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## ATOMIC WEIGHTS, 1948

*Journal of the American Chemical Society, 69, 731 (1947)*

Element	Symbol	Atomic number	Atomic weight	Element	Symbol	Atomic number	Atomic weight
Aluminum	Al	13	26.97	Molybdenum	Mo	42	95.95
Antimony	Sb	51	121.76	Neodymium	Nd	60	144.27
Argon	A	18	39.944	Neon	Ne	10	20.183
Arsenic	As	33	74.91	Nickel	Ni	28	58.69
Barium	Ba	56	137.36	Nitrogen	N	7	14.008
Beryllium	Be	4	9.02	Osmium	Os	76	190.2
Bismuth	Bi	83	209.00	Oxygen	O	8	16.0000
Boron	B	5	10.82	Palladium	Pd	46	106.7
Bromine	Br	35	79.916	Phosphorus	P	15	30.98
Cadmium	Cd	48	112.41	Platinum	Pt	78	195.23
Calcium	Ca	20	40.08	Potassium	K	19	39.096
Carbon	C	6	12.010	Praseodymium	Pr	59	140.92
Cerium	Ce	58	140.13	Protoactinium	Pa	91	231
Cesium	Cs	55	132.91	Radium	Ra	88	226.05
Chlorine	Cl	17	35.457	Radon	Rn	86	222
Chromium	Cr	24	52.01	Rhenium	Re	75	186.31
Cobalt	Co	27	58.94	Rhodium	Rh	45	102.91
Columbium	Cb	41	92.91	Rubidium	Rb	37	85.48
Copper	Cu	29	63.54	Ruthenium	Ru	44	101.7
Dysprosium	Dy	66	162.46	Samarium	Sm	62	150.43
Erbium	Er	68	167.2	Scandium	Sc	21	45.10
Europium	Eu	63	152.0	Selenium	Se	34	78.96
Fluorine	F	9	19.00	Silicon	Si	14	28.06
Gadolinium	Gd	64	156.9	Silver	Ag	47	107.880
Gallium	Ga	31	69.72	Sodium	Na	11	22.997
Germanium	Ge	32	72.60	Strontium	Sr	38	87.63
Gold	Au	79	197.2	Sulfur	S	16	32.066
Hafnium	Hf	72	178.6	Tantalum	Ta	73	180.88
Helium	He	2	4.003	Tellurium	Te	52	127.61
Holmium	Ho	67	164.94	Terbium	Tb	65	159.2
Hydrogen	H	1	1.0080	Thallium	Tl	81	204.39
Indium	In	49	114.76	Thorium	Th	90	232.12
Iodine	I	53	126.92	Thulium	Tm	69	169.4
Iridium	Ir	77	193.1	Tin	Sn	50	118.70
Iron	Fe	26	55.85	Titanium	Ti	22	47.90
Krypton	Kr	36	83.7	Tungsten	W	74	183.92
Lanthanum	La	57	138.92	Uranium	U	92	238.07
Lead	Pb	82	207.21	Vanadium	V	23	50.95
Lithium	Li	3	6.940	Xenon	Xe	54	131.3
Lutecium	Lu	71	174.99	Ytterbium	Yb	70	173.04
Magnesium	Mg	12	24.32	Yttrium	Y	39	88.92
Manganese	Mn	25	54.93	Zinc	Zn	30	65.38
Mercury	Hg	80	200.61	Zirconium	Zr	40	91.22

**INDUSTRIAL HYGIENE AND TOXICOLOGY**  
*In Two Volumes*  
**VOLUME II**

# CONVERSION TABLE FOR GASES AND VAPORS<sup>a</sup>

(Milligrams per Liter to Parts per Million and Vice Versa;  
25° C. and 760 mm. Mercury, Barometric Pressure)

Molecular Weight	1 mg./l. p.p.m.	1 p.p.m. mg./l.	Molecular Weight	1 mg./l. p.p.m.	1 p.p.m. mg./l.	Molecular Weight	1 mg./l. p.p.m.	1 p.p.m. mg./l.
1	24,450	0.0000409	51	479	0.002086	101	242.1	0.00413
2	12,230	.0000818	52	470	.002127	102	239.7	.00417
3	8,150	.0001227	53	461	.002168	103	237.4	.00421
4	6,113	.0001636	54	453	.002209	104	235.1	.00425
5	4,890	.0002045	55	445	.002250	105	232.9	.00429
6	4,075	.0002454	56	437	.002290	106	230.7	.00434
7	3,493	.0002863	57	429	.002331	107	228.5	.00438
8	3,056	.000327	58	422	.002372	108	226.4	.00442
9	2,717	.000368	59	414	.002413	109	224.3	.00446
10	2,445	.000409	60	408	.002554	110	222.3	.00450
11	2,223	.000450	61	401	.002495	111	220.3	.00454
12	2,038	.000491	62	394	.00254	112	218.3	.00458
13	1,881	.000532	63	388	.00258	113	216.4	.00462
14	1,746	.000573	64	382	.00262	114	214.5	.00466
15	1,630	.000614	65	376	.00266	115	212.6	.00470
16	1,528	.000654	66	370	.00270	116	210.8	.00474
17	1,438	.000695	67	365	.00274	117	209.0	.00479
18	1,358	.000736	68	360	.00278	118	207.2	.00483
19	1,287	.000777	69	354	.00282	119	205.5	.00487
20	1,223	.000818	70	349	.00286	120	203.8	.00491
21	1,164	.000859	71	344	.00290	121	202.1	.00495
22	1,111	.000900	72	340	.00294	122	200.4	.00499
23	1,063	.000941	73	335	.00299	123	198.8	.00503
24	1,019	.000982	74	330	.00303	124	197.2	.00507
25	978	.001022	75	326	.00307	125	195.6	.00511
26	940	.001063	76	322	.00311	126	194.0	.00515
27	906	.001104	77	318	.00315	127	192.5	.00519
28	873	.001145	78	313	.00319	128	191.0	.00524
29	843	.001186	79	309	.00323	129	189.5	.00528
30	815	.001227	80	306	.00327	130	188.1	.00532
31	789	.001268	81	302	.00331	131	186.6	.00536
32	764	.001309	82	298	.00335	132	185.2	.00540
33	741	.001350	83	295	.00339	133	183.8	.00544
34	719	.001391	84	291	.00344	134	182.5	.00548
35	699	.001432	85	288	.00348	135	181.1	.00552
36	679	.001472	86	284	.00352	136	179.8	.00556
37	661	.001513	87	281	.00356	137	178.5	.00560
38	643	.001554	88	278	.00360	138	177.2	.00564
39	627	.001595	89	275	.00364	139	175.9	.00569
40	611	.001636	90	272	.00368	140	174.6	.00573
41	596	.001677	91	269	.00372	141	173.4	.00577
42	582	.001718	92	266	.00376	142	172.2	.00581
43	569	.001759	93	263	.00380	143	171.0	.00585
44	556	.001800	94	260	.00384	144	169.8	.00589
45	543	.001840	95	257	.00389	145	168.6	.00593
46	532	.001881	96	255	.00393	146	167.5	.00597
47	520	.001922	97	252	.00397	147	166.3	.00601
48	509	.001963	98	249.5	.00401	148	165.2	.00605
49	499	.002004	99	247.0	.00405	149	164.1	.00609
50	489	.002045	100	244.5	.00409	150	163.0	.00613



Molecular Weight	1 mg./l. p.p.m.	1 p.p.m. mg./l.	Molecular Weight	1 mg./l. p.p.m.	1 p.p.m. mg./l.	Molecular Weight	1 mg./l. p.p.m.	1 p.p.m. mg./l.
151	161.9	0.00618	201	121.6	0.00822	251	97.4	0.01027
152	160.9	.00622	202	121.0	.00826	252	97.0	.01031
153	159.8	.00626	203	120.4	.00830	253	96.6	.01035
154	158.8	.00630	204	119.9	.00834	254	96.3	.01039
155	157.7	.00634	205	119.3	.00838	255	95.9	.01043
156	156.7	.00638	206	118.7	.00843	256	95.5	.01047
157	155.7	.00642	207	118.1	.00847	257	95.1	.01051
158	154.7	.00646	208	117.5	.00851	258	94.8	.01055
159	153.7	.00650	209	117.0	.00855	259	94.4	.01059
160	152.8	.00654	210	116.4	.00859	260	94.0	.01063
161	151.9	.00658	211	115.9	.00863	261	93.7	.01067
162	150.9	.00663	212	115.3	.00867	262	93.3	.01072
163	150.0	.00667	213	114.8	.00871	263	93.0	.01076
164	149.1	.00671	214	114.3	.00875	264	92.6	.01080
165	148.2	.00675	215	113.7	.00879	265	92.3	.01084
166	147.3	.00679	216	113.2	.00883	266	91.9	.01088
167	146.4	.00683	217	112.7	.00888	267	91.6	.01092
168	145.5	.00687	218	112.2	.00892	268	91.2	.01096
169	144.7	.00691	219	111.6	.00896	269	90.9	.01100
170	143.8	.00695	220	111.1	.00900	270	90.6	.01104
171	143.0	.00699	221	110.6	.00904	271	90.2	.01108
172	142.2	.00703	222	110.1	.00908	272	89.9	.01112
173	141.3	.00708	223	109.6	.00912	273	89.6	.01117
174	140.5	.00712	224	109.2	.00916	274	89.2	.01121
175	139.7	.00716	225	108.7	.00920	275	88.9	.01125
176	138.9	.00720	226	108.2	.00924	276	88.6	.01129
177	138.1	.00724	227	107.7	.00928	277	88.3	.01133
178	137.4	.00728	228	107.2	.00933	278	87.9	.01137
179	136.6	.00732	229	106.8	.00937	279	87.6	.01141
180	135.8	.00736	230	106.3	.00941	280	87.3	.01145
181	135.1	.00740	231	105.8	.00945	281	87.0	.01149
182	134.3	.00744	232	105.4	.00949	282	86.7	.01153
183	133.6	.00748	233	104.9	.00953	283	86.4	.01157
184	132.9	.00753	234	104.5	.00957	284	86.1	.01162
185	132.2	.00757	235	104.0	.00961	285	85.8	.01166
186	131.5	.00761	236	103.6	.00965	286	85.5	.01170
187	130.7	.00765	237	103.2	.00969	287	85.2	.01174
188	130.1	.00769	238	102.7	.00973	288	84.9	.01178
189	129.4	.00773	239	102.3	.00978	289	84.6	.01182
190	128.7	.00777	240	101.9	.00982	290	84.3	.01186
191	128.0	.00781	241	101.5	.00986	291	84.0	.01190
192	127.3	.00785	242	101.0	.00990	292	83.7	.01194
193	126.7	.00789	243	100.6	.00994	293	83.4	.01198
194	126.0	.00793	244	100.2	.00998	294	83.2	.01202
195	125.4	.00798	245	99.8	.01002	295	82.9	.01207
196	124.7	.00802	246	99.4	.01006	296	82.6	.01211
197	124.1	.00806	247	99.0	.01010	297	82.3	.01215
198	123.5	.00810	248	98.6	.01014	298	82.0	.01219
199	122.9	.00814	249	98.2	.01018	299	81.8	.01223
200	122.3	.00818	250	97.8	.01022	300	81.5	.01227

\* A. C. Fieldner, S. H. Katz, and S. P. Kinney, "Gas Masks for Gases Met in Fighting Fires," *U. S. Bur. Mines, Tech. Paper No. 248* (1921).



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# INDUSTRIAL HYGIENE AND TOXICOLOGY

FRANK A. PATTY, *Editor*

*Contributors:*

J. BROZEK	F. F. HEYROTH	F. A. PATTY
L. F. CURTISS	F. R. HOLDEN	L. SCHWARTZ
E. E. DART	G. W. JONES	H. SPECHT
W. B. DEICHMANN	R. A. KEHOE	J. H. STERNER
D. O. HAMBLIN	J. B. LITTLEFIELD	J. F. TREON
I. HARTMANN	C. P. MC CORD	W. N. WITHERIDGE

VOLUME II

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## USEFUL EQUIVALENTS AND CONVERSION FACTORS

<p>1 kilometer = 0.6214 mile</p> <p>1 meter = 3.281 feet</p> <p>1 centimeter = 0.3937 inch</p> <p>1 micron = 1/25,400 inch = 40 microinches</p> <p>1 foot = 30.48 centimeters</p> <p>1 inch = 25.40 millimeters</p> <p>1 square foot = 0.0929 square meter</p> <p>1 square inch = 6.452 square centimeters</p> <p>1 cubic meter = 35.315 cubic feet</p> <p>1 cubic foot = 28.32 liters = 0.0283 cubic meter</p> <p>1 cubic inch = 16.39 cubic centimeters</p> <p>1 cubic centimeter = 0.0610 cubic inch</p> <p>1 U. S. gallon = 3.7853 liters</p> <p>1 U. S. gallon = 231 cubic inches = 0.13368 cubic foot</p> <p>1 liter = 0.9081 quart (dry)</p>	<p>1 liter = 1.057 quarts (U. S. liquid)</p> <p>1 cubic foot of water = 62.43 lbs. (4° C.)</p> <p>1 U. S. gallon of water = 8.345 lbs. (4° C.)</p> <p>1 kilogram = 2.205 pounds</p> <p>1 gram = 15.43 grains</p> <p>1 pound = 453.59 grams</p> <p>1 ounce (avoir.) = 28.35 grams</p> <p>1 gram mole of a perfect gas <math>\approx</math> 24.45 liters (at 25° C. and 760 mm. Hg barometric pressure)</p> <p>1 atmosphere = 14.7 pounds per square inch</p> <p>1 foot of water pressure = 0.4335 pound per square inch</p> <p>1 inch of mercury pressure = 0.4912 pound per square inch</p> <p>1 BTU = 778 foot-pounds</p> <p>1 HP = 0.707 BTU per second = 550 foot-pounds per second</p>
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To convert degrees centigrade to degrees Fahrenheit:  $^{\circ}\text{C} \cdot (9/5) + 32 = ^{\circ}\text{F}$ .

To convert degrees Fahrenheit to degrees centigrade:  $(5/9)(^{\circ}\text{F} - 32) = ^{\circ}\text{C}$ .

For solutes in water: 1 mg./l.  $\approx$  1 p.p.m. (by weight)

Atmospheric contamination: 1 mg./l.  $\approx$  1 oz./1000 cu. ft. (approx.)

For gases or vapors in air at 25° C. and 760 mm. Hg pressure:

To convert mg./l. to p.p.m. (by volume):  $\text{mg./l.} (24,450/\text{mol. wt.}) = \text{p.p.m.}$

To convert p.p.m. to mg./l.:  $\text{p.p.m.} (\text{mol. wt.}/24,450) = \text{mg./l.}$

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**INDUSTRIAL HYGIENE AND TOXICOLOGY**

*Volume II*

## PREFACE TO VOLUME II

For the benefit of the reader who does not have Volume I immediately available we have listed on page x the contents of that volume, which deals with the broad aspects of industrial hygiene.

Volume II stresses the properties and physiological action of atmospheric contaminants, describes industrial exposures, touches upon specific analytical methods, and discusses permissible concentrations, flammability, odors, and warning properties. The last chapter is devoted to the recognition and control of industrial exposures.

FRANK A. PATTY

Detroit, Michigan  
April, 1949

## PREFACE TO VOLUME I

Industrial hygiene has been recognized and practiced from the time of Pliny down through the ages. It is the present concept of industrial hygiene that is relatively new—the concept of anticipating and recognizing potentially harmful situations and applying engineering control measures before serious injury results. There are some who question industry's ability to control all harmful exposures; and there is quite naturally a tendency to take the easy way out of a difficulty by substituting materials of low or moderate toxicity for those of a hazardous nature. Nevertheless, where incentives such as low cost, availability, or superior properties of a hazardous material justify the provision of positive engineering controls, they can be supplied promptly.

It is said that artisans are born rather than made, but there can be no doubt that industrial hygienists must be made, and it takes years to mellow some of us with sufficient understanding so that we can use our knowledge of the basic principles of industrial hygiene to the best advantage in accomplishing our goal.

Depending somewhat upon where we acquire our academic training and initial experience in field work, we are likely to start out with the concept that industry has one purpose—to make money—and that, in following that urge, the humanitarian aspects are apt to be neglected. So it is with somewhat of a shock that some of us learn that many industries are eagerly taking the initiative in improving the working environment of their employees. Our first ideas of introducing hygiene to industry are likely to involve some means of maneuvering into a position in which our recommendations for control measures are to be accepted as commandments not to be questioned and not, upon penalty of closing up shop, to be ignored. It is only gradually that we become aware of the fact that in promoting anything to the American public a sound idea "takes" more quickly and develops faster if it is "sold" rather than presented as an ultimatum. As a



people we basically resent being told bluntly that we have to do a thing: we much prefer to "discover" for ourselves that the proposed new course is correct and therefore to our advantage. Adams\* expresses these ideas well:

"The American is a composite of almost all races, nationalities, and classes . . . He hates a bit and bridle as heartily as does a young colt . . . There are dirty politicians, dirty labor leaders, dirty business men—black markets, some selfish and dirty consumers—but the Americans, now 138,000,000 of them, *the American people*, are the hope of the world and of the whole future of humanity."

The industrial hygienist becomes aware that salesmanship is a necessary part of his practice. The salesman will think of the "buyer's" point of view and, first of all, develop his recommendations for environmental controls with the understanding of an economist, and then stress all the advantages. He will simplify his work by taking advantage of the views of production engineers and occasionally going them one better by saving them money in the conservation of materials or in the recovery of a by-product. One cardinal rule he learns early is not to "bluff" or try to impress his audience with his superior knowledge. Some few persons have the ability to "get away with it," but the odds are against them and it is much safer to work on the same plane as our audience whether that means a step down or a jump up, and it helps to imagine one's self in the position of the man one is trying to influence.

Industrial hygiene may be defined as *the science and art of preserving health through the recognition, evaluation, and control of environmental causes and sources of illness in industry*. It resolves itself into the problem of finding factors or conditions in workplaces that may cause or contribute to the illness or serious discomfort of employees, and of devising methods and means of eliminating or controlling such conditions.

It would be a mistake to attempt to give the impression that industrial hygiene is pure science, or that it is restricted to the art of applying scientific principles: much of it involves a liberal use of common sense or what is perhaps better known as "horse sense." The job will never become monotonous or routine because the chemist, the engineer, and the physicist will keep introducing new and more or less hazardous materials and processes that require new developments for the evaluation and control of exposures attendant to their use. Neither is the job glamorous or spectacular, and much of it is hard work bordering on drudgery, but it has its compensations.

I should like to narrate an incident that, because of its fundamentality and at the same time dramatic departure from the daily routine of an industrial hygienist, may be worth describing without retouching. One of the pioneers in industrial medicine and hygiene whom most readers will recognize without further identification might have regarded this incident as an "acorn.†" However, since no tangible reward or token of appreciation was either anticipated or received and the only special remuneration was

\* J. T. Adams, *Big Business in Democracy*. Scribner, New York, 1946.

† C. P. McCord, *A Blind Hog's Acorns*. Cloud, Inc., Chicago, 1945.

# The Halogens

FRANCIS F. HEYROTH, M.D.

## FLUORINE AND FLUORIDES OF THE ALKALIES AND ALKALINE EARTHS

### 1. *Uses and Industrial Exposures*

Fluorine is a yellow gas, which does not occur free in nature, because of its great reactivity. With the moisture of the air it forms hydrogen fluoride. Elementary fluorine is prepared in the chemical industry for use in fluorinating organic compounds. The two chief sources of fluorine compounds are fluorspar (calcium fluoride) and cryolite (sodium aluminum fluoride,  $\text{Na}_3\text{AlF}_6$ ). The annual consumption of the former in the United States rose from 183,000 tons in 1939 to about 400,000 tons in 1943. Imports of cryolite from Greenland, its only commercial source, rose from 10,210 tons in 1939 to 18,000 tons in 1941.<sup>1</sup>

The largest use of fluorspar is in steelmaking and in the smelting of nickel, copper, gold, and silver, where it serves as a flux. Other applications are in the opacifying of glass and enamels, and in coatings for welding rods. At least 50,000 tons of it, annually, are treated with sulfuric acid for the preparation of hydrogen fluoride. Sodium fluoride is used in considerable quantities as a rodenticide and insecticide, antimony fluoride serves as a catalyst for certain organic reactions, and barium fluoride is used in baths for the electrolytic isolation of beryllium. Lesser uses of fluorides are found in the bleaching of cane for seats, in the disinfection of hides and skins, in the preservation of timbers, in the coagulation of latex, in cleaning graphite, metals, windows, and glassware, and in various ways in the optical, brewing, and dyeing industries.<sup>2</sup>

Cryolite is employed as an insecticide and, in molten form, as an electrolyte in the production of aluminum from alumina. In Danish plants for the grinding and packing of cryolite, the presence of large quantities of dust caused the fluorine content of the air to be about 0.035 mg. per liter.<sup>3</sup> Exposure to cryolite dusts also occurs in the manufacture of beryllium.

<sup>1</sup> U.S. Bureau of Mines, *Minerals Year Book* (1941).

<sup>2</sup> D. A. Greenwood, *Physiol. Rev.*, 20, 582 (1940). K. F. Stahl, *J. Eng. Chem.*, 7, 56 (1915); *Illinois Labor Bull. No. 4*, 412 (1944); *J. Ind. Hyg. Toxicol.*, 26, 103A (1944).

<sup>3</sup> K. Roholm, *Arch. Gewerbepath. Gewerbehyg.*, 7, 255 (1936).



the feeling of satisfaction that goes with accomplishing any job, assumed or assigned, it was considered all in the day's work.

While busily engaged at my office one morning in the industrial hygienist's favorite occupation of poring over survey reports, I received a telephone call: "This is Dr. \_\_\_\_\_, chemist over at \_\_\_\_\_ Dry Dock. Here's something I think you should know about and maybe you will want to come over and look around. We just sent a man to the hospital and we have two more who are laid up and in a serious condition. The \_\_\_\_\_ was docked here just two weeks ago for repairs and conversion and out of the 2000 men working on her, over 100 are affected with some sort of breaking out and itch and all the men are threatening to quit if we don't find out what's wrong and correct it. The boat's been in the tropics for some time and the workmen fear some tropical disease is responsible for this outbreak."

Yes, I did want to look around, and within an hour was aboard the ship and observed many of the afflicted men at work. There was considerable grumbling and an abundance of dirty looks. Several men wore bandages over vesicular patches and on a few there was evidence of a generalized fine vesiculation. We went through the ship from stem to stern and forecastle to bilge. It was like a beehive: men were cutting with torches, sawing out panels, knocking off plaster, shoveling out debris and filth, scrubbing, and removing the interior furnishings preparatory to refitting the boat completely. Admittedly the ship was dirty—in fact, in some areas it was filthy—but so what! Next we went to the first-aid room to see the attendant and find out what, if any, information could be obtained there. The place was crowded with patients, and while we waited to see the attendant first-aid man we could hear the grumblings of the waiting patients, who complained of "filthy working conditions" and that, if the health department were not called in to condemn the place, everyone should quit before they became ill—that the place was "infested with fleas" and that they didn't "want any tropical fevers." Finally the harassed attendant came to us, but had little to offer except that the cases and complaints were getting more numerous and he certainly hoped we could do something.

We had seen the situation: a once luxuriant ship, somewhat filthy in spots, an explosive outbreak of dermatitis in nearly ten per cent of the 2000 men at work on the ship, no reported cases among the many thousands of workmen in adjacent areas of the same shipyard, and, unless something were done quickly, work on this desperately needed troop ship and possibly in the entire yard would stop.

The job looked interesting if not easy. We collected samples of everything we could get loose—plaster, upholstery, hair stuffing, sweepings, scrapings from panels and floors, and samples of the different woods and sawdusts, and returned to the laboratory. The samples were turned over to the chemists and microscopists to look for fumigants, insecticides, alkalies, and other common irritants, as well as any signs of insects or parasites. Two members of the staff were inveigled into joining me in making patch tests with some of the materials after saturating them with alcohol as a precautionary measure. While these tests were in progress a medical associate told me with an air of finality that our company had called in, as consultant, an authority on dermatology and that he planned to leave the matter entirely in the consultant's hands. When I took the story to my immediate superior he said it was very interesting, and sometime when he had more time I should "tell him all about it." I telephoned the consultant dermatologist and inquired if he had seen the cases and had any ideas of what might cause the difficulty. Yes, he had seen them, and, except for the fact that it didn't make sense, he would say that they resembled poison-ivy cases. That agreed with what we had seen on the job, but we had not seen any poison ivy! After all of the chemical and microscopic tests proved negative except for an insignificant amount of arsenic in the sweepings, there remained only the possibility that the patch tests might indicate an irritant. After 48 hours, and with all patch tests negative, the shipyard's chemist re-

The use of fluoride-coated welding rods offers a definite hazard.<sup>4</sup> In magnesium founding, fluorides inhibit oxidation when sprayed upon cores or mixed with the core sand to the extent of 4 to 10 per cent. They also act as fluxes when added to the melting pots.<sup>5</sup> Williams<sup>6</sup> found the following quantities, expressed as milligrams of fluoride per cubic meter of air, near various operations: core-spraying, 0.7; melting, 1.26; molding, 1.88; shakeout, 8.77. Analyses by the Illinois Department of Labor in other foundries showed the presence of fluorine equivalent to 2 p.p.m. of hydrogen fluoride at the molding operation, less than 3 p.p.m. in the shakeout areas, but as much as 7.2 p.p.m. near the pouring operation. Largent and Ferneau,<sup>7</sup> who used the urinary excretion of fluorine by workers as a measure of the severity of exposure, found the greatest exposure in the core-spraying and pouring areas.

During sulfuric acid treatment in the preparation of fertilizer from fluorine-bearing phosphate it has been estimated that 25,000 tons of fluorine per year escape into the atmosphere.<sup>8</sup> Fluorine compounds emitted by fertilizer and aluminum factories have been known to contaminate the forage of nearby areas and to cause illness among cattle and other animals. In one factory for the extraction of beryllium, the air contained fluorine equivalent to 0.996 mg. of sodium fluoride per cubic meter.<sup>9</sup>

## 2. Determination of Fluorine Compounds in Air

The sample of air may be collected in an evacuated bulb and shaken with a 1 per cent solution of sodium hydroxide, or it may be passed through an impinger. If hydrogen fluoride is the only fluorine compound present, the remaining free alkali in the absorbing solution may be titrated with acid. If dusts or other volatile fluorine compounds are present, the liquid is concentrated to a small volume, after the addition of calcium or magnesium oxide to prevent loss of fluorine. It is then distilled with perchloric acid and the fluorine determined in the distillate by the back-titration method of Dahle, Bonnar, and Wichmann.<sup>10</sup> A photocolometric method based on the ability of the fluoride ion to decolorize ferric thiocyanate has recently been used for the continuous automatic determination of concentrations of 0.001 to 0.015 mg. of hydrogen fluoride per liter.<sup>11</sup>

<sup>4</sup> P. Drinker and K. W. Nelson, *Ind. Med.*, **13**, 673 (1944).

<sup>5</sup> M. E. Brooks and A. W. Winston, *Trans. Am. Foundrymen's Assoc.*, **49**, 165 (1941).

<sup>6</sup> C. R. Williams, *J. Ind. Hyg. Toxicol.*, **24**, 277 (1942).

<sup>7</sup> E. J. Largent and I. Ferneau, *J. Ind. Hyg. Toxicol.*, **26**, 113 (1944).

<sup>8</sup> M. J. M. Schuurisma, *Chem. Weekblad*, **38**, 583, (1941).

<sup>9</sup> J. Shilen, A. E. Galloway, and J. F. Mellor, *Ind. Med.*, **13**, 464 (1944).

<sup>10</sup> D. Dahle, R. U. Bonnar, and H. J. Wichmann, *J. Assoc. Official Agr. Chem.*, **21**, 459 (1938).

<sup>11</sup> L. S. Chermodanova, *Zavodskaya Lab.*, **8**, 1248 (1939); *Chem. Abstracts*, **34**, 5785 (1940).

ported that there were several more cases, including an electrician working on the dock beside the boat, and that a walkout seemed imminent even though the ship was desperately needed for a troop transport.

The fact that an electrician who possibly had not been on the boat was affected gave an indication that the problem might be attacked from an epidemiological approach by personally interviewing some of the afflicted men. Discussion of personal matters with employees, especially shipyard workers, is ordinarily something to be avoided, but in this instance approval of such interviews was readily obtained from all parties concerned. Aided by the chemist and two safety engineers, we went out on the job and talked to some of the affected men, including the electrician, who had never been on the suspected ship, and a security policeman, who was seriously affected and had been aboard the ship only once for a few minutes. This introduced a strong element of doubt about the ship's being the contact source and diverted our attention to other possible sources of irritant material. It developed that nearly all cases were on the day shift. The electrician's case had been diagnosed "cable rash," but, since the characteristics of his lesions were similar to those of the other workmen, we did not waste time examining the cables with which he had been working. Instead, we investigated all the possible exposure sources where the men spent their time when they were off the ship: where they ate their lunch, where they loafed, and the route they took to and from work. We found what appeared to be some damaged oil drums in a pile on a sand lot where several men had spent their lunch hour within the shipyard grounds, but about a block away from the dock to which the boat was tied. The drums were punctured or otherwise damaged and, for the most part, were empty, but three or four contained some dark oily liquid. Close examination of these drums revealed lettering still visible on one which read *Cashew Shell Liquid!* The cause of the epidemic had been found.

At the shipyard, management quickly announced the facts over a public address system to the workmen so that their fears would be allayed. A strike was averted, and the ship was completed ahead of schedule. Further investigation revealed that cashew shell liquid had been spilled on the dock to some extent, in the street to a considerable amount, and extensively scattered over the sand lot in question. Many of the men working at refinishing and repairing this ship had sat on the sand, or the drums themselves, during the noon hour while they ate their lunches. Others had stretched out in the sun, bare-backed, on the contaminated sand. Checking the source of the drums revealed that a cargo of 1000 drums of the liquid had arrived and been unloaded on the opposite side of the same dock about a month previously. This work had been done by an outside contractor who had dumped the damaged drums onto the unused lot.

At our suggestion, all suspicious-looking spots were covered with chlorinated lime, the dock was cleaned and scrubbed, the drums disposed of, and dirt filled in on the sand lot. The dermatitis, which by now was starting to appear in the homes of workmen, from contact with soiled clothing, quickly disappeared. My colleague, the shipyard's chemist, however, in a sincere effort to convince himself and others of the potency of the cashew liquid, became impatient at negative results obtained in 24 hours with one tiny patch test and tried four more generous patches with samples from different drums. A few days later he joined those who had been hospitalized.

This is not a medical book nor is it intended for legal reference. Its primary purpose is not to aid in the diagnosis and treatment of disease, the winning of compensation, or the refutation of false claims. If it should prove of use in such instances by making some facts more widely available, it may be presumed that the more light that can be thrown upon these phases of industrial medicine and industrial relations the better. It is hoped that much information of use in pre-

### 3. Physiological Response

*Immediate intoxication by fluorides.* The lethal dose of sodium fluoride when administered orally to rabbits is 200 mg. per kilogram of body weight.<sup>12</sup> Because of its lesser solubility, cryolite is much less toxic: rats are not killed by the largest dose that can be administered.

The symptoms that follow the ingestion of soluble fluorides by man are listed in the order of diminishing frequency of occurrence: vomiting, abdominal pain, diarrhea, convulsions, generalized and muscular weakness, collapse, dyspnea, paresis, difficulty in articulation, thirst, weakness of the pulse, disturbed color vision, loss of consciousness, and motor unrest.<sup>13</sup> Albuminuria is frequently present. Death is primarily due to respiratory paralysis. Acute toxic nephritis, hemorrhagic gastroenteritis, and more or less definite pathologic damage to other organs are found on examination. The calcium content of the blood is reduced following the ingestion of large amounts of fluorides,<sup>14</sup> but this is not of great importance in the mechanism of the toxic action. Fluoride acts as a general protoplasmic poison, reducing the anaerobic glucolysis of many types of cells without affecting their ability to consume oxygen.<sup>15</sup> It interferes with the action of certain enzymes concerned with the conversion of phosphoglyceric acid to phosphopyruvic acid, an essential link in the chain of reactions involved in muscle metabolism.<sup>16</sup> Other enzymes, such as glycerol phosphatase,<sup>17</sup> esterases,<sup>18</sup> and liver arginase,<sup>19</sup> as well as cozymase,<sup>20</sup> are affected by the fluoride ion.

Immediate intoxication by the ingestion of fluorides is rare in industry, but various degrees of respiratory irritation may result from the inhalation of fluorides in the form of dusts. Some magnesium founders complain of a severe biting sensation in the nose when the concentration of fluorides in the air exceeds 10 mg. per cubic meter. This is accompanied after a few minutes by a discharge from the nose or by nosebleed. No such effects are noted when the concentration does not exceed 2.5 mg. per cubic meter.<sup>6</sup>

<sup>12</sup> C. W. Muehlberger, *J. Pharmacol.*, **39**, 346 (1930).

<sup>13</sup> K. Roholm, *Fluorine Intoxication*, Lewis, London, 1937. Heffter-Huebner, *Handbuch experl. Pharmacol.*, Erg. 7, 1 (1933); *Ergeb. inn. Med. u. Kinderheilk.*, **57**, 822 (1939); *Z. ges. gerichtl. Med.*, **27**, 174 (1936). F. McClure, *Physiol. Revs.*, **13**, 277 (1933). D. A. Greenwood, *ibid.*, **20**, 582 (1940). F. deEds, *Medicine*, **12**, 1 (1933).

<sup>14</sup> H. Wieland and G. Kurtzahn, *Arch. experl. Path. Pharmacol.*, **97**, 488 (1923). A. Jodlbauer, *ibid.*, **164**, 464 (1931).

<sup>15</sup> F. Lipmann, *Biochem. Z.* **206**, 171 (1929). F. Dickens and F. Simer, *Biochem. J.*, **23**, 936 (1929). K. Lohmann, *Biochem. Z.*, **222**, 324 (1930). F. Lipmann and K. Lohmann, *ibid.*, **222**, 389 (1930).

<sup>16</sup> G. Embden, A. Abraham, and H. Lange, *Z. physiol. Chem.*, **136**, 308 (1924). G. Embden and H. Hentschel, *Biochem. Z.*, **166**, 343 (1925).

<sup>17</sup> K. Inouye, *J. Biochem. (Japan)*, **7**, 433 (1927). F. Lipmann, *Biochem. Z.*, **196**, 3 (1928). V. A. Drill, J. H. Annegers, and A. C. Ivy, *J. Biol. Chem.*, **152**, 339 (1944).

<sup>18</sup> A. S. Loevenhart and G. Peirce, *J. Biol. Chem.*, **2**, 397 (1907). S. Amberg and A. S. Loevenhart, *ibid.*, **4**, 149 (1908). P. Rothschild, *Biochem. Z.*, **206**, 186 (1929).

<sup>19</sup> S. Hino, *J. Biochem. (Japan)*, **6**, 335 (1926).

<sup>20</sup> A. Lennerstrand, *Biochem. Z.*, **287**, 172 (1936).

ventive medicine is included. Diagnostic signs of absorption or of early effects, in advance of injury, are eagerly sought by the progressive industrial physician, and, although time-proved and recognized tests are disappointingly few, the research-minded industrial physician will find opportunities for increasing this field of knowledge. The object of this book is to present industrial hygiene and toxicology in simple, understandable terms in sufficient detail to be of some use to all persons interested in safeguarding the health and welfare of working people and in improving the working environment. Essential requisites for the completely successful advancement of the health and safety of the breadwinning population include: (1) competent persons in health and safety maintenance departments; (2) managerial interest and appreciation of the benefits to be derived from health and safety work; and (3) teamwork—camaraderie, and cooperative efforts among industrial hygiene, medical, and safety personnel.

The welfare of an individual workman involves not only a working environment that gives reasonable assurance of freedom from accidental injury or occupational disease, but also his mental, temperamental, and physical fitness for the work to be done. Incentive, whether in the form of tangible assets to supply the necessities and some of the pleasures of life, or some expression of interest or recognition of accomplishments, ability, and efforts may be involved indirectly, but are somewhat outside the field of industrial hygiene.

It is not possible to maintain a uniform style in a collaboration, but the collective viewpoints compensate for some variations in style. In Chapter Thirty-Five considerable variation will be noted in the length of discussions. Much of this follows a premeditated plan to give full discussion where most needed and to avoid duplication. Some, however, reflects the degree of personal familiarity of the authors of this part of the book with the occupation under discussion. Where information is desired on an industry not listed, significant processes of the industry may be found elsewhere. Many cross references of this nature have been included. The book is liberally supplied with references for the benefit of those who wish to pursue the subjects in greater detail.

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FRANK A. PATTY

Detroit, Michigan  
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*Fluorosis or chronic fluorine intoxication.* The daily ingestion by rats of a diet containing very small doses of fluorides (0.0007 to 0.0012 per cent) produces a series of fine, barely discernible lines of impaired calcification of the teeth. Dietary levels greater than 0.011 to 0.023 per cent cause some inhibition of growth, and diets containing more than 0.03 per cent cause a loss of appetite and an unhealthy appearance. When fluorine in the form of a soluble salt is present at levels above 0.09 per cent, rats die in a few days to a few months, following a period of inanition, lethargy, and weakness. When present as cryolite, fluorine is less toxic.<sup>21</sup>

Although a daily intake of fluorine of the order of 1 mg. per kilogram of body weight will produce incipient dental fluorosis, 10 to 15 mg. per kilogram per day are necessary to affect adversely the general well-being of animals. A daily intake of 20 to 25 mg. per kilogram has serious effects and a daily dose of 15 to 100 mg. per kilogram is lethal in from one to a few weeks.<sup>13</sup> Such impairment of fertility as has been found in experiments on animals,<sup>22,23</sup> may have resulted from the general state of inanition.<sup>21</sup> Relatively large doses of the order of 150 mg. of sodium fluoride per kilogram are required in order to produce inflammation of the gastric and duodenal mucosa. In pigs and dogs, nephritis has been produced in feeding experiments,<sup>13</sup> but liver damage is exceptional. Anemia has been observed in some of these experiments but is not a uniform feature of chronic fluorine intoxication.<sup>13,24</sup>

Neither dental fluorosis nor a cachectic state, the production of which requires the ingestion of relatively large daily doses of fluorides, is of great significance in industrial toxicology. Lesions of the skeletal system are of greater practical importance, since they have been observed in workers who inhaled fluorine-bearing dusts over considerable periods of time. In 1892 Brandl and Tappeiner<sup>25</sup> described crystalline deposits in the marrow spaces and Haversian canals of the bones of a dog that had been fed over 400 g. of sodium fluoride during a period of 21 months. During the last 5 months of this period the animal, in running or walking, held its spine, especially the sacral portion, in an unusually stiff position. On sacrificing the dog, the investigators noted that the tensile strength of the bones, which had an unusually white appearance, was apparently increased. More recently, similar changes were noted by Bardelli and Menzani<sup>26</sup> in the bones of cattle poisoned by fluorides, and Hauck, Steenbock, and Parsons<sup>23</sup> found that the bones of rats similarly poisoned were 18 per cent heavier than normal and had a thickened cortex that in some instances encroached upon the

<sup>21</sup> M. C. Smith and R. M. Leverton, *Ind. Eng. Chem.*, **26**, 791 (1934). H. F. Smyth and H. F. Smyth, Jr., *ibid.*, **24**, 229 (1932).

<sup>22</sup> A. R. Lamb, P. H. Phillips, E. B. Hart, and G. Bohstedt, *Am. J. Physiol.*, **106**, 350 (1933). J. A. Schulz and A. R. Lamb, *Science*, **61**, 93 (1925). P. H. Phillips, A. R. Lamb, E. B. Hart, and G. Bohstedt, *Am. J. Physiol.*, **106**, 356 (1933).

<sup>23</sup> H. M. Hauck, H. Steenbock, and H. T. Parsons, *Am. J. Physiol.*, **103**, 480, 489 (1939).

<sup>24</sup> J. T. Ginn and J. T. Volker, *Proc. Soc. Exptl. Biol. Med.*, **57**, 189 (1944).

<sup>25</sup> J. Brandl and H. Tappeiner, *Z. Biol.*, **28**, 518 (1892).

<sup>26</sup> P. Bardelli and C. Menzani, *Atti ist. Veneto sci., Pt. II*, **97**, 623 (1937-38).

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medullary cavity. The skeleton of rabbits that were given 763 p.p.m. fluorine in the diet as sodium fluoride for 92 days, or 2980 p.p.m. for 47 days, was chalky; and small areas of porous bone, varying in diameter from 1 mm. to 1 cm., were scattered throughout the vertebra, cranium, zygoma, and maxillae, with larger plaques on a markedly bulked mandible.<sup>27</sup> However, no significant changes were noted in the radiographic density of the tibiae and fibulae of these rabbits. The bony abnormalities in man produced by fluorine were first observed in routine radiographic examinations.<sup>28</sup> Similar anomalies have not as yet been produced in animals<sup>29</sup> in a clear-cut fashion. Whereas the bony alterations in man are of an osteosclerotic type, those occurring in animals have tended to be of an osteoporotic nature. In some of the earlier descriptions of animals poisoned as a result of the contamination of their forage by fluorides, the condition was confused with osteomalacia. Possibly this was due to the ingestion of fluorine at a comparatively high level,<sup>30</sup> which produced signs of general illness, while in man the osteosclerotic changes are induced by the ingestion of smaller amounts, which produce only rather indefinite symptoms of ill-health. The histologic changes in bone have been discussed by de Senarclens<sup>31</sup> and by Pachaly,<sup>32</sup> but much remains to be learned regarding the factors that cause either absorption or deposition of bone to predominate. The relation between the fluorine content of bones and their gross or histologic appearance is not as yet well understood, but it is certain that fluorine can be stored in bones and teeth in large quantities.<sup>33</sup> In the rabbits of Largent, Machle, and Ferneau,<sup>27</sup> from 1.03 to 3.98 mg. of fluorine was found per gram of wet bone, which is about 17 times the normal concentration. Bardelli and Menzani<sup>26</sup> found that the bone ash contained 2.4 times the normal amount of fluorine in the initial stages of the development of bony lesions, 3.2 times the normal amount in bones with moderate damage, and 8 times the normal amount in severely damaged bones. The grossly unaltered bones of a dog fed 65 milligrams of fluorine daily for 65 months had even more fluorine.<sup>33a</sup>

Much attention has been devoted to the possible role of calcium in relation to the development of bony abnormalities. In chronic poisoning of animals, no significant diminution in the calcium content of the blood has been found.<sup>23</sup> Fluorides must be fed at a level that produces general intoxication in order to cause a diminution in the retention of calcium,<sup>34,35</sup> or to alter the calcium content

<sup>27</sup> E. J. Largent, W. Machle, and I. F. Ferneau, *J. Ind. Hyg. Toxicol.*, **25**, 396 (1943).

<sup>28</sup> F. Møller and S. V. Gudjonsson, *Acta Radiol.*, **13**, 269 (1932).

<sup>29</sup> C. J. Sutro, *Arch. Path.*, **19**, 159 (1935).

<sup>30</sup> W. Dittrich, *Arch. exptl. Path. Pharmacol.*, **168**, 319 (1932). E. Rost, *Arch. Gewerbe-path. Gewerbehyg.*, **8**, 256 (1937).

<sup>31</sup> F. de Senarclens, *Helv. Med. Acta*, **8**, 379 (1941).

<sup>32</sup> W. I. Pachaly, *Arch. exptl. Path. Pharmacol.*, **166**, 1 (1932).

<sup>33</sup> C. Y. Chang, P. H. Phillips, and E. B. Hart, *J. Dairy Sci.*, **17**, 695 (1934).

<sup>33a</sup> E. J. Largent, *unpublished data.*

<sup>34</sup> F. J. McClure and H. H. Mitchell, *J. Biol. Chem.*, **90**, 297 (1931).

<sup>35</sup> E. M. Lantz and M. C. Smith, *Am. J. Physiol.*, **109**, 645 (1934).



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or composition of the ash in the bones.<sup>28,34,36-41</sup> There is little evidence that the phosphatase content of bone is affected.<sup>42</sup>

#### 4. Absorption and Storage of Fluorine in Man

Although the soft tissues contain fluorine to the extent of 20 to 60  $\mu\text{g.}$  per 100 grams,<sup>43</sup> ingested fluorine is stored chiefly in the bones and teeth. Roholm, who found from 0.048 to 0.21 per cent fluorine in the ash of human ribs, estimated that the total amount in the bones of a man is of the order of 1.5 to 6 g. Machle and Scott<sup>41</sup> found 0.026 per cent in the ash of human bones. Some indication of the extent to which storage can occur is found in the fact that the bones of a dog that had been given 402.9 g. of sodium fluoride over a period of nearly two years contained 29 g. of fluorine.<sup>25</sup>

In the absence of industrial exposure the chief source of fluorine is in drinking water, the fluorine content of which varies greatly in various localities. The daily intake of one human subject remained remarkably constant over a period of 16 weeks of unrestricted diet, the mean value being 0.457 mg. of fluorine. Of this, 0.155 mg. was derived from the food and 0.299 mg. from the fluid constituents of the diet. The mean daily fecal output was 0.039 mg., while the mean daily urinary output was 0.377 mg. Over the entire period, no significant storage occurred.<sup>44</sup> The daily urinary output by this subject was lower than the mean value of about 1 mg. reported by Machle, Scott, and Treon<sup>45</sup> in the case of persons in areas where the water supply did not contain excessive amounts of fluorine. In 30 Danish hospital patients, the daily urinary fluorine excretion varied from 0.18 to 1.85 mg. and the mean urinary concentration was 0.92 mg. per liter.<sup>46</sup>

A slightly more than ten-fold increase in the daily intake of fluorine in soluble form, by the subject investigated by Machle and Largent,<sup>44</sup> resulted in an increase in the urinary output to 2.42 mg. daily. By deducting the mean daily fecal output of 0.19 mg. from the daily intake of 6.47 mg. it was found that 6.28 mg. had been absorbed daily. By deducting from this the urinary output, it was concluded that 3.86 mg. or 63 per cent of the amount absorbed had been

<sup>28</sup> M. C. Smith and E. M. Lantz, *J. Biol. Chem.*, 101, 677 (1933).

<sup>27</sup> C. H. Kick, R. M. Bethke, and B. H. Edgington, *J. Agr. Research*, 46, 1023 (1933).

<sup>36</sup> C. Tolle and L. H. Maynard, *Proc. Am. Soc. Animal Production*, 15, 15 (1928).

<sup>34</sup> E. B. Forbes, *Ohio Agr. Exptl. Sta. Bull.* No. 347 (1921).

<sup>35</sup> P. A. Bishop, *Am. J. Roentgenol. Radium Therapy*, 35, 577 (1936).

<sup>41</sup> W. Machle and E. W. Scott, *J. Ind. Hyg.*, 17, 230 (1935).

<sup>45</sup> P. H. Phillips, *Science*, 76, 239 (1932). H. M. Hauck, H. Steenbock, J. T. Lowe, and J. G. Halpin, *Poultry Sci.*, 12, 242 (1933). M. C. Smith and E. M. Lantz, *J. Biol. Chem.*, 112, 303 (1935).

<sup>43</sup> A. O. Gettler and L. Ellerbrook, *Am. J. Med. Sci.*, 197, 625 (1939).

<sup>44</sup> W. Machle and E. J. Largent, *J. Ind. Hyg. Toxicol.*, 25, 112 (1943).

<sup>45</sup> W. Machle, E. W. Scott, and J. F. Treon, *Am. J. Hyg.*, 29A, 139 (1939).

<sup>46</sup> G. C. Brun, H. Buchwald, and K. Roholm, *Acta Med. Scand.*, 106, 261 (1941).

## LIST OF CONTRIBUTORS

### to Volume II

- William B. Deichmann**, Ph.D., Head, Division of Pharmacology, Union University, Albany Medical College, Albany, New York — Chapter 34: *Phenol and Phenolic Compounds*.
- Donald O. Hamblin**, M.D., Medical Director, American Cyanamid Co., New York, New York — Chapter 33: *Nitro and Amino Compounds of the Aromatic Series*.
- Francis F. Heyroth**, M.D., Associate Professor of Industrial Toxicology, Kettering Laboratory of Applied Physiology, College of Medicine, University of Cincinnati, Cincinnati, Ohio — Chapter 16: *The Halogens*. Chapter 22: *The Metals (Except Lead)*.
- Francis R. Holden**, Ph.D., Naval Radiological Defense Laboratory, San Francisco, Naval Shipyard, San Francisco, California—Chapter 35: *Potential Exposures in Industry: Their Recognition and Control*.
- Robert A. Kehoe**, M.D., Director, Kettering Laboratory of Applied Physiology, College of Medicine, University of Cincinnati, Cincinnati, Ohio — Chapter 21: *Industrial Lead Poisoning*.
- Frank A. Patty**, Director, Industrial Hygiene Service, General Motors Corp., Detroit, Michigan — Chapter 17: *Alkaline Materials*. Chapter 18: *Arsenic, Phosphorus, Selenium, Sulfur, and Tellurium*. Chapter 19: *Compounds of Oxygen, Nitrogen, and Carbon*. Chapter 23: *The Aliphatic Hydrocarbons*. Chapter 24: *Aromatic and Cyclic Hydrocarbons*. Chapter 30: *The Ketones*. Chapter 31: *Ethers, Glycols, and Glycol Ethers*. Chapter 35: *Potential Exposures in Industry: Their Recognition and Control*.
- James H. Sterner**, M.D., Director, Laboratory of Industrial Medicine, Eastman Kodak Co., Rochester, New York — Chapter 20: *The Cyanides and Cyanogen Compounds*. Chapter 25: *Halogenated Hydrocarbons*. Chapter 27: *Organic Acids*. Chapter 28: *The Esters*. Chapter 29: *The Aldehydes*. Chapter 32: *Aliphatic Nitro, Diazo, and Amino Compounds*.
- Joseph F. Treon, Jr.**, Ph.D., Kettering Laboratory of Applied Physiology, College of Medicine, University of Cincinnati, Cincinnati, Ohio — Chapter 26: *The Alcohols*.

stored. McClure, Mitchell, Hamilton, and Kinser<sup>47</sup> concluded, from experiments in which account was taken of the amounts excreted in the perspiration, that storage does not begin until the daily intake is greater than 4 mg., while Machle and Largent believed that it might begin when the daily intake is 1.5 to 2 mg. Machle and Largent found that the solubility of the fluorine compound ingested influences greatly the extent to which it can be absorbed. There are some indications that the accumulation of fluorine in the bones may exert a retarding influence upon the rate at which it is stored in prolonged experiments.<sup>48</sup> In general, however, the urinary fluoride excretion may be used as a rough measure of the rate at which fluorine is being stored. A remarkable parallelism between the fluorine content of the drinking water and the concentration of fluorine in the urine of a large number of recruits has been demonstrated by McClure,<sup>49</sup> but no relation to their susceptibility to fractures of the bones could be found.

### 5. Chronic Industrial Fluorosis

In the course of radiographic examinations of workers who had been exposed for several years to dusts in amounts sufficient to supply from 0.2 to 0.35 mg. of fluorine per kilogram of body weight daily, Møller and Gudjonsson<sup>28</sup> discovered a generalized osteosclerosis in many. Abnormal density and indistinct structure of the bones were most striking in the spinal column, pelvis, and ribs. Over half of those who had been exposed for about 10 years presented definite evidence of changes in the bone structure, varying from a fleecy thickening of the lamina or increased opacity of the bones to the appearance of excrescences and calcification of the ligamentous attachments. In some workers, the abnormalities were so pronounced as to cause stiffness of the spinal column and thorax. In a few cases, ankylosis of the joints of the vertebral column caused serious disability.

In the United States a worker in the phosphate fertilizer industry<sup>40,50</sup> was found to have bony changes that may have been related to the greatly increased fluoride concentration in his bones. A few cases of fluorosis have occurred in which drinking water was the source of the fluorine.

About half of the Danish cryolite workers complained of lack of appetite, nausea, and shortness of breath, and a smaller proportion mentioned constipation, localized pain in region of the liver, and other symptoms.<sup>51</sup> Some degree of anemia was found in half of the workers with fluorosis. The mean concentration of fluorine in the urine of these workers was 16.05 mg. per liter, the range being 2.41 to 43.41 mg. per liter. In those with less severe exposure, the mean urinary

<sup>47</sup> F. J. McClure, H. H. Mitchell, T. S. Hamilton, and C. A. Kinser, *J. Ind. Hyg. Toxicol.*, **27**, 159 (1945).

<sup>48</sup> M. Lawrenz, H. H. Mitchell, and W. A. Ruth, *J. Nutrition*, **19**, 531 (1940).

<sup>49</sup> F. J. McClure, *U. S. Pub. Health Repts.*, **59**, 1543, 1575 (1944).

<sup>50</sup> W. A. Wolff and E. G. Kerr, *Am. J. Med. Sci.*, **195**, 493 (1938).

<sup>51</sup> K. Roholm, *Fluorine Intoxication*, Lewis, London, 1937. Heffter-Heubner, *Handbuch experl. Pharmakol.*, Erg. **7**, 1 (1938). *Ergeb. inn. Med. u. Kinderheilk.*, **57**, 822 (1939). *Z. ges. gerichtl. Med.*, **27**, 174 (1936). F. McClure, *Physiol. Revs.*, **13**, 277 (1933). D. A. Greenwood, *ibid.*, **20**, 582 (1940). F. deEds, *Medicine*, **12**, 1 (1933).

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concentration was 4.81 mg. per liter, with a range of 1.78 to 11.67 mg. per liter.<sup>46</sup> A slight degree of fluorosis was found in workers exposed for 2 to 2½ years, while more definite signs were observed in those exposed nearly 5 years, and signs of moderate fluorosis appeared in those with more than 11 years of exposure. The most severe cases were those of men who had had 21 years of exposure. However, not all workers developed fluorosis, no abnormalities being detected in one man after 24 years of work. From analysis of the bones of two workers, Roholm estimated that their osseous systems contained 50 and 90 g. of fluorine, respectively. The latter amount had been deposited during 7500 working days, corresponding to an average deposition of 12 mg. per day.

### 6. *Maximum Allowable Concentration*

It is not known at present whether any rate of storage, however small, could be continued during many working years with the assurance that it would not lead to disabling skeletal abnormalities. It is, therefore, impossible to state what concentration of fluorine in the urine of workers should be regarded as evidence of potentially harmful exposure to concentrations of fluorine-bearing dusts that would be actually dangerous to some of those inhaling the air. To avoid storage completely would probably require the avoidance of more than 0.2 to 0.3 mg. per cubic meter of air.

## HYDROGEN FLUORIDE

### 1. *Uses, Properties, and Industrial Exposures*

Hydrogen fluoride, HF, is a colorless liquid, with molecular weight 20.01. It boils at 19.4° C. Its great solubility in water causes it to fume strongly in moist air. Its aqueous solution dissolves glass, reacting with the silica to form gaseous silicon tetrafluoride. Because of its solvent properties, it is used in various concentrations for frosting, etching, and polishing glass, and for removing sand from metal castings. Recently, large quantities have been used in refineries as a catalyst for the production of certain hydrocarbons for high-octane gasoline.<sup>52</sup>

1 mg./l.  $\approx$  1223 p.p.m. and 1 p.p.m.  $\approx$  0.818 mg./cu.m. at 25° C., 760 mm

### 2. *Toxicity When Inhaled by Animals*

The immediate toxicity of gaseous hydrogen fluoride when inhaled is of the order of that of hydrogen chloride or sulfur dioxide. When inhaled by rabbits and guinea pigs in a concentration of not more than 0.05 mg. per liter of air,<sup>53</sup> it induced signs of mild irritation, such as coughing and sneezing, which appeared to lessen after 5 to 15 minutes. Inhaled in higher concentrations, it acted as a severe irritant: the eyes were kept closed, paroxysms of coughing and sneezing

<sup>52</sup> C. G. Gerhold, J. O. Iverson, H. J. Nebeck, and R. J. Newman, *Petroleum Refiner*, 22, R146 (1943). J. H. Simons, *ibid.*, 22, No. 6, 83; No. 7, 83 (1943).

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## ATOMIC WEIGHTS, 1948

*Journal of the American Chemical Society, 69, 731 (1947)*

Element	Symbol	Atomic number	Atomic weight	Element	Symbol	Atomic number	Atomic weight
Aluminum	Al	13	26.97	Molybdenum	Mo	42	95.95
Antimony	Sb	51	121.76	Neodymium	Nd	60	144.27
Argon	A	18	39.944	Neon	Ne	10	20.183
Arsenic	As	33	74.91	Nickel	Ni	28	58.69
Barium	Ba	56	137.36	Nitrogen	N	7	14.008
Beryllium	Be	4	9.02	Osmium	Os	76	190.2
Bismuth	Bi	83	209.00	Oxygen	O	8	16.0000
Boron	B	5	10.82	Palladium	Pd	46	106.7
Bromine	Br	35	79.916	Phosphorus	P	15	30.98
Cadmium	Cd	48	112.41	Platinum	Pt	78	195.23
Calcium	Ca	20	40.08	Potassium	K	19	39.096
Carbon	C	6	12.010	Praseodymium	Pr	59	140.92
Cerium	Ce	58	140.13	Protoactinium	Pa	91	231
Cesium	Cs	55	132.91	Radium	Ra	88	226.05
Chlorine	Cl	17	35.457	Radon	Rn	86	222
Chromium	Cr	24	52.01	Rhenium	Re	75	186.31
Cobalt	Co	27	58.94	Rhodium	Rh	45	102.91
Columbium	Cb	41	92.91	Rubidium	Rb	37	85.48
Copper	Cu	29	63.54	Ruthenium	Ru	44	101.7
Dysprosium	Dy	66	162.46	Samarium	Sm	62	150.43
Erbium	Er	68	167.2	Scandium	Sc	21	45.10
Europium	Eu	63	152.0	Selenium	Se	34	78.96
Fluorine	F	9	19.00	Silicon	Si	14	28.06
Gadolinium	Gd	64	156.9	Silver	Ag	47	107.880
Gallium	Ga	31	69.72	Sodium	Na	11	22.997
Germanium	Ge	32	72.60	Strontium	Sr	38	87.63
Gold	Au	79	197.2	Sulfur	S	16	32.066
Hafnium	Hf	72	178.6	Tantalum	Ta	73	180.88
Helium	He	2	4.003	Tellurium	Te	52	127.61
Holmium	Ho	67	164.94	Terbium	Tb	65	159.2
Hydrogen	H	1	1.0080	Thallium	Tl	81	204.39
Indium	In	49	114.76	Thorium	Th	90	232.12
Iodine	I	53	126.92	Thulium	Tm	69	169.4
Iridium	Ir	77	193.1	Tin	Sn	50	118.70
Iron	Fe	26	55.85	Titanium	Ti	22	47.90
Krypton	Kr	36	83.7	Tungsten	W	74	183.92
Lanthanum	La	57	138.92	Uranium	U	92	238.07
Lead	Pb	82	207.21	Vanadium	V	23	50.95
Lithium	Li	3	6.940	Xenon	Xe	54	131.3
Lutecium	Lu	71	174.99	Ytterbium	Yb	70	173.04
Magnesium	Mg	12	24.32	Yttrium	Y	39	88.92
Manganese	Mn	25	54.93	Zinc	Zn	30	65.38
Mercury	Hg	80	200.61	Zirconium	Zr	40	91.22

## CONVERSION TABLE FOR GASES AND VAPORS\*

(Milligrams per Liter to Parts per Million and Vice Versa;  
25° C. and 760 mm. Mercury, Barometric Pressure)

Molec- ular Weight	1 mg./l. p.p.m.	1 p.p.m. mg./l.	Molec- ular Weight	1 mg./l. p.p.m.	1 p.p.m. mg./l.	Molec- ular Weight	1 mg./l. p.p.m.	1 p.p.m. mg./l.
1	24,450	0.0000409	51	479	0.002086	101	242.1	0.00413
2	12,230	.0000818	52	470	.002127	102	239.7	.00417
3	8,150	.0001227	53	461	.002168	103	237.4	.00421
4	6,113	.0001636	54	453	.002209	104	235.1	.00425
5	4,890	.0002045	55	445	.002250	105	232.9	.00429
6	4,075	.0002454	56	437	.002290	106	230.7	.00434
7	3,493	.0002863	57	429	.002331	107	228.5	.00438
8	3,056	.000327	58	422	.002372	108	226.4	.00442
9	2,717	.000368	59	414	.002413	109	224.3	.00446
10	2,445	.000409	60	408	.002454	110	222.3	.00450
11	2,223	.000450	61	401	.002495	111	220.3	.00454
12	2,038	.000491	62	394	.00254	112	218.3	.00458
13	1,881	.000532	63	388	.00258	113	216.4	.00462
14	1,746	.000573	64	382	.00262	114	214.5	.00466
15	1,630	.000614	65	376	.00266	115	212.6	.00470
16	1,528	.000654	66	370	.00270	116	210.8	.00474
17	1,438	.000695	67	365	.00274	117	209.0	.00479
18	1,358	.000736	68	360	.00278	118	207.2	.00483
19	1,287	.000777	69	354	.00282	119	205.5	.00487
20	1,223	.000818	70	349	.00286	120	203.8	.00491
21	1,164	.000859	71	344	.00290	121	202.1	.00495
22	1,111	.000900	72	340	.00294	122	200.4	.00499
23	1,063	.000941	73	335	.00299	123	198.8	.00503
24	1,019	.000982	74	330	.00303	124	197.2	.00507
25	978	.001022	75	326	.00307	125	195.6	.00511
26	940	.001063	76	322	.00311	126	194.0	.00515
27	906	.001104	77	318	.00315	127	192.5	.00519
28	873	.001145	78	313	.00319	128	191.0	.00524
29	843	.001186	79	309	.00323	129	189.5	.00528
30	815	.001227	80	306	.00327	130	188.1	.00532
31	789	.001268	81	302	.00331	131	186.6	.00536
32	764	.001309	82	298	.00335	132	185.2	.00540
33	741	.001350	83	295	.00339	133	183.8	.00544
34	719	.001391	84	291	.00344	134	182.5	.00548
35	699	.001432	85	288	.00348	135	181.1	.00552
36	679	.001472	86	284	.00352	136	179.8	.00556
37	661	.001513	87	281	.00356	137	178.5	.00560
38	643	.001554	88	278	.00360	138	177.2	.00564
39	627	.001595	89	275	.00364	139	175.9	.00569
40	611	.001636	90	272	.00368	140	174.6	.00573
41	596	.001677	91	269	.00372	141	173.4	.00577
42	582	.001718	92	266	.00376	142	172.2	.00581
43	569	.001759	93	263	.00380	143	171.0	.00585
44	554	.001800	94	260	.00384	144	169.8	.00589
45	543	.001840	95	257	.00389	145	168.6	.00593
46	532	.001881	96	255	.00393	146	167.5	.00597
47	520	.001922	97	252	.00397	147	166.3	.00601
48	509	.001963	98	249.5	.00401	148	165.2	.00605
49	499	.002004	99	247.0	.00405	149	164.1	.00609
50	489	.002045	100	244.5	.00409	150	163.0	.00613

Molecular Weight	1 mg./l. p.p.m.	1 p.p.m. mg./l.	Molecular Weight	1 mg./l. p.p.m.	1 p.p.m. mg./l.	Molecular Weight	1 mg./l. p.p.m.	1 p.p.m. mg./l.
151	161.9	0.00618	201	121.6	0.00822	251	97.4	0.01027
152	160.9	.00622	202	121.0	.00826	252	97.0	.01031
153	159.8	.00626	203	120.4	.00830	253	96.6	.01035
154	158.8	.00630	204	119.9	.00834	254	96.3	.01039
155	157.7	.00634	205	119.3	.00838	255	95.9	.01043
156	156.7	.00638	206	118.7	.00843	256	95.5	.01047
157	155.7	.00642	207	118.1	.00847	257	95.1	.01051
158	154.7	.00646	208	117.5	.00851	258	94.8	.01055
159	153.7	.00650	209	117.0	.00855	259	94.4	.01059
160	152.8	.00654	210	116.4	.00859	260	94.0	.01063
161	151.9	.00658	211	115.9	.00863	261	93.7	.01067
162	150.9	.00663	212	115.3	.00867	262	93.3	.01072
163	150.0	.00667	213	114.8	.00871	263	93.0	.01076
164	149.1	.00671	214	114.3	.00875	264	92.6	.01080
165	148.2	.00675	215	113.7	.00879	265	92.3	.01084
166	147.3	.00679	216	113.2	.00883	266	91.9	.01088
167	146.4	.00683	217	112.7	.00888	267	91.6	.01092
168	145.5	.00687	218	112.2	.00892	268	91.2	.01096
169	144.7	.00691	219	111.6	.00896	269	90.9	.01100
170	143.8	.00695	220	111.1	.00900	270	90.6	.01104
171	143.0	.00699	221	110.6	.00904	271	90.2	.01108
172	142.2	.00703	222	110.1	.00908	272	89.9	.01112
173	141.3	.00708	223	109.6	.00912	273	89.6	.01117
174	140.5	.00712	224	109.2	.00916	274	89.2	.01121
175	139.7	.00716	225	108.7	.00920	275	88.9	.01125
176	138.9	.00720	226	108.2	.00924	276	88.6	.01129
177	138.1	.00724	227	107.7	.00928	277	88.3	.01133
178	137.4	.00728	228	107.2	.00933	278	87.9	.01137
179	136.6	.00732	229	106.8	.00937	279	87.6	.01141
180	135.8	.00736	230	106.3	.00941	280	87.3	.01145
181	135.1	.00740	231	105.8	.00945	281	87.0	.01149
182	134.3	.00744	232	105.4	.00949	282	86.7	.01153
183	133.6	.00748	233	104.9	.00953	283	86.4	.01157
184	132.9	.00753	234	104.5	.00957	284	86.1	.01162
185	132.2	.00757	235	104.0	.00961	285	85.8	.01166
186	131.5	.00761	236	103.6	.00965	286	85.5	.01170
187	130.7	.00765	237	103.2	.00969	287	85.2	.01174
188	130.1	.00769	238	102.7	.00973	288	84.9	.01178
189	129.4	.00773	239	102.3	.00978	289	84.6	.01182
190	128.7	.00777	240	101.9	.00982	290	84.3	.01186
191	128.0	.00781	241	101.5	.00986	291	84.0	.01190
192	127.3	.00785	242	101.0	.00990	292	83.7	.01194
193	126.7	.00789	243	100.6	.00994	293	83.4	.01198
194	126.0	.00793	244	100.2	.00998	294	83.2	.01202
195	125.4	.00798	245	99.8	.01002	295	82.9	.01207
196	124.7	.00802	246	99.4	.01006	296	82.6	.01211
197	124.1	.00806	247	99.0	.01010	297	82.3	.01215
198	123.5	.00810	248	98.6	.01014	298	82.0	.01219
199	122.9	.00814	249	98.2	.01018	299	81.8	.01223
200	122.3	.00818	250	97.8	.01022	300	81.5	.01227

\* A. C. Fieldner, S. H. Katz, and S. P. Kinney, "Gas Masks for Gases Met in Fighting Fires," *U. S. Bur. Mines, Tech. Paper No. 248* (1921).

## USEFUL EQUIVALENTS AND CONVERSION FACTORS

1 kilometer = 0.6214 mile	1 liter = 1.057 quarts (U. S. liquid)
1 meter = 3.281 feet	1 cubic foot of water = 62.43 lbs. (4° C.)
1 centimeter = 0.3937 inch	1 U. S. gallon of water = 8.345 lbs. (4° C.)
1 micron = 1/25,400 inch = 40 microinches	1 kilogram = 2.205 pounds
1 foot = 30.48 centimeters	1 gram = 15.43 grains
1 inch = 25.40 millimeters	1 pound = 453.59 grams
1 square foot = 0.0929 square meter	1 ounce (avoir.) = 28.35 grams
1 square inch = 6.452 square centimeters	1 gram mole of a perfect gas $\Rightarrow$ 24.45 liters (at 25° C. and 760 mm. Hg barometric pressure)
1 cubic meter = 35.315 cubic feet	1 atmosphere = 14.7 pounds per square inch
1 cubic foot = 28.32 liters = 0.0283 cubic meter	1 foot of water pressure = 0.4335 pound per square inch
1 cubic inch = 16.39 cubic centimeters	1 inch of mercury pressure = 0.4912 pound per square inch
1 cubic centimeter = 0.0610 cubic inch	1 BTU = 778 foot-pounds
1 U. S. gallon = 3.7853 liters	1 HP = 0.707 BTU per second = 550 foot-pounds per second
1 U. S. gallon = 231 cubic inches = 0.13368 cubic foot	
1 liter = 0.9081 quart (dry)	

To convert degrees centigrade to degrees Fahrenheit:  $^{\circ}\text{C} \times (9/5) + 32 = ^{\circ}\text{F}$ .

To convert degrees Fahrenheit to degrees centigrade:  $(5/9)(^{\circ}\text{F} - 32) = ^{\circ}\text{C}$ .

For solutes in water: 1 mg./l.  $\approx$  1 p.p.m. (by weight)

Atmospheric contamination: 1 mg./l.  $\approx$  1 oz./1000 cu. ft. (approx.)

For gases or vapors in air at 25° C. and 760 mm. Hg pressure:

To convert mg./l. to p.p.m. (by volume):  $\text{mg./l.} \times (24,450/\text{mol. wt.}) = \text{p.p.m.}$

To convert p.p.m. to mg./l.:  $\text{p.p.m.} \times (\text{mol. wt.}/24,450) = \text{mg./l.}$

**INDUSTRIAL HYGIENE AND TOXICOLOGY**

*Volume II*



## CHAPTER SIXTEEN

# The Halogens

FRANCIS F. HEYROTH, M.D.

### FLUORINE AND FLUORIDES OF THE ALKALIES AND ALKALINE EARTHS

#### 1. *Uses and Industrial Exposures*

Fluorine is a yellow gas, which does not occur free in nature, because of its great reactivity. With the moisture of the air it forms hydrogen fluoride. Elementary fluorine is prepared in the chemical industry for use in fluorinating organic compounds. The two chief sources of fluorine compounds are fluorspar (calcium fluoride) and cryolite (sodium aluminum fluoride,  $\text{Na}_3\text{AlF}_6$ ). The annual consumption of the former in the United States rose from 183,000 tons in 1939 to about 400,000 tons in 1943. Imports of cryolite from Greenland, its only commercial source, rose from 10,210 tons in 1939 to 18,000 tons in 1941.<sup>1</sup>

The largest use of fluorspar is in steelmaking and in the smelting of nickel, copper, gold, and silver, where it serves as a flux. Other applications are in the opacifying of glass and enamels, and in coatings for welding rods. At least 50,000 tons of it, annually, are treated with sulfuric acid for the preparation of hydrogen fluoride. Sodium fluoride is used in considerable quantities as a rodenticide and insecticide, antimony fluoride serves as a catalyst for certain organic reactions, and barium fluoride is used in baths for the electrolytic isolation of beryllium. Lesser uses of fluorides are found in the bleaching of cane for seats, in the disinfection of hides and skins, in the preservation of timbers, in the coagulation of latex, in cleaning graphite, metals, windows, and glassware, and in various ways in the optical, brewing, and dyeing industries.<sup>2</sup>

Cryolite is employed as an insecticide and, in molten form, as an electrolyte in the production of aluminum from alumina. In Danish plants for the grinding and pecking of cryolite, the presence of large quantities of dust caused the fluorine content of the air to be about 0.035 mg. per liter.<sup>3</sup> Exposure to cryolite dusts also occurs in the manufacture of beryllium.

<sup>1</sup> U.S. Bureau of Mines, *Minerals Year Book* (1941).

<sup>2</sup> D. A. Greenwood, *Physiol. Rev.*, 20, 582 (1940). K. F. Stahl, *J. Eng. Chem.*, 7, 56 (1915); *Illinois Labor Bull.* No. 4, 412 (1944); *J. Ind. Hyg. Toxicol.*, 26, 103A (1944).

<sup>3</sup> K. Roholm, *Arch. Gewerbepath. Gewerbehyg.*, 7, 255 (1936).

The use of fluoride-coated welding rods offers a definite hazard.<sup>4</sup> In magnesium founding, fluorides inhibit oxidation when sprayed upon cores or mixed with the core sand to the extent of 4 to 10 per cent. They also act as fluxes when added to the melting pots.<sup>5</sup> Williams<sup>6</sup> found the following quantities, expressed as milligrams of fluoride per cubic meter of air, near various operations: core-spraying, 0.7; melting, 1.26; molding, 1.88; shakeout, 8.77. Analyses by the Illinois Department of Labor in other foundries showed the presence of fluorine equivalent to 2 p.p.m. of hydrogen fluoride at the molding operation, less than 3 p.p.m. in the shakeout areas, but as much as 7.2 p.p.m. near the pouring operation. Largent and Ferneau,<sup>7</sup> who used the urinary excretion of fluorine by workers as a measure of the severity of exposure, found the greatest exposure in the core-spraying and pouring areas.

During sulfuric acid treatment in the preparation of fertilizer from fluorine-bearing phosphate it has been estimated that 25,000 tons of fluorine per year escape into the atmosphere.<sup>8</sup> Fluorine compounds emitted by fertilizer and aluminum factories have been known to contaminate the forage of nearby areas and to cause illness among cattle and other animals. In one factory for the extraction of beryllium, the air contained fluorine equivalent to 0.996 mg. of sodium fluoride per cubic meter.<sup>9</sup>

## 2. Determination of Fluorine Compounds in Air

The sample of air may be collected in an evacuated bulb and shaken with a 1 per cent solution of sodium hydroxide, or it may be passed through an impinger. If hydrogen fluoride is the only fluorine compound present, the remaining free alkali in the absorbing solution may be titrated with acid. If dusts or other volatile fluorine compounds are present, the liquid is concentrated to a small volume, after the addition of calcium or magnesium oxide to prevent loss of fluorine. It is then distilled with perchloric acid and the fluorine determined in the distillate by the back-titration method of Dahle, Bonnar, and Wichmann.<sup>10</sup> A photolorimetric method based on the ability of the fluoride ion to decolorize ferric thiocyanate has recently been used for the continuous automatic determination of concentrations of 0.001 to 0.015 mg. of hydrogen fluoride per liter.<sup>11</sup>

<sup>4</sup> P. Drinker and K. W. Nelson, *Ind. Med.*, **13**, 673 (1944).

<sup>5</sup> M. E. Brooks and A. W. Winston, *Trans. Am. Foundrymen's Assoc.*, **49**, 165 (1941).

<sup>6</sup> C. R. Williams, *J. Ind. Hyg. Toxicol.*, **24**, 277 (1942).

<sup>7</sup> E. J. Largent and I. Ferneau, *J. Ind. Hyg. Toxicol.*, **26**, 113 (1944).

<sup>8</sup> M. J. M. Schuurmsma, *Chem. Weekblad*, **38**, 583, (1941).

<sup>9</sup> J. Shilen, A. E. Galloway, and J. F. Mellor, *Ind. Med.*, **13**, 464 (1944).

<sup>10</sup> D. Dahle, R. U. Bonnar, and H. J. Wichmann, *J. Assoc. Official Agr. Chem.*, **21**, 459 (1938).

<sup>11</sup> L. S. Chermodanova, *Zavodskaya Lab.*, **8**, 1248 (1939); *Chem. Abstracts*, **34**, 5785 (1940).



### 3. Physiological Response

*Immediate intoxication by fluorides.* The lethal dose of sodium fluoride when administered orally to rabbits is 200 mg. per kilogram of body weight.<sup>12</sup> Because of its lesser solubility, cryolite is much less toxic: rats are not killed by the largest dose that can be administered.

The symptoms that follow the ingestion of soluble fluorides by man are listed in the order of diminishing frequency of occurrence: vomiting, abdominal pain, diarrhea, convulsions, generalized and muscular weakness, collapse, dyspnea, paresis, difficulty in articulation, thirst, weakness of the pulse, disturbed color vision, loss of consciousness, and motor unrest.<sup>13</sup> Albuminuria is frequently present. Death is primarily due to respiratory paralysis. Acute toxic nephritis, hemorrhagic gastroenteritis, and more or less definite pathologic damage to other organs are found on examination. The calcium content of the blood is reduced following the ingestion of large amounts of fluorides,<sup>14</sup> but this is not of great importance in the mechanism of the toxic action. Fluoride acts as a general protoplasmic poison, reducing the anaerobic glucolysis of many types of cells without affecting their ability to consume oxygen.<sup>15</sup> It interferes with the action of certain enzymes concerned with the conversion of phosphoglyceric acid to phosphopyruvic acid, an essential link in the chain of reactions involved in muscle metabolism.<sup>16</sup> Other enzymes, such as glycerol phosphatase,<sup>17</sup> esterases,<sup>18</sup> and liver arginase,<sup>19</sup> as well as cozymase,<sup>20</sup> are affected by the fluoride ion.

Immediate intoxication by the ingestion of fluorides is rare in industry, but various degrees of respiratory irritation may result from the inhalation of fluorides in the form of dusts. Some magnesium founders complain of a severe biting sensation in the nose when the concentration of fluorides in the air exceeds 10 mg. per cubic meter. This is accompanied after a few minutes by a discharge from the nose or by nosebleed. No such effects are noted when the concentration does not exceed 2.5 mg. per cubic meter.<sup>6</sup>

<sup>12</sup> C. W. Muehlberger, *J. Pharmacol.*, **39**, 346 (1930).

<sup>13</sup> K. Roholm, *Fluorine Intoxication*, Lewis, London, 1937. Heffter-Huebner, *Handbuch exptl. Pharmakol.*, Erg. **7**, 1 (1938); *Ergeb. inn. Med. u. Kinderheilk.*, **57**, 822 (1939); *Z. ges. gerichtl. Med.*, **27**, 174 (1936). F. McClurc, *Physiol. Revs.*, **13**, 277 (1933). D. A. Greenwood, *ibid.*, **20**, 582 (1940). F. deEds, *Medicine*, **12**, 1 (1933).

<sup>14</sup> H. Wieland and G. Kurtzahn, *Arch. exptl. Path. Pharmakol.*, **97**, 488 (1923). A. Jodlbauer, *ibid.*, **164**, 464 (1931).

<sup>15</sup> F. Lipmann, *Biochem. Z.*, **206**, 171 (1929). F. Dickens and F. Simer, *Biochem. J.*, **23**, 936 (1929). K. Lohmann, *Biochem. Z.*, **222**, 324 (1930). F. Lipmann and K. Lohmann, *ibid.*, **222**, 389 (1930).

<sup>16</sup> G. Embden, A. Abraham, and H. Lange, *Z. physiol. Chem.*, **136**, 308 (1924). G. Embden and H. Hentschel, *Biochem. Z.*, **156**, 343 (1925).

<sup>17</sup> K. Inouye, *J. Biochem. (Japan)*, **7**, 433 (1927). F. Lipmann, *Biochem. Z.*, **196**, 3 (1928). V. A. Drill, J. H. Annegers, and A. C. Ivy, *J. Biol. Chem.*, **152**, 339 (1944).

<sup>18</sup> A. S. Loevenhart and G. Peirce, *J. Biol. Chem.*, **2**, 397 (1907). S. Amberg and A. S. Loevenhart, *ibid.*, **4**, 149 (1908). P. Rothschild, *Biochem. Z.*, **206**, 186 (1929).

<sup>19</sup> S. Hino, *J. Biochem. (Japan)*, **6**, 335 (1926).

<sup>20</sup> A. Lennerstrand, *Biochem. Z.*, **287**, 172 (1936).

*Fluorosis or chronic fluorine intoxication.* The daily ingestion by rats of a diet containing very small doses of fluorides (0.0007 to 0.0012 per cent) produces a series of fine, barely discernible lines of impaired calcification of the teeth. Dietary levels greater than 0.011 to 0.023 per cent cause some inhibition of growth, and diets containing more than 0.03 per cent cause a loss of appetite and an unhealthy appearance. When fluorine in the form of a soluble salt is present at levels above 0.09 per cent, rats die in a few days to a few months, following a period of inanition, lethargy, and weakness. When present as cryolite, fluorine is less toxic.<sup>21</sup>

Although a daily intake of fluorine of the order of 1 mg. per kilogram of body weight will produce incipient dental fluorosis, 10 to 15 mg. per kilogram per day are necessary to affect adversely the general well-being of animals. A daily intake of 20 to 25 mg. per kilogram has serious effects and a daily dose of 15 to 100 mg. per kilogram is lethal in from one to a few weeks.<sup>13</sup> Such impairment of fertility as has been found in experiments on animals,<sup>22,23</sup> may have resulted from the general state of inanition.<sup>21</sup> Relatively large doses of the order of 150 mg. of sodium fluoride per kilogram are required in order to produce inflammation of the gastric and duodenal mucosa. In pigs and dogs, nephritis has been produced in feeding experiments,<sup>13</sup> but liver damage is exceptional. Anemia has been observed in some of these experiments but is not a uniform feature of chronic fluorine intoxication.<sup>13,24</sup>

Neither dental fluorosis nor a cachectic state, the production of which requires the ingestion of relatively large daily doses of fluorides, is of great significance in industrial toxicology. Lesions of the skeletal system are of greater practical importance, since they have been observed in workers who inhaled fluorine-bearing dusts over considerable periods of time. In 1892 Brandl and Tappeiner<sup>25</sup> described crystalline deposits in the marrow spaces and Haversian canals of the bones of a dog that had been fed over 400 g. of sodium fluoride during a period of 21 months. During the last 5 months of this period the animal, in running or walking, held its spine, especially the sacral portion, in an unusually stiff position. On sacrificing the dog, the investigators noted that the tensile strength of the bones, which had an unusually white appearance, was apparently increased. More recently, similar changes were noted by Bardelli and Menzani<sup>26</sup> in the bones of cattle poisoned by fluorides, and Hauck, Steenbock, and Parsons<sup>23</sup> found that the bones of rats similarly poisoned were 18 per cent heavier than normal and had a thickened cortex that in some instances encroached upon the

<sup>21</sup> M. C. Smith and R. M. Leverson, *Ind. Eng. Chem.*, **26**, 791 (1934). H. F. Smyth and H. F. Smyth, Jr., *ibid.*, **24**, 229 (1932).

<sup>22</sup> A. R. Lamb, P. H. Phillips, E. B. Hart, and G. Bohstedt, *Am. J. Physiol.*, **106**, 350 (1933). J. A. Schulz and A. R. Lamb, *Science*, **61**, 93 (1925). P. H. Phillips, A. R. Lamb, E. B. Hart, and G. Bohstedt, *Am. J. Physiol.*, **106**, 356 (1933).

<sup>23</sup> H. M. Hauck, H. Steenbock, and H. T. Parsons, *Am. J. Physiol.*, **103**, 480, 489 (1939).

<sup>24</sup> J. T. Ginn and J. T. Volker, *Proc. Soc. Exptl. Biol. Med.*, **57**, 189 (1944).

<sup>25</sup> J. Brandl and H. Tappeiner, *Z. Biol.*, **28**, 518 (1892).

<sup>26</sup> P. Bardelli and C. Menzani, *Atti ist. Veneto sci., Pt. II*, **97**, 623 (1937-38).

medullary cavity. The skeleton of rabbits that were given 763 p.p.m. fluorine in the diet as sodium fluoride for 92 days, or 2980 p.p.m. for 47 days, was chalky; and small areas of porous bone, varying in diameter from 1 mm. to 1 cm., were scattered throughout the vertebra, cranium, zygoma, and maxillae, with larger plaques on a markedly bulked mandible.<sup>27</sup> However, no significant changes were noted in the radiographic density of the tibiae and fibulae of these rabbits. The bony abnormalities in man produced by fluorine were first observed in routine radiographic examinations.<sup>28</sup> Similar anomalies have not as yet been produced in animals<sup>29</sup> in a clear-cut fashion. Whereas the bony alterations in man are of an osteosclerotic type, those occurring in animals have tended to be of an osteoporotic nature. In some of the earlier descriptions of animals poisoned as a result of the contamination of their forage by fluorides, the condition was confused with osteomalacia. Possibly this was due to the ingestion of fluorine at a comparatively high level,<sup>30</sup> which produced signs of general illness, while in man the osteosclerotic changes are induced by the ingestion of smaller amounts, which produce only rather indefinite symptoms of ill-health. The histologic changes in bone have been discussed by de Senareclens<sup>31</sup> and by Pachaly,<sup>32</sup> but much remains to be learned regarding the factors that cause either absorption or deposition of bone to predominate. The relation between the fluorine content of bones and their gross or histologic appearance is not as yet well understood, but it is certain that fluorine can be stored in bones and teeth in large quantities.<sup>33</sup> In the rabbits of Largent, Machle, and Ferneau,<sup>27</sup> from 1.03 to 3.98 mg. of fluorine was found per gram of wet bone, which is about 17 times the normal concentration. Bardelli and Menzani<sup>28</sup> found that the bone ash contained 2.4 times the normal amount of fluorine in the initial stages of the development of bony lesions, 3.2 times the normal amount in bones with moderate damage, and 8 times the normal amount in severely damaged bones. The grossly unaltered bones of a dog fed 65 milligrams of fluorine daily for 65 months had even more fluorine.<sup>33a</sup>

Much attention has been devoted to the possible role of calcium in relation to the development of bony abnormalities. In chronic poisoning of animals, no significant diminution in the calcium content of the blood has been found.<sup>23</sup> Fluorides must be fed at a level that produces general intoxication in order to cause a diminution in the retention of calcium,<sup>34,35</sup> or to alter the calcium content

<sup>27</sup> E. J. Largent, W. Machle, and I. F. Ferneau, *J. Ind. Hyg. Toxicol.*, 25, 396 (1943).

<sup>28</sup> F. Møller and S. V. Gudjonsson, *Acta Radiol.*, 13, 269 (1932).

<sup>29</sup> C. J. Sutro, *Arch. Path.*, 19, 159 (1935).

<sup>30</sup> W. Dittrich, *Arch. exptl. Path. Pharmacol.*, 168, 319 (1932). E. Rost, *Arch. Gewerbe-path. Gewerbehyg.*, 8, 256 (1937).

<sup>31</sup> F. de Senareclens, *Helv. Med. Acta*, 8, 379 (1941).

<sup>32</sup> W. I. Pachaly, *Arch. exptl. Path. Pharmacol.*, 166, 1 (1932).

<sup>33</sup> C. Y. Chang, P. H. Phillips, and E. B. Hart, *J. Dairy Sci.*, 17, 695 (1934).

<sup>33a</sup> E. J. Largent, unpublished data.

<sup>34</sup> F. J. McClure and H. H. Mitchell, *J. Biol. Chem.*, 90, 297 (1931).

<sup>35</sup> E. M. Lantz and M. C. Smith, *Am. J. Physiol.*, 109, 645 (1934).

or composition of the ash in the bones.<sup>28,34,36-41</sup> There is little evidence that the phosphatase content of bone is affected.<sup>42</sup>

#### 4. Absorption and Storage of Fluorine in Man

Although the soft tissues contain fluorine to the extent of 20 to 60  $\mu\text{g.}$  per 100 grams,<sup>43</sup> ingested fluorine is stored chiefly in the bones and teeth. Roholm, who found from 0.048 to 0.21 per cent fluorine in the ash of human ribs, estimated that the total amount in the bones of a man is of the order of 1.5 to 6 g. Machle and Scott<sup>41</sup> found 0.026 per cent in the ash of human bones. Some indication of the extent to which storage can occur is found in the fact that the bones of a dog that had been given 402.9 g. of sodium fluoride over a period of nearly two years contained 29 g. of fluorine.<sup>25</sup>

In the absence of industrial exposure the chief source of fluorine is in drinking water, the fluorine content of which varies greatly in various localities. The daily intake of one human subject remained remarkably constant over a period of 16 weeks of unrestricted diet, the mean value being 0.457 mg. of fluorine. Of this, 0.155 mg. was derived from the food and 0.299 mg. from the fluid constituents of the diet. The mean daily fecal output was 0.039 mg., while the mean daily urinary output was 0.377 mg. Over the entire period, no significant storage occurred.<sup>44</sup> The daily urinary output by this subject was lower than the mean value of about 1 mg. reported by Machle, Scott, and Treon<sup>45</sup> in the case of persons in areas where the water supply did not contain excessive amounts of fluorine. In 30 Danish hospital patients, the daily urinary fluorine excretion varied from 0.18 to 1.85 mg. and the mean urinary concentration was 0.92 mg. per liter.<sup>46</sup>

A slightly more than ten-fold increase in the daily intake of fluorine in soluble form, by the subject investigated by Machle and Largent,<sup>44</sup> resulted in an increase in the urinary output to 2.42 mg. daily. By deducting the mean daily fecal output of 0.19 mg. from the daily intake of 6.47 mg. it was found that 6.28 mg. had been absorbed daily. By deducting from this the urinary output, it was concluded that 3.86 mg. or 63 per cent of the amount absorbed had been

<sup>25</sup> M. C. Smith and E. M. Lantz, *J. Biol. Chem.*, **101**, 677 (1933).

<sup>28</sup> C. H. Kick, R. M. Bethke, and B. H. Edgington, *J. Agr. Research*, **46**, 1023 (1933).

<sup>34</sup> C. Tolle and L. H. Maynard, *Proc. Am. Soc. Animal Production*, **15**, 15 (1928).

<sup>36</sup> E. B. Forbes, *Ohio Agr. Exptl. Sta. Bull.* No. 347 (1921).

<sup>41</sup> P. A. Bishop, *Am. J. Roentgenol. Radium Therapy*, **35**, 577 (1936).

<sup>44</sup> W. Machle and E. W. Scott, *J. Ind. Hyg.*, **17**, 230 (1935).

<sup>45</sup> P. H. Phillips, *Science*, **76**, 239 (1932). H. M. Hauck, H. Steenbock, J. T. Lowe, and J. G. Halpin, *Poultry Sci.*, **12**, 242 (1933). M. C. Smith and E. M. Lantz, *J. Biol. Chem.*, **112**, 303 (1935).

<sup>46</sup> A. O. Gettler and L. Ellerbrook, *Am. J. Med. Sci.*, **197**, 625 (1939).

<sup>47</sup> W. Machle and E. J. Largent, *J. Ind. Hyg. Toxicol.*, **25**, 112 (1943).

<sup>48</sup> W. Machle, E. W. Scott, and J. F. Treon, *Am. J. Hyg.*, **29A**, 139 (1939).

<sup>49</sup> G. C. Brun, H. Buchwald, and K. Roholm, *Acta Med. Scand.*, **106**, 261 (1941).

stored. McClure, Mitchell, Hamilton, and Kinser<sup>47</sup> concluded, from experiments in which account was taken of the amounts excreted in the perspiration, that storage does not begin until the daily intake is greater than 4 mg., while Machle and Largent believed that it might begin when the daily intake is 1.5 to 2 mg. Machle and Largent found that the solubility of the fluorine compound ingested influences greatly the extent to which it can be absorbed. There are some indications that the accumulation of fluorine in the bones may exert a retarding influence upon the rate at which it is stored in prolonged experiments.<sup>48</sup> In general, however, the urinary fluoride excretion may be used as a rough measure of the rate at which fluorine is being stored. A remarkable parallelism between the fluorine content of the drinking water and the concentration of fluorine in the urine of a large number of recruits has been demonstrated by McClure,<sup>49</sup> but no relation to their susceptibility to fractures of the bones could be found.

### 5. Chronic Industrial Fluorosis

In the course of radiographic examinations of workers who had been exposed for several years to dusts in amounts sufficient to supply from 0.2 to 0.35 mg. of fluorine per kilogram of body weight daily, Møller and Gudjonsson<sup>28</sup> discovered a generalized osteosclerosis in many. Abnormal density and indistinct structure of the bones were most striking in the spinal column, pelvis, and ribs. Over half of those who had been exposed for about 10 years presented definite evidence of changes in the bone structure, varying from a fleecy thickening of the lamina or increased opacity of the bones to the appearance of excrescences and calcification of the ligamentous attachments. In some workers, the abnormalities were so pronounced as to cause stiffness of the spinal column and thorax. In a few cases, ankylosis of the joints of the vertebral column caused serious disability.

In the United States a worker in the phosphate fertilizer industry<sup>40,50</sup> was found to have bony changes that may have been related to the greatly increased fluoride concentration in his bones. A few cases of fluorosis have occurred in which drinking water was the source of the fluorine.

About half of the Danish cryolite workers complained of lack of appetite, nausea, and shortness of breath, and a smaller proportion mentioned constipation, localized pain in region of the liver, and other symptoms.<sup>51</sup> Some degree of anemia was found in half of the workers with fluorosis. The mean concentration of fluorine in the urine of these workers was 16.05 mg. per liter, the range being 2.41 to 43.41 mg. per liter. In those with less severe exposure, the mean urinary

<sup>47</sup> F. J. McClure, H. H. Mitchell, T. S. Hamilton, and C. A. Kinser, *J. Ind. Hyg. Toxicol.*, **27**, 159 (1945).

<sup>48</sup> M. Lawrenz, H. H. Mitchell, and W. A. Ruth, *J. Nutrition*, **19**, 531 (1940).

<sup>49</sup> F. J. McClure, *U. S. Pub. Health Repts.*, **59**, 1543, 1575 (1944).

<sup>50</sup> W. A. Wolff and E. G. Kerr, *Am. J. Med. Sci.*, **195**, 493 (1938).

<sup>51</sup> K. Roholm, *Fluorine Intoxication*, Lewis, London, 1937. Heffter-Heubner, *Handbuch exper. Pharmakol.*, **Erg. 7**, 1 (1938). *Ergeb. inn. Med. u. Kinderheilk.*, **57**, 822 (1939). *Z. ges. gerichtl. Med.*, **27**, 174 (1936). F. McClure, *Physiol. Revs.*, **13**, 277 (1933). D. A. Greenwood, *ibid.*, **20**, 582 (1940). F. deEds, *Medicine*, **12**, 1 (1933).

concentration was 4.81 mg. per liter, with a range of 1.78 to 11.67 mg. per liter.<sup>46</sup> A slight degree of fluorosis was found in workers exposed for 2 to 2½ years, while more definite signs were observed in those exposed nearly 5 years, and signs of moderate fluorosis appeared in those with more than 11 years of exposure. The most severe cases were those of men who had had 21 years of exposure. However, not all workers developed fluorosis, no abnormalities being detected in one man after 24 years of work. From analysis of the bones of two workers, Roholm estimated that their osseous systems contained 50 and 90 g. of fluorine, respectively. The latter amount had been deposited during 7500 working days, corresponding to an average deposition of 12 mg. per day.

#### 6. *Maximum Allowable Concentration*

It is not known at present whether any rate of storage, however small, could be continued during many working years with the assurance that it would not lead to disabling skeletal abnormalities. It is, therefore, impossible to state what concentration of fluorine in the urine of workers should be regarded as evidence of potentially harmful exposure to concentrations of fluorine-bearing dusts that would be actually dangerous to some of those inhaling the air. To avoid storage completely would probably require the avoidance of more than 0.2 to 0.3 mg. per cubic meter of air.

## HYDROGEN FLUORIDE

### 1. *Uses, Properties, and Industrial Exposures*

Hydrogen fluoride, HF, is a colorless liquid, with molecular weight 20.01. It boils at 19.4° C. Its great solubility in water causes it to fume strongly in moist air. Its aqueous solution dissolves glass, reacting with the silica to form gaseous silicon tetrafluoride. Because of its solvent properties, it is used in various concentrations for frosting, etching, and polishing glass, and for removing sand from metal castings. Recently, large quantities have been used in refineries as a catalyst for the production of certain hydrocarbons for high-octane gasoline.<sup>52</sup>

1 mg./l.  $\approx$  1223 p.p.m. and 1 p.p.m.  $\approx$  0.818 mg./cu.m. at 25° C., 760 mm

### 2. *Toxicity When Inhaled by Animals*

The immediate toxicity of gaseous hydrogen fluoride when inhaled is of the order of that of hydrogen chloride or sulfur dioxide. When inhaled by rabbits and guinea pigs in a concentration of not more than 0.05 mg. per liter of air,<sup>53</sup> it induced signs of mild irritation, such as coughing and sneezing, which appeared to lessen after 5 to 15 minutes. Inhaled in higher concentrations, it acted as a severe irritant: the eyes were kept closed, paroxysms of coughing and sneezing

<sup>52</sup> C. G. Gerhold, J. O. Iverson, H. J. Nebeck, and R. J. Newman, *Petroleum Refiner*, 22, R146 (1943). J. H. Simons, *ibid.*, 22, No. 6, 83; No. 7, 83 (1943).

were frequent, the respirations were slowed, and there was a copious discharge from the nose and eyes.

Animals died within 5 minutes when they inhaled air containing 1.5 mg. per liter (1800 p.p.m.). The inhalation of air containing 1 mg. per liter, for 30 minutes, killed no animals but did cause damage to the tissues. All animals exposed to a concentration of 0.5 mg. per liter for 15 minutes or more showed signs of weakness and ill-health; concentrations below 0.1 mg. per liter could be tolerated for 5 hours without causing death; and 0.024 mg. per liter (30 p.p.m.) was tolerated by 6 rabbits for a total of 41 hours without fatality, although the animals subsequently lost in weight. A concentration of 0.015 mg. per liter was found tolerable.

Necropsies on animals that survived after repeated exposure to hydrogen fluoride gave evidence of damage to the lung, liver, and kidneys, of a nature that suggested that some process was involved beyond that usually produced by irritant gases. These changes in the lungs, whether caused thereby or not, were associated with retention of fluorine in this tissue. Machle's experiments demonstrated that storage of fluoride in the bones occurs as a result of repeated exposures to concentrations that are but slightly, if at all, irritant.

### 3. Injury from the Industrial Use of Hydrogen Fluoride

The highest concentration of hydrogen fluoride that can be tolerated by man for one minute is 0.1 mg. per liter of air. This causes a definite smarting of the skin, a definite sour taste, and some degree of conjunctival and respiratory irritation.<sup>53</sup> In air containing 0.05 mg. per liter, the taste was apparent and there was irritation of the eyes and nose, but no smarting of the skin. A concentration of 0.026 mg. per liter could be tolerated for several minutes, but the taste became evident after a short time, and there was mild smarting of the nose and eyes. No apparent habituation resulted from repeated brief exposures. Severe injury to the skin has resulted from exposure for 2 minutes to hydrogen fluoride in an unknown concentration,<sup>54</sup> the damage reaching its full development only after 5 or 6 days.

Contact of the skin with the anhydrous liquid produces severe burns that are felt immediately. Concentrated aqueous solutions also cause an early sensation of pain, but more dilute solutions may give no warning of injury. If not promptly removed, the skin may be penetrated by the fluoride ion, leading to the later development of painful ulcers, which heal slowly. A 0.03 per cent solution of sodium fluoride will destroy epithelium, according to Stanton and Kahn.<sup>55</sup> This observation suggests the necessity for preventing the diffusion of the fluoride ion in the treatment of serious burns.

<sup>53</sup> W. F. Machle, F. Thamann, K. Kitzmiller, and J. Cholak, *J. Ind. Hyg.*, 16, 129 (1934). W. Machle and K. Kitzmiller, *ibid.*, 17, 223 (1935).

<sup>54</sup> H. Schuermann, *Dermatol. Wochschr.*, 104, 661 (1937); *J. Ind. Hyg. Toxicol.*, 19, 234A (1937).

<sup>55</sup> D. N. Stanton and M. Kahn, *J. Am. Med. Assoc.*, 64, 1985 (1915).

After any contact with a solution of the acid, even though there be no immediate pain, the area should be flushed with copious amounts of water for at least 10 minutes, after which it may be swabbed with cotton moistened with a 10 per cent solution of 28 per cent aqueous ammonia, and again washed with water. Prolonged washing, when carried out without any delay following contact, may succeed in restoring pink color to an initially blanched area, thereby saving the tissue. Finally an ointment containing 20 per cent magnesium oxide in glycerin should be applied.<sup>56</sup> If blisters are present they should be opened by means of a sterile instrument.

In the case of more serious burns, a barrier to the spread of the fluoride ion should be set up by injecting a 10 per cent solution of calcium gluconate subcutaneously around and underneath the affected area.<sup>57</sup> This procedure has been found to be beneficial in limiting the destruction of tissue, and in giving fairly prompt relief from the deep boring pain that characterizes this type of injury.

#### 4. Maximum Allowable Concentration in Air

The concentration of 3 p.p.m. (0.0025 mg. per liter) has been adopted as the maximum allowable concentration<sup>58</sup> in 15 states and by the U. S. Public Health Service; but in Massachusetts,<sup>59</sup> the value is 1.5 p.p.m.

Precautions necessary for the safe handling of liquid hydrogen fluoride are available in the literature of petroleum technology.<sup>60</sup>

### AMMONIUM BIFLUORIDE AND SODIUM BIFLUORIDE

Sodium bifluoride,  $\text{NaHF}_2$ , is sometimes used as a welding flux or as a coating on welding rods. Sodium bifluoride is added to the mold during pouring to reduce the porosity of steel. Ammonium acid fluoride,  $(\text{NH}_4)\text{HF}_2$ , is also used as a flux in magnesium foundries. The hazards arising from their use are those of the use of fluorides in general (see Fluorine and Fluorides).

### BORON TRIFLUORIDE AND AMMONIUM BOROFLUORIDE

Boron fluoride,  $\text{BF}_3$ , is a colorless gas at ordinary temperatures, boiling at  $-101^\circ \text{C}$ . It has been used as a polymerization catalyst for certain organic reactions.<sup>61</sup> Ammonium borofluoride (fluoborate),  $\text{NH}_4\text{BF}_4$ , is a solid which has been used as a flux in magnesium founding (see Fluorine and Fluorides).

<sup>56</sup> Booklet of Universal Oil Products Company. F. Flury, *Draeger-Hefte*, No. 206, 4398 (1940); *J. Ind. Hyg. Toxicol.*, 24, 92A (1942).

<sup>57</sup> A. Paley and J. Seifter, *Proc. Soc. Exptl. Biol. Med.*, 46, 190 (1941).

<sup>58</sup> W. A. Cook, *Ind. Med.*, 14, 936 (1945).

<sup>59</sup> *Mimeographed List of Maximum Allowable Concentrations*. Massachusetts Department of Labor and Industries, Division of Occupational Hygiene, Feb., 1946.

<sup>60</sup> R. Benson, *Natl. Petroleum News*, Section 2, R532 (Nov. 3, 1943); *Petroleum Refiner*, 22, 448 (1943); *Ind. Med.*, 13, 113 (1944); C. M. Fehr, *Chem. Industries*, 53, 505 (1943); *Petroleum Refiner*, 22, 239 (1943); *Oil Gas J.*, 42, 39, 41 (1943). "Unloading Anhydrous Hydrofluoric Acid from Tank Cars and from Cylinders," *Mfg. Chemist Assoc.*, Washington, D. C., *Manual H-2 Sheet TC-5* (1943).

<sup>61</sup> *Oil Gas J.*, 43, 81 (1944).



## SILICON TETRAFLUORIDE

Silicon tetrafluoride,  $\text{SiF}_4$ , is a heavy gas, with molecular weight 104.06, and a density of 3.6 referred to air = 1. It is not employed as such in industry, but it may be discharged into the air in smelting operations as the result of the interaction of calcium fluoride with sand or with the silica present in ores. Its toxicity has not been investigated.

## HYDROFLUOSILICIC ACID AND ITS SALTS

Hydrofluosilicic acid,  $\text{H}_2\text{SiF}_6$ , molecular weight 144.08, has been employed in dilute solution as a disinfectant in breweries. Sodium and other silicofluorides (fluosilicates) are employed as fluxes in magnesium founding,<sup>62</sup> in disinfecting hides and skins, in hardening cement, in coagulating latex, and in cleaning windows.<sup>63</sup> The barium salt has been used as an insecticide. The sodium salt is used in the extraction of beryllium.

Weber and Engelhardt<sup>64</sup> exposed guinea pigs to air bearing sodium silicofluoride as a dust in concentrations ranging from 13 to 55 mg. per cubic meter and found the dust capable of causing pulmonary irritation. They concluded that the least concentration that caused death when inhaled for a period of 6 hours was 33 mg. per cubic meter.

The sodium salt is highly toxic when ingested, numerous deaths having been recorded.<sup>65</sup> The signs of poisoning resemble those seen in intoxication by fluorides.

When in contact with the skin, the acid and its salts cause redness and a burning sensation, sometimes followed by the formation of ulcers. A pustular rash has been observed among men who worked with the sodium salt.<sup>66</sup>

## CHLORINE

### 1. Chemical and Physical Properties

Chlorine,  $\text{Cl}_2$ , is a greenish-yellow gas with an irritating odor. Its molecular weight is 70.91. It is 2.49 times as heavy as air and can be condensed to a liquid, which boils at  $-33.6^\circ \text{C}$ . The latter has a high coefficient of expansion, its volume increasing by 21.9 per cent when it is heated from  $-35^\circ$  to  $60^\circ \text{C}$ . One liter of the liquid, when vaporized, forms 463.8 liters of gas at  $0^\circ \text{C}$ . and

<sup>62</sup> C. R. Williams, *J. Ind. Hyg. Toxicol.*, 24, 277 (1942).

<sup>63</sup> D. A. Greenwood, *Physiol. Revs.*, 20, 582 (1940).

<sup>64</sup> H. H. Weber and W. E. Engelhardt, *Zentr. Gewerbehyg. Unfallverhüt.*, 10, 41 (1933).

<sup>65</sup> M. Sommelet, *Bull. Sci. Pharmacol.* No. 30, 211 (1923). H. Lüthig, *Chem. Ztg.*, 48, 613 (1924); 49, 805 (1925). E. Spaeth, *Pharm. Zentralhalle*, 58, 599 (1917). F. Riechen, *Z. Nahr. Genussm.* 44, 93 (1922).

<sup>66</sup> R. P. White, *The Dermatogoses, or Occupational Affections of the Skin*. 4th ed., Lewis, London, 1934.

760 mm. pressure. The vapor pressure of liquid chlorine is 3.66 atm. at 0° C., 6.62 atm. at 20°, 8.75 atm. at 30° and 41.7 atm. at 100°. A liter of water dissolves 2.260 liters of chlorine at 20° C. The gas is readily adsorbed upon charcoal and is soluble in carbon tetrachloride, other halogenated hydrocarbons, and sulfuryl chloride. Chlorine reacts readily with metals and, by substitution or addition, with a wide variety of organic compounds.

1 mg./l.  $\approx$  344 p.p.m. and 1 p.p.m.  $\approx$  2.9 mg./cu.m. at 25° C., 760 mm.

## 2. Uses and Industrial Exposures

Chlorine is made at present by the electrolysis of chlorides, either fused or in aqueous solution. It is stored and shipped either in steel cylinders or in tank cars. Steel cylinders should be capable of resisting a pressure of 22 atmospheres and should not contain more than one kilogram of liquid per 0.8 liter of capacity. An explosion of a tank car containing 15 tons of chlorine caused injury to 85 persons, three of whom died.<sup>67</sup>

Large quantities of chlorine are used for the sterilization of water supplies and swimming pools. Chlorine, as such, or in the form of "chloride of lime," is used as a bleaching agent in laundries. It is employed in the manufacture of chlorates, perchlorates, and numerous other inorganic compounds, and has a wide variety of uses in the organic chemical industry.

## 3. Detection and Determination in Air

When present in air to the extent of 5 p.p.m., chlorine has but a slight odor. In one tenth of that concentration, it is odorless, but can be detected by its ability to give a blue color to paper impregnated with starch and potassium iodide.<sup>68</sup>

The reaction of chlorine with potassium iodide may also be used for the quantitative determination of the chlorine content of air.<sup>69</sup> In another method, a measured volume of air is passed through a solution of *o*-toluidine in hydrochloric acid, and the resultant yellow color is compared with that of standard color solutions of potassium dichromate.<sup>70</sup> An instrument has been devised for automatically giving a warning signal whenever the chlorine content of the air exceeds 0.005 volume per cent (50 p.p.m.).<sup>71</sup> It operates by measuring the conductivity of water through which the air is passed. A Russian automatic

<sup>67</sup> O. Römcke and O. K. Evensen, *Nord. Med Ark.*, 7, 1224 (1940); *Chem Abstracts*, 35, 1541 (1941). For a discussion of accidents to chlorine tanks, see T. A. Fleming, *Fire Protection*, 103, No. 8, 10, 14 (1938).

<sup>68</sup> E. Smolczyk and H. Cobler, *Gasmasker*, 2, 27 (1930), cited in F. Flury and F. Zernik, *Schädliche Gase*, Springer, Berlin, 1931, p. 121.

<sup>69</sup> A. C. Fieldner, G. G. Oberfell, M. C. Teague, and J. N. Lawrence, *Ind. Eng. Chem.*, 11, 523 (1919).

<sup>70</sup> L. E. Porter, *Ind. Eng. Chem.*, 18, 730 (1926). Am. Pub. Health Assoc., *Standard Methods of Water Analysis*. 8th ed., 1936.

<sup>71</sup> T. A. H. Jeffrey, *Power*, 87, 514 (1943); *Chem. Abstracts*, 38, 1812 (1943).

chlorine detector depends upon the ability of bromine, liberated by chlorine from potassium bromide, to bleach methyl orange.<sup>72</sup>

#### 4. Toxicity of Chlorine

*Acute effects.* Chlorine acts as a sterilizing and deodorizing agent by virtue of its ability to oxidize organic matter, and to this destructive action is probably due its irritant effect.

Brief exposure to air containing 1000 p.p.m. chlorine (3 mg. per liter) kills even large animals.<sup>73</sup> The mechanism that induces almost immediate death is unknown, but if the animals survive for a longer period death results from pulmonary edema. The exposure of cats to a concentration of 0.9 mg. per liter (300 p.p.m.) for 1 hour may cause death after a period during which the conjunctiva is inflamed and there is coughing and dyspnea.<sup>74</sup> On the other hand, it has been asserted<sup>74</sup> that dogs rarely die following a 30-minute exposure to a concentration not greater than 1.9 mg. per liter (650 p.p.m.), and never after a corresponding period of exposure to a concentration less than 0.80 mg. per liter (280 p.p.m.).

The respiratory rate of animals is increased during exposure to air containing from 200 to 1000 p.p.m.,<sup>75</sup> but when the concentration is 10,000 or more p.p.m., the inspirations occur more slowly and deeply and are finally arrested. Artificial respiration was ineffective in the case of animals exposed to concentrations greater than 50,000 p.p.m.<sup>76</sup> The pulse rate of dogs is retarded during exposure to concentrations of 180 to 200 p.p.m.<sup>76</sup> or more.<sup>77</sup> Dogs are rendered poikilothermic by exposure to concentrations of 800 to 900 p.p.m.<sup>77</sup>

The sensitivity of men to chlorine varies greatly. Men may work without interruption in air containing 0.003 to 0.006 mg. of chlorine per liter (1 or 2 p.p.m.), according to Matt.<sup>78</sup> Exposures to low concentrations, 0.01 to 0.02 mg. per liter or 3 to 6 p.p.m.,<sup>74</sup> cause a stinging and burning sensation in the eyes, nose, and throat, and sometimes headache due to irritation of the accessory nasal sinuses. There may be redness and watering of the eyes, sneezing, coughing, and huskiness or loss of the voice. Bleeding of the nose may occur and sputum from the pharynx and trachea may be blood-tinged. There is little or no chest pain other than the muscular soreness associated with excessive coughing. Exposure for  $1/2$  to 1 hour to a concentration of 0.04 to 0.06 mg. per liter (14 to 21 p.p.m.)

<sup>72</sup> I. V. Men'shchikov, *Zavodskaya Lab.*, 9, VBDJ AVTDJQ; *Chem. Abstracts* CE, 2813 (1941).

<sup>73</sup> Chlopin, *Z. ges. Schiess- u. Sprengstoffw.*, 22, 227 (1927); 23, 29 (1928); cited in F. Flury and F. Zernik, *Schädliche Gase*, Springer, Berlin, 1931, p. 118.

<sup>74</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931, p. 118.

<sup>75</sup> J. A. Gunn, *Quart. J. Med.*, 13, 121 (1920); *Chem. Abstracts*, 14, 1148 (1920).

<sup>76</sup> E. Schäfer, *Brit. Med. J.*, 1916, II, 245.

<sup>77</sup> H. G. Barbour, *J. Pharmacol.*, 14, 47, 65 (1919).

<sup>78</sup> L. Matt, *Dissertation*, Würzburg, 1889, cited in F. Flury and F. Zernik, *Schädliche Gase*, Springer, Berlin, 1931, p. 120.

is dangerous,<sup>74</sup> and a concentration of 0.29 mg. per liter (100 p.p.m.) cannot be borne for longer than one minute.<sup>79</sup>

Damage from exposures to low concentrations is limited to the nose and throat because of the solubility of chlorine in water. Higher concentrations damage the lungs, and give rise to pulmonary congestion and edema, the seriousness of which is increased by bronchoconstriction.<sup>77</sup> Many factors, which have been discussed in detail by Kehoe and Kitzmiller,<sup>80</sup> contribute to the development of a state of anoxia. The initial response to anoxia is an increase in the cardiac rate and output and in arterial and venous pressure. The victim becomes prostrated and the skin may be warm and purplish in color. Damage to the intrapulmonary vascular beds, and the decreased volume and increased viscosity of the blood resulting from the loss of water to the lung, put a severe strain upon the heart. If failure of the heart is imminent, the pulse becomes rapid and thready and the skin, especially that of the extremities, becomes cold and clammy and assumes a grayish pallor.<sup>80,81</sup>

The significance of the absorption of chlorine, and of hydrogen chloride formed by the reaction of chlorine with water, is difficult to appraise. In dogs that inhaled air containing 800 p.p.m. chlorine for 2 to 7 hours, a rapidly increasing acidosis occurred.<sup>82</sup> Among the occasional sequelae found in men gassed by chlorine in warfare are chronic bronchitis and emphysema.<sup>83</sup>

*Effects of repeated inhalation of chlorine in low concentrations.* Lehmann believed that repeated exposure of animals to chlorine may lead to the development of some tolerance.<sup>84</sup> Men lose their ability to detect the odor of chlorine in small concentrations.<sup>85</sup> Although Ronzani<sup>86</sup> found no damage in animals repeatedly exposed to a concentration of 0.002 mg./liter, Skljanskaya and Rappoport<sup>87</sup> found more recently that the repeated exposure of rabbits to concentrations ranging from 0.002 to 0.005 mg. per liter (0.7 to 1.7 p.p.m.) over periods up to nine months caused a loss of weight and an increased incidence of respiratory disease. According to Ronzani,<sup>86</sup> men exposed in bleaching rooms to concentrations of the order of 0.015 mg. per liter (5 p.p.m.) age prematurely, suffer from diseases of the bronchi, and become predisposed to tuberculosis. The teeth

<sup>79</sup> E. B. Vedder, *The Medical Aspects of Chemical Warfare*. Williams & Wilkins, Baltimore, 1925, p. 70.

<sup>80</sup> R. A. Kehoe and K. V. Kitzmiller, *Cincinnati J. Med.*, 23, 423 (1942).

<sup>81</sup> O. Klotz, *J. Lab. Clin. Med.*, 2, 889 (1917). W. H. Schultz and H. R. Hunt, *J. Pharmacol.*, 11, 179 (1918).

<sup>82</sup> A. M. Hjort and F. A. Taylor, *J. Pharmacol.*, 13, 407 (1919).

<sup>83</sup> H. L. Gilchrist and P. B. Matz, *Med. Bull. Veterans' Admin.*, 9, 229 (1933). J. C. Meakins and J. G. Priestley, *Can. Med. Assoc. J.*, 9, 968 (1919). R. G. Pearce, *J. Lab. Clin. Med.*, 5, 411 (1920).

<sup>84</sup> K. B. Lehmann, *Arch. Hyg.*, 34, 272 (1899), cited in F. Flury and F. Zernik, *Schädliche Gase*, Springer, Berlin, 1931, p. 119.

<sup>85</sup> G. Lutz, *Zentr. Gewerbehyg. Unfallverhüt.*, 14, 175 (1927), cited in F. Flury and F. Zernik, p. 119.

<sup>86</sup> E. Ronzani, *Arch. Hyg.*, 67, 287 (1908), cited in F. Flury and F. Zernik, p. 119.

<sup>87</sup> R. M. Skljanskaya and J. L. Rappoport, *Arch. exper. Path. Pharmacol.*, 117, 276 (1935).

were corroded by hydrochloric acid formed in the mouth, and inflammation or ulceration of the mucous membrane of the nose occurred. In guinea pigs the inhalation of small quantities of chlorine accelerates the course of experimental tuberculosis, according to Arloing, Berthet, and Viallier.<sup>88</sup> These experimental and clinical observations tend to controvert the belief, frequently expressed about twenty years ago, that the presence of chlorine in small quantities in the air of workrooms lessens the incidence of respiratory diseases among workmen, presumably by sterilizing the air.<sup>89</sup>

*Effects on the skin.* In high concentrations, chlorine irritates the skin, causing sensations of burning or pricking, inflammation, or even blister formation. Workers in electrolytic chlorine plants may develop a form of acne, particularly evident around the ears and on the face. It resembles that due to contact with chlorinated naphthalenes, and has been attributed to the action of some compound formed by the reaction of chlorine with agents used in the composition of the electrodes.<sup>90</sup>

#### 5. Maximum Allowable Concentration and Safety Measures

The maximum permissible limit in 13 states is 0.003 mg. per liter or 1 p.p.m.;<sup>91</sup> but Ohio and Washington have adopted 5 p.p.m. However, DallaValle<sup>92</sup> suggested that it should be less than 0.35 p.p.m.

Detailed safety measures for the handling of liquid chlorine in large quantities have been described by von Post and others.<sup>93,94</sup>

## HYDROGEN CHLORIDE

### 1. Properties, Uses, and Industrial Exposures

Hydrogen chloride, HCl, is a colorless gas with a sharp odor and an acid taste. It has a molecular weight of 36.47 and a density of 1.6397 g. per liter<sup>95</sup>

<sup>88</sup> Arloing, Berthet, and Viallier, *Presse méd.*, 48, 361 (1940); *Chem. Abstracts*, 34, 5540 (1940).

<sup>89</sup> C. Baskerville, *Science*, 50, 50 (1919); *J. Ind. Eng. Chem.*, 12, 293 (1920); 13, 568 (1921); 15, 746 (1923).

<sup>90</sup> K. Herxheimer, *Münch. med. Wochschr.*, 46, 278 (1899). G. Thibierge and P. Pagniez, *Ann. dermatol. syphilig.* 4th Sér., 1, 815 (1900). J. Nicholas and M. Pillon, *Bull. soc. franç. dermat. syphilig.*, 32, 33 (1925), cited in R. P. White, *The Dermatogoses, or Occupational Affections of the Skin*, 4th ed., 1934, Lewis, London, pp. 222, 223.

<sup>91</sup> M. Bowditch, C. K. Drinker, P. Drinker, H. H. Haggard, and A. Hamilton, *J. Ind. Hyg. Toxicol.*, 22, 251 (1940); State of California, Dept. Ind. Relations, *Minutes Ind. Accident Commission*, 1939; State of Connecticut, *Sanitary Code*, Reg. 281; cited in M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*, Interscience, New York, 1941, p. 624.

<sup>92</sup> J. M. DallaValle, *Principles of Exhaust Hood Design*. U.S. Public Health Service, Aug., 1939.

<sup>93</sup> E. Von Post, *Arbetarskyddet*, No. 1, 2; No. 2, 38 (1939); *Chem. Abstracts*, 34, 3949 (1940).

<sup>94</sup> J. Schuber and M. W. Phelps, *Paper Mill*, No. 14, 14 (1939). R. P. Belbin, *Power and Works Engr.*, 34, 293 (1939). L. L. Hedgepeth and W. S. Riggs, *J. Am. Waterworks Assoc.*, 30, 1671 (1938).

<sup>95</sup> R. W. Gray, *Proc. Chem. Soc. London*, 23, 119 (1907).

at 0° C. and 760 mm. Hg (about 1.3 times as heavy as air). Because of its great solubility in water it fumes in moist air. It may be prepared from sodium chloride by the action of sulfuric acid or sodium bisulfate. The gas itself is rarely used except in the chemical industry. Aqueous solutions containing about 35 per cent hydrogen chloride have a wide variety of uses. The impure commercial product is called muriatic acid. When employed in industries in which there is little familiarity with the handling of chemicals, the use of hydrochloric acid gives rise to numerous minor accidents. Serious intoxication from inhalation is rare because its irritant nature is such as to prevent uninterrupted work in air containing the gas in dangerous concentrations.

1 mg./l.  $\approx$  670 p.p.m. and 1 p.p.m.  $\approx$  1.47 mg./cu.m. at 25° C., 760 mm.

### 2. Determination in Air

Samples of air may be absorbed in a known quantity of an alkaline solution and determined by titration of the remaining alkali or by titration of the chloride ion with silver nitrate. Apparatus for the continuous determination of hydrogen chloride in air has been devised.<sup>96</sup> In the absence of interfering acids, hydrogen chloride can be determined in the field by the method described under Sulfuric Acid.

### 3. Physiological Response in Animals

When inhaled in sufficiently high concentration, hydrogen chloride acts as an irritant to the respiratory tract. The inhalation of air containing 6.4 mg. per liter, for 30 minutes, by rabbits and guinea pigs resulted in death,<sup>97</sup> in many instances from laryngeal spasm, laryngeal edema, or rapidly developing pulmonary edema. Lehmann<sup>98</sup> found that exposure of cats, rabbits, and guinea pigs for 1½ hours to a concentration of 5 mg. per liter (3400 p.p.m.) caused death after 2 to 6 days, while a slightly shorter exposure to a concentration of 2 mg. per liter (1350 p.p.m.) caused severe irritation, dyspnea, and clouding of the cornea. When the duration of exposure was 2 to 6 hours, a concentration of 1 mg. per liter (675 p.p.m.) caused some fatalities.<sup>97</sup> A 6-hour exposure to a concentration of 0.45 mg. per liter (300 p.p.m.) caused slight corrosion of the cornea and upper respiratory irritation. This response was but slight after a similar exposure to a concentration of 0.15 to 0.21 mg. per liter (100 to 140 p.p.m.).<sup>98</sup> The increase in respiratory rate associated with elevation of environmental temperature increases absorption and thus adds to the danger of exposures to low concentration.<sup>99</sup>

An exposure of 6 hours daily to a concentration of 0.15 mg. per liter (100 p.p.m.), repeated for 50 days, caused only slight unrest and irritation of the eyes

<sup>96</sup> E. C. White, *J. Am. Chem. Soc.*, 50, 2148 (1928).

<sup>97</sup> W. Machle, K. V. Kitzmiller, E. W. Scott, and J. F. Treon, *J. Ind. Hyg. Toxicol.*, 24, 222 (1942).

<sup>98</sup> Lehmann, *Arch. Hyg.*, 5, 16 (1886); 67, 57 (1908). K. B. Lehmann and A. Burek, *ibid.*, 72, 343 (1910); cited in F. Flury and F. Zernik, *Schädliche Gase*, Springer, Berlin, 1931, p. 126.

<sup>99</sup> Leites, *Arch. Hyg.*, 102, 91 (1929), cited in F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, p. 126.

and nose of rabbits, guinea pigs, and pigeons.<sup>100</sup> The hemoglobin content of the blood was only slightly diminished. Twenty exposures of 6 hours each to a concentration of 0.05 mg. per liter (33 p.p.m.) caused no harm to a monkey or to smaller animals.<sup>97</sup> Repeated exposure to higher concentrations resulted in a loss of weight that paralleled the severity of the exposure.

When inhaled in high concentrations, the gas causes necrosis of the tracheal and bronchial epithelium, as well as pulmonary edema, atelectasis, and emphysema, and damage to the pulmonary blood vessels. Detailed descriptions of the lesions in the liver and other organs have been given by Machle, Kitzmiller, Scott, and Treon.<sup>97</sup> The insufflation of weak aqueous solutions of hydrochloric acid into the bronchi of rabbits sets up inflammatory processes resembling those seen in influenza or after exposure to certain chemical warfare agents.<sup>101</sup>

The repeated oral administration of dilute hydrochloric acid to dogs induces acute and chronic gastritis and duodenitis, and leads to the appearance of ulcers of the pylorus,<sup>102</sup> while toxic doses lower the alkaline reserve of the blood.<sup>103</sup>

#### 4. Effects of Hydrogen Chloride on Man

According to Matt,<sup>104</sup> work is impossible when one inhales air containing hydrogen chloride in concentrations of 0.075 to 0.15 mg. per liter (50 to 100 p.p.m.), is difficult but possible when the air contains concentrations of 0.015 to 0.075 mg. per liter (10 to 50 p.p.m.), and is undisturbed at a concentration of 0.015 mg. per liter (10 p.p.m.). Prolonged exposure to low concentrations causes erosion of the teeth. Mists of heated metal-pickling solutions may cause bleeding of the nose and gums, and ulceration of the nasal and oral mucosa, and render the skin of the face so tender that shaving becomes painful.<sup>105</sup> Exposure of the skin to gaseous hydrogen chloride, escaping from leaks in apparatus or piping, has caused severe burns. Contact with concentrated solutions of hydrogen chloride (muriatic acid), in cleaning metal, gives rise to small burns and ulcerations of the hands.<sup>106</sup>

#### 5. Maximum Allowable Concentration

Elkins<sup>107</sup> proposed 0.015 mg. per liter (10 p.p.m.) as the maximum allowable concentration. According to Hirt,<sup>108</sup> a concentration three and a half times as

<sup>100</sup> E. Ronzani, *Arch. Hyg.*, 70, 217 (1909), cited in F. Flury and F. Zernik, p. 127.

<sup>101</sup> M. C. Winternitz, G. H. Smith, and F. P. McNamara, *J. Exptl. Med.*, 32, 199, 205 (1920).

<sup>102</sup> W. J. Gallagher, *Arch. Surg.*, 17, 613 (1928).

<sup>103</sup> A. Loewy and F. Münzer, *Biochem. Z.*, 134, 437 (1923).

<sup>104</sup> L. Matt, *Dissertation*, Würzburg, 1889, cited in F. Flury and F. Zernik, p. 128.

<sup>105</sup> W. Ludewig, *Arch. Gewerbepath. Gewerbehyg.*, 11, 296 (1942); L. Carozzi, *Occupation and Health*.

<sup>106</sup> R. P. White, *The Dermatogoses, or Occupational Affections of the Skin*, 4th ed., Lewis, London, 1934. *Illinois Labor Bull.*, 4, 10 (1943).

<sup>107</sup> H. B. Elkins, *Ind. Med.*, 8, 426 (1939).

<sup>108</sup> Hirt, cited in F. Flury and F. Zernik, *Schädliche Gase*, Springer, Berlin, 1931, p. 127.

great as this cannot be detected by taste or odor. Methods for the safe handling of acids have been described by Parks.<sup>109</sup>

## BLEACHING POWDER AND HYPOCHLORITES

Bleaching powder, "chloride of lime," is made by passing chlorine over finely divided slaked lime in closed chambers. It is a hygroscopic white powder with an odor of chlorine. Its exact chemical nature is controversial, some chemists regarding it as a double calcium salt of hydrochloric and hypochlorous acids,  $\text{CaCl}(\text{ClO})$ , and others as a mixture of calcium chloride,  $\text{CaCl}_2$ , and calcium hypochlorite,  $\text{Ca}(\text{ClO})_2$ . It evolves chlorine, especially in moist air. The evolution of oxygen under the catalytic influence of impurities such as iron and manganese has led to the building up of dangerous pressures in closed containers, especially when heated.<sup>110</sup> This was more common at a time when chlorine was made by the Weldon process. Bleaching powder is explosive when heated suddenly above  $100^\circ\text{C}$ .<sup>111</sup> and deflagration occurs when it is mixed with combustible substances.<sup>112</sup>

Bleaching powder is used as a disinfecting, oxidizing, and chlorinating agent. As a bleaching agent, it is employed in the making of paper and textiles. The inhalation of dusts may damage the teeth, conjunctiva, and respiratory tract. It has been much employed by dyers to remove stains from the hands. If used as a paste with excessive rubbing for more than three to four minutes, it sometimes causes a moderate to severe degree of damage to the skin.<sup>113</sup>

Javel water, a solution of sodium hypochlorite, used for the removal of stains from textiles, has been reported as a cause of dermatitis among laundresses.<sup>114</sup> Hypochlorites have sensitizing properties.<sup>115</sup>

## BROMINE

### 1. Preparation, Properties, and Uses

Although formerly prepared by the action of chlorine upon bromides present in the mother liquors in salt manufacture, bromine, ( $\text{Br}_2$ ) is now obtained in large quantities from sea water.<sup>116</sup> It is a deep reddish-brown liquid, with molecular weight 159.83, and a density of 3.12 at  $15^\circ\text{C}$ . It solidifies at  $-7.3^\circ$  and boils at  $58.8^\circ$ . Its vapor is about 5.5 times as heavy as air. The vapor pressure is equivalent to 77.3 mm. Hg at  $4^\circ\text{C}$ ., 172 mm. at  $20.6^\circ$ , and 378 mm. at  $30.6^\circ$ .

<sup>109</sup> R. W. Parks, *Safety Eng.*, 71, 245 (1936); 72, 29, 32 (1936). Moebus, *Feuerschutz*, 20, 2 (1940); *Chem. Abstracts*, 34, 2490 (1940).

<sup>110</sup> A. H. Gill, *Ind. Eng. Chem.*, 16, 577 (1924).

<sup>111</sup> S. Ochoa, *J. Chem. Soc. Japan*, 26, 978 (1923).

<sup>112</sup> J. Weichherz, *Chem. Ztg.*, 52, 729 (1928).

<sup>113</sup> J. Lebduvska, J. Pidra, and F. Pokorny, *Arch. expll. Path. Pharmacol.*, 193, 629 (1939).

<sup>114</sup> H. Rabeau and Mille. Ukrainczyk, *Ann. dermatol. syphilig.*, 10, 656 (1939); *Chem. Abstracts*, 53, 8773 (1939).

<sup>115</sup> P. Ravaut and Koang, *Bull. soc. franç. dermatol. syphilig.*, 37, 655 (1930); cited in R. P. White, *The Dermatogoses, or Occupational Affections of the Skin*. 4th ed., Lewis, London, 1934, p. 243.

<sup>116</sup> C. M. A. Stine, *Ind. Eng. Chem.*, 21, 434 (1929). L. C. Stewart, *ibid.*, 26, 361 (1934).



Bromine is soluble in water to the extent of 3.21 parts per 100 parts at 20° C. It is very soluble in alcohol, ether, chloroform, and carbon disulfide. Liquid bromine, or its aqueous solution, is widely used as an oxidizing agent in chemical laboratories. It causes burns when spilled upon the skin. Large quantities are used in brominating hydrocarbons, and in the manufacture of fumigants, dye-stuffs, drugs, and war gases. Bromides are widely used in photography.

1 mg./l.  $\approx$  153 p.p.m. and 1 p.p.m.  $\approx$  6.53 mg./cu.m. at 25° C., 760 mm.

### 2. Determination in the Atmosphere

The bromine content of air may be determined by passing a measured volume through a solution of potassium iodide, and titrating the liberated iodine with a standard solution of sodium thiosulfate.<sup>117</sup> It also may be absorbed in alkali, oxidized to bromate by sodium hypochlorite, and estimated iodometrically.<sup>118</sup> After absorption in alkali, bromine may also be liberated by chlorine water and determined colorimetrically, either in the aqueous solution or after extraction with carbon tetrachloride.<sup>119</sup>

### 3. Toxicity for Animals

Like chlorine, bromine exerts a strong irritant action upon the respiratory tract, a concentration of 3.5 mg. per liter of air (about 550 p.p.m.) being immediately fatal to animals.<sup>120</sup> An exposure of 7 hours to air containing 0.15 mg. per liter (23 p.p.m.) provoked only irritation of the respiratory tract and slight dyspnea in cats, rabbits, and guinea pigs, while a similar exposure to air containing 1.2 mg. of bromine per liter (180 p.p.m.) caused clouding of the cornea (rabbits and guinea pigs), severe irritation of the respiratory tract, dyspnea, reduction of the respiratory rate, and some fatalities (rabbits). An exposure of 3 hours to air containing 2 mg. of bromine per liter (300 p.p.m.) caused, in addition, definite disturbances of function of the central nervous system. Guinea pigs died during the exposure and rabbits died a few hours later. The hair of rabbits became yellow and brittle. Necropsy revealed the presence of edema of the lungs, a pseudomembranous deposit on the trachea and bronchi, and hemorrhages of the gastric mucosa. Foci of bronchopneumonia were found in animals that died several days after exposure.

The effect of repeated exposure to air containing bromine in low concentrations has not been adequately investigated. Henderson and Haggard<sup>121</sup> concluded that the depressant action of the bromine absorbed and converted to the bromide ion was insignificant, even under the conditions of prolonged exposure to air

<sup>117</sup> F. H. Goldman and J. M. DallaValle, *U.S. Pub. Health Repts.*, 54, 1728 (1930).

<sup>118</sup> I. M. Kolthoff and H. Yutzy, *Ind. Eng. Chem., Anal. Ed.*, 9, 75 (1937).

<sup>119</sup> M. Lane, *Ind. Eng. Chem., Anal. Ed.*, 14, 149 (1942).

<sup>120</sup> K. B. Lehmann and R. Hess, *Arch. Hyg.*, 7, 335 (1887); cited in F. Flury and F. Zernik, *Schädliche Gase*, Springer, Berlin, 1931, p. 122.

<sup>121</sup> Y. Henderson and H. Haggard, *Noxious Gases*. 2nd ed., Reinhold, New York, 1944. p. 133.

containing bromine vapor. Flury<sup>122</sup> believes that bromine can be absorbed through the skin during exposure to the vapor.

#### 4. Effects on Man

The symptoms arising in man following the inhalation of bromine in small amounts include: coughing, nosebleed, a feeling of oppression, dizziness, and headache, followed after some hours by abdominal pain and diarrhea, and sometimes by a measles-like eruption on the trunk and extremities. Oppenheim<sup>123</sup> mentioned the frequency with which discharging pustules and furuncles appear in exposed areas of the skin of men who handle bromine. Brief contact of the liquid with the skin leads to the formation of vesicles and pustules. If not removed at once, it produces deep, painful ulcers.

#### 5. Safe Concentrations of Bromine Vapor in Air

Undisturbed work is possible when the respired air contains 0.001 to 0.002 mg. bromine per liter (0.15 to 0.3 p.p.m.); it becomes difficult in the presence of 0.002 to 0.003 mg. per liter (0.3 to 0.45 p.p.m.); and impossible at 0.004 mg. per liter (0.6 p.p.m.), according to Matt.<sup>124</sup> Zederbaum<sup>125</sup> found that no serious effects resulted from an exposure to 0.026 mg. per liter (about 4 p.p.m.); Henderson and Haggard<sup>121</sup> considered this the maximum concentration allowable for an exposure of less than one hour, and believed that even brief exposures to air containing 40 to 60 p.p.m. would be dangerous. The latter investigators regarded the concentration of 0.1 to 0.15 p.p.m. as the maximum allowable one for prolonged exposure, although Hess<sup>120</sup> noted that a concentration of 0.15 p.p.m. induced some effects after several hours. Further investigation is needed for setting the upper limit of a safe concentration for the daily working atmosphere; but 5 states have adopted 1 p.p.m. as the maximum allowable concentration. The least concentration that gives a detectable odor is of the order of 3.5 p.p.m. according to Fieldner, Katz, and Kinney.<sup>126</sup>

## IODINE AND IODIDES

### 1. Properties and Uses

Iodine, I<sub>2</sub>, a crystalline, blackish-violet element with a metallic luster and a characteristic odor has a molecular weight of 253.84. Iodine melts at 114° C. and boils at 184° C. It sublimates readily, giving off a violet vapor that colors the skin. Its vapor pressure is equivalent to 0.03 mm. Hg at 0° C., 0.131 mm. at

<sup>122</sup> F. Flury, *Festschr. Zangger*, 2, 836 (1935); *Chem. Abstracts*, 31, 6711 (1937).

<sup>123</sup> M. Oppenheim, *Wien. klin. Wochschr.*, 28, 1273 (1915); cited in R. P. White, *The Dermatogoses, or Occupational Affections of the Skin*. 4th ed., Lewis, London, 1934, p. 178.

<sup>124</sup> L. Matt, *Dissertation, Würzburg*, 1889; cited in F. Flury and F. Zernik, *Schädliche Gase*. Berlin, 1931, p. 123.

<sup>125</sup> D. Zederbaum, *Gigiene truda*, 1927, p. 68; cited in F. Flury and F. Zernik, *Schädliche Gase*, Springer, Berlin, 1931, p. 123.

<sup>126</sup> A. C. Fieldner, S. H. Katz, and S. P. Kinney, *U.S. Bur. Mines Tech. Paper No. 248* (1921).

15° C., 0.309 mm. at 25° C., 0.467 mm. at 30° C., 0.699 mm. at 35° C., 1.027 mm. at 40° C., and 2.144 mm. at 50° C.<sup>127</sup> It is slightly soluble in water, easily soluble in chloroform, carbon disulfide, or alcohol. Formerly obtained from the ash of seaweed, it is now obtained chiefly from the mother liquors remaining in the preparation of Chile saltpeter. It is liberated from its salts by the action of oxidizing agents and purified by sublimation. Iodine and its compounds are used in analytical chemistry, medicine, photography, and in the making of dyestuffs and numerous organic compounds.

1 mg./l.  $\approx$  96.5 p.p.m. and 1 p.p.m.  $\approx$  10.38 mg./cu.m. at 25° C., 760 mm.

## 2. Determination of Iodine

Fritted-glass scrubbers have been recommended for the absorption of iodine from air samples.<sup>128</sup> Standard volumetric procedures are available for its determination by titration with sodium thiosulfate, using starch-iodide indicator. Methods for the microdetermination in blood and tissues have been described by Salter and McKay<sup>129</sup> and by Stephens.<sup>130</sup>

## 3. Toxicity of Iodine

Iodine is an essential element in nutrition, being required by the thyroid for the elaboration of its hormone, thyroxin. Because of its use in medicine in the treatment of hypothyroidism and other diseases, and because of the addition of iodides to salt for the prevention of endemic goiter, the pharmacology and metabolism of iodine have been the subjects of many investigations, which are described in texts on pharmacology and in reviews.<sup>131</sup> Because industrial poisoning by iodine is rare, a detailed consideration of its biological significance will not be given here.

Iodine vapor acts as an irritant when inhaled, and is capable of causing a rapidly developing pulmonary edema.<sup>132</sup> Systemic poisoning may result from its absorption through various portions of the respiratory tract.

Lacrimation and a burning sensation in the eyes, blepharitis, rhinitis, catarrhal stomatitis, and chronic pharyngitis have been noted following industrial exposure.

Matt,<sup>133</sup> in experiments upon himself, found that work is undisturbed when the concentration of iodine vapor in the air is 0.1 p.p.m., difficult when it is 0.15 to 0.2 p.p.m., and not possible when it is 0.3 p.p.m. In one recent case of fatal

<sup>127</sup> L. J. Gillespie and L. H. D. Fraser, *J. Am. Chem. Soc.*, **58**, 2260 (1936).

<sup>128</sup> *Am. Pub. Health Assoc. Yearbook (1939-40)*, p. 92.

<sup>129</sup> W. T. Salter and E. A. McKay, *Endocrinology*, **35**, 380 (1944).

<sup>130</sup> C. D. Stephens, *J. Lab. Clin. Med.*, **22**, 1074 (1937).

<sup>131</sup> R. E. Remington, *J. Chem. Education*, **7**, 2590 (1930). C. Oppenheimer, *Chem. Ztg.*, **53**, 925, 968 (1929). T. von Fellenberg, *Ergeb. Physiol.*, **25**, 176 (1926).

<sup>132</sup> Luckhardt, Koch, Schroeder, and Weiland, *J. Pharmacol.*, **15**, 1 (1920).

<sup>133</sup> L. Matt, *Dissertation*, Würzburg, 1889, cited in F. Flury and F. Zernik, *Schädliche Gase*, Springer, Berlin, 1931, p. 124.

poisoning from the ingestion of iodine,<sup>184</sup> nitrogen retention and anuria occurred, but no significant renal lesions were found at necropsy.

Experiments have not been performed upon the effects of the repeated inhalation of iodine by animals.

Chronic intoxication resulting from the ingestion of excessive amounts of iodides is characterized by signs of irritation and nervousness. Determinations of the basal metabolic rate of workers exposed to iodine do not appear to have been made. Von Fellenberg<sup>185</sup> found that the average daily urinary excretion of iodine by five normal subjects is 173 micrograms. Administered iodine is rapidly excreted in the urine and in smaller quantities in saliva, milk, sweat, bile, and other secretions. The storage of iodine in the thyroid depends upon the functional state of the gland.

Although iodine is an irritant to the skin, the repeated application of its aqueous or alcoholic solution upon the skin of white mice during a period of 18 months did not induce hyperkeratotic changes.<sup>186</sup> A vesicular or impetigenous eruption of the face, with acne and folliculitis, occurring among photographers, physicians, and nurses has been ascribed to iodine or iodides.

## HYDROGEN IODIDE

Hydrogen iodide, hydriodic acid, HI, is a colorless gas with molecular weight of 127.93. It is 4.4 as heavy as air. Hydrogen iodide melts at  $-50.8^{\circ}$  C. and boils at  $-35.5$ . It is soluble in alcohol and very soluble in water. It has a limited use in industry and may cause injury by virtue of its acid nature (see Hydrogen Chloride). Quantitative data are not available.

<sup>184</sup> R. Finkelstein and M. Jacobi, *Ann. Internal Med.*, 10, 1283 (1937).

<sup>185</sup> T. von Fellenberg, *Biochem. Z.*, 184, 85 (1927).

<sup>186</sup> J. Rosenstirn, *J. Cancer Research*, 10, 61 (1926). K. Fritzler, *Arch. exptl. Path. Pharmacol.*, 114, 6 (1926).

# Alkaline Materials

FRANK A. PATTY

The caustic alkalis, in solid form or concentrated liquid solution, have a more corrosive local action on the tissues than do most acids. The free caustic dusts, mists, and sprays may cause irritation of the eyes and respiratory tract, and erosion of the nasal septum. Strong alkalis combine with tissue to form albuminates, and with natural fats to form soaps. They gelatinize tissue to form soluble compounds and by doing so may produce deep and painful destruction of tissue. Potassium and sodium hydroxides and oxides are the most active, while less active members of the group are calcium oxide and hydroxide, ammonia gas and ammonium hydroxide, sodium and potassium carbonates, trisodium phosphate, and sodium metasilicate. Even dilute solutions of the stronger alkalis tend to soften the epidermis and emulsify or dissolve the skin fats. Soaps readily dissociate and, when unbuffered, may act as free alkalis to irritate the skin.

When first encountered, atmospheres contaminated with alkalis may be quite irritant, but the effect soon becomes less noticeable. Workmen frequently are found working unconcernedly in an atmosphere that causes coughing and very painful throat and nasal irritation in a person unaccustomed to the exposure.

## AMMONIA

### 1. *Source, Uses, and Industrial Exposures*

Ammonia is produced as a by-product in the distillation of coal, by the action of steam on cyanamide, and by the catalytic combination of nitrogen and hydrogen gases at high temperature and pressure. Ammonia is used extensively in refrigeration and in the manufacture of fertilizers, nitric acid, explosives, dyes, plastics, and other chemicals. It is also encountered in the silvering of mirrors, in glue making, in tannery work, and around nitriding furnaces.

### 2. *Physical and Chemical Properties*

Ammonia,  $\text{NH}_3$ , is a gas at ordinary temperatures. It has a molecular weight of 17.03. The density of the gas is 0.59 (air = 1) at  $25^\circ \text{C}$ . and 760 mm. The melting point is  $-77.7^\circ \text{C}$ . and the boiling point,  $-33.35^\circ$ . The solubility of ammonia in water is 90 g. per 100 ml. at  $0^\circ \text{C}$ . and 7.4 g. at  $100^\circ$  and the solubility in alcohol is 13.2 grams per 100 ml. at  $20^\circ$ . A 1 per cent solution in

water has a pH of about 11.7. The gas is compressed to a liquid and stored or transported in steel cylinders or tank cars. A 28 per cent solution of ammonia in water (sp.g. 0.90 at 25°/25° C.)—called ammonium hydroxide or stronger ammonia water—is the common form in which ammonia is supplied and used. It is also available in 10 per cent solution. Ammonium carbonate and ammonium carbamate are crystalline solids containing 34 and 44 per cent ammonia, respectively. They decompose in the air to release ammonia. Compressed ammonia gas is obviously the greatest inhalation hazard because high atmospheric concentrations can be developed more rapidly by compressed gases, if released, than by vaporization from an aqueous solution or by gradual decomposition of the salts exposed to the air.

1 mg./l.  $\approx$  1438 p.p.m. and 1 p.p.m.  $\approx$  0.7 mg./cu.m. at 25° C., 760 mm.

### 3. Determination in the Atmosphere

In the method of determination most applicable to field use in low concentrations of ammonia, the atmosphere is aspirated at a measured rate through a scrubber containing 0.01 *N* sulfuric acid and methyl red or other suitable indicator (see page 208). The amount of standard acid that is to be used will depend upon the concentration of ammonia anticipated, 1 or 2 ml. made up to 10 ml. with water being sufficient for concentrations on the order of 100 p.p.m. or less, if the rate of sampling is on the order of 2 liters per minute. Since 1 ml. 0.01 *N* sulfuric acid is equivalent to 0.17 mg. or 0.2445 ml. of ammonia gas at 25° C. and 760 mm. Hg pressure, results may be computed as follows:

$$C = \frac{\text{ml. } 0.01 \text{ } N \text{ H}_2\text{SO}_4 \times 0.2445 \times 1000}{\text{rate of sampling} \times \text{time}}$$

where *C* = concentration of ammonia in the atmosphere expressed in parts per million, rate of sampling is expressed in liters per minute, time is the minutes of sampling required to change the color of the indicator in the scrubber, and 1000 is a factor that converts the milliliters of ammonia per liter of air (parts per thousand) to parts per million. When 1 ml. of 0.01 *N* sulfuric acid is used and the sampling rate is 2.83 liters per minute (as with the use of a midget impinger) the equation becomes:

$$C = \frac{86}{\text{sampling time}}$$

With reasonable care this method yields results that are within 5 per cent of the amount of ammonia present. If fritted scrubbers are used, an antifoaming agent may be required.

If preferred, the sample may be collected by scrubbing through an excess of standard sulfuric acid or 4 per cent boric acid solution and titrated,<sup>1</sup> or be collected in 0.1 *N* sulfuric acid and nesslerized.

<sup>1</sup> M. B. Jacobs, *The Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

#### 4. Physiological Response

*Acute effects.* Ammonia either in the gaseous state or in aqueous solution, when in high concentrations, is an irritant and is corrosive to mucous surfaces. The effects of various concentrations of ammonia are given in Table 1.

TABLE 1  
*Physiological Response to Ammonia<sup>a</sup>*

Response	Concentration, p.p.m.
Maximum concentration for prolonged exposure.....	100
Maximum amount for 1 hr.....	300-500
Least amount causing immediate irritation of eyes, nose, and throat....	400-700
Dangerous for as little as ½ hr.....	2500-6500
Rapidly fatal for short exposures.....	5000-10,000

Boyd, MacLachlan, and Perry<sup>3</sup> exposed rabbits and cats to static atmospheres with initial concentrations on the order of 5000 to 10,000 p.p.m. ammonia, for 1 hour, and found this exposure to be approximately LD 50. They found that the noses, mouths, and throats of the animals were severely affected, but that because the ammonia was absorbed upon these mucous surfaces the tracheae and bronchi were partially protected. However, the epithelial lining of the less resistant bronchioles was damaged; congestion, edema, atelectasis, hemorrhage, and emphysema were found in the alveoli; and there was an increase in respiratory-tract fluid.

In human beings, 140 p.p.m. is slightly irritant<sup>4</sup> to the eyes and nose but as much as 350 p.p.m. can be endured for more than an hour, during which time the odor and irritation gradually become less noticeable. Concentrations greater than 2500 p.p.m. are dangerous to life even for short exposures, and concentrations of 5000 to 10,000 p.p.m. (0.5 to 1.0 per cent) are rapidly fatal.

High concentrations of ammonia, in addition to their corrosive action on mucous surfaces, which can cause permanent injury to the cornea, extensive damage to the throat and the upper respiratory tract, chronic bronchial catarrh, and edema, may affect heart action or cause cessation of respiration by reflex action. One per cent (10,000 p.p.m.) ammonia in the atmosphere is mildly irritant to the moist skin, 2 per cent has a more pronounced action, and concentrations of 3 per cent or greater cause a stinging sensation and may produce chemical burns with blistering after a few minutes' exposure.

*Chronic effects.* Rabbits given 50 to 80 ml. of 0.5 per cent ammonia solution by ingestion at intervals of 1 to 2 days, for periods of 1 to 17 months, are said<sup>5</sup> to have developed a chronic acidosis and necrotic changes in the muscle

<sup>2</sup> Y. Henderson and H. W. Haggard, *Noxious Gases*. Reinhold, New York, 1943.

<sup>3</sup> E. M. Boyd, M. L. MacLachlan, and W. F. Perry, *J. Ind. Hyg. Toxicol.*, 26, 29 (1944).

<sup>4</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

<sup>5</sup> J. von Balo, *Frankfurt Z. Path.*, 52, 205 (1938).

fiber and elastic tissue of the aorta and arteries. Regeneration occurred in mild cases, and calcification in seven cases.

Although the alkaline properties of ammonia might be expected to upset the normal pH of the human system after prolonged exposure to low concentrations, no data have yet been presented to show that such is the case. On the contrary, according to Sollmann,<sup>6</sup> ammonia in the body is rapidly converted to urea and ceases to act as ammonia. Concentrations below the amount that causes irritation are not known to have any adverse effect regardless of the length of exposure.

Part of any ammonia reaching the alveoli is neutralized by the carbon dioxide normally present, and part may be absorbed unchanged into the circulation. After exposure, traces of ammonia have been found in the sweat, urine, and exhaled air.<sup>4</sup> Since ammonia is a normal constituent of blood and urine, analysis of these fluids does not offer satisfactory tests to indicate the degree of exposure.

#### **5. Maximum Permissible Concentration, Warning Properties, and Inflammability**

The maximum permissible concentration is accepted to be 100 p.p.m. (70 mg. per cubic meter). This amount has a moderately strong odor, and is moderately irritant to the nose. Ammonia is detectable by odor in concentrations of less than 5 p.p.m., and concentrations of 20 p.p.m. are easily noticeable. A standard based upon comfort would be somewhat less than 100 p.p.m.

Ammonia-air mixtures are inflammable within the range of 15.5 to 26.6 per cent ammonia by volume (see Chapter Thirteen).

## **SODIUM HYDROXIDE**

### **1. Uses and Industrial Exposures**

Sodium hydroxide, caustic soda, is made chiefly from the electrolysis of brine, though some is manufactured in conjunction with the ammonia-soda process for the manufacture of sodium carbonate by the causticization of sodium carbonate with lime, after which it is evaporated to solid caustic, 98 per cent sodium hydroxide, or liquid caustic, 45 to 75 per cent sodium hydroxide.

Caustic is used in the manufacture of rayon, mercerized cotton, soap, paper, explosives, and dyestuffs. It is also used in the chemical industries, in metal cleaning, electrolytic extraction of zinc, tin plating, oxide coating, laundering, bleaching, and dish washing.

### **2. Physical and Chemical Properties**

Sodium hydroxide, NaOH, is a white deliquescent solid with molecular weight 40.01 and a density of 2.130. It melts at 318.4° C. and boils at 1390°. Its solubility in water is 42 g. per 100 ml. at 0° C. and 347 g. at 100° and it is freely soluble in glycerin or alcohol. The pH of a 1 per cent solution in water is about 12.4.

\*T. Sollmann, *A Manual of Pharmacology*. 6th ed., Saunders, Philadelphia, 1944.



### **3. Determination in the Atmosphere**

Caustics and other alkaline materials in the atmosphere, whether gases, mists, or dusts, may be determined by scrubbing a measured volume of air through a measured amount of standard sulfuric acid and titrating the excess acid with standard alkali. The analysis may be completed in the field by using a suitable quantity of standard sulfuric acid scrubbing agent containing methyl red or other appropriate indicator, and noting the time required for scrubbing a measured rate of air until the indicator changes color.

### **4. Physiological Response**

No physiological response has been described except the corrosive action discussed under alkalies. In mists the alkali is, of course, partly converted to carbonate and bicarbonate by the action of carbon dioxide in the atmosphere. After lodging in the respiratory tract a considerable portion is probably soon converted to bicarbonate as a result of the action of carbon dioxide in the exhaled breath.

### **5. Maximum Permissible Concentration**

No permissible limit has been established or suggested, and no published information on concentrations encountered is available. Judging, however, from the irritant effects of caustic mists encountered in concentrations of 1 to 40 mg. per cubic meter of air, 2 mg. sodium hydroxide per cubic meter is believed to represent a concentration that is noticeably, but not excessively, irri'ant. This figure for a total alkalinity computed as sodium hydroxide might be used, on the basis of irritant effects, as a temporary bench mark of permissible atmospheric contamination until further information is presented.

## **POTASSIUM HYDROXIDE**

Potassium hydroxide, caustic potash, KOH, is similar in appearance to caustic soda. Its molecular weight is 56.10 and its density is 2.044 at 20°/4° C. It melts at 360° C. and boils at 1320°. One part potassium hydroxide is soluble in 0.9 part of water, 3 parts of alcohol, or 2.5 parts of glycerin at 25° C. The pH of a 1 per cent solution in water is about 13.0. Potassium hydroxide is prepared by methods similar to those given under sodium hydroxide and its uses and dangers are similar to those of caustic soda.

## **SODIUM PEROXIDE**

Sodium peroxide, Na<sub>2</sub>O<sub>2</sub>, is a yellowish white powder with a molecular weight 77.99. It has a specific gravity of 2.805. It is very soluble in hot or cold water, forming sodium hydroxide and hydrogen peroxide. It is an aggressive oxidizing agent which may ignite organic matter upon contact. It is used as a

bleaching agent, a carbon dioxide absorbent, and a reagent chemical oxidizing agent.

### **SODIUM CARBONATE**

Sodium carbonate, soda ash,  $\text{Na}_2\text{CO}_3$ , is a white hygroscopic powder, with molecular weight 106.0. The specific gravity is about 2.53 at  $20^\circ/4^\circ$  C. It melts at  $851^\circ$  C. Its solubility in water is 7.1 g. per 100 ml. at  $0^\circ$  C. and 45.5 g. per 100 ml. at  $100^\circ$ . The pH of a 1 per cent solution in water is about 11.2. When crystallized with 10 moles of water, it is called decahydrate, sal soda, and washing soda.

Sodium carbonate is manufactured by several processes; chief of which is the Solvay process in which carbon dioxide is passed through a strongly ammoniacal solution of common salt thereby precipitating sodium bicarbonate, which is then converted to the carbonate by calcining. It is used in the manufacture of sodium compounds including glass and soap, in washing and cleaning, in bleaching cotton and linen fabrics, in washing wool, in softening water, in dyeing and dye manufacture, in photography, and as a reagent chemical.

### **TRISODIUM PHOSPHATE**

Trisodium phosphate, T.S.P.,  $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$ , has a molecular weight of 380.21. Its specific gravity is 1.62 at  $20^\circ/4^\circ$  C. It melts at about  $75^\circ$  C. Its solubility in water is 25.8 g. per 100 g. at  $20^\circ$  C., and 157 g. per 100 g. at  $70^\circ$ . The pH of a 1 per cent solution in water is about 11.6. Trisodium phosphate is used in detergents, in clarifying sugar, in photographic developers, in removing boiler scale, in softening water, in manufacturing paper, and in tanning leather.

### **SODIUM SILICATES**

There are several sodium silicates with different formulas and various amounts of water of crystallization. They are variously soluble in water to form alkaline solutions ranging in pH between 11.5 and 12.0. They are used for preserving eggs, in cements, in water softeners, as detergents, in fireproofing fabrics, in waterproofing, and as adhesives.

### **CALCIUM OXIDE**

Calcium oxide, CaO, lime, burnt lime, quicklime, is in the form of white lumps. Its molecular weight is 56.08 and its specific gravity is 3.40. It melts at  $2572^\circ$  C. One gram dissolves in 835 ml. of water at  $25^\circ$  C., or in 1670 ml. at  $100^\circ$ . It is produced by burning limestone in kilns. It combines with water, with evolution of considerable heat, to form calcium hydroxide. Calcium oxide is used in making mortar, plaster, and chlorinated lime, in dehairing hides, in deodorizing vegetable oils, as a dehydrating agent, and in many other ways. Upon exposure to the air it absorbs water and carbon dioxide to form calcium carbonate, becoming air slaked and losing most of its causticity. Lime is an irritant and, although it

has been reported to have caused pneumonia, the severe irritation of the upper respiratory tract ordinarily causes persons to avoid more serious exposure.

### **CALCIUM HYDROXIDE**

Calcium hydroxide, slaked lime,  $\text{Ca}(\text{OH})_2$ , has a molecular weight of 74.10 and a specific gravity of 2.34. One gram dissolves in 590 ml. of water at 25° C. and in 1300 ml. at 100°. The pH of a saturated calcium hydroxide solution in water at 25° C. is about 12.8. The uses of calcium hydroxide are similar to those of calcium oxide, from which it is formed.



# Arsenic, Phosphorus, Selenium, Sulfur, and Tellurium

FRANK A. PATTY

## ARSENIC

The element arsenic,  $As_4$ , occurs free to some extent in nature, but more frequently as a sulfide and in associations with metals. Elementary arsenic exists in several forms but the most stable one is a gray, crystalline, metal-like solid. It alloys with metals at high temperatures and is added to lead, for instance, in the manufacture of lead shot. Neither elementary arsenic nor arsenic sulfide is considered very toxic. However, several toxic compounds of arsenic are widely encountered in industry.

## SOLID COMPOUNDS OF ARSENIC

### 1. *Uses and Industrial Exposures*

The compounds of arsenic are used in medicine, in glass manufacture, in pigment production, in rodent poisons, in insecticides and fungicides, in weed killers, in textile printing, in tanning and taxidermy preservatives, in antifouling paints, and to control sludge formation in lubricating oils. The most serious exposures to fumes and dusts occur in connection with the smelting of copper, lead, zinc, iron, and other ores, and in the manufacture of insecticides. Nonindustrial absorption of arsenic from eating sprayed fruits and vegetables, and from the use of medicinal arsenicals, should always be considered when tracing exposures. In insecticide manufacture exposures to various arsenic compounds, such as calcium arsenate, arsenic trioxide, sodium arsenite, Paris green, Scheele's green, and others, occur. The greatest exposures in this industry are usually in mixing, screening, drying, bagging, and drum-filling operations, concentrations ranging from 0.5 to 45 mg. arsenic per cubic meter of air being not uncommon. Respirators are frequently, but not universally, worn in such an environment.

In the smelting of arsenical ores many opportunities for exposures within, and even above, this range exist. Among the highest exposures are those encountered in the cleaning of dust collectors and flues, and in loading and transporting the flue dust. The dust is very fine and disperses readily wherever it is agitated, as in grinding, screening, shoveling, sweeping, transferring from or to wheelbarrows, cars, hoppers, bins, settling rooms, and collectors. The repairing and

cleaning of furnaces and other equipment at intervals give rise to high exposures. The effluent from smelter stacks poses an atmospheric pollution problem, and vegetation for a considerable distance may have a high arsenic content, up to 350 times normal. Samples of soil in the province of Quebec, Canada, two miles distant from smelter stacks have been found to contain as much as 0.06 per cent arsenic. Respirators are sometimes used in the industry, but contamination frequently involves areas where no protection is provided. The experience under these conditions has not been as adverse as might be expected in view of the American Standards Association war standard allowable concentration of 1.5 mg. arsenic per 10 cubic meters of air. Unless these industries are more or less completely rebuilt on new engineering principles, it is difficult to see how it will be practical for them to maintain all exposures on a level below 1.5 mg. per 10 cubic meters, or even approaching this order of magnitude. Further study of concentrations and experience may justify a somewhat higher figure. Many orchardists exposed for 2 or 3 months to concentrations of spray mists up to 4.8 mg. arsenic per 10 cubic meters of air have not evidenced significant intoxication.

In occupations where exposures to arsenic compounds exist, workmen prefer respirators in which no rubber touches the face, because of the serious arsenic irritation resulting on the moist surface under and alongside the area covered by rubber. Cotton batting  $\frac{1}{2}$  to 1 in. thick is popular, and somewhat effective, as a filter when properly adjusted to the face.

## 2. Physical and Chemical Properties

*Arsenic trioxide*, also called arsenious anhydride, white arsenic, and arsenious acid,  $As_2O_3$ , is a white solid that may be either crystalline, vitreous, or amorphous. Its specific gravity ranges from 3.74 to 4.15. It sublimes at  $193^\circ C$ . Crystalline forms are soluble in water to the extent of 2.04 g. per 100 ml. at  $25^\circ C$ . and 11.5 g. per 100 ml. at  $100^\circ$ . The vitreous or amorphous forms are slightly more soluble at  $25^\circ C$ . and slightly less so at  $100^\circ$ .

*Calcium arsenate*,  $Ca_3(AsO_4)_2$ , is a white powder containing 37.64 per cent arsenic.

*Calcium arsenite*, an indefinite mixture of arsenite and arsenate, is a white granular powder with variable percentages of arsenic.

*Copper aceto-arsenite* (Imperial, Schweinfurth, Vienna, Parrot, or Paris green) is an emerald-green powder with the approximate composition of  $3Cu(AsO_2)_2 \cdot Cu(COOCH_3)_2$ , and has an arsenic content of 44.3 per cent.

*Cupric arsenite* (Scheele's green, Swedish green) is approximately  $CuHAsO_3$ , a yellowish green powder containing about 40 per cent arsenic.

*Sodium arsenite*, approximate formula  $NaAsO_2$ , is a hygroscopic gray powder containing 57.6 per cent arsenic.

*Lead arsenate*, approximately  $PbHAsO_4$  with 59.7 per cent lead and 21.6 per cent arsenic, is a dense, white powder with a specific gravity of 5.79.

*Lead arsenite*, approximately  $\text{Pb}(\text{AsO}_2)_2$ , with 49.2 per cent lead and 35.6 per cent arsenic, is likewise a dense, white powder. Its specific gravity is 5.85.

It is probable that the arsenic exposure from lead arsenate and lead arsenite need not be seriously considered because of the relatively greater hazard of the lead content of these insecticides.

### 3. Determination in the Atmosphere

Arsenic dusts and mists may be collected by impingement into dilute alkali or other media, or by the electrostatic precipitator. Fumes are more reliably collected by the precipitator. Estimation can then be made by the Gutzeit<sup>1</sup> or other methods.<sup>2,3</sup>

### 4. Physiological Response

*Acute effects.* Acute or subacute industrial poisoning from ingestion, skin contact, or inhalation of arsenical dusts is not common. Symptoms include gastrointestinal disturbances, irritation of the nose and conjunctiva, skin eruptions, and inflammation. Laryngitis, bronchitis, and huskiness of the voice can result from relatively brief, massive doses of arsenicals by inhalation. Systemically, arsenic relaxes the capillaries<sup>4</sup> and increases their permeability, simulating inflammation, and this dilation introduces changes in the circulation that cause disturbances in organic function.

*Chronic effects.* After chronic exposure to arsenic compounds perforation of the nasal septum is a common occurrence, as well as irritation, and occasionally ulceration, of the skin. Pigmentation also may be produced. Peripheral neuritis<sup>5</sup> is said to occur in less than 5 per cent of the cases, tremors in 10 per cent, gastric symptoms in one third, and rashes in the majority of cases of chronic poisoning. Loss of nails and hair may result. Carcinoma of the lung is said to have been produced experimentally in animals with arsenic compounds, but no evidence has been presented to indicate such occurrence among human beings from industrial exposures.

Small amounts of arsenic are thought to have a beneficial effect in treating leukemias, anemias, and skin diseases. Arsenic in organic forms is used in the treatment of syphilis: for example, Mapharsen or the arsphenamines. Arsenic was formerly used extensively, even indiscriminately,<sup>4</sup> as an alterative and tonic in all kinds of blood disturbances. Small amounts of arsenic have been found to have a beneficial effect upon animals, especially animals on a diet containing selenium.<sup>6</sup>

<sup>1</sup> M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

<sup>2</sup> D. M. Hubbard, *Ind. Eng. Chem., Anal. Ed.*, 13, 915 (1941).

<sup>3</sup> K. Bambach, *Ind. Eng. Chem., Anal. Ed.*, 14, 265 (1942).

<sup>4</sup> T. Sollmann, *A Manual of Pharmacology*, 6th ed., Saunders, Philadelphia, 1944.

<sup>5</sup> T. Legge, *Industrial Maladies*. Oxford Univ. Press, London, 1934.

<sup>6</sup> A. L. Moxon, C. R. Paynter, and A. W. Halverson, *J. Pharmacol.*, 84, 115 (1945).

### 5. Absorption, Retention, and Excretion

Arsenic may be absorbed industrially by inhalation, ingestion, and through the skin. It is largely eliminated in the urine, some in the feces, hair, epithelium, nails, and possibly small amounts in the exhaled breath. Excretion is slow, requiring up to ten days after an acute absorption; sometimes more than a year after prolonged absorption. After subcutaneous injection of potassium arsenite, human beings, and all animals except rats, showed very small amounts of arsenic in the blood<sup>7</sup> and no evidence of accumulation in rapidly growing tissues. Arsenic is retained and stored in all the tissues, the bones, and especially the hair. It is said that the arsenic content of long hair, in relation to that of close-cropped hair, can be used to give an indication of the time and extent of absorption. Arsenic content of the hair several years after death has been presented as evidence of nonindustrial arsenic poisoning.

### 6. Tests Indicating Exposure

The arsenic content of the urine of exposed persons is significant in evaluating their exposure. The normal excretion of arsenic has been found to be about 0.015 mg. As per liter,<sup>8</sup> with occasional values up to 0.06 mg. per liter. The average urinary arsenic excretion among orchardists during periods of relatively high exposures averaged 0.22 to 0.24 mg. per liter, with many values above 0.5 and one value as high as 2.0 mg., although no signs of adverse effects from the arsenic were exhibited. Values as high as 3 mg. arsenic per liter of urine have been reported elsewhere without detectable signs of intoxication. Just where on this scale a mark can be chosen to indicate excessive exposure will require further study. Kunkele<sup>9</sup> considers amounts above 0.1 mg. arsenic per liter of urine, and 3 micrograms arsenic per gram of head hair, to indicate poisonings, but reports results as high as 1.5 mg. per liter of urine and 120 micrograms per gram of hair. Young and Rice<sup>10</sup> were unable to distinguish between internally and externally deposited arsenic in the hair and question the value of tests for arsenic in the hair.

In isolated instances, men exposed to up to 0.6 mg. per cubic meter arsenicals (computed as arsenic trioxide) in the atmosphere, during the manufacture of arsphenamine and related compounds over an extended period, excreted from 1 to 5 mg. arsenic (computed as the trioxide) per liter of urine, and exhibited minor symptoms of arsenic poisoning.<sup>11</sup>

<sup>7</sup> F. T. Hunter, A. F. Kip, and J. W. Irvine, Jr., *J. Pharmacol.*, 76, 207 (1942).

<sup>8</sup> P. A. Neal, W. C. Dreessen, T. I. Edwards, W. H. Reinhart, S. H. Webster, H. T. Castberg, and L. T. Fairhall, *U.S. Pub. Health Service Bull.* No. 267 (1941).

<sup>9</sup> E. F. Kunkele, *Chem. Ztg.*, 64, 29 (1940).

<sup>10</sup> E. G. Young and F. A. H. Rice, *J. Lab. Clin. Med.*, 29, 439 (1944).

<sup>11</sup> R. M. Watrous and M. B. McCaughley, *Ind. Med.*, 14, 639 (1945).



### 7. Maximum Permissible Concentrations

Maximum permissible concentrations that vary from 0.15 to 5.0 mg. per cubic meter of air have been proposed. The higher limit may permit excessive amounts, but the lower limit appears unnecessarily severe and too low to be of practical value from an engineering standpoint. A value on the order of 1 to 2 mg. per cubic meter appears more logical, but the problem requires further study.

## ARSINE

Arsine,  $\text{AsH}_3$ , is a gas that results whenever nascent hydrogen is formed in an acid, alkaline, or neutral solution containing arsenic.

### 1. Industrial Exposures

Exposure to arsine gas may result from the action of acids on metals containing arsenic, from the use of impure sulfuric acid made from pyrites containing arsenic, or from the use of hydrochloric acid made from impure sulfuric acid that contained arsenic. Arsine poisoning has resulted from slushing out steel tanks that had previously contained a commercial grade of sulfuric acid, the diluted acid acting upon the metal tank to generate hydrogen, which combined with arsenic impurities in the acid. Arsine may arise from the pickling of any metal containing arsenic; it has been formed from the action of water on metallic arsenides or hot dross containing arsenic and aluminum. Arsine may occur as an impurity in acetylene and present an exposure either in its manufacture or use. It may occur in soldering, etching, lead plating, electrolysis of arsenious solutions, by the action of moisture on ferrosilicon or from the use of impure or inhibited acids<sup>12</sup> for scale removal. It has not been a hazard associated with the manufacture, maintenance, or use of lead storage batteries in the United States, where arsenic-free lead and sulfuric acid are used.

### 2. Physical and Chemical Properties

Arsine,  $\text{AsH}_3$ , is a colorless gas with a slightly obnoxious odor somewhat resembling garlic. It is 2.7 times as heavy as air. It boils at  $-55^\circ \text{C}$ . and decomposes at  $230^\circ$ . It is soluble in water to the extent of about 20 volumes in 100 volumes at  $20^\circ \text{C}$ . It is inflammable.

1 mg./l.  $\approx$  313 p.p.m. and 1 p.p.m.  $\approx$  3.19 mg./cu.m.  $\text{AsH}_2$  (or  $\approx$  3.07 mg.  $\text{As}_4$  or  $\approx$  4.05 mg.  $\text{As}_2\text{O}_3$ ) at  $25^\circ \text{C}$ ., 760 mm.

### 3. Determination in the Atmosphere

Arsine can be collected by scrubbing the atmosphere through normal nitric acid and estimated by the Gutzeit method<sup>1</sup> or other means. If 1 p.p.m. arsine is considered the maximum permissible concentration, 2 to 4 liters of air makes a conveniently sized sample, but it is desirable to collect an excess and use an aliquot. Qualitative and semiquantitative tests<sup>1</sup> with either silver nitrate or

<sup>12</sup> G. F. Hawlick and E. B. Ley, *Occupational Med.*, 1, 388 (1946).

mercuric chloride<sup>13</sup> test papers are of some use. The reaction is obscured by hydrogen sulfide, phosphine, and stibine. Hydrogen sulfide can be readily filtered out with lead acetate paper, while stibine and phosphine have a comparable order of toxicity to arsine so that for control purposes this simple test may give useful information, especially if the colors are compared with freshly prepared standards obtained with gas-air mixtures of known compositions.

#### 4. Physiological Response

*Acute effects.* It is thought that arsine first combines with the hemoglobin in the blood corpuscles<sup>14</sup> in some manner, and soon thereafter hemolysis of the cells occurs, resulting in the destruction of the cells and solution of the hemoglobin in the serum. More arsenic has been demonstrated in the corpuscles than in the serum. During the ensuing anemia the blood count falls rapidly and hemoglobin is excreted in the urine. Within a few days destruction of the red cells may progress to the point where death occurs from anoxemia, and may be considered a form of chemical asphyxia. It is said that death frequently occurs from pulmonary edema<sup>15</sup> resulting either from primary irritation or secondary to failure of the circulation. Symptoms are similar to those observed in other forms of anoxemia: headache, weakness, vertigo, and nausea. Pain in the kidneys and liver develops,<sup>4</sup> and the kidneys may be blocked. Jaundice, both from disintegration of red blood cells and from disorder of the liver, appears and blends its yellow with the cyanotic pallor to create a peculiar bronze tint of the skin. The symptoms of arsenic poisoning (as opposed to those of arsine) may be present in addition to the ones described. Death may occur 2 to 9 days following exposure or, if due to nephritis from arsenic, may be delayed. Recovery, even from severe poisoning, is possible in the majority of instances where the cause is recognized early<sup>16</sup> and prompt measures taken.

TABLE 1  
*Physiological Response to Various Concentrations of Arsine<sup>15</sup>*

Response	Concentration, p.p.m.
Maximum concentration allowable for prolonged exposure.....	1
Slight symptoms after exposure of several hours.....	3-10
Maximum concentration that can be inhaled 1 hr. without serious consequences. . . .	6-30
Dangerous after exposure of 30 to 60 min.....	16-60
Fatal after exposure of 30 min.....	250

*Chronic effects.* In prolonged exposure to low concentrations of arsine the symptoms bear more relation to effects produced by dusts and fumes of arsenic

<sup>13</sup> *Dept. Sci. Ind. Research (London), Leaflet No. 9 (1939).*

<sup>14</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

<sup>15</sup> Y. Henderson and H. W. Haggard, *Noxious Gases*. 2nd ed., Reinhold, New York, 1943.

<sup>16</sup> C. A. Nau, W. Anderson, and R. E. Cone, *Ind. Med.*, 13, 308 (1944).

compounds, and albumen may appear along with hemoglobin in the urine. Prolonged exposure of animals to low concentrations of arsine<sup>17</sup> produced a compensated destruction of red blood cells, which gradually deteriorated to a stationary level of anemia. There was little injury to other organs. Chronic arsine poisoning<sup>18</sup> occurred in a group of nine men exposed several months to undetermined amounts of arsine in the cyanide extraction of gold. These men complained of headache, weakness, nausea, and vomiting, the attacks increasing in frequency and severity. Puffiness of face and eyelids, tingling sensation in the toes, lumbar and epigastric pains, garlic-like odor of the breath, and change of complexion were also common symptoms. The red blood cells were markedly reduced, eight of nine cases having lows of 0.4 to 2.4 million per cubic millimeter. The arsenic content of the urine ranged from 0.3 to 3.3 mg. per liter (0.37 to 4.3 mg. As<sub>2</sub>O<sub>3</sub>). The maximum arsenic excretions in the urine of seven of the nine men ranged from 1.0 to 3.3 mg. As per liter, with an average of 2 mg. per liter. Three months later one man was excreting slightly above 1 mg. per liter, one 0.4 mg. per liter, and the others were approaching normal levels. All of the men recovered.

#### 5. Absorption and Excretion

Arsine is absorbed through the lungs, and the arsenic is largely excreted through the kidneys. The arsenic content of the urine is indicative of the extent of exposure when other possible sources of As have been considered.

#### 6. Maximum Permissible Concentration and Warning Properties

The maximum permissible concentration of arsine in the atmosphere has frequently been placed at 1 p.p.m. This is equivalent to 3.2 mg. arsenic per cubic meter of air. A figure of 1/2 p.p.m. (1.6 mg./per cubic meter) would appear to be a more logical limit. The odor of this concentration of arsine is easily noticeable, but does not constitute a satisfactory warning. The inflammable properties of the gas present no hazard of interest to industrial hygienists because concentrations in the inflammable range do not occur in industry.

### ARSENIC TRICHLORIDE

Arsenic trichloride, AsCl<sub>3</sub>, is an oily liquid boiling at 130.2° C. It is said to have been tried experimentally in mosquito-control work, and has been considered for use as an irritant war gas. It fumes when exposed to the air, and decomposes in an excess of water. Industrial exposures, except in its manufacture, are improbable. Its property of decomposition in moist, warm air makes it more effective in the lungs than on the upper respiratory tract. In addition to its strong, irritant action are, of course, the effects of arsenic.

<sup>17</sup> M. Kiese, *Arch. exptl. Path. Pharmacol.*, 186, 337 (1937).

<sup>18</sup> F. M. R. Bulmer, H. E. Rothwell, S. S. Pollack, and D. W. Stewart, *J. Ind. Hyg. Toxicol.*, 22, 111 (1940).

## Organic Arsenic Compounds

There are a number of trivalent and pentavalent arsenic compounds produced for medicinal use in the control of protozoan parasites: trypanosomes, amebae, and plasmodia, as well as spirochetes. In the manufacture of these compounds there exist exposures not only to arsenical raw materials and by-products, but also to the organic, finished products.

These organic arsenicals are nonionized and do not immediately produce arsenic effects when inhaled or ingested. They are only slowly broken down in the body and the ingested portion may be largely excreted unchanged. Inhaled dusts may be more or less readily absorbed in relation to their solubilities, and only slowly produce the toxic effects of inorganic arsenic. The threshold of harm from such exposures is even more obscure than that from inorganic arsenic compounds, but permissible concentrations probably are greater for the organic compounds. It is possible that the amount of arsenic in the urine could be directly compared with that resulting from exposures to other arsenic compounds, as a measure of excessive exposure.

Many organic arsenicals of varied, toxic properties have been investigated for their possible use in chemical warfare, but are not of industrial importance except in their manufacture, so need not be discussed here.

## PHOSPHORUS

Yellow phosphorus is one of the elements early to be recognized as a cause of occupational disease. Its use in the match industry in the United States was eliminated in 1912 by a prohibitive tax on matches made from yellow phosphorus; and for a decade it was more or less a laboratory curiosity. It was revived in fireworks manufacture, where it caused injuries and several deaths; consequently an agreement was reached in 1926 to discontinue the use of yellow phosphorus in fireworks. Other forms of phosphorus, such as the sesquisulfide, have been substituted safely in match manufacture. Phosphorus is used in the manufacture of phosphor-bronze.

### 1. *Industrial Exposures*

Recently phosphorus was encountered as a by-product and intermediate in the smelting of phosphate rock for the manufacture of phosphate fertilizer (see *Fertilizer Manufacture*, Chapter 35. In this process phosphate rock, sand or clay, and coke are heated in an electric furnace and phosphorus vapor is condensed to solid elemental phosphorus or burned to phosphorus pentoxide, depending upon which product is in demand. More recently, military needs for tracers, incendiaries, and smokes diverted this source to production of yellow phosphorus and the exposures, although controlled, were considerably multiplied. Phosphorus should be kept under water and vapors escaping from the water must be controlled by

ventilation. Pre-employment and periodic dental x-rays are vital factors in the control program.<sup>19</sup> Experience, which is admittedly somewhat brief, has been sufficient to indicate that present control practices are successful in combating the rather terrifying phosphorus necrosis of the jaw. This is an outstanding example of what can be accomplished by modern control methods.

## 2. Physical and Chemical Properties

Elemental phosphorus, P<sub>4</sub>, is prepared in four forms: yellow (or white), red, violet, and black. Only the first two are industrially important, and only the first one is outstandingly toxic. Red phosphorus at times may contain amounts up to 0.6 per cent of yellow phosphorus. Yellow (white) phosphorus is a waxy, translucent, yellowish solid, which, upon exposure to the air, turns white, by oxidation to phosphoric oxide, and ignites spontaneously in air at 34° C. The molecular weight is 124.08. Its density is 1.82 at 20°/4° C. Its melting point is 44.1° C. and its boiling point is 280°. Its solubility in water is only 0.3 mg. per 100 ml. but it is exceedingly soluble in carbon disulfide, quite soluble in ether, chloroform, and benzene, and also in alkalis. It is kept under water, in order to prevent its spontaneous combustion. Phosphorus combines with oxygen to form either P<sub>2</sub>O<sub>5</sub>, the anhydride of phosphoric acid, or P<sub>2</sub>O<sub>3</sub>, the anhydride of phosphorus acid. The vapor of elemental phosphorus can occur and persist in the atmosphere. It has a characteristic and distinct odor. Phosphorus and its vapor in contact with the air have the property of glowing in the dark, phosphorescence; and the vapor forms a milky, colloidal suspension in water.

## 3. Determination in the Atmosphere

Phosphorus and phosphine in the air may be determined by aspirating the atmosphere through a series of three scrubbers, each containing 10 ml. of 0.01 N potassium permanganate solution plus 1 ml. of 5 per cent sulfuric acid solution.<sup>20</sup> The solutions are combined, and decolorized by heating with 10 ml. of 0.01 N oxalic acid solution. Phosphoric acid in the resultant solution is determined colorimetrically by the Bell-Doisy-Briggs method. Another method utilizes bromine water as the scrubbing medium, and the excess bromine is expelled by boiling before the phosphoric acid is determined colorimetrically, as before.

1 mg./l.  $\approx$  197 p.p.m. and 1 p.p.m.  $\approx$  5.07 mg./cu.m. at 25° C., 760 mm.

## 4. Physiological Response

*Acute effects.* The acute effects of phosphorus absorption have not been demonstrated industrially. This is probably due to the relatively low concentrations ordinarily encountered, the slow absorption, and delayed effects.

*Chronic effects.* Gastrointestinal upsets, jaundice, and sometimes a phosphorus odor of the breath are said to be early signs of phosphorus poisoning. There is loss of appetite, and natural metabolism is slowed. The formation of

<sup>19</sup> H. Heimann, *J. Ind. Hyg. Toxicol.*, **28**, 142 (1946).

<sup>20</sup> W. Muller, *Arch. Hyg. Bakt.*, **129**, 286 (1943).

glycogen is inhibited<sup>21</sup> and the normal enzymic liver function is thought to be paralyzed, while autolytic processes continue and lead to toxic decomposition products. Cachexia results and jaundice is common and intense. Prolonged intake of phosphorus causes densification and changes of bone but does not cause calcification of cartilage. The bones become fragile and their resistance to infection is diminished. Necrosis of the jaw, which is thought to be fostered by defective teeth, has occurred in a small percentage of the persons exposed for a prolonged period; therefore, persons with defective teeth should not be subjected to exposure. The first symptom of necrosis may be a toothache occurring after prolonged exposure or even after termination of exposure. Suppurative ulceration of the gums around carious teeth, or abscesses that fail to heal after the extraction of teeth, may develop and progress into suppurating fistulas and necrosis of the jaw bone.

### 5. Absorption and Excretion

Phosphorus can be absorbed through the skin, by ingestion, and through the respiratory tract, but the latter is the chief industrial mode. Phosphorus burns on the skin may be deep and painful and unless the resultant phosphoric acid is removed, or neutralized, the corrosive action continues. A 2 to 5 per cent copper sulfate solution has been used to wash the skin where particles of phosphorus may be in contact with it; the theory is that any elemental phosphorus present would be coated with metallic copper and absorption or reaction prevented. Phosphorus is excreted chiefly in the urine in the combined forms, such as phosphates. The normal daily excretion is 1.5 to 1.75 g. of phosphorus. In phosphorus poisoning, insignificant amounts of phosphorus may be excreted in the exhaled breath as well as in the sweat. Elemental phosphorus may be found in the breath, blood, and feces, but not in the urine. The odor and phosphorescent property of phosphorus offer two excellent means of identifying its presence in the air or biologic materials. An increase in nitrogen excretion and the amount of amino acids<sup>22</sup> in the urine are aids in diagnosing phosphorus absorption. Recent extensive biological experimentation<sup>23</sup> has shown a considerable normal variation in urinary amino acid nitrogen but the amino acid/creatinine ratio is a very significant criterion of adverse physiological effects.

### 6. Maximum Permissible Concentration

Animal experiments have indicated that bone changes may arise in animals from daily doses<sup>24</sup> of phosphorus greater than 0.05 mg. per kilogram and that

<sup>21</sup> F. Fischler, *Munch. med. Wochschr.*, 621 (1941).

<sup>22</sup> T. Sollman, *A Manual of Pharmacology*. 6th ed., Saunders, Philadelphia, 1944.

<sup>23</sup> Harold C. Hodge and A. Rothstein, University of Rochester, Rochester, N. Y.

<sup>24</sup> R. B. L. Fleming, J. W. Miller, and V. R. Swayne, Jr., *J. Ind. Hyg. Toxicol.*, 24, 154 (1942).

deaths may result from daily doses on the order of 0.8 mg. per kilogram when injected subcutaneously. There are no published data on maximum permissible limits for man, but from experience with animals it appears advisable to limit exposures to about 1 mg. per cubic meter of air where the length of exposure is 6 or 8 hours per day for prolonged periods. The odor of such a concentration of phosphorus vapor, though it can be smelled upon entering, does not give adequate warning.

## PHOSPHINE

Phosphine,  $\text{PH}_3$ , molecular weight 34.04, is a gas that results whenever nascent hydrogen is formed in a solution containing phosphorus. It may occur during the manufacture of phosphorus, from the action of water on metallic phosphides, from the action of moisture on ferrosilicon containing phosphorus, and in fact may frequently accompany arsine because arsenic and phosphorus often occur together as impurities of metals. Phosphine also occurs as an impurity of acetylene.

### 1. Physical and Chemical Properties

Phosphine is a colorless gas with a foul odor slightly resembling decayed fish. It is 1.17 times as heavy as air. Its melting point is  $-133.5^\circ\text{C}$ . and its boiling point is  $-87.4^\circ$ . Twenty-six volumes of the gas are soluble in 100 volumes of water at  $17^\circ\text{C}$ . Phosphine ignites spontaneously in the air.

### 2. Determination in the Atmosphere

Phosphine can be determined in the same manner as arsine, and the two gases occurring together may be absorbed by scrubbing through bromine water, and the combined arsenic and phosphorus determined in an aliquot after expelling the bromine. The Denigès<sup>25</sup> (molybdenum blue) method is satisfactory. Phosphine also can be estimated by exposing mercuric chloride test paper to a measured volume of phosphine-air mixture and comparing the resultant color with similarly prepared standards. Also see method given under determination of phosphorus.

1 mg./l.  $\approx$  719 p.p.m. and 1 p.p.m.  $\approx$  1.39 mg./cu.m. at  $25^\circ\text{C}$ ., 760 mm.

### 3. Physiological Response

*Acute effects.* Phosphine differs in its action from that of arsine in that it does not hemolyze the red blood cells. Early symptoms of poisoning are a feeling of coldness and a pain in the region of the diaphragm. Dyspnea, weakness, vertigo, bronchitis, edema, convulsions, and death may result from exposure to phosphine.

<sup>25</sup>M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

TABLE 2  
*Response of Men to Inhalation of Phosphine*<sup>14</sup>

Response	Concentration, p.p.m.
Rapidly fatal.....	2000
Death occurs following 1/2 to 1-hr. exposure.....	400-600
Dangerous to life after 1 hr.....	290-430
Maximum amount for 1/2 to 1 hr. without serious effects.....	100-200
Serious effects after several hours.....	7
Limit of perceptibility.....	1.5-3

*Chronic effects.* The chronic effects produced by phosphine are essentially the same as those produced by phosphorus

#### 4. Maximum Permissible Concentration

The permissible limit has not been well established, but probably should not exceed 1 p.p.m. for exposures of 8 hours per day for prolonged periods. One part per million of phosphine is equivalent to 1.27 mg. phosphorus per cubic meter of air. The warning effects of this concentration are of no practical value: even though the gas has an offensive odor in higher concentrations, the odor of 1 p.p.m. is very faint.

### Other Compounds of Phosphorus

Other compounds of phosphorus of some importance in the chemical industry and of toxicological interest follow.

*Phosphorus trichloride*,  $\text{PCl}_3$ , is a colorless liquid with molecular weight 137.39, and a specific gravity of 1.574 at 21°/4° C., a melting point of -91°, and a boiling point of 75.5°. It decomposes in water or moist air to phosphoric acid and hydrochloric acid. Determination may be made by scrubbing through a train containing dilute alkali, 5-10 per cent, and titrating the chlorides. Hydrogen chloride, of course, interferes and if hydrolysis has occurred in the air the results will be high by the amount of the liberated hydrochloric acid. The vapors of phosphorus trichloride have an intense, irritant action upon the respiratory tract, and are believed to be irritant in concentrations of 1 p.p.m. or higher. Therefore, this is suggested as the tentative maximum permissible concentration.

1 mg./l.  $\approx$  179 p.p.m. and 1 p.p.m.  $\approx$  5.62 mg./cu.m. at 25° C., 760 mm.

*Phosphorus pentachloride*,  $\text{PCl}_5$ , is a pale, yellowish, fuming, crystalline mass, with molecular weight 208.31. It sublimes at 100° C.; under increased pressure it melts at 148° and boils at 160°. It is irritant to all mucous surfaces and has a pungent, unpleasant odor. It decomposes in water or moist air. It may be estimated in the air by the same method as the trichloride. Its toxicity and action are similar to those of the trichloride.



1 mg./l.  $\approx$  117.3 p.p.m. and 1 p.p.m.  $\approx$  8.52 mg /cu.m. at 25° C., 760 mm.

*Phosphorus sesquisulfide*,  $P_4S_3$ , phosphorus trisulfide, is a yellow crystalline material with molecular weight 220.26, and a specific gravity of 2.03, melting point 172.5° C., and boiling point 407.5°. It is insoluble in cold water and decomposes in hot water. Phosphorus trisulfide is used in making matches and friction strips for safety-match boxes. Its toxicity is minor compared with that of elemental phosphorus. Unless contaminated with yellow phosphorus this compound is not sufficiently volatile to present a vapor hazard, but its dust is irritant to the eyes, the respiratory tract, and the skin. It may cause a generalized dermatitis and has been credited with causing one case of necrosis. Obviously its dust should not be uncontrolled, but should be kept within reasonable limits. There are insufficient data to indicate the maximum permissible limit, but it probably should fall between 10 and 30 mg. per cubic meter. The inflammable nature of the dust must be recognized, since its ignition temperature in air is 95° to 100° C. Phosphorus trisulfide also forms explosive mixtures with oxidizing agents. The dust may be caught in an impinger or thimble and weighed, or ashed and determined as phosphorus pentoxide,  $P_2O_5$ .

## SELENIUM

Selenium, though relatively scarce in quantity, is widely distributed in nature. It is recovered from flue dust collected during the burning of pyrites for the manufacture of sulfuric acid. Selenium, together with tellurium, occurs as an impurity in most sulfide ores of copper, gold, nickel, and silver, and during the course of refining these ores the selenium and tellurium must be removed. As a result these by-products, though relatively rare materials, are sufficiently moderately priced to be used commercially to a considerable extent. The 1940 production of selenium approached 1,000,000 lb.

### 1. Uses and Industrial Exposures

Selenium is used in the manufacture of pigments, in insecticides, in rubber compounding, in the manufacture of rectifiers and photoelectric cells, to remove the green (iron) tint of glass, to produce pink, ruby and black glass glaze, to improve the machinability of copper alloys and stainless steel, to improve the grain, structure, and ductility of cast steel, to increase the depth of chill in cast iron, as a flameproofing agent for textiles and wire-cable coverings, and in chemical manufacture. Exposures to selenium may result during the smelting and refining of ores containing selenium, in the refining of copper, silver, and gold to remove the selenium, or from the use of selenium compounds.

### 2. Physical and Chemical Properties of Selenium and Some of Its Compounds

*Selenium*,  $Se_8$ , has an atomic weight of 78.96, and is a nonmetallic element of the sulfur group. It exists in five forms: an amorphous red powder, a colloidal dark red powder, vitreous dark brown mass, monoclinic red crystals, and trigonal

gray metallic crystalline form, with densities of 4.26 to 4.79 at 20°/4° C. The several forms melt at from 170° to 217° C. and it boils at 688°. It is insoluble in water but soluble in strong acids, and also in carbon disulfide. Selenium vapor at the boiling point is dark red.

*Selenium dioxide*,  $\text{SeO}_2$ , is a white crystalline powder with a molecular weight of 110.96 and specific gravity of 3.95 at 15°/15° C. It melts at 340° C. under increased pressure, but under ordinary atmospheric pressure it does not melt, subliming instead at 315°. It is readily soluble in hot or cold water to form *selenious acid*,  $\text{H}_2\text{SeO}_3$ .

*Selenium trioxide*,  $\text{SeO}_3$ , is a very hygroscopic, yellowish white powder with a molecular weight of 126.96 and a specific gravity of 3.6. It combines with water to form *selenic acid*,  $\text{H}_2\text{SeO}_4$ , a hygroscopic, corrosive acid similar in some respects to sulfuric acid.

*Sodium selenite*,  $\text{Na}_2\text{SeO}_3 \cdot 5\text{H}_2\text{O}$ , is a white powder, with molecular weight 263.04. It dissolves freely in water to form a slightly alkaline solution. The salt contains 30 per cent selenium.

*Sodium selenate*,  $\text{Na}_2\text{SeO}_4$ , occurs as colorless crystals with or without 10 moles of water. It has a molecular weight equal to 188.95. It is very soluble in water.

### 3. Determination in the Atmosphere

Dusts and fumes containing selenium or its compounds can be sampled with the electrostatic precipitator, and gases or vapors may be scrubbed through 40 to 48 per cent hydrobromic acid containing 5 to 10 per cent free bromine. The effluent side of such a scrubber should be provided with a soda-lime tube to absorb the corrosive vapors of hydrobromic acid and bromine. Soda lime has also been used to collect hydrogen selenide, and it is probable that silica gel could be used for any selenium compound in the gaseous or vapor state. After the sample has been collected the selenium compounds may be separated by distillation<sup>26-28</sup> with an excess of hydrobromic acid and bromine, and the selenium content estimated by gravimetric, volumetric, or colorimetric methods. Selenium dioxide can be collected in 10 ml. of water with the midget impinger and determined by a modification of Chernyi's method,<sup>29</sup> 5 ml. of c.p. hydrochloric acid being added and the sample being made up to 20 ml. Take 5 ml. in a Nessler tube, add 1 ml. of 5 per cent gum arabic solution and 1 ml. of a 10 per cent stannous chloride solution. Make up to 20 ml. with a mixture of 1 part hydrochloric acid and 3 parts water, shake, and compare the resultant color with similarly prepared standards that have stood a corresponding length of time. Amounts in the range of 0.01 to 0.1 mg. are satisfactory for comparison and it is possible to compare amounts up to 0.5 mg. The remainder of the sample can be used if desired to

<sup>26</sup> W. O. Robinson, H. C. Dudley, K. T. Williams, and H. G. Byers, *Ind. Eng. Chem., Anal. Ed.*, 6, 274 (1934).

<sup>27</sup> H. C. Dudley, *Am. J. Hyg.*, 24, 227 (1936).

<sup>28</sup> G. Wernimont and F. J. Hopkinson, *Ind. Eng. Chem., Anal. Ed.*, 12, 308 (1940).

<sup>29</sup> M. E. Chernyi, *Chem. Abstracts*, 37, 5925 (1943).

repeat the test with a greater or less amount as indicated by the intensity of the color. For sampling concentrations below 3 mg. per 10 cubic meters it is necessary to sample more than ten minutes and to use the entire sample. Dilution may be omitted and a smaller volume used for comparison as long as the same ratio of hydrochloric acid is maintained. The standard impinger is more satisfactory than the midget for concentrations below 1 mg. per 10 cubic meters.

#### 4. *Physiological Response*

*Acute effects.* Selenium somewhat resembles arsenic and tellurium in its physiological action. The relative toxicities of compounds of selenium, tellurium, and arsenic have been determined<sup>30</sup> by intraperitoneal injection and the minimum fatal doses in milligrams per kilogram (75 per cent of animals dying within 48 hours) found to be as follows:  $\text{Na}_2\text{SeO}_3$ , 3.25–3.5;  $\text{Na}_2\text{SeO}_4$ , 5.35–5.75;  $\text{Na}_2\text{TeO}_3$ , 2.25–2.5;  $\text{Na}_2\text{TeO}_4$ , 20.0–30.0;  $\text{Na}_2\text{HAsO}_3$ , 4.25–4.75;  $\text{Na}_2\text{HAsO}_4$ , 14.0–18.0. Selenium can be acquired from inhalation of the dust, vapors, gases, and fumes of the metal or its compounds, by ingestion, and to some extent by absorption through the skin. The first signs of acute selenium poisoning<sup>31</sup> are nervousness and fear followed by vomiting, then quietness and somnolence. Respiration becomes difficult, dyspnea develops, followed by opisthotonos, tetanic spasm, clonic spasm, falling blood pressure, and respiratory failure resulting from action on the central nervous system. Acute effects other than garlicky breath have not been reported from industrial exposure. The odor of the breath may be due to tellurium accompanying the selenium.

*Chronic effects.* According to Dudley,<sup>32</sup> prolonged exposure to the inhalation of selenium compounds during extraction, purification, and processing of selenium-bearing ores has given rise to marked pallor, coated tongues, gastrointestinal disorders, nervousness, and a pronounced garlicky odor of the breath. Moxon and Rhian<sup>31</sup> report a very odoriferous selenium breath resulting from chronic selenium poisoning and enumerate such effects as nervous disorders, small local hemorrhages, severe ascites, liver and splenic damage, emaciation, apathy, and progressive anemia. Hamilton<sup>33</sup> also mentions the garlic odor as well as the irritation of nose, throat and bronchi, pain in the lumbar region, nasal inflammation resembling that accompanying a cold, and night sweats. Waitkins, Bearnse, and Shutt<sup>34</sup> state that the garlicky breath, which is known to result from absorption of tellurium and has been observed after exposure to selenium, is believed not to result from absorption of selenium but to be due to tellurium impurities present in the selenium. Commercial selenium now, however, is being refined in the United States to a tellurium content of less than 0.1 per cent. This amount is said not to have been known to cause garlicky breath, and selenium workers, not also exposed to tellurium, henceforth would not be expected to develop this symptom.

<sup>30</sup> K. W. Franke and A. L. Moxon, *J. Pharmacol.*, **58**, 454 (1936); **61**, 89 (1937).

<sup>31</sup> A. L. Moxon and M. Rhian, *Physiol. Revs.*, **23**, 305 (1943).

<sup>32</sup> H. C. Dudley, *Am. J. Hyg.*, **23**, 181 (1936).

<sup>33</sup> A. Hamilton, *Industrial Toxicology*. Harper, New York, 1934.

<sup>34</sup> G. R. Waitkins, A. E. Bearnse, and R. Shutt, *Ind. Eng. Chem.*, **34**, 899 (1942).

Naturally occurring selenium compounds in the soil of sections of the northwestern plain states have produced grains and vegetation of sufficient selenium content to poison livestock. Foodstuffs such as cereals, vegetables, eggs, meats, and milk in such areas contain from 0.16 mg. to 18.0 mg. selenium per kilogram of foodstuff. Members of the rural population in these areas excrete from 0.10 mg. to 2.00 mg. selenium per liter of urine,<sup>35</sup> a condition indicating absorption of selenium, but they do not evidence definite symptoms of selenium poisoning. High protein diets are protective against selenium poisoning, and sodium arsenite or arsenate prevents<sup>36</sup> normally toxic amounts of selenium from causing hepatic injury and destruction of hemoglobin. This action is independent of the route of administration of the arsenite<sup>37</sup> and therefore is not due to an inhibition of absorption of the selenium.

### 5. Absorption and Excretion

Industrially, absorption results essentially from inhalation, though ingestion occurs to some extent, and skin absorption may occur to a lesser degree. Fifty to 80 per cent of ingested<sup>35</sup> selenium is excreted through the kidneys. Three to ten per cent of subcutaneously injected<sup>38</sup> selenium is exhaled within 24 hours (half in the first 3 hours) in the form of an unidentified volatile compound of selenium. Farm animals with "alkali disease," as selenium poisoning of animals is known in seleniferous areas, excrete 0.6 mg. to 3.0 mg. selenium per liter of urine. Selenium is stored in the liver, kidneys, spleen, pancreas, muscle, heart, lungs, and other tissues. As in arsenic poisoning, the amount stored in the hair may serve as a criterion of length of exposure and degree of storage. Urinary excretion closely parallels intake. The normal excretion<sup>39</sup> of persons outside seleniferous areas and not exposed to selenium, except through the normal ingestion with cereals, has been found to be from 0.01 mg. to 0.15 mg. per liter of urine. Dudley<sup>32</sup> determined the selenium content of the urine of a number of men engaged in extracting and processing large quantities of selenium. These men were exposed to undetermined amounts of selenium dioxide, selenium dust, and presumably some hydrogen selenide. He reports a maximum finding of 0.069 mg. per liter of urine with only minor ill effects none of which could be definitely ascribed to selenium.

### 6. Tests Indicating Exposure

The most conclusive test of exposure is that of selenium in the urine<sup>28,32,40</sup> and when amounts in excess of 0.1 mg. per liter are found, it may be accepted as evidence of unusual absorption. Amounts greater than 0.2 mg. per liter indicate potentially harmful exposures, and amounts of 0.5 mg. or more per liter of urine warrant immediate consideration of corrective or control measures.

<sup>28</sup> M. I. Smith, *J. Am. Med. Assoc.*, 116, 562 (1941).

<sup>32</sup> M. Rhian and A. L. Moxon, *J. Pharmacol.*, 78, 249 (1943).

<sup>37</sup> A. L. Moxon, C. R. Paynter, and A. W. Halverson, *J. Pharmacol.*, 84, 115 (1945).

<sup>38</sup> K. P. McConnell, *J. Biol. Chem.*, 145, 55 (1942).

<sup>39</sup> J. H. Sterner and V. Lidfeldt, *J. Pharmacol.*, 73, 205 (1941).

<sup>40</sup> M. I. Smith and R. D. Lillie, *Natl. Inst. Health Bull. No. 174* (1940).

### 7. Maximum Permissible Concentration

The maximum permissible concentration of selenium in the air has not been determined and inhalation exposures have not been measured extensively. The threshold of daily ingestion is on the order of 7.5 to 15.0 mg. and, since respiratory absorption is usually more effective, it appears logical to keep atmospheric concentrations below 10 mg. per 10 cubic meters, or 1 mg. per cubic meter.

## HYDROGEN SELENIDE

### 1. Occurrence and Physical and Chemical Properties

Hydrogen selenide,  $H_2Se$ , is a colorless, toxic gas with an odor resembling that of decayed horseradish. Its molecular weight is 80.98. It is 2.79 times as heavy as air, has a melting point of  $-64^\circ C.$  and a boiling point of  $-42^\circ C.$  It is very soluble in water, 270 volumes per 100 volumes at  $22.5^\circ C.$  It is formed by the action of acids on metallic selenides and may be suspected of being present wherever selenium compounds contact acids in the presence of metals capable of reducing the acids. It decomposes slowly in moist air and deposits elemental selenium on moist surfaces.

1 mg./l.  $\approx$  302 p.p.m. and 1 p.p.m.  $\approx$  3.31 mg./cu.m. at  $25^\circ C., 760$  mm.

The determination of hydrogen selenide has been discussed under selenium.

### 2. Physiological Response

*Acute effects.* Guinea pigs exposed to 0.3 to 2.1 p.p.m. hydrogen selenide, 0.001 to 0.007 mg. per liter, for 8 hours exhibited no objective symptoms<sup>41</sup> during exposure other than the appearance of a nasal discharge, colored red by its content of amorphous selenium. Delayed deaths, 1 to 30 days following exposure, occurred in 50 per cent of the animals exposed to from 0.3 to 1.2 p.p.m. while only 10 per cent of the control animals died in a similar period. Eighty to ninety per cent of the guinea pigs exposed to 1.8 to 2.1 p.p.m. for 8 hours died, nearly half of the deaths occurring within 1 to 5 days following exposure. Concentrations of 6 p.p.m. and higher caused immediate evidence of eye and nasal irritation of the animals. Exposure to 1.8 p.p.m. for 2 hours did not cause a significant increase in deaths over those occurring among controls, but 1.8 to 2.1 p.p.m. for 4 hours caused approximately 22 per cent of the animals to die within 1 to 20 days. Concentrations of 10 p.p.m. for as little as 2 hours resulted in a high percentage of fatalities. All animals exposed to lethal concentrations lost weight markedly during the first 5 days following exposure. Sublethal exposures also produced some weight loss and recovery appeared to begin 8 to 10 days after exposure. Liver pathology, which was found early, gradually subsided and moderate changes in the spleen were found. Changes in kidney, liver, and heart were not significant. Deaths appeared to be due primarily to irritation of the pulmonary tissue resulting in pneumonitis, which may persist in a subacute form.

<sup>41</sup> H. C. Dudley and J. W. Miller, *J. Ind. Hyg. Toxicol.*, **23**, 470 (1941).

*Chronic effects.* No data have been presented on the chronic effects of hydrogen selenide, but it is logical to assume that when the concentration of the gas is low enough to avoid the irritant effects, only the systemic effects of selenium would be prominent, and it is doubtful whether in the low amounts involved, less than 1 mg. per cubic meter, this would be a significant factor.

### 3. *Maximum Permissible Concentration*

Since guinea pigs are ordinarily more susceptible than man, and than most other animals, to the effects of lung irritants, we may, in the absence of other data, assume that man will not be more seriously affected than the guinea pigs were. Concentrations of 0.3 to 0.6 p.p.m., 1 to 2 mg. hydrogen selenide (or selenium) per cubic meter, appear to be logical bench marks to use until additional data are obtained.

### 4. *Warning Properties and Inflammability*

Concentrations of 0.3 p.p.m. are readily detected by odor but have no noticeable irritant effect. Concentrations of 1.5 p.p.m. and higher are strongly irritant to the eyes and nasal passages. As in the case of hydrogen sulfide, the odor of hydrogen selenide in concentrations below 1 p.p.m. rapidly disappears because of olfactory fatigue. The odor and irritating effects are useful to an experienced investigator in estimating the concentration, but do not offer a dependable warning to the workman who may be exposed to gradually increasing amounts.

Hydrogen selenide is an inflammable gas but this fact is of little industrial significance because inflammable concentrations are not approached, owing to the extreme toxicity and irritant effects of even low concentrations.

## SELENIUM OXYCHLORIDE

Selenium oxychloride,  $\text{SeOCl}_2$ , a powerful chlorinating agent, has found industrial use as a solvent and plasticizer of natural and synthetic resins. It is corrosive to metals. It is a clear, slightly yellow liquid with molecular weight 165.87, a density of 2.42 at 22° C., a melting point of 8.5°, and boiling point of 176.4°. Its vapor pressure is about 0.05 mm. at 20° C. It is hydrolyzed by water into hydrochloric and selenious acids. It is strongly vesicant<sup>42</sup> and will rapidly destroy the skin upon contact unless immediately removed by washing. Less than 0.01 ml. on the skin of rabbits has proved fatal within 24 hours, and selenium could be demonstrated in the blood and liver. Dudley<sup>42</sup> found the minimum lethal dose, when applied to the skin of a rabbit, to be 7 mg. per kilogram. This would be equivalent to approximately 0.2 ml. applied to a man of average size. The application of less than 0.005 ml. to the arm of a man caused a painful burn with swelling, and its healing required a month. The vapors of selenium oxychloride are toxic, but their irritant and corrosive action on the

<sup>42</sup>H. C. Dudley, *U.S. Pub. Health Repts.*, 53, 94 (1938).

respiratory tract is not as great as might be supposed, because the vapor readily decomposes in air; also, the low vapor pressure limits the concentration to the order of 60 or 70 p.p.m. when in contact with dry recirculated air. Under ordinary conditions the concentration would be less than that. Data pertaining to the inhalation hazard have not been presented.

## SULFUR

Elemental sulfur is mined in great quantities in Texas and Louisiana. It is widely used and there are numerous operations, such as shoveling, grinding, screening, and bagging, where sulfur dust in considerable amount is found in the atmosphere. The dust is a very mild irritant and may irritate sensitive skins. No injurious effects have been ascribed to the inhalation of the dust in the United States,<sup>43</sup> but cases of "thiopneumoconiosis" have been described elsewhere.<sup>44</sup> Common sense dictates that excessive concentrations of sulfur dust or any other dust are not compatible with the maintenance of health. Sulfur burns in the air with a bluish flame and the dust is inflammable, the lower inflammable limit being 30 mg. per liter.

## SULFUR DIOXIDE

Sulfur dioxide is formed whenever sulfur is burned in the air, and its odor is frequently described as that of burning sulfur. It is perhaps the most widely encountered and best known irritant gas, not only because of its wide usage but also because of its frequent occurrence as an undesired by-product in the smelting of sulfide ores, in paper manufacture, in the combustion of sulfur-bearing coals and petroleum fuels, and in the action of sulfuric acid on reducing agents. Sulfur dioxide is one of the most prominent gases contributing to atmospheric pollution in large cities and in areas surrounding smelters. Sweetening plants for petroleum products sometimes dispose of sulfide gases by burning them to sulfur dioxide and discharging it from high stacks. The terrain, height of stack, rate of gas discharge, and atmospheric conditions present variable factors that have made the success of this dilution method unpredictable and frequently disappointing. The gas rises vertically for some distance above the stack, then spreads out laterally. The important factors in its dispersion are fog, wind direction, velocity, and turbulence. Sulfur dioxide in moist air or fogs combines with the water to form sulfurous acid, but is only very slowly oxidized to sulfuric acid.

### 1. Uses and Industrial Exposures

Sulfur dioxide is an intermediate in the manufacture of sulfuric acid. It is also used in the manufacture of sodium sulfite and in other chemical processes. Large quantities are used in refrigeration, in bleaching, fumigating, and pre-

<sup>43</sup> S. S. Pinto, R. A. Brown, and B. H. Carlton, *J. Ind. Hyg. Toxicol.*, **25**, 149 (1943).

<sup>44</sup> G. P. Schiavina, *Rass. Med. Ind.*, **12**, 173, 244 (1941).

servicing. It is used as an antioxidant in melting and pouring magnesium where it is applied as the gas or generated by adding powdered sulfur to the surface of the molten metal in the ladle and on the surface of the poured casting. Sulfur dioxide up to 0.5 per cent is also used for the prevention of oxidation in controlled-atmosphere heat-treat ovens for magnesium. Breathing zone concentrations of sulfur dioxide in magnesium foundries are highly variable and range from fractions of a part per million to over 10 p.p.m. as an average concentration with occasional peak concentrations of short duration in excess of 50 p.p.m.

### 2. Physical and Chemical Properties

Sulfur dioxide,  $\text{SO}_2$ , is a colorless gas with a strong, suffocating odor. It has a molecular weight of 64.06, a specific gravity of 1.434 in the liquid phase, and in the gaseous phase is 2.2 times as heavy as air. It melts at  $-72.7^\circ \text{C}$ . and boils at  $-10^\circ$ . Its solubility in water to form sulfurous acid is 8.5 g. per 100 g. at  $25^\circ \text{C}$ . and 17.7 g. per 100 g. at  $0^\circ$ . Its solubility in methyl or ethyl alcohol is greater than in water. It is also soluble in acetic acid, sulfuric acid, chloroform, and ethyl ether.

1 mg./l.  $\approx$  382 p.p.m. and 1 p.p.m.  $\approx$  2.62 mg./cu.m. at  $25^\circ \text{C}$ ., 760 mm.

### 3. Determination in the Atmosphere

Aspirate the sample through two scrubbers, the first of which contains a measured quantity of 0.01 *N* standard iodine in potassium iodide solution, and the second about one half as much 0.01 *N* sodium thiosulfate solution. Wash the contents of the two scrubbers into a beaker and titrate with 0.01 *N* sodium thiosulfate, using starch indicator. One millimeter of 0.01 *N* iodine solution  $\approx$  0.1223 ml. sulfur dioxide gas at  $25^\circ \text{C}$ . and 760 mm. Hg pressure. Determination may also be made by aspiration of the atmosphere at known rate through standard 0.002 *N* iodine-starch solution until the color is just discharged, or better, to a very faint blue. The amount of iodine required to produce a faint blue in the scrubber must be considered. Hydrogen sulfide, hydrogen cyanide, and other reducing agents give the same reaction. A blank should be run parallel on air free from reducing gases, or air filtered through silica gel or activated carbon.

The atmosphere also may be scrubbed through an oxidizing solution such as 5 per cent potassium chlorate<sup>45</sup> and evaluated by acidifying with hydrochloric acid, adding barium chloride solution, and comparing with standards of potassium sulfate treated in a similar manner. Automatic recorders<sup>46</sup> are available and are widely used.

### 4. Physiological Response

*Acute effects.* Sulfur dioxide is an irritant gas: 6 to 12 p.p.m. causes immediate irritation to nose and throat. Three tenths to 1 p.p.m. can be detected by

<sup>45</sup> S. Plisetskaya, *Lab. Prakt. (U.S.S.R.)*, No. 12, 25 (1939).

<sup>46</sup> M. D. Thomas, O. J. Ivie, J. N. Abersold, and R. H. Hendricks, *Ind. Eng. Chem., Anal. Ed.*, 15, 287 (1943).



the average individual, probably by taste rather than by odor, and 3 p.p.m. has an easily noticeable odor. About 20 p.p.m. is the least amount irritating to the eyes. One per cent is irritant to moist areas of the skin within a few minutes. Although sulfur dioxide dissolves readily and its inhalation affects chiefly the upper respiratory tract and bronchi, it may cause edema of the lungs or glottis and can produce respiratory paralysis.<sup>47</sup>

*Chronic effects.* A period of exposure of over 2 years to variable concentrations on the order of 30 p.p.m. with occasional peaks of up to 100 p.p.m. was found to have produced a significantly higher than normal incidence of nasopharyngitis,<sup>48</sup> an alteration of the senses of smell and taste, high urinary acidity, and increased fatigue. There was also an extension of the duration of colds, but not a significant change in their incidence. Exposure of mice and guinea pigs to concentrations of 10, 25, 33, 65, 100, 150, 300, and 1000 p.p.m.<sup>49</sup> sulfur dioxide revealed no significant effects in concentrations of 33 p.p.m. or less. In 65 p.p.m. one third of the animals evidenced acute distention of the stomach on the ninth day, and in 100 p.p.m. on the fourth day, at which time perforations of the stomach began to appear. The median lethal concentration for mice was 130 p.p.m. for 24 hours, 340 p.p.m. for 6 hours, 610 p.p.m. for 1 hour, and 1350 p.p.m. for 10 minutes. Less than 1 p.p.m. is believed to be injurious to plant foliage.

#### 5. Maximum Permissible Concentration and Warning Properties

The accepted permissible limit for prolonged exposure is 10 p.p.m. The irritating effects of this concentration are sufficient to provide ample warning. Fifty to 100 p.p.m. is considered the maximum permissible amount for 30 to 60 minutes' exposure, while 400 to 500 p.p.m. is immediately dangerous to life. Men are not likely to voluntarily enter concentrations high enough to be immediately harmful. The gas is not inflammable.

## SULFUR TRIOXIDE AND SULFURIC ACID MIST

### 1. Industrial Exposures and Physical and Chemical Properties

Sulfur trioxide and sulfuric acid mist exposures occur in the manufacture of sulfuric acid, in pickling operations, in the charging of storage batteries, and wherever mist or spray of the acid is formed or the acid is heated in an open container. Sulfur trioxide,  $\text{SO}_3$ , the anhydride of sulfuric acid, is a colorless gas with a molecular weight of 80.06. It is 2.8 times as dense as air. It melts at  $16.83^\circ\text{C}$ . and boils at  $44.8^\circ\text{C}$ . It combines with water to form sulfuric acid, which freezes at  $10.49^\circ\text{C}$ . and boils at  $330^\circ$ .

1 mg./l.  $\approx$  306 p.p.m. and 1 p.p.m.  $\approx$  3.21 mg./cu.m. at  $25^\circ\text{C}$ ., 760 mm.

<sup>47</sup> R. T. Johnstone, *Occupational Diseases*. Saunders, Philadelphia, 1942.

<sup>48</sup> R. A. Kehoe, W. F. Machle, K. Kitzmiller, and T. J. LeBlanc, *J. Ind. Hyg.*, 14, 159 (1932).

<sup>49</sup> F. R. Weedon, A. Hartzell, and Carl Setterstrom, *Contrib. Boyce Thompson Inst.*, 10, 281 (1939).

### **2. Determination in the Atmosphere**

Sulfuric acid mists may be collected either in scrubbers or impingers and titrated with 0.01 *N* alkali with a suitable indicator such as methyl red. Standard alkali may also be used with methyl red in a scrubber and air scrubbed at a measured rate through it until a color change of the indicator shows that neutralization has occurred, after which the atmospheric concentration is computed from the sampling rate and time. Sampling of the minute particles in sulfuric acid "fumes" or fog requires either very efficient scrubbing, or electrostatic collectors employing acid-resistant linings or glass tubes.

### **3. Physiological Response**

Sulfur trioxide is a strong irritant and the inhalation of concentrations of around 1 p.p.m. causes a choking sensation in the uninitiated. Persons accustomed to the exposure are unable to notice concentrations of this order of magnitude. Sulfur trioxide is irritant and corrosive to all mucous surfaces, causing inflammation of the upper respiratory tract, and possible lung injury. Sulfuric acid also attacks the enamel of the teeth.

The permissible limit has been variously stated at from 2 to 10 p.p.m. If the concentration is maintained below that which causes coughing, choking, and severe discomfort in unaccustomed persons, no injury is to be expected.

## **HYDROGEN SULFIDE**

### **1. Uses and Industrial Exposures**

Exposure to hydrogen sulfide results occasionally from its use as an industrial chemical, and frequently, from its occurrence as a by-product in industrial or natural processes wherever proteins decompose. It is encountered in mining, especially where sulfide ores are found; in excavating in swampy or filled ground, and hence sometimes in wells, caissons, and tunnels; in natural gas; in the production and refining of petroleum; in the waters of certain natural springs; in volcanic gases; in the low temperature carbonization of coal; in the manufacture of chemicals, dyes, and pigments; in the rayon industry; in the rubber industry; in tanneries; in the manufacture of glue; in the washings from sugar beets; and in sewer gases. Since hydrogen sulfide is soluble in water and oil, it may flow for a considerable distance from its place of origin to escape at unexpected areas. Many budding chemists have developed a casual disregard for the toxicity of hydrogen sulfide because of its general, and sometimes careless, use in the teaching of qualitative and quantitative analysis, and it is with great surprise that they later learn that the gas they used so consistently has a toxicity comparable to that of hydrogen cyanide. It is detectable by odor at about 1/400 of the lowest amount that can cause injurious effects.

## 2. Physical and Chemical Properties

Hydrogen sulfide,  $H_2S$ , is a colorless gas, which in low concentrations has an offensive odor described as that of rotten eggs. With prolonged exposure or higher concentrations the odor grows markedly less, apparently as a result of olfactory fatigue. The molecular weight of  $H_2S$  is 34.08 and its specific gravity is 1.19 (air = 1). Hydrogen sulfide melts at  $-82.9^\circ C.$  and boils at  $-61.8^\circ$ . It is soluble in water to the extent of 437 ml. in 100 ml. at  $0^\circ C.$  and 186 ml. in 100 ml. at  $40^\circ$ . It is also soluble in alcohol, petroleum solvents, and crude petroleum. It ignites at  $558^\circ F.$  and burns in the air forming sulfur dioxide and water. With insufficient oxygen, some free sulfur is formed and this reaction has been utilized to make sulfur from "sour" natural gas.

## 3. Determination in the Atmosphere

Hydrogen sulfide in the atmosphere is readily detected by its blackening of moistened lead acetate paper. It may be determined quantitatively by scrubbing the air through a cadmium chloride solution and estimating iodometrically<sup>50</sup> or colorimetrically.<sup>51</sup> In the absence of interfering oxidizing or reducing gases, hydrogen sulfide may be determined, in the field, by scrubbing through water containing a measured amount of 0.01 *N* standard iodine solution<sup>52</sup> and starch indicator. The midget impinger pump with a calibrated, fritted glass, or other suitable scrubber, is satisfactory for either the cadmium chloride or the iodine method. In the case of iodine a 0.01 *N* solution may be carried into the field in a glass-stoppered bottle, measured into the scrubber with a pipette, and the starch added. Air can be drawn through the scrubber at a measured rate to a pre-determined fading or almost complete loss of color and, since 1 ml. of 0.01 *N* solution  $\approx$  0.1223 ml. hydrogen sulfide at  $25^\circ C.$  and 760 mm. Hg pressure, the concentration of hydrogen sulfide in the air may be estimated by the following equation:

$$\frac{\text{ml. 0.01 } N \text{ iodine} \times 0.1223 \times 1000}{\text{sampling time (min.)} \times \text{sampling rate (l./min.)}} = \text{p.p.m.}$$

or where the rate is 1 liter per minute:

$$\frac{\text{ml. 0.01 } N \text{ iodine} \times 122.3}{\text{sampling time (min.)}} = \text{p.p.m. hydrogen sulfide}$$

When a control test is made in hydrogen sulfide-free air and allowance made for the amount of iodine necessary to produce a detectable color in the scrubbing liquid, this method can give results of at least 95 per cent accuracy. The M.S.A.

<sup>50</sup> M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1944.

<sup>51</sup> F. H. Goldman, A. A. Coleman, H. B. Elkins, and H. H. Schrenk, *Am. J. Pub. Health*, 33, 862 (1943).

<sup>52</sup> A. C. Fieldner, G. G. Oberfell, M. C. Teague, and J. N. Lawrence, *Ind. Eng. Chem.*, 11, 523 (1919).

hydrogen sulfide detector<sup>53</sup> offers another rapid, convenient, and fairly accurate method. An automatic detection and control system has been described by Clough.<sup>54</sup>

#### 4. Physiological Response

*Acute effects.* By far the greatest danger from the inhalation of hydrogen sulfide is from its acute effects. Whether the effects are to be acute, or subacute and chronic, depends upon the concentration of the gas in the atmosphere. Concentrations of 700 p.p.m. (0.07 per cent by volume) and above may result in acute poisoning and, although the gas is an irritant, the systemic effects from absorption of hydrogen sulfide into the blood stream<sup>55</sup> overshadow the irritant effects. These acute systemic effects result from the action of free hydrogen sulfide in the blood stream and occur whenever the gas is absorbed faster than it can be oxidized to pharmacologically inert compounds such as thiosulfate or sulfate. Such oxidation occurs rapidly in man or animals and, even following inhalation exposure to concentrations up to 700 p.p.m. hydrogen sulfide in the atmosphere, hydrogen sulfide does not appear in the exhaled breath. Relatively massive doses are required to overcome this protective activity of the body. Sodium sulfhydrate, NaHS, solution injected intravenously into dogs rapidly disappears from the circulating blood<sup>56</sup> when a rate equivalent to 0.1 to 0.2 mg. hydrogen sulfide per kilogram of body weight per minute is not exceeded.

When the amount absorbed into the blood stream exceeds that which is readily oxidized, systemic poisoning results, with a general action on the nervous system, hyperpnea occurs shortly, and respiratory paralysis may follow immediately. This condition may be reached almost without warning as the originally detected odor of hydrogen sulfide may have disappeared, as a result of olfactory fatigue. Unless the victim is removed to fresh air within a very few minutes, and breathing stimulated or induced by artificial respiration, death occurs. Unconsciousness and collapse occur within seconds in high concentrations and for that reason many persons have lost their lives attempting to save a victim who has collapsed from exposure. In such a case, holding the breath will permit a brief stay in the atmosphere, while to inhale it would cause almost immediate collapse.

As an example of the rapidity of these effects and recovery may be cited the experimental results observed with a dog exposed to a concentration on the order of 1000 p.p.m. When first placed in the atmosphere, the animal frisked playfully for a short time, stopped and stood still momentarily, breathing laboriously, fell on his side, gasped once or twice, then remained motionless with legs extended. At the end of 1 minute the dog was removed from the chamber and given artificial respiration; within 1 or 2 minutes he resumed his frisking as though nothing

<sup>53</sup> J. B. Littlefield, W. P. Yant, and L. B. Berger, *U.S. Bur. Mines Repts. Investigations*, No. 3278 (1935).

<sup>54</sup> J. Clough, *J. Soc. Chem. Ind.*, 63, 210 (1944).

<sup>55</sup> Y. Henderson and H. W. Haggard, *Noxious Gases*. 2nd ed., Reinhold, New York, 1943.

<sup>56</sup> V. A. Tichonravov, *Farmakol. i Toksikol.*, 6, No. 5, 36 (1943).

had occurred. Had breathing not been induced by artificial respiration, the heart would have stopped within a very few minutes: death would have resulted from asphyxiation. The mechanics of this respiratory paralysis formerly were thought to involve a chemical reaction with the respiratory enzymes or with the hemoglobin or both; but, in high concentrations of the gas, are now believed to be due to reflexes resulting from irritation of the carotid sinus.<sup>57</sup> Moderately high concentrations cause apne vera after overstimulation of the respiratory center.<sup>55</sup> Regardless of the exact mechanism of the cessation of respiration, if the victim is removed to pure air and respiration set in motion by any means before heart action has ceased, rapid recovery may be expected.

*Subacute effects.* Hydrogen sulfide is an irritant gas and exposure to concentrations between 70 and 700 p.p.m. may irritate the mucous membranes of the eyes and of the respiratory tract. Pulmonary edema<sup>57</sup> or bronchial pneumonia is likely to follow prolonged exposure to concentrations on the order of 250 to 600 p.p.m. These levels of exposure may cause such symptoms as headache, dizziness, excitement, nausea or gastrointestinal disturbances, dryness and sensation of pain in the nose and throat and chest, and coughing. Table 3 indicates responses to various concentrations of hydrogen sulfide in the atmosphere.

TABLE 3  
*Physiological Response to Various Concentrations of Hydrogen Sulfide*<sup>55</sup>

Response	Concentration, p.p.m.
Maximum allowable concentration for prolonged exposure.....	20
Slight symptoms after several hours.....	70-150
Maximum concentration for 1 hr. without serious consequences.....	170-300
Dangerous after exposure of 1/2 to 1 hr.....	400-700

Among the subacute and chronic effects of exposure to hydrogen sulfide irritation resulting in conjunctivitis or "gas eyes"<sup>58</sup> is the most common, ranging from mild to severe with extent and intensity of exposure, manifested by itching and smarting, a feeling of sand in the eyes, marked inflammation, swelling, cloudy cornea, destruction of the epithelial layer with scaling and in blurring of vision. Exposure to light may increase the painful effect. Atmospheric concentrations above 50 p.p.m. and up to 300 p.p.m. are considered dangerous conditions.

### 5. Absorption and Excretion

The absorption of hydrogen sulfide is almost exclusively through the respiratory tract. Absorption through the skin has been demonstrated and reported, but that this is not a significant source of systemic poisoning is indicated by the fact that the routine for gas mask approval

<sup>57</sup> T. Sollmann, *A Manual of Pharmacology*, 6th ed. Saunders, Philadelphia

<sup>58</sup> W. P. Yant, *Am. J. Pub. Health*, 22, 598 (1930).

United States Bureau of Mines has included the wearing of gas masks for 30-minute periods in atmospheres containing 2 per cent (20,000 p.p.m.) hydrogen sulfide. During these tests, which include strenuous exercise, the subjects have noted slight skin irritation but no systemic effects indicative of hydrogen sulfide absorption and no discoloration of the skin. When free sulfide exists in the circulating blood a certain amount of hydrogen sulfide is excreted in the exhaled breath. This is sufficient to be detected by odor. The greater portion, however, is excreted in the urine, chiefly as sulfate, but some also as sulfide.

There are no known reliable tests, applicable to the exposed individual, that are indicative of the degree of exposure.

#### **6. Maximum Permissible Concentration and Warning Properties**

The accepted maximum permissible concentration for prolonged exposure is 20 p.p.m. Although the characteristic odor of the gas is detectable in concentrations as low as 0.025 p.p.m., is distinct at 0.3 p.p.m., is offensive and moderately intense at 3 to 5 p.p.m., is strong and marked but not intolerable at 20 to 30 p.p.m., the odor of higher concentrations does not become more intense, and above about 200 p.p.m. the disagreeable odor appears less intense. These perceptions are based upon initial inhalations, and with continuous inhalation the olfactory sense fatigues rapidly.

Hydrogen sulfide is inflammable within the limits of 4.3 and 45.5 per cent by volume in air (see Chapter Thirteen).

### **Alkaline Sulfides**

The sulfides of potassium, sodium, calcium, and barium are solids that, in presence of water or acids, liberate hydrogen sulfide into the air. They are so because of formation of free alkali by hydrolysis.

## **SULFUR**

### **and Industrial Exposures**

Carbon disulfide is used in the xanthation of cellulose in the preparation of rayon and exposures exist not only in the xanthating process but also during washing of the viscose. In the rubber industry carbon disulfide has been used as a solvent for sulfur or as a diluent for sulfur chloride in vulcanizing and as a solvent for rubber cement. It has been used as an insecticide and in the rubber industry as a solvent for phosphorus, fats, oils, resins, and waxes. It is used in the manufacture of optical glass, to fill glass prisms. Carbon disulfide is used in the destructive distillation of coal.

### **and Chemical Properties**

Carbon disulfide (bisulfide),  $CS_2$ , is a colorless, toxic liquid with molecular weight, <sup>25</sup> 1.6232, and specific gravity 1.2628 at 20°/4° C. The vapor is heavier than air. It melts at -108.6° C. and boils at 46.3°. The vapor

pressure equals 360 mm. Hg at 25° C., corresponding to a concentration of 47.4 per cent vapor in a "saturated" vapor-air mixture, which mixture has a density 1.74 times that of air. The solubility of carbon disulfide in water is 0.22 g. per 100 ml. at 22° C. and it is miscible with alcohol, ether, and benzene.

1 mg./l.  $\approx$  321 p.p.m. and 1 p.p.m.  $\approx$  3.12 mg./cu.m. at 25° C., 760 mm.

### 3. Determination in the Atmosphere

Scrub the atmosphere through two fritted glass scrubbers containing a solution of 0.5 per cent each diethylamine and triethanolamine and 0.001 per cent cupric acetate in 95 per cent ethyl alcohol.<sup>59</sup> The sampling rate should be 0.5 to 1 liter per minute. One to fifty micrograms of carbon disulfide develops sufficient color and comparison can be made with prepared standards. The determination is more satisfactorily made by means of a photometer. The vapor of carbon disulfide may also be determined directly in the air by means of an ultraviolet photometer. Satisfactory results can be obtained by the methods of Viles<sup>60</sup> or Matuzak.<sup>61</sup> The interferometer may also be used successfully (see page 204).

### 4. Physiological Response

*Acute effects.* Table 4 lists six representative levels of effect upon man, with corresponding ranges of concentration of inhaled carbon disulfide. The

TABLE 4  
*Effects of Various Concentrations of Carbon Disulfide on Man*<sup>62</sup>

Effects	Concentration	
	mg./l.	p.p.m.
Slight or no effect.....	0.5- 0.7	160- 230
Slight symptoms after several hours.....	1.0- 1.2	320- 390
Symptoms after 1/2 hr.....	1.5- 1.6	420- 510
Serious symptoms after 1/2 hr.....	3.6	1150
Dangerous to life after 1/2 hr.....	10.0-12.0	3210-3850
Fatal in 1/2 hr.....	15.0	4815

predominant effect of high concentrations of carbon disulfide is narcosis, and death may result from respiratory failure. Less severe exposures may result in headache, giddiness, respiratory disturbances, precordial distress, and gastrointestinal disturbances.<sup>63</sup> The possibility of injury to the central nervous system from a single severe acute exposure is reported by Lewy.<sup>64</sup>

<sup>59</sup> R. W. McKee, *J. Ind. Hyg. Toxicol.*, 23, 151 (1941).

<sup>60</sup> F. J. Viles, *J. Ind. Hyg. Toxicol.*, 22, 188 (1940).

<sup>61</sup> M. P. Matuzak, *Ind. Eng. Chem., Anal. Ed.*, 4, 98 (1932).

<sup>62</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

<sup>63</sup> U.S. *Pub. Health Reports*, 56, 574 (1941).

<sup>64</sup> F. H. Lewy, *Penna. Dept. Labor Industry Bull.* No. 36 (1938).

**Chronic effects.** Repeated brief exposures to high concentrations or prolonged exposures to low concentrations are of much greater industrial importance than are the single acute exposures. Among the subjective complaints that characterize chronic carbon disulfide poisoning are: fatigue, loss of memory, insomnia, listlessness, headache, excessive irritability, melancholia, vertigo, weakness, loss of appetite, gastrointestinal disturbances, and impairment of sexual functions. Visual disturbances, loss of reflexes, hallucinations, mania, or chronic dementia may occur. Lung irritation has been reported. Degenerative changes in the blood and blood-forming organs are reported to occur sometimes after poisoning has progressed. Dermatitis, and even blistering, may result from contact of vapor or liquid with the skin or mucous surfaces. Rubin and Arieff<sup>65</sup> studied 100 workers exposed for 4 years to average concentrations of 1.0 to 5.5 p.p.m. hydrogen sulfide and 1.9 to 26.4 p.p.m. carbon disulfide, or a combined sulfide gas and vapor concentration of 2.9 to 31.9 p.p.m., and found no indication of intoxication. Improvement or complete recovery is to be expected if the exposure is discontinued before severe damage results. Barthelemy,<sup>66</sup> reporting on 10 years of experience in the manufacture of viscose rayon, cites three cases of poisoning due to excessive exposure to carbon disulfide: one mental derangement, and two with impaired motor nerves adversely affecting the leg muscles. All three workmen completely recovered within a few months after termination of exposure. He further states that when the carbon disulfide in the air was kept below 30 p.p.m. and the hydrogen sulfide below 20 p.p.m. no trouble whatsoever was experienced.

Mice and rats exposed 8 hours per day for 20 weeks to an average concentration of 37 p.p.m. (0.114 mg. per liter) carbon disulfide showed evidence of toxic effects.<sup>67</sup> This was interpreted as an indication that carbon disulfide in workroom atmospheres should be kept below 0.1 mg. per liter.

### 5. Absorption and Excretion

The absorption of carbon disulfide is mainly through the lungs, where it enters the blood stream and is distributed throughout the body. Limited absorption can occur through the skin, and if swallowed, it is absorbed from the gastrointestinal tract. Saturation of the body occurs rapidly (see page 188). Eighty-five to ninety per cent of the carbon disulfide is metabolized<sup>68</sup> and eliminated in the urine as inorganic sulfates and other sulfur compounds; the balance is eliminated unchanged: 8 to 13 per cent in the exhaled breath, 1/2 per cent in the urine, and none in the feces. It is probable that a trace is also eliminated in the sweat, but this has not been demonstrated.

<sup>65</sup> H. H. Rubin and A. J. Arieff, *J. Ind. Hyg. Toxicol.*, 27, 123 (1945).

<sup>66</sup> H. L. Barthelemy, *J. Ind. Hyg. Toxicol.*, 21, 141 (1939).

<sup>67</sup> F. H. Wiley, W. C. Hueper, and W. F. von Oettingen, *J. Ind. Hyg. Toxicol.*, 18, 733 (1936).

<sup>68</sup> R. W. McKee, C. Kipper, J. H. Fountain, A. M. Riskin, and P. Drinker, *J. Am. Med. Assoc.*, 122, 217 (1943).



### **6. Tests Indicating Exposure**

Although the total sulfur in the urine of exposed persons is considerably elevated, there are many other factors that cause that same result. Carbon disulfide in the blood or urine, however, is indicative of exposure, and its concentration can give some indication of the severity of the exposure.

### **7. Maximum Permissible Concentration and Warning Properties**

Concentrations of carbon disulfide in the air varying all the way from 3 to 30 p.p.m. have been given as maximum safe limits. The present accepted maximum permissible concentration is 20 p.p.m. (0.0624 mg. per liter). Carbon disulfide has a foul, slightly ethereal, odor that, however, does not offer adequate warning in the lower harmful concentrations.

### **8. Inflammability**

Carbon disulfide has a range of inflammability of 1.25 to 50.0 per cent by volume in air. The flash point by the closed-cup method is  $-22^{\circ}$  F. and the ignition temperature is  $248^{\circ}$  F., a temperature commonly encountered in steam pipes, electric light bulbs, and elsewhere. These properties make carbon disulfide vapor one of the outstanding explosion hazards.

## **CARBONYL SULFIDE**

### **1. Occurrence and Physical and Chemical Properties**

Carbonyl sulfide, carbon oxysulfide, COS, is a colorless gas frequently associated with hydrogen sulfide and carbon disulfide. It is encountered in the destructive distillation of coal and the purification of petroleum. The molecular weight is 60.07. The gas is 2.1 times denser than air. It has a melting point of  $-138.2^{\circ}$  C. and a boiling point of  $-50.2^{\circ}$ . The solubility in water is 0.54 ml. per milliliter at  $20^{\circ}$  C., in alcohol 8 ml. per milliliter at  $22^{\circ}$ , and in toluene 15 ml. per milliliter at  $22^{\circ}$ . It decomposes in moist air to carbon dioxide and hydrogen sulfide.

1 mg./l.  $\approx$  408 p.p.m. and 1 p.p.m.  $\approx$  2.55 mg./cu.m. at  $25^{\circ}$  C., 760 mm.

### **2. Determination in the Atmosphere**

Carbonyl sulfide in the air can be determined by absorption in alcoholic potassium hydroxide solution, and precipitation of sulfide with cadmium chloride or other suitable means; or it may be oxidized with hydrogen peroxide or bromine and the sulfate determined by precipitation with barium chloride. The gas can also be determined readily with the gas interferometer.

### **3. Physiological Response**

The gas carbonyl sulfide is only slightly irritant to the lungs. It acts principally upon the central nervous system with death resulting mainly from

respiratory paralysis. Rabbits<sup>62</sup> showed some ill effects after an exposure of 1/2 hour to 1300 p.p.m., convulsions and death following an exposure of 1 hour to 3200 p.p.m. With mice<sup>69</sup> death occurred in 3/4 minute when they were exposed to 8900 p.p.m., 1 1/2 minutes to 2900 p.p.m., and 35 minutes to 1200 p.p.m. Sixteen minutes' exposure to 900 p.p.m. caused no perceptible effects.

Experience with exposure of human beings has not been recorded. It is probable that the effects can be assigned to the action of the hydrogen sulfide resulting from partial decomposition in the lungs and after absorption into the blood stream. It is also probable that the permissible limit should be somewhat higher than for hydrogen sulfide.

Pure carbonyl sulfide has inadequate warning properties. It is inflammable between the range of 11.90 to 28.50 per cent by volume in air.

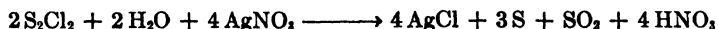
### SULFUR MONOCHLORIDE

Sulfur monochloride is used in vulcanizing and in curing rubber. In the manufacture of rubber-coated fabrics, sulfur chloride has been used in oven "curing" atmospheres, and in some such operations has been poured into open containers and placed on steam coils on the floor of the curing oven. The leakage into the room in such an instance causes pronounced irritation to the eyes and nose of anyone working in the room. The distribution and collection of open containers involve brief exposures to relatively high concentrations. Men who do this sometimes inadvisedly rely upon holding their breath during the period of exposure to high vapor concentration, rather than wearing a gas mask. Sulfur monochloride is also used in the manufacture of organic chemicals, printer's inks, varnishes, and cements; in hardening soft woods; and as an agricultural insecticide.

Sulfur monochloride, S<sub>2</sub>Cl<sub>2</sub> (sometimes given as SCl), is a yellowish-red viscous liquid with molecular weight 135.03 and density 1.678 at 20°/4° C. It boils at 135.6° C. and freezes at -80°.

1 mg./l.  $\approx$  181 p.p.m. and 1 p.p.m.  $\approx$  5.52 mg./cu.m. at 25° C., 760 mm.

The vapor decomposes in water or moist air to form sulfur, hydrochloric acid, and sulfur dioxide. The sulfur monochloride vapor in the air may be determined by scrubbing through two scrubbers containing a measured quantity of 0.1 N silver nitrate acidified with nitric acid. When sampling has been completed, add 0.1 N sodium chloride solution equivalent to the silver nitrate used, and titrate the excess chloride with additional 0.1 N silver nitrate. The reaction is as follows:



Sulfur chloride has a suffocating odor and it is strongly irritant to the eyes, nose, and throat. A concentration of 150 p.p.m. has been stated<sup>62</sup> to be fatal to mice after an exposure of 1 minute, but the degree of toxicity has not yet been well established. The irritant effects are due to the sulfur dioxide and hydrochloric

<sup>69</sup> A. Klemenc, *Ber.*, B76, 299 (1943).

acid liberated by hydrolysis. Since this occurs rather readily, most of the irritant action is expended upon the upper respiratory tract. However, if the hydrolysis should not be completed in the upper respiratory tract, injury to the bronchioles and alveoli would result. Further observations of the action of this vapor must be made before threshold limits can be established, but it is probable that the safe limit for prolonged inhalation lies below 10 p.p.m.

### THIONYL CHLORIDE

Thionyl chloride,  $\text{SOCl}_2$ , molecular weight 118.97, is used as a chlorinating agent in chemical manufacture. It melts at  $-105^\circ \text{C}$ . and boils at  $75.5^\circ$ . The vapor pressure is 110 mm. at  $26^\circ \text{C}$ ., corresponding to 14.5 per cent vapor in the air. The specific gravity of the liquid is 1.655 at  $10^\circ/4^\circ \text{C}$ ., of the vapor, 4.1 (air = 1) and of the vapor-saturated air, 1.5 (air = 1) at  $26^\circ$ .

1 mg./l.  $\approx$  205 p.p.m. and 1 p.p.m.  $\approx$  4.87 mg./cu.m. at  $25^\circ \text{C}$ ., 760 mm.

Thionyl chloride decomposes in moisture and sunlight into sulfur dioxide, sulfur, chlorine, sulfur monochloride, and hydrochloric acid. Thionyl chloride vapor is irritant to the respiratory tract and its toxicity is probably similar to, and possibly greater than, that of sulfur monochloride. An exposure of 17.5 p.p.m. for 20 minutes is said to have proved fatal to cats.<sup>82</sup>

No maximum permissible limit has been proposed. Such a limit would probably lie below 5 p.p.m.

Thionyl chloride in the air can be determined in the same manner as sulfur monochloride.

### SULFURYL CHLORIDE

Sulfuryl chloride is used in chemical manufacture as a chlorinating and sulfonating agent for aromatic and aliphatic compounds, and for treating wool to make it unshrinkable.

Sulfuryl chloride,  $\text{SO}_2\text{Cl}_2$ , is a colorless, pungent liquid of molecular weight 134.97 and specific gravity 1.667 at  $20^\circ/4^\circ \text{C}$ . Sulfuryl chloride melts at  $-54.1^\circ \text{C}$ . and boils at  $69.1^\circ$ . Its refractive index is 1.444 at  $20^\circ \text{C}$ . The density of the vapor is 4.7 times that of air.

1 mg./l.  $\approx$  181 p.p.m. and 1 p.p.m.  $\approx$  5.52 mg./cu.m. at  $25^\circ \text{C}$ ., 760 mm.

Sulfuryl chloride is soluble in benzene and acetic acid but decomposes in water and moist air into hydrochloric and sulfuric acids. Although its irritant properties have not been described in detail, in view of its decomposition products it would be expected to be very irritant to the lungs, possibly more so than either sulfur monochloride or thionyl chloride.

Sulfuryl chloride can be absorbed by scrubbing through an alkaline medium, hydrolyzed, and determined either as the chloride or the sulfate.

No maximum permissible limit has been proposed; because of the chemical properties of sulfuryl chloride such a limit would be expected to be less than 5 p.p.m.

## TELLURIUM

### 1. Uses and Industrial Exposures

The world's production of tellurium in 1940 was about 200,000 lbs. or one fifth that of selenium, along with which it is found in sulfide ores. Tellurium is used as a rubber improver; in tellurium vapor "daylight" lamps; in cast iron, where minute amounts stabilize the iron carbide and appreciably increase the depth of the chill. The gray iron industry uses hundreds of tons annually, a considerable amount being for hardening the surface of car wheels. It is also used in malleable iron to improve ductility and in stainless steel for machinability. A fraction of 1 per cent alloyed with lead improves the corrosion resistance, strength, and hardening properties of the lead. Tellurium is used to increase the machinability of copper and bronze, and to improve other metals and alloys. It is also used in several chemical processes, including use as a catalyst.

### 2. Physical and Chemical Properties

Tellurium, Te, atomic weight 127.61, exists in two forms: a blue-white, silvery material with a metallic luster, specific gravity 6.24 at 20°/4° C.; and an amorphous, brownish black powder, specific gravity 6.00 at 20°/4°. It melts at 452° C. and boils (in hydrogen) at 1390°. It will burn in air with a greenish blue flame to form the oxide, TeO<sub>2</sub>. Chemically, it belongs to the sulfur group and has many properties in common with arsenic and selenium. It dissolves in 1:1 nitric acid, concentrated sulfuric acid, potassium hydroxide, and potassium cyanide. It is insoluble in carbon disulfide and water.

### 3. Determination in the Atmosphere

Dusts and fumes are satisfactorily collected by the electrostatic precipitator, while hydrogen telluride or methyl telluride can be absorbed by scrubbing through 48 per cent hydrobromic acid containing 5 to 10 per cent bromine, as in the collection of hydrogen selenide. The amount of sample needed will depend upon the collection apparatus available and the concentration in the air. Determination may be made by the method of Steinberg, Massari, Miner, and Rink.<sup>70</sup> Best results are obtained when the aliquot used for comparison with standards contains between 5 and 50 micrograms of tellurium.

### 4. Physiological Response

*Acute effects.* The actions of tellurium and selenium are similar to those of inorganic arsenic, especially the injurious effect on the capillaries.<sup>71</sup> A garlic odor is imparted to the breath by brief and minor exposures to tellurium compounds. This may result from a single short inhalation exposure, or from skin absorption from handling tellurium compounds. The garlic odor may persist for

<sup>70</sup> H. H. Steinberg, S. C. Massari, A. C. Miner, and R. Rink, *J. Ind. Hyg. Toxicol.*, **24**, 183 (1942).

<sup>71</sup> T. Sollman, *A Manual of Pharmacology*. 6th ed., Saunders, Philadelphia, 1944.

months if the amount of tellurium absorbed was significant. Suppression of the sweat, nausea, metallic taste, and somnolence may also result from significant acute inhalation exposures. More serious effects have not been reported from acute exposures.

*Chronic effects.* The toxic effects of tellurium on animals are similar to those of arsenic. Steinberg and his associates<sup>72</sup> report that workmen, exposed 2 years to amounts ranging from 0.1 mg. to 7.4 mg. tellurium and tellurium oxide per 10 cubic meters of air, exhibited in decreasing frequency: garlic odor of the breath, dryness of the mouth, metallic taste, somnolence, garlic odor of the sweat, loss of appetite, nausea; but there was no suppression of sweat, nor evidence of intoxication. Approximately 90 per cent of the air samples ranged between 0.1 mg. and 1.0 mg. tellurium per 10 cubic meters of air. However, since the symptoms recorded over the 2-year period could also occur from brief exposure to higher concentrations, it is not possible to say that concentrations below 1 mg. per 10 cubic meters would produce all of these symptoms. It is reasonable to think that where concentrations do not rise above 1 mg. per 10 cubic meters, serious illness is not to be expected.

#### 5. Absorption and Excretion

Tellurium compounds can be absorbed through the skin, by ingestion, and by inhalation. They are excreted in the exhaled breath, sweat, urine, and feces.

#### 6. Tests Indicating Exposure

Exposure is indicated by a garlic odor of the breath, or by the presence of amounts of 0.01 mg. or more tellurium per liter of urine. Concentrations up to 0.06 mg. per liter have been found in the absence of any evidence of intoxication from tellurium.

#### 7. Maximum Permissible Concentration

The maximum permissible concentration in the atmosphere depends upon the criterion. If a foul breath is to be avoided, the maximum permissible concentration is on the order of 0.1 mg. or 0.2 mg. tellurium per 10 cubic meters of air. If the manifestation of toxic effects is to be the criterion, 1 mg. per 10 cubic meters appears quite safe, and indications are that the toxic level is probably in excess of 8 mg. per 10 cubic meters. It seems somewhat logical that for practical purposes the presence or absence of the characteristic tellurium breath can be relied upon to indicate exposure, and if this is heeded as an indication of the necessity for control measures, injurious exposures are not likely to occur.

## HYDROGEN TELLURIDE

Hydrogen telluride,  $H_2Te$ , which has no industrial uses, is a colorless gas, with a molecular weight of 129.63. In the pure state it is 4.5 times as dense as

<sup>72</sup> H. H. Steinberg, S. C. Massari, A. C. Miner, and R. Rink, *J. Ind. Hyg. Toxicol.*, 24 183 (1942).

air. It melts at  $-51^{\circ}$  C. and boils at  $-4^{\circ}$ . It dissolves and decomposes in water, precipitating elemental tellurium. It has an odor somewhat resembling hydrogen sulfide, and is irritant in relatively low concentrations. Its actions on the human system are believed to be similar to those of other tellurium compounds. Its degree of toxicity has not been established but, owing to its ready decomposition, it is believed to be less toxic than arsine or hydrogen selenide.

1 mg./l.  $\approx$  189 p.p.m. and 1 p.p.m.  $\approx$  5.3 mg./cu.m. at  $25^{\circ}$  C., 760 mm.

## CHAPTER NINETEEN

# Compounds of Oxygen, Nitrogen, and Carbon

FRANK A. PATTY

### OXYGEN

#### 1. Occurrence, Properties, and Uses

Oxygen, O<sub>2</sub>, is a colorless, odorless gas with a molecular weight of 32, melting point of  $-218.4^{\circ}$  C., and boiling point of  $-183^{\circ}$ . Its solubility in water is 4.89 cc. in 100 ml. water at  $0^{\circ}$  C. Oxygen (20.95 per cent by volume) is a normal constituent of the air we breathe. Men and animals are dependent upon the presence of oxygen and can live only a few minutes in its absence. Oxygen is required by the body for combustion in the tissues in amounts proportional to energy expenditures. Henderson and Haggard<sup>1</sup> give the approximate energy expenditures, oxygen consumption, and volume of breathing of an average (154 lb.) man as follows in Table 1. For variations due to age see page 66 (Vol. I).

TABLE 1  
*Energy Expenditure, Oxygen Consumption, and Volume of Breathing of Man*

Activity	Cal./min.	Oxygen consumption, l./min. ( $0^{\circ}$ C., 760 mm.)	Vol. of air breathed, l./min. ( $20^{\circ}$ C.)
Rest in bed, fasting.....	1.15	0.240	6
Sitting.....	1.44	0.300	7
Standing.....	1.72	0.360	8
Walking 2 m.p.h.....	3.12	0.650	14
Walking 4 m.p.h.....	5.76	1.200	26
Slow run.....	9.60	2.000	43
Maximum exertion.....	14-20	3.000-4.000	65-100

Oxygen inhalation during decompression has been used to prevent compressed-air illness.<sup>2</sup>

<sup>1</sup> Y. Henderson and H. W. Haggard, *Noxious Gases*. Reinhold, New York, 1943.

<sup>2</sup> R. R. Jones, J. W. Crosson, F. E. Griffith, R. R. Sayers, H. H. Schrenk, and E. Levy, *J. Ind. Hyg. Toxicol.*, **22**, 427 (1940).

## 2. *Physiological Response to Increased Concentrations*

*Effects on man.* The inhalation of 100 per cent oxygen for periods up to 16 hours per day for many days at atmospheric pressure has caused no observed injury to man. It is believed to have no serious adverse effect for a continuous exposure of 24 to 48 hours.<sup>3</sup> Pure oxygen for 24 hours at atmospheric pressure causes some substernal distress, but none at  $1/2$  atm. (equivalent of 18,000 ft. altitude).<sup>4</sup> Mixtures of up to 65 per cent oxygen in air may be inhaled for extended periods with no known ill effects. The inhalation of pure oxygen at 3 atm. pressure (30 lb. gage) is safe for man for a period of 30 minutes.<sup>5</sup> Longer periods or higher pressures may produce oxygen poisoning. Convulsions have occurred in man after oxygen has been breathed for 45 minutes at 4 atm. pressure,<sup>6</sup> while, after 1 to 3 hours at 1 atm. pressure, neuromuscular co-ordination and the power of attention were adversely affected. In most subjects they were impaired or at least increased effort was required to maintain them.

Oxygen<sup>7</sup> at 3 atm. pressure can be breathed by young, healthy men for 3 hours without distressing symptoms. During the fourth hour, a progressive contraction of the visual field with dilatation of the pupils and some impairment in central vision is the most constant criterion of oxygen toxicity. Circulatory changes indicative of peripheral vascular constriction are associated with the visual impairment and culminate during the fourth hour in an abrupt rise in systolic and diastolic blood pressure, increase in pulse rate, and extreme pallor. At this stage the subjects experience dizziness and a feeling of impending collapse, with partial stupefaction. Rapid and complete recovery, attended by a feeling of alertness and stimulation, results within an hour after air is substituted for oxygen.

*Effects on dogs.* Among dogs<sup>8</sup> inhaling pure oxygen at atmospheric pressure, oxygen poisoning begins to develop after 36 hours, causes distress within 48 hours, and death in 60 hours. Ninety per cent oxygen in air requires double the exposure period for similar results; and in 80 per cent oxygen in air the animals did not die but were ill at the end of a continuous exposure of 1 week. A decline in oxygen saturation of the blood, rise in hemoglobin, lung congestion and edema, right heart failure, and liver congestion were frequent findings in oxygen poisoning.

## 3. *Fire Hazards of Increased Concentrations*

In the use of air containing oxygen in concentrations above 21 per cent, or air at increased pressures, all materials are more readily oxidized than in the

<sup>3</sup> T. Sollman, *A Manual of Pharmacology*. 6th ed. Saunders, Philadelphia, 1944.

<sup>4</sup> J. H. Comroe, Jr., R. D. Dripps, P. R. Dumke, and M. Deming, *J. Am. Med. Assoc.*, 128, 710 (1945).

<sup>5</sup> A. R. Behnke, L. A. Shaw, C. W. Shilling, R. M. Thomson, and A. C. Messer, *Am. J. Physiol.*, 107, 13 (1934).

<sup>6</sup> A. R. Behnke, F. S. Johnson, J. R. Poppen, and E. P. Motley, *Am. J. Physiol.*, 110, 565 (1935).

<sup>7</sup> A. R. Behnke, H. S. Forbes, and E. P. Motley, *Am. J. Physiol.*, 114, 436 (1936).

<sup>8</sup> J. R. Paine, A. Keys, and D. Lynn, *Am. J. Physiol.*, 133, 406 (1941).



normal atmosphere and therefore will ignite more easily and burn more rapidly, thus presenting a greater fire hazard. Great care must be exercised to assure that cylinders, gages, valves, or lines to be used with compressed oxygen do not become contaminated with traces of oil or other readily oxidized material. If such contamination exists, explosive oxidation may occur when contact is made with the compressed oxygen.

## OXYGEN DEFICIENCY

### 1. Occurrence

Oxygen deficiency is of much more concern in industry than are high concentrations or high pressures of oxygen. It may be encountered in numerous situations such as in tanks, vats, holds of ships, silos, mines, or in any poorly ventilated area where the air may be diluted or displaced by gases or vapors of volatile materials, or where the oxygen may be consumed by chemical or biological reaction processes.

### 2. Determination in the Atmosphere

The analysis of the atmosphere for its oxygen content may be done with the Haldane or Orsat<sup>9</sup> gas-analysis apparatus. Safety lamps<sup>10</sup> are used for detecting oxygen deficiency, and where there was no danger of encountering inflammable gases a lighted candle has been used to indicate unsafe atmospheres (less than 16.5 per cent oxygen). If the candle burns, there is believed to be sufficient oxygen to support life. This, however, has been demonstrated to be unreliable (see page 147, Vol. I). Oxygen-recording devices covering the range of 0 to 15 per cent oxygen are available.

### 3. Physiological Response

When the concentration of oxygen in the atmosphere falls below 16 per cent, symptoms of anoxia begin to appear. These may be classified by stages<sup>1</sup> as given in Table 2.

TABLE 2  
*Response of Man to the Inhalation of Atmospheres Deficient in Oxygen*

Stage	Oxygen, volume per cent	Symptoms or phenomena
1	12-16	Breathing and pulse rate increased, muscular co-ordination slightly disturbed
2	10-14	Consciousness continues, emotional upsets, abnormal fatigue upon exertion, disturbed respiration
3	6-10	Nausea and vomiting, unable to move freely, loss of consciousness may occur; may collapse and though aware of circumstances be unable to move or cry out
4	Below 6	Convulsive movements, gasping respiration; respiration stops and a few minutes later heart action ceases

<sup>9</sup> G. A. Burrell and F. M. Seibert, revised by G. W. Jones, *U.S. Bur. Mines Bull.* No. 197 (1926).

<sup>10</sup> A. B. Hooker, E. J. Coggeshall, and G. W. Jones, *U.S. Bur. Mines Repts. Investigations* No. 3527 (1937).

Mixtures of 2 per cent oxygen with nitrogen have been administered for 3 or 4 minutes in the treatment of certain forms of insanity<sup>11</sup> with only an occasional respiratory failure. There is almost immediate loss of consciousness, progressive stimulation of respiration, tachycardia and irregularity of heart action, muscular twitching, and opisthotonos. One or two inflations with oxygen are said to produce complete recovery. The suddenness with which oxygen-deficient atmospheres can cause unconsciousness and death may be explained as follows:

During the inhalation of normal air the arterial blood leaves the lungs about 95 per cent saturated with oxygen, and, with a subject standing at rest, the venous blood returns to the lungs about 60 to 70 per cent saturated. During 1 minute approximately 360 cc. of oxygen are used up. After a forced deep inspiration the normal lung volume is about 5 to 5.5 liters, 1 liter of which is oxygen, or nearly a 3-minute oxygen supply should the breath be held. However, when a subject inhales normally, the lung volume is only about 2.5 to 3 liters and if an oxygen-depleted atmosphere is inhaled at the rate of about 8 liters per minute, the 2.5 to 3 liters of atmosphere in the lungs is depleted of its oxygen by ventilation much more rapidly than by absorption. Since the initial effects of anoxia are increased rate of breathing and circulation, these processes are speeded up, the oxygen percentage in the lung atmosphere falls below 10 per cent, and the arterial blood supply to the brain very quickly (seconds, rather than minutes) becomes insufficiently oxygenated to maintain consciousness. Respiratory failure and cessation of heart action soon follow unless the subject is returned to respirable air.

There is considerable personal variation in susceptibility to anoxia. Because of impaired compensation, persons with cardiac and pulmonary deficiencies are more susceptible. Hyperthyroid persons normally consume more oxygen and are therefore more susceptible, while the reverse is true of hypothyroid persons. Whenever anoxia is prolonged, recovery is slow and there are apt to be sequelae such as hallucinations, excitement, headache, nausea, and apathy extending over several hours; these are thought to result from pressure of cerebral edema. When the anoxia is severe and prolonged, with unconsciousness, irreversible degenerative changes<sup>12</sup> in the nervous system, especially in the cerebral cortex and basal ganglia, may occur. These result in paralyses, amnesia, and other manifestations of permanent injury. The condition is perhaps more often seen following prolonged unconsciousness due to carbon monoxide poisoning. There is a marked difference in survival time<sup>13</sup> of different nerve tissues when cut off from their blood supply, the cerebrum and cerebellum having the shortest, 8 and 13 minutes, and the myenteric plexus longest, 180 minutes (see Table 9). Likewise, the cortical center of the brain can revive after an interruption of blood supply not to exceed 5 minutes, but the cardioregulatory, vasomotor, and respiratory centers may

<sup>11</sup> F. A. D. Alexander and H. E. Himwick, *Am. J. Physiol.*, 126, 418 (1939).

<sup>12</sup> A. T. Steegmann, *Arch. Neurol. Psychiat.*, 41, 955 (1939).

<sup>13</sup> C. K. Drinker, *Carbon Monoxide Asphyxia*. Oxford Univ. Press, New York, 1938.

survive up to 30 minutes interruption. It is evident, then, why severe anoxia, whether from the inhalation of an oxygen-deficient atmosphere or from any other cause, may result in cerebral damage even though respiration may not have stopped.

#### 4. *Warning Properties*

The warning properties of an atmosphere deficient in oxygen are completely inadequate and, although a trained observer may, when alert, recognize the increase in the pulse and rate of breathing in time to return to good air, the average individual fails to recognize the danger until he is too weak to save himself, especially where the return to good air involves climbing stairs or a ladder. The fire hazard of oxygen-deficient atmospheres is below normal and where the oxygen content of the air is below 16 per cent many common materials will not burn.

## OZONE

### 1. *Occurrence and Uses*

Ozone,  $O_3$ , in very small amounts, is a frequent and variable constituent of the atmosphere we breathe. During and following electrical storms it may reach sufficient concentrations to be readily recognizable by odor—on the order of 0.01 to 0.05 p.p.m. by volume. Reports of concentrations up to 100 times that amount in the outdoor air must be regarded with some skepticism. Ozone can be generated by a high-tension nonsparking discharge in air or oxygen. It is used for the sterilization of water; for bleaching oils, paper, and flour; for aging liquor; and in combating odors, in lieu of proper ventilation. Claims that ozone will detoxify exhaust gases, freshen or purify the air, kill bacteria in the atmosphere of inhabited spaces, and other equally fantastic feats have not been substantiated.

### 2. *Physical Properties*

Ozone has a molecular weight of 48.00. It is 1.7 times as dense as air. It melts at  $-251^\circ C.$  and boils at  $-112^\circ$ . Its solubility in water is 49 cc. in 100 ml. water at  $0^\circ C.$

1 mg./l.  $\approx$  509 p.p.m. and 1 p.p.m.  $\approx$  1.96 mg./cu.m. at  $25^\circ C., 760$  mm.

### 3. *Determination in the Atmosphere*

In the absence of other oxidizing gases such as nitrogen oxides and hydrogen peroxide, the atmosphere to be sampled may be scrubbed through an acidified solution of potassium iodide and titrated with 0.1 *N* sodium thiosulfate.<sup>14</sup> In the presence of interfering gases, the sample should first be scrubbed through chromic acid and potassium permanganate.

<sup>14</sup> M. B. Jacobs, *The Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

#### 4. Physiological Response

Ozone is very irritant to all mucous membranes and significant exposures may cause pulmonary edema. Its prolonged inhalation in concentrations above 0.05 p.p.m. is inadvisable because of the danger of pulmonary irritation. The effects of various concentrations have been tabulated by Witheridge and Yaglou<sup>15</sup> as given in Table 3.

TABLE 3  
*Effects of Ozone in Various Concentrations*

Observed effect	Concentration, p.p.m.
Threshold of odor, normal person.....	0.01-0.015
Maximum allowable concentration.....	0.04
Objectionable to all normal persons, irritates the nose and throat of most persons	0.10
Disorders breathing, reduces oxygen consumption, and shortens lives of guinea pigs.....	0.5-1.0
Inhibits fungus and mold growth in cold storage rooms.....	0.3-1.5
Headache, respiratory irritation, and possible coma.....	1-10
Lethal to small animals within 2 hours.....	15-20
Lethal in a few minutes.....	>1700
Germicidal for air-borne organisms.....	6500

These investigations confirmed the findings of others, that ozone does not destroy odors, but masks the odor and appears to "freshen" the air by lowering the perceptibility of odors. Odors of high intensity cannot be successfully masked by concentrations of ozone regarded as safe for prolonged inhalation. Flury and Zernik<sup>16</sup> state: (1) that men, when exposed to ozone, suffer eye, nasal, and throat irritation, cramps in the chest, frontal headache and vertigo, increasing fatigue, and lowering of blood pressure, owing to the centrally conditioned dilatation of the peripheral blood vessels; (2) that 0.5 p.p.m. causes distinct irritation; (3) that 1 p.p.m. for an hour causes cough and serious fatigue; and (4) that a brief period of inhalation of 5 to 10 p.p.m. accelerates the pulse and causes stupefaction and continuous body pain.

## NITROGEN

Nitrogen, N<sub>2</sub>, is a colorless, odorless, physiologically inert gas that normally constitutes about 78 per cent of the atmosphere by volume. Its molecular weight is 28.02. It melts at -209.86° C. and boils at -195.8°. Its solubility in water is 2.33 cc. at 0° C. and 1.02 cc. at 45° C. per 100 ml. water.

The only physiological effects due to inhalation of nitrogen result from oxygen dilution, and nitrogen must be present in sufficient amount to reduce the partial pressure of oxygen below about 100 mm. Hg equivalent before serious effects of

<sup>15</sup> W. N. Witheridge and C. P. Yaglou, *Trans. ASHVE*, 45, 509 (1939).

<sup>16</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

anoxia result (see Oxygen Deficiency, page 601). Saturation of the body with nitrogen occurs rapidly (page 188). During rapid lowering of the pressure of the environmental atmosphere, nitrogen may separate as bubbles in the tissue, capillaries, and veins, causing "bends" (see Chapter Six). Helium, because of its higher rate of diffusion, has been found useful<sup>17,18</sup> as an oxygen diluent in the prevention of "bends." Undiluted oxygen has likewise been used for this purpose.<sup>19</sup>

## NITROUS OXIDE

Nitrous oxide,  $N_2O$ , molecular weight 44.02, is a colorless gas having a sweetish taste. Its melting point is  $-102.4^\circ C.$  and its boiling point is  $-89.5^\circ$ . Its solubility in water is 60 cc. per 100 ml. of water at  $25^\circ C.$  It is weakly narcotic and is used as an anesthetic: where it is mixed with air, it acts chiefly as an asphyxiant by lowering the oxygen percentage; when mixed with oxygen, the percentage of nitrous oxide must be more than 80 in order to produce deep anesthesia. Nitrous oxide is of little interest to industrial hygienists.

## NITRIC OXIDE

Nitric oxide,  $NO$ , molecular weight 30.01, is a colorless gas slightly heavier than air. Its boiling point is  $-151.8^\circ C.$  and its melting point is  $-163.6^\circ$ . Its solubility in water is 7.34 cc. in 100 ml. water at  $0^\circ C.$

1 mg./l.  $\approx$  815 p.p.m. and 1 p.p.m.  $\approx$  1.23 mg./cu.m. at  $25^\circ C.$ , 760 mm.

Nitric oxide is rapidly oxidized in the air to nitrogen dioxide and so, for practical purposes, its toxicity need not be given marked attention, because the resulting nitrogen dioxide is much more insidious. Nitric oxide is not an irritant, but in animals it has been found to act upon the central nervous system to produce paralysis phenomena and convulsions.<sup>16</sup> It combines with hemoglobin and this is oxidized by oxygen in the blood to methemoglobin, with resultant anoxia.

Mice exposed to 2500 p.p.m. for 6 or 7 minutes were narcotized and death occurred within 12 minutes, but if the narcotized animals were returned to fresh air within 4 to 6 minutes, recovery was rapid.<sup>16</sup> Poisoning of man has not been reported.

## NITROGEN DIOXIDE AND NITROGEN TETROXIDE

### 1. Industrial Exposures

Nitrogen dioxide,  $NO_2$ , and its polymer nitrogen tetroxide,  $N_2O_4$ , are always found together at normal environmental temperatures. Nitrogen dioxide can be

<sup>17</sup> R. R. Sayers, W. P. Yant, and C. Hildebrand, *U.S. Bur. Mines Repts. Investigations* No. 2670 (1925).

<sup>18</sup> R. R. Sayers and W. P. Yant, *Anesthesia and Analgesia*, 5, 127 (1926).

<sup>19</sup> R. R. Jones, J. W. Crossen, F. E. Griffith, R. R. Sayers, H. H. Schrenk, and E. Levy, *J. Ind. Hyg. Toxicol.*, 22, 427 (1940).

used to nitrate benzene, anthracene, and naphthalene at 20 to 60° C. but has not been extensively applied. It is a by-product of many operations and results whenever nitric acid acts upon metals, as in bright dipping, pickling, and etching, or upon organic material, as in the nitration of cotton or other cellulose. It is a by-product of the manufacture of many chemicals including explosives, dyes, lacquers, and celluloid. It also results, in significant amounts, from the slow burning of explosives or the detonation of explosives having a high oxygen balance; from electric arcs or electric- and gas-welding or gas-shrinking operations in confined and unventilated areas; from the burning of nitrocellulose; from the accidental spillage of nitric acid; during operations incidental to the manufacture or recovery of nitric acid; from the reduction of nitrates as, for instance, in the accidental pollution of a molten nitrate salt, heat-treat bath with some readily oxidizable matter.

The brown mixture arising from the bright dipping of copper or brass, or from nitration reactions is essentially a pure mixture of  $\text{NO}_2$  and  $\text{N}_2\text{O}_4$ . So far as industrial exposures are concerned, it matters little whether the nitrogen oxides enter the air as  $\text{NO}$ ,  $\text{NO}_2$ , or  $\text{N}_2\text{O}_4$ , since the  $\text{NO}$  rather rapidly changes to  $\text{NO}_2$  and the  $\text{NO}_2$ - $\text{N}_2\text{O}_4$  balance mentioned in the next paragraph then comes into play. This mixture has frequently been erroneously referred to as nitrous fumes, but it is not nitrous oxide,  $\text{N}_2\text{O}$ , and it is a gaseous mixture not a fume. It may, for convenience, more properly be called nitrogen dioxide.

### 2. Physical Properties

Nitrogen dioxide is a dark chocolate-brown gas, with molecular weight 46.01. Its polymer, nitrogen tetroxide,  $\text{N}_2\text{O}_4$ , with molecular weight 92.02, is colorless. At  $-9.3^\circ\text{C}$ . and below, the oxides are a colorless solid composed completely of nitrogen tetroxide. At temperatures of  $135^\circ\text{C}$ . and above, the gas is a very dark chocolate-brown, composed essentially of  $\text{NO}_2$ . At temperatures within this range, the gases are always present as a mixture of the two. At  $37.5^\circ\text{C}$ ., the temperature of the body and therefore the temperature at which the gases react upon the human lung, the ratio of  $\text{NO}_2$  to  $\text{N}_2\text{O}_4$  is 30 to 70.<sup>20</sup> Both gases are frequently referred to as the dioxide, and computations such as the following conversion factors are almost always made on the same basis as though the mixture were all  $\text{NO}_2$ . The gas reacts with water to form a mixture of nitrous acid,  $\text{HNO}_2$ , and nitric acid,  $\text{HNO}_3$ . The relative proportions are frequently assumed to be equal, but may vary with circumstances.

1 mg./l.  $\approx$  532 p.p.m. and 1 p.p.m.  $\approx$  1.88 mg./cu.m. at  $25^\circ\text{C}$ ., 760 mm.

### 3. Determination in the Atmosphere

Perhaps the most satisfactory laboratory method of determining the concentration of nitrogen dioxide in the air is the phenoldisulfonic acid method described

<sup>20</sup> Y. Henderson and H. W. Haggard, *Noxious Gases*. 2nd ed., Reinhold, New York, 1943.

by Beatty, Berger, and Schrenk.<sup>21</sup> The method, however, is exacting and time consuming, and unless meticulous care is employed it frequently gives low results. It does not differentiate between the dusts of nitrates and nitrites, or between the brown oxide gases and nitric acid, and its result is in terms of the total as nitrates. A satisfactory field method<sup>22</sup> for the determination of nitrogen dioxide has been developed from the  $\alpha$ -naphthylamine-nitrite reaction. A sampling kit, with permanent dyed cellophane standards, Luer syringes, and reagent bottles, is available commercially.<sup>23</sup> The total time required for sampling and determination in the field is less than 10 minutes. Results obtained under controlled conditions in the laboratory, as well as in nitration plants, acid manufacture, bright dipping, welding, and mining operations, indicate that the method is reliable and convenient. Another method, applicable to various nitrogen compounds, has been proposed.<sup>24</sup> Samples collected by this method must be transported to a laboratory for evaluation, and the nitrogen compounds are determined as total nitrate.

#### 4. Physiological Response

*Acute effects.* Nitrogen dioxide, in concentrations from 100 to 1000 p.p.m. or more, caused death in five species of animals—cats, guinea pigs, mice, rats, and rabbits—by asphyxia resulting from pulmonary edema induced by irritation of the lung tissue.<sup>25</sup> As related to the concentrations of gas, the average durations

TABLE 4

*Concentrations of Nitrogen Dioxide and Average Time to Produce Death in Animals*

Concentration, p.p.m.	Time, min.
30.....	No deaths
100.....	318
150.....	90
400.....	58
600.....	32
800.....	29
1000.....	19

of exposure causing death were found to be as tabulated in Table 4. This indicates a higher order of toxicity, but is not in serious disagreement with findings reported by Flury and Zernik<sup>16</sup> for mice, rabbits, and cats as tabulated in Table 5.

<sup>21</sup> R. L. Beatty, L. B. Berger, and H. H. Schrenk, *U.S. Bur. Mines Repts. Investigations*, No. 3687 (1943).

<sup>22</sup> F. A. Patty and G. M. Petty, *J. Ind. Hyg. Toxicol.*, 25, 361 (1943).

<sup>23</sup> Mine Safety Appliances Co., Pittsburgh, Pa.

<sup>24</sup> H. Yagoda and F. H. Goldman, *J. Ind. Hyg. Toxicol.*, 25, 440 (1943).

<sup>25</sup> L. W. Latowsky, E. L. MacQuiddy, and J. P. Tollman, *J. Ind. Hyg. Toxicol.*, 23, 129 (1941).

TABLE 5  
*Concentrations of Nitrogen Dioxide and Time of Exposure Causing Death of Animals  
 within 24 Hours*

Concentration, p.p.m.	Time, min.
110- 125.....	360-420 (no effects)
225- 230.....	315-420
340- 410.....	60-105
1000.....	30- 50
3350-7500.....	8- 10

With man, concentrations considered dangerous for short exposures, above 50 p.p.m., are moderately irritating to the eyes and nasal passages. Higher concentrations, up to 150 p.p.m., cause an acid taste but are not painfully irritant. There have been many deaths resulting from acute exposure to nitrogen dioxide and, although there is little information on attendant atmospheric concentrations, there is reason to believe that the results of exposure of man are similar to those of animals, where death has been found to be due to asphyxia resulting from a pulmonary edema and not due to the effects of nitrite.

Most water-soluble, irritant gases exert their strongest effects at the earliest point of contact with moist mucous surfaces, but not so nitrogen dioxide. This difference has been accounted for by the fact that nitrogen dioxide hydrolyzes slowly in water or humid air to form nitrous and nitric acids. The theory is that during inhalation the relatively dry gas-air mixture reacts little with the slightly moist surfaces of the respiratory passages, whereas after reaching the alveoli the humid air, moist surfaces, and extended time promote almost complete hydrolysis in intimate contact with the alveolar tissue. According to Sollmann,<sup>26</sup> this always results in edema, and a person who has been exposed to lethal concentrations of nitrogen dioxide may feel no discomfort for several hours after the end of exposure, but as long as eight hours later may become distressed by the accumulation of fluid in his lungs. Whenever fluid collects in the lungs, it interferes with oxygen exchange and asphyxia may result. Symptoms may include weakness, a cold feeling, nausea, abdominal pain, coughing with a foamy yellow or brownish expectorate, accelerated heart action, severe cyanosis with convulsions. Sollmann<sup>26</sup> points out that the slightest exertion under such circumstances may produce dyspnea, cyanosis, cardiac dilatation, and collapse; and, when this situation terminates fatally, death occurs in most cases within 8 to 48 hours following exposure. Where the pulmonary edema is survived, infectious pneumonia is a probable sequela that may cause death some weeks later. It has been pointed out by von Oettingen<sup>27</sup> that acute nitrogen dioxide poisoning may not always follow the usual pattern, but may cause a reversible type, characterized by dyspnea,

<sup>26</sup> T. Sollmann, *A Manual of Pharmacology*. 6th ed., Saunders, Philadelphia, 1944.

<sup>27</sup> W. F. von Oettingen, *U.S. Pub. Health Bull.* No. 272 (1941).



cyanosis, vomiting, vertigo, somnolence, loss of consciousness, and methemoglobinemia, without pulmonary edema, from which the victim may recover completely if removed from exposure early. Another type, termed "shock type," is described in which a person exposed to a sudden, high concentration of nitrogen dioxide (and possibly nitric oxide) suffers asphyxiation, convulsions, and respiratory arrest. The similarity between nitrogen dioxide poisoning and phosgene poisoning is noteworthy.

*Chronic effects.* The nitrite effect, resulting from absorption of nitrous acid hydrolyzed from nitrogen dioxide, is a factor to be considered along with pulmonary irritation in prolonged exposure to concentrations between 25 and 100 p.p.m. In concentrations above 100 p.p.m. it is probable that the effects of irritation outweigh others. Adverse effects of exposures well below 25 p.p.m. have been reported by the Institute of Hygiene of Labor and Industrial Diseases, Leningrad,<sup>28</sup> but our experience in the United States does not lend support to these findings.

Men observed by the author working 6 to 8 hours daily in nitric acid recovery and fortification plants, where exposures ranged from 5 to 30 p.p.m. and averaged 10 to 20 p.p.m., for periods up to 18 months, evidenced no significant ill health nor were any characteristic adverse effects detected by periodic medical examinations.

From experimental exposures of guinea pigs and rats to filtered carbon-arc fumes, Tollman, MacQuiddy, and Schonberger<sup>29</sup> concluded that nitrogen dioxide inhaled in concentrations in excess of 100 p.p.m. 4 hours per day will lead, in time, to fatal results.

McCord, Harrold, and Meek,<sup>30</sup> studying the effects of welding fumes on rabbits and rats, found that exposure to fumes containing up to 24 p.p.m. nitrogen dioxide for 6 hours per day, 5 days a week, to a total of 45 days, produced an average of 2.9 per cent methemoglobin in rabbits and 15 per cent in rats; but they concluded that no permanent, harmful effects were demonstrated by prolonged exposure of rabbits and rats to atmospheres containing up to 70 p.p.m. nitrogen dioxide. They also reported 2.3 to 2.6 per cent methemoglobin in the blood of welders exposed to from 3.9 to 5.4 p.p.m. nitrogen dioxide, and suggest that methemoglobin might be useful as a measure of degree of exposure to welding fumes.

Other harmful effects, which are more or less common to all irritant acid gases, have been described by von Oettingen.

It has been stated that proof is lacking that nitrogen oxides, as such, are irritant. In support of the general opinion that they are irritant, it may be of

<sup>28</sup> N. A. Vigdortschik, E. C. Andreeva, I. Z. Matussevitsch, M. M. Nikulina, L. M. Frumina, and V. A. Striter, *J. Ind. Hyg. Toxicol.*, 19, 469 (1937).

<sup>29</sup> J. P. Tollman, E. L. MacQuiddy, and S. Schonberger, *J. Ind. Hyg. Toxicol.*, 23, 269 (1941).

<sup>30</sup> C. P. McCord, G. C. Harrold, and S. F. Meek, *J. Ind. Hyg. Toxicol.*, 23, 200 (1941).

interest to mention a personal experience concerning the action of the gas on normal dry skin. During the breaking of many glass ampules of pure nitrate-free  $\text{NO}_2\text{-N}_2\text{O}_4$  (purity attested by analysis at two different laboratories), whenever the liquid or the concentrated gas came in contact with the dry skin corrosion resulted. The corroded area had the same appearance that results from contact with nitric acid or its concentrated vapors except that the action was not as intense.

#### 5. *Warning Properties and Permissible Concentration*

The author has found the odor of nitrogen dioxide to be characteristic and distinct in concentrations below 5 p.p.m. In concentrations of 10 to 20 p.p.m. the gas is mildly irritant to the eyes, nose, and upper respiratory mucosa. There is very little difference in intensity of odor and irritation, however, between concentrations of 20 and 100 p.p.m. In well-lighted areas nitrogen dioxide-air mixtures of 100 p.p.m. or more nitrogen dioxide have a visible, reddish-brown tint. These properties of the gas can in no way be considered adequate warning. *It should be pointed out with emphasis that the ordinary type A, acid gas, or type AB, acid gas and organic vapor, canister gas masks, with soda-lime or soda-lime activated carbon fills, do not offer satisfactory protection against nitrogen dioxide gas.* This information appears in small print on the approval label.

Safe limits for nitrogen dioxide in air ranging from 5 to 70 p.p.m. have been proposed. The safe limit set by the American Standards Association is 25 p.p.m.

### NITROGEN CHLORIDE

Nitrogen chloride,  $\text{NCl}_3$ , is a yellowish, oily liquid, molecular weight 120.38, with a boiling point below  $71^\circ \text{C}$ . and a melting point below  $-40^\circ$ . Its vapor pressure is equivalent to about 150 mm. Hg at  $20^\circ \text{C}$ . It is relatively insoluble in water, but readily dissolves in carbon tetrachloride, chloroform, benzene, and carbon disulfide. It is subject to explosive decomposition from temperatures above  $60^\circ \text{C}$ ., from impact, or from the effect of supersonic waves.

1 mg./l.  $\approx$  203 p.p.m. and 1 p.p.m.  $\approx$  4.92 mg./cu.m. at  $25^\circ \text{C}$ ., 760 mm.

Possible industrial exposures occur in the bleaching of flour and fumigation of citrus fruit.

Vapor-air mixtures have a characteristic odor and are irritant to mucous membranes. Information on the degree of toxicity is not available, but according to Flury and Zernik,<sup>31</sup> nitrogen chloride is less irritant to the respiratory organs than is chlorine. The use of nitrogen chloride for bleaching flour has been criticized.

### NITROSYL CHLORIDE

Nitrosyl chloride,  $\text{NOCl}$ , is a yellowish gas, molecular weight 65.47, with a boiling point of  $-5.5^\circ \text{C}$ . and melting point of  $-64.5^\circ$ . It decomposes in water. Exposure may occur whenever aqua regia is made or used.

The gas is an irritant. Cats exposed 20 minutes to a concentration of 100

p.p.m. died with evidence of lung hemorrhage.<sup>31</sup> Other significant data have not been presented.

1 mg./l.  $\approx$  373 p.p.m. and 1 p.p.m.  $\approx$  2.68 mg./cu.m. at 25° C., 760 mm.

## AMMONIA

For a discussion of ammonia, NH<sub>3</sub>, see Alkaline Materials, Chapter Seventeen.

## CARBON MONOXIDE

Of all the gases that have poisonous effects upon man and animals, carbon monoxide is the most widely encountered. It exerts its effects by combining with the hemoglobin of the blood and interrupting the normal oxygen supply to the body tissues. Although this resultant oxygen deficiency is a reversible chemical asphyxia, nevertheless, damage done by severe asphyxia from any cause may not be reversible.

### 1. Industrial Exposures

Exposures to carbon monoxide in industry, or in private life, may occur whenever carbonaceous matter such as coal, wood, paper, oil, gas, gasoline, or any other organic material, is burned. Carbon monoxide is a product of incomplete combustion, and is not likely to result where a flame burns in an abundant air supply without contacting any surface. Whenever a flame touches a surface that is cooler than the ignition temperature of the gaseous part of the flame, carbon monoxide may result. Notorious in this respect are water heaters: the temperature of the water-filled coils cannot rise appreciably above the boiling point of water at the pressure involved; if a flame is allowed to play on the coils, a substantial amount of carbon monoxide is produced; and where the heater is not effectively vented to the exterior, contamination of the room atmosphere results.

Gas or coal heaters in the home and gas space heaters in industry have been frequent sources of carbon monoxide when not provided with effective vents. Gas heaters, though they may be properly adjusted when installed, may become hazardous sources of carbon monoxide if not correctly maintained. Automobile exhaust gas in garages, especially small private garages, is perhaps the most familiar source of carbon monoxide exposures.

Additional potential exposures occur in: the manufacture and use of illuminating gas, or "manufactured gas"; the manufacture of synthetic methanol or other organics from carbon monoxide; carbide manufacture; the distillation of coal or wood; operations near furnaces, ovens, stoves, forges, and kilns, which are especially likely to produce excessive carbon monoxide during the period in which they are being brought to normal operating temperature after a period of idleness; controlled atmosphere heat-treatment of metals; fire fighting; mines, following fires or the use of explosives; testing internal combustion engines; and many

<sup>31</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

other exposure sources. Salamander stoves are dangerous sources of carbon monoxide in poorly ventilated areas. Among the situations less commonly warranting concern are: faulty exhaust discharge equipment on automobiles, busses, airplanes, and cabin cruisers; improperly located air inlets for automobile interiors; and compressed air for respiratory protective devices when supplied by reciprocating compressors (rarely, carbon monoxide may occur due to excessive overheating of the compressor).

The extent of room atmospheric pollution by carbon monoxide from any source, as for instance an automobile, can be computed from the rate of production of carbon monoxide, where constant, and the amount of general ventilation by use of the formula,<sup>32</sup>

$$C = \frac{100K(1 - e^{-Rt})}{RV}$$

where  $C$  = per cent carbon monoxide in a room after a given time,  $t$ ,  $R$  = air changes per hour,  $t$  = time in hours,  $V$  = volume of room in cubic feet,  $K$  = cubic feet of carbon monoxide liberated per hour, and  $e$  = the base of the natural system of logarithms.

It is obvious from inspection of the formula that as  $R$  or  $t$  increases, the factor  $(1 - e^{-Rt})$  approaches 1 and equilibrium is reached—more quickly for larger values of  $R$ . Where  $V$  is relatively small the concentration builds up rapidly.  $100K/RV$  = the equilibrium concentration. This formula can be used in computing general ventilation rates, the concentration of any gas or vapor in the air, or the rate of admitting any gas or vapor to the room, providing all the other factors are known.

The amount of carbon monoxide produced by an automobile varies with the richness of the gasoline-air mixture, speed, temperature, piston displacement, and other factors, but has been found by Yant, Jacobs, and Berger<sup>33</sup> to approximate 30 to 100 cu.ft. per hour. The concentration of carbon monoxide in exhaust gas may exceed 6 or 7 per cent by volume. Yant<sup>33</sup> found 0.4 per cent carbon monoxide 10 minutes after starting a car in a closed 3000-cu.ft. garage, sufficient to cause unconsciousness in 10 to 12 minutes. The average amount to be expected in a 1500-cu.ft. garage with engine racing would be about 0.5 per cent at the end of 6 minutes and, assuming equal distribution, unconsciousness could occur in 5 to 8 minutes after the engine was started.

## 2. Physical Properties

Carbon monoxide is a colorless, odorless, nonirritant gas with a molecular weight of 28.01 and a density essentially the same as that of air, but slightly less. It melts at  $-207^{\circ}$  C. and boils at  $-190^{\circ}$ . Its solubility in water is 3.5 cc. per 100 ml. at  $0^{\circ}$  C. and 1.5 cc. at  $60^{\circ}$  C., and in alcohol, 20 cc. at  $20^{\circ}$  C.

<sup>32</sup> G. W. Jones, L. B. Berger, and W. F. Holbrook, *U.S. Bur. Mines Tech. Paper No. 337* (1923).

<sup>33</sup> W. P. Yant, W. A. Jacobs, and L. B. Berger, *Ind. Eng. Chem.*, 16, 1047 (1924).

### 3. Determination in the Atmosphere

As with so many other compounds, the choice of a method of determining carbon monoxide will depend upon many factors, and no one method is satisfactory for all circumstances. Perhaps the most widely used is the catalytic oxidation indicator, which may be of the recorder type,<sup>34</sup> or one of the portable types described on page 207. The pyrotannic acid method<sup>35</sup> is fairly reliable, accurate within less than 0.03 per cent when good standards are used. Standards supplied with a commercial device utilizing the pyrotannic acid method have been found to vary as much as 25 per cent. The iodine pentoxide method is slow and requires meticulous attention to details and possible interfering gases. It is reliable and has been widely used as a laboratory method.

The Haldane or Orsat gas absorption devices may be used in certain instances, and when only small samples are available. The carbon monoxide can be burned and the resultant carbon dioxide absorbed; or the carbon monoxide can be absorbed as such in a mixture of cuprous sulfate, beta naphthol, and sulfuric acid. The limit of accuracy of the Orsat is 0.2 to 0.4 per cent, and the Haldane 0.02 to 0.04 per cent.

The use of sealed palladium chloride ampules, containing palladium chloride in a water-acetone mixture, is a very convenient method of roughly estimating the carbon monoxide content of the air. When the ampule is crushed, the contents moisten its cotton covering and, when suspended in the air for 10 minutes, it blackens in relation to the concentration of carbon monoxide. The method is not satisfactory in temperatures approaching 0° F.

The above methods have been described in detail by Jacobs.<sup>36</sup> An additional laboratory method, which is dependable for low concentrations and requires only a small volume of sample, is described by Polis, Berger, and Schrenk.<sup>37</sup> The National Bureau of Standards recently developed a simple and practical indicator,<sup>38</sup> silica gel treated with sulfuric acid, ammonium molybdate, and palladium sulfate; these silica gel granules, contained in tubes, change color characteristically when air containing as little as 10 p.p.m. carbon monoxide is passed through the tube. The equipment is commercially available.

<sup>34</sup> S. H. Katz, D. A. Reynolds, H. W. Frevert, and J. J. Bloomfield, *U.S. Bur. Mines Tech. Paper No. 355* (1926).

<sup>35</sup> R. R. Sayers, W. P. Yant, and G. W. Jones, *U.S. Pub. Health Rept.*, 38, 2311 (1923) (Reprint No. 872).

<sup>36</sup> M. B. Jacobs, *The Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

<sup>37</sup> R. D. Polis, L. B. Berger, and H. H. Schrenk, *U.S. Bur. Mines Repts. Investigations No. 3785* (1944).

<sup>38</sup> M. Shepard, "A Preliminary Report on the NBS Colorimetric Indicating Gel for the Rapid Determination of Small Amounts of Carbon Monoxide," *Natl. Bur. Standards* (June 29, 1946).

#### 4. Determination in the Blood

The pyrotannic acid method<sup>35,39</sup> discussed under Determination in the Atmosphere is equally applicable to the determination of carbon monoxide in the blood. The Van Slyke<sup>40</sup> gasometric method, employing a manometric gas-analysis apparatus, requires a 2-ml. sample and is accurate to about  $\pm 0.025$  volume per cent carbon monoxide. Spectrophotometric methods<sup>41-43</sup> are rapid and of various degrees of accuracy.

Blood for CO determinations must be kept from contact with the air or the carbon monoxide will soon be displaced. Blood out of contact with air will retain its carbon monoxide for indefinite periods and is best preserved by adding 0.3 per cent sodium fluoride as anticoagulant. Carbon monoxide may be demonstrated in exhumed bodies, even months after death but, since the plasma and cells may not be in their original proportions, all determinations of CO in blood taken from bodies after death should be referred to the same sample after complete saturation with CO.

Any sample of blood to be transported or stored before the determination of CO is accomplished should be kept in well-filled and sealed containers. If blood is obtained from a puncture wound, it must be collected promptly into a measuring pipette or other container to exclude air or else part of the carbon monoxide will be displaced by oxygen.

#### 5. Physiological Response

*Acute effects.* The symptoms caused by various percentages of CO hemoglobin in the blood have been tabulated by Sayers and Yant<sup>44</sup> as given in Table 6.

TABLE 6  
*Symptoms Caused by Various Amounts of Carbon Monoxide Hemoglobin in the Blood*

Blood saturation in per cent of CO hemoglobin	Symptoms
0-10	No symptoms
10-20	Tightness across forehead; possibly slight headache, dilation of cutaneous blood vessels
20-30	Headache and throbbing in temples
30-40	Severe headache, weakness, dizziness, dimness of vision, nausea, vomiting, and collapse
40-50	Same as previous item with more possibility of collapse and syncope, and increased respiration and pulse
50-60	Syncope, increased respiration and pulse, coma with intermittent convulsions, and Cheyne-Stokes respiration
60-70	Coma with intermittent convulsions, depressed heart action and respiration, and possibly death
70-80	Weak pulse and slow respiration, respiratory failure, and death

<sup>35</sup> R. R. Sayers and W. P. Yant, *U.S. Bur. Mines Tech. Paper No. 373* (1927).

<sup>40</sup> P. B. Hawk and O. Bergeim, *Practical Physiological Chemistry*, 11th ed. Blakiston, Philadelphia, 1937.

<sup>41</sup> B. L. Horecker and F. S. Brackett, *J. Biol. Chem.*, 152, 669 (1944).

<sup>42</sup> H. Hartman, *Ergeb. Physiol. biol. Chem. exptl. Pharmakol.*, 39, 413 (1937).

<sup>43</sup> R. R. Sayers, F. V. Meriwether, and W. P. Yant, *U.S. Pub. Health Repts.*, 37, 1127 (Reprint No. 748).

<sup>44</sup> R. R. Sayers and W. P. Yant, *U.S. Bur. Mines, Repts. Investigations No. 2476* (1923).

In carbon monoxide poisoning, as in any other form of asphyxia, there are many factors that may cause a greater susceptibility than the average. Notable among these factors as pointed out by Drinker<sup>45</sup> are: any impairment in circulation, heart disease in any form, anemia, asthma, lung impairment, any condition that speeds metabolism, any increase in activity, high temperature and high humidity, and low barometric pressure (high altitude).

Carbon monoxide combines with hemoglobin and reaches a state of equilibrium more slowly in low concentrations as shown in Table 7. The rate of combining is more rapid at first and slows as equilibrium is approached as indicated graphically in Figure 1. Both the rate of combining and the symptoms of poisoning are increased by exercise.

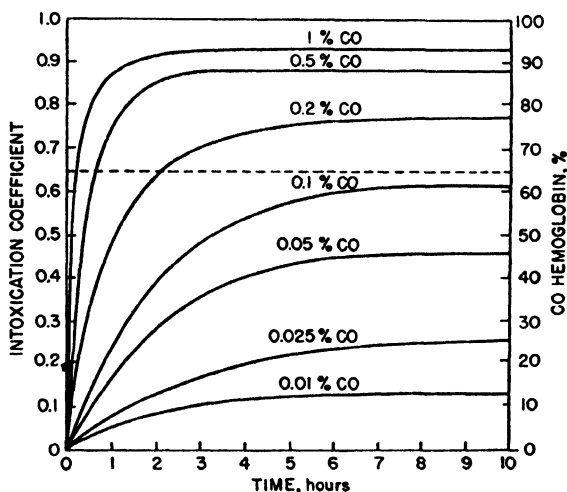


FIG. 1. Speed of saturation of hemoglobin with different concentrations of CO until equilibrium between the concentration of CO in air and blood is produced.<sup>46</sup>

TABLE 7

*Time for Various Concentrations of Carbon Monoxide to Produce 80 Per Cent Equilibrium Value of Blood Saturation<sup>44</sup>*

CO in air (inclusive), vol. per cent	Percentage blood satn. (80% of approx. equil. values)	Time, hours
0.02-0.03	23-30	5-6
0.04-0.06	36-44	4-5
0.07-0.10	47-53	3-4
0.11-0.15	55-60	1 <sup>1</sup> / <sub>2</sub> -3
0.16-0.20	61-64	1-1 <sup>1</sup> / <sub>2</sub>
0.20-0.30	64-68	1 <sup>1</sup> / <sub>2</sub> -3 <sup>1</sup> / <sub>4</sub>
0.30-0.50	68-73	20-30 (min.)
0.50-1.00	73-76	2-15 (min.)

<sup>45</sup> C. K. Drinker, *Carbon Monoxide Asphyxia*. Oxford Univ. Press, New York, 1938.

<sup>46</sup> W. F. von Oettingen, *U.S. Pub. Health Bull.* No. 290 (1944).

As with many other gases, the degree of harm from carbon monoxide is a product of concentration times the length of exposure. Henderson and Haggard<sup>47</sup> have proposed the following equations as a rough guide in estimating probable effects—obviously it does not apply to exposures longer than a few hours:

Hours × p.p.m. = 300	(no perceptible effect)
Hours × p.p.m. = 600	(just perceptible effect)
Hours × p.p.m. = 900	(headache and nausea)
Hours × p.p.m. = 1500	(dangerous to life)

The more precise figures (Table 8) of Henderson, Haggard, Teague, Prince, and Wunderlich<sup>48</sup> are also of interest.

TABLE 8  
*Physiological Response to Various Concentrations of Carbon Monoxide*

Response	CO, p.p.m. by vol. in air	Volume per cent
Concentration allowable for an exposure of several hours.....	100	0.01
Concentration inhaled for 1 hr. without appreciable effect.....	400- 500	0.04-0.05
Concentration causing just appreciable effects after 1 hr. of exposure	600- 700	0.06-0.07
Concentration causing unpleasant, but not dangerous, symptoms after 1 hr. of exposure....	1000-1200	0.1 -0.12
Dangerous concentration for exposure of 1 hr.....	1500-2000	0.15-0.2
Concentrations fatal in exposures of less than 1 hr.....	4000 and above	0.4 and above

Persons suffering prolonged unconsciousness from exposure to carbon monoxide may have permanent ill effects. As described by Drinker,<sup>45</sup> these include, rarely, damage to the heart, blood vessels, and various visceral organs, but more frequently to the brain and the nervous system. The most common neurological sequela of carbon monoxide poisoning is the "basal ganglia syndrome" as a result of injury to the brain tissue from anoxemia.

The dissociation curve of oxyhemoglobin in the presence of various quantities of CO hemoglobin, Figure 2, illustrates why a normal person with 50 per cent saturation with carbon monoxide is unable to undergo physical exertion comparable to that of an anemic person with only 50 per cent of the normal amount of hemoglobin.

If the oxygen saturation of the available hemoglobin of the venous blood of each person is reduced to say 75 per cent at rest, the anemic person has a remaining tension of oxygen of 44 mm. while the person with 50 per cent carbon monoxide saturation will have only 28 mm. of oxygen tension. Then if each person exercises, the venous blood becomes less saturated with oxygen—say 60 per cent—and the anemic person retains a partial pressure of around 36 mm. of oxygen,

<sup>47</sup> Y. Henderson and H. W. Haggard, *Noxious Gases*. 2nd ed., Reinhold, New York, 1943.

<sup>48</sup> Y. Henderson, H. W. Haggard, M. C. Teague, A. L. Prince, and R. M. Wunderlich, *J. Ind. Hyg.* 3, 79, 137 (1921).



which is still ample to oxidize tissue but the person with 50 per cent CO hemoglobin has suffered a drop in oxygen tension to less than 20 mm., which is probably insufficient to prevent fainting.<sup>49</sup> Other factors influence the dissociation of both oxyhemoglobin and CO hemoglobin: carbon dioxide, for instance, enhances the dissociation of each.

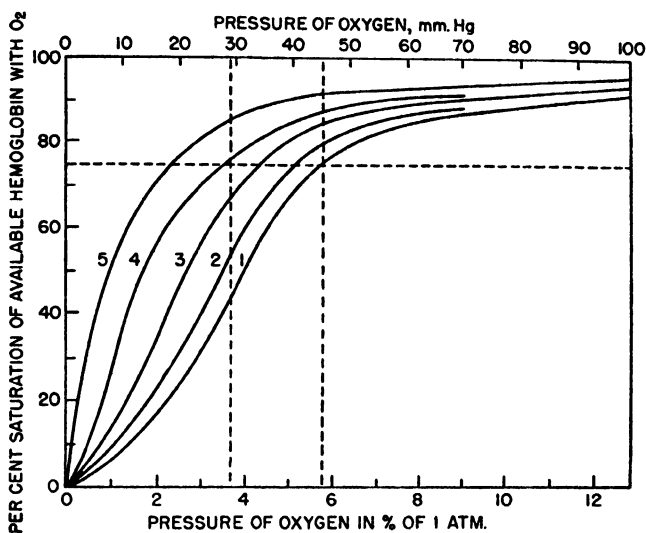


FIG. 2. Dissociation of oxyhemoglobin in the presence of various quantities of carbon monoxide hemoglobin: 1 = 0 per cent, 2 = 10 per cent, 3 = 25 per cent, 4 = 50 per cent, 5 = 75 per cent.<sup>48</sup>

*Chronic effects.* The well-known effects of prolonged exposure to carbon monoxide are no different from the acute effects: headache, nausea, impaired senses, general debility, weakness, vertigo, and ataxia. Increase in hemoglobin and red cells as well as many more obscure effects have been attributed to chronic poisoning, some of them being reputed sequelae of acute poisoning as well. In evaluating such statements as far as acute poisoning is concerned, proof of prolonged unconsciousness should be an important factor; and, in the case of chronic poisoning, the certainty and degree of exposure and of carbon monoxide absorption are of vital concern.

Claims have been made of permanent, harmful effects from prolonged exposure to low concentrations of carbon monoxide, but they are not readily substantiated. Such possibilities have been discussed by von Oettingen<sup>48</sup> and have been demonstrated<sup>50</sup> in dogs. Every smoker, as well as everyone present in a room

<sup>48</sup> For a more complete discussion of the physiology of this situation, consult page 18 of Drinker's *Carbon Monoxide Asphyxia*.

<sup>50</sup> F. H. Lewey and D. L. Drabkin, *Am. J. Med. Sci.*, 208, 502 (1944).

filled with tobacco smoke, is exposed to small amounts of carbon monoxide. Cigarette smoke, as inhaled, contains 200 to 800 p.p.m. carbon monoxide, while cigar or pipe tobacco smoke has considerably more, and smokers' blood may become saturated with carbon monoxide to the extent of 5 per cent or greater within a period of 2 hours.<sup>51</sup>

That repeated exposures of persons to low but significant amounts of carbon monoxide do not ordinarily cause permanent ill effects has been demonstrated many times by carefully controlled experiments. Sayers, Meriwether, and Yant<sup>43</sup> exposed men to 200, 300, and 400 p.p.m. for periods of 6 hours, several times, during which their blood reached 15 to 28 per cent saturation with carbon monoxide. There were no indications of prolonged ill effects at the time, and any one who knows the subjects would feel certain they have suffered no cerebral damage or other permanent ill effects.

Again, Sayers, Yant, Levy, and Fulton<sup>52</sup> subjected 6 men, 4 to 7 hours daily for 68 days, to exhaust gas containing concentrations ranging from 200 to 400 p.p.m. carbon monoxide. The blood of these men acquired 20 to 40 per cent CO hemoglobin upon each of the 68 days, and the men suffered the usual acute symptoms. Although these men were subjected to exhaustive examinations and tests, no symptoms of a permanent or semipermanent nature were found during or following the exposures, other than a significant increase in hemoglobin and red cells, a few instances of urinary sugar, and a slight tendency toward poorer performance on a prolonged steadiness test. There were no apparent signs that the exposures produced deleterious effects upon the health and physical well-being of the subjects at the time or in the years following these experiments.

Considerably more convincing evidence of the absence of any signs of chronic carbon monoxide poisoning, especially where exposures are too low to cause acute symptoms, is the report by Sievers, Edwards, Murray, and Schrenk<sup>53</sup> on the results of clinical and laboratory examinations of 156 traffic officers stationed in the Holland tunnel in New York. These men had been on duty 13 years in an exposure which averaged 65 to 85 p.p.m. carbon monoxide from exhaust gas, and the CO hemoglobin in their blood ranged from 0.5 to 13.1 per cent. They were found to be in exceptionally good physical condition.

*Pathology.* Carbon monoxide poisoning has been variously reported to have caused a vast assortment of ailments involving injury to practically all visceral organs.<sup>46</sup> No very satisfactory evidence has ever been presented, however, to indicate that permanent ill effects in men or animals are to be expected from a single acute exposure to carbon monoxide where the exposed person or animal remains conscious throughout.

<sup>51</sup> G. W. Jones, W. P. Yant, and L. B. Berger, *U.S. Bur. Mines Repts. Investigations No. 2539* (1923).

<sup>52</sup> R. R. Sayers, W. P. Yant, E. Levy, and W. B. Fulton, *U.S. Pub. Health Bull. No. 186* (1929).

<sup>53</sup> R. F. Sievers, T. I. Edwards, A. L. Murray, and H. H. Schrenk, *J. Am. Med. Assoc.*, 118, 585 (1942).

Where poisoning is severe enough to cause unconsciousness, however, some damage to the brain, central nervous system, and circulation may occur, related in degree to the length and severity of the asphyxia. The following tabulation<sup>45</sup> shows the survival time of different nerve tissues when completely deprived of blood, and readily explains the often observed loss of cerebation in individuals severely poisoned by carbon monoxide.

TABLE 9  
*Survival Time of Nerve Tissues When Deprived of Blood*

Tissue	Survival time, min.
Cerebrum, small pyramidal cells.....	8
Cerebellum, Purkinje's cells.....	13
Medullary centers.....	20-30
Spinal cord.....	45-60
Sympathetic ganglia.....	60
Myenteric plexus.....	180

Single exposures of dogs to concentrations of carbon monoxide causing unconsciousness and death within 30 minutes produced circulatory changes characterized by dilatation, stasis, perivascular hemorrhage, and edema. There were diffuse degenerative changes throughout the entire brain.<sup>54</sup> The neuropathology was quite similar to that resulting from asphyxiation by nitrogen in a similar time. Dogs dying in 11 to 15 minutes showed considerably less damage; while dogs kept in a state of unconsciousness and near death for several hours, by exposure to carbon monoxide, evidenced much more extensive damage; and dogs surviving this exposure for periods up to 165 days supplied evidence that much of the damage to the brain was of a permanent nature.

#### 6. Absorption and Elimination

*Absorption.* Carbon monoxide is absorbed only through the lungs, where it enters the blood stream in the same manner as does oxygen. Carbon monoxide exerts its acute harmful effects by displacing oxygen in the blood. It has a greater affinity for hemoglobin than has oxygen and therefore forms a more stable compound. Douglas and Haldane<sup>55</sup> found that hemoglobin in equilibrium with atmospheres containing carbon monoxide and not less than 14 per cent oxygen was all in combination with one or the other of these gases and that the affinity of carbon monoxide for hemoglobin was approximately 300 times as great as that of oxygen. The relation<sup>47</sup> between the partial pressures of oxygen and carbon monoxide in the lungs and their combinations with hemoglobin can be expressed by the equations on the following page:

<sup>54</sup> W. P. Yant, J. Chorynak, H. H. Schrenk, F. A. Patty, and R. R. Sayers, *U.S. Pub. Health Bull.* No. 211 (1934).

<sup>55</sup> C. G. Douglas, J. S. Haldane, and J. B. S. Haldane, *J. Physiol.*, 44, 275 (1912).

$$\frac{\text{PCO} \times 300}{\text{PO}_2} = \frac{\text{COHb}}{\text{O}_2\text{Hb}} \text{ and}$$

$$\text{Per cent CoHb} = \frac{\text{PCO} \times 300 \times 100}{\text{PO}_2 + (\text{PCO} \times 300)}$$

where Hb represents hemoglobin, and PCO and PO<sub>2</sub> represent the partial pressures of carbon monoxide and oxygen, respectively.

Prince<sup>56</sup> pointed out that this relation made it easy to compute the concentration of carbon monoxide in an atmosphere that is in equilibrium with blood, where the partial pressure of oxygen and the amount of hemoglobin combined

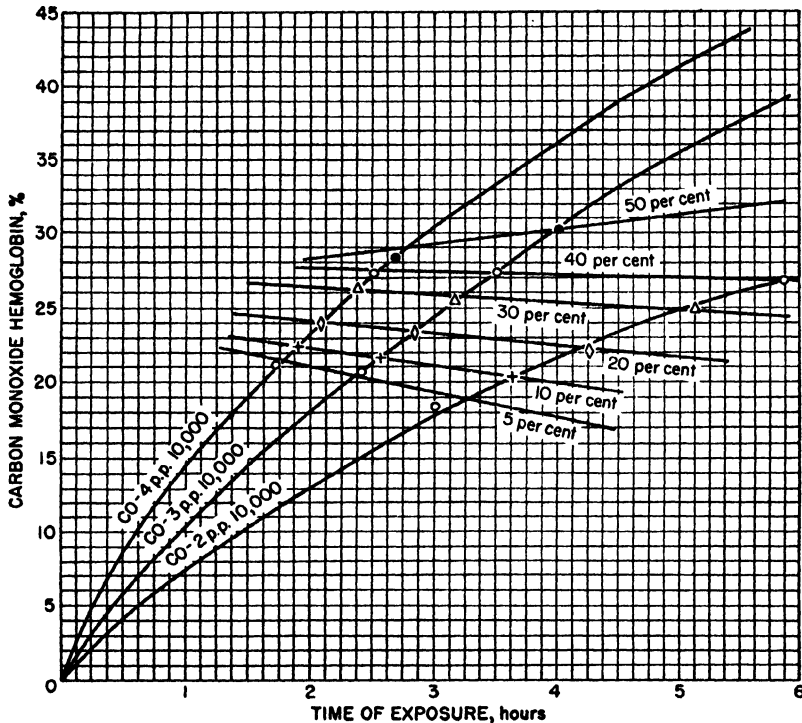


FIG. 3. Rate of saturation of blood with carbon monoxide, subjects exercising mildly during exposures to 200, 300, and 400 p.p.m. carbon monoxide. The per cent lines refer to the frequency of frontal headaches.<sup>53</sup>

with either oxygen or carbon monoxide is known. Sayers, Yant, and Jones<sup>57</sup> developed a convenient method for the determination of CO hemoglobin and applied it to the determination of carbon monoxide in the air. Henderson and Haggard<sup>47</sup> have pointed out that in using this formula to compute concentrations of CO hemoglobin in the body, or concentrations of carbon monoxide inhaled, the

<sup>53</sup> A. L. Prince, *Report of New York State Bridge and Tunnel Commission, Sec. 9, Appendix 4, p. 188 (1921).*

partial pressure of the gases in the lungs must be used, and this is given as 15 per cent for oxygen. At equilibrium the partial pressure of carbon monoxide upon inhalation would be reduced somewhat, but not to such an extent as that of oxygen, the reduction being primarily due to increase in the partial pressure of water vapor. Recent information<sup>58</sup> indicates that the ratio of CO hemoglobin to oxyhemoglobin is 210 instead of the previously believed 300 and, in that case, the factor 210 should replace 300 in the formulas above.

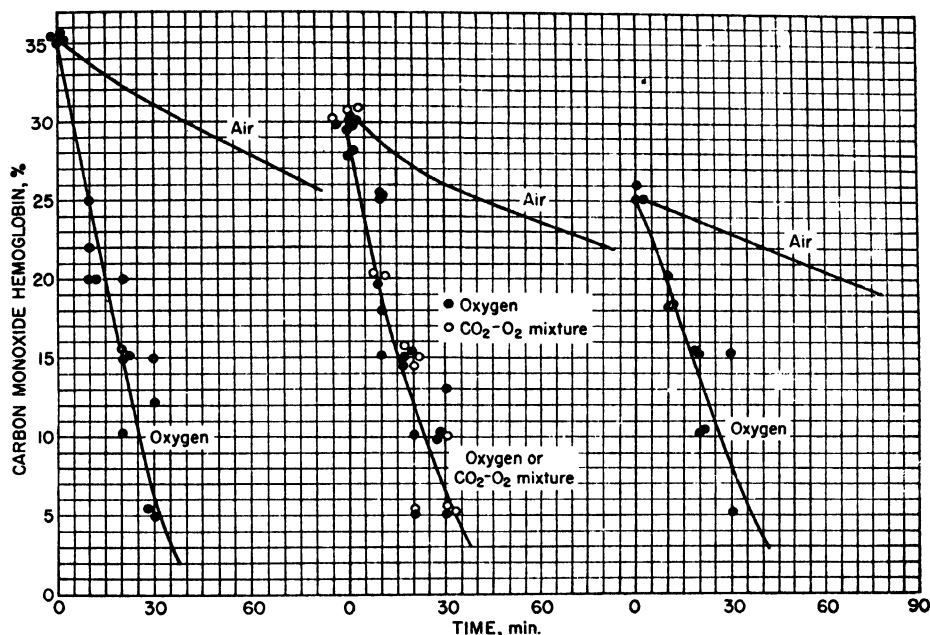


FIG. 4. Elimination of carbon monoxide from the blood as effected by breathing oxygen or a mixture of 5 per cent carbon dioxide in oxygen.<sup>58</sup>

Henderson and Haggard<sup>47</sup> determined that an average adult man at rest inhaling carbon monoxide absorbs enough in one hour to reach a maximum of 50 per cent of the equilibrium figure. Experiments conducted at the United States Bureau of Mines<sup>52,59</sup> with carbon monoxide-air mixtures support this finding, in that men exposed to concentrations of 200 to 400 p.p.m. acquired in 1 hour a maximum of 45 per cent of the expected equilibrium value at rest, only slightly over 50 per cent of the equilibrium value at strenuous exercise, and somewhat less

<sup>57</sup> R. R. Sayers, W. P. Yant, and G. W. Jones, *U.S. Pub. Health Repts.* 38, 2311 (1923) (Reprint No. 872).

<sup>58</sup> J. L. Lilienthal, Jr., R. L. Riley, D. D. Proemmeland, and R. E. Franke, *Am. J. Physiol.* 146, 351 (1946).

<sup>59</sup> R. R. Sayers, F. V. Meriwether, and W. P. Yant, *U.S. Pub. Health Repts.*, 37, 1127 (1922) (Reprint No. 748).

than 50 per cent with mild exercise. This last is indicated by the absorption curves shown in Figure 3.

In the development of safety standards the figure of 50 per cent of equilibrium as being the maximum attainment in 1 hour for adults at rest or doing light work may be utilized in connection with atmospheric pollution with CO below 0.1 per cent.

*Elimination.* The elimination of carbon monoxide is solely through the lungs and similar in many ways to the absorption. Although elimination is rapid at first, the last traces are eliminated very slowly. Exercise speeds elimination but is inadvisable because it may cause collapse. Increasing the partial pressure of oxygen by inhaling pure oxygen, or oxygen with 5 to 7 per cent carbon dioxide added, speeds the elimination. Curves presented by Sayers and associates<sup>52</sup> as portraying the elimination of carbon monoxide are reproduced in Figure 4. For each percentage saturation with CO, the upper curve shows the elimination when breathing air, and the lower one, when breathing oxygen.

### **7. Permissible Limit**

One hundred parts per million has been adopted by the American Standards Association as the maximum average concentration of carbon monoxide for work-room air where the exposure may be of several hours' duration. Other values for brief exposures can be taken from Table 8.

### **8. Inflammability and Warning Properties**

Carbon monoxide is inflammable within the range of 12.5 per cent and 74.2 per cent by volume in air (see Chapter Thirteen) and it has no warning properties.

## **CARBON DIOXIDE**

### **1. Uses and Industrial Exposures**

Carbon dioxide is a normal constituent of the atmosphere, about 0.31 per cent by volume; the exhaled breath contains up to 5.6 per cent; the gas is also widely encountered in industry in harmless concentrations. Carbon dioxide may be recovered from lime or cement kilns, from flue gases, from fermentation processes, and from some natural gas wells. It is first purified, then dehydrated, and compressed. If solid carbon dioxide, "dry ice," is desired, it is then manufactured from the compressed liquid. When the pressure upon this compressed, liquefied CO<sub>2</sub> is suddenly released, a portion of it solidifies to "snow" as the balance expands to a gas again and is drawn off and recompressed. The snow is then pressed into 220-lb. blocks of solid "dry ice." The compressed and bottled gas is used for carbonating beverages and the "dry ice" is used for preserving foods, especially during transportation. Other incidental uses are for chilling aluminum rivets and shrinking cylinder liners or bearing inserts. Industrial exposures may occur in mines, caves, tunnels, wells, the holds of ships, as well as tanks, vats, or any place where fermentation processes may have depleted the

oxygen with formation of carbon dioxide. The manufacture, storage, and use of "dry ice" also offers exposures, as do carbon dioxide fire extinguishers when operated in confined areas.

## 2. Physical and Chemical Properties

Carbon dioxide,  $\text{CO}_2$ , has a molecular weight of 44.01 and is about 1.5 times denser than air. It melts at  $-56.6^\circ \text{C}$ . under 5.2 atm. pressure, and sublimates under ordinary atmospheric pressure at  $-78.5^\circ$ . One hundred milliliters of water at  $0^\circ \text{C}$ . dissolves about 180 ml. carbon dioxide, and half that amount at  $20^\circ \text{C}$ . Carbon dioxide has no odor, but in high concentrations it causes a prickly sensation to mucous membranes. Its solution in water is weakly acid.

1 mg./l.  $\approx$  approximately 556 p.p.m. and 1 p.p.m.  $\approx$  approximately 1.8 mg./cu.m. at  $25^\circ \text{C}$ ., 760 mm.

## 3. Determination in the Atmosphere

From the viewpoint of industrial hygiene there is seldom occasion for making an analysis of the air for carbon dioxide. The Haldane or Orsat gas absorption devices (see page 206) are convenient means of estimation. In the absence of interfering alkaline or acid materials, air to be analyzed may be aspirated through a scrubber containing standard bicarbonate solution and phenolsulfonphthalein indicator, and the air concentration of carbon dioxide determined by comparison with prepared color standards.<sup>60</sup> The color developed is not influenced by volume or rate of sampling but depends entirely upon the percentage of carbon dioxide in the air. Circumstances requiring the analysis will also dictate the choice of method, from among these or other methods, of which there are many.

## 4. Physiological Response

*Acute effects.* Except as a contributor to oxygen deficiency, a very real danger, carbon dioxide does not offer serious industrial exposures. The initial effect of inhalation of excessive carbon dioxide is noticed in concentrations of about 2 per cent, 20,000 p.p.m., when the breathing becomes deeper and the tidal volume is increased.<sup>61</sup> The depth of respiration is markedly increased at 4 per cent; at 4.5 to 5 per cent breathing becomes labored, and distressing to some individuals. Concentrations of 8 to 10 per cent have been inhaled by men for periods up to 1 hour with no evident, harmful effects. The role of carbon dioxide in oxygen deficiency need not be elaborated upon, as it acts similarly to any other diluent gas. It is worth noting that in many instances the carbon dioxide may have been formed by processes, such as combustion or fermentation, that were at the same time depleting the oxygen supply in the air. Up to 10 per cent of carbon dioxide mixed with oxygen is given therapeutically<sup>62</sup> to improve respiration and lung ventilation and hasten the elimination of anesthetic gases or carbon monoxide.

<sup>60</sup> H. L. Higgins and W. M. Marriott, *J. Am. Chem. Soc.*, 39, 68 (1917).

<sup>61</sup> T. Sollman, *A Manual of Pharmacology*. 6th ed., Saunders, Philadelphia, 1944.

<sup>62</sup> Y. Henderson and H. W. Haggard, *Noxious Gases*. 2nd ed., Reinhold, New York, 1943.

*Chronic effects.* Although repeated, daily 1-hour exposures to 8 per cent carbon dioxide increased the hemoglobin and red cells, and improved the gaseous exchange in the blood, no marked, deleterious effects were observed.<sup>63</sup> Cohn, Tannenbaum, Thalimer, and Hastings,<sup>64</sup> however, warn against such a procedure in the presence of pneumonia or other pulmonary or cardiovascular diseases. In such diseases excessively rapid or deep respirations are an added burden to an already overburdened respiratory and cardiovascular system.

There appears no reason to establish a maximum permissible concentration for carbon dioxide. Its percentage is usually a corollary to the more important factor of oxygen percentage.

## PHOSGENE

### 1. Uses and Industrial Exposures

Phosgene may be encountered in certain chemical manufacturing operations, where it is used in many organic syntheses. It is also used in metallurgy to separate ores by chlorination of the oxides and volatilization. It is produced commercially by the catalytic chlorination of carbon monoxide and supplied in liquid form in steel cylinders. It was an effective combat gas used in chemical warfare from 1915 to 1918. Its chief importance in industrial hygiene, however, lies in its occurrence as one of the products of combustion whenever a volatile chlorine compound, such as a chlorinated solvent or its vapor, comes in contact with a flame or very hot metal. This ordinarily does not produce a serious threat to health except where ventilation is not satisfactory, the area is confined, or considerable quantities of chlorinated vapors are involved. It may be encountered in the use of carbon tetrachloride<sup>65</sup> for extinguishing fires in confined spaces.

### 2. Physical and Chemical Properties

Phosgene,  $\text{COCl}_2$ , carbonyl chloride, is an irritant gas with a distinctive odor sometimes described as that of musty hay. Anyone, who wishes to recognize or identify the odor, may generate a quantity ample for such a purpose by placing a drop or two of carbon tetrachloride, on a glass rod, into the reducing cone of a Bunsen burner flame. Phosgene has a molecular weight of 98.92. The concentrated gas is about 3.4 times as dense as air, but gas-air mixtures in the lower toxic range have the same density as air. It melts at  $-104^\circ \text{C}$ . and boils at  $8.3^\circ$ . Phosgene dissolves freely in many solvents, but in water decomposes to hydrochloric and carbonic acids. While the dry gas is noncorrosive to steel and only moderately so to tissue, the moist gas hydrolyzes to hydrogen chloride and carbon dioxide and the nascent hydrogen chloride is quite active.

<sup>63</sup> W. Tomaszewski, J. Oszacki, and E. Dumoulin, *J. Am. Med. Assoc.*, 108, 1016 (1937).

<sup>64</sup> D. J. Cohn, A. Tannenbaum, W. Thalimer, and A. B. Hastings, *J. Biol. Chem.*, 128, 109 (1939).

<sup>65</sup> W. P. Yant, J. C. Olsen, H. H. Storch, J. B. Littlefield, and L. Scheffan, *Ind. Eng. Chem., Anal. Ed.*, 8, 20 (1936).



1 mg./l.  $\approx$  247 p.p.m. and 1 p.p.m.  $\approx$  4.05 mg./cu.m at 25° C., 760 mm.

### 3. Determination in the Air

The best method for the determination of phosgene in concentrations of 2 p.p.m. or greater is the diphenylurea<sup>65</sup> method, but for concentrations below this amount the method requires more than ordinarily careful technique and is not reliable. These low concentrations can be determined more satisfactorily, perhaps, by the use of phosgene test paper.<sup>66,67</sup>

### 4. Physiological Response

Phosgene is mildly irritant to mucous surfaces in concentrations below 10 p.p.m., and very irritant to the entire respiratory tract in considerably higher concentrations. A single, shallow respiration of a moderately high concentration causes a rasping, burning sensation in the nose, pharynx, and larynx that is not readily forgotten. One-half part per million by volume of phosgene can be recognized in air, through the sense of smell, by normal persons acquainted with its odor, and 1 p.p.m. is easily noticeable. At 2 p.p.m., the odor is moderately strong and the irritant action on eyes, nose, and throat is barely detectable.

The principal action of phosgene is that of a lung irritant. Only a relatively small portion of the inhaled gas hydrolyzes in the respiratory passages, but in the moist atmosphere of the terminal spaces of the lungs complete hydrolysis occurs with irritant effects upon the alveolar walls and blood capillaries.<sup>68</sup> The result of this action is a gradually increasing edema, until as much as 30 to 50 per cent of the total blood plasma has accumulated in the lungs, causing "dry land drowning." The air spaces grow less and less; the blood is thickened by loss of plasma, which results in slowed circulation; oxygen exchange is slowed; and the overworked heart, with insufficient oxygen, weakens. The end result may be either asphyxiation or heart failure, and this may be delayed. High concentrations of phosgene are immediately corrosive to lung tissue and result in sudden death by suffocation.

The normal responses to slight gassing are, besides a dryness or burning sensation in the throat, numbness, vomiting, pain in the chest, bronchitis, and possibly dyspnea. There is sometimes a latent effect: the period between inhaling low concentrations of the gas and the appearance of dyspnea may be several hours, almost free of symptoms. The action of phosgene and its sequelae resemble in some respects those of nitrogen dioxide (see section on Nitrogen Dioxide). Flury and Zernik give the following table of response to various concentrations of phosgene in air.

<sup>65</sup> A. C. Fieldner, G. G. Oberfeld, M. C. Teague, and J. N. Lawrence, *Ind. Eng. Chem.*, 11, 519 (1919).

<sup>66</sup> F. A. Patty, *Am. J. Pub. Health*, 30, 1191 (1940).

<sup>67</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

TABLE 10  
*Physiological Response to Phosgene Gas*

Response	Concentration, p.p.m.
Maximum amount for prolonged exposure.....	1
Dangerous to life, for prolonged exposure.....	1.25- 2.5
Cough or other subjective symptoms within 1 min.....	5
Irritation of eyes and respiratory tract in less than 1 min...	10
Dangerous to life in 30 to 60 min.....	12.5
Severe lung injury within 1 to 2 min.....	20
Dangerous to life for as little as 30 min.....	25
Rapidly fatal (30 min. or less).....	90

### 5. *Warning Properties*

The odor is characteristic and can be recognized even in safe concentrations by the trained observer, but the odor and irritant properties of the gas are wholly inadequate to cause persons to avoid dangerous exposures.

### *Metal Carbonyls*

Carbonyls of nickel, chromium, iron, cobalt, molybdenum, ruthenium, tungsten, rhenium, osmium, and iridium have been prepared.

Iron carbonyl has been prepared in three combinations,  $\text{Fe}(\text{CO})_4$  and  $\text{Fe}_2(\text{CO})_9$ , which are crystalline, and  $\text{Fe}(\text{CO})_5$  a viscous yellow liquid melting at  $-21^\circ \text{C}$ . and boiling at  $102.5^\circ$ . The chemical properties and reactions of the iron and other carbonyls are similar to those of nickel carbonyl; and they are believed to produce a similar physiological response, except that the iron carbonyls are believed to be less toxic. The pathology caused by the carbonyls has not received sufficient study and needs much more attention before atmospheric concentrations of even as much as 10 p.p.m. can be regarded as acceptable for prolonged exposures. See Nickel Carbonyl and Iron Carbonyl, Chapter Twenty-Two.

## NICKEL CARBONYL

### 1. *Industrial Exposures, and Physical and Chemical Properties*

Industrially, nickel carbonyl is most often encountered as an intermediate in the Mond process of refining nickel. In this process carbon monoxide is passed over the nickel ore, and the nickel carbonyl that results is later decomposed by heat to yield nickel and carbon monoxide. Nickel carbonyl,  $\text{Ni}(\text{CO})_4$ , is a colorless liquid with a molecular weight 170.73 and a specific gravity of 1.29832 at  $25^\circ \text{C}$ . It melts at  $-25^\circ \text{C}$ . and boils at  $43.33^\circ$ . The vapor pressure is equal to 349.7 mm. Hg at  $24.26^\circ \text{C}$ . The density of the vapor is 5.9 (air = 1) and "saturated" air at  $24.26^\circ \text{C}$ . contains 46 per cent vapor and has a density of 3.2 (air = 1). It is only slightly soluble in water, but soluble in most organic

solvents. It decomposes upon standing, forming colloidal nickel, which settles out later as a deposit. It is decomposed by strong sulfuric acid to form nickel sulfate.

1 mg./l.  $\approx$  143 p.p.m. and 1 p.p.m.  $\approx$  6.98 mg./cu.m. at 25° C., 760 mm.

### 2. Determination in the Atmosphere

Nickel carbonyl vapor in the atmosphere may be estimated by scrubbing the air sample through strong sulfuric acid, or by drawing it through a heated tube to decompose the nickel carbonyl and deposit the nickel on the walls of the tube; afterward the nickel can be dissolved in acid. In either case the nickel is then determined by a suitable chemical method.

### 3. Physiological Response

Nickel carbonyl is toxic even when inhaled in small amounts from the atmosphere, and the liquid may be absorbed through the skin. The immediate symptoms of intoxication are said<sup>69</sup> to be indistinguishable from the symptoms caused by inhalation of carbon monoxide, which is frequently associated with the carbonyls. This initial stage passes off, and the exposed workman may feel well enough to return to work, then 12 to 18 hours later develop a soreness in the chest accompanied by an unproductive cough and dyspnea. The symptoms and sequelae depend upon the severity of the exposure: the early symptoms may progress, cyanosis may develop, and the temperature may rise. Severe exposures usually produce a widespread vascular congestion of the lungs that may almost obliterate the air sacs. Degenerative changes in the pulmonary epithelium, with desquamation of cells into the alveoli, may occur. Hemorrhage and exudation are said to be uncommon, and consolidation does not occur.

Nickel carbonyl is thought to be absorbed, unchanged, into the blood stream, and it is believed that damage to the pulmonary epithelium is due to the action of the nickel carbonyl. Flury and Zernik<sup>68</sup> are of the opinion that the action is that of a catalytic poison, which influences especially the central nervous system and the metabolic processes. They also believe that colloidal nickel separates in the lungs and other tissues, and they compare the action of nickel carbonyl to that of zinc fumes. Krafft<sup>70</sup> has suggested that the action on the lung surfaces may be allergenic, as found in diseases of the skin. Brandes<sup>71</sup> reports damage to capillaries and arterioles, with multiple small hemorrhages in the lungs, and likens the irritation in some respects to that resulting from phosgene. Further light on the mechanics of these injuries is desired. Following exposure, nickel has been found in the urine of men and animals, and in the livers of the animals.

### 4. Permissible Limit

There is little information upon which to base a suggestion for a maximum permissible concentration, but 180 p.p.m. is said to have been fatal to a rabbit

<sup>69</sup> A. J. Amor, *Occupation and Health, Suppl.*, International Labor Office, Sept. 1938.

<sup>70</sup> E. Krafft, *Ber. 8 intern. Kongr. Unfallmed. u. Berufskrankh.*, 2, 1054 (1939).

<sup>71</sup> W. W. Brandes, *J. Am. Med. Assoc.*, 101, 1204 (1934).

after an exposure of 1 hour. If the issue were to be decided upon the basis of carbon monoxide, since there are 4 volumes of carbon monoxide from 1 of carbonyl, that would place the limit at 25 p.p.m. There is no evidence that this would be logical, and the safe amount for 8-hour exposures is probably somewhat below that figure.

#### **5. *Warning Properties and Inflammability***

Nickel carbonyl is inflammable and burns with a yellow flame. It may decompose violently when heated at 60° C. in the presence of air or oxygen. Ten parts per million in the atmosphere is sufficient to impart luminosity to alcohol or carbon monoxide flames: this may be used as a semiquantitative test. Although nickel carbonyl has a characteristic odor in low concentrations, this is considered to give inadequate warning.

# The Cyanides and Cyanogen Compounds\*

JAMES H. STERNER, M.D.

## I. Physiological Response to Compounds Containing Cyanogen

### A. SYMPTOMS IN ANIMALS

The simple volatile cyanide and nitrile compounds have a similar effect on the animal body, and in acute poisoning produce one of the most rapid modes of death. The symptoms of acute poisoning are an initially increased respiration, followed by a labored respiration, paralysis, loss of consciousness, convulsions, suffocation, and finally cessation of breathing. With lower toxic concentrations there is irritation of the eyes and upper respiratory tract, and vomiting frequently occurs.

At higher concentrations cyanogen bromide and cyanogen chloride are slightly less toxic but similar in action to hydrogen cyanide. At lower concentrations the halogen cyanides are much more irritant, and the lacrimatory and pulmonary irritation effects are more like those of phosgene. Cyanogen, acetonitrile, propionitrile, and acrylonitrile are somewhat less toxic than hydrogen cyanide, but slightly more irritating.

The ingestion of sodium and potassium cyanides produces symptoms similar to, and only slightly less rapid than, those from the inhalation of the volatile cyanides. Calcium cyanamide is much less toxic.

### B. GROSS PATHOLOGY IN ANIMALS

The extremely rapid action of the higher concentrations of the cyanides causes death with surprisingly little gross pathology. Following inhalation of hydrogen cyanide (HCN), the lungs may show scattered petechial hemorrhages, and there may be some congestion of the brain, liver, kidneys, and spleen. There frequently is more evidence of injury at the lower, fatal concentrations, for here the effects of asphyxia have more opportunity to develop. The blood is usually of bright "arterial" color, even in the veins. With the halogen cyanides, CNBr and CNCl, especially at the lower effective concentrations, the injury to the respira-

\* Most of the physical data given in this chapter not specifically credited by reference notes were taken from Beilstein's *Handbuch der organischen Chemie*.

tory tract is marked, with hemorrhagic exudate of the bronchi and trachea, and a hemorrhagic edema of the lungs. With the lower concentrations of acrylonitrile, moderate interstitial nephritis, subacute bronchopneumonia, and liver damage (this last in cats only) were observed.

### C. ABSORPTION AND EXCRETION IN MAN

The cyanides are rapidly absorbed, in quickly fatal amounts, through the gastrointestinal tract, the lungs, and the skin—the last two portals of entry being the much more important in industrial exposures. With high concentrations of hydrogen cyanide, unconsciousness and labored respirations may result after 10 to 20 seconds, and death may occur within a few minutes, indicating the rapidity with which cyanide is absorbed through the lungs and transported through the entire body. Absorption through the skin is much slower, but guinea pigs and rabbits are readily killed by absorption of hydrogen cyanide gas through the skin, though intact.

Absorption of sodium cyanide ( $\text{NaCN}$ ), potassium cyanide ( $\text{KCN}$ ), calcium cyanide [ $\text{Ca}(\text{CN})_2$ ], and calcium cyanamide ( $\text{CaCN}_2$ ) may occur by the inhalation of dust, or by skin absorption from solutions of these salts.

The cyanides are carried in solution in the plasma with little or no direct combination with hemoglobin. However, if methemoglobin is present, cyanide forms a complex with it, cyanmethemoglobin, which is reconverted to hemoglobin at a slow rate, with the gradual release of cyanogen.

The cyanides undergo relatively rapid decomposition or modification in the body: part combines with sulfur to form thiocyanate, an important if not the chief detoxication mechanism; and probably some cyanide is excreted as such through the lungs, in the saliva, and in the urine.

An increased thiocyanate excretion in the urine has been correlated with excessive cyanide absorption in animals, although the rate of formation and excretion varies considerably with species. Identification of excessive amounts of cyanide in the blood and tissues of human acute poisoning cases is an important diagnostic aid. The determination of thiocyanate in the blood or in the urine has little or no practical application in the control of industrial exposures to cyanide compounds.

### D. MODE OF ACTION AND CAUSE OF DEATH IN ANIMALS

The characteristic cyanide effect is that of an "internal" asphyxia due to inhibition of oxidative processes in the cells. The symptoms of intoxication are those of asphyxia with the exception that the blood remains saturated with oxygen, and the cyanosis associated with an "obstructive" asphyxia is absent. The oxidative enzyme systems are apparently not destroyed, for the inhibitory effect of hydrogen cyanide can be reversed when a mechanism is introduced that binds the cyanide more or less firmly.

Death is due to paralysis of the respiratory center, as the result of "internal" asphyxia of central nervous system cells. The respiration ceases considerably before the heart, the latter finally stopping in systole, and being capable of transient resumption on stimulation.

### E. EFFECTS ON MAN

With high concentrations the action of the cyanides on man is similar to that on the lower animals. The symptoms following acute pulmonary absorption are constriction of the throat, fullness and flushing of the head, vertigo, nausea, and vomiting. Increased respiration may be followed quickly by slow, shallow, irregular breathing, and unconsciousness and convulsions. With lower concentrations the subjective phenomena—nausea, headache, vertigo, and a feeling of suffocation—may persist for hours after removal from exposure.<sup>1</sup>

Chronic intoxication is rare, with gastrointestinal symptoms predominating.

Irritation of the skin and mucous membranes may be severe in exposures to the dust of calcium cyanamide or the vapors of the halogen cyanides.<sup>2</sup>

## II. Specific Compounds

### HYDROGEN CYANIDE (Prussic Acid)

#### 1. Source

Hydrogen cyanide (HCN) is prepared by treating a cyanide salt with dilute sulfuric acid.<sup>3</sup>

#### 2. Uses and Industrial Exposures

For fumigating ships, buildings (high concentrations are encountered), citrus trees; as a reagent in industry. It is found in certain industrial processes in concentrations that may be dangerous, as in blast furnaces, dyestuff works, gas works, coke ovens, tanneries, fertilizer plants, metal cleaning, electroplating, and in industries of gold mining and gilding.

#### 3. Chemical and Physical Properties

Physical state: colorless liquid  
 Molecular weight: 27.03  
 Melting point:  $-13.4^{\circ}$  C.  
 Boiling point:  $25.7^{\circ}$  C.  
 Refractive index: 1.2619 at  $20^{\circ}$  C.  
 Vapor density: 0.94 (air = 1)  
 Vapor pressure: 807.23 mm. Hg at  $27.22^{\circ}$  C.

Percentage in "saturated" air: 100 at  $25.7^{\circ}$  C.  
 Miscible with water, alcohol, and ether  
 Volatility of vapor: 873 mg./l. at  $20^{\circ}$  C.<sup>4</sup>  
 Persistence: summer, 5 minutes in open,  
 10 minutes in woods; winter, 10 minutes  
 in open, 1 hour in woods<sup>4</sup>

1 mg./l.  $\approx$  905 p.p.m. and 1.104 mg./cu.m. at  $25^{\circ}$  C., 760 mm.

<sup>1</sup> R. T. Johnstone, *Occupational Diseases*. Saunders, Philadelphia, 1941.

<sup>2</sup> T. Sollmann, *A Manual of Pharmacology*. 6th ed., Saunders, Philadelphia, 1942.

<sup>3</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

<sup>4</sup> A. M. Prentiss, *Chemicals in War*. McGraw-Hill, New York, 1937.

#### 4. Determination in the Atmosphere

Methods have been described by Robbie and Leinfelder<sup>5</sup> and by Jacobs.<sup>6</sup> See also page 209.

#### 5. Physiological Response

See Tables 1 and 2.

Relative toxicity: 16.5 (compared with chlorine = 1.0).<sup>6</sup>

Fatal dose by ingestion: about 0.05 g.<sup>2</sup>

TABLE 1

*Physiological Response to Various Concentrations of Hydrogen Cyanide—Animals<sup>7,8</sup>*

Animal	Concentration		Response
	mg./l.	p.p.m.	
Mouse	1.45	1300	Fatal after 1 to 2 min.
Cat, dog	0.350	315	Quickly fatal
Guinea pig, rabbit	"	"	Fatal
Guinea pig	0.23	200	Toleration 1½ hr. without symptoms
Cat	0.20	180	Fatal
Cat	0.14	125	Markedly toxic in 6 to 7 min.
Monkey	"	"	Distinctly toxic after 12 min.
Rabbit	0.13	120	No marked toxic symptoms
Dog	0.125	115	Fatal
Mouse	0.12	110	Fatal after ¾ hr. exposure
Rat	"	"	Fatal after 1½ hr. exposure
Dog	0.1	90	May be tolerated for hours; death after exposure
	0.07-0.04	65-35	Vomiting, convulsions, recovery; may be fatal
Mouse	0.05	45	Fatal after 2½ to 4 hr. exposure
	0.044	40	No symptoms after 7 hr.
Dog	0.035	30	May be tolerated

TABLE 2

*Physiological Response to Various Concentrations of Hydrogen Cyanide—Man<sup>4,8</sup>*

Response	Concentration	
	mg./l.	p.p.m.
Immediately fatal.....	0.3	270
Fatal after 10 min.....	0.2	181
Fatal after 30 min.....	0.15	135
Fatal after ½ to 1 hr. or later, or dangerous to life.....	0.12-0.15	110-135
Tolerated for ½ to 1 hr. without immediate or late effects	0.05-0.06	45-54
Slight symptoms after several hours.....	0.02-0.04	18-36

#### 6. Suggested Maximum Allowable Concentration

20 p.p.m.<sup>7</sup>

<sup>5</sup> W. A. Robbie and P. J. Leinfelder, *J. Ind. Hyg. Toxicol.*, **27**, 136 (1945).

<sup>6</sup> M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

<sup>7</sup> H. C. Dudley, T. R. Sweeney, and J. W. Miller, *J. Ind. Hyg. Toxicol.*, **24**, 255 (1942).

<sup>8</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.



**7. Inflammability**

Inflammable within the range of 5.60 to 40.00 per cent by volume in air (see Chapter Thirteen).

**8. Odor and Warning Properties**

Penetrating odor of bitter almonds, burns with violet flame. Odor detectable at 1 mg./cu.m. (0.9 p.p.m.).<sup>4</sup> Recognition of the odor of 2 to 5 p.p.m. HCN requires training.

**CYANOGEN CHLORIDE****1. Source**

Cyanogen chloride (CNCl) is produced by the action of chlorine on moist sodium cyanide suspended in carbon tetrachloride and kept cooled to  $-3^{\circ}$  C., followed by distillation.<sup>3</sup>

**2. Uses and Industrial Exposures**

Cyanogen chloride is used in organic synthesis and in the manufacture of military poison gases.<sup>3</sup> It has also found use as a warning agent in fumigant gases.

**3. Chemical and Physical Properties**

Physical state: colorless gas

Molecular weight: 61.47

Melting point:  $-7^{\circ}$  C.

Boiling point:  $15.5^{\circ}$  C.

Vapor density: 2 (air = 1)

Vapor pressure: 1000 mm. Hg at  $20^{\circ}$  C.<sup>4</sup>

Solubility in water: 1 vol.  $H_2O$ : 25 vol.

CNCl at  $20^{\circ}$  C.

Solubility in ethyl alcohol: 1 vol.: 100 vol. CNCl at  $20^{\circ}$  C.

Solubility in ether: 1 vol.: 50 vol. CNCl at  $20^{\circ}$  C.

Dissolves readily in all organic solvents<sup>4</sup>

Persistency: summer, 10 minutes in open, 20 minutes in woods; winter, 20 minutes in open, 2 hours in woods<sup>4</sup>

1 mg./l.  $\approx$  398 p.p.m. and 1 p.p.m.  $\approx$  2.51 mg./cu.m. at  $25^{\circ}$  C., 760 mm.

**4. Determination in the Atmosphere**

Methods have been described by Jacobs.<sup>6</sup>

TABLE 3

*Physiological Response to Various Concentrations of Cyanogen Chloride—Animals<sup>6</sup>*

Animal	Concentration		Response
	mg./l.	p.p.m.	
Rabbit	3.0	1200	Fatal in 2 min.
Goat	2.5	1000	3 min. exposure fatal after 70 hr.
Mouse, cat	1.0	400	Fatal
Dog	0.8	320	Fatal
Mouse	0.3	120	Fatal to some animals
Cat	"	"	Fatal
Dog	"	"	Severe injury, but recovery
Mouse	0.2	80	Tolerated by some animals
Dog	0.12	48	After 6 hr. exposure fatal
Cat	0.1	40	18 min. exposure, fatal in 9 days

**5. Physiological Response**

See Tables 3 and 4.

Relative toxicity: 13.5 (compared with chlorine = 1.0).<sup>6</sup>

TABLE 4

*Physiological Response to Various Concentrations of Cyanogen Chloride—Man*<sup>4,5</sup>

Response	Concentration	
	mg./l.	p.p.m.
Fatal after 10 min.....	0.4	159
Fatal after 30 min.....	0.12	48
Intolerable concentration, 1 min. exposure.....	0.05	20
Intolerable concentration, 10 min. exposure.....	0.005	2
Lowest irritant concentration, 10 min. exposure.....	0.0025	1

**6. Maximum Allowable Concentration**

Less than 0.5 p.p.m.

**7. Odor and Warning Properties**Pungent odor. Odor detectable at 2.5 mg./cu.m. (1 p.p.m.).<sup>4</sup>**CYANOGEN BROMIDE****1. Source**

Cyanogen bromide (CNBr) may be prepared either by the action of bromine on potassium cyanide or the interaction of sodium bromide, sodium cyanide, sodium chlorate, and sulfuric acid.<sup>3</sup>

**2. Uses and Industrial Exposures**

In organic synthesis; parasiticide; fumigating compositions; rat exterminator; cyaniding reagent in gold-extraction processes; cellulose-products treating agent; war gas.<sup>3</sup>

**3. Chemical and Physical Properties**

Physical state: colorless crystals (needles or cubes)

Molecular weight: 105.93

Specific gravity: 2.015 at 20°/4° C.

Melting point: 52° C.

Boiling point: 61.4° C.

Vapor density: 3.17 (air = 1)

Vapor pressure: 92.0 mm. Hg at 20° C.

Density of "saturated" air: 1.3 (air = 1) at 20° C.

Per cent in "saturated" air: 12.1 at 20° C.

Soluble in water, but hydrolyzes

Soluble in alcohol and ether

1 mg./l.  $\approx$  230.9 p.p.m. and 1 p.p.m.  $\approx$  4.33 mg./cu.m. at 25° C., 760 mm.**4. Determination in the Atmosphere**Methods have been discussed by Jacobs.<sup>6</sup>**5. Physiological Response**

See Tables 5 and 6

**TABLE 5**  
*Physiological Response to Various Concentrations of Cyanogen Bromide—Animals<sup>8</sup>*

Concentration		Response	
mg./l.	p.p.m.	Mice	Cats
1	230	Fatal	Fatal
0.3	70	Paralysis after 3 min. exposure	Paralysis after 3 min. exposure
0.15 to 0.05	35-12	—	Severe injury; fatal on prolonged inhalation

**TABLE 6**  
*Physiological Response to Various Concentrations of Cyanogen Bromide—Man<sup>4,5</sup>*

Response	Concentration	
	mg./l.	p.p.m.
Fatal after 10 min.....	0.4	92
Intolerable concentration, 1 min. exposure.....	0.085	20
Intolerable concentration, 10 min. exposure.....	0.035	8
Lowest irritant concentration, 10 min. exposure.....	0.006	1.4

Concentration preventing "fighting efficiency" in a few seconds: 35 mg./cu.m. (8 p.p.m.).<sup>8</sup>

**6. Suggested Maximum Allowable Concentration**

Less than 0.5 p.p.m.

**7. Odor**

Penetrating odor and bitter taste.

**METHYL CYANIDE (Acetonitrile, Ethanenitrile)**

**1. Source**

Methyl cyanide ( $\text{CH}_3\text{CN}$ ) is prepared by heating acetamide with glacial acetic acid.<sup>3</sup>

**2. Uses and Industrial Exposures**

Organic synthesis; perfumes; extracts; denaturant.<sup>3</sup>

**3. Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 41.05

Specific gravity: 0.7768 at 25°/4° C.

Melting point: -41° C.

Boiling point: 81.6° C.

Refractive index: 1.34596 at 16.5° C.

Miscible with water, alcohol, benzol, ether, acetone

1 mg./l.  $\approx$  595.3 p.p.m. and 1 p.p.m.  $\approx$  1.68 mg./cu.m. at 25° C., 760 mm.

#### 4. *Physiological Response—Animals*

The median lethal subcutaneous dose for rats is 0.5 ml. per 100 g. body weight for very pure acetonitrile. Impure material may be much more toxic.<sup>9</sup>

#### 5. *Suggested Maximum Practical Working Level*

20 p.p.m.

#### 6. *Odor, Warning Properties, and Inflammability*

Ethereal odor, burning sweetish taste. Burns with a luminous, peach-blossom colored flame.

### ETHYL CYANIDE (Propionitrile, Propanenitrile)

#### 1. *Source*

Ethyl cyanide is made by heating barium ethyl sulfate and potassium cyanide, with subsequent distillation.<sup>3</sup>

#### 2. *Uses and Industrial Exposures*

Organic synthesis.<sup>3</sup>

#### 3. *Chemical and Physical Properties*

Physical state: colorless liquid

Molecular weight: 55.08

Specific gravity: 0.7770 at 25°/4° C.

Boiling point: 97.1° C.

Melting point: -103.5° C.

Refractive index: 1.3659 at 24° C.

Fairly soluble in water

Soluble in ether and alcohol<sup>10</sup>

1 mg./l.  $\approx$  444.4 p.p.m. and 1 p.p.m.  $\approx$  225 mg./cu.m. at 25° C., 760 mm.

#### 4. *Suggested Maximum Practical Working Level*

20 p.p.m.

#### 5. *Odor*

Ethereal odor.

### ACRYLONITRILE (Vinyl Cyanide)

#### 1. *Source*

Acrylonitrile (CH<sub>2</sub>:CHCN) may be prepared either by dehydration of  $\beta$ -hydroxypropionitrile; or pyrolysis of cyanethyl acetate.<sup>3</sup>

#### 2. *Uses and Industrial Exposures*

Synthetic rubber; plastics; organic synthesis.<sup>3</sup>

<sup>9</sup>L. Cuny and D. Quivy (Toxicity of Acetonitrile for Rats), *Chem. Abstracts*, 34, 3362 (1940).

<sup>10</sup>*Handbook of Chemistry and Physics*. 28th ed., Chemical Rubber Publishing Co., Cleveland, 1944-45.

**3. Chemical and Physical Properties**

Physical state: colorless, volatile liquid

Molecular weight: 53.06

Specific gravity (liquid): 0.8004 at 25°/4° C.<sup>11</sup>

Freezing point: -83° C.

Boiling point: 77.3° C.

Refractive index: 1.3885 at 25° C.<sup>11</sup>Vapor density: 1.9 (air = 1)<sup>11</sup>Vapor pressure: 110-115 mm. Hg. at 25° C.<sup>11</sup>

Per cent in saturated air: 14.5 at 25° C.

Solubility in water: 7.3 per cent by weight<sup>11</sup>Soluble in all common organic solvents<sup>8</sup>1 mg./l.  $\approx$  460.5 p.p.m. and 1 p.p.m.  $\approx$  2.168 mg./cu.m. at 25° C., 760 mm.**4. Determination in the Atmosphere**

Acrylonitrile, cyanogen chloride, or hydrogen cyanide may be collected by adsorption or other means, acidified with sulfuric acid then distilled from an excess of caustic solution into dilute hydrochloric acid, nesslerized and compared.<sup>12</sup>

**5. Physiological Response**

See Table 7.

TABLE 7  
*Physiological Response to Various Concentration of Acrylonitrile—Animals*<sup>7</sup>

Animal	Concentration		Response
	mg./l.	p.p.m.	
Rat	1.38	635	Fatal after 4 hr. exposure
Guinea pig	1.25	576	Fatal during or after exposure
Cat	0.60	276	Markedly toxic
Guinea pig	0.58	267	Slight transitory effect
Rabbit	0.56	258	Fatal during or after exposure
Cat	0.33	152	Markedly toxic, sometimes fatal
Monkey	"	"	Definite toxic effects
Rabbit	0.29	133	Marked transitory effects
Rat	0.28	129	Slight transitory effect
Dog	0.24	110	Fatal to three fourths of the dogs
	0.213	98	Convulsions and coma; no death
Rat, rabbit	0.21	97	Slight transitory effects
Dog	0.12	55	Transitory paralysis; 1 dog died
	0.063	29	Very slight effects

**6. Suggested Maximum Practical Working Level**20 p.p.m. (43 mg./cu.m.).<sup>7</sup>**7. Inflammability**

Inflammable within the range of 3.05 to 17.00 per cent by volume in air (see Chapter Thirteen).

<sup>11</sup> H. C. Dudley and P. A. Neal, *J. Ind. Hyg. Toxicol.*, 24, 27 (1942).<sup>12</sup> W. R. Bradley, *personal communication*.

**8. Odor**

Mild odor.

**CYANOGEN****1. Source**

Cyanogen (N:CC:N) is prepared by slowly dropping potassium cyanide solution into copper sulfate solution or by heating mercury cyanide.<sup>3</sup>

**2. Uses and Industrial Exposures**Organic synthesis; war gas.<sup>3</sup>**3. Chemical and Physical Properties**

Physical state: colorless gas

Molecular weight: 52.04

Melting point:  $-34.4^{\circ}$  C.Boiling point:  $-27.17^{\circ}$  C.

Vapor density: 1.67 (air = 1)

Solubility in water: 450 cc./100 ml. water at  $20^{\circ}$  C.<sup>10</sup>Solubility in ethyl alcohol: 2300 cc./100 ml. alcohol at  $20^{\circ}$  C.<sup>10</sup>Solubility in ethyl ether: 500 cc./100 ml. ether at  $20^{\circ}$  C.<sup>10</sup>1 mg./l.  $\approx$  469.6 p.p.m. and 1 p.p.m.  $\approx$  2.127 mg./cu.m. at  $25^{\circ}$  C., 760 mm.**4. Determination in the Atmosphere**

Cyanogen may be determined in the presence of HCN by first scrubbing out the HCN with silver nitrate solution and then estimating the cyanogen by the ferrocyanide or thiocyanate methods.<sup>6</sup>

**5. Physiological Response**

See Table 8.

TABLE 8

*Physiological Response to Various Concentrations of Cyanogen—Animals\**

Animal	Concentration		Response
	mg./l.	p.p.m.	
Mouse	31.5	15,000	Fatal in a few sec.
	5.5	2,600	Fatal after 12 min. exposure
Cat	4.26	2,000	Fatal after 13 min. exposure
Rabbit	0.84	400	Fatal after 1 $\frac{1}{4}$ hr. exposure
Mouse	0.63	300	Fatal after 3 $\frac{1}{2}$ hr. exposure
	0.5	235	Tolerated a 15 min. exposure
Rabbit	0.42	200	Slight symptoms after 4 hr. exposure
Cat	"	"	Fatal after 1 $\frac{1}{2}$ hr. exposure
Rabbit	0.21	100	Little effect after 4 hr. exposure
Cat	"	"	Fatal after 2 to 3 hr. exposure
Cat	0.16	75	Fatal 2 days after 4 hr. exposure
Cat	0.1	50	Severely ill after 4 hr. exposure. Recovered

**6. Inflammability**

Inflammable within the range of 6.60 to 42.60 per cent by volume in air (see Chapter Thirteen). Burns with peach-blossom red flame.

### 7. Odor

Pungent odor.

## SODIUM CYANIDE

### 1. Source

Sodium cyanide (NaCN) is prepared by the following process: sodamide is produced from sodium and ammonia; the sodamide is heated with charcoal; and the resultant sodium cyanamide is then heated with an excess of charcoal resulting in the formation of sodium cyanide. It may also be prepared by the fusion of calcium cyanamide, sodium chloride, and a small amount of calcium carbide.<sup>3</sup>

### 2. Uses and Industrial Exposures

Extraction of gold and silver from ores; electroplating; heat treatment of metals; making hydrocyanic acid; insecticide.<sup>3</sup>

### 3. Chemical and Physical Properties

Physical state: white crystalline solid, deliquescent

Molecular weight: 49.02

Melting point: 564° C.

Boiling point: 1496° C.<sup>10</sup>

Vapor pressure: 0.76 mm. Hg at 800° C.

Readily soluble in water

Slightly soluble in alcohol

### 4. Physiological Response—Effects on Man

Fatal dose of sodium cyanide by ingestion: 0.2–0.3 g.<sup>13</sup>

### 5. Odor

Slight odor of HCN, released by deliquescence and hydrolysis.

## POTASSIUM CYANIDE

### 1. Source

Potassium cyanide (KCN) is prepared by heating potassium carbonate and carbon in a current of ammonia. The fused mass is extracted with alcohol, the latter distilled off, and the cyanide fused. It can be made from calcium cyanamide which is prepared from calcium carbide and nitrogen and is then fused with caustic potash. Potassium cyanide can also be made from by-products of beet-sugar manufacture.<sup>3</sup>

### 2. Uses and Industrial Exposures

Extraction of gold and silver from ores; electroplating; heat treatment of steel; reagent in analytical chemistry; insecticide; reagent in manufacture of various intermediate organic cyanogen derivatives; paper manufacture; pharmaceutical preparations; fixative in photography; process engraving and lithography; fumigant for raw cotton; fumigant for grain elevators; fumigant for citrus fruits.<sup>3</sup>

<sup>13</sup> C. H. Thienes, *Clinical Toxicology*. Lea & Febiger, Philadelphia, 1940.

**3. Chemical and Physical Properties**

Physical state: white crystalline solid, deliquescent

Molecular weight: 65.11

Melting point: 636° C.

Specific gravity: 1.560

Readily soluble in water: at 25° C.

1000 g. dissolves 716 g. KCN

Slightly soluble in alcohol: at 19.5° C.

100 g. dissolves 0.875 g. KCN

**4. Physiological Response—Effects on Man**

Fatal dose of potassium cyanide by ingestion 0.2 to 0.3 g.<sup>2</sup>

**5. Odor**

Like that of HCN—bitter almond, released by deliquescence and hydrolysis.

**CALCIUM CYANIDE****1. Source**

Calcium cyanamide,  $\text{Ca}(\text{CN})_2$ , is fused with sodium chloride to give a crude mixture of calcium cyanide and sodium cyanide along with sodium chloride and other impurities. This is the chief source of industrial cyanides.

**2. Uses and Industrial Exposures**

Killing ants, rats, mice, moles, and other similar burrowing insects and rodents; also for fumigating greenhouses, mushroom houses, flour mills, grain and seed; for fumigating citrus trees under tents for control of scale insects.<sup>3</sup>

**3. Chemical and Physical Properties**

Physical state: amorphous white powder

Molecular weight: 92.12

Readily soluble in water (with gradual liberation of HCN<sup>14</sup>)

Soluble in alcohol

**4. Odor and Warning Properties**

Smells rather strongly of HCN, released by deliquescence and hydrolysis, inadequate warning odor.

**CALCIUM CYANAMIDE****1. Source**

Calcium cyanamide ( $\text{CaCN}_2$ ) is prepared from calcium carbide, which is finely powdered and heated in an electric oven, into which pure nitrogen is passed. The charge remains in the furnace 24 to 36 hours. It is then removed and any uncombined calcium carbide is leached out.<sup>3</sup>

**2. Uses and Industrial Exposures**

Fertilizers; nitrogen products; hardening iron and steel.<sup>3</sup>

<sup>14</sup> *The Merck Index*, 5th ed., Merck, Rahway, N. J., 1940.



**3. Chemical and Physical Properties**

Physical state: white crystalline solid

Molecular weight: 80.11

Boiling point: 1190° C.<sup>10</sup>

Specific gravity: 2.3<sup>8</sup>

Decomposes in water, liberating ammonia<sup>9</sup>

**4. Physiological Response—Effects on Man**

Fatal dose: about 40 to 50 g.<sup>2</sup>



# Industrial Lead Poisoning

ROBERT A. KEHOE, M.D.

## I. Occurrence of Lead Poisoning in Industry

There are no reliable statistics on the frequency of occurrence of occupational lead poisoning in the United States of America as a whole, by localities, or by occupations. This situation arises out of a number of conditions, among which must be mentioned the frequency of errors of diagnosis, the lack of adequate medical supervision of many industrial plants in which there is hazardous occupational lead exposure, and the failure on the part of certain of the states to set up mechanisms for accurately reporting or adequately compensating cases of industrial lead poisoning. As the application of state compensation laws becomes more effective and more precise in relation to this occupational disease, the statistical data will approach adequacy, but for the present the industrial hygienist will be well advised to rely only upon those recorded in areas in which the mechanisms for collecting and recording the facts are known by him to be reliable. On this account, any statements concerning the incidence of industrial lead poisoning must of necessity be based in large part upon the observations and experience of an individual writer, without benefit of the collective case records of his colleagues.

Such evidence as is recorded would seem to demonstrate that fatal lead poisoning has decreased in frequency more or less regularly and progressively during the past twenty-odd years. Just how much of this decrease has resulted from progressive changes in medical viewpoints, with reference to the primary cause of death of persons with a history of apparently significant occupational lead exposure, cannot be determined. It is quite certain, however, that the more severe forms of lead poisoning are seen relatively infrequently at the present time, and that primary fatal industrial lead poisoning is infrequent in its occurrence. These facts argue that the more hazardous types of occupational lead exposure have been brought under some degree of control, and the experience of industrial physicians and hygienists serves to validate this argument.

It is by no means so certain that there has been any very significant decrease in the incidence of the milder forms of industrial lead poisoning. The experience of the writer leads him to believe that within recent years occupational lead

exposure has been brought under some measure of control in the large proportion of American industries. On the other hand, the opportunities for hazardous exposure have not been controlled to the degree that is required to eliminate lead poisoning as the cause of partial and temporary disability among a large number of workmen in a wide variety of industrial occupations. Regardless of statistics or the lack of them, it is apparent to any informed observer that industrial lead poisoning occurs with a frequency that bears no reasonable relationship to the accuracy of present criteria for differentiating safe from dangerous occupational lead exposure, or to the adequacy of presently available medical and engineering means for controlling lead exposure within safe limits.

The causes for the present unnecessarily high incidence of industrial lead poisoning are manifold, but certain outstanding factors should be understood by those interested in eliminating this disease from the industrial community. First in importance among these causes is the prevailing lack of understanding, on the part of industrial management and many of its medical and technical advisers, of the primary factors that determine the frequency and severity of lead poisoning in a given occupation, and of the means now available for recognizing and appraising these factors. Certain confused and confusing ideas have persisted for a long time in connection with the lead trades. Variations in the "susceptibility" of individuals have given rise to the belief that there is no means of predicting the occurrence of lead poisoning, when it will strike, and what severity or duration of exposure will cause it. Moreover, the comparative mildness of the disease as commonly seen and the fairly regular subsidence of symptomatology when exposure is discontinued for a brief time tend to create and support the viewpoint that occupational conditions are reasonably satisfactory and "much better than they used to be." This viewpoint, as will be apparent, is especially prevalent in the long-established lead trades.

A second factor that exerts an important influence upon the incidence of intoxication is the continually changing pattern of modern industrial production whereby new processes and products create new, and sometimes unrecognized, opportunities for occupational lead exposure. By this means lead hazards are introduced into industrial plants where there is no knowledge of such hazards and no experience in coping with them. In other plants new lead hazards may be added to recognized pre-existing hazards that were well under control, thereby, perhaps, increasing the lead exposure above threshold levels and giving rise to cases of saturnism.

A third factor, and one that came into recent prominence by reason of the demands of World War II, is to be found in a large and abrupt increase in the number and volume of lead-bearing materials and commodities. Under such circumstances production schedules are likely to take precedence over precautionary measures, and the lead exposure may well increase by an increment that is greatly disproportionate to the increase in production. Such increased exposure comes about through actual increase in the variety and volume of materials

handled, through increased frequency of failures of plant equipment under the stress of production schedules, through the mistakes and failures of inadequately trained personnel, through inadequacies in supervision, and perhaps through deficiencies in plant housekeeping and in facilities and training in relation to personal hygiene.

Whatever may be the cause or combination of causes that gives rise to lead poisoning in a specific plant or industry, the means of prevention can be found in the careful study of the origin, nature, and magnitude of the lead exposure by methods now readily available, and in the application of certain comparatively simple procedures that can be counted upon to reduce the exposure to a level compatible with the safety of plant personnel. This is not to say that there are no difficult problems to be met in certain industries. It is merely to say that the specifications for the maintenance of safety can be prescribed with adequate accuracy, and that the engineering skill required to meet such specifications need not be of a higher order than that so generously expended upon problems of production. There are few types of occupational lead exposure that offer insurmountable or even serious obstacles to modern engineering methods of attack. What is required is a sound understanding of the problem that is to be solved, and a genuine determination to solve it, not by brilliant excursions into prophylactic medical therapy, but by the application of orthodox engineering principles and equipment. It is the purpose of the following paragraphs to outline the practical means by which the hazards of industrial lead exposure may be understood, measured, and eliminated.

## II. Types of Industrial Lead Exposure

Generally speaking, there are two means for the entrance of inorganic lead compounds into the human body under industrial conditions: (a) by way of the respiratory tract, through inhalation of vapor, fume, dust, or mist; and (b) by way of the gastroenteric tract, through swallowing lead compounds trapped in the upper respiratory tract, or introduced into the mouth on food, tobacco, tools, fingers, or other objects. Certain organic lead compounds, such as tetraethyl lead, penetrate the normal intact skin with comparative rapidity and thus enter the body, but this route of absorption is of no practical importance in the case of the more common industrial lead compounds. These portals of entry are mentioned for the purpose of calling attention to the forms in which lead compounds must exist if they are to gain entrance into the body. The presence of vapor, fume, or fine dust of lead compounds in the air breathed by workmen is the most important factor in occupational lead exposure. However, lead compounds that contaminate the hands or food, tobacco, or other objects taken into the mouth may not be ignored as sources of exposure. In this connection, the not uncommon practice among workmen in certain plants of keeping food or bottles of milk in convenient places in dusty workrooms or in locker rooms inadequately protected

against factory dust is a source of significant hazard. Likewise, the rooms in which workmen eat their lunches are all too frequently contaminated with dust from plant operations.

The quantities of lead vapors that are given off from pots containing molten lead at temperatures under 1000° C. are insufficient in themselves to create an important lead hazard, but alloys of high lead content prepared and handled at higher temperatures—often near, and sometimes above, the boiling point of lead (1629° C., 2984° F.)—give rise to dangerous concentrations of lead vapors in the air. Even at the lower temperatures, however, a slight contribution made by lead vapor to the total lead exposure of workmen may have sufficient importance to warrant its elimination. Molten lead is easily oxidized at its surface, and when it is skimmed, stirred, poured, or otherwise agitated in the presence of air, variable quantities of finely divided lead oxide may be thrown into the air. For these reasons, the handling of molten lead or molten alloys of high lead content, in all plant processes not enclosed or adequately ventilated, is always associated with some degree of lead exposure for the workmen. The hazard of such exposure is especially prominent in certain foundry operations in which castings of lead-containing alloys are made. The latter include a wide variety of bearings for automobiles and ships and rail-car brake shoes. The alloys are brought to high temperatures, which vary with their composition, and in the usual type of foundry are transported on overhead rails to the desired site for being poured into molds. In transit a considerable proportion of the fume escapes into the atmosphere of the plant, thereby creating an exposure for molders and numerous other employees whose work otherwise would be free from lead hazard. Similar hazards are to be found in automobile-body plants in which metallic lead is used to smooth out the welds on "turret" tops. (A more significant hazard of this procedure is that of finely divided metallic lead distributed into the air through the use of abrasives with power-driven equipment employed to give the cooled metal a smooth and properly shaped surface.) A wide variety of plant procedures create lead exposure of this type, including soldering in the manufacture of automobile radiators, tin cans, and other receptacles, as well as the manufacture and reclamation of babbitt metal, the manufacture of lead shot and bullets, and the production of granular metallic surfaces by means of a finely divided spray of molten alloy. One rather common procedure in many types of chemical plants—that of lining tanks and reaction vessels with metallic lead and repairing these linings from time to time—is a source of significant exposure to lead fume, especially when the work has to be done on the inside of extensively corroded receptacles. Indeed, lead burning in general, which includes the operations just referred to, may be a highly hazardous occupation under unfavorable conditions involving prolonged or regularly repeated exposure to vapor and fume. Somewhat similar techniques, from the aspect of lead exposure, are those involving the cutting, welding, or reshaping of metal surfaces heavily coated with lead-bearing paints or with other corrosion-resisting layers of high lead content such as that of

terneplate. The application of a cutting flame to lead-containing alloys or to leaded steel likewise results in the release of lead fume, which under suitable conditions may give rise to hazardous lead exposure.

By far the most frequent industrial lead exposures are those that arise from handling or processing lead compounds in such a way as to introduce dust into the surrounding air. Metallic lead or any of its compounds when present in finely divided form in the atmosphere breathed by workmen must be regarded as dangerous, unless the quantities present in the air remain within limits known to be safe. The industrial processes responsible for the creation of lead-containing dust are too numerous to mention and too familiar to require discussion.

Lead compounds are sometimes thrown into the atmosphere as mist, when paints, enamels, or glazes are applied as a spray. The inhalation of such mists constitutes a potential hazard, which is not different in principle from that in which fume or dust is involved.

Certain organic lead compounds, of which only tetraethyl lead is manufactured and used in any considerable quantity at present, are liquids that are sufficiently volatile at ordinary temperatures to give rise to dangerous concentrations of vapor. These liquid lead compounds when handled in undiluted form or in concentrated solutions, as in their manufacture and in the plants in which they are mixed with gasoline, also give rise to lead exposure by contact with the skin, through which they are absorbed. Any open receptacle that contains these liquids in high concentration, or any container, article of clothing, floor, or other object that has not been cleaned thoroughly after contact with them, may subject to serious lead exposure persons who are nearby or whose skin may come in contact with them. The acute and frequently fatal character of lead intoxication from absorption of organic lead compounds of this type justifies special precautions for the avoidance of exposure to them. Differentiation should be made between the occupations involving opportunities for exposure to tetraethyl lead in concentrated form and those concerned only with the handling of gasoline containing tetraethyl lead in the concentrations in which it is employed in commercial motor fuels. Dilution of tetraethyl lead with gasoline to such an extent that there are 1000 parts or more of gasoline by volume to 1 part of tetraethyl lead effectively prevents the absorption of appreciable quantities of tetraethyl lead through human skin. At the same time the vaporization of tetraethyl lead from such dilute solutions in gasoline is so slight as to be practically insignificant under the conditions of handling and use that are normally required to avoid the risks of fire and explosion. For these reasons, the normal commercial distribution and use of leaded gasoline as a motor fuel involves no hazardous lead exposure. (Attention is called to the fact that under the unique conditions that exist within tanks in which leaded gasoline has been stored, there may be highly dangerous exposure to tetraethyl lead and its decomposition products, as well as to obviously toxic gasoline vapors, for the men who enter the tanks to clean or repair them. Moreover under any set of conditions in which large quantities of leaded gasoline

are spilled, sprayed, or otherwise vaporized into an enclosed, unventilated or inadequately ventilated space the lead concentration in the air may exceed safe levels. Leaded gasoline is intended for use as a motor fuel only. It should not be used for other purposes, excepting under conditions that will prevent hazardous lead exposure.)

### III. Detection of Industrial Lead Exposure

The *existence* of occupational lead exposure can usually be recognized by careful observance of the activities of an industrial plant. Some experience is required before one can attempt to judge the *severity* of the exposure, and even then it is best to reserve judgment until the results of more precise methods of study are available. Nevertheless, systematic examination of procedures and equipment, while following the flow of materials through manufacturing processes, will give valuable information concerning conditions that require further study. Therefore frequent trips of inspection should be made throughout a potentially hazardous plant as part of a general program of hygienic supervision. Attention should be paid to the cleanliness and orderliness of the workrooms and to the condition of sanitary facilities as an index of the care being given to matters of health and safety.

In lieu of precise measurements of lead exposure, which will be referred to more extensively later, it may sometimes be desirable to arrive at a prompt conclusion concerning the severity of the lead exposure of an industrial establishment. Here, resort may be had to an examination into the hygienic status of the workmen. This may be done in several ways, depending upon the information and facilities available. An experienced physician may find it possible to establish the facts by examination of a limited number of carefully selected and representative workmen. Examination of employment records, if such are available, will reveal the extent of the labor turnover, and if the latter is excessive, the records may suggest the reasons, especially if there are wide differences in this respect among the different occupations. Records of absenteeism and illness also may contribute highly significant information. The recorded incidence of lead poisoning among the workmen carries its own significance, but an unduly high rate of illness of any type, regardless of its classification, calls for interpretation.

### IV. Measurement of Industrial Lead Exposure

#### A. ANALYSIS OF AIR AS A MEANS OF MEASURING LEAD EXPOSURE

Poisoning from the ingestion of lead compounds is of relatively infrequent occurrence in industry, partly because of the general excellence of washroom and lunchroom facilities, particularly in large industrial plants, and the resultant promotion of cleanly habits among the workmen, but chiefly because of the preponderant opportunities for developing intoxication through the inhalation of



particulate lead compounds that contaminate the atmosphere of workrooms. In other words, the ingestion of lead compounds in the course of the day's work can be and is largely prevented through the exercise of ordinary care, whereas the prevention of lead inhalation is much more difficult. As might be expected, therefore, an overwhelming proportion of cases of industrial lead poisoning are due to inhaled lead. For these reasons, determinations of the respirable lead in the atmosphere of workrooms yield fairly adequate information as to the magnitude of the occupational lead hazard in such rooms. Satisfactory methods for estimating the atmospheric lead content have been devised and employed extensively in a variety of industries, not only in hygienic surveys but also in the routine periodic testing of plant conditions. For detailed information the student of this subject should consult standard texts and official reports, some of which are listed at the end of this chapter. The development of these methods, their practical application to the study of plant processes, and the correlation of data obtained by their use with the results of clinical studies on workmen have provided a practical means for the appraisal of industrial lead hazards. As experience has been gained it has become increasingly apparent that it is feasible to express the magnitude of the lead hazards of a plant and of its individual operations in terms of the lead content of properly selected air samples, and to anticipate with reasonable accuracy the results of exposure thereto.

The satisfactory application of the methods of air sampling and analysis requires sound technical knowledge of the principles involved in their use, as well as experience in handling the equipment and in selecting the sites for samples. As to the actual analysis, a number of methods are available (see references at end of chapter). The choice of method must be based upon the quantities of lead that are to be dealt with, and upon the presence or absence of other, interfering substances in the atmosphere of the plant. Highly specific and sensitive methods must be used if the quantities of lead are small and if other metals are present in significant quantities. These matters should be considered carefully, and the choice and application of methods should be made by competent chemists.

In the case of a single analytical survey of a plant, a sufficient number of air samples must be taken to give a comprehensive picture of all parts of the plant. Moreover, samples must be collected over a sufficient length of time and with sufficient frequency in any one location to yield representative results. If air analyses are employed as part of a regular program for controlling the lead exposure of a plant, they should be made either continuously at selected representative sites or at such intervals as will reveal the effects of any changes in environmental conditions, whether due to changing weather or to operating conditions within the plant. It should be recognized that a sample collected over a period of hours may not reveal the existence of intense exposures of short duration, thereby failing to yield a true picture of the existing hazard. Especially should the effects of all alterations in plant processes be checked by air analyses.

## B. ANALYSIS OF BLOOD, URINE, AND FECES OF EXPOSED WORKMEN AS A MEANS OF MEASURING LEAD EXPOSURE

A second method that is available for measuring the lead hazards of an occupation or an industry is based upon the physiological behavior of lead in the human body. Thus, the periodic determination of the lead content of the blood or the urine of exposed workmen will demonstrate the general magnitude of their lead absorption, while examination of their feces for lead will give an approximate, but useful, measure of the extent of their lead intake by inhalation and ingestion during the day or two immediately preceding the date of collection of the sample.

The general physiological background on which the interpretation of the results of lead analyses on the blood and excreta must be based will be presented later in this chapter. The methods for collecting samples also will be described there, and reference will be made to reliable methods of analysis. These matters play an important part in the medical supervision of workmen in certain lead industries, and therefore they are discussed fully in that connection. They are referred to here only in relation to the measurement of lead exposure, and the differentiation of safe from dangerous exposure.

## V. Safe Occupational Lead Exposure (Permissible Limits)

Experience has shown that when occupational lead exposure is insufficient to cause at least occasional toxic episodes resembling those characteristic of plumbism, little or no evidence is found of vague general disorders or impairments of the health of workers that differ in frequency or degree from those seen in any comparable group of unexposed industrial employees. It is possible, however, that the standards now employed to define safe lead exposure may be subject to slight change, both qualitatively and quantitatively. Of the various standards that might be considered, there are two which, by reason of their sound practical and theoretical background, are most likely to endure.

(1) Expressed in terms of air analyses, the upper limit of safety for industrial lead exposure is taken to be a concentration of 1.5 mg. lead per 10 cubic meters of air. One interpretation of this standard holds that "when the air of workrooms regularly contains not more than 1.5 mg. lead per 10 cubic meters of air, as measured by standard methods, cases of disabling lead intoxication do not occur among the men who work regularly in such workrooms, and cases of questionable or mild intoxication are rare. In practice, the attempt is made to maintain the lead content of the air within such limits as will yield an average of not more than 1.5 mg. lead per 10 cubic meters throughout the working day, while preventing the occurrence of materially higher concentrations (5 mg. per 10 cubic meters, or more)." Evidence of the validity of this standard has been provided elsewhere and need not be enlarged upon here.

(2) The comprehensive character of the information available on the urinary excretion of lead under a variety of conditions gives a unique value to urinary lead analysis as a means of measuring the lead exposure of workmen. On this account, the definition of safe lead exposure in physiological terms is given only on the basis of urinary lead excretion.

The upper limit of safe lead exposure as defined on the basis of the urinary lead excretion of exposed workmen is represented by a mean value of approximately 0.10 mg. lead per liter for samples that do not exceed 0.15 mg. per liter frequently and rarely exceed 0.20 mg. per liter.

In order that there may be no opportunity for misinterpretation of a standard, that includes a range of values as well as a mean, the results obtained on a representative group of men, whose occupational exposure failed to cause cases of lead poisoning over a period of 12 years, are given in Table 1. Table 2, on the

TABLE 1

*Distribution of Results Obtained in the Analysis of One Series of Samples of Urine of Large Volume from a Representative Group of Workmen in an Occupation Involving Lead Exposure Maintained for Years near the Threshold of Toxicity*

Lead, mg./l. urine	Frequency of occurrence of results indicated
0.000-0.019.....	0
0.020.....	3
0.040.....	14
0.060.....	17
0.080.....	10
0.100.....	9
0.120.....	6
0.140.....	9
0.160.....	4
0.200.....	1
0.220.....	1
Total.....	74
Mean and its standard deviation..	0.097 ± 0.004
Standard deviation of the series...	± 0.045

other hand, shows the excretory status of a similar group of men in the same occupation, but in another plant, at a time when mild but unquestionable cases of lead intoxication began to develop. It should be understood that not all of the individuals represented in the data of Table 2 had symptoms of lead poisoning. Moreover no line can be drawn at any point in the list of rubrics of Table 2 whereby the men who were free from symptoms can be separated from those with symptoms. Rather, we are illustrating, by means of one series of urinary lead determinations, a general level of occupational lead exposure which, if maintained, may be expected to give rise to some cases of lead poisoning. Some of the jobs in this plant involved less lead exposure than others, and therefore there was

considerable variation in the general level of lead excretion among individuals in the group. Moreover, there was some variation from day to day both in the severity of the exposure of any one individual and in his physiological (excretory) response to the prevailing lead exposure. That such environmental and physiological variability is well represented in the one set of illustrative observations has been established by a number of corresponding observations made from time to time over a period of months, with corresponding results for the group as a whole. Cases of lead poisoning occurred only among those men employed in the occupations of this plant that gave rise to the most consistently severe lead exposure as demonstrated by the higher sustained levels of urinary lead excretion. However, for present purposes, we are concerned with the group data representative of the plant as a whole, rather than with individuals. In this sense the

TABLE 2

*Distribution of Results Obtained in the Analysis of a Series of Samples of Urine of Large Volume from a Representative Group of Workmen in an Occupation Involving Lead Exposure Sufficient to Induce a Number of Cases of Mild but Definite Lead Intoxication*

Lead, mg./l. urine	Frequency of occurrence of results indicated
0.000-0.039.....	1
0.04 .....	15
0.08 .....	22
0.120.....	20
0.160.....	8
0.20 .....	7
0.24 .....	4
0.28 .....	5
0.32 and above.....	2
Total.....	84
Mean and its standard deviation..	0.148 ± 0.006
Standard deviation of the series..	± 0.079

frequencies of the results, the pattern of their distribution, and the mathematical expression of the mean value with its deviation illustrate, in practical and reproducible terms, hazardous conditions of lead exposure in one industrial plant.

## VI. Control of Industrial Lead Exposure

### A. ENGINEERING METHODS

The elimination of hazardous lead exposure from the many industrial operations that involve the use of lead compounds is primarily a technical problem. Its satisfactory solution in any instance depends upon adequate knowledge of how the specific industrial product can be made satisfactorily, economically, and

safely. The choice of the materials (with respect to lead content or physical state, that is, whether solid, powder, or paste), the processes and the equipment will determine the general character of the plant that is to be built or adapted for the purpose. The potential health hazards should influence all of these choices, and in addition will introduce their own requirements into the project. For these reasons a new plant should be designed and built, or an old one should be remodeled, only after taking into account all the factors that have to do with the safety and health of the employees.

Certain general principles of procedure have been found to be worthy of attention in the construction and arrangement of industrial plants, and in the remodeling of old ones.

(1) Hazardous exposures should not be distributed throughout a plant if it is possible to localize them in specific areas where they can be subjected to concentrated measures of control. The application of this principle has a bearing upon the movement of materials through a plant, the arrangement of equipment within it, and the manner of employing ventilating equipment (whether local or general or both). For these and other reasons, it determines the layout of the plant, its structural characteristics, and thereby, to a considerable extent, its cost.

(2) The equipment should be arranged with reference to the hazards and the means of their control, as well as to convenience and speed in production. For example, ventilation can rarely be introduced as an afterthought, with completely satisfactory results. There must be space for fans and ducts and for the heating equipment that may be required to temper the air.

(3) The matter of ventilation in general is dealt with elsewhere in this volume, and therefore little need be said here. Three points, however, merit specific mention in connection with particulate lead compounds: (a) the necessity for the use of carefully designed local exhaust systems to remove fume and dust at their points of origin, (b) the exercise of great care to prevent the reintroduction of exhausted air into workrooms, and (c) the desirability of collecting exhausted dust and fume so as not to contribute to the community problem of atmospheric pollution. The importance of these points will be appreciated only by those who have had broad experience, or by those who, lacking experience, have undertaken to solve these practical problems by methods of trial and error. It is of considerable importance, also, to so design the ventilation system as to ensure that its operation will be independent of weather conditions and the personal predilections of workmen (see Chapter Ten).

(4) The construction and arrangement of the plant must be such as to promote cleanliness and good housekeeping. Floors, window ledges, walls, and working spaces in general must be designed with specific reference to the materials to be used and the methods of housekeeping that will be employed. For example, floors that are to be hosed down must have regular surfaces and adequate drainage, and must not be too slippery when wet. Similar purposes may be served by metal grills overlying a secondary floor equipped with adequate drains. Areas

*and equipment that are to be cleaned by vacuum must be smooth, regular, and free from all unnecessary obstructions and sharp angles.*

**(5) Facilities for medical services must be designed on the basis of the medical program that is contemplated, and not on what remains of space and location after other requirements have been satisfied.**

**(6) Toilets, washrooms, locker rooms, lunchrooms, and sanitary equipment in general, including a satisfactory supply of drinking water, should be so planned as to encourage their use. Convenience, comfort, and adequacy in relation to the number of employees are first considerations. Almost without exception in lead-using industries, it is necessary for workmen to change clothing completely on going to work, and to change and bathe at the end of the day's work. Therefore, there must be double lockers for the two sets of clothing, and good bathing facilities. Workmen must not eat in workrooms, and therefore a clean and comfortable lunchroom must be provided, in which hot or cold beverages and perhaps hot food should be available. Good washroom facilities are required to enable the men to cleanse themselves properly before entering the lunchroom. All these rooms and spaces must be so located or otherwise designed as to prevent their contamination with dust-laden or fume-laden air, and to facilitate frequent and thorough cleaning.**

The problem of coping with the lead exposure of a plant already built and in operation resolves itself into two distinct parts. First, it is necessary to determine the origin and the extent of the lead exposure associated with the various occupations and parts of the plant. Second, come the choice and application of the methods for control. The simplest means by which the first step can be achieved has been mentioned previously, but certain practical points are worthy of some elaboration. Adequate systematic sampling of the air of workrooms while work is in progress and the use of accurate methods for the analysis of such samples will indicate the distribution and the order of severity of the lead hazards. In a plant in which the quality of sanitary facilities and of the general hygienic performance is good, the results of air analyses will demonstrate the hazard or the lack of it with considerable accuracy, and will indicate clearly what is to be done and where to begin. It may happen, however, that hygienic conditions in general are unsatisfactory, that the instruction and supervision of the workmen in precautionary measures are defective, and that as a consequence the men are inadequately informed and indifferent in matters of safety. Under these conditions the extent of their occupational lead absorption can be expected to be considerably greater than that which would naturally follow from the magnitude of the contamination of the air. In addition there is an educational problem to be met, both among the workmen and the management, as a first step toward the accomplishment of the task that lies ahead. Both must be brought to recognize the actuality of the hazards, while at the same time they are informed of their respective roles and responsibilities in a comprehensive plan for the solution of the problem.

The methods for controlling the lead exposure will depend upon the circum-

stances and the nature of the plant processes. In a generally well-designed and well-managed plant the problem is straightforward and comparatively simple. Mechanical measures of control can be applied where and as they are needed, the results being checked by air sampling and analysis until the desired condition has been achieved. Under the unsatisfactory conditions referred to above, however, and even under the best of conditions, considerable time may be required to obtain and install the necessary equipment. It may be highly important, therefore, to do all that can be done to reduce existing lead hazards, pending their elimination by more adequate or permanent means. In such instances, the use of respirators is fully justified as a temporary expedient for the control of otherwise unavoidable respiratory lead exposure. Moreover, every effort should be made to prevent the wholly unnecessary ingestion of lead that may result from inadequacies in the instruction of personnel and in plant practices, with respect to personal cleanliness and the handling of food, beverages, and tobacco during working hours. Improvement of sanitary facilities, instruction of workmen through talks, formal regulations, and placards, as well as provision for adequate hygienic supervision in the performance of the day's work, may be highly necessary and helpful in alleviating the situation.

As was suggested above, respirators should be regarded as merely temporary means for preventing the inhalation of lead compounds. Occasional situations arise that necessitate the use of respiratory equipment of some type, but in the main lead exposure should be prevented by other means, not only for the sake of the comfort and efficiency of the workman, but also on account of the continual care and supervision that are required to see that this type of equipment is used properly and effectively. As to the selection of respirators or masks in relation to specific lead hazards, as well as the necessities for proper use and maintenance, the reader is referred to Chapter Fourteen. It should be emphasized, however, that no aspect of this matter should be left to the workman. The care of such equipment, including inspection, cleansing, maintenance, and replacement, as well as all decisions as to when and how it is to be used, must be set up under the control of trained and responsible personnel.

In a potentially hazardous lead industry all the operations of production, repair and replacement of equipment, the investigative work on processes, the laboratory control of materials and products, and even general housekeeping involve opportunities for lead exposure and therefore come within the province of industrial hygiene. What is often forgotten in dealing with pounds and tons of material is that one is concerned with mere milligrams of lead compounds in matters of human health. The technical background and experience required to grasp and retain this quantitative concept as an effective principle of daily work are not common among production personnel, and therefore the industrial hygienist must supply and implement this viewpoint. The continuous search for the small departures from satisfactory practice, for the small sources of lead exposure that pass unnoticed otherwise, is his responsibility. In setting these upon a firm

and understandable quantitative basis, in terms of accepted standards of air contamination, he eliminates mystery and conjecture and thereby may gain the effective assistance of technical and production personnel. A single demonstration of the efficacy of a procedure recommended for the elimination of air contamination, by means of "before and after" analytical results, will have a more salutary effect than volumes of verbal propaganda.

The orderly and effective application of safe methods for the performance of many items of plant procedure, especially those involving repair and maintenance of equipment, often calls for written instructions and regulations. The preparation of such instructions requires a sound understanding of operating processes, as well as of hygienic and physiologic principles. Here, and at many other points of contact, there must be effective collaboration between the industrial hygiene engineer, the physician, and the production personnel. It is highly important, therefore, that the organization of the activities of a plant in relation to industrial health in general be such as to facilitate teamwork of this type.

## B. MEDICAL METHODS

As has been indicated previously, the control of occupational lead exposure through the maintenance of a safe environment is essentially a mechanical problem, which, therefore, lies within the province of the engineer. If the maintenance of a safe level of atmospheric lead contamination were accepted as a necessary condition of plant hygiene in the lead trades generally, there would seem to be no medical problem. The situation is not quite so simple, however. There is a great deal of misunderstanding on this score on the part of industrial management, engineers, and even the physicians themselves. Actually safe conditions, with respect to occupational lead exposure, are not generally achieved in industry; and there is an unfortunate belief that it is the function of the industrial physician, by some special clinical skill or legerdemain, to convert hazardous work into safe, or at least to avert the more serious consequences of hazardous lead exposure. Let us clear the air by admitting that this cannot be done except to a limited degree, and then only through the use of highly specialized physiological tools. The physician may find it possible to recognize the early clinical manifestations of saturnism, and thereby prevent the development of the more serious and disabling forms of lead poisoning among industrial workers. Under actually hazardous conditions of lead exposure, however, he will not always succeed in this attempt, as experience has amply demonstrated. He also may alleviate suffering and shorten the period of disability through proper care of poisoned workmen, but by no stretch of the imagination can this be regarded as preventive medicine. Indeed, to the extent that such medical practice tends to obscure the hazardous character of an occupation, it is an obstacle rather than an aid to the achievement of industrial health. There are, however, certain functions in the



control of industrial lead hazards that can best be served by the industrial physician. It is these we wish to emphasize.

The first and foremost function of the physician in the lead trades is to recognize the earliest manifestations of lead intoxication. The proper performance of this function serves a threefold purpose: (1) It enables him to recognize the existence of hazardous lead exposure, thereby demonstrating that measures being taken for the control of lead exposure are inadequate. (2) The recognized occurrence of lead poisoning, when related to the work location and the duration of the exposure of affected individuals, often serves to reveal the source and nature of the lead hazard, thereby pointing the way for its elimination. (3) The existence of plumbism in one or more members of an occupational group will demonstrate the need for prompt protection of the others in the group, whether by special means or by temporary discontinuance of the job until the hazard has been eliminated.

It should be apparent to all students of the subject that our criteria for the safety of any type of occupational lead exposure are based upon the sensitivity of clinical methods for the recognition of the signs of lead intoxication. Such present criteria are wholly pragmatic and practical, since they have been derived from the correlation of analytical data and clinical observations. If new and better clinical methods based upon more complete understanding of the toxicology of lead compounds should be developed, these criteria might well be modified. The importance of continued clinical investigation in the lead industries is quite obvious therefore.

There is also, of course, the matter of nonoccupational illnesses among industrial workmen. The differentiation of these—especially the chronic diseases of obscure origin—from saturnism is a problem the complexity of which varies considerably with conditions that have little relation to clinical diagnosis as such. The inevitable tendencies of the workmen, members of their families, their legal advisers, and their sympathetic and sometimes ill-informed family physicians to attribute any illness to the effects of lead absorption are heightened tremendously by unsatisfactory labor-management relations, by stringent general, local, and individual economic conditions, and by local professional friction. Nevertheless, the clinical problem itself is sometimes difficult to solve, requiring a high degree of technical expertness and general professional judgment, as well as complete freedom from prejudice. It is not enough for the physician to determine to his own satisfaction that an illness is or is not due to lead absorption. Proper professional standards, as well as medicolegal considerations, demand that he put forth every effort, consonant with current medical knowledge, not only to convict or exclude lead as an etiologic or contributory factor in an illness, but also to demonstrate the actual nature of the disease in question.

A second function of the physician in the lead trades lies in the application of physiological methods for the measurement of lead exposure, and the interpretation of the data obtained under his supervision for this purpose, when such

information is required. Reference has been made previously to a criterion for the differentiation of safe from dangerous lead exposure in terms of the concentration of lead in the urine of exposed persons. Other more or less comparable data can be obtained by analysis of the blood and also the feces of exposed persons. The analysis of these materials calls for the services of a competent analytical chemist. The collection of suitable samples of such biological materials, on the other hand, should be done by, or under the direct guidance of, persons whose familiarity with the workmen and their working conditions is complete, and whose understanding of the physiological and technical background of the sampling procedures is comprehensive. There appears to be considerable uncertainty as to the proper role of analytical data of this type in the control of industrial lead exposure. The specific meaning of various types of analytical data will be considered elsewhere in this chapter, but questions concerning the desirability and the need for such data in the given instance can be answered briefly and simply. In general, when the lead exposure of an occupation, a plant, or an industry is of such type and character as to be substantially uniform and readily controlled by mechanical means, so that essentially safe occupational conditions are regularly maintained, there is no real need for systematic determination of the lead content of the blood or excreta of workmen. In comparison with the sampling and analysis of the air of workrooms, the sampling and analysis of blood and excreta of the workmen are difficult, time-consuming, and expensive while, under the conditions indicated, the former procedures may well be entirely adequate to maintain safe working conditions. In such circumstances the analysis of biological materials is required only occasionally, if at all, in connection with medical or medicolegal differential diagnoses.

On the other hand, when the lead exposure of an industry is highly variable for technical or other reasons, or when the control of the lead exposure is difficult to achieve and maintain, precise analytical data, especially through analyses of suitable samples of the urine of exposed persons, become a necessity. Only by such means can one protect those who are actually involved in hazardous exposure. The medical problem in such a situation is to determine how long an individual or a group may safely continue to work. When workmen reach a level of lead absorption at which it is no longer safe for them to accept the common or unusual opportunities for lead exposure associated with their day's work, they must be removed and transferred to work involving less exposure or perhaps none at all. The quantity of lead that is retained in the tissues of workmen under a given set of occupational conditions is determined largely by the factor of time, that is, by the duration of continuous employment in the specific occupation. The influence of the time factor in relation to a known intensity of lead exposure can be estimated roughly, but in a number of industries and occupations it can be ascertained with adequate assurance only by physiological means. For this reason, in the medical supervision of occupations in which

the lead exposure is uncertain or near the threshold of danger, the use of such methods is generally advantageous and sometimes indispensable.

A third function of the industrial physician is the maintenance of adequate records of pre-employment and periodic examinations, and the use of such records to determine the hygienic status of individuals and occupational groups of plant personnel. The necessity and propriety of comprehensive examinations of this type in hazardous occupations is beyond argument and requires no discussion here. It is not so commonly recognized that the information that can be gained thereby, in matters of general industrial health or in relation to specific hazards, is of such importance as to justify considerable expenditure of time and effort in the accumulation of complete and precise records, and in periodic systematic study of the data contained therein. Obviously, much of the information in such records must be held in proper professional confidence, but the essential data related to the main problems of industrial hygiene rarely have individual or personal implications.

### C. SPECIFIC MEDICAL PROCEDURES

The preceding paragraphs are intended merely to outline the general professional methods of the physician in the lead industries. Certain specific procedures and practices merit detailed discussion, however, for the reason that their significance is not always fully understood, nor are they always applied in a satisfactory manner. These are concerned primarily with the detection of dangerous levels of lead absorption prior to the development of toxic manifestations. The evidences of lead absorption, as distinguished from those of intoxication, consist in: (a) certain blood changes, of which the most important are apparently the result of some degree of stimulation of the blood-forming tissues with the release of increased numbers of juvenile forms of erythrocytes (reticulocytes and erythrocytes with basophilic granulation); (b) the development of punctate sulfide deposits in the gum tissues and in the mucosa of the colon and anus; and (c) an elevation of the lead content of the blood and excreta (or tissues) above the normal level. The first two of these cannot be regarded as specific evidence of lead absorption, since many stimuli affect the hematopoietic tissues, and since any metal that will form a black sulfide may cause a blue line in the gum tissues or a bluish-black deposit in the anal mucosa. The third, on the contrary, is entirely specific and reliable in indicating the extent of the absorption of lead.

#### 1. *Significance of "Stippling" of the Erythrocytes*

The limits of normal numerical variation of the several formed elements of the blood, which are specifically involved in lead absorption, have been observed and reported upon by various workers. Discussion herein will be limited to

punctate basophilia, or "stippled" erythrocytes. (References are given at the end of this chapter to articles on these and other blood elements, and on methods.) The latter occur normally in human blood, as reported by Sanders, in numbers from 1 or 2 up to 6000 per million erythrocytes. Some 6 per cent of a group of several thousand apparently healthy persons, free from occupational lead exposure, showed 1000 or more stippled erythrocytes per million erythrocytes, while the mean figure for 784 persons was  $339.18 \pm 9.72$  per million. The number of stippled erythrocytes in the blood shows little or no change with small increments of increased lead intake, but at higher levels of exposure and absorption their number in the circulating blood shows a somewhat irregular tendency toward an increase. Considerable variation in the degree of individual response is observed, and fairly wide variations occur from day to day, but with increasingly severe conditions of lead exposure there is a trend toward increasing numbers of stippled erythrocytes in the blood of exposed workmen, if comparisons are based on groups rather than on individuals. Unfortunately the trend in this direction is neither striking nor dependable, and a sizable proportion of the results of any series of such observations is always within the range of normal values.

The above facts, stated briefly and somewhat too simply, show clearly why it is impossible to rely upon this and related hematological tests for estimating the severity of the lead exposure of individuals and occupational groups with sufficient promptness and exactitude for practical purposes. And yet some modification of this procedure is the common, and in many instances the only, method employed for this purpose. It is high time that industrial physicians in the lead trades should recognize the inadequacy of these procedures, except as clinical adjuncts to other more specific and sensitive methods.

Certain additional facts demonstrate the value of blood examinations of this type in relation to clinical diagnosis, when properly employed and interpreted. Under the conditions of hazardous lead exposure, an abrupt and *progressive* increase in stippled erythrocytes above the previous normal level of the individual is strongly suggestive of increased lead absorption, and should be so regarded unless there is adequate evidence to the contrary. Such an increase cannot be taken as evidence of the existence or imminence of lead intoxication, for large variations occur without symptoms or signs of illness; but they should be considered as harbingers of danger, somewhat in proportion to their magnitude and speed of development. On the other hand, the absence of stippled erythrocytes in the blood, in a suspected or alleged case of lead poisoning during a period of active intoxication, constitutes very nearly conclusive evidence that the toxemia is due to some factor other than lead. The only exceptions, in our experience, are found in cases of acute overwhelming intoxication from a single or very brief massive exposure, and in cases of poisoning by tetraethyl lead. The absorption of the latter compound has never been found to result in hematological abnormalities.

## 2. *Significance of the "Lead Line"*

A lead line may appear in gum margins that are somewhat inflamed by bacterial invasion—that is, when hydrogen sulfide is produced locally—whenever the lead content of the involved tissues is sufficiently elevated. We have observed the appearance of a faint punctate blue line in the tissue overlying an infected gum pocket in one person whose blood contained lead only to the extent of 0.05 mg. per 100 grams. Easily identified lead lines usually signify somewhat higher levels of lead absorption. Obvious deposits of lead sulfide are seen in the gums of persons with no demonstrable symptoms or signs of intoxication, but the development and extension of a lead line may be accepted as an indication of progressive lead absorption and thereby as a warning of danger. The lead line must be differentiated from similar deposits resulting from the precipitation of other metallic sulfides, notably of bismuth; and they must not be confused with the normal pigment of Negroes and correspondingly dark-skinned peoples. The former differentiation is sometimes provided by the medical history of the person in question, but may require analyses of the blood, or urine, or both; the latter can usually be made by careful study of the locus and appearance of the pigment. The natural pigment is rarely found in the gum tissue on the lingual side, while despite the scant attention given the fact by clinicians in general, a favored site for the first appearance of a lead line is in the extreme lingual edge of the gum opposite the bicuspid and lower molars. The bluish-purple line of gingival congestion may be taken for a lead line by the inexperienced, especially if examination is not made after expression of the blood by means of a transparent applicator (such as a glass slide). More commonly, the stained, or discolored surface of a tooth just visible beneath a thin layer of gum tissue is called a lead line. The differentiation is not always easy, and resort must sometimes be had to the use of a hand lens, or even to biopsy followed by microchemical, or better, spectrographic analysis.

## 3. *Significance of Results of Lead Analyses of Blood and Excreta*

These reliable and specific procedures are of such importance as to require extensive elaboration. As a background for the practical considerations that follow, it is advisable to review briefly certain facts with respect to human lead metabolism.

## VII. **General Character of Lead Metabolism**

The general character of the lead metabolism of the average normal healthy North American adult may be described with considerable accuracy. He ingests with his food and drink quantities of lead varying from 0.05 mg. to somewhat more than 2.00 mg. per day, the mean daily quantity over a period of months being approximately 0.30 mg. He inhales air containing a small quantity, which

probably rarely exceeds 0.15 mg. per 24 hours, and of which only a portion—doubtless a variable but otherwise unpredictable portion—is retained by the respiratory membranes and eventually absorbed into the tissues, the remainder being either exhaled or trapped in the upper respiratory tract and subsequently swallowed. (The quantity absorbed is so small as to be barely apparent in prolonged studies in which the total lead output in the feces and urine is balanced against lead intake by ingestion only; and is, therefore, quite small.) Only a small proportion (10 per cent or less) of ingested lead is actually absorbed into the body. Most of it traverses the alimentary tract unabsorbed and appears in the feces. The portion absorbed is distributed to the tissues of the body, including the liver, from which it is partially secreted back into the alimentary tract with the bile. The effect of the poor alimentary absorption together with the biliary secretion (and perhaps other lead-containing secretions into the alimentary tract) is to make the daily fecal lead output almost equivalent to the total intake by ingestion. The small quantity that escapes elimination in the feces finds its way into the tissues, the blood, the body fluids, and secretions. The concentration of lead in the blood at any specific time depends upon two main factors: the rate of absorption from the intestine or other avenue of entry, and the quantity of lead in the body as a whole. Thus, the whole blood of normal healthy North American adults usually contains from 0.01 mg. to 0.05 mg. per 100 grams, with a mean concentration of approximately 0.03 mg. per 100 grams. (Concentrations as high as 0.06 mg. per 100 grams occasionally are found.) Very little of this is in the plasma, 95 per cent or more being found in the erythrocytes. Lead is found normally in physiologically representative volumes of urine in quantities that vary from 0.01 mg. to 0.08 mg. per liter, with a mean concentration slightly in excess of 0.03 mg. per liter, and in the sweat in concentrations of the same order of magnitude. The lead in the tissues is distributed in accordance with a definite pattern. The major portion is found in the skeleton—the long bones, such as the femur, containing higher concentrations than the flat. Measurable and fairly constant concentrations are found in the other tissues. The average gross quantity of lead present in the body of the normal human adult in the United States of America is not less than 100 mg. nor more than three times this quantity, with due regard to variations in body weight. Present evidence indicates that there is little or no progressive lead accumulation under average conditions of lead intake in the United States of America.

#### A. EFFECT OF INCREASED EXPOSURE

When there is an increase in the lead exposure of an individual above his usual or average normal level, a number of things occur promptly. If the additional lead is ingested or if it is inhaled in the form of dust, there is an immediate rise in the alimentary lead content, as revealed in the feces—a rise that bears a direct relation to the quantity ingested or inhaled, since most of such lead passes through the alimentary tract unabsorbed. Some absorption takes place

from both lung and alimentary tract, and the concentrations of lead in the tissues, the blood, and the urine (also to a less readily demonstrable degree in the feces) gradually increase. Each of a series of normal subjects, studied under laboratory conditions, to whom a constant small quantity of lead was administered daily, showed such an increase, which occurred at a substantially constant rate over the entire period of months or years of lead administration. The rate of increase varied among the subjects according to the size of the daily dose of lead being administered. The conditions of industrial lead exposure differ from those set up in these experiments in that they are less uniform, both quantitatively and on a time base, but there is scant reason to question the essential similarity of the results under the two conditions. Whether or not progressive lead accumulation occurs in the case of industrial workers would seem to depend upon the intensity and the constancy (or intermittency) of the prevailing exposure. Any interruption in the exposure, even that involved in a long week end, may be expected to decrease the rate of lead accumulation in the body and may be sufficient to neutralize it under conditions of slight occupational lead exposure.

#### B. EFFECT OF DISCONTINUANCE OF LEAD EXPOSURE

After the discontinuance of lead exposure, the lead retained in the body during the period of increased absorption maintains the lead concentration of the tissues, the blood, and the urine above normal levels for a period of time that depends upon both the quantity of lead retained and the time over which it was absorbed. Thus, the concentration of lead in the blood and urine decreases progressively, reaching the normal range in a period that varies from a few weeks to considerably more than one year. The alimentary tract, on the contrary, is emptied of its abnormal lead content to a very large extent within a few days after the discontinuance of the lead exposure. From then on the alimentary lead output is so largely composed of ordinary ingested lead as to be indistinguishable therefrom, except under carefully controlled conditions, in which the total lead content of the ingested food and beverages is ascertained by analysis of representative samples. The lead content of the tissues of the body diminishes in accordance with the rate of elevated lead excretion, there being some lag but by no means immobility in this regard on the part of the skeleton. Available analytical data indicate that approximately normal lead concentrations in the tissues are commonly reached within twelve to eighteen months, the skeleton being the last to return to the normal range.

The importance of the facts outlined in the foregoing paragraphs cannot be overemphasized in their relation to the problem of industrial lead exposure. They demonstrate clearly that lead occurs in the human body without prejudice to normal health, and that a toxic effect on the part of this element is a matter of concentration. Combined with other experimental and clinical evidence, they also indicate that the absorption and excretion of quantities of lead considerably in excess of the usual and normal levels are wholly compatible with normal and

healthy human life and activity, and that lead intoxication is not to be anticipated if certain limits of exposure and absorption are not exceeded.

### C. EARLY SIGNS OF ELEVATED LEAD ABSORPTION

#### 1. *Increased Rate of Urinary Excretion*

The earliest and most delicate sign of elevated lead absorption, and one that fortunately is specific, is found in an increased rate of urinary lead excretion. The excretory increase, furthermore, bears a direct relation to the quantity and rate of the lead absorption. The demonstration of a small increase requires careful procedures for the collection of samples and adequate control of the physiological factors involved in the urinary excretion of lead. Urinary samples of small volume obtained at random are subject to considerable variation in their lead content. In individual cases, the latter varies chiefly with the urinary volume during the period of collection—that is, if the urine is concentrated the lead concentration is relatively high, if dilute from high water intake or diuresis the lead concentration is relatively low. This factor can be controlled, in small volumes, by proper selection of the time of sampling so as to avoid extremes of water intake and output; it can be corrected for in large measure by determination of the specific gravity of the urine and by applying a factor derived therefrom; it can be eliminated altogether by collecting one or more liters of urine, and by making sure that no unusual quantities of liquid are taken by the subject in order to speed up the collection of the sample.

Of primary importance is the avoidance of contamination of urinary samples—and the smaller the sample the greater must be the care in this respect. Samples of urine collected during working hours in the usual type of washrooms or medical quarters in manufacturing plants, or obtained by customary hospital procedures, or, in fact, secured by any other than by precise methods controlled by the analyst, are not only valueless but grossly misleading as to their lead content. Lead is ubiquitous, and it is difficult under the most favorable circumstances to avoid all sources of contamination. In this connection it should be pointed out that a urinary lead concentration in excess of 0.5 mg. per liter is a rarity, that concentrations higher than 0.3 mg. per liter occur only under conditions of dangerous lead exposure and absorption, while values exceeding 0.20 mg. per liter are not found in association with casual or questionable types of lead exposure, but rather with admittedly hazardous conditions. It must be emphasized also that such values are found only during the period in which such exposure occurs, or within the period of a few weeks thereafter, and not after prolonged intervals of freedom from exposure. High results are to be regarded with suspicion, unless the conditions of current exposure are in keeping with them, and results beyond a maximum of 1 mg. per liter, or perhaps slightly more in exceptional cases of massive brief exposure, must be discarded as obviously erroneous. In any case, single results must not be relied upon.



## 2. *Increased Lead Concentration in Blood*

An increase in the lead concentration in the blood above normal levels also is indicative of abnormal lead exposure and absorption. However, in view of the high concentration of lead in whole blood as compared with that in the urine, a slight elevation of the lead in the blood is difficult to evaluate, because it may be within or near the limits of error of the methods involved in the analysis of samples of blood of the size that are commonly and conveniently obtained. As a general rule, the comparatively small changes in the lead concentration in the blood in response to lead absorption are considerably magnified in their urinary representation, and are thus more readily demonstrated and interpreted.

In view of the relatively slight variability of the lead concentration in the blood, except in response to changing conditions of lead exposure and absorption, determinations of the lead in the blood serve a very useful purpose. Moreover blood samples can be obtained without the active help of the exposed individual and, under ideal conditions, without risk of their contamination. (The fact that the lead in the blood is contained largely in the erythrocytes has given rise to the suggestion that the lead in the plasma or serum should be determined, rather than that in the whole blood, or that the partition of lead within the blood should be determined analytically. It should be recognized, however, that the partition has physiological significance only if determined by prompt examination of a *fresh* sample of blood, and that the accurate analysis of small quantities of serum or plasma requires an extraordinary degree of precision, because of the minute quantities of lead involved. For these reasons these procedures are practicable only under special conditions.)

Analyses of the blood have one other advantage in relation to the problem of lead exposure, in that they reveal the abnormality in the lead content of the body in the exceedingly rare instance in which analyses of the urine fail to do so because of impairment in the ability of the kidney to secrete lead.

Blood samples must be obtained with the utmost precautions if contamination with lead is to be avoided. A chemically clean evacuated glass tube equipped with a sterile, lead-free needle, prepared in the chemical laboratory, seems to offer the best and simplest means of obtaining uncontaminated blood under a wide range of conditions. Otherwise it is necessary to take the samples in a special dust-free room (into which persons exposed to lead compounds may come only after bathing and donning clean clothes) by means that will insure that the blood cannot come in contact with anything except lead-free needles, syringes, and containers.

## 3. *Value of Analysis of Feces*

The value of the analysis of the feces of groups of exposed workmen as a means of determining the relative magnitude of their lead exposure by ingestion and inhalation has been mentioned previously. Suffice it here to point out that

a considerable proportion of the dust in respired air is caught in the upper respiratory tract and subsequently swallowed, and therefore the quantity of lead appearing in the feces provides an approximate measure of the exposure for the period represented by the fecal sample. The lead in the feces is predominantly, and indeed almost wholly, ingested or inhaled (subsequently swallowed) lead under any other than the most unusual circumstances. Considerable quantities of lead may be secreted into the alimentary tract for a brief period following the absorption of large amounts of lead but, in the main, the true alimentary excretion of lead is small. The quantity is rarely more than twice or three times greater per day than that excreted in the urine, and it may be of the same order of magnitude or even less than that of the urine under certain circumstances. The true alimentary lead excretion of the normal individual with no occupational exposure is completely masked by the much larger quantity of unabsorbed lead that has been ingested with the food, except under carefully controlled experimental conditions. It is quite impossible to determine its magnitude or even its occurrence when lead-containing dusts have been inhaled, for under these conditions it is an exceedingly minute fraction of the fecal lead. For these reasons the fecal lead, as such, bears no significant relation to the lead content of the body of an individual, and indicates practically nothing with respect to absorbed lead. Yet these very facts, which militate against the usefulness of analyses of the lead content of the feces for diagnostic purposes, establish the rationale for the collection of such data in relation to the severity of the respiratory lead exposure of individuals and occupational groups.

### **VIII. Recommended Procedures and Interpretations**

Taking all of the foregoing facts into account in relation to the problems of sampling and the interpretation of analytical data, there are several types and combinations of practical procedures that can be employed in the medical supervision of workmen in hazardous lead trades. A regimen that has proved its efficacy over a period of many years may be worthy of presentation.

As a means of demonstrating the type, location, and severity of the lead exposure associated with a series of different occupations in a plant, quarterly analyses have been carried out by collecting a large sample of urine (2 liters or more) and one ordinary fecal evacuation from each of a group of men chosen to represent the several occupations and work locations of the plant. These samples are obtained by the workmen during the time spent at their homes, having bathed and discarded their work clothing at the plant. Verbal and written instructions are provided for their guidance, so as to cultivate their informed co-operation, and to avoid, as far as possible, errors of sampling. The analytical data are subjected to careful study from time to time, and as the occupational groups are maintained substantially constant, the status of the lead hazards in the plant is shown. The location of exposure to dusts, and the relative severity of such exposure from time to time are clearly defined by the fecal results. The level

of the lead absorption of individuals and groups also is portrayed by the urinary data in relation both to work location and duration of employment.

In order to augment the data obtained above, and as a means of checking clinical judgments in individual cases, spot samples of urine and duplicate samples of blood are obtained from individuals or groups that have been subjected to an unusual or accidental exposure, or whose clinical condition or occupational exposure is open to question at the time of a regular or special medical examination. The combination of these analytical data enable the physician to establish the significance of the factor of lead exposure without the doubts that otherwise arise concerning the possibility of errors of sampling and analysis.

#### CRITERIA FOR INTERPRETATION OF RESULTS

Criteria for the interpretation of analytical results and for appropriate action based thereon have been adopted as follows:

1. When analytical data are available in the presence of symptomatology of any type,
  - a. the symptomatology should be interpreted without reference to analytical data and a conclusion arrived at as to its significance, taking into account the hematological and other laboratory findings;
  - b. a cause-and-effect relationship between lead absorption and nonspecific symptomatology, on the part of men who have been working up to the time of sampling, may be excluded, when
    - (1) the results on a sample of blood and a spot sample of urine are well within safe limits: less than 0.06 mg. per 100 grams whole blood; less than 0.12 mg. per liter urine; or when
    - (2) repeated results on spot samples of urine are within safe limits as defined above, or when
    - (3) the result on a large sample of urine is within safe limits as defined above;
  - c. a cause-and-effect relationship between lead absorption and nonspecific symptomatology may be assumed to exist, when
    - (1) other causes of symptomatology have been excluded beyond reasonable doubt and the analytical results are above safe limits; or when
    - (2) the background of the symptomatology is quite uncertain, and the analytical results are within the dangerous range, that is, 0.08 to 0.15 mg. per 100 grams whole blood, 0.18 to 0.40 mg. per liter urine;
  - d. a cause-and-effect relationship between lead absorption and strongly suggestive or specific symptomatology may be assumed to exist, when
    - (1) the analytical results are within the dangerous range; or when
    - (2) it is known that the analytical results were well above safe levels during a period of lead exposure that has now been discontinued for some weeks.
2. When no symptoms of any kind exist, persons should be removed from lead exposure or transferred to work involving greatly reduced exposure, when
  - a. the analytical results are consistently within dangerous limits, that is,
    - (1) results on a blood sample and a spot urine sample are in agreement at high levels of more than 0.08 mg. per 100 grams whole blood and more than 0.18 mg. per liter urine; or

- (2) repeated results on spot urine samples are consistently within the high range indicated above; or
  - (3) the result on a large sample of urine is within the range given above (0.18 mg. per liter or more). (An exception may be made in this rule when it can be established that a high result is of short duration and is followed by a rapid drop in the results, as in case of a brief severe exposure.)
3. Men with no symptomatology may be returned to the work from which they were transferred or removed because of excessive lead absorption, when
- a. the analytical results have fallen to levels that are consistently safe, that is,
    - (1) the blood results are down to 0.05 mg. per 100 grams or lower, and the urinary results are not higher than 0.10 mg. per liter; or
    - (2) the results on urine samples of large volume (1 liter or more) are not in excess of 0.10 mg. per liter, and a representative sample of feces for a twenty-four hour period contains under 0.40 mg. lead. (In general, the length of the period of reduced or discontinued lead exposure should be more extended in the case of persons whose employment under conditions of potentially hazardous exposure has been prolonged, that is, the longer the period of exposure, the longer should be the period of freedom from exposure.)

## IX. Medical Problems of Industrial Lead Poisoning

The diagnosis and treatment of lead poisoning are problems of clinical medicine that can scarcely be dealt with adequately in a discussion devoted primarily to the control of occupational lead exposure and the prevention of occupational illness. Reference has been made previously to the importance of the recognition of the earliest evidences of lead intoxication as a means of detecting the existence of hazardous lead exposure. Obviously, the knowledge and experience required of the physician for this purpose will not have been obtained or greatly augmented by the consideration of these matters as they might be summarized here. Accordingly, attention is called to adequate sources of information in the references at the end of this chapter. Certain related medical problems are worthy of brief comment.

### A. PROPHYLAXIS

When incipient or well-defined lead intoxication has appeared in an individual case, certain steps should be taken at once. (See the preceding section for criteria for disposition of men in relation to analytical results.) The first requirement is the elimination of further lead exposure on the part of the affected person. The means by which this is done will depend upon the circumstances. If the lead exposure has resulted from accidental and unforeseen causes, and if the resultant illness is slight and fleeting, it may be sufficient to see that the opportunities for subsequent exposure are reduced or dispensed with; after which the workman may resume his work. If the cause was carelessness, ineptitude, or inattention to instructions on the part of the workman, it may be satisfactory to transfer him to other, less exacting work. If the illness is somewhat more serious, or if it does not lend itself to immediate diagnosis, it is advisable to make

sure that no further lead exposure is encountered, either by transferring the workman to work that involves no exposure, or by giving him temporary leave, under observation. Obviously the onset of real illness usually involves cessation of work and of further exposure. It must be recognized, however, that some men pay but little attention to minor illness and discomfort and attempt to continue their work when they should not do so.

Prophylactic measures in the form of dietary supplements for lead workers, such as acid beverages, milk, and vitamin preparations are not to be recommended in lieu of adequate measures for the control of lead exposure. If they are employed in addition to such measures of control, as a means of improving the quality of the food and preventing the dietary deficiencies that commonly exist, they are less open to criticism. Even here, however, it seems probable that advice and instruction in matters of diet, such as may be given by the industrial physician to individuals and groups of workmen, may better serve the purpose.

Likewise the regular administration of cathartic medication is to be condemned unreservedly, and this practice, often resorted to by the workmen themselves, should not be condoned. Constipation is a common human ailment, and for the worker in the lead-using trades it is especially disadvantageous since it promotes lead absorption from the alimentary tract. To the degree that it is caused by lead absorption, this symptom is a sign of lead intoxication, and should be cured by the control of the lead exposure, not by cathartics, but to the degree that it is due to other causes, such as carelessness and faulty diet, it should be dealt with by the recognition and elimination of these causes. The physician in industry has an important advisory and educational function to perform in this and many other hygienic matters.

Since the quantity of lead absorbed by an individual is dependent on the length of his exposure as well as on the severity, it is important to consider the time factor in employment as well as the environmental conditions. (Incidentally, this factor is taken into account when the hygienic significance of occupational lead exposure is measured in terms of urinary lead excretion.) For this reason, the physician should be especially vigilant in periods of accelerated industrial production, when hours of work per day and per week tend to increase. At such times it may be advantageous, or even necessary, to resort to the rotation of men and jobs so as to reduce the time spent by individuals in jobs that involve the greatest lead exposure. No specific rule can be given by which to adapt such rotation to the requirements of the situation, but the guiding principle lies in the fact that the period required for the elimination of lead that has been retained in the tissues is considerably longer than the period over which the lead accumulation occurred. In practical terms, this is equivalent to saying that the length of the period of freedom from exposure (or of reduced exposure) should be at least as long as the period of exposure, if the most satisfactory results are to be obtained. Nevertheless, any regularly occurring break in the lead exposure will result in reduction of the lead absorption, if the break is of sufficient duration

(several days) to provide for the evacuation of the absorbable lead from the alimentary tract.

### B. MANAGEMENT AFTER RECOVERY

The recovery of the industrial worker from an episode of lead poisoning resolves one problem and creates another, in that the question of re-employment then arises. Should the workman return to his former job, and if not, what work should he undertake? In general it may be said that if the conditions that were responsible for his illness have been identified and corrected, he may return to his previous work. Otherwise provision should be made for his employment in a position that will not subject him to potentially hazardous lead exposure. This will not present unsurmountable difficulties in an industry that can provide varied types of employment. Nor is it likely to be difficult in the case of an industrial organization that has adequate information on the lead exposure associated with all of its activities. It must be pointed out, however, that the signs of illness usually disappear long before lead has been eliminated from the body of the workman, and that until such time as the tissues and excreta have reached substantially normal levels of lead concentration, he may be in danger from lead exposures that are not hazardous for other workmen. Therefore, before he takes or resumes an occupation that involves lead exposure at or near the threshold of danger, he should have an interval of freedom from lead exposure sufficient to bring about a material reduction in the lead content of his tissues and excreta. In any case he should be kept under careful observation to make sure of the safety of his work.

It should be noted that the recommendation above is for an interval of time, rather than a period of therapeutic de-leading. The clinical and experimental observations of the writer indicate that the latter procedure is of little or no avail. Even if it were, it would be unnecessary, since time will accomplish the desired result.

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# The Metals (Except Lead)

FRANCIS F. HEYROTH, M.D.

## ALUMINUM

Aluminum, Al, atomic weight 26.97, density 2.70, melting point 648° C., boiling point 1800°, is prepared by the electrolysis of bauxite in a bath of molten cryolite. Dusts in the reduction rooms contain alumina, cryolite, sodium hydroxide, and fluorides of sodium, aluminum, and calcium.

Following the ingestion of salts of aluminum, or the powdered metal, little if any of the metal is absorbed into the tissues. If poisoning occurs, it is due not to aluminum but rather to the absorption of acid liberated from the salts by hydrolysis. Gardner<sup>1</sup> has repeatedly administered colloidal alumina intravenously to rabbits without inducing intoxication. When inhaled by animals, powdered aluminum is rapidly phagocytosed in the alveolar epithelium of the lungs.<sup>2,3</sup> Rabbits exposed for 12 hours daily during 14 months to air bearing 7000 particles per cubic centimeter ( $200 \times 10^6$  particles per cubic foot), gained in weight. No fibrosis was found in the lungs, which appeared normal except for a uniformly distributed mottling of the pleural surfaces, the dark areas consisting of aggregates of dust-filled cells, which almost completely filled the adjacent alveolar spaces.<sup>4</sup>

In Germany during World War II several fatal cases of pulmonary disease ("aluminum dustlung")<sup>5</sup> occurred among men engaged in the stamping and sifting of aluminum pyrotechnic powder, although prior to the war no such illness had occurred. Some investigators<sup>6</sup> attributed the disease to causes other than

<sup>1</sup> L. Gardner, *Ann. Repts. Saranac Laboratory* (1942); *J. Ind. Hyg. Toxicol.*, 26, 48A, 211 (1944).

<sup>2</sup> A. Policard, *Compt. rend. soc. biol.*, 135, 961 (1941); *J. Ind. Hyg. Toxicol.*, 24, 39A (1942); *Bull. Acad. Nat. Med.*, 131, 543 (1947); *J. Ind. Hyg. Toxicol.*, 30, 105A (1948).

<sup>3</sup> O. Ehrismann, *Z. Hyg. Infektionskrankh.*, 122, 166 (1939).

<sup>4</sup> J. J. W. Denny, W. D. Robson, and D. A. Irwin, *Bull. Inst. Mining Met.*, No. 145 (1939); *Ind. Med.*, 8, 133 (1939); *Can. Med. Assoc. J.*, 37, 1 (1937). L. U. Gardner, M. Dworski, and A. B. Delahant, *J. Ind. Hyg. Toxicol.*, 26, 211 (1944).

<sup>5</sup> K. W. Joetten and Eichhoff, *Reichsarbeitsblatt*, 22, Part III, *Arbeitsschutz*, 1942, 102, 342; *Arch. Hyg. Bakt.*, 127, 344 (1942). Goralewski, *Deut. Tuberk.-Blatt*, 17, No. 3 (1943); *J. Ind. Hyg. Toxicol.*, 26, 7A (1944); *Arch. Gewerbepath. Gewerbehyg.*, 9, 676 (1939); 10, 334 (1940); 11, 102, 108 (1941). Jaeger and Jaeger, *ibid.*, 11, 117 (1941).

<sup>6</sup> Koelsch, *Beitr. Klin. Tuberk.*, 97, 688 (1942); *J. Ind. Hyg. Toxicol.*, 25, 100A (1943). M. Doese, *Arch. Gewerbepath. Gewerbehyg.*, 8, 501 (1938).

aluminum, and it has recently been reported<sup>6a</sup> that during the war, when stearine was no longer available as a lubricant, an artificial petroleum jelly prepared by the hydrogenation of coal was used. Investigations of men engaged in the reduction of aluminum ore in Great Britain<sup>7</sup> and elsewhere and of men exposed to alumina in dust form<sup>8</sup> have given no evidence of fibrotic changes in the lungs. The work of Denny, Robson, and Irwin<sup>9</sup> has, on the contrary, demonstrated that the addition of 1 per cent of powdered aluminum to the dust in mines tends to protect miners from silicosis. The protective action is believed to be due to the adsorption of a layer of crystalline  $\alpha$ -monohydrate of aluminum upon the particles of silica,<sup>10</sup> which, by lessening their rate of solution in the fluids of the pulmonary tissues, interferes with their ability to cause the fibrotic lesions of silicosis. Favorable results, both prophylactic<sup>4,11</sup> and therapeutic,<sup>11</sup> were claimed to have been obtained by having the miners inhale air containing aluminum dust before or during exposure to silica. Subsequent investigations of these claims<sup>11a</sup> tend to indicate that the use of aluminum or alumina for this purpose is harmless, at least in the case of men without tuberculosis, but that further carefully controlled work will be needed to establish its field of practical utility. Objective evidence that is capable of reversing or delaying the development of silicosis is lacking, although several observers have noted that subjective evidence of improvement of the symptoms of the disease may occur.<sup>11b</sup> Claims for the prophylactic value of aluminum are difficult to evaluate but the consensus is that its use is not a proper substitute for other measures for controlling the dustiness of the atmosphere. Aluminum should not be used indiscriminately but should be restricted to places

<sup>6a</sup> F. C. Frary, *FIAT Final Rept., 991, Office of Military Government for Germany*, March 6, 1947.

<sup>7</sup> Industrial Pulmonary Disease Committee of the British Medical Research Council, *Lancet*, 2, 1478 (Dec. 19, 1936); *Brit. Med. J.*, 1273 (1936). D. Hunter, R. Milton, K. M. A. Perry, and D. R. Thompson, *Brit. J. Ind. Med.*, 1, 159 (1944).

<sup>8</sup> C. L. Sutherland, A. Meiklejohn, and F. N. R. Price, *J. Ind. Hyg. Toxicol.*, 19, 312 (1937). W. I. Clark and E. B. Simmonds, *J. Ind. Hyg.*, 7, 345 (1925). W. I. Clark, *ibid.*, 11, 92 (1929).

<sup>9</sup> J. J. W. Denny, W. D. Robson, and D. A. Irwin, *Can. Med. Assoc. J.*, 40, 213 (1939).

<sup>10</sup> L. H. Germer and K. H. Storks, *Ind. Eng. Chem., Anal. Ed.*, 2, 583 (1939).

<sup>11</sup> D. W. Crombie, J. L. Blaisdell, and G. MacPherson, *Can. Med. Assoc. J.*, 50, 318 (1944); *J. Ind. Hyg. Toxicol.*, 28, 114A (1944).

<sup>11a</sup> W. D. Robson, *Trans. Canadian Inst. Mining Met.*, 47, 172 (1944); *J. Ind. Hyg. Toxicol.*, 27, 49A (1945); J. W. G. Hannon, *Trans. Canadian Inst. Mining Met.*, 47, 180 (1944); *J. Ind. Hyg. Toxicol.*, 27, 50A (1945); A. W. Jacob, *Trans. Canadian Inst. Mining Met.*, 47, 185 (1944); *J. Ind. Hyg. Toxicol.*, 27, 50A (1945); E. J. King, N. Rogers, and M. Gilchrist, *J. Path. Bact.*, 57, 281 (1945); P. J. Bamberger, *Ind. Med.*, 14, 477 (1945); I. R. Tabershaw and B. D. Tebbens, *ibid.*, 14, 709 (1945); D. R. Johns and S. J. Petronella, *Monthly Bull. Indiana State Bd. Health*, 48, 203, 216 (1945); *J. Ind. Hyg. Toxicol.*, 28, 55A (1946).

<sup>11b</sup> Report of Council on Industrial Health and Council on Pharmacy and Chemistry of the American Medical Association, *J. Am. Med. Assoc.*, 130, 1223 (1946); J. W. G. Hannon, *Ind. Med.*, 15, 527 (1946); W. E. George, *Suppl. to New South Wales Ind. Gaz.*, Sept., 1946; *J. Ind. Hyg. Toxicol.*, 29, 90A (1947); A. Meiklejohn and W. W. Jones, *J. Ind. Hyg. Toxicol.*, 30, 160 (1948); A. R. Riddell, *U.S. Div. Labor Standards Bull.*, 94, 25 (1948); *J. Ind. Hyg. Toxicol.*, 30, 90A (1948).

where conventional control measures are not feasible.

The manufacture of an abrasive (corundum) from bauxite, iron, and coke in electric furnaces involves an exposure of the furnace men to a dense white fume consisting of very finely divided amorphous material, 0.01 to 0.5  $\mu$  in diameter, and containing 85 to 90 per cent of alumina, the remainder being silica, iron oxide, and other materials.<sup>11c</sup> In one plant, from 7.5 to 122 mg. of this material were found per cubic meter of air.

Of 344 workers in four plants employing this process, 23 were found by Shaver and Riddell<sup>11d</sup> to exhibit a type of pulmonary disease unlike any previously known pneumoconiosis. Seven of the men died and others were seriously disabled. The disease consisted essentially of a nonnodular, interstitial pulmonary fibrosis, in which broad bands of pigmented scar tissue were located, chiefly in the depths of the lungs. Emphysematous blebs and bullae occurring on the visceral pleura in many instances ruptured spontaneously, giving rise to pneumothoraces. Riddell,<sup>11d</sup> who published some of Gardner's uncompleted observations on the ability of the stack fumes to produce bands of fibrosis several months after inoculation into experimental animals, is of the opinion that the current belief in the harmlessness of aluminum when inhaled in large quantities may require some revision. Although the incrimination of any one of the components of the fume as the causal agent offers a difficult problem, it is of interest that the cases of pulmonary disease attributed by Goralewski<sup>5</sup> to the inhalation of aluminum dust bore some resemblance to these more recent cases, although the nature of the exposure in Germany was quite different.

Aluminum filings rubbed into the skin of man or animals, and aluminum splinters embedded in the skin, do not induce a state of hypersensitivity.<sup>12</sup> Repeated contact of the skin with certain salts of aluminum results in irritation, due to acid liberated by hydrolysis, rather than to the aluminum ion, since aluminum acetate is nonirritating. A congestive, anesthetic condition of the fingers known as acroanesthesia<sup>13</sup> occurs among wet bobbin winders in cotton mills as a result of long contact of the skin with alum.

The ease of ignition of powdered aluminum has caused many fires and explosions.<sup>14</sup> When the diameter of an average particle is 0.14  $\mu$ , the lower

<sup>11c</sup> C. M. Jephcott, J. H. Johnston, and G. R. Findlay, *J. Ind. Hyg. Toxicol.*, 30, 145 (1948).

<sup>11d</sup> C. G. Shaver and A. R. Riddell, *J. Ind. Hyg. Toxicol.*, 29, 145 (1947). A. R. Riddell, *Occupational Med.*, 4, 56 (1947).

<sup>12</sup> E. Sedlacek, *Arch. Gewerbepath. Gewerbehyg.*, 10, 445 (1941). F. Marquardt, *Med. Welt*, 1939, 1317; *Zentr. Gewerbehyg. Unfallverhüt.*, 27, 130 (1940); *J. Ind. Hyg. Toxicol.*, 24, 158A (1942).

<sup>13</sup> R. P. White, *The Dermatogoses or Occupational Affections of the Skin*. 4th ed., Lewis, London, 1934.

<sup>14</sup> H. R. Brown, *U.S. Bur. Mines Information Circ. No. 7148* (Mar. 1941); *J. Ind. Hyg. Toxicol.*, 23, 127A (1941). G. H. Durston and W. Bleyburg, *Light Metals*, 4, 127 (1941). R. E. Maginnis, *Safety Eng.*, 79, No. 4, 39 (1940). F. Ritter, *Z. Ver. deut. Ing.*, 74, 145 (1930). G. M. Babcock and F. B. Rethwisch, *Chem. & Met. Eng.*, 60, No. 1, 82 (1943).

limiting explosive concentration is 40 to 50 mg. per liter of air.<sup>15</sup> Large fires must be isolated and allowed to burn out, but small ones may be controlled by the use of sand, of talc, or of sodium chloride<sup>16</sup> (see Chapter Thirteen, in Volume One).

## ANTIMONY

### 1. Properties, Uses, and Industrial Exposures

Antimony, Sb, is a silver-white metal of atomic weight 121.76 and density 6.70, which melts at 630° C. and boils at 1440°. It is usually obtained by roasting the mineral stibnite and smelting the resultant oxide with charcoal. Dusts or fumes containing the metal, its oxides, or sulfides may be inhaled by those who crush the ores, tend or clean the extraction chambers, or collect the oxide dusts from the roasting chambers.

Antimony enters into the composition of type and babbitt metals, certain dental alloys, and storage battery grids. Foundry workers, linotypers, monotypers, and stereotypers may be exposed to fumes that contain antimony. Stibine, SbH<sub>3</sub>, a highly toxic gas with a characteristic odor, may be liberated by storage batteries on overcharge.<sup>17</sup> The gas was evolved when a hot aluminum dross contaminated with antimony was sprinkled with water.<sup>18</sup>

Antimony trioxide, Sb<sub>2</sub>O<sub>3</sub>, is used in ceramics, in the manufacture of pigments, and as a mordant in dyeing and printing textiles. Antimony pentasulfide, Sb<sub>2</sub>S<sub>5</sub>, enters into the composition of matches, fireworks, and explosives. It is also used in the compounding of rubber.<sup>18a</sup> Minor uses of the metal and its compounds in metal polishing and decoration, in the chemical industry, and in medicine have not given rise to serious hygienic problems.<sup>18b</sup>

Antimony may be determined colorimetrically by methods employing Rhodamine B<sup>19</sup> or 9-methyl-2,3,7-trihydroxyfluor-6-one.<sup>20</sup> It may also be determined spectrographically.<sup>20a</sup>

### 2. Toxicity of Antimony and Its Compounds

The toxicity of elementary antimony is of the same nature as that of elementary arsenic,<sup>21</sup> its lethal dose when administered intraperitoneally to rats being 100 mg. per kilogram of body weight.<sup>22</sup> It causes dyspnea and convulsions,

<sup>15</sup> R. B. Mason and C. S. Taylor, *Ind. Eng. Chem.*, **29**, 626 (1937); **32**, 67 (1940).

<sup>16</sup> D. J. Price and R. W. Bader, *Chem. & Met. Eng.*, **29**, 878 (1923).

<sup>17</sup> H. F. Haring and K. G. Compton, *Trans. Electrochem. Soc.*, **63**, 283 (1935).

<sup>18</sup> C. A. Nau, W. Anderson, and R. E. Cone, *Ind. Med.*, **13**, 308 (1944). C. U. Dernehl, F. M. Stead, and C. A. Nau, *ibid.*, **13**, 361 (1944).

<sup>18a</sup> R. S. Quimby, *J. Ind. Hyg.*, **8**, 108 (1926).

<sup>18b</sup> F. M. R. Bulmer and J. H. Johnston, *J. Ind. Hyg. Toxicol.*, **30**, 26 (1947).

<sup>19</sup> W. G. Fredrick, *Ind. Eng. Chem., Anal. Ed.*, **13**, 922 (1941). A. Gellhorn, M. E. Krahl, and J. W. Fertig, *J. Pharmacol.*, **87**, 159 (1946).

<sup>20</sup> S. H. Webster and L. T. Fairhall, *J. Ind. Hyg. Toxicol.*, **27**, 183 (1945). P. Wenger, R. Duckert, and C. P. Blancpain, *Mikrochim. Acta*, **3**, 13 (1938).

<sup>20a</sup> J. Cholak and D. M. Hubbard, *J. Ind. Hyg. Toxicol.*, **28**, 121 (1946).

<sup>21</sup> O. Rybak, *Lék. rozhledy*, **2**; *Chem. Abstracts*, **8**, 1165 (1914).

<sup>22</sup> W. R. Bradley and W. G. Fredrick, *Ind. Med., Ind. Hyg. Sect.*, **2**, 15 (1941).

impairs the action of the heart,<sup>23</sup> and damages the liver. Its oxides and sulfides are less toxic than those of arsenic, the trivalent compounds being slightly more toxic than the pentavalent ones.<sup>24</sup> Expressed as milligrams per kilogram of body weight, the dosages of various compounds required to kill half of the rats injected intraperitoneally are: antimony trisulfide, 1000; antimony pentasulfide, 1500; antimony trioxide, 3250; and antimony pentoxide, 4000.<sup>22</sup> Brachmachari,<sup>25</sup> however, found that the lethal dose of the trioxide when administered intramuscularly to guinea pigs is between 20 and 25 mg. per kilogram.

Intoxication by antimony induces myocardial congestion and edema, dilatation of the right chambers of the heart, and congestion of the viscera with occasional interstitial hemorrhages.<sup>22</sup>

After having inhaled air bearing antimony trioxide fumes in an average concentration of 45.4 mg. of  $Sb_2O_3$  per cubic meter for 2 or 3 hours per day over varying periods, guinea pigs developed an interstitial pneumonitis with fatty degeneration of the liver, and the number of leucocytes in their circulating blood diminished.<sup>25a</sup> Fairhall and Hyslop<sup>25b</sup> report that the dust of the free metal is more toxic on inhalation than any of its sulfides or oxides.

The growth of rats is not affected by the daily oral administration, on five days, of 4 mg. of either of the oxides of antimony, but it is slightly retarded when 200 mg. of antimony trioxide is given daily.<sup>24</sup> Cats lose weight when given daily 450 mg. of either oxide. No tolerance develops. The number of leucocytes in the blood of cats or rabbits given antimony is diminished,<sup>26</sup> but the proportion of mononuclear cells, lymphocytes, and especially eosinophiles is relatively increased.<sup>22</sup> There is some evidence that antimony compounds may be detoxified by conversion to sulfides.<sup>27</sup>

### 3. Industrial Intoxication

Sir Thomas Oliver<sup>28</sup> found no signs of illness in six men engaged in the production of antimony oxide. Schrupf and Zabel<sup>28</sup> noted leucopenia and signs and symptoms of chronic intoxication resembling mild lead poisoning among a group of type founders, and attributed them to the absorption of antimony because they were unable to detect the presence of lead in the urine. The inadequacy of the analytical method then available renders their conclusions of little significance. The concentration of antimony in the blood or excretions in alleged cases of poisoning has not been adequately investigated, and there are no quantitative data that can be used to establish a relationship between the degree of exposure to antimony dust or fumes and the severity of intoxication. No maximum safe concentration for antimony in the air of workrooms has been proposed.

<sup>23</sup> G. A. Masson, *J. Pharmacol.*, 30, 68 (1926).

<sup>24</sup> F. Flury, *Arch. exptl. Path. Pharmacol.*, 126, 87 (1927).

<sup>25</sup> U. N. Brachmachari, *Indian J. Med. Research*, 11, 196 (1923); cited by W. R. Bradley and W. G. Fredrick, *Ind. Med., Ind. Hyg. Sect.*, 2, 15 (1941).

<sup>25a</sup> C. V. Dernehl, C. A. Nau, and H. H. Sweets, *J. Ind. Hyg. Toxicol.*, 27, 256 (1945).

<sup>25b</sup> L. T. Fairhall and F. Hyslop, *U.S. Pub. Health Repts., Suppl. No. 195* (1947).

<sup>26</sup> P. Schrupf and B. Zabel, *Arch. exptl. Path. Pharmacol.*, 63, 242 (1910).

<sup>27</sup> E. Hesse, *Arch. exptl. Path. Pharmacol.*, 122, 354 (1927).

<sup>28</sup> Sir Thomas Oliver, *Brit. Med. J.* 1933, I, 1094.

Men exposed to antimony fumes in foundries,<sup>28,29</sup> and in the handling of antimony salts in textile dyeing,<sup>30</sup> have developed a maculopustular rash. Keratitis and ulceration of the nasal septum also have resulted from exposure to antimony-bearing dusts. The role played in the production of these lesions by arsenic as a contaminant has not been determined.

## BERYLLIUM

### 1. Properties, Uses and Industrial Exposures

Beryllium, Be, is a light metal (atomic weight 9.02, specific gravity 1.85, melting point 1285° C., boiling point 2780°) that is used in the making of precision instruments and nonsparking tools, in x-ray apparatus, and in research in nuclear physics. Alloys of copper and beryllium possess great resistance to fatigue and are used in diaphragms of altimeters, in electrical equipment, and for a wide variety of purposes. Beryllium compounds enter into the composition of phosphors used in the manufacture of fluorescent lamps.

Extraction of the metal from beryl (beryllium aluminum silicate), its chief source, is difficult. In one German process,<sup>31</sup> the powdered mineral was heated with sodium fluoride and silicofluoride in order to form soluble sodium beryllium fluoride, which was then leached from the powdered mass with water. The beryllium was precipitated as hydroxide, and converted into the fluoride either by dissolving it in a 40 per cent solution of hydrofluoric acid or, after drying, by fusing it with ammonium bifluoride. The metal was liberated by electrolyzing the molten beryllium fluoride in a graphite crucible, using iron or copper cathodes, fluorides of other metals including barium being added to increase the conductivity. Exposure to dusts of beryl, beryllium fluoride, and various other fluorine-containing compounds, as well as hydrogen fluoride, may occur during the extraction.<sup>32</sup>

In the manufacture of copper-beryllium alloys, beryllium hydroxide is converted to beryllium oxide by calcination, mixed with copper oxide and carbon powder and melted in an electric arc furnace, charged with additional amounts of pure copper. The resulting alloy is remelted with more copper in coke-fired crucible furnaces.

### 2. Determination of Beryllium

Cholak and Hubbard<sup>33</sup> have described a spectrographic method for the determination of beryllium in urine, blood, and animal tissues, or in dusts in the air. Unlike previously described colorimetric or fluorimetric methods,<sup>34</sup> it is suitable for the determination of the small amounts encountered in toxicologic investigations.

<sup>28</sup> A. Feil, *Presse méd.*, 47, 1133 (1939).

<sup>29</sup> A. B. Selisky, *Dermatol. Wochschr.*, 86, 723 (1928).

<sup>30</sup> H. H. Weber and W. E. Engelhardt, *Zentr. Gewerbehyg. Unfallverhüt.*, 10, 41 (1933).

<sup>31</sup> J. Shilen, A. E. Galloway, and J. F. Mellor, Jr., *Ind. Med.*, 13, 464 (1944).

<sup>32</sup> J. Cholak and D. M. Hubbard, *Anal. Chem.*, 20, 73, 970 (1948).

<sup>33</sup> F. Hyslop, E. D. Palmes, W. C. Alford, A. R. Monaco, and L. T. Fairhall, *Natl. Inst. Health Bull.* No. 181 (1943).



### 3. Toxicity of Beryllium for Animals

Recent reports of the occurrence of a large number of cases of industrial pulmonary disease which could be ascribed only to the inhalation of beryllium compounds, and the use of beryllium in the development of atomic energy have led several laboratories to repeat and amplify the older observations on the toxicity of beryllium. Even so recently as 1943, a bulletin issued by the U. S. Public Health Service,<sup>34</sup> which contained a review of the older toxicological observations together with original experimental work performed at the Institute of Health, stated that beryllium and its insoluble compounds were intrinsically nontoxic, the toxicity of the soluble compounds, when administered intraperitoneally,<sup>34a</sup> being ascribed to their tendency to hydrolyze with the liberation of strong acid.

Subsequent experimental work has shown that this concept must be revised. Experiments conducted at the University of Rochester<sup>34b</sup> have shown the LD<sub>50</sub> of beryllium sulfate, when administered intravenously to rats, is only 7.2 mg. per kg., corresponding to 0.36 mg. of beryllium per kg. This dose is far too small for the lethal action to be ascribed to the sulfate ion. Microscopic observations of the tissues of rats given such doses revealed the presence of mid-zonal focal necrosis of the liver, an epithelial necrosis of the distal third of the proximal convoluted tubules of the kidney, and some degenerative changes in the hemopoietic system. Of greater interest is the observation by Gardner at Saranac,<sup>34c</sup> subsequently confirmed elsewhere,<sup>34d</sup> that the intravenous administration to rabbits of a series of doses of a suspension of an insoluble beryllium compound (oxide, phosphate, or zinc beryllium silicate) was followed after several months to a year by the development of osteosarcoma.

In experiments in which beryllium compounds were given orally to animals, beryllium sulfate and beryllium oxyfluoride induced hemorrhagic necrosis of the gastric mucosa,<sup>34</sup> but the metal is poorly absorbed from the digestive tract, the rate varying from animal to animal. In the case of a dog given 30 mg. of the metal as sulfate, 94 per cent of the dose appeared in the feces and 1.6 per cent in the urine.<sup>34</sup> Storage is chiefly in the bones, only small amounts being found in the soft tissues.

Metallic beryllium or beryllium oxide can be incorporated to the extent of 5 per cent in the diet of rats without affecting their rate of growth over long periods,<sup>34e</sup> but the presence of 5 per cent of beryllium carbonate in their diet

<sup>34a</sup> E. A. Maynard, W. L. Downs, and H. C. Hodge, *U.S. Atomic Energy Commission, Report MDDC-1233* (1947); *Federation Proc.*, 7, 227 (1948).

<sup>34b</sup> J. K. Scott, *U.S. Atomic Energy Commission, Report MDDC-1237* (1947); *Arch. Path.*, 45, 354 (1948).

<sup>34c</sup> L. U. Gardner, *Trans. 11th Ann. Meeting Ind. Hyg. Foundation*, 88 (1946); *J. Ind. Hyg. Toxicol.*, 29, 71A (1947).

<sup>34d</sup> F. R. Dutra and E. J. Largent, *unpublished observations*.

<sup>34e</sup> E. A. Maynard, W. L. Downs, and H. C. Hodge, *U.S. Atomic Energy Commission, Report MDDC-1234* (1947); *Federation Proc.*, 7, 244 (1948).

completely inhibited their growth. Beryllium sulfate interfered with the growth of guinea pigs when the dietary level was 1.4 per cent, while beryllium oxy-fluoride was toxic at a level of 0.1 per cent.<sup>34</sup> It has been shown repeatedly that the continued dietary administration of beryllium compounds produces a rachitic state, presumably by interfering with the normal absorption of phosphorus.<sup>34f</sup>

When solutions of beryllium fluoride, beryllium sulfate and beryllium oxy-fluoride were administered intratracheally to rats, the lethal dosages were, respectively, 15, 10, and 2 mg. per kg.,<sup>34g</sup> but the administration in this fashion of suspensions of beryllium dust or of insoluble beryllium compounds in saline solution in the largest dosages that could be given without causing mechanical interference with pulmonary function was not immediately lethal. The administration of a single dose of 100 mg. per kilogram of either of these suspensions failed to affect the growth of rats over the following 200 days, and in animals killed after periods of up to 100 days no evidence of scarring, fibrosis, or granulomatous lesions of the lungs could be found. An undue proportion of the injected animals died from 100 to 300 days following injection, and exhibited severe lung damage with various combinations and degrees of edema, hemorrhage, consolidation, and ulceration.

Experiments in which animals inhaled air-borne dusts of metallic beryllium,<sup>34h</sup> such insoluble beryllium compounds as beryllium oxide,<sup>31</sup> beryl,<sup>34</sup> or beryllium carbonate<sup>34</sup> gave little evidence of any immediate toxic effects. However, in one experiment in which guinea pigs were subjected over a period of 107 days to a series of 90 exposures of 30 to 40 minutes to air bearing 188.9 mg. of beryllium as carbonate per cubic meter, the mortality was 44 per cent, and the deaths of some, at least, of the animals were ascribed to a "dust pneumonia." Fabroni<sup>34i</sup> proposed the name "berylliosis" for a pulmonary condition induced by the inhalation of beryllium carbonate. However, in no published report was evidence advanced for the production of a granulomatous lesion of the type recently found to occur in beryllium workers, possibly because the animals were sacrificed before sufficient time had elapsed following the exposure to permit of the development of this type of lesion. At a recent symposium<sup>35</sup> it was stated that the long-continued inhalation of zinc beryllium silicate dust,

<sup>34f</sup> H. D. Branion, B. L. Guyatt, and H. D. Kay, *J. Biol. Chem.*, *92*, Proc. ii (1931). H. D. Kay, *ibid.*, *99*, 85 (1932). H. D. Kay and D. I. Skill, *Biochem. J.*, *28*, 1222 (1934). A. E. Sobel, A. R. Goldfarb, and B. Kramer, *J. Biol. Chem.*, *108*, 395 (1935). C. W. Duncan and E. J. Miller, *J. Nutrition*, *11*, 371 (1936). J. H. Jones, *Am. J. Physiol.*, *124*, 230 (1938).

<sup>34g</sup> C. W. LaBelle and M. R. Cucci, *U.S. Atomic Energy Commission, Report MDDC-1232* (1947); *Federation Proc.*, *7*, 236 (1948). H. Wurm and H. Ruger, *Beitr. Klin. Tuberk.*, *98*, 296 (1942).

<sup>34h</sup> I. Gelman, *J. Ind. Hyg. Toxicol.*, *18*, 371 (1936). M. Berkovitz and B. Israel, *Klin. Med. (U.S.S.R.)*, *18*, 117 (1940).

<sup>34i</sup> S. M. Fabroni, *Med. del Lavoro*, *26*, 297 (1935); cited by S. Caccuri, *Rass. Med. Ind.*, *11*, 307 (1940).

<sup>35</sup> Sixth Saranac Symposium, Sept. 29 to Oct. 3 (1947).

in experiments performed at the Saranac Laboratory, induced after a period of 2.5 years a pulmonary picture simulating that encountered in man.

On the other hand, the inhalation of beryllium sulfate dust in a concentration of approximately 90 mg. per cubic meter of air for 6 hours daily over a period of 2 weeks<sup>36</sup> was highly toxic to animals of several species, pulmonary edema being encountered in mice, rabbits, and rats, but not in guinea pigs. All animals, irrespective of species, exhibited a superficial ulceration of the bronchial epithelium, with an inflammatory exudate in the lumens of the terminal bronchi. Guinea pigs and dogs developed conjunctivitis and some of them, a severe ulcerative keratitis.

#### 4. Industrial Intoxication

Recognition of beryllium as an industrial hazard was delayed because the first outbreaks of disease occurred in German<sup>31</sup> and Russian<sup>34h</sup> plants for the preparation of beryllium compounds by processes which involved a concomitant exposure to fluorides. As described by Gelman,<sup>34h</sup> men exposed to beryllium oxyfluoride or other dusts or fumes encountered in such processes became ill with typical metal fume fever. This lasted only a few hours, but was followed after 1 to 5 days by the onset of an extensive bronchioloalveolitis, with coughing, dyspnea, rapid respirations, fever, and cyanosis, which persisted for 6 to 10 days and was occasionally followed by a relapse. However, in 1942, Meyer<sup>37</sup> described several cases of an acute pulmonary disease akin to pneumonia, 6 of them serious and 3 fatal, that occurred among men who had been engaged for a few months in the preparation of beryllium by a process that did not involve an exposure to fluorides.

In 1945, 170 cases of illness occurred in certain Ohio beryllium plants, the incidence being greatest among men whose work involved exposure to the soluble beryllium salts.<sup>38</sup> In most of the cases the disease consisted of an edematous papulovesicular contact dermatitis, or a conjunctivitis, but 38 of the patients developed nasopharyngitis, tracheobronchitis or pneumonitis, with cough, substernal pain, dyspnea, cyanosis, anorexia, and fatigue. Five of these patients died.

A delayed chemical pneumonitis, now usually designated as pulmonary granulomatosis, has also been found to occur among beryllium workers,<sup>35,38a</sup> some of whom were exposed to dusts of the phosphors used in the manufacture of fluorescent lamps, or were engaged in the manufacture of beryllium copper alloys.

The incidence of pulmonary granulomatosis among exposed workers is

<sup>36</sup> G. F. Sprague, A. G. Pettengill, and H. E. Stokinger, *Federation Proc.*, 7, 257 (1948). J. K. Scott, *U.S. Atomic Energy Commission, Report MDCC-1237* (1947).

<sup>37</sup> H. E. Meyer, *Beitr. Klin. Tuberk.*, 98, 388 (1942). H. Wurm and H. Rüger, *ibid.*, 98, 396 (1942).

<sup>38</sup> H. S. Van Ordstrand, R. Hughes, J. M. De Nardi, and M. G. Carmody, *J. Am. Med. Assoc.*, 129, 1084 (1945). D. E. Kress and K. R. Crispell, *Guthrie Clin. Bull.*, 13, 91 (1944).

<sup>38a</sup> H. L. Hardy and I. R. Tabershaw, *J. Ind. Hyg. Toxicol.*, 28, 197 (1946). J. Pyre and W. H. Oatway, Jr., *Arizona Med.*, 4, 21 (1947). H. L. Hardy, *Bull. New Engl. Med. Center*, 9, 16 (1947). L. M. Pascucci, *Radiology*, 50, 23 (1948). S. A. Wilson, *ibid.*, 50, 770 (1948).

believed to be low, and attempts to relate the incidence of the disease to the degree of exposure have been unsuccessful.<sup>34c</sup> An interesting feature is the fact that the onset may be delayed for months or years after the last exposure of the victim to beryllium. This form of the disease, the first few cases of which were confused with Boeck's sarcoid, which it resembles in several respects, begins insidiously with loss in weight, anorexia, dyspnea, and cough after a latent period of from about 3 months to 3 years. Its course is of long duration and is usually, but not always, progressive. The mortality is high, death following a period of cachexia, progressive dyspnea, and heart failure. The pulmonary lesions consist of focal intraalveolar compact granules composed of proliferating cells with widely scattered multinucleated giant cells. Beryllium has been found in the lungs in the few cases in which an appropriate analytical method has been employed in searching for it. In one case,<sup>38b</sup> it was found widely disseminated throughout the tissues, the amounts present in  $\mu\text{g.}$  per 100 g. of wet tissue being: lung, 12; liver, 8.4; spleen, 4.3; bones, 13.5; and kidneys, 27.2. In some cases, cutaneous granulomas have also been described, and it has been reported that cuts of the skin by broken fluorescent lamp bulbs have given rise to subcutaneous granulomas about unremoved bits of a beryllium phosphor.<sup>38c</sup> No sarcoidlike lesions have been found in the bones.

### 5. Maximum Safe Working Concentrations

Efforts have been made to determine the concentration and nature of the dusts or fumes to which men were exposed in plants in which the acute phase of the pulmonary disease, or the dermatitis has occurred. In one survey, beryllium dust concentrations of 0.050 to 0.53 mg. per cubic meter of air, with fluoride concentrations of the same order, were found near a rotary kiln drier, but the particle size was quite large. Greater concentrations (1.4 to 4.7 mg. of beryllium and 1.7 mg. of fluoride per cubic meter) were found near a beryllium metal furnace.<sup>38d</sup> Eisenbud, Berghout, and Steadman<sup>38e</sup> state that an exposure of only 20 minutes to beryllium fluoride was responsible for 3 cases. In areas where only a fraction of a milligram of either the sulfate or the fluoride could be inhaled daily, the incidence of the acute phase of the disease has been high. All cases were associated with exposure to concentrations in excess of 0.1 mg. per cubic meter, and 8 employees exposed to a concentration of 0.015  $\mu\text{g.}$  of the sulfate per cubic meter failed to develop the disease.

No data are available upon which to base a value for the maximum concentration of any beryllium compound that can be inhaled without producing beryllium granulomatosis in at least a few of a number of exposed persons.

<sup>34b</sup> H. S. Martland, H. A. Brodtkin, and H. S. Martland, Jr., *J. Med. Soc. New Jersey*, 45, 5 (1948).

<sup>34c</sup> R. S. Grier, P. Nash, and D. G. Freiman, *J. Ind. Hyg. Toxicol.*, 30, 228 (1948).

<sup>34d</sup> S. Laskin, R. A. N. Turner, and H. E. Stokinger, *Federation Proc.*, 7, 236 (1948).

<sup>34e</sup> M. Eisenbud, C. F. Berghout, and L. T. Steadman, *J. Ind. Hyg. Toxicol.*, 30, 281 (1948).

## CADMIUM

### 1. *Properties, Uses, and Industrial Exposures*

Cadmium, Cd, atomic weight 112.41, is obtained from the mineral greenockite, CdS, or more usually as a by-product in the smelting of impure zinc ores. It is a ductile, malleable, silver-white metal which takes a high polish and is resistant to corrosion. It has a density of 8.65 at 20°; melts at 320.9° C., and boils at 767°. Cadmium vapor, which is about 3.88 times as heavy as air, burns with a bright flame emitting brown fumes of the oxide. The latter is only slightly volatile at 700° C., but decomposes at 1000°.

Cadmium vapor lamps have a limited use in physical laboratories. Alloys of cadmium are used in electrical conductors, solders, antifriction and bearing metals, alkaline storage batteries, and jewelry. Cadmium compounds are used in electroplating, ceramics, process engraving, and photography. The pigment, cadmium yellow, CdS, is sometimes used in the coloring of glass and in certain paints. In 1940 it was estimated that more than 30,000 workers in the United States were potentially exposed to cadmium and its compounds<sup>39</sup>: in smelting ores, plating with cadmium, manufacturing cadmium compounds, welding, soldering or heat-treating cadmium-containing or cadmium-plated metals, or otherwise.<sup>40</sup> Nearly 60 cases of acute industrial poisoning by inhalation of cadmium-bearing fumes have been reported since 1858.<sup>41</sup> Fumes emitted in the smelting of impure zinc ores have contained as much as 5 per cent cadmium. Air in the vicinity of a tank in which cadmium had been leached from a roasted zinc ore by acid contained 29.3 mg. of cadmium per 10 cubic meters.<sup>42</sup> Several fatal cases of poisoning occurred among workers who flanged cadmium-plated steel pipe by heating it to redness with a blowpipe.<sup>41</sup> Other operations that have led to poisoning include the welding of cadmium-plated levers on electrical switch boxes and the heating of cadmium-plated rivets in a furnace at 1400 to 1500° F. In such operations the fumes of cadmium oxide may be inhaled in fatal concentrations without causing immediate discomfort. In a fire caused by the ignition of the dust on the floor of a cadmium-recovery chamber the fumes affected 23 persons.

Cadmium salts are toxic when ingested. Nearly 300 cases of nonindustrial poisoning have been reported,<sup>43</sup> many of them having resulted from food contaminated by the use of cadmium-coated metal in food containers.<sup>44</sup>

### 2. *Determination in the Atmosphere*

Cadmium-bearing dusts may be obtained from samples of air by the use of a standard impinger or, especially in the case of fumes, an electrostatic precipita-

<sup>39</sup> J. J. Bloomfield, V. M. Trasko, R. R. Sayers, R. T. Page, and M. F. Peyton, *U.S. Pub. Health Bull.* No. 259 (1940).

<sup>40</sup> Prodan, *J. Ind. Hyg.*, 14, 132, 151 (1932). L. I. Dublin and R. T. Vane, *U.S. Bur. Labor Statistics Bull.* No. 582, 32 (1933).

<sup>41</sup> L. W. Spolyar, J. T. Keppler, and H. G. Porter, *J. Ind. Hyg. Toxicol.*, 26, 232 (1944).

<sup>42</sup> *Illinois Labor Bull.* No. 3, July 31, 1942; *J. Ind. Hyg. Toxicol.*, 25, 12A (1943).

<sup>43</sup> U.S. Pub. Health Service, Div. Ind. Hyg., *U.S. Pub. Health Repts.*, 67, 601 (1942).

<sup>44</sup> J. J. Schiftner and H. Mahler, *Am. J. Pub. Health*, 33, 1224 (1943).

tor. Many reagents have been used in the colorimetric determination of cadmium, among the most satisfactory being dithizone<sup>45</sup> and di- $\beta$ -naphthylthiocarbazone.<sup>46</sup> For quantities down to 1 mg., a volumetric method based upon the use of  $\beta$ -naphthoquinoline and titration with potassium iodate may be employed.<sup>47</sup> Quantities of the order of 1.5 to 500  $\mu$ g. can be determined polarographically.<sup>46,48</sup> Cholak and Hubbard<sup>46</sup> also describe a spectrographic method for quantities of the order of 0.4 to 200  $\mu$ g., using the 3261A line of cadmium and the 3209A line of molybdenum.

### 3. Toxicity of Cadmium

Cadmium chloride is a powerful emetic, the minimum effective dose for cats being 4 mg. per kilogram of body weight.<sup>49</sup> Kobert<sup>50</sup> gave 0.15 to 0.30 g. per kilogram as the lethal oral dose in the case of rabbits. The ingestion of 33 mg. by a man caused nausea and vomiting, but an amount ten times as great failed to cause permanent injury.<sup>51</sup> A boy died 1 $\frac{1}{2}$  hr. after he had taken about 8.9 g. of cadmium chloride, mistaken for a purgative.<sup>52</sup> Ingestion of a cadmium salt induces salivation, choking attacks, persistent vomiting, abdominal pain, tenesmus and diarrhea, attacks of vertigo, and loss of consciousness. Catarrhal and ulcerative gastroenteritis, congestion and pulmonary infarcts, and subdural hemorrhages are found at necropsy.

When injected subcutaneously, cadmium salts induce inflammation, and coagulation necrosis at the site of administration. The irritant action apparently is due to the metal rather than to the acid radical, since cats suffer fatal pulmonary irritation as the result of 15 minutes of enforced inhalation of the fumes produced by burning metallic cadmium in oxygen.<sup>40</sup> The inhalation of air containing 2 mg. of cadmium fumes per liter for a period of 5 to 15 minutes on each of 10 to 16 days induced fatal pneumonia, according to the observations of Otto.<sup>53</sup>

Values for the LD<sub>50</sub> of fumes from a cadmium arc, when inhaled by animals of various species, have been determined recently by Barrett, Irwin, and

<sup>45</sup> A. K. Klein and H. S. Wichmann, *J. Assoc. Official Agr. Chem.*, **28**, 257 (1935). F. W. Church, *J. Ind. Hyg. Toxicol.*, **29**, 34 (1947).

<sup>46</sup> J. Cholak and D. Hubbard, *Ind. Eng. Chem., Anal. Ed.*, **16**, 333 (1944).

<sup>47</sup> Subcommittee on Chemical Methods of Analyses, Am. Pub. Health Assoc., *Am. J. Pub. Health*, **33**, 862 (1943); H. A. Bewick, A. J. Cruikshank, and F. E. Beamish, *Anal. Chem.*, **19**, 269 (1947).

<sup>48</sup> F. L. Feicht, H. H. Schrenk, and C. E. Brown, *U.S. Bur. Mines, Rept. Investigations 3639* (May 1942); *J. Ind. Hyg. Toxicol.*, **25**, 21A (1943). J. J. Lingane, *Ind. Eng. Chem., Anal. Ed.*, **16**, 147 (1944). D. P. Malyuga, *J. Gen. Chem. (U.S.S.R.)*, **13**, 391 (1943).

<sup>49</sup> Alsberg and Schwartze, *J. Pharmacol.*, **13**, Proc. 504 (1919).

<sup>50</sup> R. Kobert, *Lehrbuch der Intoxikationen*, **II**, 1906, 399.

<sup>51</sup> Griebel and Weiss, *Pharm. Zentralhalle*, **72**, 689 (1931); cited in *U.S. Pub. Health Repts.*, **57**, 601 (1942).

<sup>52</sup> W. J. Palmer, *Indian Med. Gaz. (Calcutta)*, **1**, 156 (1866); cited in *U.S. Pub. Health Repts.*, **57**, 601 (1942).

<sup>53</sup> A. Otto, *Zentr. Gewerbehyg.*, **2**, 309 (1925); cited in Prodan, *J. Ind. Hyg.*, **14**, 132 (1932).

Semmons.<sup>53a</sup> Expressed in terms of the product (CT) of minutes of exposure and concentration in mg. per cubic meter, they are: rats, 500; mice, less than 700; rabbits, 2500; guinea pigs, 3500; dogs, 4000; and monkeys, 15,000. It is estimated that the CT value in the case of 2 fatal human cases was of the order of 2500 and certainly not greater than 2900 mg. minutes per cubic meter. In the case of dogs exposed to an aerosol of cadmium chloride, the CT<sub>90</sub> value was 9600,<sup>53b</sup> death being due to pulmonary injury.

Although some investigators<sup>53b</sup> have reported that British anti-lewisite (BAL) reduces the mortality in such experiments, others<sup>53c</sup> have found that its use may induce a fatal renal disease, presumably due to the reabsorption of the cadmium-BAL compound, in the tubules. The glucoside of BAL is preferable because it is less readily reabsorbed.

Our knowledge of chronic poisoning is derived from experiments in which cadmium salts have been incorporated in the food of animals. The largest tolerable proportion of cadmium in the diet of cats (without inducing vomiting) was 200 p.p.m.<sup>49</sup> Cadmium prevented the growth of rats, and induced fatal poisoning when present to the extent of 250 p.p.m. in their diet.<sup>54</sup> In the case of male cats, the presence of 125 p.p.m. cadmium in the diet caused death in 50 days or less, but a dietary concentration of 62.5 p.p.m. had no effect on growth. The daily administration of 0.56 mg. of cadmium revealed no cumulative action.

An interesting phenomenon observed when rats were fed diets containing cadmium was a bleaching of the teeth, proportional in intensity to the amount of cadmium administered.<sup>55</sup> Unmistakable bleaching occurred at a dietary level of 16 p.p.m., while at 31 p.p.m. the rate of growth was affected. Severe anemia (sufficient in extent to induce cardiac hypertrophy) was noted when the food contained 62 p.p.m. Prodan<sup>40</sup> found severe degenerative changes in the liver and kidneys of some, but not all, cats fed cadmium phosphate or carbonate.

#### 4. Storage and Excretion

Cadmium appears to be stored chiefly in the liver, kidneys, and bones.<sup>40,56,57</sup> Little is known regarding its presence in normal tissues. Malyuga<sup>58</sup> reported the

<sup>53a</sup> H. M. Barrett, D. A. Irwin, and E. Semmons, *J. Ind. Hyg. Toxicol.*, 29, 279 (1947); H. M. Barrett and B. Y. Card, *ibid.*, 29, 286 (1947).

<sup>53b</sup> H. E. Harrison, H. Bunting, N. K. Ordway, and W. S. Albrink, *J. Ind. Hyg. Toxicol.*, 29, 302 (1947).

<sup>53c</sup> A. Gilman, F. S. Philips, R. B. Allen, and E. S. Koelle, *J. Pharmacol.*, 87, Supplement 85 (1946); J. M. Tobias, C. C. Lushbaugh, H. M. Patt, S. Postel, M. N. Swift, and R. W. Gerard, *ibid.*, 87, Supplement 102 (1946); F. P. Simon, A. M. Potts, and R. W. Gerard, *Arch. Biochem.*, 12, 283 (1947).

<sup>54</sup> A. D. Johns, C. O. Finks, and C. L. Alsberg, *J. Pharmacol.*, 21, 59 (1923).

<sup>55</sup> R. Wilson and F. DeEds, *Science*, 90, 498 (1939). R. Wilson, F. DeEds, and A. J. Cox, Jr., *J. Pharmacol.*, 71, 222 (1941). J. T. Ginn and J. F. Volker, *Proc. Soc. Exptl. Biol. Med.*, 57, 189 (1944).

<sup>56</sup> G. Hessel, *Biochem. Z.*, 177, 146 (1926).

<sup>57</sup> Stephens, *J. Ind. Hyg.*, 2, 129 (1920).

<sup>58</sup> D. P. Malyuga, *Compt. rend. acad. sci. U.S.S.R.*, 31, 145 (1941); *J. Ind. Hyg. Toxicol.*, 25, 128A (1943).

presence of 0.38 mg. of cadmium per 100 g. of kidney of a man who died of heart disease and 3.3 mg. in that organ in a fatal case of lead poisoning. When given intravenously, cadmium disappears rapidly from the blood. It appears in the urine within 1 or 2 days, but does not appear in the feces before 4 or 5 days after the injection. The complete elimination of 10 to 12 mg. of cadmium given in repeated intravenous doses requires 4 weeks.<sup>56</sup>

The amounts of cadmium found in the lungs of experimental animals after the inhalation of an LD<sub>50</sub> dose of cadmium fumes varied from 1 mg. per 100 g. of dried tissue in the case of rats to 10 mg. in that of monkeys.<sup>53a</sup> After having been stored in formalin for 5 years, the lungs of 2 fatally poisoned men were found to contain 1.7 to 1.8 mg. per 100 g. of dried tissue.

### 5. Industrial Intoxication

Attention was attracted to the serious hazard that attends the heating of metals containing cadmium by the publication by Bulmer, Rothwell, and Frankish,<sup>59</sup> in 1938, of a report of a number of cases of acute intoxication. Early symptoms include: dryness of the throat, coughing, a sense of constriction in the chest, shivering, headache, and, less commonly, nausea and vomiting. Later, a pneumonitis develops and causes excruciating pain in the chest, severe dyspnea, and prostration. In nonfatal cases, the intensity of the respiratory distress may increase for a few days, with recovery after 8 days to 2 weeks.<sup>60,61</sup> Even in severe cases, the physical signs are not marked, râles being absent or few, and fever moderate, except shortly before death. No large areas of pulmonary consolidation are found, and radiologic examination reveals only widespread patchy bronchopneumonia.

At necropsy, the findings include congestion, edema, hemorrhage, and partial collapse of the lungs. Histologic examination reveals an interstitial pneumonitis characterized by a marked proliferation of the lining cells of the alveolar spaces.

Examination of the lungs of experimental animals sacrificed at various intervals of time following exposure has shown that acute pulmonary edema appears in a few hours, and that the fluid is reabsorbed as the proliferative process develops.<sup>61a</sup>

Little attention has been devoted as yet to the possibility of chronic industrial intoxication. In six alleged cases, radiographic examinations are said to have revealed the presence of striae in the entire skeletal system, especially evident in the neck of the femur.<sup>62</sup> The metal has been detected spectrographically in

<sup>59</sup> F. M. R. Bulmer, N. E. Rothwell, and E. R. Frankish, *Can. Pub. Health J.*, 29 (Jan. 1938).

<sup>60</sup> M. Richnow, *Samml. Vergiftungsfällen*, 10A, 77 (1939); *J. Ind. Hyg. Toxicol.*, 23, 75A (1941).

<sup>61</sup> E. R. Hayhurst, *Ohio Industrial Bull.*, 1, No. 2 (1939); cited by R. T. Johnstone, *Occupational Diseases*, Saunders, Philadelphia, 1941, p. 279.

<sup>61a</sup> J. C. Patterson, *J. Ind. Hyg. Toxicol.*, 29, 294 (1947).

<sup>62</sup> A. Lafitte and A. Gros, *Presse méd.*, 60, 399 (1942); *J. Ind. Hyg. Toxicol.*, 26, 96A (1944).



the blood, but not in the excretions, of cadmium platers who complained of headache, abdominal pain, nausea, vomiting, and diarrhea. In view of the results of animal experimentation, the need for an adequate investigation of this aspect of intoxication by cadmium seems apparent. Inflammation of the pharynx and ulceration of the nasal septum have occurred among cadmium platers.<sup>63</sup>

The appearance of a yellow ring on the teeth has been described as a sign of chronic exposure to cadmium.<sup>63a</sup> It is reported to be unrelated to the hygienic condition of the teeth or gums and was the only positive finding in a group of men who had been exposed for periods ranging from 6 months to 22 years to atmospheric concentrations which varied from 0.04 to 31.30 mg. of cadmium per cubic meter of air. The average blood and urinary concentrations of cadmium found among these men were less than 0.040 mg. per 100 g. of blood and less than 0.1 mg. per liter of urine.

#### 6. Maximum Allowable Concentration

The maximum allowable concentration of cadmium is 1 mg. per 10 cubic meters of air.<sup>58a,64,64a</sup>

In cadmium plating, exhaust ventilation of the type used in chromium plating is recommended. The Sanitary Code of the City of New York prohibits the use of cadmium-plated articles in the preparation of food or beverages.

## CHROMIUM

### 1. Properties, Uses, and Industrial Exposures

Chromium, Cr, is a gray metal, with atomic weight 52.01 and a specific gravity of 7.1, which melts at 1615° C. and boils at 2200°. Chromium confers hardness upon steels used for armor, shell heads, ball bearings, and tools. It is usually added in the form of ferrochrome, which may contain 60 to 70 per cent chromium, and which is commonly prepared by the direct reduction of chromite ore in an electric furnace. Chromium plating is widely employed because of the resistance of the plate to tarnishing.

Sodium chromate is obtained by sintering chrome-iron ore with sodium carbonate in a reverberatory furnace at 900 to 1000° C. and leaching the mass with water. Treatment with sulfuric acid yields potassium dichromate. Chromic oxide is formed by fusing the dichromate with sulfur in iron kettles. It may be reduced to the metal by means of charcoal or aluminum. The metal also may be deposited electrolytically from a solution of chromous chloride.

Chromates and dichromates have many applications in lithography, textile printing, tanning, dyeing, photography, and in the manufacture of dyes, pigments,

<sup>63</sup> G. Manciola, *Rass. med. applicata lavoro ind.*, 11, 632 (1940).

<sup>63a</sup> P. Barthelemy and R. Moline, *Paris Med.*, 36, 7 (1946); *J. Ind. Hyg. Toxicol.*, 29, 123A (1947).

<sup>64</sup> *Am. Standards Assoc. Pub. Z37.5* (1941); H. B. Elkins, *Ind. Med.*, 8, 426 (1939).

<sup>64a</sup> F. Princi, *J. Ind. Hyg. Toxicol.*, 29, 315 (1947); H. L. Hardy and J. B. Skinner, *ibid.*, 29, 321 (1947).

wallpaper, electric cells, explosives, matches, and rubber goods. Many of their uses depend upon their oxidizing properties.

Chromous salts, which have fewer uses, and metallic chromium do not give rise to serious industrial hazards; but chromium trioxide, chromates, and dichromates are important because of their irritant properties. The occurrence of systemic illness as a result of the absorption of chromium is rare<sup>65</sup> but dermatologic lesions arising from contact with solutions, dusts, or mists that contain hexavalent chromium are frequent. In one factory where dichromates were made the air of the crushing room contained 3.30 to 6.30 mg. of dichromate dust per cubic meter and that of the packing house 1.5 mg. per cubic meter.<sup>66</sup> In unventilated chromium-plating establishments, mist from the bath, carried into the air by the evolution of hydrogen at the cathodes, may introduce chromium into the air to the extent of 2.5 to 6.5 mg.  $\text{CrO}_3$  per cubic meter.<sup>67</sup> Exposure may occur also in magnesium foundries when the castings are treated with chromic-acid solutions to increase their weather resistance<sup>68</sup>; likewise, in the anodizing of aluminum.<sup>69</sup> The deposition of chromium on metals from the vapor of chromyl chloride,  $\text{CrO}_2\text{Cl}_2$ , is another source of danger. Of 233 chromium platers examined by Schwartz and Seike<sup>70</sup> in 1930, 42.6 per cent gave evidence of dermatitis, ulceration, or scars, and in 52 per cent of these the membrane of the nose was damaged. Injury occurs also in chrome tanning, to some degree in lithography, and in other industries in which chromates are used.

## 2. Determination in Atmosphere

Samples of air may be collected in a Greenburg-Smith impinger, or one of its modifications, with a normal solution of sodium hydroxide as the collecting fluid. Potassium iodide is added, the liquid is acidified and the liberated iodine titrated with sodium thiosulfate. Small quantities may be determined by a colorimetric method employing hematoxylin<sup>67</sup> or *s*-diphenylcarbazine.<sup>71,71a</sup> Spectrographic<sup>72</sup> and polarographic methods also may be used. In cases in which the chromium is not present as chromate, it may be oxidized by bromine or potassium persulfate.

## 3. Toxicity of Chromium Compounds

Chromic oxide,  $\text{Cr}_2\text{O}_3$ , and the trivalent salts of chromium are generally believed to have only a low order of toxicity and have given rise to little if any industrial illness. Akatsuka and Fairhall<sup>73</sup> found no illness, loss of weight, or

<sup>65</sup> *J. Am. Med. Assoc.*, 110, 1060 (1938). W. Goertz, *Arbeitschutz*, 183 (1939); *J. Ind. Hyg. Toxicol.*, 21, 192A (1939); *Chem. Abstracts*, 36, 3285 (1942).

<sup>66</sup> R. P. White, *The Dermatogoses or Occupational Affections of the Skin*. 4th ed., Lewis, London, 1934, p. 190.

<sup>67</sup> W. Blum and J. J. Bloomfield, *U.S. Pub. Health Repts.*, 43, 2330 (1928).

<sup>68</sup> N. Hypher, *Practitioner*, 146, 92 (1941); *Bull. Hyg.*, 16, 253 (1941).

<sup>69</sup> J. T. Gresh, *J. Ind. Hyg. Toxicol.*, 26, 127 (1944).

<sup>70</sup> L. Schwartz and F. Seike, *Zentr. Gewerbehyg. Unfallverhüt.*, 17, 232 (1930).

<sup>71</sup> G. A. Gorodetzki and S. L. Makhover, *Hig. Truda i Tekh. Bezopasnosti*, 16, No. 1, 84 (1937); *Chem. Abstracts*, 32, 2452 (1938). K. Akatsuka and L. T. Fairhall, *J. Ind. Hyg.*, 16, 1 (1934).

<sup>71a</sup> L. Silverman and J. F. Ege, Jr., *Am. Ind. Hyg. Assoc. Quart.*, 8, No. 1, 12 (1947).

<sup>73</sup> E. Letterer, *Arch. Gewerbepath. Gewerbehyg.*, 9, 498 (1939).

tissue damage in cats given daily in their food as much as 1000 mg. of chromium carbonate or phosphate. No injury resulted when cats inhaled chromium carbonate dust over a period of 17 weeks.<sup>73</sup> Letterer<sup>72</sup> attributes a hitherto unknown form of interstitial and alveolar chronic pneumonia to inhalation of chromic oxide, Cr<sub>2</sub>O<sub>3</sub>. Under the name "chrome rouge" this substance is employed as an abrasive in polishing certain metal articles.

On the other hand, chromates and dichromates act as protein precipitants and are therefore irritant in action. Administered subcutaneously to rabbits and guinea pigs, they damage the kidney, the urine containing albumin and an abundance of casts of various types,<sup>74,75</sup> and in severe poisoning uremic symptoms may appear.<sup>76</sup> Fatal nephritis has occurred in man as a result of the cauterization of a wound with chromic acid.<sup>77</sup> Lewin<sup>78</sup> found that the chromate ion can be absorbed through the skin of rabbits in amounts sufficient to induce systemic intoxication.

The inhalation of chromic acid dust (CrO<sub>3</sub>) by rabbits induced pulmonary hyperemia and inflammation. Guinea pigs exposed to the air over a chromium-plating bath for 1/2 to 3 hours daily during a period of 45 days developed lesions of the mucosa and submucosa of the respiratory tract, as well as changes in the spleen and kidney.<sup>79</sup>

Apart from the fact that chromium is present in teeth,<sup>80</sup> little is known of its occurrence in the tissues of normal men or animals. Brard<sup>81</sup> has studied its distribution in dogs following the administration of dichromates and other chromium compounds. The metal was found in the blood, urine, feces, and stomach content of a patient who died following the use of a scabies ointment in the preparation of which a chromate had been mistakenly substituted for sulfur. Chromium has been detected in the urine of workers with chromates.<sup>82</sup>

#### 4. Occupational Diseases among Workers with Chromium

Systemic diseases definitely attributable to the handling of chromium compounds are rare. Interstitial pneumonia in a sandblaster of ferrochrome may have been the result of the inhalation of chromic oxide Cr<sub>2</sub>O<sub>3</sub>.<sup>72</sup>

Pfeil,<sup>83</sup> Teleky,<sup>84</sup> Koelsch,<sup>85</sup> and Alwens, Bauke, and Jonas<sup>86</sup> have recently found an unduly high incidence of pulmonary carcinoma<sup>86a</sup> among workers with

<sup>73</sup> K. Akatsuka and L. T. Fairhall, *J. Ind. Hyg.*, 16, 1 (1934).

<sup>74</sup> W. Ophüls, *Proc. Soc. Exptl. Biol. Med.*, 9, 11, 13 (1911).

<sup>75</sup> W. C. Hunter and J. M. Roberts, *Am. J. Path.*, 8, 665 (1932).

<sup>76</sup> H. Brieger, *Zentr. exptl. Med.*, 25, 111 (1921).

<sup>77</sup> R. H. Major, *Bull. Johns Hopkins Hosp.*, 33, 56 (1922).

<sup>78</sup> L. Lewin, *Chem. Ztg.*, 31, 1076 (1907).

<sup>79</sup> S. Galloro, *Folia Med.*, 24, 1256 (1938); *J. Ind. Hyg. Toxicol.*, 21, 98A (1939).

<sup>80</sup> F. Lowater and M. M. Murray, *Biochem. J.*, 31, 837 (1937).

<sup>81</sup> M. D. Brard, *J. pharm. chim.*, 30, 549 (1934); 21, 5 (1935).

<sup>82</sup> *J. Am. Med. Assoc.*, 110, 1060 (1938).

<sup>83</sup> E. Pfeil, *Deut. med. Wochschr.*, 61, 1197 (1935).

<sup>84</sup> L. Teleky, *J. Ind. Hyg. Toxicol.*, 19, 75 (1937).

<sup>85</sup> F. Koelsch, *Acta unio intern. contra cancerum* (Paris), 3, 243 (1938); *C.A.*, 35, 3732 (1941).

<sup>86</sup> W. Alwens, E. E. Bauke, and W. Jonas, *Arch. Gewerbepath. Gewerbehyg.*, 7, 69 (1936).

<sup>86a</sup> E. Gross, *Arch. Gewerbepath. Gewerbehyg.*, 12, 164 (1943).

chromates, 25 cases being on record. The disease is compensable in Germany when it occurs in men with a history of past exposure to chromium compounds.<sup>87</sup> On the other hand, attempts to produce it experimentally have failed and ulcers of the skin caused by chromates do not undergo carcinomatous degeneration. Chromium has been found in some of the pulmonary carcinomas<sup>88</sup> and also in human tumors of nonoccupational origin.

The most common injury produced by chromates is a characteristic penetrating ulcer of the hands and forearms known as a "chrome hole," apparently first described in 1826.<sup>89</sup> The most frequent sites of these lesions are the roots of the nails, the skin between the fingers, the creases of the knuckles, and the hairy parts of the backs of the hands and forearms. According to White,<sup>90</sup> their location is determined by the mouths of the follicles on hairy parts, by creases of the skin, or by slight abrasions of the cuticle. The lesions begin as painless papules or vesicles of pinhead size that eventually form ulcers which penetrate deeply but slowly. They are punched-out in appearance with thick, rounded edges that are indurated but not inflamed. They are not painful and interfere with work only when they occur on the knuckles. If further contact with the irritant is prevented early, the ulcers may heal in a few weeks with a permanent scar; otherwise they persist indefinitely. They are usually treated by means of a reducing agent, such as sodium bisulfite or sodium hyposulfite, with the object of reducing chromates to trivalent compounds.<sup>91</sup>

Lesions also occur in the nose, and may lead to atrophy of the mucous membrane, ulceration, or perforation of the septum,<sup>70</sup> the latter lesions usually being limited to the cartilaginous portion. Detailed descriptions have been given by Schwartz,<sup>92</sup> Zvaifler,<sup>93</sup> and Manciola.<sup>94</sup> Cases have been described in which multiple small ulcers have been found on the soft palate, posterior surface of the tongue, and floor of the mouth.<sup>95</sup>

Generalized dermatitis also may occur.<sup>90,96-97a</sup> It is not uncommon among lithographers. Chromium-plated objects such as wrist watches and bracelets have caused dermatitis.<sup>98</sup>

<sup>87</sup> W. C. Hueper, *Occupational Tumors and Allied Diseases*. Thomas, Springfield, 1942, p. 410.

<sup>88</sup> W. Alwens and W. Jonas, *Arch. Gewerbepath. Gewerbehyg.*, 7, 532 (1936).

<sup>89</sup> Cumming, *Edinburgh Med. Surg. J.*, 26, 134 (1826).

<sup>90</sup> R. P. White, *The Dermatogoses or Occupational Affections of the Skin*. 4th ed., Lewis, London, 1934, p. 152. C. P. McCord, H. G. Higginbotham, and J. C. McGuire, *J. Am. Med. Assoc.*, 94, 1043 (1930). J. Blair, *ibid.*, 90, 1927 (1928).

<sup>91</sup> B. J. Slater, *N. Y. State J. Med.*, 36, 1731 (1936); *J. Am. Med. Assoc.*, 96, 633 (1931).

<sup>92</sup> L. Schwartz, *U.S. Pub. Health Bull. No. 249*, 44 (1939).

<sup>93</sup> N. Zvaifler, *J. Ind. Hyg. Toxicol.*, 26, 124 (1944).

<sup>94</sup> G. Manciola, *Rass. med. applicata lavoro ind.*, 9, 258 (1938).

<sup>95</sup> Liebermann, *New England J. Med.*, 225, 132 (1941).

<sup>96</sup> W. E. Engelhardt and R. L. Meyer, *Arch. Gewerbepath. Gewerbehyg.*, 2, 140 (1931). H. Parkhurst, *Arch. Dermatol. Syphilol.*, 12, 253 (1925).

<sup>97</sup> A. R. Smith, *J. Am. Med. Assoc.*, 97, 95 (1931).

<sup>97a</sup> H. T. Schrus and H. Bürk, *Arch. Gewerbepath. Gewerbehyg.*, 12, 217 (1944).

### 5. Maximum Allowable Concentration

The maximum safe concentration of chromium trioxide in air is usually given as 0.1 mg. per cubic meter<sup>99</sup>; but it should be noted that, according to some investigators,<sup>100</sup> damage to the nasal mucosa has been produced as a result of exposure to this concentration.

### 6. Suggested Preventive Measures

Detailed suggestions for the housekeeping and ventilation of chromium-plating and anodizing establishments have been given by Riley and Goldman<sup>101</sup> and by Gresh<sup>99</sup> (see also Chapter Ten). In some Russian and German plants, the bath is covered by a 1.5- to 2-cm. layer of a petroleum product,<sup>102</sup> but certain difficulties are encountered when this type of production is employed.<sup>103</sup> A layer of plastic "chips" of various sizes and shapes has been used in the United States.<sup>103a</sup> Gloves should be worn and frequent medical examinations are essential. Approved mist respirators are a temporary expedient. To avoid explosions, containers for chromium trioxide should be kept clean and free from organic matter (see Electroplating).<sup>103b</sup>

## COBALT

### 1. Properties and Uses

Cobalt, Co, a silver-white metal, atomic weight 58.94, specific gravity 8.9, which melts at 1478° C. and boils at 2900°, occurs in the minerals cobaltite (CoAsS) and smaltite (CoAs<sub>2</sub>). It is, however, usually extracted from copper and silver ores, in which it occurs as an impurity. After roasting the ores to remove arsenic and sulfur, cobalt compounds are leached from the residue by means of an acid solution and, after purification by chemical means, the cobalt is precipitated as carbonate. The latter may be reduced with charcoal in an electric furnace.

Cobalt is used to impart hardness to steel<sup>104</sup> and various alloys. Cobalt compounds are used in the making of pigments and enamels.

<sup>99</sup> N. Toomey, *Med. Times and Long Island Med. J.*, 60, 223 (1932).

<sup>100</sup> H. G. Dyktor, *Monthly Rev. Am. Electroplaters' Soc.*, 27, 597 (1940); *J. Ind. Hyg. Toxicol.*, 24, 11A (1942). H. Elkins, *Ind. Med.*, 8, 426 (1929). M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*, Interscience, New York, 1941, p. 629.

<sup>101</sup> S. Ginsburg, A. Iljinskaya, and R. Leites, *Gigiena Truda*, 1935, No. 3, 80; *J. Ind. Hyg.*, 17, 128A (1935).

<sup>102</sup> E. C. Riley and F. H. Goldman, *U.S. Pub. Health Repts.*, 52, 172 (1937).

<sup>103</sup> N. P. Lapin, W. F. Warganow, S. L. Druskin, I. G. Woro chopin, and W. W. Sapolski, *Gigiena Truda*, 1934, No. 5, 51; *J. Ind. Hyg.*, 17, 23A (1935). R. I. Verkhovskaya, *Hig. Truda i Tekh. Bezopasnosti*, 15, No. 2, 33 (1937); *Chem. Abstracts*, 32, 4441 (1938). Rassow and Wolf, *Chem. Ztg.*, 55, 73 (1931).

<sup>103b</sup> C. Wolters and A. Brandt, *Metallwaren-Ind. Galvano-Tech.*, 30, 206 (1932).

<sup>103a</sup> J. E. Molos, *Ind. Med.*, 16, 404 (1947); L. Silverman and R. M. Thomson, *J. Ind. Hyg. Toxicol.*, 30, 303 (1948).

<sup>103b</sup> Goertz, *Arbeitsschutz*, 1935, 323.

<sup>104</sup> Kalmus and Harper, *J. Ind. Eng. Chem.*, 7, 6 (1915).

## 2. Determination

Cobalt may be detected in tissues by a colorimetric procedure using nitroso-R-salt.<sup>105</sup> This method can be applied satisfactorily to microgram samples of cobalt collected from the atmosphere. The polarograph and spectrograph are also applicable.

## 3. Toxicity for Animals

Smaltite applied as a dust to the cornea of the eye of an animal induced slowly a serious reaction; but dust of cobaltite, similarly applied, caused only a slight reaction.<sup>106</sup>

The effects of the dietary administration of small quantities of cobalt compounds have been repeatedly investigated for two reasons. First, the element has been found essential in nutrition: a deficiency in its content in the forage of sheep and other grazing animals gives rise to a disease known in Scotland as "pining" and in New Zealand as "bush sickness".<sup>107</sup> Recovery from this disease may be effected by supplying 0.1 to 0.3 mg. daily to sheep, or 1.0 to 1.3 mg. to cattle.<sup>108</sup> Second, cobalt has been shown by many investigators to induce a state of polycythemia,<sup>109</sup> studied recently because of an interest in the possibility that it might be of value in improving the ability to work under anoxic conditions. The mechanism by which cobalt increases erythropoiesis is not understood, and it does not appear effective in the nutritional anemia of rats.<sup>110</sup>

In the course of these investigations, it has been shown that the presence of 2 per cent of cobalt in the diet of rats causes death within 5 or 6 weeks. The presence of 1 per cent in the diet causes a loss in weight in about 7 weeks, but a diet containing 0.5 per cent may be given for 7 months without affecting the rate of growth, although fertility is decreased. Rats given drinking water containing 0.1 mg. of cobalt per milliliter for 14 weeks and then killed showed only a generalized vascular congestion of all the tissues and no abnormalities in the heart, liver, or kidneys.

Cobalt is widely distributed in the tissues of normal animals. Bertrand<sup>111</sup> found 470 and 350 mg. per kilogram of fresh tissue in human liver and spleen, re-

<sup>105</sup> K. J. McNaught, *Analyst*, 64, 23 (1939); 67, 97 (1942).

<sup>106</sup> A. Policard and J. Rollet, *Compt. rend. soc. biol.*, 132, 192 (1939).

<sup>107</sup> K. V. Beeson, "Literature on Cobalt in Soil and Its Connection with Deficiency Diseases in Animals," *U.S. Dept. Agr., Misc. Pub. No. 369*, 1941; cited by O. Baudisch, *J. Am. Med. Assoc.*, 123, 961 (1943).

<sup>108</sup> W. M. Neal and C. S. Ahman, *J. Dairy Sci.*, 20, 406 (1937); cited by O. Baudisch, *J. Am. Med. Assoc.*, 123, 961 (1943).

<sup>109</sup> K. Waltner and K. Waltner, *Klin. Wochschr.*, 8, 313 (1929). Q. D. Schubmehl, I. R. Wood, and C. O. Warren, *Am. J. Physiol.*, 142, 173 (1944). J. E. Davis, *ibid.*, 122, 397 (1938); 127, 322 (1939); 129, 140 (1940). S. S. Dorrance, G. W. Thorn, M. Clinton, Jr., H. W. Edmunds, and S. Farber, *ibid.*, 139, 399 (1943). J. M. Orten, *ibid.*, 114, 414 (1936). M. E. Shils and E. V. McCollum, *J. Am. Med. Assoc.*, 120, 609 (1942).

<sup>110</sup> F. A. Underhill, J. M. Orten, and R. C. Lewis, *J. Biol. Chem.*, 91, 13 (1931). E. J. Underwood and C. A. Elvehjem, *ibid.*, 124, 419 (1938).

<sup>111</sup> Bertrand and Machebaeuf, *Bull. soc. chim.*, 37, 554 (1925); 39, 942 (1926); *Compt. rend.*, 183, 5, 257 (1926).

spectively. Experiments with a radioactive isotope have shown that it is but incompletely absorbed from the digestive tract: when administered orally, 40 per cent of the dose is eliminated in the feces and 18.5 per cent in the urine; while, injected subcutaneously, 63.5 per cent of the dose appears in the urine and only 8.4 per cent in the bile.<sup>112</sup> Storage occurs in the liver, kidney, and the other tissues generally.

#### 4. Industrial Intoxication

There are no well-authenticated cases of industrial intoxication, although one case of acute illness characterized by hematemesis and fever was reported as having occurred in a man who inhaled dust near a cobalt-acetate drier.<sup>113</sup> Arsenic cannot be excluded as the cause of the hyperkeratosis observed among workers of cobalt ores.<sup>114</sup> Sensitivity to cobalt is uncommon,<sup>115,115a</sup> but according to Haxthausen<sup>116</sup> has been induced experimentally.

## COPPER

### 1. Properties, Uses, and Industrial Exposures

Copper, Cu, is a reddish metal, atomic weight 63.57, specific gravity 8.92, which melts at 1083° C. and boils at 2310°.<sup>117</sup> Because of its electrical conductivity, it is used in the manufacture of electrical equipment. Marketed as castings, sheets, rods, tubing, and wire, it is used in chemical apparatus and equipment, cooking utensils, roofing, coinage, and for the formation of many copper compounds. Its important alloys include those with zinc (brass), with tin (bronze), and with nickel (German silver).

It occurs free in nature as native copper, as well as in several oxide ores, carbonate ores, and sulfide ores, the latter predominating. The processes employed for its extraction vary with the nature of the ore. In general, they involve the operations of crushing, concentration by flotation, roasting at 600 to 800° C. to remove part of the sulfur, and smelting at 1100 to 1600° C. for the production of matte. The latter may contain 30 to 35 per cent copper as sulfide, together with iron sulfide. Treatment of molten matte with air in a converter removes the sulfur, and the addition of a siliceous flux permits the iron to be removed as an oxide slag. The product is brittle blister copper, which contains some sulfur, iron, and, at times, precious metals. It may be further refined with charcoal or coke

<sup>112</sup> D. H. Copp and D. M. Greenberg, *Proc. Natl. Acad. Sci. (U.S.)*, **27**, 153 (1941). D. M. Greenberg, D. H. Copp, and E. N. Cuthbertson, *J. Biol. Chem.*, **147**, 751 (1943).

<sup>113</sup> J. Hagen, *Samml. Vergiftungsfällen*, **11**, 25 (1940); *J. Ind. Hyg. Toxicol.*, **23**, 33A (1941).

<sup>114</sup> R. P. White, *The Dermatogoses or Occupational Affections of the Skin*. 4th ed., Lewis, London, 1934, p. 162. Margain, *J. maladies cutanées et syphilitiques*, **16**, 94 (1904); *Brit. J. Dermatol. Syphilis*, **16**, 395 (1904).

<sup>115</sup> H. Rabeau and Mlle. Ukrainczyk, *Bull. soc. franç. dermatol. syphilig.*, No. 45, 1872 (1938); *Chem. Abstracts*, **33**, 5069 (1939). S. G. Stuart, *Arch. Internal. Med.*, **51**, 427 (1933).

<sup>115a</sup> L. Schwartz, S. M. Peck, K. E. Blair, and K. E. Markuson, *J. Allergy*, **16**, 51 (1945).

<sup>116</sup> H. Haxthausen, *Arch. Dermatol. u. Syphilis*, **174**, 17 (1936).

<sup>117</sup> H. C. Greenwood, *Chem. News*, **100**, 39, 40 (1909).

in a reverberatory furnace, or cast into anodes and subjected to electrolytic refining, using as a bath an acid solution of copper sulfate.<sup>118</sup> In the latter process, precious metals are recovered from the slime that collects at the bottom of the tanks.

Mining and extraction processes are attended by the hazard of silicosis, and exposure to dusts of compounds of such elements as arsenic, antimony, bismuth, lead, selenium, tellurium, zinc, mercury, silver, and gold. Sulfur dioxide is encountered in charging the roasting furnaces and acid vapors are present near the electrolytic cells.

## 2. Determination

Volumetric methods based upon the liberation of iodine in a cupric-cuprous iodide reaction, and colorimetric procedures employing potassium ethyl xanthate, sodium diethyldithiocarbamate, and dithizone are available.<sup>119</sup>

## 3. Biological Significance

Copper bears a somewhat paradoxical relationship to living organisms for, although it is widely distributed in plant and animal tissues in concentrations several times those in which other trace metals occur,<sup>120</sup> it is, when present in minute amounts in water, toxic for algae, bacteria,<sup>121</sup> and other unicellular forms. The mechanism of the extreme toxicity of copper for these lower forms of life—its so-called oligodynamic action<sup>122</sup>—is but poorly understood. It has been suggested that it may act upon the surface of the cell.<sup>123</sup> Copper interferes with the action of several enzymes including lipase,<sup>124</sup> intracellular diastase,<sup>125</sup> and certain of those connected with the metabolism of glucose.<sup>126</sup> Copper salts are unreliable as germicides,<sup>127</sup> although they are used for the extermination of algae and agricultural parasites.

The significance of the presence of copper in the tissues of the higher forms of life is but incompletely understood. According to Stotz, Harrer, and King,<sup>128</sup> it is the active substance in so-called "ascorbic-acid oxidase." Oxyhemocyanin,

<sup>118</sup> C. R. Hayward, *An Outline of Metallurgical Practice*. 2nd ed., Van Nostrand, New York, 1940, p. 16.

<sup>119</sup> M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

<sup>120</sup> F. Eichholtz, in Heffter-Heubner, *Handbuch expt. Pharmakol.*, 3, Pt. 3, 1928 (1934). C. A. Elvehjem, *Physiol. Revs.*, 15, 471 (1935). Hahn and Fairman, *J. Biol. Chem.*, 113, 161 (1936). H. W. Severy, *ibid.*, 59, 79 (1923).

<sup>121</sup> K. Spiro, *Münch. med. Wochschr.*, 62, 1601 (1915). S. F. Cook, *J. Gen. Physiol.*, 9, 735 (1926).

<sup>122</sup> J. Schwaibold and F. Fischler, *Biochem. Z.*, 232, 240 (1931). P. L. Violle and A. Giberton, *Compt. rend.*, 188, 409 (1929). G. Tammann, *Forschungen u. Fortschr.*, 5, 257 (1929). S. Hocs, *Helv. Chim. Acta*, 13, 153 (1930).

<sup>123</sup> P. Reznikoff, *J. Gen. Physiol.*, 10, 9 (1926).

<sup>124</sup> R. A. Corran, *Biochem. J.*, 23, 188 (1929).

<sup>125</sup> A. W. Peters and O. Burres, *Science*, 27, 909; *J. Biol. Chem.*, 6, 65 (1909).

<sup>126</sup> T. Wagner-Jauregg and Rzeppa, *Z. physiol. Chem.*, 243, 166 (1936).

<sup>127</sup> L. M. Dewitt and H. Sherman, *J. Infectious Diseases*, 18, 368 (1916).

<sup>128</sup> E. H. Stotz, C. J. Harrer, and C. G. King, *Science*, 86, 35 (1937).



the blue oxygen-carrying pigment of the blood of snails and crabs, contains copper rather than iron. In the course of evolution, the significance of copper for hemopoiesis has not been entirely lost, for iron must be supplemented by copper in order that rats may recover from the nutritional anemia that is produced by a deficient diet.<sup>129</sup>

#### 4. Toxicity for Animals

*Acute effects.* When orally administered, copper sulfate, because of its local irritant action, acts as an emetic in all species that are capable of vomiting. A dose of 50 mg. per kilogram of body weight is toxic for rabbits, which cannot vomit. The lethal dose of copper carbonate is 159 mg. per kilogram for rabbits and 420 mg. per kilogram for goats.<sup>130</sup> In man, a large quantity of copper sulfate has caused dizziness, exhaustion, icterus,<sup>131</sup> convulsions, shock, coma, and death.<sup>132</sup> Symptoms attributable to damage to the nervous system and kidney have occurred. When administered subcutaneously to rabbits, 2.5 ml. of 1 per cent cupric chloride solution caused local necrosis, and loss in weight.<sup>133</sup> Moderate amounts of finely powdered copper are not toxic to dogs when administered intravenously.<sup>134</sup> Colloidal copper compounds given by this route vary in toxicity with their solubility,<sup>135</sup> but the soluble salts are very toxic.<sup>136</sup>

*Chronic effects.* Mallory<sup>137-139</sup> observed pigment deposits and other changes in the liver of animals given copper compounds over long periods, and suggested that "bronze diabetes" or hemochromatosis in man might be due to copper poisoning. Although more recent work has shown that hemochromatosis is, instead, a disease of iron metabolism, copper poisoning in animals does result in damage

<sup>129</sup> E. B. Hart, H. Steenbock, J. Waddell, and C. A. Elvehjem, *J. Biol. Chem.*, **77**, 797 (1928). J. S. McHargue, D. J. Healy, and E. S. Hill, *ibid.*, **78**, 637 (1928). J. Waddell, H. Steenbock, and E. B. Hart, *ibid.*, **83**, 115, 243, 251 (1929). R. W. Titus and J. S. Hughes, *ibid.*, **83**, 463 (1929). C. A. Elvehjem and E. B. Hart, *ibid.*, **84**, 131 (1929). E. C. Meyers and H. H. Beard, *J. Am. Med. Assoc.*, **93**, 1210 (1929). D. L. Drabkin and C. S. Waggoner, *J. Biol. Chem.*, **89**, 51 (1930). E. B. Hart, C. A. Elvehjem, H. Steenbock, A. R. Kemmerer, G. Bohstedt, and J. M. Fargo, *J. Nutrition*, **2**, 277 (1930). Elden, Sperry, Robscheit-Robbins, and Whipple, *J. Biol. Chem.*, **79**, 577 (1928).

<sup>130</sup> R. Attia, *Ministry of Agr. of Egypt, Tech. and Sci. Service Bull. No. 105* (1931); *Chem. Abstracts*, **26**, 243 (1932).

<sup>131</sup> C. G. Santesson, *Skand. Arch. Physiol.*, **61**, 79 (1931); *Chem. Abstracts*, **25**, 1589 (1931).

<sup>132</sup> Raestrup, *Deut. Z. ges. gerichtl. Med.*, **3**, 36 (1924); *Chem. Abstracts*, **18**, 2384 (1924). Esser, *ibid.*, **28**, 430 (1936); *J. Ind. Hyg. Toxicol.*, **13**, 159A (1936). M. Meerovich and L. Moisseyeva, *ibid.*, **11**, 189 (1928); *Chem. Abstracts*, **23**, 2760 (1929). V. Reichmann, *Münch. med. Wochschr.*, **60**, 181 (1913).

<sup>133</sup> H. Eggers, *Beitr. Klin. Tuberk.*, **47**, 373 (1921); *Chem. Abstracts*, **16**, 2359 (1922).

<sup>134</sup> G. B. Zanda, *Giorn. accad. med. Torino*, **85**, 249 (1922); *Chem. Abstracts*, **18**, 2038 (1924).

<sup>135</sup> G. Spagnol, *Boll. soc. biol. sper.*, **1**, 587 (1926); *Chem. Abstracts*, **21**, 3083; *Arch. sci. biol.*, **9**, 132 (1926); *Chem. Abstracts*, **21**, 3959 (1927).

<sup>136</sup> P. Mascherpa, *Boll. soc. ital. biol. sper.*, **15**, 226 (1940).

<sup>137</sup> F. B. Mallory, F. Parker, and R. N. Nye, *J. Med. Research*, **42**, 461 (1921).

<sup>138</sup> F. B. Mallory, *Am. J. Path.*, **1**, 117 (1925).

<sup>139</sup> E. M. Hall and E. M. Butt, *Arch. Path.*, **6**, 1 (1925).

to the liver.<sup>140</sup> In the case of sheep poisoned in Texas<sup>141-143</sup> by access for 25 to 86 days to salt licks that contained from 5 to 9 per cent copper sulfate, there was a sudden onset of depression, loss of appetite, hemolytic anemia, icterus, and hemoglobinuria, followed after a day or two by death. It was estimated that the total amount of copper sulfate ingested by fatally poisoned sheep was of the order of 40 to 49 g. or less. At necropsy the liver, spleen, and kidneys showed severe degenerative changes. The livers of three animals contained 283, 530, and 1470 mg. of copper per kilogram, respectively, whereas the normal content ranges from 4.8 to 41.9 mg. per kilogram.

The inhalation of copper dust by one rabbit during 20 days induced a proliferation of connective tissue in the lungs, according to Goralewski.<sup>144</sup> Pulmonary edema has developed in dogs following a brief exposure to dusts containing copper acetate.<sup>145</sup> Dusts of copper stearate cause an acute reaction, but the deposits are subsequently absorbed without inducing any progressive changes of a pneumoconiotic nature.<sup>146</sup>

### 5. Absorption, Storage, and Excretion

Kehoe, Cholak, and Story,<sup>147</sup> after reviewing the work of others on the distribution of copper in the tissues of men and animals, reported the content of copper in various human organs in milligrams per 100 grams of fresh tissue, as follows: liver, 0.710; kidney, 0.166; heart, 0.190; spleen, 0.085; lung, 0.110; muscle, 0.125; stomach, 0.107; intestines, 0.110; rib, 0.37 to 0.47; and long bone, 1.19. The content in the liver is increased (2.40 mg. per 100 grams) in infancy.<sup>148</sup> It is moderately increased in hemochromatosis<sup>149</sup> and Wilson's disease,<sup>150</sup> while in Laennec's cirrhosis as much as 27.4 mg. of copper per 100 grams of liver has been found.<sup>151</sup> Relatively large quantities (0.22 to 0.68 mg. per 100 grams) are found in the brain.<sup>152,153</sup> Blood contains 0.114 mg. per 100 grams,<sup>147,149</sup> there being slightly more in the cells than in the plasma.

<sup>140</sup> L. Schindel, *Beitr. path. Anat.*, 87, 768 (1931). F. Oshima and P. Siebert, *ibid.*, 84, 106 (1930). F. Oshima, S. Kamamoto, and K. Adachi, *Trans. Japanese Path. Soc.*, 22, 209 (1932); *Chem. Abstracts*, 27, 4592 (1934). C. C. Santesson, *Skand. Arch. Physiol.*, 61, 79 (1931). J. H. Shelton, *Lancet*, 2, 1031 (1934). R. G. Mills, *J. Am. Med. Assoc.*, 84, 1326 (1925). See, however, C. J. Polson, *Brit. J. Exptl. Path.*, 10, 241 (1929) and F. B. Flinn and W. F. von Glahn, *J. Exptl. Med.*, 49, 5 (1929).

<sup>141</sup> J. B. Boughton and W. T. Hardy, *Texas Agr. Expt. Sta. Bull.* No. 499 (1934).

<sup>142</sup> T. P. Chou and W. H. Adolph, *Biochem. J.*, 29, 476 (1935).

<sup>143</sup> N. Bisset, *Vet. J.*, 90, 405 (1934); *Chem. Abstracts*, 29, 431 (1935).

<sup>144</sup> Goralewski, *Arch. Gewerbepath. Gewerbehyg.*, 9, 686 (1939). K. W. Jötten, C. von Marwyh, and H. Reploh, *Arch. Hyg. Bakter.*, 124, 1 (1940).

<sup>145</sup> I. Brodskii, *Arch. Gewerbepath. Gewerbehyg.*, 5, 91 (1933).

<sup>146</sup> P. T. Knies, *J. Lab. Clin. Med.*, 25, 726 (1940).

<sup>147</sup> R. A. Kehoe, J. Cholak, and R. V. Story, *J. Nutrition*, 19, 582 (1940); 20, 85 (1940).

<sup>148</sup> D. B. Morrison and T. P. Nash, Jr., *J. Biol. Chem.*, 88, 479 (1930). N. Andrianoff and S. Ansbacher, *Deut. med. Wochschr.*, 56, 357 (1930).

<sup>149</sup> F. Oshima and R. Schönheimer, *Z. physiol. Chem.*, 180, 249, 252 (1929).

<sup>150</sup> F. Haurowitz, *Z. physiol. Chem.*, 190, 72 (1930).

<sup>151</sup> R. Schönheimer and W. Herkel, *Klin. Wochschr.*, 9, 1449 (1930).

<sup>152</sup> S. L. Tompsett, *Biochem. J.*, 29, 480 (1935).

<sup>153</sup> M. Bodansky, *J. Biol. Chem.*, 48, 361 (1921).

The normal concentration in the urine is low, being on the average 0.034 mg. per liter.<sup>147</sup> The mean daily amount ingested with the food and drinking water is about 2 mg., most of which is eliminated in the feces.<sup>142,153</sup> Leverton and Binckley<sup>154</sup> found that 65 subjects, with an average daily intake of 2.65 mg., retained on the average 0.85 mg. of copper daily. The metal is stored chiefly in the liver.<sup>139,141</sup> It is eliminated through the liver<sup>155</sup> and to some extent through the mammary gland. Excretion by the kidney is slow.

### 6. Industrial Intoxication

Few instances of alleged illness from working with copper or its compounds have been reported, although dusts containing copper compounds may irritate the upper respiratory passages. Men exposed to dusts containing copper acetate<sup>145</sup> have complained of sneezing, coughing, digestive disorders, and fever. Congestion of the nasal mucous membrane, with superficial sloughing, was observed in 17 employees in a plating plant, but was attributed to an alkaline mist that contained sodium copper cyanide.<sup>156</sup>

Although many copper salts are irritating to the skin, the handling of copper or brass seldom gives rise to dermatitis.<sup>157</sup>

## GERMANIUM

Germanium, Ge, is a grayish-white metal, atomic weight 72.60, specific gravity 5.47, and hardness 6.25, which melts at 958° C.<sup>158</sup> and boils at about 2600°. It is but slightly volatile at 1500° C. It is obtained from germanium-bearing zinc ores.

Germanium is used in certain alloys and in the electrical industry. Neither germanium nor its compounds have been the cause of reported occupational intoxication.<sup>159</sup>

According to Hammett, Müller, and Nowrey,<sup>160</sup> the lethal dose of germanium dioxide when administered intraperitoneally to guinea pigs was 586 mg. per kilogram. Nevertheless, damage to the visceral organs of rabbits could be produced by a subcutaneous dose as small as 4 mg. per kilogram.<sup>161</sup> Hueper<sup>162</sup> found that a toxic dose decreases the blood pressure and leads to dehydration. In the chief parenchymatous tissues he found massive deposits of a brown pigment, hydropic degeneration, and cellular atrophy. No proliferative changes were found in the

<sup>154</sup> R. M. Leverton and E. S. Binckley, *J. Nutrition*, **27**, 43 (1944).

<sup>155</sup> S. G. Serebryanaya, *Voprosy Pitaniya*, **5**, No. 6, 123 (1936); *Chem. Abstracts*, **31**, 4400 (1937). A. Eden, *J. Agr. Sci.*, **31**, 145 (1941); *Chem. Abstracts*, **35**, 2574 (1941).

<sup>156</sup> M. H. Barsky, *N. Y. State J. Med.*, **37**, 1031 (1937).

<sup>157</sup> A. Hamilton, *Industrial Poisons in the United States*. Macmillan, New York, 1925, p. 278.

<sup>158</sup> W. Biltz, *Z. anorg. allgem. Chem.*, **72**, 313 (1911).

<sup>159</sup> G. C. Harrold, S. Meek, and C. P. McCord, *Ind. Med.*, **13**, 236 (1944).

<sup>160</sup> F. S. Hammett, J. H. Müller, and J. E. Nowrey, Jr., *J. Pharmacol.*, **19**, 337 (1922); *J. Exptl. Med.*, **35**, 173 (1922).

<sup>161</sup> G. H. Bailey, P. B. Davidson, and C. H. Bunting, *J. Am. Med. Assoc.*, **84**, 1722 (1925).

<sup>162</sup> W. C. Hueper, *Am. J. Med. Sci.*, **181**, 820 (1931).

lungs after intraperitoneal or intrapleural administration of germanium dioxide.<sup>159</sup> No local action on man or animals could be demonstrated by patch tests.

## IRON

### 1. Occurrence and Properties

Iron, Fe, is a silvery metal with atomic weight 55.85, a specific gravity of 7.86, melting point 1535° C., and boiling point 3000°. Iron is lustrous, malleable, ductile, and the only temperable metal. It is derived from the smelting of oxide ores with coke, charcoal, or coal. Depending upon the process, wrought iron, cast iron, or steel may be produced. Iron was one of the first metals to be used by man, and is still the metal of choice today for many purposes where strength and durability are paramount to weight.

### 2. Hazards in the Iron and Steel Industry

The mining, loading, and unloading of iron ores afford opportunity for the inhalation of both silica and iron oxide in the form of dusts. Carbon monoxide is a hazard in the operation of blast furnaces for the production of pig iron. The use of fluorspar in steelmaking may give rise to the evolution of gases containing silicon tetrafluoride and other fluorine compounds, while the manufacture of alloy steels introduces the hazards attendant upon the use of such metals as chromium, manganese, nickel, vanadium, tungsten, molybdenum, and copper. The "pickling" of iron that contains arsenic or phosphorus in large quantity may liberate arsine or phosphine. Certain grades of ferrosilicon used in steelmaking decompose with explosive violence on contact with moist air, evolving various toxic gases, such as acetylene, hydrogen sulfide, silicon tetrahydride, phosphine, and arsine. Numerous fatal intoxications have occurred from such accidents during the transportation of this material, particularly by sea.<sup>163</sup>

### 3. Toxicity of Iron and Its Salts

Although the extreme toxicity of iron salts and of colloidal iron when introduced into the circulation has been repeatedly demonstrated,<sup>164</sup> the toxicity of iron compounds by oral administration is low.<sup>165</sup> The daily administration to dogs of 0.2 to 0.8 g. of ferrous chloride induced no noteworthy changes in physiologic behavior.<sup>166</sup> The absorption of iron from the digestive tract is slow and

<sup>159</sup> J. Rambousek, *Industrial Poisoning*, trans. by T. M. Legge, Arnold, London, 1913, p. 149. C. E. Pellew, *J. Soc. Chem. Ind.*, 33, 779 (1914). H. Hognested, *Med. Rev.*, 48, 409 (1931). A. Jerwell and M. Haaland, *ibid.*, 47, 145 (1930); *Chem. Abstracts*, 26, 3858 (1932).

<sup>164</sup> H. Hold, *Klin. Wochschr.*, 21, 1040 (1942). L. Sabbatani, *Arch. fisiol.*, 19, 57, 197 (1921). E. Starkenstein, *Arch. exptl. Path. Pharmacol.*, 118, 131 (1926); 127, 101 (1927). E. Starkenstein and H. Weden, *ibid.*, 134, 300 (1928); *Z. ges. exptl. Med.*, 68, 425 (1929).

<sup>165</sup> McGuigan, *J. Lab. Clin. Med.*, 12, 790 (1927).

<sup>166</sup> R. Sanders, *Arch. exptl. Path. Pharmacol.*, 151, 1 (1930). F. Hendych and K. Klinaesches, *ibid.*, 178, 178 (1935).

incomplete.<sup>167</sup> The average daily intake of iron by man is of the order of 11 to 19 mg.<sup>168</sup> Experiments with a radioactive isotope of iron<sup>169</sup> have shown that the liver plays a part in the excretion of iron. The liver, spleen, and lymph nodes are the chief sites of storage, irrespective of the route of administration. Experiments, in which guinea pigs were forced to inhale massive doses of iron dust or hematite dust, did not indicate that either dust is likely to constitute a serious hazard.<sup>170</sup>

#### 4. Mottling of the Lungs by Iron

The hygienic significance of the mottling of lungs—siderosis—that results from the long-continued inhalation of iron or its oxides in the form of welding fumes has been the subject of much recent discussion. Harrold, Meek, and McCord,<sup>171</sup> found that the concentration of iron oxide in the air of certain welding chambers varied between 90 and 682 mg. per cubic meter.

*Animal experimentation.* Somewhat lower concentrations—35 to 250 mg. per cubic meter—were used in experiments of Titus, Warren, and Drinker,<sup>172</sup> in which animals were subjected to the inhalation of welding fumes. These investigators ascribed the irritant action of the fumes to the presence of ozone and nitrogen oxide, since it persisted when the iron oxide was removed by filtration. Inhalation of iron oxide dust alone caused no pulmonary irritation.<sup>172a</sup> Gardner and McCrum<sup>173</sup> found no iron deposits in the pulmonary lymphatics of animals that had inhaled welding fumes repeatedly. Roentgenograms of the lungs, made after their removal from the body, afforded slight evidence of an accumulation of iron. It was believed that the accumulation was due to large collections of phagocytes containing iron granules and lying within the alveoli. Repeated exposure of animals did not increase their natural susceptibility to tuberculosis and did not reactivate pre-existing, partially healed pulmonary tubercles.

*Observations on man.* In 1936, Doig and McLaughlin<sup>174</sup> observed radiographically a very fine pseudonodulation in the lungs of six arc welders; and shortly thereafter Enzer and Sander<sup>175</sup> found discrete nodular shadows in roent-

<sup>167</sup> Henriques and Roche, *Bull. soc. chim. biol.*, 12, 404 (1930). R. Nicolaysen, *Norsk Mag. Laegevidenskab.*, 96, 842 (1935). C. V. Moore, V. Minnich, and J. Welch, *J. Clin. Investigation*, 18, 543 (1939). C. V. Moore, W. R. Arrowsmith, J. Welch, and V. Minnich, *ibid.*, 18, 553 (1939). O. Firth and R. Scholl, *J. Pharmacol.*, 53, 14 (1936). W. Linzel, *Biochem. Z.*, 263, 173 (1933). C. A. Elvehjem, E. B. Hart, and W. C. Sherman, *J. Biol. Chem.*, 103, 61 (1933); 107, 383 (1934).

<sup>168</sup> H. C. Sherman, *U.S. Dept. Agr. Off. Exptl. Sta. Bull.* No. 185 (1944).

<sup>169</sup> D. M. Greenberg, D. H. Copp, and E. M. Cuthbertson, *J. Biol. Chem.*, 147, 749 (1943).

<sup>170</sup> H. M. Carleton, *J. Hyg.*, 26, 227 (1927); *J. Ind. Hyg. Toxicol.*, 10, 12A (1928).

<sup>171</sup> G. C. Harrold, S. F. Meek, and C. P. McCord, *J. Ind. Hyg. Toxicol.*, 22, 347 (1940); 23, 204 (1941).

<sup>172</sup> A. C. Titus, H. Warren, and P. Drinker, *J. Ind. Hyg.*, 17, 121 (1935).

<sup>172a</sup> H. E. Harding, *Brit. J. Ind. Med.*, 2, 32 (1945). H. E. Harding, J. L. A. Grout, and T. A. L. Davies, *ibid.*, 4, 223 (1947).

<sup>173</sup> L. U. Gardner and D. S. McCrum, *J. Ind. Hyg. Toxicol.*, 24, 173 (1942).

<sup>174</sup> A. T. Doig and A. I. McLaughlin, *Lancet*, 1, 771 (1936).

<sup>175</sup> N. Enzer and O. A. Sander, *J. Ind. Hyg. Toxicol.*, 20, 333 (1938).

genograms of welders who had worked in confined spaces. The borders of the nodules were more sharply defined than those of silicotic nodules and the shadows at the hilum were less prominent. There was no evidence of proliferation of fibrous tissue. In one case, re-examined after 5 years,<sup>176,176a</sup> it was found that a tuberculosis lesion had healed despite continued welding. The occurrence of this condition in a certain proportion of welders or hematite miners has since been repeatedly confirmed and its significance discussed.<sup>177</sup> Sander prefers the term "iron pigmentation" to either "siderosis" or "iron pneumoconiosis," since the first does not imply the occurrence of fibrous proliferation. Chemical data on the iron content of the lungs of men in dusty trades have been given by Gerstel in a 1941 report.<sup>178</sup>

Physical examinations and tests of the capacity for work of welders with iron pigmentation have shown that it causes little or no disability<sup>177</sup> and induces no symptoms and no predisposition to tuberculosis. In one nontypical case there was an ulcerated granulating lesion in the right main bronchus.<sup>179</sup> Gardner<sup>180</sup> regarded iron oxide as a retardant of the development of conglomerate silicotic fibrosis.

### 5. Maximum Allowable Concentration

Enzer and Sander<sup>181</sup> suggest that the fume concentration should be kept below that at which the accumulation of iron in the lungs occurs. Drinker, Warren, and Page<sup>182</sup> in 1935 suggested 10 mg. per cubic meter as a safe limit, but later Drinker<sup>183</sup> expressed the belief that this might be revised to 30 mg. per cubic meter. The lower limit is difficult to maintain in carrying on certain types of work, but tests at the Oregon Shipbuilding Company revealed that the higher limit was not exceeded.<sup>184</sup>

<sup>176</sup> O. A. Sander, *J. Ind. Hyg. Toxicol.*, **26**, 79 (1944).

<sup>176a</sup> O. A. Sander, *Am. J. Roentgenol.*, **58**, 277 (1947).

<sup>177</sup> R. Fawcitt, *Brit. J. Radiol.*, **16**, 323 (1943). J. A. Groh, *Ind. Med.*, **13**, 598 (1944). J. Brodie, *Calif. and Western Med.*, **59**, 13 (1943); *J. Ind. Hyg. Toxicol.*, **25**, 199A (1943). O. A. Sander, *Ind. Med.*, **8**, 177 (1939). Koelsch, *Arch. Gewerbepath. Gewerbehyg.*, **10**, 519 (1941). J. A. Britton and E. L. Walsh, *J. Ind. Hyg. Toxicol.*, **22**, 125 (1940). N. Enzer, E. Simonson, and A. M. Evans, *ibid.*, **27**, 147 (1945). K. Humperdinck, *Deut. med. Wochschr.*, **68**, 16 (1942); *J. Ind. Hyg. Toxicol.*, **25**, 64A (1943). W. E. Fleischer, K. W. Nelson, and P. Drinker, *J. Maine Med. Assoc.*, **35**, 223 (1944); *J. Ind. Hyg. Toxicol.*, **27**, 94A (1945).

<sup>178</sup> Gerstel, *Arch. Gewerbepath. Gewerbehyg.*, **10**, 616 (1941).

<sup>179</sup> H. R. Nayer, *J. Am. Med. Assoc.*, **119**, 1500 (1942).

<sup>180</sup> L. U. Gardner, *Ann. Repts. Saranac Laboratory* (1942); *J. Ind. Hyg. Toxicol.*, **26**, 48A (1944).

<sup>181</sup> N. Enzer and O. A. Sander, *J. Ind. Hyg. Toxicol.*, **26**, 79 (1944).

<sup>182</sup> P. Drinker, H. Warren, and R. Page, *J. Ind. Hyg.*, **17**, 133 (1935).

<sup>183</sup> P. Drinker, *U.S. Dept. Labor, Division of Labor Standards, Spec. Bull. No. 5* (1941).

<sup>184</sup> J. Beeman, W. A. David, W. C. Hunter, and F. R. Menne, *J. Ind. Hyg. Toxicol.*, **26**, 125A (1943).

## IRON CARBONYL

### 1. Properties, Uses, and Industrial Exposures

Iron carbonyl,  $\text{Fe}(\text{CO})_5$ , is a highly toxic, pale yellow liquid, with molecular weight 195.90 and a density of 1.4565 at  $21.1^\circ \text{C}$ .,<sup>185</sup> formed by the interaction of carbon monoxide with finely divided iron. It melts at  $-21^\circ \text{C}$ ., boils at  $102.5^\circ$  at 760 mm. Hg pressure, and has a high vapor pressure equivalent to 25.9 mm. Hg at  $16.1^\circ \text{C}$ . and 52.0 mm. at  $35^\circ$ . It is soluble in alcohol, benzene, mineral oils, and pyridine. In sunlight it undergoes decomposition with the formation of carbon monoxide and orange-red crystals of  $\text{Fe}_2(\text{CO})_9$ .

In small quantities, iron carbonyl may be formed during acetylene welding.<sup>186</sup> It contaminates carbon monoxide kept in steel cylinders, being formed by the action of carbon monoxide on the metal.<sup>187</sup> Under the name Motalin, iron carbonyl has been used in Germany as a knock inhibitor in gasoline.<sup>188</sup> It is also used as an intermediate compound in the preparation of pure iron.

### 2. Determination in the Atmosphere

Iron carbonyl may be determined by decomposing it by passage through a heated silica tube or through sulfuric acid, after which the liberated iron is estimated by any suitable method.<sup>189</sup>

### 3. Toxicity and Inflammability

Iron carbonyl is extremely toxic when inhaled, ingested, or absorbed through the intact skin. The lethal dose when orally or intravenously administered to rabbits is 17.5 mg. per kilogram of body weight.<sup>190</sup> The mechanism by which it acts is not fully understood<sup>191</sup> (see Nickel Carbonyl). It appears to be excreted by the lungs, which are found congested and acutely edematous, regardless of the mode of administration.

The ease with which iron carbonyl decomposes with the formation of carbon monoxide and finely divided iron renders it a fire hazard.<sup>192</sup>

<sup>185</sup> J. Dewar and H. O. Jones, *Proc. Roy. Soc. London*, 71, 427 (1903); *A76*, 558 (1905); *A79*, 66 (1907); 80, 229 (1908).

<sup>186</sup> Kienitz, *Z. kompr. flüss. Gase*, 34, 97, 113 (1939); *J. Ind. Hyg. Toxicol.*, 22, 184A (1940).

<sup>187</sup> H. Bunte and E. Terres, *Gas- u. Wasserfach*, 65, 145 (1922). H. Fichler and H. Walenda, *Brennstoff-Chem.*, 21, 133 (1940); *Chem. Abstracts*, 35, 3207 (1941). L. M. Liddle, *Ind. Eng. Chem.*, 8, 89 (1916).

<sup>188</sup> A. Mittasch, *Z. angew. Chem.*, 41, 827 (1928).

<sup>189</sup> R. H. Griffith and G. C. Holliday, *J. Soc. Chem. Ind.*, 47, 311 (1928). M. B. Jacobs, *The Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941, p. 239.

<sup>190</sup> Unpublished observations of W. Deichmann.

<sup>191</sup> Amor, *J. Ind. Hyg.*, 14, 216 (1932).

<sup>192</sup> H. Fischer, *Gluckauf*, 73, 717 (1937); *Chem. Abstracts*, 32, 2323 (1938).

## MAGNESIUM

### 1. *Properties, Uses, and Industrial Exposures*

Magnesium, Mg, is a light metal of atomic weight 24.32 and specific gravity 1.75, which melts at 651° C. and boils at 1107°.<sup>193</sup> At high temperatures it reacts violently with water, forming magnesium oxide and hydrogen. Large quantities of magnesium have been extracted from sea water<sup>194</sup> and used for the fabrication of airplane parts. Alloys with aluminum, manganese, or zinc also are used for varied purposes. Powdered magnesium is used in incendiary bombs, flares, and flashlight powders. Compounds of magnesium are used in the coatings of welding rods. The oxide is used in rubber compounding.

In casting magnesium, fluoride fluxes and certain inhibitors of oxidation are employed.<sup>195</sup> During the melting of the metal in steel crucibles, fluxes (ammonium acid fluoride, ammonium borofluoride, ammonium silicofluoride) are sprinkled on the metal and stirred in when the metal is molten. The charge is then heated to about 900° C., and removed from the furnace to a station where the dross is skimmed off and a mixture of sulfur and borax or some other inhibitor of oxidation is added, producing a brief but violent evolution of gas and fumes. After the metal is cooled to 700 to 800° C. more inhibitor is added, and the metal is then poured. Inhibitor is also added to the metal in the pouring basins and risers, so that a blanket of sulfur dioxide may prevent the metal from burning.<sup>196</sup> The molding sand is usually mixed with inhibitor and the cores are sprayed with fluorine compounds and sometimes with sulfur dust. In some foundries the castings are heat-treated in an atmosphere of sulfur dioxide.

The hazards arising from the use of fluorides in magnesium founding have been discussed under Fluorine and Fluorides. The hazard from the use of sulfur dust in coremaking is satisfactorily controlled by the precautions required to keep silica dust within safe limits.<sup>197</sup>

Sulfur dioxide concentrations of 3.0 p.p.m. have been found in the air of the general molding floor, 15.7 p.p.m. at the shakeout area, 24.6 p.p.m. at the core knockout, and 35.2 p.p.m. near the pouring operation.<sup>197</sup> Ventilation control is required.

Concentrations of magnesium oxide great enough to cause metal-fume fever<sup>198</sup> have not been encountered, the air in the melting room containing from 0.8 to 7.0 mg. per 10 cubic meters.<sup>199</sup> Fine particles of magnesium dispersed in the air during the trimming, filing, or buffing of castings may cause irritation to the mucous membranes.<sup>194</sup> The treatment of finished castings with chromic acid to increase

<sup>193</sup> Greenwood, *Chem. News*, 100, 39, 49.

<sup>194</sup> H. Gay, *Iron Age*, 150, No. 23, 60 (1942).

<sup>195</sup> M. E. Brooks and A. W. Winston, *Trans. Am. Foundrymen's Assoc.*, 49, 165 (1941).

<sup>196</sup> A. B. Guise, C. V. Mars, and K. S. Wilson, *Light Metal Age*, 1, No. 3, 10, 20 (1943).

<sup>197</sup> *Illinois Labor Bull.*, 3, No. 3, 8 (Sept. 30, 1942).

<sup>198</sup> P. Drinker, R. M. Thomson, and J. L. Finn, *J. Ind. Hyg.*, 9, 187 (1927). K. R. Drinker and P. Drinker, *ibid.*, 10, 56 (1928).

<sup>199</sup> C. R. Williams, *J. Ind. Hyg. Toxicol.*, 24, 277 (1942).



their weather resistance introduces the hazards to nasal mucosa and skin discussed under Chromium.

### 2. Determination of Magnesium Oxide in Air

Williams<sup>190</sup> used Titan yellow in a colorimetric method for determining magnesium in samples collected by the aid of an electrostatic precipitator.

### 3. Toxicity of Magnesium

When administered intravenously, the magnesium ion is toxic, producing narcosis<sup>200</sup> and exerting a profound action upon the circulatory, neuromuscular, and respiratory systems.<sup>201</sup> The lethal dose for dogs is 0.23 to 0.28 g. per kilogram. When magnesium salts are ingested in large amounts, only very small quantities of the metal are absorbed; the osmotic action of the ion withdraws water from the intestinal walls, with resulting purgation. However, fatal intoxication has occurred under certain circumstances. Magnesium is regarded as a constituent of certain enzymes, such as phosphatase<sup>202</sup> and carboxylase.<sup>203</sup> It is essential in normal nutrition, its deficiency in the diet of animals giving rise to a condition known as "grass staggers,"<sup>204</sup> characterized by hyperexcitability, muscular spasticity, convulsions, and cardiac arrhythmia.<sup>205</sup> However, the incorporation of magnesium sulfate in the diet of animals in concentrations of 15,000 to 25,000 p.p.m. has a toxic effect.<sup>206</sup>

Gardner and Delahant<sup>207</sup> observed no damage of the lungs of cats and guinea pigs following their inhalation of finely divided metallic magnesium. They consider it very improbable that serious injury of the lungs will occur in manufacturing processes that permit the inhalation of an appreciable amount of the dust of magnesium. The effects of the inhalation of magnesium oxide over prolonged periods have not been determined.

### 4. Occupational Disabilities

Industrial intoxication by magnesium has not been reported. Examination of 95 men exposed to magnesium oxide dust in the preparation of magnesia revealed only slight irritation of the eyes and nose, although the magnesium content of the serum of 60 per cent of the examined persons was greater than the

<sup>190</sup> J. Auer and S. J. Meltzer, *J. Exptl. Med.*, 23, 643 (1916). C. J. Peth and S. J. Meltzer, *J. Am. Med. Assoc.*, 67, 1131 (1916). J. T. Gwathmey, *ibid.*, 35, 1482 (1925).

<sup>201</sup> S. A. Mathews and W. S. Austin, *Am. J. Physiol.*, 79, 708 (1927). S. J. Meltzer, *Proc. Soc. Exptl. Biol. Med.* (June 22, 1907). S. J. Meltzer and D. R. Lucas, *J. Exptl. Med.*, 9, 298 (1907). G. Crisler, *Am. J. Physiol.*, 86, 552 (1928). D. R. Joseph and S. J. Meltzer, *J. Pharmacol.*, 1, 1 (1909).

<sup>202</sup> K. Lohmann, *Naturwissenschaften*, 17, 624 (1929); cited by O. Baudisch, *J. Am. Med. Assoc.*, 123, 959 (1943).

<sup>203</sup> P. Ostern, T. Baranowski, and F. Terzakowec, *Z. physiol. Chem.*, 251, 258 (1938).

<sup>204</sup> S. W. Hoobler, H. D. Kruse, and E. V. McCollum, *Am. J. Hyg.*, 25, 86 (1937).

<sup>205</sup> M. Sullivan and V. J. Evans, *Bull. Johns Hopkins Hosp.*, 73, 59 (1943).

<sup>206</sup> V. G. Heller and C. H. Larwood, *Science*, 71, 223 (1930). Barlow and Biskind, *Am. J. Physiol.*, 86, 594 (1928).

<sup>207</sup> I. U. Gardner and A. B. Delahant, *Am. J. Pub. Health*, 33, 153 (1943).

normal upper limit of 3.5 mg. per cent.<sup>208</sup> Dermatitis from working with magnesium compounds is rare.

It has been asserted by many observers<sup>209</sup> that fragments of magnesium or light metal alloys, if allowed to remain in wounds, lead to extensive inflammation and difficult healing. Some investigators attributed this to a reaction with the tissue fluids in which bubbles of hydrogen are evolved,<sup>210</sup> along with magnesium hydroxide. The latter, because of its alkalinity, exerts a necrotizing influence<sup>211</sup> which increases susceptibility to infection. This action is probably more severe in the case of alloys. Gay<sup>194</sup> asserts that during 1,500,000 man-days of work in a large magnesium foundry no man lost a single hour as a result of injury from a foreign body composed of magnesium or a magnesium alloy.

### 5. Fire Hazard

Fires<sup>212</sup> arise from the molten metal or from the ignition of dust or swarf. Molten metal burns with explosive violence in the presence of excessive moisture in the molding sand, or when air or water is trapped in the mold runway. This type of fire is quite common and gives rise to severe burns.<sup>213</sup> Swarf fires result from the ignition of particles between 1 and 3 mm. in diameter or from fine threads of metal formed in filing, grinding, or machining the castings. They are controlled by powdered pumice stone or other antiburning powders.

Methods for disposing of dust and grindings and other fire-preventive measures have been described.<sup>214</sup> Fireproof clothing, shoes, gloves, and face shields are essential<sup>215</sup> (see Chapter Thirteen).

## MANGANESE

### 1. Properties, Uses, and Industrial Exposures.

Manganese, Mn, is a gray-pink metal, atomic weight 54.93 and specific gravity 7.2, which melts at 1260° C. and boils at 1900°.<sup>215</sup> It may be obtained from manganese dioxide by an aluminothermic process, or, after treatment with

<sup>208</sup> A. Pleschtizer, *Arch. Gewerbepath. Gewerbehyg.*, 7, 8 (1936).

<sup>209</sup> W. Ehrlich, *Arch. Gewerbepath. Gewerbehyg.*, 7, 517 (1936). C. P. McCord, J. J. Prendergast, S. F. Meek, and G. C. Harrold, *Ind. Med.*, 11, 71 (1942); *J. Ind. Hyg. Toxicol.*, 24, 142 (1942).

<sup>210</sup> W. Gerlach, *Bruns Beitr.*, 159, 129 (1934); cited by W. Ehrlich, *Arch. Gewerbepath. Gewerbehyg.*, 7, 517 (1936).

<sup>211</sup> R. Z. Schulz and C. W. Walter, *J. Ind. Hyg. Toxicol.*, 24, 148 (1942).

<sup>212</sup> G. H. Durston and W. Bleyberg, *Light Metals*, 4, 89, 127 (1941); *Ind. Hyg. Digest*, 6, 1122 (Dec., 1942). Lenze, Metz, and Rubens, *Jahresber. chem.-tech. Reichsanstalt*, 8, 12 (1930). H. R. Brown, *U. S. Bur. Mines Information Circ. No. 7148* (1941). Hartmann, Nagy, and Brown, *U. S. Bur. Mines Repts. Investigations No. 3722* (1943). A. B. Guise, *Chem. & Met. Eng.*, 48, No. 6, 85 (1945). Kremer, *Reichsarbeitsblatt*, 18, III, 190 (1938). Thrune, *Trans. Am. Foundrymen's Assoc.*, 51, 213, 234 (1943). A. C. Stern and B. A. Ford, *Iron Age*, 153, No. 25, 64 (1943). R. Twelvetrees, *Machinery (London)*, 63, 89 (1943).

<sup>213</sup> F. J. Zarzynka, *Ind. Med.*, 12, 427 (1943).

<sup>214</sup> R. I. Thrune, *Natl. Safety News*, 46, 99 (1942); *J. Ind. Hyg. Toxicol.*, 25, 117A (1943). J. M. Kane, *Trans. Am. Foundrymen's Assoc.*, 51, 228, 234 (1943); *J. Ind. Hyg. Toxicol.*, 26, 196A (1944).

<sup>215</sup> H. C. Greenwood, *Chem. News*, 100, 39, 49 (1909).

sulfuric acid, by an electrolytic process. Manganese commonly enters commerce in the form of the alloys spiegeleisen and ferromanganese, which are made directly from the ores in blast or electric furnaces. They are used in steelmaking as deoxidizing agents and to impart strength and shock resistance. Manganin, an alloy composed of 83 per cent copper, 13 per cent manganese, and 4 per cent nickel, is used in electrical resistance coils. Manganese also enters into the composition of manganese bronze and certain alloys with desirable magnetic properties.

Large quantities of manganese dioxide are used in dry cells for depolarization. Manganese dioxide is also employed in glass making and in ceramics. Manganese salts are used in the chemical industry for a wide variety of purposes. Several of its salts may serve as driers for linseed oil. The manganates and permanganates, in which manganese with a valence of 6 or 7 is in the anion, are oxidizing agents used in disinfecting and bleaching and in laboratory work.

Mining, transporting, crushing, and sieving of the ore may disperse manganese-bearing dusts in the air, while manganese fumes may be present near reduction furnaces.<sup>216-218</sup> At one plant having imperfect dust control, the air in the vicinity of the pulverizer contained 173 mg. of manganese per cubic meter, while the average content in the air breathed by laborers was 40 mg. per cubic meter. Near an electric furnace in which manganese was added to steel, the fumes contained 18 per cent manganese.<sup>219</sup> The milling and sifting of ferromanganese also may give rise to exposure.<sup>220</sup> Relatively few cases of intoxication have occurred as a result of the use of manganese in the metal trades, despite the fact that they consume 90 to 95 per cent of the total output of the metal. Most of the many reported cases have been acquired during the mining, transporting, grinding, and smelting of the ore.

The use of manganese in the coatings of welding rods is a source of contamination of the air.<sup>221</sup> Analysis of the coatings have revealed the presence of considerable quantities of manganese.<sup>221,222</sup> The air in a welding chamber has been found to contain from 2 to 23 mg. of manganese per cubic meter.<sup>223</sup> No severe intoxication has been reported from this use of the metal, alleged symptoms in a few men having been of minor psychic character.

It has been estimated that the number of workers potentially exposed to manganese and its compounds in the United States was 23,340 in 1939.<sup>224</sup> Acute

<sup>216</sup> R. H. Flinn, P. A. Neal, and W. B. Fulton, *J. Ind. Hyg. Toxicol.*, **23**, 374 (1941).

<sup>217</sup> R. F. Gayle, *J. Am. Med. Assoc.*, **85**, 2008 (1925).

<sup>218</sup> R. H. Flinn, P. A. Neal, W. H. Reinhart, J. M. DallaValle, W. B. Fulton, and A. E. Dooley, *U.S. Pub. Health Service Bull.* No. 247 (1940).

<sup>219</sup> G. G. Davis and W. B. Huey, *J. Ind. Hyg.*, **3**, 231 (1921).

<sup>220</sup> H. Voss, *Arch. Gewerbepath. Gewerbehyg.*, **9**, 456 (1939).

<sup>221</sup> E. Beintker, *Zentr. Gewerbehyg. Unfallverhüt.*, **19**, 207 (1932); cited in J. A. Britton and E. L. Walsh, *J. Ind. Hyg. Toxicol.*, **22**, 134 (1940).

<sup>222</sup> J. A. Britton and E. L. Walsh, *J. Ind. Hyg. Toxicol.*, **22**, 134 (1940).

<sup>223</sup> C. P. McCord, G. C. Harrold and S. F. Meek, *J. Ind. Hyg. Toxicol.*, **23**, 204 (1941).

<sup>224</sup> J. J. Bloomfield, V. M. Trasko, R. R. Sayers, R. T. Page, and M. F. Peyton, *U.S. Pub. Health Bull.* No. 269 (1940).

intoxication is almost unknown and chronic intoxication, a serious and disabling condition, is relatively infrequent.<sup>225</sup>

## 2. Determination of Manganese

A volumetric bismuthate method may be employed for the determination of manganese in samples of dust collected in impinger flasks containing distilled water.<sup>216</sup> The metal may be oxidized to permanganic acid,<sup>226</sup> by such oxidizing agents as potassium periodate, and the latter determined by the usual methods. The metal may also be determined polarographically.<sup>227</sup> For its determination in biological materials, a spectrographic method is suitable.<sup>228</sup>

## 3. Toxicity for Animals

*Acute effects.* Although a large number of investigations have dealt with the immediate toxicity of manganese compounds when administered subcutaneously or intravenously, the results are of but limited significance for industrial toxicology, since occupational poisoning occurs only following the inhalation of dusts or fumes over long periods. Details of the immediate toxic action of manganese may be found in the review by von Oettingen.<sup>229</sup> In general, the lethal dose of most soluble manganese salts by the intravenous route lies between 18 and 50 mg. per kilogram, the precise figures varying with the salt chosen and the species to which it is administered.<sup>230</sup> Convulsions and paralysis may follow the administration of a large dose, and damage occurs in the liver<sup>231</sup> and kidney.<sup>232</sup>

*Chronic effects.* Experiments in which small oral doses have been given repeatedly over prolonged periods are more pertinent to the problem of industrial intoxication. Several such experiments in which moderate amounts of manganese or its salts were fed gave no evidence of harm,<sup>233</sup> and, indeed, in some, a favorable effect from small quantities upon the growth of the animals was found.<sup>234</sup> When manganese is present in the diet to the extent of 100 p.p.m. growth is stimulated.

<sup>225</sup> F. W. Bickert, *Arch. Gewerbepath. Gewerbehyg.*, 4, 674 (1933).

<sup>226</sup> C. K. Reiman and A. S. Minot, *J. Biol. Chem.*, 42, 329 (1920).

<sup>227</sup> E. Levine, *J. Ind. Hyg. Toxicol.*, 27, 175 (1945).

<sup>228</sup> R. A. Kehoe, J. Cholak, and R. V. Story, *J. Nutrition*, 19, 581 (1940).

<sup>229</sup> W. F. von Oettingen, *Physiol. Rev.*, 15, 175 (1935).

<sup>230</sup> F. Cervinka, *Compt. rend. soc. biol.*, 102, 262 (1929); cited by W. F. von Oettingen, *Physiol. Rev.*, 15, 175 (1935). L. Sabbatani, *Bull. soc. ital. biol. sper.*, 3, 268 (1928); *Chem. Abstracts*, 22, 3231 (1928). T. Sato, *Arch. Intern. Pharmacodynamie*, 36, 49 (1929); cited by W. F. von Oettingen, *Physiol. Rev.*, 15, 175 (1935). R. E. Carratalá and C. L. Carboneschi, *Rev. med. leg. jurisprud. med.*, 1, 405 (1935); *Chem. Abstracts*, 31, 8697 (1937). H. Handovsky, H. Schulz, and M. Staemler, *Arch. exptl. Path. Pharmacol.*, 110, 265 (1925). F. Faludi, *Z. deut. ges. exptl. Med.*, 58, 370 (1927). D. Escobar-Bordoy, *Arch. exptl. Path. Pharmacol.*, 178, 167 (1935).

<sup>231</sup> Hurst and Hurst, *J. Path. Bact.*, 31, 303 (1928). Findley, *Brit. J. Exptl. Path.*, 5, 92 (1924). Kobert, *Arch. exptl. Path. Pharmacol.*, 16, 361 (1883).

<sup>232</sup> E. M. Butt, *Arch. Path.*, 10, 859 (1930).

<sup>233</sup> Richet, Gardner, and Goodbody, *Compt. rend.*, 181, 1105 (1925). W. F. von Oettingen and T. Sollman, *J. Ind. Hyg.*, 9, 48 (1927). Hendych and Klimesch, *Arch. exptl. Path. Pharmacol.*, 178, 178 (1935).

<sup>234</sup> Ehrismann, *Z. Hyg. Infektionskrankh.*, 117, 662 (1935). R. E. Carratalá and C. L. Carboneschi, *Rev. med. leg. jurisprud. med.*, 1, 405 (1935); *Chem. Abstracts*, 31, 8697 (1937).

but its presence in a concentration of 600 p.p.m. is deleterious.<sup>235</sup>

By repeated intraperitoneal injections of manganous chloride into monkeys over a period of 18 months, Mella<sup>236</sup> succeeded in producing symptoms resembling those known to appear as a result of lesions of the basal nucleus. The animals exhibited movements of a choreic type, and later showed a rigidity of the muscles, disturbances of motility, and tremors and contractions of the hands. Histological examination, besides showing acute hepatitis and liver necrosis, revealed marked changes in the corpus striatum, in the globus pallidus of the lenticular nucleus, along with degenerative changes in the caudate and striate nuclei, and in the large ganglion cells of the cortex and basal ganglia. Somewhat similar changes have been observed in the brains of dogs after repeated subcutaneous injections, as well as in those of rabbits after repeated large oral doses.<sup>237</sup>

Despite the fact that occupational intoxication results from exposure to dust containing manganese, few experiments have been carried out to learn the effects of the inhalation of such dusts by animals. Ehrismann<sup>234</sup> subjected rabbits for 4 hours daily over a period of 3 to 6 months to air bearing manganese dioxide in concentrations of 10 to 20 mg. per cubic meter, and observed a decrease in the hemoglobin content and in the number of erythrocytes in the blood. Pneumonia did not occur, but a pulmonary condition resembling silicosis appeared. Analyses of the tissues gave evidence that manganese had been absorbed through the lungs.

Signs of manganese intoxication were observed in a monkey that inhaled manganese dioxide in the form of an aerosol for an hour on each of 95 days.<sup>234a</sup>

#### 4. Absorption and Excretion

That manganese is but poorly absorbed from the digestive tract<sup>238</sup> accounts for the fact that little harm was encountered in feeding experiments except when fairly large amounts were given. Following the oral administration of a soluble compound containing a radioactive isotope of manganese, rats eliminated most of the metal in the feces.<sup>239</sup> Even less absorption occurs when insoluble powdered ores are fed,<sup>240</sup> but the metal can be detected in the liver, kidney, and thyroid. Manganese is an essential element for normal nutrition,<sup>241</sup> being required by the animal body for the action of certain enzymes. A deficiency of manganese in the

<sup>234a</sup> L. van Bogaert and M. J. Dallempagne, *Monatschr. Psychiat. Neurol.*, **111**, 60 (1945). *J. Ind. Hyg. Toxicol.*, **28**, 119A (1946).

<sup>235</sup> V. E. Nelson, J. M. Evvard, and W. E. Sewel, *Proc. Iowa Acad. Sci.*, **36**, 267 (1929); *Chem. Abstracts*, **25**, 1565 (1931).

<sup>236</sup> H. Mella, *Arch. Neurol. Psychiatr.*, **11**, 405 (1924).

<sup>237</sup> T. Matsumura, *Fukuoka Acta Med.*, **26**, 61 (1933); cited by W. F. von Oettingen, *Physiol. Rev.*, **15**, 175 (1935). A. M. Grunstein and N. Popowa, *Arch. Psychiat. Nervenkrankh.*, **87**, 742 (1929); cited by W. F. von Oettingen, *loc. cit.*

<sup>238</sup> Skinner, Peterson, and Steenbock, *Biochem. Z.*, **250**, 392 (1932).

<sup>239</sup> D. M. Greenberg, D. H. Copp, and E. M. Cuthbertson, *J. Biol. Chem.*, **147**, 749 (1943). H. J. Born, H. A. Timofeeff-Ressovsky, and P. M. Wolf, *Naturwissenschaften*, **31**, 246 (1943); *Chem. Abstracts*, **38**, 134 (1944).

<sup>240</sup> C. K. Reimann and A. G. Minot, *J. Biol. Chem.*, **42**, 133 (1920).

<sup>241</sup> Orent and McCollum, *J. Biol. Chem.*, **92**, 651 (1931). A. L. Daniels and G. J. Everson, *J. Nutrition*, **9**, 191 (1935). L. W. Wachtel, C. A. Elvehjem, and E. B. Hart, *Am. J. Physiol.*, **140**, 72 (1943).

diet of chicks of certain breeds causes a condition known as "slipped tendon," which results from an osteoporotic condition of the bones.<sup>242</sup>

The human diet provides a daily intake of about 4 mg. of manganese,<sup>228</sup> most of which is evacuated in the feces, a concentration somewhat less than 0.01 mg. per liter being excreted regularly in the urine.<sup>228</sup> The blood contains from 0.012 to 0.015 mg. per 100 ml.<sup>228,240</sup> Small quantities are found in most of the tissues, the bones, liver, and lymph nodes having the greatest concentrations.

The liver plays an important role both in storing and excreting the metal following its intravenous administration.<sup>243</sup> When very fine particles of manganese dioxide are so administered some may be recovered from the lungs. Under these experimental conditions, symptoms of derangement of the nervous system resembling those encountered in chronic human intoxication were not observed.

### 5. Occupational Intoxication

Manganism usually begins with languor, sleepiness, and a feeling of weakness in the legs. Occasionally, bronchitic symptoms, an enlargement of the lymph nodes, and an increase in the hemoglobin content of the blood have been noted.<sup>244</sup> A characteristic spastic difficulty in walking develops. Muscular twitching and nocturnal cramps occur in the calves, and the legs become stiff. On rising, the victim tends to fall backward, and in walking he leans forward.<sup>216</sup> Rigidity is felt in passive movements of the legs of the patient, who may lose the ability to carry out fine movements of the hands because of a stiffness of the muscles. The voice becomes monotonous and the face masklike. Some, but not all, patients develop gross rhythmic movements of the arms, legs, and trunk, or a fine tremor of the hands, which is sometimes of the intentional type. In severe intoxication, the victim falls when he closes his eyes or when he attempts to walk backward. The tendon reflexes are exaggerated. Sensation usually remains unimpaired, the pupillary reflexes are usually normal, and the peripheral nerves are unaffected. Aside from some paresis of the facial muscles, which may lead to escape of saliva, the cranial nerves are seldom affected.<sup>245-247</sup> The neurological signs may re-

<sup>228</sup> Meyerhof and Ohlmeyer, *Biochem. Z.*, 290, 334 (1937). von Euler, Adler, Günther, and Vestin, *Z. physiol. Chem.*, 247, 127 (1937). Richard and Hellerman, *J. Biol. Chem.*, 134, 237 (1940). Edlbacher and Zeller, *Z. physiol. Chem.*, 245, 65 (1936). Edlbacher and Pinösch, *ibid.*, 250, 241 (1937). H. S. Wilgus, Jr., L. C. Norris, and G. F. Heuser, *Science*, 84, 252 (1936); *J. Nutrition*, 14, 155 (1937). C. D. Caskey, W. D. Gallup, and L. C. Norris, *ibid.*, 17, 407 (1939).

<sup>242</sup> Lund, Shaw, and Drinker, *J. Exptl. Med.*, 33, 23, 77 (1921). Drinker, Shaw, and Drinker, *ibid.*, 37, 829 (1923). Findlay, *Brit. J. Exptl. Path.*, 5, 92 (1924).

<sup>244</sup> V. S. Surat, A. P. Sapozhnikov, and A. P. Shilova, *Kazan Med. Zhur.*, 32, 149 (1936); *Chem. Abstracts*, 33, 2219. G. G. Davis and W. B. Huey, *J. Ind. Hyg.*, 3, 231 (1921). E. W. Baader, *Zentr. Gewerbehyg. Unfallverhüt.*, 9, 1 (1932). Schwarz and Pagels, *Arch. Hyg.*, 92, 77 (1923).

<sup>245</sup> D. L. Edsall, F. P. Wilbur, and C. K. Drinker, *J. Ind. Hyg.*, 1, 183 (1919).

<sup>246</sup> W. D. McNally, *Ind. Med.*, 4, 581 (1935).

<sup>247</sup> J. LeClerq, *Arch. Gewerbepath. Gewerbehyg.*, 5, 337 (1934).

semble those encountered in other diseases of the nervous system,<sup>248</sup> and the clinical picture may show considerable variation in different patients.

Observers differ in regard to the incidence of psychic changes. Some believe that they are rare,<sup>248</sup> but others have noted mental dullness<sup>245,249</sup> and an indifference on the part of the patient to his condition. Some patients complain of insomnia, but more are drowsy. Others have emotional disturbances, such as undue elation or uncontrollable laughter. Disturbances in sexual function are common.

At necropsy, lesions have been found in the basal ganglia, caudate and lenticular nuclei, corpus striatum, globus pallidus, pons, internal capsule, peduncle, and putamen, with occasional changes in the frontal and parietal cortex, and more rarely, in other portions of the central nervous system.<sup>250</sup>

The general health of the patient remains unaffected. If he is removed from exposure soon after the first evidence of the disease appears, the symptoms regress or disappear, but when once well established the disease is crippling but does not shorten life. Erythrocyte counts usually remain normal throughout most of the course of the disease, except for an elevation during its early stages.<sup>216,218</sup> Changes in the bone marrow have been described in two cases. The leucocyte count tends to be lowered.<sup>216,218</sup> The gold curve of the cerebrospinal fluid may exhibit a slight rise in the middle zone,<sup>216</sup> and the fluid may contain an abnormal amount of manganese,<sup>251</sup> and an excess of albumin.<sup>252</sup> Little is known, as yet, of a relationship between the severity of the symptoms and the manganese content of the blood.

Fairhall and Neal<sup>253</sup> believe that a high urinary content of manganese is indicative of past exposure, but that it does not reflect the severity of the symptoms. In a plant in which there was great exposure, the urine of 82 per cent of the affected men contained 4 to 48  $\mu$ g. of manganese per liter, the average being 10  $\mu$ g. per liter, while the urinary concentration averaged 14  $\mu$ g. per liter in the case of 70 per cent of the unaffected men. The feces of one pyrolusite worker contained 7.5 mg. of manganese per 100 grams, according to Dantin-Gallego.<sup>254</sup> Manganese in smaller quantities has been found in the feces 10 to

<sup>248</sup> J. R. Charles, *Brain*, 50, 30 (1927); *J. Neurol. Psychopath.*, 3, 262 (1922). M. Dragonette, *Rass. med. applicata lavoro ind.*, 9, 94 (1938). H. Voss, *Arch. Gewerbepath. Gewerbehyg.*, 10, 550 (1941).

<sup>249</sup> A. Meyer, *Samml. Vergiftungsfällen*, 1A, 34, 79 (1930). Salmon and Planque, *Ann. d'hyg.*, 11, 196 (1933).

<sup>250</sup> C. C. Lund, L. A. Shaw, and C. K. Drinker, *J. Exptl. Med.*, 33, 231 (1921). L. Casamajor, *J. Am. Med. Assoc.*, 60, 646 (1913). M. M. Canavan, S. Cobb, and C. K. Drinker, *Arch. Neurol. Psych.*, 32, 501 (1934). E. W. Baader, *Arch. med. soc. hyg.*, 2, 776 (1939); *Chem. Abstracts*, 36, 3287 (1942). H. Voss, *Arch. Gewerbepath. Gewerbehyg.*, 10, 550 (1941).

<sup>251</sup> A. W. Bryan, *Arch. Neurol. Psych.*, 37, 1448 (1937).

<sup>252</sup> F. Grewel and E. Sassen, *Nederland Tijdschr. Geneeskunde*, 83, 5464 (1939).

<sup>253</sup> L. T. Fairhall and P. A. Neal, *Natl. Inst. Health Bull.* No. 182 (1943).

<sup>254</sup> J. Dantin-Gallego, *Rev. san. hig. publica*, 9, 270 (1934); *J. Ind. Hyg.*, 17, 60A (1935).

16 months after the last exposure.<sup>255</sup> The right and left lungs of one man contained 3.07 and 4.87 mg. of manganese per 100 grams, respectively, indicating a store of metal that might be slowly absorbed and excreted. Progressively smaller amounts were found in the liver, intestine, kidney, bone, heart, stomach, and brain.<sup>218</sup>

The first report of human manganese poisoning was made by Couper in 1837,<sup>256</sup> after which no further mention was made of it until 1901. By 1943, 353 cases were on record,<sup>253</sup> most of them involving miners or handlers of ore. Some investigators believe that only a small proportion of men are susceptible, since in certain mines only a few of the exposed workers became intoxicated. Those affected usually began to exhibit<sup>254,257,258</sup> symptoms within the first two years of exposure to dust, but in Egypt, where severe intoxication has been reported, cases are believed to have developed within a few weeks to six months.<sup>259</sup>

Statistical evidence, supplemented by some experimental observations on animals,<sup>260</sup> suggests that there is a high incidence of a fatal form of pneumonia among workers exposed to pyrolusite (manganese dioxide).

#### 6. Maximum Allowable Concentration and Preventive Measures

In the surveys conducted by the United States Public Health Service,<sup>216,218</sup> no cases of typical manganism developed among men exposed to air bearing any concentration less than 38 mg. of manganese per cubic meter; but one man exhibited symptoms after 10 months of exposure to that concentration, and another after an exposure of less than 1 year to a concentration of 50 mg. per cubic meter. Two of eleven men exposed to concentrations between 30 and 59 mg. per cubic meter, and eight of ten exposed to more than 90 mg. per cubic meter, were victims of chronic intoxication.

The tentative proposal of 60 mg. manganese per 10 cubic meters, arrived at in these surveys, was adopted as a war standard of maximum allowable concentration by the American Standards Association.<sup>261</sup> However, the maximum permissible concentration in California is somewhat more liberal, 50 mg. per cubic

<sup>255</sup> Leschke, *Münch. med. Wochschr.*, 79, 140 (1932). E. W. Baader, *Zentr. Gewerbehyg. Unfallverhüt.*, 9, 1 (1932).

<sup>256</sup> Couper, *Brit. Anal. Med. Pharm.*, 1, 41 (1837); *J. chim. med. pharm. toxicol.*, 3, 233 (1837); cited in R. H. Flinn, P. A. Neal, and W. B. Fullerton, *J. Ind. Hyg. Toxicol.*, 23, 374 (1941).

<sup>257</sup> L. Schwarz, *Arch. Hyg. Bakt.*, 129, 265 (1943); *J. Ind. Hyg. Toxicol.*, 26, 75A (1944).

<sup>258</sup> M. Kaffman, J. Oyarzun, and E. Concha, *Rev. medica Chile*, 70, 892 (1942); *J. Ind. Hyg. Toxicol.*, 25, 174A (1943); J. A. Jiménez, E. Uiberall, and E. Escudero, *Prensa Med. Argentina*, 33, 1684 (1946); *J. Ind. Hyg. Toxicol.*, 29, 70A (1947); J. Ansola, E. Uiberall, and E. Escudero, *Rev. Med. Chile*, 72, 222, 311 (1944); *J. Ind. Hyg. Toxicol.*, 27, 77A (1945).

<sup>259</sup> A. Scander and H. A. Sallam, *J. Egypt Med. Assoc.*, 19, 57 (1936); *J. Ind. Hyg. Toxicol.*, 18, 124A (1936). E. W. Baader, *J. Am. Med. Assoc.*, 113, 521 (1939); *Arch. Gewerbepath. Gewerbehyg.*, 9, 477 (1939).

<sup>260</sup> E. W. Baader, *Aerzt. Schverst. Ztg.*, 43, 75 (1937). Schopper, *Arch. Hyg. Bakt.*, 104, 155 (1930). H. E. Büttner and E. Lenz, *Arch. Gewerbepath. Gewerbehyg.*, 7, 672 (1937). Freise, *ibid.*, 4, 1 (1932). K. W. Jötten, H. Reploh, and G. Hegemann, *ibid.*, 9, 314 (1939). T. A. L. Davies, *Brit. J. Ind. Med.*, 3, 111 (1946).

<sup>261</sup> American Standards Association, Pamphlet No. 237.6, July 16, 1942.



meter.<sup>262</sup> The enclosure of processing equipment, the use of mechanical conveyors, and exhaust ventilation have been found effective in lessening the hazard in ore-crushing plants.<sup>216</sup> Further precautionary measures have been described by Hassinger.<sup>263</sup>

## MERCURY

### 1. Refining of Mercury

Mercury, a highly toxic metal, occurs as cinnabar, HgS, and as free metal in minute droplets in rock layers in Spain, Italy, parts of the United States, and elsewhere. The ore, after being crushed, is dried at a moderate temperature and then roasted at 500 to 600° C. in the presence of air. This removes the sulfur as sulfur dioxide, while the mercury distills. The types of furnaces—shaft furnaces, rotary kilns, and small retort furnaces—and also the arrangements for condensing and collecting the liquid metal, vary greatly. Along with the condensed mercury is a black deposit called stupp: a mixture of ore dust, ash, fine droplets of mercury, and mercury oxide. The liquid metal is tapped from the condensing chambers and filtered through chamois or canvas into weighed steel flasks. In modern installations dust catchers are used with mechanical furnaces and the filtering and weighing are carried on automatically. Mercury is recovered from the stupp by mechanically stirring the latter with lime on a perforated iron pan, the metal forming globules which issue from the holes. The residue is returned to the roasting furnace or decomposed by lime in a retort furnace.

### 2. Properties of Mercury

Mercury, Hg, is a heavy liquid of atomic weight 200.61, and density 13.534 at 25° C., melting point -38.87° C., and boiling point 357.3°. Its vapor pressure, the subject of many investigations,<sup>264</sup> has been given by Hill<sup>265</sup> as 0.000775 mm. Hg at 10° C., 0.00182 mm. at 20°, 0.00407 mm. at 30°, and 0.00787 mm. at 40°, these values being slightly higher than those given by Knudsen.<sup>266</sup> On this basis air at 760 mm. pressure, "saturated" with mercury vapor, would contain 19.9 mg. per cubic meter at 20° C., 43.3 mg. per cubic meter at 30°, and 80.9 mg. per cubic meter at 40°. Because layering of the heavy vapor interferes with vaporization, such equilibrium concentrations are rarely found in air as a result of the evaporation of mercury. Nevertheless, the toxicity of mercury vapor is so great that contamination of air, especially that of laboratories, is of great hygienic signifi-

<sup>262</sup> *State of California, Dept. Ind. Relations, Minutes Ind. Accident Commission*, Nov. 1939; cited by M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

<sup>263</sup> C. C. Hassinger, *Penna. Dept. Labor Ind., Safe Practice Bull. No. 70* (1941).

<sup>264</sup> A. W. C. Menzies, *Z. physik. Chem.*, 130, 90 (1927). D. D. van Laar, *Z. anorg. allgem. Chem.*, 171, 42 (1928).

<sup>265</sup> Hill, *Phys. Rev.*, 18, 113 (1921); 20, 259 (1922).

<sup>266</sup> Knudsen, *Ann. Physik*, 29, 179 (1909). See also F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931, p. 232.

cance. A stream of air passed at the rate of 1 liter per minute over a surface of 10 sq. cm. of mercury at 20° C. becomes about 15 per cent saturated and acquires about 3 mg. of mercury vapor per cubic meter.<sup>267</sup> When mercury is spilled on floors or dirty tables, evaporation is facilitated: dust and grease prevent the minute globules that are formed from uniting into larger ones, so that very large surfaces are exposed to air.

1 mg./l.  $\approx$  121.9 p.p.m. and 1 p.p.m.  $\approx$  8.2 mg./cu.m. at 25° C., 760 mm.

### 3. Uses of Mercury and Industrial Exposures

The metal is used in physical and chemical laboratories in measuring columns, as a confining liquid for handling gases, and in pumps for the production of high vacuums. In a recent investigation of 61 laboratories in this country, the air in ten contained from 0.02 to 0.07 mg. of mercury per cubic meter. In 28, less than 0.004 mg. per cubic meter was present, and in most of the others the concentration was less than 0.02 mg. per cubic meter.<sup>268-269a</sup>

At one time many cases of intoxication resulted from the use of the metal or its amalgams in the "silvering" of mirrors and in the "water gilding" of metals, processes now largely abandoned. The manufacture of mercury-vapor lamps and rectifiers, thermometers, barometers, and other scientific instruments involves the use of considerable quantities of mercury. Users of such instruments are not always aware of the hazard that may arise from failure to remove all accidentally spilled mercury from floors and tables. Large quantities of the metal are employed as electrodes in numerous electrochemical processes. The use of hot mercury in induction furnaces has caused acute intoxication, a concentration of 7 mg. per liter having been recorded in the surrounding air in one instance.<sup>270</sup> The use of mercury as a heat-transfer liquid in boilers for power generation is a potential source of danger. Large quantities of the metal are used also in metallurgy in the extraction of gold and silver. The use of alloys of mercury, known as amalgams, offers a source of exposure. In one instance, the air in a room in which copper amalgam was heated contained 8.5 mg. of mercury per cubic meter.<sup>271</sup> Amalgams for filling teeth are commonly prepared by dentists by rubbing up an alloy with mercury either in a mortar or sometimes in the palm of the hand. Dental technicians have occasion, at times, to heat dental amalgams.

The danger of intoxication in the mining and extraction of mercury has been recognized for centuries. A recent examination disclosed the presence of 1.8 mg.

<sup>267</sup> A. C. Giese, *Science*, 91, 476 (1940).

<sup>268</sup> M. Shepherd, S. Schuhmann, R. H. Flinn, J. W. Hough, and P. A. Neal, *J. Research Natl. Bur. Standards*, 26, 357 (1941).

<sup>269</sup> C. F. McCarroll, *U.S. Bur. Mines, Repts. Investigations No. 3475* (1939).

<sup>269a</sup> J. Gillis, *Mededeel. Vlaamsh. Chem. Ver.*, 7, 223, 300 (1945); *J. Ind. Hyg. Toxicol.*, 26, 137A (1946); L. E. Renes and H. E. Seifert, *Ind. Hyg. Quart.*, 7, 21 (1946).

<sup>270</sup> Jordan and Barrows, *Ind. Eng. Chem.*, 16, 898 (1924).

<sup>271</sup> R. H. Markwith, *Ohio Dept. Health* (1940); cited in P. A. Neal, A. S. Gray, and others, *U.S. Pub. Health Bull. No. 263* (1941); *J. Ind. Hyg. Toxicol.*, 22, 144A (1940).

of mercury per cubic meter of air in a mine in California,<sup>272</sup> but it was found that this could be lowered to 0.1 to 0.2 mg. per cubic meter by the use of a spray containing calcium polysulfides. Two factors tend to limit the severity of exposure in mining. The temperature is usually not high enough to cause decomposition of the cinnabar, and the humidity is great enough to interfere with the dispersal of dusts. When modern airtight equipment is used for the extraction of the metal, exposure occurs only during the discharge of the hot residues and during the cleaning and repair of the equipment.

#### 4. Uses of Mercury Compounds and Industrial Exposures

The salts of mercury have many uses that give rise to occupational hazards. The most widespread hazard is from the use of mercurous nitrate in the carroting of rabbit fur for the manufacture of felt hats. Detailed descriptions of the processes, and the magnitude of the exposures associated with the various operations, have been given by the United States Public Health Service in reports of surveys in the fur-cutting, and felt hat manufacturing industries.<sup>273,274</sup> In these industries the air contains fur dusts that include mercury compounds, in addition to smaller quantities of mercury vapor resulting from their decomposition. Freshly carroted fur contains as much as 2.41 per cent mercury, but a large fraction of it is lost during subsequent operations. A finished hat contains 0.85 per cent, according to Minot,<sup>275</sup> or more, according to Stock.<sup>276</sup> The following concentrations, expressed as milligrams per cubic meter, have been found in the air in various departments in fur cutting and felt hat making: fur storage, mixing, and blowing, 0.5; hardening, 0.25; starting, wetting down, and sizing, 0.21; fur shipping, 0.72; blowing, 0.46; blown-fur packing, 0.38; brushing, 0.12–0.31; cutting, 0.18–0.40. The operation of carroting itself involves little exposure, but mercury concentrations as high as 2.05 mg. per cubic meter have been found in the vicinity of the blowers. New carroting processes that do not involve the use of mercury are being introduced.

Mercuric sulfide is used as the pigment vermilion; mercuric chloride is employed in taxidermy, and as a disinfectant; and calomel, mercurous chloride, besides being used in medicine, has minor uses in industry, as has the nitrate. Mercury fulminate enters into the making of percussion caps; and several alkyl mercury derivatives are used as fungicides. The preparation of organic mercurials consumes large quantities of mercury salts. About eighty occupations involve some hazard from mercury or its compounds.<sup>277</sup>

<sup>272</sup> M. Randall and H. B. Humphrey, *U.S. Bur. Mines Circ. No. 7206* (1942); *Chem. Abstracts*, 36, 6699 (1942).

<sup>273</sup> J. J. Bloomfield and J. M. DallaValle, *Am. J. Pub. Health*, 27, 167 (1937).

<sup>274</sup> P. A. Neal, A. S. Gray, and others, *U.S. Pub. Health Bull. No. 263* (1941). P. A. Neal, R. R. Jones, J. J. Bloomfield, J. M. DallaValle, and T. I. Edwards, *ibid.*, No. 234 (1937).

<sup>275</sup> Minot, *J. Ind. Hyg.*, 4, 253 (1922). See also, Lloyd and Gardner, *J. Soc. Chem. Ind.*, 31, 1109 (1912).

<sup>276</sup> A. Stock, *Angew. Chem.*, 51, 33 (1938).

<sup>277</sup> L. I. Dublin and R. J. Vane, *Bur. Labor Statistics Bull. No. 532* (1933).

### 5. Detection and Determination of Mercury

When it is known that all of the mercury is present in air as vapor, it is possible to employ optical methods of determination based upon the ability of the vapor to absorb the ultraviolet resonance line at 2537Å. The source may be a germicidal lamp, and the measurement may be made by means of a narrow-band photoelectric cell and microammeter.<sup>278</sup> By the use of two photoelectric cells with balanced circuits, it has been possible to construct indicators that are capable of detecting the presence of about 5 µg of mercury per cubic meter of air,<sup>279</sup> especially if the mercury is first condensed by passing the air through a bath of liquid air. Paper coated with selenium sulfide blackens in mercury vapor because of the formation of mercury sulfide, a reaction that has been made the basis of commercial apparatus devised primarily for detecting the occurrence of leaks in mercury boilers.<sup>280</sup> Gold chloride on silica gel also blackens or turns gray in mercury vapor when the concentration exceeds 1 µg. per liter.<sup>281</sup>

When mercury-containing dusts are present in the air, they may be caught in an impinger apparatus, and dissolved in aqua regia, acidified potassium permanganate, or potassium iodide-iodine solution. Various colorimetric procedures of analysis, involving the use of diphenylcarbazide<sup>282</sup> and dithizone,<sup>283</sup> have been described. For the determination of mercury in urine, spectrographic<sup>277,284</sup> and electrodeposition<sup>285</sup> methods have been employed, as well as a colorimetric procedure employing di-β-naphthylthiocarbazon.<sup>286</sup> In determining mercury in tissues, Stock<sup>287</sup> employed the method of Bodnár and Szép,<sup>288</sup> in which the mercury is distilled and condensed into a droplet the size of which is measured microscopically. A more recent dithizone method for determining mercury in tissues was developed by Laug and Nelson.<sup>289</sup>

To determine the hazard to glass blowers that results from sucking air through a side tube containing a drop of mercury, Goodman, Irvine, and Horan<sup>290</sup> added a known amount of a radioactive isotope of mercury, and measured the radioactivity of the air, the method being capable of detecting 10<sup>-8</sup> g. of mercury.

<sup>278</sup> A. E. Ballard and C. D. W. Thornton, *Ind. Eng. Chem., Anal. Ed.*, **13**, 893 (1941).

<sup>279</sup> K. Müller, *Z. Physik*, **65**, 739 (1930).

<sup>280</sup> L. R. Biggs, *J. Ind. Hyg. Toxicol.*, **20**, 161 (1938).

<sup>281</sup> K. Grosskopf, *Draeger-Hefte*, **191**, 3589 (1937); *J. Ind. Hyg. Toxicol.*, **20**, 21A (1938).

<sup>282</sup> Stock and Pohland, *Z. angew. Chem.*, **39**, 791 (1926). O. Stelling, *Svensk Kem. Tid.*, **41**, 80 (1929); *Chem. Abstracts*, **24**, 2182 (1930).

<sup>283</sup> van Zwet and Duran, *Chem. Weekblad*, **38**, 186 (1941). Gettler and Lehmann, *Am. J. Clin. Path.*, **8**, 161 (1938).

<sup>284</sup> Browning, *J. Chem. Soc.*, **111**, 236 (1917). A. M. Fraser, *J. Ind. Hyg.*, **16**, 67 (1934).

<sup>285</sup> E. D. Storlazzi and H. B. Elkins, *J. Ind. Hyg. Toxicol.*, **23**, 459 (1941).

<sup>286</sup> D. M. Hubbard, *Ind. Eng. Chem., Anal. Ed.*, **12**, 768 (1940). J. Cholak and D. M. Hubbard, *ibid.*, **18**, 149 (1946).

<sup>287</sup> A. Stock, *Biochem. Z.*, **316**, 108 (1943).

<sup>288</sup> D. Bodnár and O. Szép, *Biochem. Z.*, **307**, 79 (1940).

<sup>289</sup> E. P. Laug and K. W. Nelson, *J. Assoc. Official Agr. Chem.*, **25**, 399 (1942).

<sup>290</sup> C. Goodman, J. W. Irvine, Jr., and C. F. Horan, *J. Ind. Hyg. Toxicol.*, **25**, 274 (1943).

### 6. Acute Toxicity of Mercury

Mercury acts as a general protoplasmic poison. Attempts<sup>291</sup> to distinguish between the effects of the absorption of atomic mercury into the blood from the lungs, and those of ionic mercury absorbed after the ingestion of mercury salts, seem premature in view of the present speculative state of our knowledge regarding the mode in which mercury is transported in the blood and liberated in the tissues. A more significant determinant of the type of the toxic response is the rate at which mercury is introduced into the body. The inhalation of small amounts of the vaporized metal over prolonged periods gives rise to a chronic form of intoxication in which nervous symptoms predominate. When large amounts are inhaled the type of poisoning assumes a more acute form, and to the nervous manifestations are added symptoms and signs that arise from damage to the various organs—kidney, intestine, and salivary glands—which play a part in the elimination of the metal from the body.

Relatively little is known of the effects of the ingestion of small quantities of mercury or its salts over prolonged periods,<sup>292</sup> but intoxication following the ingestion of larger quantities of mercuric chloride has been the subject of numerous investigations. This form of intoxication, which is of greater clinical than occupational interest, is characterized by pharyngitis, dysphagia, abdominal pain, nausea and vomiting, bloody diarrhea, and shock. Later, swelling of the salivary glands, stomatitis, with loosening of the teeth, nephritis, enuria, and hepatitis occur. The lethal dose of mercuric chloride when administered orally to dogs is 10 to 15 mg. per kilogram.<sup>293</sup> When administered intravenously, it is about 4 to 5 mg. per kilogram for dogs<sup>294</sup> and somewhat more for cats.<sup>295</sup> Poisoning can also occur following inunction of mercury, absorption occurring through the skin.<sup>296</sup>

Acute intoxication from the inhalation of mercury vapor in high concentration, although formerly common among those who extracted the metal from its ores, is now relatively infrequent. However, several recent case reports have been collected.<sup>300</sup> The condition is characterized by a metallic taste, nausea, abdominal pain, vomiting, diarrhea, headache, and sometimes cardiac weakness. The urine may contain albumin. After a few days the salivary glands swell, stomatitis and gingivitis develop, and a dark line of mercury sulfide forms on the inflamed gums.

<sup>291</sup> I. Gelman and G. Derviz, *J. Ind. Hyg. Toxicol.*, 19, 215 (1937). F. Domenici, *Rass. med. applicata lavoro ind.*, 10, 703 (1939). H. Hoff, *Jahrb. Psychiat. u. Neurol.*, 46, 209 (1929); cited by F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931, p. 238.

<sup>292</sup> S. Stimegi and J. Putnoky, *Arch. Gewerbepath. Gewerbehyg.*, 9, 571 (1939).

<sup>293</sup> R. E. Carratalá and C. Guerra, *Rev. asoc. médica argentina*, 49, 926 (1936).

<sup>294</sup> Samsun, *J. Am. Med. Assoc.*, 70, 824 (1918).

<sup>295</sup> W. Modell and S. Krop., *Proc. Soc. Exptl. Biol. Med.*, 55, 80 (1944).

<sup>296</sup> J. F. Schamberg, G. W. Raiziss, and G. L. Garvan, *J. Am. Med. Assoc.*, 70, 142 (1918). C. Stein, *Deut. med. Wochschr.*, 34, 2126 (1908). Moncorps, *Arch. exptl. Path. Pharmacol.*, 155, 51 (1930).

<sup>300</sup> G. Ricker and W. Hesse, *Arch. path. Anat.*, 317, 267 (1915). D. Gutman, *Am. J. Syphilis*, 7, 1, 145, 326 (1923). G. Francioni, *Biochem. therap. sper.*, 16, 545 (1929); *Chem. Abstracts*, 24, 1155 (1930). M. Adamo, *Rass. med. applicata lavoro ind.*, 10, 684 (1939).

The teeth may loosen, and ulcers may form on the lips and cheeks. In milder cases recovery occurs within 10 to 14 days, but in others poisoning of the chronic type may ensue, accompanied by muscular tremors and psychic disturbances. Some of the acute cases have been found in association with exposure to concentrations of the order of 1.2 to 8.5 mg. of mercury per cubic meter of air. Cases also have been encountered among men engaged in welding operations on tanks equipped with mercury seals.<sup>300a</sup>

#### 7. Chronic Intoxication by the Inhalation of Mercury Vapor

*Animals.* Symptoms suggestive of those encountered in industrial intoxication—tremor, loss of weight, and hypertonia—have been observed in guinea pigs and rabbits that inhaled mercury vapor over periods of 1 or 2 months.<sup>297</sup> Kidney lesions were found in rabbits and guinea pigs so exposed, and hyperemia of the lungs and lesions of the intestines were found both in these animals and in mice and rats. Menesini<sup>298</sup> observed lesions in the central nervous system in such experiments. Very few quantitative data have been provided with reference to the mercury concentrations to which animals had been exposed. Fraser, Melville, and Stehle<sup>299</sup> found that dogs that inhaled air containing 1.89 mg. of mercury vapor per cubic meter for 8 hours, on each of 40 days, were unharmed, and that the least concentration that produced chronic toxic effects was 3.05 mg. per cubic meter.

*Man.* An insidious chronic form of mercurialism is now the more commonly encountered one.<sup>300,301</sup> It may appear after a few weeks of exposure, or its onset may be delayed for a year or two. Psychic or emotional disturbances are characteristic. The victim becomes excitable and irascible, especially when criticized. He loses the ability to concentrate and becomes fearful, indecisive, or depressed and may complain of headache, fatigue, weakness, loss of memory, and either drowsiness or insomnia. Objectively, he exhibits a fine tremor, and is unsteady in attempts to perform fine motions. The tremor may affect the hands, lips, head, tongue, or jaw. He may be able to write a few words normally, after which his writing tends to become illegible. This is readily seen in the progressive changes that occur in repetitions of the patient's signature.<sup>302</sup> A letter may be omitted or a wrong one substituted. Other neurological disturbances may include paresthesias, affections of taste and smell, neuralgia, and dermographism. Stock<sup>303</sup> has

<sup>297</sup> G. Menesini, *Zacchia*, 3, No. 2, 538 (1939); *Chem. Abstracts*, 36, 3288 (1942).

<sup>299</sup> A. M. Fraser, K. I. Melville, and R. L. Stehle, *J. Ind. Hyg.*, 16, 77 (1934).

<sup>300</sup> Fühner, *Klin. Wochschr.*, 6, 1545 (1927). Warren, *U.S. Veterans' Bur. Med. Bull.* No. 6, 39 (1930).

<sup>300a</sup> J. E. Williams and C. F. N. Schram, *Ind. Med.*, 6, 490 (1937).

<sup>301</sup> K. Fellinger and F. Sweitzer, *Arch. Gewerbepath. Gewerbehyg.*, 9, 269 (1938); M. Buchell, D. Hunter, R. Milton, and K. M. A. Perry, *Brit. J. Ind. Med.*, 3, 55 (1946).

<sup>302</sup> E. Holstein, *Deut. med. Wochschr.*, 68, 170 (1942); *J. Ind. Hyg. Toxicol.*, 25, 65A (1943). H. Steck, *Schweiz. Arch. Neurol. Psychiat.*, 45, 248 (1940); *J. Ind. Hyg. Toxicol.*, 22, 145A (1940).

<sup>303</sup> A. Stock, *Arch. Gewerbepath. Gewerbehyg.*, 7, 388 (1936); *Z. angew. Chem.*, 39, 461 (1926).

concluded that many cases of so-called neurasthenia, particularly those occurring in chemists, are due to the absorption of small amounts of mercury. Some caution may well be exercised in the too literal acceptance of this thesis.

Other signs of systemic disease appear with less regularity,<sup>274</sup> signs of kidney disease being often encountered. Chronic nasal catarrh and epistaxis are not unusual.<sup>304,305</sup> Salivation, gingivitis, and digestive disturbances are common. Stomatitis is sometimes severe. Ocular lesions, such as amblyopia and scotomas, have been seen. In some patients a cachectic state develops. There are no characteristic changes in the nature of the cellular elements of the blood, although some observers believe that at least a slight degree of anemia is common. Atkinson,<sup>306</sup> using a slit lamp and low power objective, observed a brownish reflex from the anterior capsule of the lens in 37 of 70 thermometer makers. Since less than half of those who exhibited this reflex showed signs of mercurialism, he regarded it as a possible early diagnostic sign.

Most patients show slow improvement when removed from exposure, but no specific treatment is known to aid recovery.

#### 8. Excretion and Storage of Mercury

According to Stock<sup>303</sup> and Borinski,<sup>305</sup> normal persons excrete 0.5  $\mu\text{g}$ . of mercury in the urine and 10  $\mu\text{g}$ . in the feces daily. Experiments on animals designed to learn the efficiency with which inhaled mercury is absorbed have not been conclusive.<sup>299,306,307</sup> Most attempts to learn the sites of storage have been concerned with the fate of ingested mercuric chloride. The liver and kidney appear to be the organs in which most is held,<sup>308</sup> but some has been found in many other tissues. Uncertainty regarding the validity of the analytical methods employed renders much of the work of doubtful significance. In unexposed persons, the organs contain from 0.1 to 1  $\mu\text{g}$ . of mercury per 100 g. of fresh tissue, according to Stock,<sup>309</sup> although the kidney may contain up to 58  $\mu\text{g}$ . per 100 grams.

Mercury may be found in the urine and feces for months after exposure has ceased, the average urinary concentration decreasing logarithmically with time.<sup>271</sup> Urine samples collected from 23 workers during the fourth, ninth, eighteenth, and

<sup>303</sup> S. D. Reiselmann, *Arch. Gewerbepath. Gewerbehyg.*, 1, 496 (1930). Holtzmann, *Z. angew. Chem.*, 40, 438 (1927).

<sup>305</sup> P. Borinski, *Klin. Wochschr.*, 10, 149 (1931). Briggemann, *Z. Laryngol.*, 16, 187 (1926); cited by F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931, p. 238.

<sup>306</sup> W. S. Atkinson, *Am. J. Ophthalmol.*, 26, 685 (1943). H. N. Cole, A. D. Gericke, and T. Sollmann, *Arch. Dermatol. Syphilol.*, 5, 18 (1922). A. Stock and W. Zimmerman, *Biochem. Z.*, 216, 1, 243 (1929). W. Wirth, *Arch. exptl. Path. Pharmacol.*, 184, 91 (1936). K. M. Vogel and O. I. Lee, *Med. Record*, 89, 58 (1916).

<sup>307</sup> M. Shepherd, S. Schuhmann, R. H. Flinn, J. W. Hough, and P. A. Neal, *J. Research Natl. Bur. Standards*, 26, 357 (1941).

<sup>308</sup> Sollman and Schreiber, *Arch. Int. Med.*, 57, 46 (1936). A. Stock, *Biochem. Z.*, 304, 160 (1940). T. H. Maren, J. A. Epstein, and W. C. Hand, *J. Am. Pharm. Assoc.*, 33, 91 (1944). Rosenbloom, *J. Biol. Chem.*, 20, 123 (1923). Burmeister and McNally, *J. Med. Research*, 36, 87 (1917). Blumenthal, *Deut. med. Wochschr.*, 38, 543 (1912). Duhamel, *Compt. rend. soc. biol.*, 82, 724 (1919). Lomholt, *Biochem. J.*, 18, 693 (1924). Lee, *J. Am. Med. Assoc.*, 81, 1748 (1923).

<sup>309</sup> A. Stock, *Biochem. Z.*, 304, 162 (1940). D. Bodnár, O. Szép, and B. Westprémy, *ibid.*, 302, 384 (1939). O. Szép, *ibid.*, 307, 79 (1940).

thirty-first weeks following the cessation of exposure to mercury vapor in high concentration contained the following average concentrations, respectively, 0.54, 0.32, 0.17, 0.07 mg. per liter, but the range of variation was wide.

Unfortunately, it appears from presently available evidence that the elimination of mercury in the urine is too irregular to be of value in determining the severity of occupational exposure; and its absence from the urine in occasional typical cases makes a search for it of uncertain value as a means of determining that exposure has occurred previously.<sup>310</sup> Dentists may eliminate 0.05 mg. of mercury daily in the urine.<sup>311</sup> In general, when little mercury is found in the urine despite a known exposure, the inference is that the metal has been fixed in the tissue. The average urinary concentration rises with increasing exposure along an S-shaped curve. Neal<sup>274</sup> found 0.017 mg. per liter in the urine of men exposed to air bearing 0.05 mg. per cubic meter, and 0.709 mg. per liter in that of 19 men exposed to a concentration of 0.5 mg. per cu. meter. When the exposure ranged from 0.21 to 0.27 mg. per cubic meter, he<sup>270</sup> found an average urinary concentration of 0.297 mg. per liter (range 0.0 to 1.1 mg. per liter) in definitely poisoned persons, 0.415 mg. per liter (range 0.0 to 1.80) in association with borderline cases, and 0.413 mg. per liter (0.0 to 2.7) in unaffected men. The range of variation increased steadily with increasing exposure, while the percentage of men with low urinary concentrations decreased. Storlazzi and Elkins<sup>285</sup> believe that the value of the ratio (U/A) of the urinary concentration, expressed as milligrams per liter, to the mercury concentration in air, expressed as milligrams per 10 cubic meters, affords a measure of the extent to which retention occurs. When so expressed, Neal's data gave a lower value than that of 0.2 to 0.3 found by Storlazzi and Elkins, who noted that the urinary concentrations reported by the Public Health Service were lower than theirs. Only four of 79 samples that Storlazzi and Elkins obtained from felt hat makers indicated that less than 0.1 g. of mercury was being excreted per day, whereas Neal reported that a number of samples from heavily exposed workers contained no mercury. The belief of Koelsch<sup>312</sup> that signs of poisoning are usually present when 0.1 g. of mercury is excreted daily is not confirmed by the data of Neal. Leischner<sup>313</sup> believes that only in the cerebrospinal fluid is the mercury content directly related to the severity of the damage to the central nervous system, but data are not available to substantiate this concept.

#### 9. Incidence of Mercury Poisoning in Various Occupations

Intoxication among miners and workers in the extraction of mercury, although formerly very common, is now becoming unusual. The most severe cases in recent years have occurred as a result of heating amalgams or working near

<sup>270</sup> P. A. Neal and R. R. Jones, *J. Am. Med. Assoc.*, 110, 337 (1938). H. Ilzhöfer, *Münch. med. Wochschr.*, 66, 14 (1919).

<sup>311</sup> H. Schulte, *Arch. Hyg.*, 83, 43 (1914); *Chem. Abstracts*, 9, 105 (1915).

<sup>312</sup> Koelsch, in Abderhalden, *Handbuch der biologischen Arbeitsmethoden*, Vol. IV. 16 (2), 438 (1932).

<sup>313</sup> A. Leischner, *Med. Welt*, 1940, 716; *Chem. Abstracts*. 36. 3288 (1942).



induction furnaces.<sup>314</sup> The incidence of mild chronic intoxication among laboratory workers is difficult to estimate.<sup>315</sup> In the fur-cutting and hat-making trades, the incidence of various degrees of intoxication has been greater than 50 per cent in many shops, although there have been notable exceptions. In the United States in 1936, Bloomfield and DallaValle<sup>316</sup> reported 43 cases of chronic poisoning among 529 workers in 36 plants in these two industries, an incidence of 8.1 per cent. A more recent survey<sup>317</sup> showed that the incidence was somewhat greater among hat felters (11 per cent, or if borderline cases are included, 20 per cent) than among fur cutters (8 per cent). The incidence of psychic or emotional changes was 3.7 per cent, or about that found in industrial workers generally, among 107 cutters exposed to concentrations not in excess of 0.1 mg. of mercury per cubic meter; but it was 17.4 per cent in a group of 144 men exposed to concentrations greater than 0.25 mg. per cubic meter. In areas in which the concentration exceeded 0.1 mg. per cubic meter, the incidence of mercurialism increased with the duration of employment.

Exposure to both mercury and to mercuric oxide occurs during the manufacture of dry batteries of the Ruben type.<sup>317a</sup> The mercury concentrations in 107 samples of urine from men engaged in this work showed little relation to the atmospheric concentrations to which the men were exposed, and widely different urinary concentrations were encountered in the case of men exposed to the same degree of atmospheric contamination.

Relatively few cases of intoxication have occurred as the result of handling other salts of mercury. Two masons were severely poisoned by working in a vat that had contained a solution of mercuric chloride. Spray-painting of ships with an antifouling resinous paint that contained added salts of mercury, lead, and arsenic poisoned 9 of 17 painters.<sup>318</sup>

The irritant nature of mercuric chloride, nitrate, and iodide has been the cause of damage to the skin of those required to handle these substances.<sup>319</sup>

#### 10. Toxicity of Organic Compounds of Mercury

Methyl mercuric iodide and methyl mercuric nitrate when given to rats in an average total dose of 34 to 36 mg. over a period of 29 days caused serious intoxication, with clumsiness and ataxia in the use of the hind legs.<sup>320</sup> Rats and

<sup>314</sup> Turner, *U.S. Pub. Health Repts.*, 39, 229 (1924).

<sup>315</sup> E. H. Christensen, M. Krogh, and M. Nielsen, *Skand. Arch. Physiol.*, 76, 273 (1937); *J. Ind. Hyg. Toxicol.*, 19, 220A (1937).

<sup>316</sup> J. J. Bloomfield and J. M. DallaValle, *Am. J. Pub. Health*, 27, 167 (1937).

<sup>317</sup> P. A. Neal, A. S. Gray, and others, *U.S. Pub. Health Bull.*, No. 263 (1941). P. A. Neal, R. R. Jones, J. J. Bloomfield, J. M. DallaValle, and T. I. Edwards, *ibid.*, No. 254 (1937).

<sup>317a</sup> C. R. Williams, M. Eisenbud, and S. E. Pihl, *J. Ind. Hyg. Toxicol.*, 29, 378 (1947).

<sup>318</sup> L. J. Goldwater and C. P. Jeffers, *J. Ind. Hyg. Toxicol.*, 24, 21 (1942).

<sup>319</sup> R. P. White, *The Dermatogoses or Occupational Affections of the Skin*. 4th ed., Lewis, London, 1934, p. 137.

<sup>320</sup> D. Hunter, R. R. Bomford, and D. S. Russell, *Quart. J. Med.*, 9, 193 (1940); *Brit. Med. Res. Council* (1937-38); *J. Ind. Hyg. Toxicol.*, 21, 3A, 134A (1939).

a monkey subjected to the inhalation of these compounds responded similarly. The inhalation of closely related compounds used as fungicides has given rise to several cases of severe intoxication, characterized by ataxia, dysarthria, constricted visual fields, and altered plantar reflexes. There is an intense, widespread degeneration of certain sensory nerve paths, the peripheral nerves and posterior spinal roots being affected first, and the spinal cord later. There is also a degeneration of certain neurones of the middle lobe of the cerebellum. Such compounds in the form of dust are also irritating to the skin<sup>321</sup> and may be the cause of severe dermatitis.

The use of phenyl mercury oleate as a fungicide and wood preservative offers a dermatologic hazard.<sup>322</sup>

Diethyl mercury is extremely toxic, producing a state that combines the features just described with those typical of ordinary acute mercurialism.<sup>323</sup> Even small amounts cause weakness that lasts for weeks or months. Two chemists who had a part in the early chemical investigation of this substance were fatally poisoned. Two stenographers whose desks were 15 feet from a place in which 20,000 pounds of diethyl mercury was stored also were fatally poisoned.

Mercury fulminate causes many cases of dermatitis, with erythema, intense itching, edema, papules, pustules, and deep ulcers ("powder holes"),<sup>324</sup> especially on the tips of the fingers. Fatigue, headache, and irritation of the conjunctiva and respiratory tract may be noted, along with allergic manifestations in some persons exposed to mercury fulminate. Sensitized persons may show a fall in blood pressure, leucopenia, albuminuria, and edema of the face. True mercurialism is rare. Preventive measures have been described.<sup>325</sup> A soap has been devised that turns yellow in the presence of 0.01 mg. of mercury ion per square meter of skin. Washing should be continued until its color disappears.<sup>326</sup>

### 11. Maximum Allowable Concentration

The allowable concentration of the American Standards Association is 0.1 mg. mercury per cubic meter of air.<sup>327</sup> Stock<sup>328</sup> has stated that 0.2 mg. per cubic meter is dangerous, but concentrations less than 0.003 mg. per cubic meter are not ordinarily injurious. Detailed descriptions of preventive measures for the

<sup>321</sup> F. J. Vintinner, *J. Ind. Hyg. Toxicol.*, **22**, 297 (1940).

<sup>322</sup> C. P. McCord, S. F. Meek, and P. A. Neal, *J. Ind. Hyg. Toxicol.*, **23**, 466 (1941).

<sup>323</sup> Hepp, *Arch. exper. Path. Pharmacol.*, **23**, 91 (1887). W. H. Hill, *Can. Pub. Health J.*, **34**, 158 (1943); *J. Ind. Hyg. Toxicol.*, **25**, 151A (1943).

<sup>324</sup> L. Naro, *Acta Med. Scand.*, Suppl., **120**, 95 (1941). R. P. White, *The Dermatogoses or Occupational Affections of the Skin*, 4th ed., Lewis, London, 1934, p. 134. Swanston, *Proc. Roy. Soc. Med.*, **36**, 633 (1943). MacLeod, *Brit. J. Dermatol.*, **28**, 135 (1916); A. Jordi, *Schweiz. med. Wochschr.*, **77**, 621 (1947).

<sup>325</sup> *Natl. Safety News*, **44**, 38 (1941); *J. Ind. Hyg. Toxicol.*, **24**, 93A (1942).

<sup>326</sup> H. S. Mason and I. Botvinnick, *U.S. Pub. Health Repts.*, **58**, 1183 (1943).

<sup>327</sup> *Am. Standards Assoc.*, Pub. Z57.8 (1943).

<sup>328</sup> A. Stock, *Z. angew. Chem.*, **51**, 33 (1938); *Arch. Gewerbepath. Gewerbehyg.*, **7**, 388 (1936); *Z. physik. Chem.*, **A189**, 63 (1944). A. Stock and Cucuel, *Ber. deut. chem. ges.*, **67**, 122 (1934).

fur-cutting industry have been given by the United States Public Health Service,<sup>317</sup> and laboratory precautions by various authors.<sup>306,315,328a,328b</sup>

Ahlmark<sup>328b</sup> tentatively suggests that the maximum allowable concentration of methyl mercury compounds should be less than 0.01 mg. per cubic meter, and that no exposure that gives rise to a urinary concentration of 10 to 15  $\mu$ g. per liter should be permitted.

## NICKEL

### 1. Properties, Uses, and Industrial Exposures

Nickel, Ni, is a metal of silver-like color, with atomic weight 58.69 and specific gravity 8.5, which melts at 1450° C. and boils at 2150°. It is extracted in Canada from pentlandite, a mixed iron and nickel sulfide, which usually contains copper, and to a lesser extent in the South Pacific from garnierite, a hydrosilicate of nickel and magnesium. The process of extraction varies with the nature of the ore. Copper-nickel concentrates are treated by methods similar to those used in the production of copper, to obtain a mixture of copper and nickel oxides, which may be reduced directly to Monel metal, an alloy containing 28 per cent copper and 67 per cent nickel. If nickel alone is desired, a separation is effected at an earlier stage, while the metals are in the form of sulfides, by fusion with coke and sodium sulfate. The nickel sulfide, which forms a lower layer, is reduced by means of coke in a suitable furnace. The final purification is electrolytic.

In the Mond process, the mixed nickel and copper sulfides are converted to oxides and reduced by heating with water gas at 350 to 400° C. The cooled mixture of nickel and copper is then subjected to the action of carbon monoxide at 60° C. The nickel unites with the carbon monoxide to form volatile nickel carbonyl, Ni(CO)<sub>4</sub>, which is decomposed by passage over nickel pellets heated to 180° C., very pure nickel being deposited upon the pellets. Leakage of the apparatus may lead to exposure to both carbon monoxide and nickel carbonyl. The latter is a nearly colorless liquid, which boils at 45° C., forming a very toxic gas with a peculiar sooty odor, detectable in a concentration of 1 vol. in 2,000,000 of air. Many cases of intoxication, with several fatalities, have occurred.

Nickel is used in steelmaking and in the form of alloys with iron, chromium, and tungsten. The metal itself is used for making cooking utensils and chemical apparatus. Its salts are widely used in electroplating, in preparing storage batteries, and in the chemical industry. Nickel oxide is used as a catalyst for the hydrogenation of oils.

### 2. Determination in the Atmosphere

Fairhall<sup>329</sup> employed potassium dithiooxalate for the colorimetric determination of nickel. The content of nickel carbonyl in air may be determined by

<sup>328a</sup> W. F. Houghton, *Ind. Eng. Chem., News Ed.*, 18, 998 (1940). A. Stock, *Z. angew. Chem.*, 42, 999 (1929).

<sup>328b</sup> A. Ahlmark, *Brit. J. Ind. Med.*, 5, 117 (1948).

<sup>329</sup> K. R. Drinker, L. T. Fairhall, G. B. Ray, and C. K. Drinker, *J. Ind. Hyg.*, 6, 346 (1924). L. T. Fairhall, *ibid.*, 8, 528 (1926). J. H. Yoe and F. H. Wirsing, *J. Am. Chem. Soc.*, 54, 1866 (1933).

aspirating a known volume of filtered air through aqua regia and determining the quantity of nickel in the solution.

### 3. Toxicity for Animals

*Nickel and its salts.* When administered intravenously to dogs, a dose of 10 to 20 mg. of colloidal nickel or of nickel chloride per kilogram of body weight is lethal, affecting the respiratory and cardiac nerve centers<sup>330</sup> and producing edema, hemorrhage, and degenerative changes in the heart, brain, lung, liver, and kidney.<sup>331</sup> The administration of a repeated intravenous dose of 0.5 to 1 mg. of colloidal nickel is tolerated by guinea pigs,<sup>332</sup> but larger doses damage the endothelium of the capillaries. Armit<sup>331</sup> found that the lethal subcutaneous dose of nickel administered in the form of various soluble salts ranges from 7 to 8 mg. per kilogram for rabbits, to 9 to 16 mg. per kilogram for cats. Although the oral administration to dogs of 1 to 3 g. of powdered nickel per kilogram induced vomiting, dyspnea, convulsions, and collapse, the animals did not die. The toxic symptoms produced by the oral administration of nickel salts resemble those caused by arsenic.<sup>333</sup> However, nickel salts incorporated in the diet of animals in fairly high levels can be fed for considerable periods without harm.<sup>334</sup> Lehmann<sup>335</sup> fed 15 cats and 4 dogs from 4 to 12 mg. of nickel per kilogram daily, as chloride or acetate, for periods of 1 to 200 days without affecting their health. There is no evidence of harm from the use of nickel utensils in cooking.<sup>336</sup>

*Nickel carbonyl.* The vapor of nickel carbonyl is at least five times as toxic as carbon monoxide.<sup>331</sup> The inhalation of air containing 0.018 volume per cent (180 p.p.m.) for 65 minutes is sufficient to kill rabbits. Its action is insidious, there being only transient restlessness and dyspnea during the exposure. Twelve to 36 hours later dyspnea, cyanosis, and fever appear. In the lungs, there is vascular congestion and edema so severe as to cause an almost complete obliteration of the air sacs.<sup>337</sup> Capillary hemorrhages in the brain are found also. The mechanism of the intoxication is not completely understood. It is certain that the formation of carboxyhemoglobin in the blood plays an insignificant role.<sup>331</sup> McKendrick and Snodgrass<sup>338</sup> and Armit<sup>331</sup> regard either nickel or its hydrated carbonate, formed following the decomposition of nickel carbonyl within the

<sup>330</sup> J. Caujolle and G. Canal, *J. pharm. chim.*, 29, 391, 410 (1939); *J. Ind. Hyg. Toxicol.*, 22, 125A (1942).

<sup>331</sup> H. W. Armit, *J. Hyg.*, 7, 525 (1907); 8, 565 (1908).

<sup>332</sup> L. Pozzi, *Arch. farmacol. sper.*, 43, 183 (1927); *Chem. Abstracts*, 22, 458.

<sup>333</sup> F. Wohlwill, *Arch. exptl. Path. Pharmacol.*, 56, 403 (1907).

<sup>334</sup> Hanzlik and Presho, *J. Pharmacol.*, 21, 145 (1923). Waltner, *Arch. exptl. Path. Pharmacol.*, 141, 123 (1929). M. Polonovski and S. B. Briskas, *Compt. rend. soc. biol.*, 129, 493 (1938); *J. Ind. Hyg. Toxicol.*, 21, 116A (1941).

<sup>335</sup> K. B. Lehmann, *Arch. Hyg.*, 68, 421 (1913).

<sup>336</sup> W. S. Dzergowsky, S. K. Dzergowsky, and F. O. Schurnoff-Sieder, *Biochem. Z.*, 2, 190 (1906). K. R. Drinker, L. T. Fairhall, G. B. Ray, and C. K. Drinker, *J. Ind. Hyg.*, 6, 308 (1924).

<sup>337</sup> A. J. Amor, *Occupation and Health, Suppl.*, International Labor Office, Geneva, 1938.

<sup>338</sup> D. B. McKendrick and W. Snodgrass, *Brit. Med. J.*, 1, 1215 (1891).

lungs, as the toxic agent, although Vahlen<sup>339</sup> has suggested that the molecule as a whole may be toxic.

#### 4. Industrial Intoxication

*Nickel carbonyl poisoning.* No well-authenticated cases of acute or chronic industrial intoxication by nickel<sup>340</sup> or its compounds, other than nickel carbonyl, have been reported. Nickel carbonyl has, however, been the cause of several fatalities. The symptoms and treatment have been described by Armit,<sup>331</sup> Amor,<sup>337</sup> Bayer,<sup>341</sup> and Kötzing.<sup>342</sup> In suspected cases, it is important to examine the blood for carbon monoxide, because exposure to nickel carbonyl usually implies a concomitant exposure to carbon monoxide, since both are involved in the Mond process for the purification of nickel. No maximum allowable concentration for nickel carbonyl vapor in air has been proposed. Blue flames of carbon monoxide are kept burning in various parts of some plants, since the presence of small concentrations of nickel carbonyl in the air will cause them to burn with a yellow color, thus warning of a leak. It has been asserted that a change in the color of a Bunsen flame will occur when the air contains one part nickel carbonyl in 400,000 parts of air.<sup>343</sup>

*Dermatitis, sensitization, and malignancy.* Numerous cases of dermatitis have been observed among nickel platers.<sup>344</sup> The "nickel itch," which is variable in nature, usually begins with a sensation of burning and itching in the hand, followed by erythema and a nodular eruption on the web of the fingers, wrists, and forearms. The nodules may become pustules or may ulcerate. The acute stage is sometimes accompanied by fever. Recovery usually occurs after a week, although in a few cases the dermatitis has persisted for weeks. There has been much discussion<sup>345</sup> as to the incidence of the condition, and particularly of the role played by degreasing agents in its causation. Some persons are highly susceptible<sup>346</sup> and dermatitis in such persons has resulted from the wearing of a

<sup>339</sup> Vahlen, *Arch. exptl. Path. Pharmacol.*, 48, 117 (1902).

<sup>340</sup> Chomiakow, *Gig. Truda*, 1925, No. 5, 94; cited in *Occupation and Health*, International Labor Office, Geneva, 1934, p. 322.

<sup>341</sup> O. Bayer, *Arch. Gewerbepath. Gewerbehyg.*, 9, 592 (1939).

<sup>342</sup> K. Kötzing, *Arch. Gewerbepath. Gewerbehyg.*, 4, 500 (1933).

<sup>343</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931, p. 252.

<sup>344</sup> A. Müllschitzky, *Wien. med. Wochschr.*, 89, 717 (1939). N. Wedroff, *Arch. Gewerbepath. Gewerbehyg.*, 6, 179 (1935). Stockinger and Schittenhelm, *Z. ges. exptl. Med.*, 45, 58 (1925). R. P. White, *The Dermatogoses or Occupational Affections of the Skin*, 4th ed., Lewis, London, 1934, p. 193. F. M. Carlsen, *Metal Ind. (London)*, 52, 511 (1938); *J. Ind. Hyg. Toxicol.*, 21, 15A (1941).

<sup>345</sup> E. Kolzowa, *Gig. Truda*, 1927, No. 4, 36; cited in *Occupation and Health*, International Labor Office, Geneva, 1934, p. 322. Jadassohn and Schaaf, *Arch. Dermatol. u. Syphilis*, 1929, 572; Schultz, *Aertzl. Sachsverständ. Ztg.*, 1912; *Chem. Abstracts*, 7, 2160 (1913). R. P. White, *The Dermatogoses or Occupational Affections of the Skin*, 4th ed., Lewis, London, 1934, p. 289.

<sup>346</sup> K. R. Drinker, L. T. Fairhall, G. B. Ray, and C. K. Drinker, *J. Ind. Hyg.*, 6, 307 (1924). L. Goldman, *Arch. Dermatol. Syphilol.*, 28, 688 (1933).

nickel spectacle frame,<sup>347</sup> nicked zippers,<sup>348</sup> dentures,<sup>349</sup> and identification tags,<sup>350</sup> and from contact with plastics in which nickel occurred, presumably as the result of its use as a catalyst.<sup>351</sup>

Experimental sensitization to nickel salts has been induced in animals.<sup>352</sup> Rostenberg and Sulzberger,<sup>353</sup> after testing over 500 substances for sensitizing properties, concluded that nickel ranks high as a sensitizing material. Some investigators believe that a high temperature near nickel-plating baths is an important predisposing factor.<sup>354</sup>

In England, an unusual number of cases of malignancy of the accessory nasal sinuses and lungs has been encountered among refiners of nickel. Whether they are to be ascribed to the presence of arsenic in the dusts of the ores, to nickel, or to other causes is in need of further investigation.<sup>355</sup>

## OSMIUM (Os)

### 1. Properties, Uses, and Industrial Exposures

Osmium, Os, is a hard, bluish-white metal of the platinum group with atomic weight 190.2. It melts at 2700 to 2900° C. It has a specific gravity of 22.48 (the heaviest substance known) and is nearly insoluble in all acids, including aqua regia. When heated to 400° C., it burns, forming the tetroxide, OsO<sub>4</sub>, called osmic acid (sometimes called osmium peroxide or perosmic acid). Osmium is reclaimed from the residues left after platinum has been extracted from its ores. Once it was used in the filaments of incandescent lamps, and it is used in the manufacture of metal parts for electrical contacts. Alloyed with iridium, it finds its chief use in tipping gold nibs for fountain pens, and in compass bearings and engraving tools. It may contaminate the platinum-iridium alloys used in jewelry. It has minor uses as a catalyst. Osmic acid, molecular weight 254.2, a crystalline material of burning taste and chlorinelike odor, which melts at 40° C., boils at about 135°, and is quite volatile at ordinary temperatures, is used in staining tissues for histological examination.

1 mg./l. osmium tetroxide  $\approx$  96 p.p.m. and 1 p.p.m.  $\approx$  10.43 mg./cu.m. at 25° C., 760 mm.

<sup>347</sup> Dubois, *Ann. dermat. syphilig.*, 24, 750 (1927). Stewart, *Arch. Internal Med.*, 51, 427 (1933).

<sup>348</sup> L. Goldman and H. L. Claassen, *Arch. Dermatol. Syphilol.*, 45, 578 (1942).

<sup>349</sup> K. K. Deissler and G. R. Sheets, *Calif. and Western Med.*, 57, 354 (1942).

<sup>350</sup> P. N. Unger, *Military Surgeon*, 92, 67 (1943).

<sup>351</sup> Unpublished observations of the author.

<sup>352</sup> Haxthausen, *Arch. Dermatol. u. Syphilis*, 174, 17 (1936).

<sup>353</sup> Rostenberg and Sulzberger, *Arch. Dermatol. Syphilol.*, 35, 433 (1937). C. Carrie, *Dermatol. Wochschr.*, 1940, 1, 619; *Chem. Abstracts*, 36, 3285. H. H. Johnson, Jr., *Arch. Dermatol. Syphilol.*, 43, 575 (1941).

<sup>354</sup> C. DuBois, *Schweiz. med. Wochschr.*, 61, 278 (1931). F. M. R. Bulmer and E. A. Mackenzie, *J. Ind. Hyg.*, 8, 517 (1926).

<sup>355</sup> F. Koelsch, *Monatschr. Krebsbekämpfung*, 5, 7 (1937); *J. Ind. Hyg. Toxicol.*, 19, 194A (1939). A. J. Amor, *Ber. 8th Intern. Congr. Unfallmed. u. Berufskrankh.*, 2, 941 (1939); *Acta Univ. Intern. Contra Cancrum (Paris)*, 3, 243, 253 (1938); *Chem. Abstracts*, 35, 3731, 3732.

As a metal osmium is innocuous, but osmic acid is extremely toxic. It develops slowly at room temperature when the powdered metal is exposed to air. The gentle heat required for annealing platinum or for making pen nibs causes the evolution of poisonous fumes.<sup>356</sup>

## 2. Toxicity

The instillation of one drop of a 1 per cent solution of osmic acid into the conjunctival sac of rabbits causes a slowly developing but intense conjunctivitis, with corneal ulceration. The acute phase begins to subside after about 10 days. In the experiments of Brunot,<sup>356</sup> all rabbits exposed for 30 minutes to air bearing the vapor of osmic acid in somewhat uncertain concentrations died. Their lungs were dark red, voluminous, and doughy, and presented a striking appearance when cut, the bronchi standing out prominently because of a black staining of the epithelial lining by reduced osmium. The trachea, epiglottis, and the interior of the larynx were jet black. In other respects, the lesions resembled those produced by chlorine. The very slight exposure of the investigator, which resulted from opening four 0.25 g. ampoules and placing them in the exposure chamber, an operation completed within 2 minutes, was followed 30 minutes later by a smarting of the eyes with lacrimation. This progressed to a degree such that after 3 hours reading became difficult, and street lights appeared as though seen through a rather dense fog. The chemist, Deville, suffered serious derangement of his vision as a result of his work on the preparation of osmic acid. Even small amounts, if inhaled over a considerable period, caused headache, insomnia, digestive disturbances, and pharyngeal and laryngeal distress.<sup>357,357a</sup>

## 3. Maximum Allowable Concentration

The maximum allowable concentration has not been determined. It has been stated by Lehmann and Hess that it is possible to breathe air bearing 0.001 mg. per liter (0.1 p.p.m.) for  $\frac{1}{2}$  hour without harm. The highest concentration that could be tolerated for 6 hours was 0.000001 mg. per liter (0.01 mg. per 10 cubic meters) or 0.0001 p.p.m.<sup>357a</sup>

## PALLADIUM

Palladium, Pd, a silvery metal of the platinum group, with atomic weight 106.7 and specific gravity 12.0 melts at 1555° C., boils at 2200° C., and is soluble in aqua regia and hot sulfuric acid. It is used to a slight extent in jewelry, and in the making of dental alloys. Because of its remarkable ability to adsorb hydrogen, it finds use in chemical laboratories in gas analysis.

The subcutaneous administration to rats of as much as 24 mg. of palladium chloride per kilogram in buffered solution caused no harm.<sup>358</sup> The daily admin-

<sup>356</sup> B. M. Hoke, *Jewelers Circ., Brass World*, 20, 242 (1924); *Chem. Abstracts*, 18, 2673 (1924). F. R. Brunot, *J. Ind. Hyg.*, 16, 137 (1933).

<sup>357</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931, p. 253.

<sup>357a</sup> A. J. McLaughlin, R. Milton, and K. M. A. Perry, *Brit. J. Ind. Med.*, 3, 183 (1946).

<sup>358</sup> S. F. Meek, G. C. Harrold, and C. P. McCord, *Ind. Med.*, 12, 447 (1943).

istration of 5 mg. of palladium to rabbits during a period of 2 months caused no disturbance of health.<sup>359</sup> Patch tests with a buffered solution of palladium chloride on the skin of seven subjects caused no reaction in 24 hours. Solutions of palladium chloride are acid and if not neutralized might be expected to cause irritation of the skin.

No industrial intoxication by palladium or its salts has been reported.

## RUTHENIUM

Ruthenium, Ru, is a hard, brittle, gray metal associated with platinum ores. Its atomic weight is 101.7 and its specific gravity 12.2 (crystalline form). It is nearly insoluble in acids, melts at 2450° C., and resembles osmium chemically. Like osmium, when heated in air, ruthenium also forms fumes that are injurious to the eyes and lungs.<sup>360</sup> Ruthenium tetroxide, RuO<sub>4</sub>, molecular weight 165.70, is a yellow crystalline compound that melts at 25.5° C. and is explosive and volatile, with an odor resembling ozone.

Ruthenium red, Ru<sub>2</sub>(OH)<sub>2</sub>Cl<sub>4</sub>·7NH<sub>3</sub>·3H<sub>2</sub>O, an ammoniated basic ruthenium chloride, is a brownish red powder used as a microscopic stain and as a test for pectin, gum, and so forth.

## THALLIUM

### 1. Properties, Uses, and Industrial Exposures

The chief source of thallium is pyrites, in which it occurs as an impurity. During the roasting of the ore for the production of sulfur dioxide, it passes into the dust which settles on the flues, or accumulates in the sludge in the lead chambers of sulfuric acid factories. Compounds of thallium have been used in rodent control, in pyrotechnics, in the preparation of catalysts, in the analytical laboratory, in extending the life of the tungsten filaments of lamps, and in imparting a high refractive index to glass.<sup>360a</sup>

In appearance, thallium, Tl, resembles tin, but it is soft and malleable like lead. It has an atomic weight of 204.39, specific gravity 11.85, melting point 300° C., and boiling point about 1482°. It forms univalent thallos salts and trivalent thallic salts; the latter are more or less readily hydrolyzable by water and on boiling tend to be reduced to thallos compounds. Thallos acetate is soluble in cold water but thallos chloride, iodide, and hydroxide are insoluble. In general, thallium salts are somewhat more soluble.

1 mg./l.  $\approx$  119.7 p.p.m. and 1 p.p.m.  $\approx$  8.36 mg./cu.m. at 25° C., 760 mm.

<sup>359</sup> M. Kauffmann, *Münch. med. Wochschr.*, 60, 525 (1913).

<sup>360</sup> R. A. Cooper, *J. Chem. Met. Mining Soc. S. Africa*, 22, 152 (1922); *Chem. Abstracts*, 16, 2101 (1922).

<sup>360a</sup> H. K. Sessions and S. Goren, *U.S. Naval Med. Bull.*, 47, 545 (1947).



## 2. Determination

Thallium can be detected readily by means of the spectroscope, since it emits a green line at 535  $\mu$ . Volumetric methods for its determination are based upon the ability of the thallic ion, formed by the use of an oxidizing agent, to liberate iodine from potassium iodide.<sup>361,361a</sup>

## 3. Toxicity for Animals

Salts of thallium are extremely toxic, causing widespread damage to the nervous system, digestive tract, and to a lesser extent, the kidneys and circulatory system. The lethal dose is the equivalent of 12 to 15 mg. of the metal per kilogram of body weight, when administered orally to dogs.

The repeated administration of daily doses of 0.2 mg. of thallium acetate to young rats retards growth<sup>362</sup> and causes bony abnormalities,<sup>363</sup> cataracts,<sup>361,364</sup> neoplastic lesions of the forestomach,<sup>365</sup> and an almost complete but temporary loss of hair.

## 4. Absorption and Excretion

Thallium compounds are readily absorbed through the skin and from the digestive tract. The metal appears quickly in the feces, urine, tears, sweat, and milk but persists for long periods in the urine. It does not occur normally in the tissues, but when ingested is widely distributed therein.<sup>366</sup>

## 5. Human Intoxication

Although over 778 cases of human poisoning by thallium have been reported,<sup>367</sup> only about a dozen, all of them chronic, have been attributed to industrial exposure<sup>368,369</sup> in the handling of pyrites, or thallium salts, or from exposure to thallium-bearing dusts. Symptoms included excitement and sleeplessness, followed by anorexia, loss of weight, fatigue, depression, salivation, vomiting, diarrhea, and hysterical laughter. After a few weeks or months, the hair was lost and signs of polyneuritis appeared. Scotomata and optic atrophy have resulted.

No attempts have been made to determine a maximum permissible concentration of thallium-bearing dusts in the air.

<sup>361</sup> R. Fridli, *Deut. Z. ges. gerichtl. Med.*, 15, 478 (1930); A. O. Gettler and L. Weiss, *Am. J. Clin. Path.*, 13, 322, 368 (1943); Samaan and Mikhail, *Quart. J. Pharm. Pharmacol.*, 16, 342 (1944).

<sup>361a</sup> H. H. Ackerman, *J. Ind. Hyg. Toxicol.*, 30, 300 (1948).

<sup>362</sup> A. Buschke and B. Peiser, *Med. Klin.*, 13, 731 (1922).

<sup>363</sup> A. Buschke, L. Loewenstein, and O. W. Joel, *Klin. Wochschr.*, 7, 515 (1928).

<sup>364</sup> S. Ginsburg and A. Buschke, *Klin. Monatsbl. Augenheilk.*, 71, 285 (1923).

<sup>365</sup> A. Buschke, L. Loewenstein, and O. W. Joel, *Med. Klin.*, 25, 462 (1929).

<sup>366</sup> A. O. Gettler and L. Weiss, *Am. J. Clin. Path.*, 13, 422 (1943).

<sup>367</sup> J. C. Munch, *J. Am. Med. Assoc.*, 102, 1929 (1934).

<sup>368</sup> I. Teleky, *Wiener med. Wochschr.*, 73, 506 (1928).

<sup>369</sup> Rube and Hendricks, *Med. Welt*, 1, 733 (1927).

## TIN

**1. Properties, Uses, and Industrial Exposures**

Tin, Sn, atomic weight 118.70, specific gravity 7.3, is the most fusible of the solid metals, melting at 233° C. and boiling at 2270°. <sup>370</sup> It is extracted from its ores (cassiterite—SnO<sub>2</sub>, stannite—FeCu<sub>2</sub>SnS<sub>4</sub>, and tealite—PbSnS<sub>2</sub>) by methods that may involve exposure to silica, lead, and, more readily, fluorides. Arsenic and antimony may be encountered as impurities. Utensils of many types are made of tin because it changes but little in moist air. In the form of foil, it is used in the packaging of foods, but for this purpose it is being supplanted by aluminum. Sheets of scoured steel for the manufacture of cans are plated by dipping them into molten tin. The metal is recovered from waste cans by exposing them to chlorine that converts the tin to liquid tin tetrachloride. The addition of a soda solution, along with carbon dioxide, precipitates stannic acid, which can be reduced to metallic tin by charcoal. In another process, the scrap is immersed in a solution of copper sulfate, the tin dissolving and the copper precipitating. Tin enters into the composition of many important alloys such as bronze, white metal, and solders.

Stannous chloride is a reducing agent employed as a discharge in calico printing. Hydrated stannic acid, sodium metastannate, hydrated stannic chloride, and ammonium stannic chloride are used as mordants in dyeing and in the weighting of silk.

**2. Determination**

Tin may be determined by spectrographic, <sup>371</sup> electrolytic, <sup>372</sup> or colorimetric <sup>373</sup> methods, reagents for the latter including substituted benzene-*o*-dithiols and toluene-3,4-dithiol. <sup>374</sup>

**3. Toxicity of Tin and Its Compounds**

When parenterally administered, tin salts are toxic, causing spasms and fatal paralyses, <sup>375</sup> and inducing hyperemia, vascular changes, and bleeding in the central nervous system, liver, heart, and other organs. <sup>376</sup> There is little difference in the toxicity of stannous and stannic salts. <sup>377</sup> The lethal intravenous dose of a compound of tin with citric acid corresponds to about 100 mg. of tin per kilogram of body weight. <sup>378</sup>

<sup>370</sup> H. C. Greenwood, *Chem. News*, 100, 39, 49 (1909).

<sup>371</sup> J. Cholak and R. V. Story, *Ind. Eng. Chem., Anal. Ed.*, 10, 619 (1938).

<sup>372</sup> D. Rafaelli, *Ann. chim. applicata*, 33, 16 (1943).

<sup>373</sup> G. S. Buchanan and S. B. Schryver, *Brit. Food J.*, 11, 101 (1909); *Chem. Abstracts*, 3, 2329 (1909).

<sup>374</sup> R. E. D. Clark, *Analyst*, 61, 242 (1936). R. DeGiacomi, *ibid.*, 65, 216 (1940).

<sup>375</sup> M. Mitolo, *Arch. fisiol.*, 28, 89 (1930).

<sup>376</sup> A. A. Mamontova, *Voprosy Pitaniya*, 9, No. 6, 13 (1940); *Chem. Abstracts*, 38, 2118 (1944).

<sup>377</sup> Salant and Rieger, *Proc. Soc. Exptl. Biol. Med.*, 11, 178 (1914).

<sup>378</sup> Seifter and Rambousek, *J. Lab. Clin. Med.*, 28, 1344 (1943).

When orally administered, a very large dose of metallic tin will induce vomiting. However, the daily administration to pigeons of 0.25 g. of powdered tin per kilogram for 27 days caused no harm.<sup>379</sup> Little evidence of toxicity has been obtained in experiments of a similar nature on other species.<sup>380</sup> Men and dogs can tolerate 800 to 1000 mg. of the metal daily, according to Mamontova.<sup>376</sup> Soluble salts, such as the chloride or tartrate, are tolerated by rats and by cats in daily doses of not more than 30 to 50 mg. per kilogram.<sup>381</sup> The diet of normal American men contains on the average 17.14 mg. of tin per day,<sup>382</sup> much of it derived from canned goods. Buchanan and Schryver,<sup>373</sup> after reviewing alleged cases of poisoning from canned goods, concluded that there is little likelihood of chronic intoxication from this source.

Experiments on the effects of the inhalation of tin in the form of dust are lacking. The tetrachloride, which fumes strongly in moist air because of hydrolysis to hydrochloric acid and tin hydroxide, is doubtless a source of danger, although Pedley<sup>383</sup> found that a guinea pig withstood an exposure of 10 minutes to air containing 3 p.p.m. of this compound.

#### 4. Absorption and Excretion

But little absorption of tin (at least in the form present in canned food) occurs from the alimentary tract.<sup>384</sup> The mean content of tin in the blood of normal Americans is 0.014 mg. per 100 grams,<sup>382</sup> practically all of it being in the cells, and the urine contains 0.011 mg. per liter.<sup>382</sup> The excretion of tin in the feces and urine of man balances the intake when the latter does not exceed 130 mg. per day,<sup>373</sup> but some accumulates in the tissues when the intake is greater. In the organs of Americans, Kehoe, Cholak, and Story<sup>382</sup> found the following amounts of tin, expressed as milligrams of metal per 100 g. of wet tissue: kidney, 0.020; heart, 0.022; liver, 0.060; spleen, 0.022; lung, 0.045; muscle, 0.011; long bone, 0.080; rib, 0.050; stomach, 0.050; intestine, 0.016; brain, 0.0. After the intravenous administration of tin compounds, fairly large amounts may be recovered from the kidney, with smaller amounts in the liver, lung, spleen, and other organs.<sup>378</sup> Very little is found in the brain. Excretion appears to occur chiefly through the liver and intestines, rather than in the urine,<sup>376,383a</sup> although some investigators<sup>373</sup> believe the opposite.

#### 5. Incidence of Occupational Injury from Tin

Acute industrial intoxication from exposure to tin is not known to have occurred; and there are reports of but three questionable cases of chronic poisoning.<sup>383</sup> The metal itself is not a cause of dermatitis. Stannic chloride, because of its acidity, is irritating to the skin, nose, and eyes.

<sup>379</sup> Hanzlik, McIntyre, and Presho, *Proc. Soc. Exptl. Biol. Med.*, 19, 192 (1922).

<sup>380</sup> Waltner, *Arch. exptl. Path. Pharmacol.*, 141, 123 (1929).

<sup>381</sup> Salant, *J. Ind. Hyg.*, 2, 72 (1920).

<sup>382</sup> R. A. Kehoe, J. Cholak, and R. V. Story, *J. Nutrition*, 19, 582 (1940); 20, 85 (1940).

<sup>383</sup> F. G. Pedley, *J. Ind. Hyg.*, 9, 43 (1927).

<sup>383a</sup> Salant, Rieger, and Treuthardt, *J. Biol. Chem.*, 17, 265 (1914).

Pendergrass and Pryde<sup>384</sup> have reported a case of benign pneumoconiosis in a man who had been engaged in bagging tin oxide over a period of 15 years.

## VANADIUM

### 1. *Properties, Uses, and Industrial Exposures*

Vanadium, V, a light gray, crystalline metal, very malleable, soft, and ductile, with atomic weight 50.95, density 5.7, melting point 1720° C., boiling point 3000°, is used in steelmaking. It is obtained as soluble sodium vanadate,  $\text{Na}_3\text{VO}_4$ , by sintering its ores with soda ash and leaching with water. The addition of sulfuric acid precipitates vanadium pentoxide,  $\text{V}_2\text{O}_5$ , which is dried and fused. By treating the pentoxide with iron in an aluminothermic process, or by electric smelting, an alloy with iron called ferrovandium is obtained. This is the usual form in which vanadium enters commerce.

Vanadium compounds have some limited use as catalysts, in photography, in printing and dyeing, and in inkmaking.

Vanadium may be determined spectrographically, using chromium as an internal standard.<sup>385</sup>

### 2. *Toxicity of Vanadium*

Expressed as  $\text{V}_2\text{O}_5$ , the lethal dose of colloidal vanadium pentoxide and of ammonium metavanadate,  $\text{NH}_4\text{VO}_3$ , when administered to mice, guinea pigs, rats, and rabbits, is of the order of 1 to 2 mg. per kilogram<sup>386</sup> while sodium vanadate and vanadyl sulfate,  $(\text{VO})_2(\text{SO}_4)_3$ , are somewhat less toxic.<sup>387</sup> Vanadium pentoxide is a respiratory irritant,<sup>388</sup> and when ingested vanadium compounds cause vomiting, distress, salivation, increased peristalsis, and diarrhea.<sup>389</sup> After the administration of a fatal dose, the central nervous system is affected, there being somnolence, paralysis of the hind legs, clonic convulsions, and coma. In animals poisoned by sodium vanadate, the lungs and intestines are hyperemic, with the bone marrow, brain, and cord somewhat less congested.<sup>389</sup> There is acute enteritis, mild fatty degeneration of the liver and kidney tubules, and the spleen is reduced in size.

Heimberger<sup>390</sup> found that cats die within 60 hours following a 5-minute exposure to air containing 5 mg. of vanadium pentoxide per liter, or within 40

<sup>384</sup> E. P. Pendergrass and A. W. Pryde, *J. Ind. Hyg. Toxicol.*, 30, 119 (1948).

<sup>385</sup> E. P. Daniel, E. M. Hewston, and M. W. Kies, *Ind. Eng. Chem., Anal. Ed.*, 14, 921 (1942).

<sup>386</sup> F. Proescher and H. A. Seil, *Am. J. Syphilis*, 1, 347 (1917); *Chem. Abstracts*, 11, 1858 (1917).

<sup>387</sup> Franke and Moxon, *J. Pharmacol.*, 58, 454 (1936).

<sup>388</sup> F. Molfino, *Rass. med. applicata lavoro ind.*, 9, 362 (1938); *J. Ind. Hyg. Toxicol.*, 21, 96A (1939).

<sup>389</sup> E. P. Daniel and R. D. Lillie, *U.S. Pub. Health Repts.*, 53, 765 (1938).

<sup>390</sup> Heimberger, *Dissertation Würzburg*, 1929; cited in F. Flury and F. Zernik, *Schädliche Gase*, Springer, Berlin, 1931, p. 250.

minutes following a 23-minute exposure to air containing 0.5 mg. per liter. Cats survived after an exposure of 3 hours to a concentration of 0.04 mg. per liter. The effects of the inhalation of vanadium-bearing dusts over prolonged periods have not been investigated.

The daily oral administration to rats of 2 to 4 mg. of vanadium in the form of soluble vanadates leads to poisoning in 2 to 4 days.<sup>386</sup> Symptoms appear when a vanadate is added to the diet in the proportion of 92 p.p.m. or 50 p.p.m.<sup>387</sup> but not when it is present to the extent of 23 p.p.m.

Vanadium has been detected in the urine of rabbits after the administration of the pentoxide. The element is temporarily stored in the liver, kidney, stomach, and intestine; and is eventually completely eliminated, mainly in the feces.<sup>386</sup>

### 3. Industrial Intoxication

The evidence for the occurrence of chronic intoxication as a result of exposure to vanadium-bearing dusts is inadequate.<sup>391</sup> Balestra and Molfino<sup>392</sup> called attention to pulmonary damage in men who handled a dust that contained 85 per cent vanadium pentoxide. Symanski,<sup>393</sup> who examined 19 workers engaged in the production of ferrovandium, observed among them conjunctivitis, sometimes suppurative, rhinitis, dryness of the pharynx, continuous and more or less productive coughing, and some degree of subacute or chronic bronchitis, confirmed by radiographic examinations. No tuberculosis was found, and there were no signs of inflammatory infiltration of the pulmonary parenchyma. There was no anemia, and gastritis was rare. Symanski called attention to the fact that none of the men examined had been exposed for more than a few years. Ten cases have recently been described by Wyers.<sup>393a</sup>

There is no evidence upon which to base a maximum allowable concentration of vanadium in air. In view of the toxic effects of the absorption of vanadium compounds upon animals, further investigation is needed.

## ZINC

### 1. Properties, Uses, and Industrial Exposures

In the metallurgy of zinc, sulfide ores are converted to zinc oxide by roasting; and carbonate ores, by ignition. The oxide is reduced in multiple small retorts by the action of coal or coke at a temperature of about 1100° C., and the liberated zinc, which boils at 930°, distills. The metal is received in fireclay condensers and cast in blocks called spelter, which may be refined by redistillation. Associated hazards in the metallurgy of zinc arise from the presence of arsenic, cadmium, manganese, copper, silver and, very commonly, lead.

Zinc, Zn, atomic weight 65.38, specific gravity 7.14, melts at 419° C., and at temperatures of 120 to 150° C. can be rolled into sheets. It burns in air forming

<sup>381</sup> Dutton, *J. Am. Med. Assoc.*, 56, 1648 (1911).

<sup>382</sup> G. Balestra and F. Molfino, *Rass. med. applicata lavoro ind.*, 13, 5 (1942); *Chem. Abstracts*, 37, 3591 (1943); *J. Ind. Hyg. Toxicol.*, 26, 7A (1944).

<sup>383</sup> Symanski, *Arch. Gewerbepath. Gewerbehyg.*, 9, 295 (1939).

<sup>383a</sup> H. Wyers, *Brit. J. Ind. Med.*, 3, 177 (1946).

the oxide. When formed at temperatures higher than 650° C., the latter tends to be colloiddally dispersed in the air, the particles being less than 0.3 to 0.4  $\mu$  in diameter.<sup>394</sup> Powdered zinc is a powerful reducing agent, decomposing water with the liberation of hydrogen and the evolution of heat.

The uses of zinc are too numerous to list. The frequent presence of arsenic in zinc is a source of danger whenever the metal is dissolved in acids or alkalies, because arsine will be liberated. Many cases of intoxication by arsine have occurred in the pickling of galvanized iron, or from the use of powdered impure zinc as a reducing agent in dyeing. Zinc oxide is widely used as a filler in rubber and linoleum, as a pigment, and in pharmacy. Other zinc compounds, such as the sulfide and chromate, are also used as pigments. Zinc chloride, a corrosive salt, is used as a preservative for wood, in soldering, in taxidermy, and for numerous other purposes.

### 2. Determination in the Atmosphere

Samples of fumes of zinc oxide in air may be collected by means of a Greenburg-Smith impinger, an electrostatic precipitator, or by passing the air through cotton moistened with dilute nitric acid. The determination may be made by a colorimetric procedure using dithizone or di- $\beta$ -naphthylthiocarbazone, or it may better be made polarographically.<sup>395</sup> In the air of nonferrous foundries, concentrations greater than 15 mg. of zinc oxide per cubic meter are seldom encountered, the highest being found at the time of pouring.<sup>396</sup>

### 3. Toxicity of Zinc Compounds

Zinc salts are astringent and corrosive, the soluble chloride and sulfate being irritating and capable of causing severe damage to the skin. When taken internally, they act as emetics, because of the local action of the metal upon the tissues of the digestive tract. Zinc is ordinarily too poorly absorbed to give rise to acute systemic intoxication. After large doses have been ingested, fatal collapse may occur as a result of serious damage to the buccal and gastroenteric mucous membranes. The lethal dose of the zinc ion when administered orally to mice is 57 mg. per kilogram.<sup>397</sup> Jaeger<sup>397</sup> found that a subcutaneous injection of zinc lactate or valerate equivalent to 57 mg. of zinc per kilogram killed a cat, death occurring after 3 days. When parenterally introduced, zinc depresses the central nervous system and causes tremors and paralyzes of the extremities. Acute human intoxication has resulted from drinking limeade that had been kept in a galvanized iron container.<sup>398</sup>

<sup>394</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931, p. 229.

<sup>395</sup> J. Cholak, D. Hubbard, and R. Burkey, *Ind. Eng. Chem., Anal. Ed.*, 16, 754 (1943).

<sup>396</sup> Wisconsin State Board of Health, Industrial Hygiene Unit, *J. Ind. Hyg. Toxicol.*, 25, 61A (1943).

<sup>397</sup> H. Jaeger, *Arch. exptl. Path. Pharmacol.*, 159, 139 (1931).

<sup>398</sup> G. R. Callender and C. J. Gentzkow, *Military Surgeon*, 80, 67 (1939). J. W. Sale and C. H. Badger, *Ind. Eng. Chem.*, 16, 164 (1924).

Drinker, Thompson, and Marsh<sup>399</sup> gave 175 to 1000 mg. of zinc oxide per day, over periods of 3 to 53 weeks, to dogs and cats with little evidence of harm. Glycosuria occurred in the dogs, and a fibrous degeneration of the pancreas in some of the cats was found at necropsy. No harm resulted to rats from the administration of 0.5 to 34.4 mg. of the oxide per day over periods of 1 month to 1 year. Similar negative results from zinc carbonate were reported by Lehmann. On the other hand, Waltner and Waltner<sup>400</sup> were able to inhibit the growth of rats and induce anemia and osteoporosis by feeding this salt, whereas no injurious effect resulted from the presence of 2 per cent of metallic zinc in the diet of rats. In the experiments of Salant,<sup>401</sup> no injury resulted when rats were given 10 to 15 mg. of zinc acetate daily for 4 months, or when cats were given 50 mg. of zinc in the form of malate daily for periods of 10 days to 2 months. Sutton and Nelson<sup>402</sup> found that 0.1 per cent zinc could be incorporated in the diet of rats without injury, but that more than 0.5 per cent lessened their ability to reproduce, while 1 per cent inhibited growth and caused severe anemia and death. Zinc salts appear to be somewhat more toxic when added to the diet of pigs.<sup>403</sup>

#### 4. Absorption and Excretion

There is evidence that zinc is required in normal nutrition.<sup>404</sup> It is a component of the enzymes carbonic anhydrase<sup>405</sup> and uricase, and activates the enzyme carboxylase.<sup>406</sup> Zinc occurs in many animal tissues, particularly the pancreas.<sup>407</sup> According to Batchelor, Fehnel, Thomson, and Drinker,<sup>408</sup> the blood of normal men contains 0.32 to 0.46 mg. of zinc per 100 ml.; more is present in the cells than in the plasma.<sup>409</sup> The daily urinary output averages 0.64 mg. and the fecal output 9.3 mg., the range of variation being very wide in both.<sup>410</sup> From 1.3 to 39.3 mg. per liter were found in the urine and from 8 to 133 mg. in the

<sup>399</sup> K. R. Drinker, P. K. Thompson, and M. Marsh, *Am. J. Physiol.*, *80*, 31, 65 (1927); *81*, 284 (1927).

<sup>400</sup> K. Waltner and K. Waltner, *Arch. experl. Path. Pharmacol.*, *141*, 123 (1929); *146*, 310 (1929).

<sup>401</sup> Salant, *J. Ind. Hyg.*, *2*, 72 (1920).

<sup>402</sup> W. R. Sutton and D. E. Nelson, *Proc. Soc. Experl. Biol. Med.*, *36*, 211 (1937).

<sup>403</sup> R. E. N. Grimmett, I. G. McIntosh, E. M. Wall, and C. S. M. Hopkirk, *New Zealand J. Agr.*, *54*, 216 (1937).

<sup>404</sup> K. R. Drinker and E. S. Collier, *J. Ind. Hyg.*, *8*, 257 (1926); W. R. Todd, C. A. Elvehjem, and E. B. Hart, *Am. J. Physiol.*, *107*, 146 (1934). E. Hove, C. A. Elvehjem, and E. B. Hart, *Am. J. Physiol.*, *119*, 768 (1937). D. M. Hegsted, J. M. McKibben, and C. K. Drinker, *U.S. Pub. Health Service*, Suppl. No. 179 to *Pub. Health Repts.* (1945).

<sup>405</sup> E. Keilin and T. Mann, *Biochem. J.*, *34*, 1163 (1940). E. Hove, C. A. Elvehjem, and E. B. Hart, *J. Biol. Chem.*, *136*, 425 (1940). J. N. Davidson, *Biochem. J.*, *32*, 1306 (1938). C. G. Holmberg, *Biochem. J.*, *33*, 1901 (1939).

<sup>406</sup> Lohmann and Kossel, *Naturwissenschaften*, *27*, 595 (1939).

<sup>407</sup> D. A. Scott and A. M. Fisher, *J. Pharmacol.*, *55*, 206 (1935). *Am. J. Physiol.*, *121*, 253 (1938). R. E. Lutz, *J. Ind. Hyg.*, *8*, 177 (1926).

<sup>408</sup> R. P. Batchelor, J. W. Fehnel, R. M. Thomson, and K. R. Drinker, *J. Ind. Hyg.*, *8*, 322 (1926).

<sup>409</sup> A. Burstein, *Biochem. Z.*, *216*, 449 (1929).

<sup>410</sup> P. Drinker, J. W. Fehnel, and M. Marsh, *J. Biol. Chem.*, *72*, 375 (1927). L. T. Fairhall and L. H. Hoyt, *J. Clin. Investigation*, *7*, 537 (1929).

daily feces of zinc smelters.<sup>408,410</sup> Only very small amounts of zinc were absorbed and stored in the tissues of rats, cats, and dogs fed zinc compounds over long periods,<sup>399</sup> the chief sites of storage being the liver and pancreas. No increase in the urinary zinc concentration could be detected, in the case of a man, following the ingestion of a meal that contained between 225 and 275 mg. of zinc.<sup>410</sup> Recent investigations in which radioactive zinc ( $Zn^{65}$ ) was injected intravenously,<sup>411</sup> confirmed the early observations that zinc is stored in the liver, pancreas, and kidney, and showed that from 5 to 11 per cent of the amount injected is eliminated in the pancreatic juice. Very little was eliminated in the bile. Relatively large amounts were found in the muscular and mucosal layers of the small intestine. In 170 hours following injection mice excrete over 50 per cent of the injected amount in the feces and only 2 per cent in the urine.

### 5. Industrial Intoxication Other than Metal-Fume Fever

Metal-fume fever,<sup>412</sup> described below, is a definite acute clinical syndrome induced by exposure to zinc fumes. The older literature reports many cases of chronic intoxication among zinc smelters, but it is now believed that these were caused by such impurities as lead and arsenic in the ores.<sup>408</sup> Batchelor, Fehnel, Thomson, and Drinker<sup>408</sup> found no acute or chronic illness directly attributable to zinc in their examination of 24 men who had been exposed, from 2 to 35 years, to air bearing zinc oxide in amounts equivalent to 0.3 to 1.64 mg. of zinc per cubic foot. The mean zinc content of the blood of these men was only very slightly greater than that of unexposed men. Exposure to fumes or mists bearing zinc salts may possibly give rise to irritation of the respiratory or gastroenteric tracts, but the evidence for these effects is not conclusive.<sup>413</sup>

Zinc oxide lacks irritant properties, and is used externally in the treatment of many disorders of the skin. It has been stated that zinc oxide, as dust, may block the ducts of sebaceous glands and give rise to a papulopustular eczema in men engaged in packing the compound into barrels.<sup>414</sup> Sensitivity to zinc oxide is extremely rare.<sup>415</sup>

Zinc chloride, because of its caustic action, causes ulceration of the fingers, hands, and forearms of those who use it as a flux in soldering. This condition has been observed among men who handled railway ties impregnated with this

<sup>408</sup> G. E. Sheline, I. L. Chaikoff, H. B. Jones, and M. L. Montgomery, *J. Biol. Chem.*, **147**, 409 (1943); **149**, 139 (1943); *J. Exptl. Med.*, **78**, 151 (1943).

<sup>409</sup> C. C. Sturgis, P. Drinker, and R. M. Thomson, *J. Ind. Hyg.*, **9**, 88 (1927). P. Drinker, R. M. Thomson, and J. L. Finn, *ibid.*, **9**, 98, 187, 331 (1927); **10**, 13 (1928).

<sup>410</sup> C. P. McCord and A. Friedlander, *Am. J. Pub. Health*, **16**, 274 (1926). Gocher, *Northwest Med.*, **40**, 467 (1941).

<sup>411</sup> J. A. Turner, *U.S. Pub. Health Repts.*, **36**, 2727 (1921). J. G. Downing, *J. Ind. Hyg.*, **17**, 147, 150 (1935).

<sup>412</sup> H. E. Freeman, *J. Am. Med. Assoc.*, **119**, 1016 (1942).

<sup>413</sup> C. P. McCord and C. H. Kilker, *J. Am. Med. Assoc.*, **76**, 442 (1921). L. W. Fetzer, *Ind. Eng. Chem.*, **14**, 456 (1922).



substance.<sup>416</sup> Animal experimentation has led some investigators to regard zinc chloride as carcinogenic.<sup>417</sup>

#### 6. Metal-Fume Fever

The inhalation of fumes of zinc oxide causes a malaria-like illness, which has its onset some hours after the exposure has ended. This illness is variously known as brass chills, zinc chills, smelter shakes, and brass-founders ague. The term "metal-fume fever" is now preferred because this same type of illness can follow the inhalation of fumes of several other metals, and does not represent a specific toxic response to zinc. Indeed, in animals the subcutaneous injection of finely powdered zinc does not cause it.<sup>418</sup> In industry, zinc causes it more frequently than do other metals because of its low boiling point, and widespread use and because zinc fumes tend to be dispersed so finely that they penetrate to the alveoli of the lungs. When the larger particles of ordinary zinc oxide are inhaled they settle quickly or adhere to the tracheal mucosa and fail to induce the characteristic symptoms.

Lehmann<sup>418</sup> suggested that finely divided zinc fumes in contact with epithelial cells in the lower portions of the respiratory tract damage their protein. The subsequent absorption of denatured protein, according to his theory, is the cause of the physiologic response, which resembles that due to the injection of a foreign protein, as in vaccine therapy. This interpretation of the mechanism is supported by the observation of Schmidt-Kehl<sup>419</sup> that elevation of the temperature could be produced by injecting into an animal blood serum that had been denatured by spraying it into a chamber containing fumes of zinc.

In general, typical metal-fume fever is not easily produced in animals, the usual response being an immediate fall in body temperature with no subsequent elevation.<sup>420</sup> However, the typical illness has been produced repeatedly in human volunteers<sup>412</sup> who inhaled the fumes of zinc, or of freshly burned magnesium, or a suspension of very finely divided and heated zinc oxide, the particles of which were of a size of  $0.4 \mu$ , for a few minutes. Burstein<sup>421</sup> is the only investigator who has suggested that the effect is due to an action of zinc after absorption into the circulation, and he alone claimed that the syndrome could be induced by the subcutaneous or intravenous administration of zinc salts.

The illness begins a few hours after the exposure or, more frequently, during the night. The symptoms include a sweet taste, dryness of the throat, cough, fatigue, yawning, weakness, aching of the head and body, chills and fever, which rarely exceeds  $102^{\circ}$  F., nausea, and sometimes vomiting. After a few hours, the victim sweats profusely, and the temperature begins to fall. The condition rarely

<sup>417</sup> Cook, Haslewood, Hewett, Hieger, Kennaway, and Mayneord, *Am. J. Cancer*, **29**, 219 (1937).

<sup>418</sup> K. B. Lehmann, *Arch. Hyg.*, **72**, 358 (1910).

<sup>419</sup> Schmidt-Kehl, *Zentr. Gewerbehyg.*, **5**, 273 (1928); *J. Ind. Hyg.*, **12**, 115A (1930).

<sup>420</sup> J. A. Turner and L. R. Thomson, *U.S. Pub. Health Bull. No. 157* (1926). K. R. Drinker and P. Drinker, *J. Ind. Hyg.*, **10**, 56 (1928).

<sup>421</sup> A. Burstein, *Gig. Truda*, **3**, 17 (1925); *J. Ind. Hyg.*, **8**, 110A (1926).

lasts a day and is never fatal. Occasionally, glucose is found in the urine, but albuminuria is rare. Mental confusion and convulsions may be present. The pulmonary and bronchitic symptoms may be a prominent feature. The vital capacity of one man was halved and that of another reduced by 18 per cent, this condition persisting about 15 hours. Very slight, afebrile attacks, simulating a beginning chill, with leucocytosis as the only objective sign, may be more common than the more severe attacks.<sup>412,421</sup>

In 36 of 100 cases observed by Natvig,<sup>421a</sup> the condition recurred weekly or more frequently. Leucocytosis (12,000 to 16,000 leucocytes per cubic millimeter) persists for 12 hours after the temperature has returned to normal.<sup>412</sup> While it persists<sup>412</sup> there is a measure of immunity. Workers are more susceptible on Mondays and on weekdays following a holiday than on other working days. Metal-fume fever has been observed among welders or oxyacetylene cutters who work on galvanized metal in poorly ventilated spaces.<sup>422</sup>

#### 7. Maximum Allowable Concentration in Air

Drinker, Thomson, and Finn<sup>412</sup> believe that 15 mg. of zinc as oxide per cubic meter is the maximum concentration that can be inhaled for several hours daily without production of symptoms of metal-fume fever. In laboratory experiments, a concentration of 45 mg. per cubic meter was tolerated for 20 minutes by man.

#### 8. Inflammability

Powdered zinc offers the hazard of explosion. If stored in damp storehouses, there is danger of spontaneous combustion.<sup>423</sup> Residues from laboratory reduction experiments may start a fire if thrown into waste buckets, with paper (see Chapter Thirteen).

<sup>421a</sup> H. S. Natvig, *Tidsskr. Norske Laege foreningen*, 57, 456 (1937); *J. Ind. Hyg. Toxicol.*, 19, 227A (1937); J. R. Kuh, M. F. Collen, and C. Kuh, *Permanente Found. Med. Bull.*, 4, No. 4, 145 (1946); *J. Ind. Hyg. Toxicol.*, 29, 35A (1947).

<sup>422</sup> J. Brodie, *Calif. and Western Med.*, 59 (July 1943). F. Molino, *Rass. med. applicata lavoro ind.*, 8, 341 (1937); 9, 374 (1938). J. W. Hammond, *J. Ind. Hyg. Toxicol.*, 26, 117 (1944).

<sup>423</sup> H. R. Brown, *U.S. Bur. Mines Circ. No. 7148* (1941). S. H. Katz and J. J. Bloomfield, *U.S. Bur. Mines Repts. Investigations No. 2335* (1922); Wehrli, *Chem. Fabrik*, 1940, 362; *Chem. Abstracts*, 35, 625 (1941). H. Berger, *Metallwirtschaft*, 20, 475 (1941); *Chem. Abstracts*, 36, 4339 (1942).

# The Aliphatic Hydrocarbons

FRANK A. PATTY

## *The Paraffins*

### I. General Considerations

#### 1. *Source and Uses*

The lower homologs of the paraffin series, methane, ethane, propane, and butane, are gaseous and they flow in huge quantities from oil and gas wells. All of them are widely used for fuels and the last three, as refrigerants also. The next homologs, pentane to octane, are volatile solvents and may be encountered wherever solvents or thinners are used. Those paraffins above octane are also solvents but are not sufficiently volatile to warrant serious consideration as vapor hazards at normal room temperatures unless confined to a tank or other enclosure where vapor-saturated air is encountered. The aliphatic group includes some of the most widely used solvents in industry, whose major application is in the manufacture of paints, enamels, varnishes, and lacquers; in dry cleaning; and in degreasing.

These solvents are obtained by the fractionation of crude petroleum and are encountered as mixtures with other members of the series as well as with other hydrocarbons, such as the acetylenes, olefines, cyclics, and aromatics. Pentane, hexane, heptane, and octane form azeotropes with acetic acid, formic acid, and many of the common esters, alcohols, and ketones. Some common commercial petroleum solvents are: petroleum ether, boiling range about 30 to 70° C.; gasoline, boiling range about 60 to 120°, although fractions boiling from 40 to 205° occur; petroleum spirit, boiling range 80 to 130°; V. M. and P. naphtha, boiling range 100 to 160°; mineral spirit, 90 per cent boiling below 200°; and kerosene, boiling range 150 to 270°.

#### 2. *Industrial Exposures*

Prolonged exposures to relatively low concentrations of gasoline vapor in air with brief periods of higher concentrations are common to garage workers and filling station attendants. Evidence of ill effects from such exposures where gasoline did not enter the lungs in a liquid state and was not swallowed has not been convincing. More serious exposures may be encountered where the more volatile solvent fractions are used for dry cleaning, for degreasing, or as a thinner for

TABLE 1 Physical and Chemical Properties of the Paraffins

Property	Methane	Ethane	Propane	Butane	Pentane	Hexane	Heptane	Octane
	CH <sub>4</sub>	C <sub>2</sub> H <sub>6</sub>	C <sub>3</sub> H <sub>8</sub>	C <sub>4</sub> H <sub>10</sub>	C <sub>5</sub> H <sub>12</sub>	C <sub>6</sub> H <sub>14</sub>	C <sub>7</sub> H <sub>16</sub>	C <sub>8</sub> H <sub>18</sub>
Formula								
Molecular weight	16.04	30.07	44.09	58.12	72.15	86.17	100.20	114.22
Density of liquid (25°/4° C.)	—	—	0.4923 <sup>a</sup>	0.5730 <sup>a</sup>	0.62139	0.65481	0.67949	0.69855
F.p., ° C.	-182.48	-183.23	-187.65	-138.33	-129.723	-95.320	-90.595	-56.798
B.p., ° C. (760 mm.)	-161.49	-88.63	-42.07	-0.5	36.073	68.740	98.426	125.665
Vapor density (air = 1)	0.55	1.04	1.52	2.01	2.49	2.97	3.52	3.94
Vapor pressure (mm. Hg at 25° C.)	Gas	Gas	8.8 atm. (20°)	1823	500 (24.34°)	150 (24.81°)	47.7	10.45 (20°)
n <sub>D</sub> (25° C.)	—	—	—	—	1.35466	1.37226	1.38517	1.39580
Per cent in saturated air (25° C., 760 mm.)	100	100	100	100	66.0	19.7	6.3	1.4
Density of air saturated with vapor (25° C., 760 mm., air = 1)	0.55	1.04	1.52	2.01	1.98	1.39	1.18	1.04
Solubility in water (20° C.)	0.09 cc./g.	0.04724 vol. in 1 vol.	0.065 vol. in 1 vol. (17.8°)	0.15 vol. in 1 vol. (17°)	0.036 g. in 100 ml. (16°)	0.0023 wt. per cent (20°)	0.005 wt. per cent (15.5°)	0.0014 wt. per cent (16°)
Solubility in ethyl alcohol, (20° C.)	0.60 cc./g.	2.3344 vols. in 1 vol.	7.90 vol. in 1 vol. (16.6°)	18.83 vol. in 1 vol. (17°)	Miscible	50 g. in 100 ml.	100 g. in 100 ml.	Slightly soluble
Solubility in ether (20° C.)	0.91 cc./g.	—	1 vol. (16.6°) Gas	29.8 vol. in 1 vol. (18°) Gas	Miscible	Soluble	Miscible	Soluble
Flash point (° F.)	Gas	Gas	—	—	-40	-15	25	56
Specific dispersion	—	—	—	—	97.9	97.9	97.9	97.9
P.p.m. ≈ 1 mg./l.	1524	813	557	421	340	284	244	214
Mg./cu.m. ≈ 1 p.p.m.	0.656	1.230	1.804	2.376	2.94	3.52	4.10	4.67
Inflammable limits (% by vol. in air)	5.00-15.00	3.10-12.45	2.10-10.10	1.86-8.41	1.40-7.80	1.25-6.90	1.00-6.00	0.95-3.20
Suggested max. permissible limit	1.00 vol. per cent <sup>a</sup>	0.62 vol. per cent <sup>b</sup>	0.42 vol. per cent <sup>b</sup>	0.37 vol. per cent <sup>b</sup>	0.2 vol. per cent	700 p.p.m.	300 p.p.m.	200-300 p.p.m.
and its attendant warning properties	None	None	None	Odor 0-1	Odor 3	Odor 3	Odor 3-4	Odor 4

<sup>a</sup> At saturation pressure.<sup>b</sup> Based upon 20 per cent of the lower inflammable limit rather than upon physiological effects.

paints and other finishes, and with inadequate ventilation. The production filling of containers with petroleum distillates in poorly ventilated areas offers serious exposures the same as it does with practically all other volatile solvents. Perhaps the greatest exposures occur during cleaning, repairing, or other work conducted in storage tanks on land or in tankers. It is "approved" practice to permit workmen to work in "gas-free" compartments of tankers and gas-free certificates are issued where the concentration as indicated by an explosimeter or other combustible gas indicator registers 20 per cent of the lower inflammable limit, approximately 2000 p.p.m. for gasoline. Safe practice leaflets<sup>1</sup> state that "more than 0.2 per cent hydrocarbon vapors is not safe for men to breathe for more than a short time"; and again, "atmosphere within a tank which registers more than 14 to 20 per cent of the lower combustible limit is considered unsafe for breathing even for a short period of time." These statements seem to imply that concentrations up to 0.2 per cent (2000 p.p.m.) gasoline can be breathed with impunity; and experience has shown that it is not uncommon to find men working without respiratory protection in atmospheres approaching this level.

### 3. *Physical and Chemical Properties*

The physical and chemical properties of paraffins are given in Table 1.

### 4. *Determination in the Atmosphere*

In the most dependable method of analysis for petroleum gases and vapors either the Haldane or the Orsat gas apparatus is used. Portable electrical indicating devices such as the methane detector and combustible gas indicators are, however, more convenient. When carefully calibrated, the more sensitive devices, which give a positive indication at 2 per cent of the lower inflammable limit, are sufficiently accurate for most purposes. The interferometer (page 204, Vol. I) is also very satisfactory for these gases and vapors.

### 5. *Physiological Response*

The paraffin series of hydrocarbons, methane to octane, have primarily a simple anesthetic action affecting the central nervous system. In the vapor stage they are also mildly irritant to all mucous surfaces, increasing in intensity from pentane to octane. "Simple" is used here to denote the absence of major toxic effects and not to indicate that the little understood phenomena of anesthesia are simple. Although the anesthetic condition has been recognized and utilized for many years, the mechanics of the phenomenon causing it are obscure and explanation has been attempted by several conflicting theories with which we need not be concerned here. Haggard,<sup>2</sup> using straight-run gasoline and dogs, found that for short exposures the time element is much less significant than the concentration. He found that convulsions occurred at about 1 per cent when the concentration was gradually increased from zero, even though the time during which the

<sup>1</sup> *Accident Prevention Manuals 1A, and 1B*. American Petroleum Institute, New York, 1942.

<sup>2</sup> H. W. Haggard, *J. Pharmacol.*, 16, 401 (1920).

concentration was being built up varied from 12 to 35 minutes. Immobility followed at a concentration of about 1.6 per cent, regardless of variations of from 16 to 44 minutes in the time of reaching that concentration. Anesthesia resulted with one animal at 2.3 per cent and 4 minutes later, at a concentration of 2.6 per cent, death occurred. These concentrations are of a magnitude similar to those of hexane and heptane found by Fühner<sup>3</sup> to cause narcosis and death in mice and rats.

In experiments with a man,<sup>4</sup> gasoline vapor, gradually increased from zero to 1.1 per cent in 9 minutes and to 2.2 per cent in 3 more minutes, caused confused vision and inability to stand without holding to a support. Another man was made quite dizzy by 10 to 12 inhalations of an air mixture containing 2.6 per cent gasoline vapor.

Many fatalities have occurred from the inhalation of gasoline vapors and they frequently have been attributed to asphyxiation from oxygen want or to impurities in the gasoline. There is ample evidence that gasoline and the paraffin hydrocarbons pentane to octane produce anesthetic or narcotic action in men and animals; and the margin between narcosis and death in animals is narrow. It is reasonable to expect that the concentrations proving fatal to mice and dogs are of the same general order as for man: amounts on the order of 2 per cent may be considered immediately dangerous to life. Although degenerative action on the kidneys and fatty infiltration of the liver have been reported,<sup>5</sup> and anemia is believed to result from hemolytic action, evidence of serious systemic injury from the prolonged inhalation of low concentrations of these vapors is scanty and inconclusive. It seems probable that concentrations low enough to produce no immediate response in susceptible persons will, upon long-repeated exposures, cause no serious chronic illness in man, but this point has yet to be established. Machle<sup>6</sup> notes that the first symptoms of chronic intoxication are neurasthenic manifestations followed by muscular weakness and cramps, listlessness and a feeling of dullness, fatigue, and loss of weight. Conjunctivitis with lachrimation, and cough with expectoration, are common evidences of irritation. The central nervous system may evidence a wide variety of symptoms such as: mental confusion or impairment, memory loss, depression, irritability and nervousness, apathy, numbness, paresthesia, pains in the limbs, nerve tenderness, neuritis, and paralysis of peripheral or cranial nerves. Ataxia occurs occasionally and may be accompanied by inco-ordination. The sequelae can involve the higher centers and may be general or focal, but such have never been recorded except in cases of severe acute intoxication involving coma.

The aliphatic petroleum distillates are fat solvents and for that reason are

<sup>3</sup> H. Fühner, *Biochem. Z.*, 116, 235 (1921).

<sup>4</sup> A. C. Fieldner, S. H. Katz, and S. P. Kinney, *U.S. Bur. Mines Tech. Paper No. 272* (1921).

<sup>5</sup> K. B. Lehman and F. Flury, "*Toxicology and Hygiene of Industrial Solvents.*" Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

<sup>6</sup> W. Machle, *J. Am. Med. Assoc.*, 117, 1965 (1941).

skin irritants. Considerable variation in the intensity of this irritant action is thought to be influenced by the degree of saturation and by the viscosity. Unidentified minor constituents of some petroleum products have been found to be carcinogenic. Some still residues are highly carcinogenic.<sup>7</sup> Systemic effects through skin absorption do not occur. Rather, these solvents are acquired by inhalation or ingestion and they are largely excreted unchanged in the exhaled air. A small portion has been found in the urine.

#### 6. Maximum Permissible Concentrations

Although in general the explosion hazard overshadows the dangers from inhalation of the aliphatic hydrocarbons, some members of the group have been accorded a degree of immunity beyond their merits in the matter of their effects upon the human system. The figure of 1000 p.p.m., widely quoted in literature regarding industrial health, as a "safe limit" for prolonged exposure to gasoline or benzene vapor, is not well founded upon facts. It is contrary to experimental data presented to the effect that 0.1 per cent gasoline,<sup>8,9</sup> as well as heptane,<sup>10</sup> produces adverse symptoms including drowsiness, unsteadiness, giddiness, headache, and nausea within 6 to 60 minutes. Luce<sup>11</sup> reported a considerable number of moderate illnesses in a rubber factory. The adverse effects included slight blood changes (anemia, leucocytosis, and basophilia) arising from an exposure to benzene vapors averaging about 750 p.p.m. (3 mg. per liter) and ranging from 220 to 2200 p.p.m. (0.9 to 9 mg. per liter) benzene. Machle,<sup>6</sup> after studying more than 2000 workmen with varying degrees of exposure to gasoline vapors, concluded that functional neuroses and other symptoms may develop after exposure to concentrations on the order of 300 to 500 p.p.m. One wonders why the figure of 1000 p.p.m. was proposed as a safe working atmosphere for prolonged exposures and why it has not been revised. A single figure for maximum permissible solvent vapors of materials distributed under the names of gasoline, benzene, petroleum naphtha, and so forth, is not practical because of the wide variation in the chemical composition of such petroleum distillates, as regards their content of hexane, heptane, octane, unsaturates, cyclics, and aromatics. For example, gasoline made by cracking processes may contain over 50 per cent unsaturates. Other variables are introduced in the petroleum distillates by the presence of up to 40 per cent aromatics in some crude oils, while still others have a considerable percentage of cyclic compounds. Tetraethyl lead and other "antiknock" agents, added to gasolines to be used in internal combustion engines, furnish yet another variable.

Because of the wide variation in the composition of gasolines the toxicities

<sup>7</sup> E. V. Cowdry, St. Louis Free Skin and Cancer Institute, *personal communication*.

<sup>8</sup> R. R. Sayers, A. C. Fieldner, W. P. Yant, and B. G. H. Thomas, *U.S. Bur. Mines Monograph No. 2* (1927).

<sup>9</sup> P. Drinkler, C. P. Yaglou, and M. F. Warren, *J. Ind. Hyg. Toxicol.*, **25**, 225 (1943).

<sup>10</sup> F. A. Patty and W. P. Yant, *U.S. Bur. Mines Repts. Investigations No. 2979* (1929).

<sup>11</sup> F. Luce, *Gasmasker*, **10**, 85 (1938).

must necessarily vary and can possibly best be arrived at by considering the additive effects of their constituents on the basis of the chemical composition. The maximum permissible concentrations might well range from about 250 to 700 p.p.m. depending upon the chemical composition.

## II. Specific Paraffins

### METHANE

The toxicity of the paraffins, methane to octane, increases with the molecular weight. Methane ( $\text{CH}_4$ ) has no appreciable physiological action except that due to lowering the partial pressure of oxygen in the air enough to cause oxygen want. It has no warning odor. Although its chief danger in the coal mining industry is as an explosion hazard, it may, due to its low density, accumulate in poorly ventilated areas, especially in the upper strata, so as to produce an asphyxiating atmosphere. Natural gas contains on the order of 85 per cent methane.

### ETHANE

Ethane ( $\text{C}_2\text{H}_6$ ) likewise is of little significance physiologically, no definite symptoms being observed in concentrations below 5 per cent. It is found in natural gas to the extent of 12 to 15 per cent.

### PROPANE

Propane ( $\text{C}_3\text{H}_8$ ) up to 1 per cent by volume causes no symptoms in man upon brief exposures<sup>10</sup> and cannot be detected by odor below 2 per cent. For more complete information concerning the odor intensities of the paraffins, propane to heptane, see Figure 2 in Chapter Eight (Vol. I). Ten per cent propane is not noticeably irritating to the eyes, nose, and respiratory passages but it produces slight dizziness within a few minutes. It has not been established but it is probable that concentrations up to 1 or 2 per cent by volume could be inhaled indefinitely without causing ill effects.

### BUTANE

Butane ( $\text{C}_4\text{H}_{10}$ ) gas causes noticeable drowsiness within ten minutes at a concentration of 1 per cent but no other symptoms were observed.<sup>10</sup> Its odor cannot be detected below about 0.5 per cent and, judging from the scanty information available, there is little reason to believe that ill effects would result from the prolonged, repeated inhalation of this amount.

### PENTANE

Pentane ( $\text{C}_5\text{H}_{12}$ ) is the lowest member of the series to be liquid under normal conditions. Its vapor causes narcosis<sup>8</sup> in mice in the range of 9 to 12 per cent by volume within 5 to 60 minutes, with only a small margin between narcosis, convulsions, and death. Brief exposures of human beings (10 minutes) to 0.5 per cent pentane produced no symptoms or irritation though its odor was definite. Informa-



tion on a maximum safe amount for prolonged exposure is lacking but, with consideration of available evidence, 0.2 per cent is suggested as a maximum permissible concentration for prolonged daily exposure.

## HEXANE

Hexane ( $C_6H_{14}$ ), on a volume basis, is three times as toxic<sup>3</sup> for mice as is pentane. Narcosis was caused in less than an hour by concentrations on the order of 3 per cent by volume, while convulsions and death occurred in a similar time in concentrations of 3.5 to 4 per cent.

With men, 0.2 per cent hexane produced no symptoms in 10 minutes while 0.5 per cent caused distinct dizziness and giddiness.<sup>10</sup> As with pentane, there are few data from which a safe limit can be set, but a tentative figure of 700 p.p.m. is suggested as a maximum concentration for prolonged daily exposure.

## HEPTANE

Heptane ( $C_7H_{16}$ ), in concentrations of 1 to 1.5 per cent by volume, produced narcosis<sup>3</sup> in mice within  $1/2$  to 1 hour. Tetanic convulsions and death occurred in concentrations of about 1.5 to 2.0 per cent. Men developed slight vertigo<sup>10</sup> within 6 minutes while inhaling 0.1 per cent heptane vapor in air and within 4 minutes, in 0.2 per cent. Exposure to 0.5 per cent heptane vapor for 4 minutes was without noticeable irritation to nose and eyes but caused marked vertigo, inability to walk along a straight line, hilarity, and inco-ordination of space. Fifteen minutes of exposure to this concentration resulted in a condition resembling intoxication from ethyl alcohol, with a period after removal of exposure of up to 30 minutes of uncontrolled hilarity in some individuals and dolefulness in others. It is a common phenomenon in petroleum intoxication that the condition is frequently first noticeable or more pronounced at the moment of entering uncontaminated air following exposure. A taste suggestive of gasoline persisted for a few hours after exposure. Slight nausea was common, with a temporary loss of appetite. With no data on the chronic effects of low concentrations of heptane available, it is difficult even to suggest a maximum concentration for prolonged exposure but a figure of 300 p.p.m. appears reasonable for tentative use.

## OCTANE

Octane ( $C_8H_{18}$ ), in concentrations of 0.66 to 1.37 per cent by volume, caused narcosis<sup>3</sup> in mice within  $1/2$  to  $1 1/2$  hours. No deaths resulted with concentrations below 1.37 per cent and convulsions did not occur. Data on the inhalation exposure of men have not been presented. A range of 200 to 300 p.p.m. is suggested as a maximum permissible concentration until data to establish a more definite figure are available.

TABLE 2  
*Physical and Chemical Properties of the Unsaturated Aliphatic Hydrocarbons*

Property	Ethylene	Propylene	Butylene (1-butene)	1,3-Butadiene	Acetylene
Formula	C <sub>2</sub> H <sub>4</sub>	C <sub>3</sub> H <sub>6</sub>	C <sub>4</sub> H <sub>6</sub>	C <sub>4</sub> H <sub>6</sub>	C <sub>2</sub> H <sub>2</sub>
Molecular weight	28.05	42.08	56.10	54.09	26.04
B. p., ° C. (760 mm.)	-103.71	-47.70	-6.26	-4.41	-83.6
M. p., ° C.	-169.15	-185.25	-185.35	-108.915	-81.8
n <sub>D</sub> (25° C.) and satn. pressure	—	0.5053	0.5888	0.6149	—
Density of gas (air = 1)	0.97	1.45	1.94	1.87	0.90
Solubility in water	25.6 vol. in 100 vol. (0° C.)	44.6 vol. in 100 vol.	Slightly soluble	Very low	100 vol in 100 vol. (18° C.)
Solubility in ethyl alcohol	360 vol. in 100 vol.	1250 vol. in 100 vol.	Soluble	Very soluble	600 vol. in 100 vol. (18° C.)
Inflammable <sup>a</sup> limits (% by vol.)	2.75-28.6	2.00-11.10	1.98-9.65	2.0-11.5	2.5-80.0
Suggested max. permissible <sup>b</sup> limit (% by vol.) and its attendant warning properties	0.55 Faint sweet odor	0.40 Weak odor	0.40 Weak odor	0.40 Faint odor	0.50 Faint odor

<sup>a</sup> See Chapter Thirteen.

<sup>b</sup> Based on 20 per cent of the lower inflammable limit rather than on physiological effects.

## *The Unsaturated Aliphatic Hydrocarbons: Olefins, Diolefins, and Acetylene*

### I. General Considerations

The only members of these groups that have attained industrial importance are ethylene, butadiene, and acetylene—all gases. The olefins have a greater narcotic action than have the corresponding paraffins and also a greater margin of safety between narcosis and death. See Table 2.

### II. Specific Compounds

#### ETHYLENE (Ethene)

##### 1. Uses and Determination

Ethylene, a by-product of the distillation of petroleum, is added to manufactured gas as an illuminant. It is used as a fuel in welding, as an anesthetic, and in the conditioning and coloring of fruits and the blanching of vegetables.

Analytical methods for the estimation of ethylene in air are similar to those for the paraffin series. In addition, its reactivity with sulfuric acid permits its estimation by absorption<sup>12</sup> in a gas analysis pipette.

##### 2. Physiological Response and Permissible Limit

Ethylene ( $\text{CH}_2:\text{CH}_2$ ) has a slightly sweet odor and mixed with oxygen is used as an anesthetic in concentrations on the order of 75 to 90 per cent. Except for its wide inflammable range and its property, common to all gases, of causing asphyxiation by lowering the oxygen content of the atmosphere, ethylene is not hazardous. Its maximum permissible limit in workroom air should not exceed 5500 p.p.m., however, this being 20 per cent of the lower inflammable limit.

1 mg./l.  $\approx$  872 p.p.m. and 1 p.p.m.  $\approx$  1.15 mg./cu.m. at 25° C., 760 mm.

#### PROPYLENE (Propene, Methylene)

Propylene ( $\text{CH}_2:\text{CHCH}_3$ ) is a gas that has little industrial application. It has been used as an anesthetic. It can be estimated in the air in the same manner as ethylene and its physiological properties are similar. The inflammable range is 2.00 to 11.10 per cent by volume in air. The suggested maximum permissible limit is 4000 p.p.m., one fifth of the lower inflammable limit.

1 mg./l.  $\approx$  581 p.p.m. and 1 p.p.m.  $\approx$  1.72 mg./cu.m. at 25° C., 760 mm.

#### BUTYLENES: 1-Butene, Ethylethylene; 2-Butene, *sym*-Dimethylethylene; and Isobutylene, 2-Methylpropene, *unsym*-Dimethylethylene

The butylenes are colorless gases resulting from the cracking of petroleum and are used in the polymerization process to produce high octane aviation gasoline. Methods of determination in the atmosphere are similar to those for ethylene. Butylene and its isomers are similar in their narcotic action and about

<sup>12</sup> M. P. Matuszak, *Ind. Eng. Chem., Anal. Ed.*, 10, 354 (1938).

4.5 times as toxic as ethylene.<sup>13</sup> Unless encountered in sufficient amounts to cause asphyxiation and narcotization, the butylenes do not appear to warrant serious consideration for their effects upon the health of workmen, either from prolonged exposure to low concentrations or from short exposures to high concentrations. The inflammable range of normal butylene is 1.98 to 9.65 per cent by volume in air. This property should place the maximum permissible concentration for workroom atmospheres at 4000 p.p.m.

1-Butene,  $\text{CH}_3\text{CH}_2\text{CH}:\text{CH}_2$ ; 2-butene,  $\text{CH}_3\text{CH}:\text{CHCH}_3$ ; isobutylene,  $\text{CH}_2:\text{C}(\text{CH}_3)\text{CH}_3$ .

1 mg./l.  $\approx$  436 p.p.m. and 1 p.p.m.  $\approx$  2.30 mg./cu.m. at 25° C., 760 mm.

## 1,3-BUTADIENE (Divinyl, Biethylene)

### 1. Occurrence and Determination

Butadiene ( $\text{CH}_2:\text{CHCH}:\text{CH}_2$ ) is a colorless gas with a characteristic odor that has been termed "aromatic." It is produced from petroleum and from ethyl alcohol and is used as an intermediate in the manufacture of synthetic rubber. It may be determined in the air by the methods mentioned under the paraffins and ethylene, or by its reaction with iodine pentoxide.<sup>14</sup>

### 2. Physiological Response

Butadiene causes narcosis in men and animals. Carpenter, Shaffer, Weil, and Smyth<sup>14</sup> found that 25 per cent butadiene in air produced progressive anesthesia in rabbits after an average time of 1.6 minutes, and death in 23 minutes. One rabbit survived 34 daily inductions into deep anesthesia without evidence of any damage to lungs, liver, or kidneys. No significant and consistent change was found in the blood pictures, nor was there significant progressive injury in any of a group of animals (dog, guinea pigs, rats, and rabbits) exposed 7½ hours a day, 6 days a week, for 8 months to a concentration of 6700 p.p.m. Men exposed to 8000 p.p.m. for a single period of 8 hours noted no significant symptoms other than odor and slight irritation, with no resulting ill effects.

No permanent ill effects are anticipated from the accidental anesthetization of workmen if they are promptly removed from exposure while respiration and heart action are strong.

### 3. Maximum Permissible Concentration

The maximum permissible concentration for prolonged exposure should not exceed 4000 p.p.m., one fifth of the lower inflammable limit. Butadiene upon contact with the air may form explosive peroxides<sup>15</sup> that necessitate extra precautions in handling.

1 mg./l.  $\approx$  452 p.p.m. and 1 p.p.m.  $\approx$  2.22 mg./cu.m. at 25° C., 760 mm.

<sup>13</sup> W. F. von Oettingen, *U.S. Pub. Health Bull.* No. 255 (1940).

<sup>14</sup> C. P. Carpenter, C. B. Shaffer, C. S. Weil, and H. F. Smyth, Jr., *J. Ind. Hyg. Toxicol.*, **26**, 69 (1944).

<sup>15</sup> P. K. Frolick and C. E. Morell, *Chem. Eng. News*, **21**, 1139 (1943).

## ACETYLENE

### 1. Source and Uses

The acetylene ( $\text{CH} : \text{CH}$ ) of commerce is a colorless gas with a characteristic odor due in part to impurities, such as traces of phosphine. It is generated by the action of water on calcium carbide and is usually compressed in cylinders partly filled with acetone, which dissolves acetylene to the extent of 25 times its volume per atmosphere of pressure. Acetylene compressed to 2 atm. without the presence of acetone may explode spontaneously, but in the presence of acetone it is routinely compressed at 10 atm. and is permitted by the Interstate Commerce Commission regulations at 250 lb. pressure. Acetylene is used as a fuel in welding and cutting; it is also used in chemical synthesis, and has been used as an anesthetic.

### 2. Determination in the Atmosphere

Acetylene may be determined by the use of a combustible gas indicator, providing the instrument is equipped with suitable screens and orifices to prevent flash back. The interferometer is satisfactory, the limit of sensitivity for the 50 cm. portable type being about 110 p.p.m. Acetylene may also be determined by the Ilosvay test.<sup>16</sup>

### 3. Physiological Response

The inhalation of 10 per cent acetylene has only a slightly intoxicating effect upon man.<sup>13</sup> Marked intoxication occurs at 20 per cent, inco-ordination at 30 per cent, while 35 per cent produces unconsciousness within 5 minutes. Acetylene does not adversely affect the blood picture nor cause other damage upon repeated exposures. Up to as much as 0.06 per cent phosphine has been reported to be present in impure grades of acetylene, and the possibility of this and other impurities must be considered in the evaluation of exposures.

### 4. Inflammability and Permissible Limit

The inflammable range for acetylene is extremely wide, 2.50 to 80.0 per cent by volume in air. In view of the lower explosive limit of 2.5 per cent, acetylene should not be permitted to exceed 0.5 per cent (5000 p.p.m.) in any working environment.

1 mg./l.  $\approx$  937 p.p.m. and 1 p.p.m.  $\approx$  1.065 mg./cu.m. at 25° C., 760 mm.

<sup>16</sup> M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.



# Aromatic and Cyclic Hydrocarbons

FRANK A. PATTY

## BENZENE

Benzene, benzol,  $C_6H_6$ , is derived chiefly from the destructive distillation of coal, and is therefore a by-product in the illuminating gas and coke industries. It can also be made by the catalytic cyclization and aromatization of the paraffin hydrocarbons, a process used in re-forming gasoline to increase the octane rating and reduce the "knock" factor.

### 1. *Uses and Industrial Exposures*

Benzene is one of the best organic solvents known and, for that reason, is widely used for solvent and extraction purposes. Perhaps its chief use for extraction is found in the chemical and drug industries. Other extensive uses of benzene occur in the manufacture of dyes and intermediates, in organic synthesis, in rotogravure printing, in the manufacture of rubber cement, and in the manufacture of artificial leather, linoleum, and oilcloth. It is encountered as a paint remover and as a thinner in stains and varnishes, lacquers, and airplane dopes. In this connection it is well to note that it is frequently supplied to the trade as a thinner under a number or trade name that completely hides its identity. Benzene is also used in coating paper; in the cleaning industry for spotting clothing; and sometimes for bench degreasing of small articles such as precision bearings for small motors. Unfortunately, it is sometimes used for cleaning and degreasing large objects around repair shops. Upon one occasion, the author found two mechanics in an airplane hangar unconcernedly washing large aluminum parts on a table in the middle of this large room in which more than fifty people were working. The two men were removing grease and dirt by means of a rag which they dipped in a water pail full of benzene. It had been a routine daily practice for several weeks with the knowledge and assent of the safety director, and concentrations of 100 to 1000 p.p.m. benzene were found for a radius of several feet in the surrounding atmosphere. The large volume of air involved diluted the benzene vapor except near the bucket. The practice was discontinued, but not without some dissension on the part of supposedly safety-minded persons.

### 2. *Physical and Chemical Properties*

The physical and chemical properties of benzene are given in Table 1.

TABLE 1. *Physical and Chemical Properties of Some Aromatic and*

Property	Benzene, C <sub>6</sub> H <sub>6</sub>	Toluene, C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	Xylene, C <sub>6</sub> H <sub>4</sub> (CH <sub>3</sub> ) <sub>2</sub>			Ethyl- benzene, C <sub>6</sub> H <sub>5</sub> C <sub>2</sub> H <sub>5</sub>	Cumene, C <sub>6</sub> H <sub>5</sub> - CH(CH <sub>3</sub> ) <sub>2</sub>
			<i>o</i> -	<i>m</i> -	<i>p</i> -		
Mol. wt.	78.11	92.13	106.16	106.16	106.16	106.16	120.19
B.p., °C.	80.103	110.623	144.414	139.102	138.348	136.187	152.393
F.p., °C.	5.533	-94.991	-25.175	-47.872	13.263	-94.950	-96.028
<i>n</i> <sub>D</sub> at 25°	1.49790	1.49405	1.50282	1.49455	1.49319	1.49319	1.48874
Vapor pressure	100 mm. at 26.085°	30 mm. at 26.04°	10 mm. at 32.11°	10 mm. at 28.26°	10 mm. at 27.30°	10 mm. at 25.90°	10 mm. at 38.33°
Density at 25°/4°	0.87368	0.86220	0.87583	0.85985	0.85666	0.86258	0.85748
Vapor density (air = 1)	2.7	3.2	3.7	3.7	3.7	3.7	4.2
Per cent in satd. air, 760 mm.	13.15 at 26°	3.94 at 26°	1.32 at 32°	1.32 at 28.3°	1.32 at 27.3°	1.32 at 26°	1.32 at 38.3°
Density of satd. va- por—air mixt. at 760 mm. (air = 1)	1.22 at 26°	1.09 at 26°	1.03 at 32°	1.03 at 28°	1.03 at 27°	1.03 at 26°	1.03 at 38°
Specific dispersion	189.6	184.4	180.3	181.1	181.8	174.6	166.2
Solubility in water at 20°	0.082 g. per 100 ml. (at 22°)	0.047 g. per 100 ml. (at 16°)	Insoluble	Insoluble	Insoluble	0.014 g. per 100 ml. (at 15°)	Insoluble
Solubility in ethyl alcohol	Miscible	Miscible	Very soluble	Very soluble	Very soluble	Miscible	Soluble
Solubility in ethyl ether	Miscible	Miscible	Very soluble	Very soluble	Very soluble	Miscible	Soluble

<sup>a</sup> A mixture, chiefly *α*-pinene, C<sub>10</sub>H<sub>16</sub>.

<sup>b</sup> Also very soluble in most other organic liquids.



*Cyclic Hydrocarbons (All Temperatures in Degrees Centigrade)*

Styrene, C <sub>8</sub> H <sub>8</sub> CH: CH <sub>2</sub>	Cyclo- hexane, C <sub>6</sub> H <sub>12</sub>	Methyl- cyclo- hexane, C <sub>7</sub> H <sub>14</sub> CH <sub>2</sub>	Naphtha- lene, C <sub>10</sub> H <sub>8</sub>	Tetralin, C <sub>10</sub> H <sub>12</sub>	Decalin, C <sub>10</sub> H <sub>18</sub>		Turpentine <sup>a</sup>
					<i>cis</i> -	<i>trans</i> -	
104.14	84.16	98.18	128.16	132.20	138.25	138.25	Approx. 133
145.2	80.738	100.934	217.9	207.2	194.6	185.5	153-175
-30.628	6.554	-126.597	80.22	-30	-43.26	-31.47	-50 to -60
1.5441	1.42354	1.42056	1.58218 (at 99.6°)	1.54614 (at 20.2°)	1.48113 (at 20°)	1.46994 (at 18°)	1.459 to 1.47 (at 20°)
4.3 mm. at 15°	103.67 mm. at 26.347°	43 mm. at 25°	approx. 0.082 mm. at 25°	---	---	---	---
0.9021	0.77389	0.76501	1.145 at 20°/4°	0.971 at 20°/4°	0.8963 at 20°/4°	0.8699 at 20°/4°	0.86-0.88
3.6	2.9	3.4	4.4	4.6	4.8	4.8	4.6
0.57 at 15°	13.66 at 26.3°	5.65 at 25°	0.01 at 25°	---	---	---	---
1.02 at 15°	1.23 at 26°	1.14 at 25°	1.00 at 25°	---	---	---	---
265	96.1	97.8	---	---	---	---	---
0.031 g. per 100 ml. (at 25°)	Insoluble	Insoluble	3 mg./100 ml.	Insoluble	Insoluble	Insoluble	Insoluble
Miscible	Miscible	---	4.2 g. per 100 ml. (at 20°)	Very soluble	Soluble	Soluble	Miscible
Miscible	Miscible	---	Very soluble <sup>b</sup>	Very soluble	Soluble	Soluble	Miscible

### 3. Determination in the Atmosphere

Perhaps the most satisfactory chemical method for the determination of benzene in the atmosphere is the nitration method of Schrenk, Pearce, and Yant,<sup>1</sup> especially when benzene is present with other vapors. Smyth's method<sup>2</sup> is reliable but somewhat cumbersome. The interferometer is quite satisfactory (page 204). The benzol indicator is useful providing it has been carefully serviced and calibrated. Adsorption methods are less desirable possibilities.

1 mg./l.  $\approx$  313 p.p.m. and 1 p.p.m.  $\approx$  3.19 mg./cu.m. at 25° C., 760 mm.

The exposure of an individual at any particular moment may be rather accurately determined by analysis of the benzene in a sample of arterial blood<sup>3</sup> and computation of the corresponding concentration in the air from the distribution coefficient<sup>4</sup> of benzene between blood and room air. The over-all or integrated exposure may be best arrived at by determining the ratio of inorganic to organic sulfates<sup>5,6</sup> in a sample of urine collected near the end of the day's exposure, or within one hour after cessation of the day's exposure.

### 4. Physiological Response

*Acute effects.* Acute poisoning by benzene is due to its narcotic action and in many respects resembles that from petroleum. Flury<sup>7</sup> gives the following figures for a single exposure for man:

3000 p.p.m.—endurable for 0.5 to 1 hour.  
7500 p.p.m.—dangerous after 0.5 to 1 hour.  
20,000 p.p.m.—fatal after 5 to 10 minutes.

Symptoms from inhaling a high concentration may start with exhilaration and this is followed by drowsiness, fatigue, vertigo, nausea, and headache. With higher concentrations or prolonged time, toniclonic spasms followed by paralysis and loss of consciousness may result. An initially rapid respiration soon slows and circulatory collapse may result. Death may ensue quickly from respiratory paralysis after severe exposure. Dautrebande<sup>8</sup> has demonstrated that with dogs inhalation of benzene causes initial hypertension by irritation of the fifth cranial nerve in the nose and that it quickly causes paralysis of the vasomotor system by action on the smooth muscular fiber of the blood vessels. High vapor concentra-

<sup>1</sup> H. H. Schrenk, S. J. Pearce, and W. P. Yant, *U.S. Bur. Mines. Repts. Investigations* No. 3287 (1935).

<sup>2</sup> H. F. Smyth, Jr., *J. Ind. Hyg.*, 11, 338 (1929); 13, 227 (1931).

<sup>3</sup> S. J. Pearce, H. H. Schrenk, and W. P. Yant, *U.S. Bur. Mines Repts. Investigations* No. 3302 (1936).

<sup>4</sup> H. H. Schrenk, W. P. Yant, S. J. Pearce, F. A. Patty, and R. R. Sayers, *J. Ind. Hyg. Toxicol.*, 23, 20 (1941).

<sup>5</sup> W. P. Yant, H. H. Schrenk, R. R. Sayers, A. A. Horvath, and W. H. Reinhart, *J. Ind. Hyg. Toxicol.*, 18, 69 (1936).

<sup>6</sup> W. P. Yant, H. H. Schrenk, and F. A. Patty, *J. Ind. Hyg. Toxicol.*, 18, 349 (1936).

<sup>7</sup> F. Flury, *Arch. exptl. Path. Pharmacol.*, 138, 65 (1928).

<sup>8</sup> L. Dautrebande, *Arch. intern. pharmacodynamie*, 44, 394 (1933).

tions of benzene have a moderately irritant action on the respiratory tract and liquid benzene is irritant to the skin.

It is probable that repeated brief exposures to high concentrations can produce chronic benzene poisoning, and it is not good practice to encourage or to condone men entering concentrations of 1000 p.p.m. or more for even brief exposures without suitable respiratory protection. Emergency situations can arise which would warrant such brief exposures but the greatest danger is that the brief, severe exposure may be repeated or may be in addition to a routine exposure to moderate amounts (less than 100 p.p.m.).

*Chronic effects.* It is the chronic effects of the inhalation of small amounts of benzene that are of the greatest importance industrially. The symptoms and hemotological picture of chronic benzene poisoning, as has been pointed out by Hamilton,<sup>9</sup> do not necessarily follow a typical picture of aplastic anemia. As Schwartz and Teleky<sup>10</sup> also have pointed out, the classical picture of chronic benzene poisoning, loss of red corpuscles resulting in profound anemia, loss of clotting power with resultant hemorrhage, and loss of white blood cells and substances concerned with defending the body against bacterial infection, is confused by regenerative activity. The resulting picture depends upon the ratio of regenerative activity to the destruction effect of benzene, and normal red and white cell counts may indicate only that a compensation veils the chronic destruction of these cells. Greenburg and his associates,<sup>11</sup> in a study of the rotogravure industry in New York, found that among 102 workmen exposed to benzene and receiving complete blood studies, 74 were affected: 22 of these severely poisoned, 43 early cases, and 9 showing only macrocytosis. They found that the white cell count alone revealed only 40.5 per cent of these cases. They list the percentages of poisoning cases revealed by single tests as follows: increase in the mean corpuscular volume of the erythrocytes above 94 cubic microns in 64.9 per cent of cases, a diminution of erythrocytes to less than 4.5 million in 63.5 per cent, a reduction of blood platelets to less than 100,000 in 41.9 per cent, a reduction of white blood cells to less than 5000 in 40.5 per cent, and reduction of hemoglobin to less than 13 g. per 100 ml. of blood in 40.5 per cent. Men with clinical pictures of benzene poisoning were found whose blood appeared normal, and serious blood abnormalities were found in the complete absence of symptoms or physical signs. A few men developed positive blood pictures in a 60-day period after removal from exposure, indicating that harmful effects can occur in advance of any detectable blood changes and continue to develop even after removal from exposure. The bone marrow of persons poisoned by benzene may be normal, aplastic, or hyperplastic. As pointed out before, objective symptoms may be absent but headache, dizziness, fatigue, loss of appetite, irritability, nervousness, nosebleed, and other hemorrhagic manifestations are common in benzene poisoning.

<sup>9</sup> A. Hamilton, *Industrial Toxicology*. Harper, New York, 1934.

<sup>10</sup> E. Schwartz and L. Teleky, *J. Ind. Hyg. Toxicol.*, **23**, 1 (1941).

<sup>11</sup> L. Greenburg, M. R. Mayers, L. Goldwater, and A. R. Smith, *J. Ind. Hyg. Toxicol.*, **21**, 395 (1939).

### 5. *Absorption and Excretion*

Industrial benzene poisoning results almost exclusively from the inhalation of benzene in the atmosphere. Saturation of the circulating blood occurs rapidly, with 70 to 80 per cent saturation being reached within 30 minutes. (See page 188 and Figures 2 and 3 for absorption and elimination curves for benzene.) However, it requires a period of days to approach complete saturation of the body and the same is true of elimination. Benzene is rather insoluble in blood and the equilibrium constant or coefficient of distribution of benzene between room air and the blood of animals breathing such air (dogs) is 6.58, that is, milligrams benzene per liter of blood/milligrams benzene per liter of air. This may also be stated as: at equilibrium each 100 p.p.m. benzene in the inhaled air will produce an average concentration of 2.1 milligrams benzene per liter of blood. As the blood circulates, however, it comes to equilibrium with the tissues and the fatty tissues store quantities<sup>4</sup> of benzene in this manner. Elimination involves the same process in reverse because most of the benzene is eliminated through the lungs, being picked up by the blood in the capillaries and carried to the lungs, where equilibrium with the alveolar air is rapidly established as previously explained.

Unquestionably, small amounts of benzene are absorbed through the skin wherever the liquid touches the skin but it is not probable that systemic poisoning can arise from immersing the hands in benzene because in order to do extensive damage it would have to enter the circulation and would then be subject to rapid elimination by the lungs, as explained above. However, well-recognized results of skin contact with benzene include skin defatting with erythema, dry scaling, and even secondary infections. In this respect, however, benzene is not considered to be as severe as toluene, xylene, and many other solvents, including certain of the petroleum distillates.

Some benzene is eliminated unchanged in the urine. Some is oxidized in the body to phenols and diphenols which, in turn, are conjugated in the liver with sulfate ions and excreted in the urine, thus increasing the ratio of ethereal or organic sulfates to total sulfates in the urine. This is the basis of a dependable control test to determine the severity of the over-all daily exposure to benzene.

### 6. *Tests Indicating Exposure*

The ratio of inorganic sulfates to total sulfates in the urine is normally 85 per cent or above. Upon exposure to benzene this ratio is decreased and the decrease is related quantitatively to the severity of the exposure to the point where nearly all sulfates are eliminated as organic sulfates. Ratios of less than 70 per cent inorganic are abnormal and may be indicative of benzene exposure: they warrant investigation of exposure sources with a view toward correction. Ratios of 60 per cent or less inorganic indicate dangerous exposures warranting immediate correction and termination. Concurrent exposure to carbon tetrachloride, or any other material having an adverse effect upon the liver, may decrease the sulfate response so that ratios on the order of 70 per cent inorganic

would indicate exposures of great significance. As was pointed out in the original paper,<sup>5</sup> the sulfate test must be made while the worker is on the job, and it is not to be considered a method for diagnosing benzene poisoning, because the changes are merely indicative of exposure, not of poisoning nor of damage. It is therein that the great preventive value of this test lies, the indication occurs in advance of any demonstrable harmful effects, but forewarns of their coming if exposures are not reduced. However, in complete disregard of these well-known facts, case histories of benzene poisoning too often carry enlightening comments to the effect that from a prognostic viewpoint repeated blood studies on the hospitalized patient are of greater value than concurrent repeated urinary sulfate determinations!

It seems logical to make periodic, hematological studies of the blood of all workers coming in contact with any benzene vapors, perhaps every 30 days, and urine sulfate tests, perhaps weekly. Air analyses for benzene in suspected atmospheres should be made frequently. If these three control measures are consistently performed, and heeded, as a guide for elimination of significant exposures, it is believed that no fear need be entertained regarding the careful use of benzene in industrial processes.

#### **7. Maximum Permissible Concentration**

The generally accepted figure for a maximum permissible concentration of benzene in workroom atmospheres is 100 p.p.m. Some authorities believe that this figure should be reduced to 50 or 35 p.p.m. and extremists say that any benzene vapor is too much. The figure of 100 p.p.m. will probably stand until more clear-cut information regarding the harmful effects of concentrations below this amount is presented. It has been demonstrated<sup>12</sup> that the toxic effects of crude, commercial, and pure benzene are dependent primarily upon the concentration of benzene and are independent of the impurities usually present. There is little information regarding the combined effects of benzene with other solvents. The American Standards Association has adopted the figure of 100 p.p.m.

#### **8. Warning Properties and Inflammability**

Benzene vapor within the range of 1.35 and 6.75 per cent by volume in air is inflammable (see Chapter Thirteen). The flash point by the closed-cup method is 12° F. The odor is distinctive and should be familiar to all industrial hygienists. However, the warning properties of benzene are inadequate, 100 p.p.m. having 0 irritation and an odor intensity between 1 and 2.

## **TOLUENE**

#### **1. Source and Uses**

Toluene, toluol, methylbenzene,  $C_6H_5CH_3$ , is a by-product of the coke industry. Huge quantities also have been made more recently by the catalytic

<sup>12</sup> H. H. Schrenk, W. P. Yant, S. J. Pearce, and R. R. Sayers, *J. Ind. Hyg. Toxicol.*, **22**, 53 (1940).

cyclization and aromatization of petroleum. The solvent properties of toluene are similar to those of benzene, making it a popular extraction agent as well as a thinner in paints, varnishes, enamels, and lacquers. Although it is not, in itself, a solvent for cellulose esters, it can be used successfully in large proportions as a diluent in finishes containing these esters. Toluene is used extensively in chemical manufacture, as for instance in the manufacture of benzoic acid, benzaldehyde, dyes, and T.N.T.

## 2. Physical and Chemical Properties

The physical and chemical properties of toluene are given in Table 1.

## 3. Determination in the Atmosphere

A satisfactory chemical method of determining toluene in the air is one developed at the United States Bureau of Mines,<sup>13</sup> in which the vapors are nitrated in fuming nitric acid and the 2,4-dinitrotoluene thus formed is extracted with butanone and made alkaline to develop a reddish blue color. The color is compared with standards prepared in a similar manner. The interferometer is very satisfactory and can be used to determine toluene alone, or in vapor mixtures where the components and relative proportions are known. The M.S.A. benzene indicator can be used successfully if correctly calibrated for toluene. It registers total combustibles and vapors other than toluene must be considered.

1 mg./l.  $\approx$  266 p.p.m. and 1 p.p.m.  $\approx$  3.76 mg./cu.m. at 25° C., 760 mm.

## 4. Physiological Response

*Acute effects.* Toluene is a more powerful narcotic than benzene and its acute toxicity is greater. Smyth and Smyth<sup>14</sup> found animals severely affected, but alive, after 18 daily exposures to 1250 p.p.m. toluene, while fatalities occurred after a few daily, 4-hour exposures to 4000 p.p.m. A comparison of the acute toxicities of the aromatic hydrocarbons for mice can be made from the values given by Lazarew<sup>15</sup> as presented in Table 2.

TABLE 2  
*Acute Toxicity of Some Aromatic Hydrocarbons—Mice*

Compound	Minimum concentrations of vapors which cause			
	Prostration		Death	
	Mg./l.	Vol. per cent <sup>a</sup>	Mg./l.	Vol. per cent <sup>a</sup>
Benzene	15	0.47	45	1.41
Toluene	10-12	0.27-0.32	30-45	0.80-1.20
<i>o</i> -Xylene	15-20	0.35-0.46	30	0.69
<i>m</i> -Xylene	10-15	0.23-0.35	50	1.15
<i>p</i> -Xylene	10	0.23	15-35	0.35-0.81
Ethyl benzene	15	0.35	45	1.04

<sup>a</sup> Volume per cent times 10,000 equals parts per million.

<sup>13</sup> W. P. Yant, S. J. Pearce, and H. H. Schrenk, *U.S. Bur. Mines Repts. Investigations* No. 3323 (1936).

<sup>14</sup> H. F. Smyth and H. F. Smyth, Jr., *J. Ind. Hyg.*, 10, 261 (1928).

<sup>15</sup> N. W. Lazarew, *Arch. exper. Path. Pharmacol.*, 143, 223 (1929).

Early data on toluene and xylene are colored by the effects of benzene, which frequently occurred as a contaminant. Toluene of high purity is now available commercially and recent, controlled exposures<sup>16</sup> of human beings to concentrations of 50 to 800 p.p.m. indicate that exposure to a concentration of 200 p.p.m. for a period of 8 hours produces mild fatigue, weakness, confusion, and paresthesias of the skin. The fatigue persisted for hours and moderate insomnia and restlessness resulted. The same symptoms were more pronounced with 300 p.p.m. With 400 p.p.m. mental confusion was added to the list of symptoms. With 600 p.p.m. extreme fatigue, mental confusion, exhilaration, nausea, headache, and dizziness resulted by the end of 3 hours. After 8 hours, the mental confusion, weakness, dizziness, and nausea were pronounced. The pupils were dilated and accommodation to light was impaired. The subjects evidenced inco-ordination, with a staggering gait. The conditions persisted for hours and the subjects complained of insomnia. Fatigue and nervousness were still present on the second day. With 800 p.p.m. the same symptoms were more pronounced and aftereffects, characterized by severe nervousness, muscular fatigue, and insomnia, lasted for several days. Exposures to 50 and 100 p.p.m. failed to present distinct symptoms or aftereffects.

*Chronic effects.* The experiments described above, totaling 15 exposures, over a period of 3 months, to concentrations of toluene ranging from 50 to 800 p.p.m., did not cause definite changes in the white blood cell picture. Greenburg and his co-workers<sup>17</sup> studied a group of 106 painters in an airplane factory. These men, who were spraying, dipping, and brushing, were exposed, for the most part, to concentrations of toluene ranging from 100 to 800 p.p.m., though the average exposures of a few men were higher: 900, 1000, and 1100 p.p.m., respectively. The paints and finishes contained relatively small proportions of other solvents including acetone, ethyl alcohol, ethyl acetate, butyl alcohol, butyl acetate, petroleum naphtha, and xylene. Besides the solvents, these finishes contained zinc chromate, magnesium silicate, titanium oxide, iron pigments, zinc oxide, nitrocellulose, and resins. Some of the brush paints contained aluminum, cadmium, and barium pigments. The toluene exposure exceeded that of all other vapors combined, and only the toluene was quantitated in the study. The exposure period ranged from a few weeks to five years. None of these men experienced any symptoms throughout the study other than occasional dermatitis. Five men had perforated nasal septums (probably due to zinc chromate) and 32 were found to have enlargement of the liver (as determined by palpation) as the only physical evidence of toxic effects. The hematological findings were: erythrocytes—a small percentage of the workers slightly below normal; hemoglobin—slightly above normal; lymphocytes—differential normal, absolute about 20 per cent of the exposed workers were above 5000 as compared with 7.7 per cent of a control group; mean corpuscular volume—23.6 per cent were above 100 cubic microns as compared with 7.2 per cent of

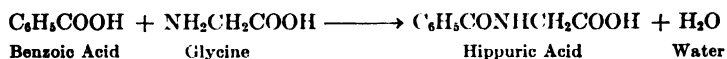
<sup>16</sup> W. F. von Oettingen, P. A. Neal, and D. D. Donahue, *J. Am. Med. Assoc.*, 118, 579 (1942).

<sup>17</sup> L. Greenburg, M. R. Mayers, H. Heimann, and S. Moskowitz, *J. Am. Med. Assoc.*, 118, 573 (1942).

controls. The leukocytes, reticulated erythrocytes, basophilic aggregation, platelets, sedimentation rate, coagulation time, hematocrit values, fragility, and serum bilirubin were all reported to be within normal limits.

### 5. Absorption and Excretion

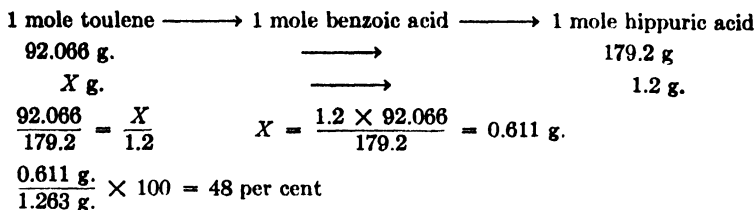
As in the case of benzene, industrial poisoning by toluene probably results only from inhalation. However, since toluene is slowly absorbed through the skin and it is also irritating to the skin, it is only common sense to avoid skin contact wherever possible. Since the solubility of toluene in water and blood is low, the circulating blood rapidly comes to equilibrium with toluene vapor in the alveolar air, as is the case with benzene. Von Oettingen, Neal, and Donahue<sup>16</sup> found 7.3 mg. toluene per liter of blood of men exposed to 300 p.p.m. toluene vapor in air. This would correspond to a coefficient of distribution of 6.5 (milligrams toluene per liter of blood/milligrams toluene per liter of room air) which is about the same as the figure for benzene. Part of the absorbed toluene is eliminated in the exhaled breath, but a large percentage is oxidized to benzoic acid, conjugated with glycine, and excreted as hippuric acid in the urine. This method of defense or detoxication is used by the human body for many organic acids, of which benzoic is perhaps the best known. The glycine for the reaction is synthesized in



the body. The normal hippuric acid excretion varies with individuals and with diet, but has been reported to be on the order of 0.7 g. per day.<sup>18</sup> The reaction takes place in the kidneys and elsewhere. The amount of hippuric acid excreted within a 24-hour day by men exposed to toluene<sup>16</sup> was found to be proportional to the concentration of toluene in the air. Within the range of 100 to 600 p.p.m. toluene vapor in air for 8-hour exposures, this amount was approximately 1.2 g. hippuric acid more than observed normals per 100 p.p.m. (0.376 mg./l.) toluene vapor. The amount of toluene absorbed and the portion excreted as hippuric acid are not known but may be roughly estimated as follows. The subjects were probably breathing at a rate of approximately 10 liters per minute or  $8 \times 60 \times 10 = 4800$  liters per 8-hour exposure period. We may safely assume that only about 70 per cent of this could have been absorbed (see page 179) regardless of how rapidly saturation of the blood with toluene, and oxidation of the toluene, occurred. We then would expect as a maximum  $4800 \times 0.70 \times 0.376 = 1263$  mg. toluene to have reached the alveoli from the exposure to 100 p.p.m. The actual proportion of this absorbed would depend upon several factors and is unknown. However, since it has been shown that approximately 1.2 g. hippuric acid results from such an exposure, we can compute the percentage of toluene converted to hippuric acid:

<sup>18</sup> P. B. Hawk and O. Bergeim, *Practical Physiological Chemistry*, 11th ed., Blakiston, Philadelphia, 1944.





Therefore it appears that approximately 48 per cent of the available toluene (portion reaching the respiratory tissue) was converted to hippuric acid in the body and excreted in the urine. It is probable that the most of the remainder was excreted unchanged in the exhaled air. Etheral sulfates do not appear in the urine in significant amounts.

### 6. Tests Indicating Exposure

Toluene in the blood may be used as an indication of exposure if the exposure period has been sufficiently long to approach equilibrium. A figure of 2.4 mg. toluene per liter of blood apparently corresponds to each 100 p.p.m. toluene in the environmental atmosphere at or near equilibrium. Since each 100 p.p.m. toluene per 8-hour day produces an excretion of approximately 1.2 g. hippuric acid, the total daily excretion of hippuric acid appears to be an index of exposure in concentrations less than 800 p.p.m. It must be remembered, however, that normal dietary constituents such as certain fruits and vegetables raise the normal level of hippuric acid excretion, and so must be considered.

### 7. Maximum Permissible Concentration

The figure of 200 p.p.m. has been suggested<sup>16</sup> as the maximum permissible concentration for an 8-hour daily exposure. This figure is based upon acute effects since there are no data to indicate that adverse effects result from prolonged exposure to amounts of this order. This exposure corresponds to 4.9 mg. toluene per liter of blood at or near equilibrium, and a daily excretion, above normal, of about 2.4 g. hippuric acid. The American Standards Association (ASA) has adopted the figure of 200 p.p.m.

### 8. Warning Properties and Inflammability

Toluene is inflammable within the range of 1.27 to 6.75 per cent by volume in air, and its flash point by the closed-cup method is 40° F. (see Chapter Thirteen). The odor intensity of 200 p.p.m. is about 3 upon entering, but olfactory fatigue occurs rapidly. The irritant effects are not distinct.

## XYLENE

### 1. Source and Uses

Xylene, xylol, dimethylbenzene,  $C_6H_4(CH_3)_2$ , exists as three isomers (ortho-, meta-, and para-) comprising the three possible relative positions of attachment of the two methyl groups to the benzene ring. Commercial xylene is a mixture of the three isomers, chiefly meta. The sources of xylene are the same as of

toluene and the uses are similar, except as modified by its higher boiling point and slower evaporation rate.

## 2. *Physical and Chemical Properties*

The physical and chemical properties of the xylenes are given in Table 1.

## 3. *Determination in the Atmosphere*

In the absence of interfering vapors such as benzene and toluene, xylene can be determined by the nitration method used for toluene. The combustible gas indicators, adsorption on silica gel or activated carbon, condensation, and the interferometer, are likewise applicable methods for the determination of xylene. Xylene and many other vapors may be determined by infrared or ultraviolet absorption methods after collection by suitable means (see Chapter Eight).

1 mg./l.  $\approx$  230 p.p.m. and 1 p.p.m.  $\approx$  4.35 mg./cu.m. at 25° C., 760 mm.

## 4. *Physiological Response*

*Acute effects.* The scope of experiments with xylene has not been as complete as with toluene and benzene, but the acute narcotic and toxic actions of xylene appear to be as great as, or greater than, those of either benzene or toluene. Investigators agree that there is a difference in the toxicity of the isomers, but disagree regarding the degree and order. The symptoms reported are similar to those arising from toluene exposure.

*Chronic effects.* Although leucocytosis is rather consistently reported by investigators, the blood picture does not indicate any marked trend or alteration, and aplasia of the bone marrow has not been reported. Studies of the toxicity of xylene leave much to be desired, especially regarding its chronic effects.

## 5. *Absorption and Excretion*

Absorption of xylene takes place chiefly through the lungs and it must be remembered, when considering solvents of relatively low vapor pressure, that volatility is not so important a factor where mists are encountered, as in the spraying of finishes thinned with xylene. The absorption of xylene through the skin is probably not of industrial significance, but skin irritation from xylene is more serious than from either benzene or toluene. The fate of xylene in the human body has not been determined, though it has been shown<sup>19</sup> that in dogs xylene is oxidized to toluic acid, conjugated with glycine, and excreted as toluric acid in a manner analogous to the fate of toluene, and it is logical to expect such a course in the human body as well. This needs further study.

## 6. *Tests Indicating Exposure*

Besides air analyses to evaluate the degree of exposures, toluric acid or other elimination products in the urine of exposed persons might well be sought.

<sup>19</sup>O. Schultzen and B. Naunyn, *Arch. Physiol.*, 349 (1867); cited by W. F. von Oettingen, *U.S. Pub. Health Bull.* No. 255 (1940).

### 7. Maximum Permissible Concentration

The generally accepted maximum permissible concentration for xylene is 200 p.p.m. However, further study may reveal that xylene in concentrations of 200 p.p.m. adversely affects the efficiency of workers, even though there may be no permanent injury. The figure of 200 p.p.m. is an ASA standard.

### 8. Warning Properties and Inflammability

The warning properties of xylene are fair, the initial odor of 200 p.p.m. having an intensity on the order of 3 and an irritation of 1. Olfactory fatigue, as in most other instances, occurs rapidly, however, and the odor is no longer detected. The inflammable range of *o*-xylene is 1.00 to 6.00 per cent by volume; and the flash point by the closed-cup method is 63° F. (see Chapter Thirteen).

## ETHYLBENZENE

### 1. Source and Uses

Ethylbenzene,  $C_6H_5C_2H_5$ , is obtained by the ethylation<sup>20</sup> of benzene. It has the same molecular weight as xylene and a similar structure, differing in that it has one ethyl side chain instead of two methyl groups. Ethylbenzene is an intermediate in the production of styrene. It has been used as a diluent in lacquers and other finishes. Suggested uses include blending in aviation gasoline for "antiknock" qualities, and general solvent uses similar to those for xylene.

### 2. Physical and Chemical Properties

The physical and chemical properties of ethylbenzene are listed in Table 1.

### 3. Determination in the Atmosphere

Ethylbenzene may be determined by the same methods as used for xylene. 1 mg./l.  $\approx$  230 p.p.m. and 1 p.p.m.  $\approx$  4.35 mg./cu.m. at 25° C., 760 mm.

### 4. Physiological Response

*Acute effects.* The acute effects for mice have been found to be greater than those of benzene and similar to toluene and *m*-xylene (see Table 2). The acute effects for guinea pigs, as found by Yant, Schrenk, Waite, and Patty,<sup>21</sup> are given in Table 3.

Ethylbenzene is mildly irritant to the lungs, but death of guinea pigs appeared to result primarily from effects upon the central nervous system. Men found 1000 p.p.m. to be very irritating to the eyes upon entering but the effect rapidly lessened. They found that 2000 p.p.m. caused immediate, severe eye irritation and lacrimation and moderate nasal irritation. The irritant effects somewhat lessened, and dizziness became quite noticeable within 6 minutes, at which time exposure was terminated. 5000 p.p.m. caused intolerable irritation of the eyes and nose.

<sup>20</sup> V. N. Ipatieff and L. Schmerling, *Ind. Eng. Chem.*, **38**, 400 (1946).

<sup>21</sup> W. P. Yant, H. H. Schrenk, C. P. Waite, and F. A. Patty, *U.S. Pub. Health Repts.*, **45**, 1241 (1930).

TABLE 3

*Acute Effects of Exposure of Guinea Pigs to Ethylbenzene Vapor*

Effects	Concentration, per cent by volume
Kills in a few minutes.....	a
Dangerous to life in 30 to 60 minutes.....	1.0
Dangerous to life after several hours.....	0.5
Maximum amount for one hour without serious symptoms.....	0.3
Maximum amount for several hours without serious disturbance....	0.1

\* Not produced by 1 per cent, the highest concentration obtained in a closed chamber by extended recirculation of air at 23° C. over wicks wet with ethylbenzene.

**Chronic effects.** Chronic inhalation exposure studies have not been reported. Although the chemical structure of ethylbenzene would indicate an action similar to that of toluene and xylene, the point is not established and the effects of prolonged exposures on the blood picture are unknown.

#### 5. Absorption and Excretion

Absorption is chiefly by inhalation. Here, as in the case of toluene, dogs dosed with ethylbenzene have been found to excrete excess hippuric acid,<sup>22</sup> while the fate of ethylbenzene in the human body has not been established. It would, however, be expected to be the same.

#### 6. Maximum Permissible Concentration

Any estimate of the maximum permissible exposure for men must be derived from the scanty information on acute effects and the similarity to better known compounds. On this basis, it is tentatively suggested that a range of concentrations of 150 to 200 p.p.m. be the maximum for 8-hour daily exposures.

#### 7. Warning Properties and Inflammability

Ethylbenzene, in a concentration of 200 p.p.m., has a definite, but transient, irritant effect upon the eyes with an intensity degree of 1 or 2, while 1000 p.p.m. has a transient irritation intensity of about 3 and causes profuse lacrimation. The odor intensity of 200 p.p.m. is about 2. The flash point by the closed-cup method is 63° F.

## CUMENE

#### 1. Source and Uses

Cumene, isopropylbenzene,  $C_6H_5CH(CH_3)_2$ , is normally found in many petroleum distillates and is frequently a significant constituent of commercial petroleum solvents in the boiling range of 150 to 160° C. It is recovered by fractionation of petroleum and is widely used as a diluent or thinner in paints and enamels, as a solvent, and in organic synthesis.

<sup>22</sup> M. Nencki and P. Giacosa, *Z. physiol. Chem.*, 4, 325 (1880).

## 2. Physical and Chemical Properties

The physical and chemical properties are given in Table 1.

## 3. Determination in the Atmosphere

The methods for the determination of cumene vapor in the air are similar to those for xylene, page 762.

1 mg./l.  $\approx$  203.5 p.p.m. and 1 p.p.m.  $\approx$  4.92 mg./cu.m. at 25° C., 760 mm.

## 4. Physiological Response

*Acute effects.* The acute toxicity of cumene is greater than that of benzene or toluene. The minimum lethal concentration of cumene<sup>23</sup> as determined by single 7-hour exposures of white mice is 10 mg. per liter, 2000 p.p.m. On a milligram-per-liter basis this is twice the toxicity of toluene and over three times that of benzene. On a volume basis the ratio is even higher, the L.D.<sub>50</sub> concentrations of cumene, toluene, and benzene being approximately 2000, 5000, and 10,000 p.p.m., respectively. Cumene is a depressant to the central nervous system, its narcotic action being characterized by slow induction and long duration. Damage to the spleen and fatty change in the liver were consistent findings. Neither renal nor pulmonary irritation was observed.

*Chronic effects.* No results of chronic exposure have been published.

## 5. Permissible Limit and Inflammability

No permissible limit can be estimated from available data. The low vapor pressure of cumene limits the exposure arising from its use in the cold in open containers or vats, but mechanical ventilation or enclosed processes are advised. The flash point is about 97° F.

# STYRENE

## 1. Source and Uses

Styrene, vinylbenzene, phenylethylene,  $C_6H_5CH:CH_2$ , occurs naturally in stryaceous trees. Monomeric styrene is produced from ethylbenzene. Because of its ease of polymerization, styrene has recently come into very extensive use in the fields of synthetic rubber and plastics manufacture, in addition to miscellaneous applications.

## 2. Physical and Chemical Properties

The physical and chemical properties of styrene are listed in Table 1.

## 3. Determination in the Atmosphere

Rowe, Atchison, Luce, and Adams<sup>24</sup> have presented techniques for the sampling and analysis of styrene by ultraviolet, infrared, and nitration methods.

<sup>23</sup> H. W. Werner, R. C. Dunn, and W. F. von Oettingen, *J. Ind. Hyg. Toxicol.*, **26**, 264 (1944).

<sup>24</sup> V. K. Rowe, G. J. Atchison, E. N. Luce, and E. M. Adams, *J. Ind. Hyg. Toxicol.*, **25**, 348 (1943).

The choice between these methods will depend upon circumstances, as discussed in the original paper. For control purposes, the interferometer, because of its rapidity and ease of manipulation, is probably the method of choice, even though it is not specific. Because of the relatively high indication given by threshold concentrations of styrene, the 25 cm. interferometer is quite satisfactory. Combustible gas indicators also may be used.

1 mg./l.  $\approx$  235.5 p.p.m and 1 p.p.m.  $\approx$  4.26 mg./cu.m. at 25° C., 760 mm.

#### 4. *Physiological Response*

*Acute effects.* Under ordinary room conditions styrene<sup>24</sup> does not vaporize sufficiently to reach vapor concentrations that kill animals (rats and guinea pigs) in a few minutes. 10,000 p.p.m. was dangerous to life in 30 to 60 minutes, 2500 p.p.m. was dangerous to life in 8 hours, while 1300 p.p.m. was the highest amount causing no serious systemic disturbance in 8 hours. All animals exposed to these amounts evidenced eye and nasal irritation. Those exposed to 2500 p.p.m. or greater showed varying degrees of weakness and stupor, followed by inco-ordination, tremors, and unconsciousness. Unconsciousness occurred in 10 hours with 2500 p.p.m., 1 hour with 5000 p.p.m., and within a few minutes at 10,000 p.p.m.

*Chronic effects.* Rats exposed<sup>25</sup> to 1300 p.p.m. styrene, 7 to 8 hours per day, 5 days per week, for 6 months, evidenced definite signs of eye and nasal irritation and appeared unkempt, though they made a normal gain in weight and presented no significant microscopic tissue changes or changes in the blood picture. Twelve rabbits exposed to 1300 p.p.m. for a similar period presented, with the exception of one unexplained death, a similar result. Of nearly 100 guinea pigs exposed to this concentration, 10 per cent died from lung irritation within a few exposures, while the remainder survived the 6 months' exposure period with no significant gross or microscopic findings. When another group of guinea pigs was similarly exposed to 650 p.p.m. styrene, the weight gain and condition of exposed animals were similar in all respects to those of the controls.

#### 5. *Absorption and Excretion*

Absorption is mainly through the respiratory tract, and in both animals<sup>25</sup> and man<sup>26</sup> styrene is metabolized to benzoic acid, conjugated with glycine, and excreted in the urine as hippuric acid. From 50 to 90 per cent of orally administered styrene has been recovered as hippuric acid in the urine. As with any other compound, so long as styrene exists as such in the circulating blood, some of it is excreted in the exhaled air.

#### 6. *Maximum Permissible Concentration*

Judged from the effects upon animals, 400 p.p.m. has been suggested<sup>25</sup> as the maximum permissible limit for repeated exposures of men. Further studies

<sup>24</sup> H. C. Spencer, D. D. Irish, E. M. Adams, and V. K. Rowe, *J. Ind. Hyg. Toxicol.*, **24**, 295 (1942).

<sup>25</sup> C. P. Carpenter, C. B. Shaffer, C. S. Weil, and H. F. Smyth, Jr., *J. Ind. Hyg. Toxicol.*, **26**, 69 (1944).

conducted with men, however, may reveal that a concentration of 400 p.p.m., which causes slight irritation and has a strong, disagreeable odor, may produce fatigue or other adverse effects in men, even if permanent ill effects do not occur. For this reason, the present maximum permissible concentration of 400 p.p.m. which has been set by the American Standards Association may have to be lowered to 200 p.p.m.

#### 7. *Warning Properties and Inflammability*

Styrene vapor in concentrations of 200 to 400 p.p.m. has, upon entering, a transient irritant effect on the eyes and nose with an intensity of 1 or 2. The initial odor intensity is 3 or 4. The inflammable limits are 1.10 to 6.10 per cent by volume vapor in air, and the flash point by the closed-cup method is 86° F. (see Chapter Thirteen).

## CYCLOHEXANE

### 1. *Source and Uses*

Cyclohexane, hexahydrobenzene,  $C_6H_{12}$ , is produced by the hydrogenation of benzene. The solvent properties and uses are similar to those of benzene.

### 2. *Physical and Chemical Properties*

The physical and chemical properties of cyclohexane are presented in Table 1 on page 753.

### 3. *Determination in the Atmosphere*

The only satisfactory methods described for determining cyclohexane in the air are general methods applicable to most solvents: the spectrometer, the interferometer, the combustible gas indicator, and combustion to  $CO_2$  with determination of the  $CO_2$ . The refractivity of 1 per cent vapor in air at 25° C. and 760 mm. is  $15.1 \times 10^{-6}$ .

1 mg./l.  $\approx$  291 p.p.m. and 1 p.p.m.  $\approx$  3.44 mg./cu.m. at 25° C., 760 mm.

### 4. *Physiological Response*

*Acute effects.* The minimum lethal dose<sup>27</sup> of cyclohexane administered orally to rabbits is 5.5 to 6 g. per kilogram. By inhalation, 2.66 per cent by volume (89.6 mg./l.) caused the death of rabbits within 1 hour. Concentrations of 1.85 per cent or less did not cause death within one 8-hour exposure. Concentrations of 0.74 per cent and above caused lethargy, increased respiration, and narcosis; 1.26 per cent and above caused, in addition, spasmodic convulsions. Concentrations of 0.333 per cent (3330 p.p.m.) caused no visible effects upon rabbits. Flury and Zernik<sup>28</sup> give comparative data for four animals as presented in Table 4.

<sup>27</sup> J. F. Treon, W. E. Crutchfield, Jr., and K. V. Kitzmiller, *J. Ind. Hyg. Toxicol.*, **26**, 199, 323 (1943).

<sup>28</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

TABLE 4

*Comparative Acute Effects of a Single Brief Exposure (0.5 Hour) to 1.8 Per Cent by Volume, Cyclohexane Vapor in Air*

Animal	Minutes to produce effect		
	Trembling	Disturbed equilibrium	Complete recumbency
Mouse	5	15	25
Guinea pig	Slight	—	—
Rabbit	6	15	30
Cat	—	11	18-25

*Chronic effects.* Ten daily exposures,<sup>27</sup> of 6 hours, to 0.74 to 1.85 per cent by volume cyclohexane in air, caused fatalities in at least part of the exposed rabbits. No symptoms and no fatalities occurred as a result of 50 daily 6-hour exposures to 0.333 per cent or less. However, minor microscopic changes were observed in the liver and kidneys of rabbits exposed to concentrations as low as 786 p.p.m. (2.65 mg./l.). A concentration of 1243 p.p.m. caused no sign of illness in a monkey during, nor any microscopic evidence of injurious effects following, 50 daily 6-hour exposures. Rabbits exposed 8 hours per day, 5 days per week, for 26 weeks, to 434 p.p.m. cyclohexane exhibited no symptoms of ill effects during or after exposure and there was no gross or microscopic evidence of tissue damage. No specific, or general, toxic effects upon the cellular elements of the peripheral blood were observed in any of the above described experiments. Pathological changes were not specific for cyclohexane, but characteristic of acute toxic reactions, and included generalized endothelial injury with vascular lesions in the brain, heart, lungs, liver, spleen, and kidneys. The lower concentrations that caused any evidence of damage caused degenerative changes in the liver and kidneys.

##### 5. Absorption and Excretion

Absorption from industrial exposure is almost exclusively through the respiratory tract. The liquid is irritant to the skin, but evidence of systemic effects from absorption of cyclohexane through the skin is lacking. Cyclohexane is partly metabolized by rabbits: some is excreted in the urine as glucuronic acid, some as ethereal sulfates. The decrease in the ratio of inorganic to total sulfates in the urine is somewhat proportional to the concentration of cyclohexane in the inhaled air, but the change is not as rapid, nor as complete, as is the case in benzene exposures. As with other hydrocarbons, some cyclohexane is doubtless excreted as such in the urine, and a considerable portion in the exhaled air.

##### 6. Tests Indicating Exposure

Data on the glucuronic acid excretion and urine sulfate ratios of exposed workmen may prove useful as measures of the degree of exposure, but such data will have to be collected and correlated with the contaminations of cyclohexane in the atmospheres before any relationships can be established.



### 7. Maximum Permissible Concentration

A concentration of 434 p.p.m. is believed to be safe for rabbits. Whether human beings will observe any narcotic effects or be fatigued at this concentration remains to be established. However, it seems unlikely that serious and lasting consequences will result from exposure to 300 p.p.m. and this should offer a satisfactory temporary bench mark until further studies are made.

### 8. Warning Properties and Inflammability

The irritation and odor produced by concentrations on the order of 300 p.p.m. are not distinct. The inflammable range for cyclohexane vapor is from 1.33 to 8.35 per cent by volume in air, and the flash point by the closed-cup method is 1° F. (see Chapter Thirteen).

## METHYLCYCLOHEXANE

### 1. Physical and Chemical Properties

The physical and chemical properties of methylcyclohexane are given in Table 1. Methylcyclohexane,  $C_6H_{11}CH_3$ , is similar to cyclohexane and it is determined in the same manner. The refractivity of 1 per cent vapor in air at 25° C. and 760 mm. is  $17.5 \times 10^{-6}$ .

1 mg./l.  $\approx$  249 p.p.m. and 1 p.p.m.  $\approx$  4.02 mg./cu.m. at 25° C., 760 mm.

### 2. Physiological Response

*Acute effects.* The oral minimum lethal dose<sup>27</sup> for rabbits is 4.0 to 4.5 g. per kilogram. By inhalation, 1.5 per cent by volume (59.9 mg./l.) caused the death of rabbits within 70 minutes. The symptoms included conjunctival congestion, salivation, labored breathing, narcosis, and convulsions.

*Chronic effects.* All rabbits died that had been exposed to 1.0 per cent vapor, 6 hours per day, 5 days per week, for 2 weeks; and one fourth of the rabbits exposed to 0.73 per cent for a similar time died. Four weeks' exposure of rabbits to 0.56 per cent caused no fatalities, and the only sign of intoxication was slight lethargy, while objective symptoms were absent with half this concentration. Likewise, concentrations of 1162 and 241 p.p.m. for a period of 10 weeks caused no signs of illness in rabbits. Also, a monkey, exposed the same length of time to 372 p.p.m., showed no signs of illness. No microscopic evidence of cellular injury was observed in rabbits exposed to 1162 p.p.m. and only minor evidence of liver and kidney damage after 300 hours' (10 weeks) exposure to 3330 p.p.m. Pathology, absorption, and excretion were similar to those observed with cyclohexane.

### 3. Maximum Permissible Concentration

Although concentrations up to 1162 p.p.m. appear to be safe for rabbits, data with human beings have not been obtained. Even though permanent damage would not be expected at concentrations up to 800 p.p.m., it is suggested that for


prolonged exposure 500 p.p.m. should not be exceeded, until data on the exposure of human beings to concentrations of this order are collected and presented.

#### 4. *Warning Properties and Inflammability*

There is no irritation to the eyes and nose, and only a weak odor in atmospheres of 500 to 800 p.p.m. methyl cyclohexane in air. The lower inflammable limit for the vapor is 1.15 per cent by volume in air and the flash point by the closed-cup method is 25° F.

## NAPHTHALENE

### 1. *Source and Uses*

Naphthalene, tar camphor, , C<sub>10</sub>H<sub>8</sub>, obtained from coal tar, is a white solid sold in scales, powder, or more familiarly in balls, in which form it is widely dispensed as a moth repellent. It is also used extensively in chemical and dye manufacturing, for carbureting illuminating gas, as a disinfectant, and in preserving wood and other materials.

### 2. *Physical and Chemical Properties*

The physical and chemical properties of naphthalene are given in Table 1.

### 3. *Determination in the Atmosphere*

Naphthalene vapor in air may be determined by weighing, after adsorption on silica gel or activated charcoal, or after collection by condensation at low temperature. It may be determined with the spectrometer, the interferometer, or by the picrate method,<sup>29</sup> or by nitration in a scrubber and subsequent analysis in the same manner as toluene if interfering vapors are absent.

1 mg./l.  $\approx$  191 p.p.m. and 1 p.p.m.  $\approx$  5.24 mg./cu.m. at 25° C., 760 mm.

### 4. *Physiological Response*

Rabbits administered naphthalene, 1 g. per kilogram daily, develop changes in the lens within 3 days,<sup>30</sup> and within 20 days the lens becomes opaque. The mechanism is little understood except that the glutathione content of the lens, as well as the vitamin C content of the aqueous humor, the lens, and the vitreous humor, are materially reduced. The naphthalene is detoxicated, in rabbits, partly by conjugation with cysteine and excretion as a mercapturic acid, and partly by excretion after conversion to an unidentified soluble compound that upon acidification yields naphthalene. Inhalation experiments with animals have not been reported. In human beings,<sup>28</sup> the inhalation of naphthalene vapors may produce headache, loss of appetite, nausea, and retching. Naphthalene dusts, or more concentrated vapors, are reported to have caused optical neuritis and injuries to

<sup>29</sup> M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

<sup>30</sup> M. C. Bourne, *Physiol. Revs.*, 17, 1 (1937).

the cornea, as well as kidney damage. Destruction of erythrocytes, or injury to blood-forming organs, has not been established. Skin irritation has been reported. Although evidence has not been established, with human beings, that cataracts or other serious injurious effects result from the inhalation of naphthalene vapors at ordinary room temperatures, there is every reason to treat these vapors with respect. Engineering and medical control should be exercised to avoid excess exposures and prevent injury.

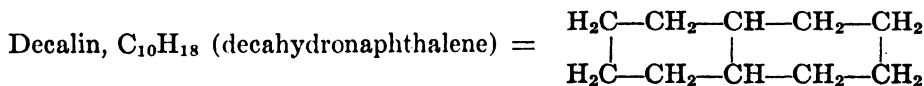
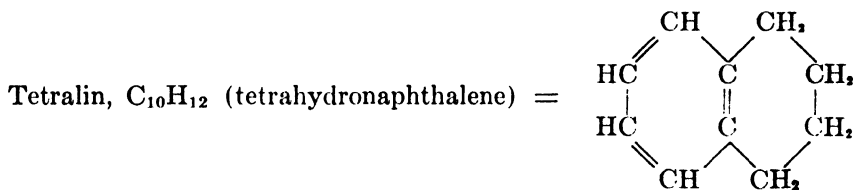
### 5. Maximum Permissible Concentration

No maximum permissible limit has been proposed. As a tentative limit, a concentration of 25 p.p.m. is hereby suggested for naphthalene vapor in air. This corresponds to 130 mg. per cubic meter and is about 25 per cent of the amount of vapor occurring in saturated air at 25° C., at which temperature the vapor pressure of naphthalene equals approximately 0.082 mm. Hg. We need correlated medical observations and concentration data.

### 6. Warning Properties and Inflammability

The flash point of naphthalene by the closed-cup method is 176° F. and the powder also produces inflammable mixtures when suspended in air. The inflammable range of the vapor is from 0.88 to 5.9 per cent by volume of air.<sup>31</sup> The initial odor of 25 p.p.m. has an intensity of about 3.

## TETRALIN AND DECALIN



### 1. Source and Uses

Tetralin and decalin, liquids with odors resembling that of naphthalene, are produced by the catalytic hydrogenation of naphthalene. They are used as solvents for oils, fats, waxes, resins, asphalt, and rubber. They are also used in paint and varnish removers, and as substitutes for turpentine in shoe polishes, oil paints, and floor lacquers. Tetralin has been used as a larvicide for mosquitoes. Their use in the United States, however, has not been so extensive as elsewhere.

### 2. Physical and Chemical Properties

The physical and chemical properties of tetralin and decalin are given in Table 1.

<sup>31</sup> G. W. Jones and G. S. Scott, *U.S. Bur. Mines Repts. Investigations No. 5381* (1946).

### 3. Determination in the Atmosphere

No specific methods of analysis have been reported. The interferometer, collection by condensation upon adsorbents for weighing, and sensitive types of combustion apparatus, should be applicable, as should infrared and ultraviolet absorption methods.

Tetralin, 1 mg./l.  $\approx$  185 p.p.m. and 1 p.p.m.  $\approx$  5.41 mg./cu.m. at 25° C., 760 mm.

Decalin, 1 mg./l.  $\approx$  177 p.p.m. and 1 p.p.m.  $\approx$  5.65 mg./cu.m. at 25° C., 760 mm.

### 4. Physiological Response

Absorption of these solvents through the skin is reported to have caused the death of cats by methemoglobin formation. They are irritant to the eyes, nose, and throat. According to Flury and Zernik,<sup>28</sup> they cause numbness, headache, nausea, and vomiting. They are reported to have caused eczema among painters. Serious poisoning in man has not been reported. The urine of exposed persons is colored blue and the hydronaphthalenes are thought to be excreted as combined glucuronic acids.

### 5. Inflammability and Suggested Limits

The flash point, by the closed-cup method, of decalin is about 136° F. and of tetralin, about 172°. No permissible limits have been proposed. It seems logical to suggest a limit of less than 100 p.p.m. Odor and irritation make this amount somewhat offensive.

## TURPENTINE

### 1. Source and Uses

Turpentine oil, or gum spirit (American), is a variable mixture containing chiefly  $\alpha$ -pinene, sometimes  $\beta$ -phellandrene,<sup>32</sup> and minor fractions of *n*-heptane and *n*-undecane. It is prepared by water or steam distillation of the resin flowing from cuts in certain varieties of growing pine trees. It is used as a solvent for oils, fats, and resins, in the manufacture of oil lacquers, shoe creams, and polishing waxes. It is also used in the manufacture of synthetic camphor, and in medicine.

### 2. Physical and Chemical Properties

The physical and chemical properties of turpentine are given in Table 1.

### 3. Determination in the Atmosphere

The general methods of atmospheric analysis mentioned under tetralin may be used for turpentine. Turpentine may be determined by being absorbed in suitable scrubbing media, a color developed with a solution of vanillin in hydrochloric acid, and the color compared with freshly made standards.<sup>29</sup> It may also

<sup>29</sup> N. T. Mirou, *Ind. Eng. Chem.*, **38**, 405 (1946).

be determined by collection in concentrated sulfuric acid, and the resulting color compared with similar, freshly made standards, or permanent dye standards. This method is said to be sensitive to approximately 0.02 mg.<sup>33</sup>

1 mg./l.  $\approx$  approximately 179 p.p.m. and 1 p.p.m.  $\approx$  approximately 5.57 mg./cu.m. at 25° C., 760 mm.

#### 4. Physiological Response

*Acute effects.* Lehmann<sup>34</sup> found that cats exposed to 3 to 4 mg. per liter, 540 to 720 p.p.m., turpentine evidenced immediate irritation of all mucous surfaces, especially the eyes, and slight convulsions developed after a few hours. Eight milligrams per liter, 1440 p.p.m., produced disturbances in equilibrium, tetanic convulsions in 30 to 60 minutes, and paralysis in 150 to 180 minutes. Double this amount caused death within 45 to 60 minutes. Lehmann and Flury<sup>35</sup> reported that, when men are exposed, concentrations of 720 to 1100 p.p.m. cause eye irritation, headache, vertigo, nausea, and an accelerated pulse. They give as the acute effects in man: headache, nausea, accelerated respiration and pulse, pain in the chest, bronchitis, coughing, lung inflammation, excitation, confusion, and disturbance of vision. Chapman<sup>36</sup> reports that in man the inhalation of turpentine may cause renal injury, with albuminuria and hematuria, but when the exposure is terminated promptly recovery usually occurs within a few weeks.

*Chronic effects.* Lehmann found that cats exposed 3.5 hours per day for 8 days to 155 to 180 p.p.m. turpentine evidenced no injury. Smyth and Smyth<sup>37</sup> found no injury to guinea pigs after prolonged daily exposure to 750 p.p.m. Excessive exposure of men may result in kidney damage (tubular nephritis). Significant adverse effects upon the blood picture have not been substantiated.

Turpentine is irritant to the skin and, apparently, hypersensitiveness can occur after years of handling. Variations in the composition cause some turpentines to be much more irritant than others. McCord<sup>38</sup> has shown that wood turpentine is much more productive of dermatitis than is gum spirit. He attributed this to impurities, such as formic acid, formaldehyde, phenols, and so forth, commonly occurring in the wood turpentine oil, which is distilled either with steam or by destructive distillation from pine wood, especially stumps. It is also recovered from sulfate liquor in the wood pulp industry. Wood turpentine, even after steam distillation, may be recognized and distinguished from gum spirit by positive tests for benzaldehyde and fenchyl alcohol.<sup>39</sup>

<sup>33</sup> P. Andreev and A. Gavrilov, *Chem. Ztg.*, 53, 870, 889 (1929).

<sup>34</sup> K. B. Lehmann, *Arch. Hyg.*, 33, 239 (1914).

<sup>35</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

<sup>36</sup> E. M. Chapman, *J. Ind. Hyg. Toxicol.*, 23, 277 (1941).

<sup>37</sup> H. F. Smyth and H. F. Smyth, Jr., *J. Ind. Hyg.*, 10, 261 (1928).

<sup>38</sup> C. P. McCord, *J. Am. Med. Assoc.*, 86, 1978 (1926).

<sup>39</sup> T. C. Chadwick and S. Palkin, *Trans. Am. Soc. Testing Materials*, 37, Part II, 574 (1937).

### **5. *Absorption and Excretion***

Turpentine may be acquired by ingestion and by skin absorption, but the significant industrial mode is by inhalation. Part of it is eliminated in the expired air, while part is excreted in the urine, some of it unchanged and some in combination with glucuronic acid. The odor of the urine of men or animals exposed to turpentine is a peculiar one, often described as the "odor of violets."

### **6. *Maximum Permissible Concentration***

For some years 700 p.p.m. turpentine vapor in air was used as the maximum permissible concentration. However, more recently official public health agencies have been inclined to regard 200 p.p.m. as the maximum permissible concentration for prolonged exposures.

### **7. *Warning Properties and Inflammability***

The odor of 200 p.p.m. turpentine in air is easily noticeable and this concentration is moderately irritant to the eyes and nasal passages. The lower inflammable limit is 0.80 per cent by volume in air, while the upper limit has not been established. The flash point by the closed-cup method is 95° F.

# Halogenated Hydrocarbons

JAMES H. STERNER, M.D.

## I. General Consideration

The halogenated hydrocarbons are among the most widely used of industrial chemicals. The excellent solvent properties, the range of volatility, and the low flammability of the members of the series satisfy many of the requirements of a good solvent, and of a good refrigerant. Unfortunately, from the viewpoint of their industrial use, all of the compounds possess an appreciable toxicity, with some of the industrially more desirable members being quite toxic. With the chlorinated aliphatic hydrocarbons, of the methane, ethane, and ethylene series, the relatively lower toxicity of the members containing fewer chlorine atoms is offset, as to industrial application, by their greater volatility and usually inferior solvent properties.

The nomenclature of the halogenated hydrocarbons frequently is confusing. The older terminology, describing the compound as an addition of the halogen to the unsaturated hydrocarbon, is often retained as the industrial name of the compound. For common example, ethylene dichloride is not a member of the *ethylene* or unsaturated series, is not synonymous with dichloroethylene, but is a saturated compound more properly called dichloroethane. Further to confuse the person who is not an organic chemist, two other, more exact systems of nomenclature defining the position of the halogen atoms are in good chemical usage: the preferable one designates the carbon atoms by number, as 1,2-dichloroethane, where the chlorine atoms are attached to different carbons; the second method indicates the carbons by the Greek letters, as  $\alpha,\beta$ -dichloroethane. Thus ethylene dichloride is synonymous with dichloroethane, 1,2-dichloroethane, or  $\alpha,\beta$ -dichloroethane.

### A. SYMPTOMS IN ANIMALS

The primary symptoms produced by the simpler halogenated aliphatic hydrocarbons are those of narcosis, with a varying pattern as to the degree of irritation of the eyes, upper respiratory tract, and lungs, and of central nervous system excitation. In exposures to high concentrations the syndrome usually begins with lachrymation, salivation, sniffing, sneezing, nose scratching, evidences of eye

and upper respiratory tract irritation; this is frequently quite rapidly followed by unsteadiness, vertigo, side position, decreased and irregular respiration, loss of consciousness, and death. Symptoms of central nervous system irritation such as restlessness, twitching, and clonic convulsions may occur, with increased excitability a not uncommon finding preceding the onset of narcosis.

Of great importance from the viewpoint of industrial hygiene are the secondary, and frequently less well-recognized, effects. This delayed action due to the later developing injury in such organs as the liver, kidneys, heart, and circulatory system is not closely related to the narcotic activity, and hence not predictable from that physiologic response. In addition, this delayed effect, the "two-phased activity" of K. B. Lehmann, may vary considerably with the effective concentration of the solvent vapor and with the species of animal exposed to it.

A logical approach in organizing the physiologic effects of these compounds is to group the substances according to the number of carbon atoms and the degree of "saturation"—for example, the methane, ethane, and ethylene series—and then compare the activities of the members of a series with the type and degree of halogenation. Cross comparisons between the important compounds of different groups will permit some orientation of this entire class of clinical substances.

#### *Methane Series*

With the three monohalogenated methane derivatives, methyl chloride or monochloromethane ( $\text{CH}_3\text{Cl}$ ), methyl bromide or monobromomethane ( $\text{CH}_3\text{Br}$ ), and methyl iodide or monoiodomethane ( $\text{CH}_3\text{I}$ ), there is a decrease in the narcotic action and an increase in toxicity with the increase in molecular weight and boiling point. A similar relation holds for the trihalogen homologues, chloroform ( $\text{CHCl}_3$ ), bromoform ( $\text{CHBr}_3$ ), and iodoform ( $\text{CHI}_3$ ).

Among the chlorine-substituted methane series, of greater importance industrially, an increase in the number of chlorine atoms is associated with an increase in hemolytic and antiseptic effects. A similar relation for the narcotic action holds only through chloroform ( $\text{CHCl}_3$ ), with the addition of a fourth chlorine atom resulting in a slightly lessened anesthetic effect. The toxicity of the compounds does not follow such a regular relation to the physicochemical properties. If the toxic action is judged by the deaths occurring during or very shortly after narcosis from high concentrations, toxicity increases with the degree of chlorination, through chloroform; but if the delayed deaths—occurring after recovery from narcosis, or after repeated subnarcotic exposures—are included, the monochlorinated compound, methyl chloride ( $\text{CH}_3\text{Cl}$ ), is the most toxic, with carbon tetrachloride ( $\text{CCl}_4$ ), chloroform ( $\text{CHCl}_3$ ), and methylene chloride ( $\text{CH}_2\text{Cl}_2$ ) following in order of decreasing toxicity. The substitution of one or two fluorine atoms for chlorine in carbon tetrachloride results in a considerably lessened narcotic action and mortality—the difluorodichloromethane being less active than the monofluorotrichloromethane.



*Ethane Series*

As was true of the methane group, the corresponding chlorine-, bromine-, and iodine-substituted compounds of the ethane series exhibit an increase in toxicity and a decrease in narcotic effect with the rise in molecular weight and in boiling point. With the chlorinated compounds, the narcotic action increases with the number of chlorine atoms through tetrachloroethane, decreasing slightly with the addition of a fifth chlorine atom. In ranking the compounds as to toxicity, it is again important to define the criteria, whether mortality is judged by those deaths occurring during or shortly after exposure to concentrations that will produce narcosis, or whether the "delayed" deaths are to be included. Again, the toxic action, as determined by the effect of repeated exposure to subnarcotic concentrations, does not follow the same pattern as the acute toxicity, an important element in its determination being the degree of injury to the liver.

The acute toxicity (as judged by deaths occurring during narcosis) increases with the number of chlorine atoms through tetrachloroethane ( $\text{CHCl}_2\text{CHCl}_2$ ), then decreases slightly. If the "delayed" death criterion is used, trichloroethane ( $\text{CH}_2\text{ClCHCl}_2$ ) is considerably more toxic, with tetrachloroethane ( $\text{CHCl}_2\text{-CHCl}_2$ ) and pentachloroethane ( $\text{CCl}_3\text{CHCl}_2$ ) intermediate in effect, and dichloroethane ( $\text{CH}_2\text{ClCH}_2\text{Cl}$ ) and monochloroethane ( $\text{CH}_2\text{ClCH}_3$ ) of a still lower order. With repeated exposures to lesser concentrations, and the hepatotoxic action (although less clearly defined) as the criterion of toxicity, tetrachloroethane ( $\text{CHCl}_2\text{CHCl}_2$ ) shows the greatest activity, with dichloroethane ( $\text{CH}_2\text{ClCH}_2\text{Cl}$ ) intermediate, a questionable activity for mono-, tri-, and pentachloroethanes, and no observed effect with hexachloroethane ( $\text{CCl}_3\text{CCl}_3$ ).

The distribution of the chlorine atoms between the carbon atoms (as contrasted with their being placed on one carbon only) results in an increased toxicity and narcotic action. For example, these effects are more marked for ethylene dichloride (1,2-dichloroethane) ( $\text{CH}_2\text{ClCH}_2\text{Cl}$ ) than for ethylidene chloride (1,1-dichloroethane) ( $\text{CHCl}_2\text{CH}_3$ ); similarly, more marked for 1,1,2-trichloroethane ( $\text{CHCl}_2\text{CH}_2\text{Cl}$ ) than for 1,1,1-trichloroethane ( $\text{CCl}_3\text{CH}_3$ ).

The partial substitution of fluorine for chlorine, as in dichlorotetrafluoroethane ( $\text{CClF}_2\text{CClF}_2$ ), as with the methane series, results in a decreased toxicity.

*Ethylene Series*

The narcotic effects of the chlorinated ethylene compounds increase with the number of chlorine atoms, the greatest increase occurring with the addition of the second chlorine. The toxicity as judged by the deaths occurring during or immediately after exposure to narcotic concentrations parallels the narcotic action, but if the "delayed" deaths are the deciding factor, dichloroethylene ( $\text{CHCl}:\text{CHCl}$ ) and trichloroethylene ( $\text{CHCl}:\text{CCl}_2$ ) are more toxic than tetrachloroethylene ( $\text{CCl}_2:\text{CCl}_2$ ). Hepatotoxic effects have been reported with di-

chloroethylene ( $\text{CHCl:CHCl}$ ), but the information is inadequate with respect to the other members of the series.

### *Propane Series*

Monochloropropane (propyl chloride, 1-chloropropane,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$ ) has a greater narcotic action, but is less toxic than monobromopropane (propyl bromide, 1-bromopropane,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$ ). Although data adequate for careful comparison are lacking, apparently an increase to two chlorine atoms, as in 1,3-dichloropropane (propylene chloride,  $\text{CH}_2\text{ClCH}_2\text{CH}_2\text{Cl}$ ), or three, as in 1,2,3-trichloropropane ( $\text{CH}_2\text{ClCHClCH}_2\text{Cl}$ ), is associated with increased narcotic action and toxicity.

### *Miscellaneous Aliphatic Halogenated Compounds*

Dichloroethyl ether ( $\beta,\beta'$ -dichloroethyl ether,  $(\text{CH}_2\text{ClCH}_2)_2\text{O}$ ) is a strong primary irritant, with animals exposed to higher concentrations showing intense irritation of the upper respiratory tract followed by unsteadiness, retching, shallow and rapid breathing, loss of consciousness, and death. With lower concentrations, delayed death is associated with liver and kidney injury. Allyl chloride or 3-chloropropene ( $\text{CH}_2\text{ClCH:CH}_2$ ) and allyl bromide ( $\text{CH}_2\text{BrCH:CH}_2$ ) also produce marked irritation of the conjunctiva, upper respiratory tract, and lungs. Chloroprene (2-chloro-1,3-butadiene,  $\text{CH}_2\text{:CHCl:CH}_2$ ) at high concentrations is markedly irritating to the respiratory tract and has considerable narcotic effect. After repeated exposures to lower concentrations, symptoms associated with anemia, and injury of the liver and kidneys are found. Ethylene chlorohydrin ( $\beta$ -chloroethyl alcohol, 2-chloroethanol,  $\text{CH}_2\text{ClCH}_2\text{OH}$ ) produces marked irritation of the respiratory tract, with delayed deaths, following exposures to lesser concentrations, being due to degenerative changes of the heart, liver, and kidneys.

### *Aromatic Halogenated Hydrocarbons*

The mono- and dichlorinated benzenes ( $\text{C}_6\text{H}_5\text{Cl}$ ,  $\text{C}_6\text{H}_4\text{Cl}_2$ ) have strong narcotic effects, and cause moderate irritation to the respiratory tract. Dichlorobenzene is more irritating and more toxic than the monochloro-derivative. Exposures to higher concentrations result in irritative and degenerative changes in the liver and kidneys.

## B. GROSS PATHOLOGY IN ANIMALS

With high concentrations of the simpler halogenated hydrocarbons, such as dichloromethane, trichloroethylene, the upper respiratory tract and lungs exhibit varying degrees of irritation from mild edema to, in the severe cases, petechial hemorrhages and cell degeneration. With certain of the more irritating compounds.

such as allyl chloride, the effects are more like those of the acid gases, producing acute pulmonary edema. At lower, but narcotic, concentrations of the less irritating compounds, single, short exposures may result in little obvious systemic gross pathology. Repeated or prolonged exposures at this level may cause injury to organs or systems other than the respiratory, with the liver and kidneys more commonly involved. If death occurs during or immediately after narcosis, as it may with sufficiently high concentrations of any of these compounds, there may be considerable edema and scattered petechial hemorrhages in the brain, lungs, heart, kidneys, liver, and other organs; but if the animal survives the immediate exposure, death is usually associated with severe degenerative changes of the liver, kidney, or both. It must be emphasized that these "delayed" deaths are much more common after exposure to certain compounds, for example, tetrachloromethane (carbon tetrachloride) and tetrachloroethane. The characteristic liver lesion is an acute yellow atrophy, with the microscopic examination showing congestion, vacuolization, fatty degeneration, and necrosis, most marked in the region of the central veins. The kidneys are congested and exhibit swelling, patchy degeneration and necrosis of the capsular and tubular epithelium.

TABLE 1  
*Toxicity of Halogenated Hydrocarbons*<sup>1</sup>

Compound	Inhalation (mouse), fatal concn., g. mole/l.	Intrav. injec. (dog), M.L.D., <sup>a</sup> mg./kg.	Oral admin. (dog) M.L.D., g./kg.	Subcut. Injec. (rabbit), M.L.D., g./kg.
Dichloromethane	0.00059	200	3.00	2.7
Chloroform	0.00029	90	2.25	0.9
Carbon tetrachloride	0.00044	125	4.00	—
Monochloroethane	0.00271	—	—	—
Dichloroethane	0.00035	175	2.50	1.6
Ethylidene chloride	0.00070	—	—	—
1,1,1-Trichloroethane	0.00049	95	0.75	0.5
1,1,2-Trichloroethane	0.00045	—	—	—
Tetrachloroethane	0.00024	60	0.70	0.5
Pentachloroethane	0.00017	100	1.75	0.7
Hexachloroethane	—	325	—	—
Dichloroethylene	—	225	5.75	3.9
Trichloroethylene	0.00032	150	—	1.8
Tetrachloroethylene	0.00024	85	—	2.2

<sup>a</sup>M.L.D. = minimum lethal dose.

With chronic exposures, that is, repeated or prolonged exposures to relatively low concentrations, degenerative effects are much less marked, and reparative processes may occur in areas adjacent to continuing injury. In the liver this repeated phenomenon may result in a cirrhosis, with gradually diminishing function of that organ. The same condition of degeneration and repair may be noted in the kidney, but usually to a lesser extent. Degenerative changes have been

<sup>1</sup>See W. F. von Oettingen, *J. Ind. Hyg. Toxicol.*, 19, 349 (1937).

found, usually of less prominence, in the adrenals, nervous system, and other organs.

### C. ABSORPTION AND EXCRETION IN MAN

The most common, and most important, mode of absorption of the halogenated hydrocarbons in industrial exposures is through the respiratory tract. All of the compounds discussed above are quickly absorbed through the pulmonary epithelium and in the higher concentrations in sufficient quantity to cause rapid systemic effects. In man, studies of the absorption of chloroform through the lungs indicate that at the beginning of the inhalation about 75 per cent of the chloroform is removed and as exposure continues, and equilibrium between the chloroform in the alveolar air and in the blood is approached, diminishing amounts of solvent are absorbed. With other members of the chlorinated hydrocarbon series, from 50 to 75 per cent disappears from the inhaled air at the beginning of exposure.\*

Absorption from the gastrointestinal tract is of lesser industrial importance, although appreciable absorption of many of these compounds has been demonstrated. The small intestine, colon, and stomach, respectively, in order of decreasing importance, are the sites of absorption.

TABLE 2  
*Narcotic Action of Chlorinated Hydrocarbons (Quoted from Lazarew)<sup>1</sup>*

Compound	Fatal concn., mole/l.	Rank <sup>a</sup>
Dichloromethane	0.00041	10
Chloroform	0.00017	4
Carbon tetrachloride	0.00032	7
Monochloroethane	0.00217	11
Dichloroethane	0.00021	6
Ethylidene chloride	0.00033	8
1,1,1-Trichloroethane	0.00034	9
1,1,2-Trichloroethane	0.00011	2
Tetrachloroethane	0.00007	1
Pentachloroethane	0.00012	3
Trichloroethylene	0.00019	5

\* According to decreasing narcotic action.

The permeability of the skin to certain of the halogenated hydrocarbons is much greater than has been generally recognized. Several investigators have demonstrated in animals appreciable absorption (sufficient to produce narcosis and death) through the intact skin, after excluding the possibility of inhalation of the solvent. Experiments defining the relationship in man are lacking, but there is good reason to assume that this mode of absorption may have been an important one in a number of instances of intoxication.

\* This represents essentially complete absorption of the vapors reaching alveolar spaces until a significant amount has been absorbed by the blood (see page 179).

The halogenated hydrocarbons are carried by the blood throughout the body; the partition in the blood between the plasma and cells depends in part upon the relative solubility of the compounds in oil and water. For example, with chloro-

TABLE 3  
*Narcotic Action of Chlorinated Hydrocarbons (Quoted from Lehmann, 1911)<sup>1</sup>*

Compound	Relative narcotic efficiency	Relative volatility
Chloroform	2.2	6.3
Carbon tetrachloride	1.0	4.1
Tetrachloroethane	9.1	0.2
Pentachloroethane	6.2	0.17
Dichloroethylene	1.7	5.8
Trichloroethylene	1.7	2.2
Tetrachloroethylene	1.6	1.0

TABLE 4  
*Narcotic Action of Chlorinated Hydrocarbons (Quoted from Müller)<sup>1</sup>*

Compound	Mole per liter	Rank*
Dichloromethane	0.00074	7
Chloroform	0.00022	2
Carbon tetrachloride	0.000325	4
Dichloroethane	0.00034	5
Ethylidene chloride	0.00041	6
Tetrachloroethane	0.000062	1
Dichloroethylene	0.00023	3
Propyl chloride	0.0015	8

\* According to decreasing narcotic action.

TABLE 5  
*Narcotic Action of Chlorinated Hydrocarbons<sup>1</sup>*

Compound	Acute narcotic action (CCl <sub>4</sub> = 1)	Compound	Acute narcotic action (CCl <sub>4</sub> = 1)
Monochloromethane	0.4	Tetrachloroethane	8.3
Dichloromethane	1.7	Pentachloroethane	6.0
Trichloromethane	2.0	<i>cis</i> -Dichloroethylene	1.7
Tetrachloromethane	1.0	<i>trans</i> -Dichloroethylene	0.9
Monochloroethane	0.5	Trichloroethylene	2.2
Dichloroethane	2.0	Tetrachloroethylene	2.5
Trichloroethane	3.3		

form and with ethyl chloride, approximately three fourths of the solvent is bound to the red blood cells, one fourth is in the plasma—a disproportionate amount in the former, based on lipid content only.

There is a variable distribution of the solvents in the various organs and

tissues, depending largely on tissue relationships and whether or not absorption is continuing. In the earlier stages the tissues containing the higher lipid content, the central nervous system and fat deposits, take up a higher proportion of the solvents. Usually, after cessation of absorption, the liver and kidneys are found to contain the materials after they can no longer be demonstrated in other organs.

The halogenated hydrocarbons are excreted chiefly through the lungs, regardless of the mode of absorption, with the rapidity of elimination being dependent upon the concentration and solubility in the blood and the volatility. With the more volatile members, for example ethyl chloride ( $\text{CH}_3\text{CH}_2\text{Cl}$ ) and monochloroethylene ( $\text{CH}_2:\text{CHCl}$ ), the greater part of the solvent is eliminated through the lungs within a few minutes after absorption stops. Methyl chloride ( $\text{CH}_3\text{Cl}$ ), despite its volatility, is apparently much more slowly eliminated, which possibly in part explains its increased toxicity. The other solvents are less rapidly eliminated, with the greater part being lost in the first few hours, and none or only traces remaining in the body 24 hours after absorption has ceased.

Small amounts of the compounds are excreted through the kidneys, with only traces eliminated through the gastrointestinal tract. The amounts that are conjugated, degraded, or otherwise metabolized vary with the specific compound, but are relatively small in any case.

#### D. MODE OF ACTION AND CAUSE OF DEATH

With the higher concentrations of the halogenated hydrocarbons, the chief action is narcotic or anesthetic, with varying degrees of stimulation seen in the preparalytic stage. All of the compounds exhibit some degree of irritation to the mucous membranes of the eyes and respiratory tract, and certain members, for example, dichloroethyl ether and allyl chloride, produce such marked inflammation of the upper respiratory tract and lungs that the irritative syndrome, resulting in pulmonary edema, overshadows the narcotic action. The majority of the compounds, however, produce a narcosis similar to that caused by chloroform or ether, and if death occurs relatively early, from the inhalation of high concentrations, the autopsy may reveal nothing more than the phenomena of death by asphyxia. With death occurring early in the narcosis, reflex stimulation of the vagus nerve, resulting from the irritation of the respiratory tract, and a direct depressant action of the chemical on the heart muscle contribute to a cardiac failure as the cause of death. With somewhat lesser concentrations and more prolonged narcosis, depression of the respiratory control centers occurs and a cessation of breathing usually precedes circulatory arrest.

The secondary effects, which may follow exposures sufficient to cause narcosis, but also may result from the absorption of amounts of material too small to produce appreciable narcotic action, are of greater importance from the industrial viewpoint. These delayed effects are the result of injury to various tissues or organs, and require some hours or even days to demonstrate their severity. Even after exposures that result in deep narcosis, an apparently satis-

factory recovery may occur with the signs of delayed injury developing some hours later. The organs more prominently involved are the liver and the kidneys. The discrepancy between the degree of involvement of these two organs, as for example with carbon tetrachloride intoxication, in the same animal species (including man) and with comparable exposures is a striking and as yet unexplained phenomenon. One organ is, of course, not seriously involved to the complete exclusion of the other, but many instances have been described in which the injury to the liver—or in other cases to the kidney—is much more marked and is the obvious primary cause of death. The compounds act, apparently, as protoplasmic poisons, in the liver producing vacuolization, fatty degeneration, swelling and necrosis of the cells, and in the kidney swelling, degeneration and necrosis, more marked in the tubular cells, but also involving the capsule.

Mention should be made of the action of methyl chloride and methyl bromide, since their behavior is somewhat different from that of the other compounds that produce the "delayed death" effect. The activity of these compounds is apparently related to their relatively greater instability in the animal body. At autopsy, even in animals succumbing to subanesthetic exposures, the chief findings are pulmonary edema and hemorrhages, hyperemia, and hemorrhages of the liver and kidney.

The evidence as to the mechanism of the toxic action of the halogenated hydrocarbons points to the whole molecule, and not the degraded components, as the effective factor. Even with methyl bromide, which is more readily broken down in the animal body, the frequently quoted theory that the toxic effects were due to the degraded methyl alcohol and the bromide ion is untenable. Amounts of methyl alcohol and sodium bromide, many times greater than the molecular equivalent of a fatal dose of methyl bromide, introduced into the animal body fail to produce an either qualitatively or quantitatively similar effect. With the compounds of higher halogen saturation and greater chemical stability, the failure to isolate appreciable amounts of conjugation or decomposition products and the converse fact of recovery of a very high percentage of the unchanged compound from the fatally poisoned animal are further indications of the essential toxic action of the whole molecule.

#### E. PHYSIOLOGICAL RESPONSE IN MAN

*Acute effects.* The effects of the halogenated hydrocarbons on the various animal species, as described above, find a reasonably close parallel in man, especially with respect to exposures to higher concentrations of the solvents. In general, industrial exposures sufficient to cause narcotic effects with loss of consciousness are now relatively uncommon. The problem of greater importance from the industrial viewpoint concerns the repeated action of lower, subnarcotic concentrations.

The symptoms of acute intoxication following exposure to relatively high

concentrations of halogenated hydrocarbons, with the exception of such highly irritating compounds as allyl chloride, follow a common pattern. The variations are chiefly in rapidity of effect, amount of prenarcoctic stimulation (from the local irritant action on the respiratory tract, and from a transient central nervous system irritability) and depth of anesthesia. Immediate mortality is rare, and even with the compounds that cause the higher proportion of fatalities, recovery may take place with little or no evidence of residual effect. Characteristically, inhalation of concentrated vapor produces irritation of the mucous membranes of the eyes and respiratory tract, with sniffing, sneezing, and coughing. This frequently is followed by a feeling of suffocation, with the respiration at first irregular, and later rapid and shallow. A preliminary stage of excitation may occur, followed by loss of reflexes and sensory functions, with final muscle flaccidity and loss of consciousness. If the individual is removed from exposure, an immediate recovery from narcosis may take place rapidly with the more volatile compounds such as methylene chloride (dichloromethane) or ethyl chloride (monochloroethane), or only after many minutes or hours, as with chloroform, carbon tetrachloride, or tetrachloroethane.

In fatal cases, if death does not occur during or immediately following narcosis, the individual may live from 3 to 12 days, ultimately succumbing to the later developing injury to liver and kidneys. The symptoms associated with these delayed effects are usually referable to the gastrointestinal tract—anorexia, nausea, vomiting. Jaundice, indicating liver damage, is a frequent finding. If the kidneys are prominently involved, as with carbon tetrachloride intoxication, headache, hypertension, increased irritability, and convulsions, associated with uremia, may develop.

The compounds that are more likely to cause these delayed deaths following the inhalation of narcotic amounts are also more apt to cause serious or even fatal effects following a single or a few exposures to subnarcotic concentrations. As stated previously, there is little relation between the acute narcotic action and the toxicity as judged by delayed mortality. With this criterion of mortality, following acute exposure, tetrachloroethane, carbon tetrachloride, and methyl chloride are the more toxic of the commonly encountered chlorinated hydrocarbons. With the other members of the series, death may follow protracted narcosis with loss of consciousness, as with trichloroethylene, but rarely has been reported following acute exposures of lesser degree.

*Chronic effects.* The symptoms and signs of chronic intoxication are not pathognomonic—that is, characteristic of the causative factor to the exclusion of other diagnoses. With compounds like trichloroethylene and tetrachloroethane, neurologic involvement may be a prominent factor, with headache, hyperirritability, vertigo, paralysis of varied parts, and optic nerve lesions. The gastrointestinal symptoms are the more common, such as anorexia, nausea, and vomiting. Loss of weight, lack of energy, difficulty in sleeping, and inability to concentrate are frequently present.



Again, as with acute intoxication, certain compounds present greater hazard, both from the viewpoint of seriousness of symptoms and disability, and from mortality. In these respects, tetrachloroethane is the most toxic. Fatalities have occurred following chronic exposures to tetrachloroethane where the warning signs, such as narcotic effect at the time of exposure, or the initial and intermediate symptoms gave no indication of the ultimate severity. The recognition of the marked toxicity of tetrachloroethane has almost banished this otherwise very excellent solvent from industrial usage. Of less, but appreciable, toxicity, in descending order as to health hazard, come the more common compounds of the series: carbon tetrachloride, ethylene dichloride, trichloroethylene, and propylene dichloride. Of the compounds discussed thus far, as to chronic toxicity, hepatic injury is more likely to occur following tetrachloroethane exposures, somewhat less so with carbon tetrachloride, and rarely with trichloroethylene or ethylene dichloride.

It should not be implied, because of the emphasis on liver and kidney injury, that other systems and organs are not involved in intoxication by the halogenated hydrocarbons. Severe degenerative changes of the brain have been reported after acute exposures. Experimental evidence has shown that the heart and circulatory system may be severely injured, apparently by a direct effect on the heart muscle. Various changes in the blood cells and in the cell-forming tissues have been reported, but apparently are not consistent. Gross metabolic disturbances occur: acidosis, depressed metabolic rate, and the derangements that accompany severe liver and kidney injury.

The discussion is not complete without some reference to psychogenic factors in exposure to these compounds, particularly since these are of importance in setting the lower working limits. It is a frequent experience that individuals who have had gastrointestinal symptoms, such as nausea and vomiting following an intoxication by a chlorinated solvent, for example ethylene dichloride, may, even months after the initial incident, have a prompt recurrence of nausea on re-exposure insufficient in degree or duration for the nausea to be of other than psychogenic origin. Other individuals are adversely affected by the sweetish characteristic odor of the solvents, such as trichloroethylene and carbon tetrachloride, and the resulting persistent loss of appetite and nausea may require their removal from exposure.

#### F. DETERMINATION OF THE HALOGENATED HYDROCARBONS<sup>a,b</sup>

The interferometer may be used successfully to determine in the air the majority of those vapors having permissible limits of 100 p.p.m. or greater. The Halide leak detector has some limited semiquantitative application, but the most

<sup>a</sup> See Chapter Eight.

<sup>b</sup> M. B. Jacobs, *The Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

TABLE 6

*Physiological Response to Various Concentrations of Methyl Chloride—Animals<sup>7,8</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Guinea pig	865.7	415,000	—	After 30 sec. loss of equilibrium; after 8 min. dyspnea
	319.2	153,000	10- 20 min.	Similar symptoms and delayed death
	298.4	143,000		
	248.2	119,000		
	198.2	95,000	—	Dizziness after 2 min. and inability to walk; delayed death in 1-4 days
	104.3- 125.2	50,000- 60,000	20- 30 min.	Unsteadiness
125.2	60,000	50 min. 20 min.	Inability to walk Delayed death in some	
Dog	94	46,000	1 hr.	After 12 min. respiratory difficulty; vomiting and ataxia in 15 min.; vertigo in $\frac{3}{4}$ hr.; death within 24 hr.
	75	37,000	1 hr.	Restlessness and salivation in 10 min.; vomiting after 18 min.; respiratory difficulty after 25 min.; recovery
Guinea pig	57.4	27,500	1- 5 min.	Slight dizziness; with 10 min., no deaths
			30 min.	One death
			90 min.	Semiconsciousness; death of all animals 6 hr. after test
	29.8- 36.8	14,300- 16,700	180-205 min.	Death of all animals during exposure
			—	Uneasiness; after 20 min. labored breathing and râles; 265 min., feeble pulse
			30 min. 90 min. 270 min.	No deaths Death of all animals within 2-4 days Death of animals 60 min. after exposure
Dog	36	17,000	1 hr.	Slight symptoms in $\frac{1}{2}$ hr.; recovery
Guinea pig	14.6- 18.8	7,000- 9,000	—	Rapid pulse in 20 min.; inactiveness in 270 min.; tremors in 350 min.
			90 min. 420 min.	Death of 1 animal after 2 days Death of all animals during 100 min. following exposure
Mouse	14	6,777	30- 45 min.	Light narcosis
Guinea pig	10.4- 11.7	5,000- 5,600	—	No marked symptoms except increased rate of respiration after 540 min.
			120-270 min.	Death of all animals within 1-2 days
	6.3	3,000	540 min.	Death of all animals after 2 $\frac{1}{2}$ -15 hr.
			810 min.	No symptoms except increased respiration and tendency toward weakness
	2.5- 3.13	1,200- 1,500	540 min. 815 min.	Death of all after 1-3 days Death of all after 8 hr. to 2 days
			—	No marked symptoms except rapid shallow respiration after 810 min.
		270 min. 540-810 min.	Death of some animals after 2-3 days Death of all animals	
Mouse	2	968	4 hr.	Death

generally applicable methods utilize other halogenated hydrocarbon combustion apparatus.

## II. Specific Compounds

### METHYL CHLORIDE (Chloromethane)

#### 1. Source

Methyl chloride,  $\text{CH}_3\text{Cl}$ , is produced by the action of hydrochloric acid on methyl alcohol in the presence of sulfuric acid.<sup>4</sup>

#### 2. Uses and Industrial Exposures

As a refrigerant; medicine.

#### 3. Pertinent Chemical and Physical Properties

Physical state: colorless gas

Molecular weight: 50.49

Specific gravity: 0.922 at 20° C.<sup>5</sup>

Melting point: -94.4° C.

Boiling point: -24.09° C.

Vapor density: 1.76 (air = 1)

Solubility in water: 1 vol.:2.2 vol.  $\text{CH}_3\text{Cl}$  at room temperature

Solubility in ethyl alcohol (absolute alcohol): 1:35 vol.  $\text{CH}_3\text{Cl}$

Soluble in ethyl ether and chloroform<sup>6</sup>

1 mg./l.  $\approx$  484.1 p.p.m. and 1 p.p.m.  $\approx$  2.086 mg./cu.m. at 25° C., 760 mm.

#### 4. Physiological Response

Acute effects (see Table 6).

Chronic effects (see Table 7).

TABLE 7  
Chronic Poisoning from Methyl Chloride—Animals<sup>6</sup>

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Mouse	30	15,323	15 min. on 2 consecutive days	No apparent effect
Guinea pig	30	15,323	15 min. on 2 consecutive days	Apparent recovery after first day; death within 24 hr. after second exposure
Mouse	6	2,905	51 15-min. exposures within 105 days and 6 1-hr. exposures	Death
Guinea pig	6	2,905	47 15-min. exposures within 112 days with 2 intervals of 10-25 days	Recovery after first 15 exposures; poor recovery after next 12 exposures; death after last 20 exposures
	6	2,905	15-min. exposures 11-15 times within 18 days	Death
	6	2,905	15-min. exposures on 3 consecutive days	Death

<sup>4</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

<sup>5</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

<sup>6</sup> *Handbook of Chemistry and Physics*. 28th ed., Chemical Rubber Pub. Co., Cleveland, 1944.

TABLE 8

*Physiological Response to Various Concentrations of Methyl Bromide—Animals*<sup>1,2</sup>

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Guinea pig	194.5	50,000	—	Uneasiness, rapid depression, struggling, convulsive respiration Death of all animals with both concentrations
	373.4	96,000	7- 15 min.	
Mouse	115	30,000	30- 45 min.	Light narcosis
	95	24,500	25 min.	Death after 75 min.
Rabbit	80-115	20,000- 30,000	25- 30 min.	Death
Guinea pig	85.6- 112.8	22,000- 29,000	7 min.	Coughing, retching
			8- 15 min.	Unsteadiness
			10 min.	Death of all animals 4-5 hr. after exposure
			30 min.	Marked weakness
			35 min.	Death immediately after exposure
Dog	52	13,500	90 min.	Side position in 45 min.; death after 90 min.
Guinea pig	50.6	13,000	—	Increased respiration, inactivity, lachrymation, <sup>1</sup> discharge from nose, weakness and unsteadiness
Dog	35.0	9,000	60 min.	Death 80 min. later
Guinea pig	27.2	7,000	30 min.	Symptoms, similar to those with 13,000 p.p.m., <sup>1</sup> death in 1-2 hr.
			90 min.	Immediate death
	21.0	5,400	10 min.	No symptoms
			20 min.	Death after 6 days
	7.78- 8.9	2,000- 2,300	30 min.	No symptoms; death after 9 hr.
			90 min.	Slight weakening; irritation of mucous membranes; death of majority after 2½ hr. or less
		170 min.	Death	
Dog	3.5	900	?	No deaths
Guinea pig	1.9- 2.3	500- 600	—	No other symptoms than slight salivation and later nasal discharge
			90 min. 270 min.	No deaths Death of all animals
Mouse	1.6	400	24 hr.	Death after 6 hr.
Guinea pig	1.2	300	270 min.	Death of 1 animal
			540 min.	Râles; death in 3 days
			810 min.	Death in 3 days
Mouse	0.8	200	—	Tolerated, narcosis after several hours; recovery
Guinea pig	0.58	150	540 min.	No symptoms; death of majority after 1-3 days
			810 min.	No deaths
	0.39	100	300-600 min.	No symptoms; no deaths

<sup>1</sup>R. R. Sayers, W. P. Yant, B. G. H. Thomas, and L. B. Berger, [response to methyl bromide, methyl chloride, ethyl bromide, and ethyl chloride], *U.S. Pub. Health Bull.* No. 185 (1929).

<sup>2</sup>F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

**5. Suggested Maximum Practical Working Level**

100 p.p.m.

**6. Inflammability**

Inflammable within the range of 8.25 to 18.70 per cent by volume in air (see Chapter Thirteen). Burns with white flame.

**7. Odor and Warning Properties**

Weak, not unpleasant. Does not give adequate warning of its presence in air in concentrations harmful to life.<sup>3</sup>

**METHYL BROMIDE (Bromomethane)****1. Source**

Methyl bromide,  $\text{CH}_3\text{Br}$ , is prepared by the action of bromine on methyl alcohol in the presence of phosphorus, with subsequent distillation.<sup>4</sup>

**2. Uses and Industrial Exposures**

Organic synthesis; fumigant; refrigerant and fire extinguisher.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless gas

Molecular weight: 94.95

Specific gravity: 1.732 at 0°/0° C.

Melting point: -93.66° C.\*

Boiling point: 4.6° C.

Vapor density: 3.26 (air = 1)

Solubility in water: 0.09 g./100 ml. water\*

Soluble in ethyl alcohol, ether, and chloroform

1 mg./l.  $\approx$  257.15 p.p.m. and 1 p.p.m.  $\approx$  3.89 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

Acute effects (see Table 8).

**5. Suggested Maximum Concentration**

50 p.p.m.

**6. Inflammability**

Inflammable within the range of 13.50 to 14.50 per cent by volume in air (see Chapter Thirteen).

**7. Odor and Warning Properties**

Burning taste; chloroformlike odor in higher concentrations, but odorless in lower concentrations, which still may be high enough to be dangerous.<sup>9</sup>

**METHYL IODIDE (Iodomethane)****1. Source**

Methyl iodide,  $\text{CH}_3\text{I}$ , is prepared by the interaction of methyl alcohol, sodium iodide, and sulfuric acid, with subsequent distillation.<sup>4</sup>

\* H. Heimann, *N. Y. State Dept. Labor, Ind. Hyg. Bull.*, **23**, 103 (1944).

**2. Uses and Industrial Exposures**

Medicine; in industry for methylations.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid (turns brown on exposure to light)	Refractive index: 1.5293 at 21.0° C.
Molecular weight: 141.95	Per cent in "saturated" air: 53 at 25° C.
Specific gravity: 2.27899 at 20°/4° C.	Density of "saturated" air: 3.04 (air = 1) at 25° C.
Melting point: -63.8° C.	Solubility in water: 1 vol. in 125 vol. water at 15° C.
Boiling point: 42.4 to 42.6° C.	Miscible with ethyl alcohol and ether <sup>8</sup>
Vapor density: 4.9 (air = 1)	
Vapor pressure: 400 mm. Hg at 25° C. <sup>10</sup>	

1 mg/l.  $\approx$  175.3 p.p.m. and 1 p.p.m.  $\approx$  5.81 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

Acute effects (see Table 9).

TABLE 9  
*Physiological Response to Various Concentrations of Methyl Iodide—Mice*  
(Quoted from Bachem, 1927)<sup>11</sup>

Concentration		Response
mg./l.	p.p.m.	
454.4	78,693	Rapid narcosis; death after 10-min. exposure
105.1	18,109	Death after 30-min. exposure
42.6	7,340	After 15-30 min. side position, no complete narcosis; death 1 hr. after beginning of exposure
21.3-31.2	3,670-5,376	Death after 2-2½-hr. exposure
0.43-4.26	73.4-734	Death of all animals within 24 hr.
0.31	53.8	No marked toxic symptoms

**METHYLENE CHLORIDE (Dichloromethane)****1. Source**

Methylene chloride, CH<sub>2</sub>Cl<sub>2</sub>, is prepared by the chlorination of methyl chloride and subsequent distillation.<sup>4</sup>

**2. Uses and Industrial Exposures**

For degreasing, in cleaning fluid, in paint removers, in artificial silk industry as a "stretching" solvent; extraction of oils, fats, perfumes, flavors and drugs; solvent for alkaloids, bitumens, crude rubber, oils, resins, waxes, and many organic compounds.

<sup>10</sup> D. H. Killeffer, *Ind. Eng. Chem.*, 30, 477, 565 (1938).

<sup>11</sup> W. F. von Oettingen, *J. Ind. Hyg. Toxicol.*, 19, 349 (1937).

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless volatile liquid	Refractive index: 1.4237 at 20° C. <sup>9</sup>
Molecular weight: 84.94	Per cent in "saturated" air: 55 at 25° C.
Specific gravity: 1.336 at 20°/4° C. <sup>12</sup>	Density of "saturated" air: 2.06 (air = 1) at 25° C.
Melting point: -96.0° C.	Solubility in water: 2.0 g./100 g. water
Boiling point: 41.5° C.	Miscible with ethyl alcohol and ethyl ether <sup>9</sup>
Vapor density: 2.92 (air = 1)	
Vapor pressure: 420 (approx.) mm. Hg at 25° C. <sup>12a</sup>	

1 mg./l.  $\approx$  288.2 p.p.m. and 1 p.p.m.  $\approx$  3.48 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (500 p.p.m.): 37.3 ml.

**4. Physiological Response in Animals**

*Acute effects* (see Table 10).

*Chronic effects* (see Table 11).

**5. Effects on Man**

See Table 12.

**6. Suggested Maximum Concentration**

500 p.p.m.<sup>12</sup>

TABLE 10  
*Physiological Response to Various Concentrations of Methylene Chloride—Mice<sup>8</sup>*

Concentration		Response
mg./l.	p.p.m.	
62-63	18,000	Side position in 6-11 min.; a 1½-hr. exposure fatal after ½ hr. to 5 da6s
50	14,500	Side position after 8-15 min.; death after 2-hr. exposure
35	10,000	A 2-hr. exposure necessary to produce deep narcosis
30-35	8,700-10,000	A 2-hr. exposure necessary to cause side position
24	7,000	Failure of a 2-hr. exposure to cause side position
20	5,800	A 6-hr. exposure caused side position after 4½ hr., deep narcosis after hr., recovery after 2-3 hr.

TABLE 11  
*Physiological Response to Various Concentrations of Methylene Chloride—Animals<sup>12</sup>*

Concentration		Duration of exposure	Rat, rabbit	Dog	Guinea pig	Monkey
mg./l.	p.p.m.					
17	5,000	Repeated 7-hr. exposure 5 days a wk. for 6 mo.	Tolerated	Tolerated	Adverse effect on rate of growth	
34	10,000	Repeated 4-hr. exposure 5 days a wk. for 7½ wk.	No microscopic evidence of liver damage	2 out of 4 showed slight to moderate fatty degeneration of the liver after 6 exposures	4 out of 6 developed liver injury	No microscopic evidence of liver damage

<sup>9</sup> L. A. Heppel, P. A. Neal, T. L. Perrin, M. L. Orr, and V. T. Porterfield, *J. Ind. Hyg. Toxicol.*, **26**, 8 (1944).

<sup>12a</sup> S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, **38**, 320 (1946).

TABLE 12  
*Physiological Response to Various Concentrations of Methylene Chloride—Man*<sup>13</sup>

Concentration		Response
mg./l.	p.p.m.	
25	7205	After 8 min. paresthesia of the extremities; after 16 min. acceleration of the pulse to 100; during the first 20 min. congestion in the head, sense of heat, slight irritation of the eyes
8	2305	No feeling of dizziness during 1 hr., but nausea after 30 min.
8	2305	After 5 min. 73 per cent was absorbed
3-4	865-1153	Dizziness after 20 min.
1.1	317	Limit of perception through smell

### CHLOROFORM (Trichloromethane)

#### 1. Source

Chloroform,  $\text{CHCl}_3$ , is produced by the reaction of chlorinated lime with acetone.<sup>14</sup>

#### 2. Uses and Industrial Exposures

Good solvent for fats, resins, rubber alkaloids; anesthetic; insecticide; plastics; dry-cleaning (solvent, spotting agent); analysis; organic synthesis.

#### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid

Molecular weight: 119.39

Specific gravity: 1.4752 at 25°/4° C.

Melting point: -63.5° C.<sup>15</sup>

Boiling point: 61.2° C.

Vapor density: 4.1 (air = 1)

Vapor pressure: 200 mm. Hg at 25° C.

Refractive index: 1.4433 at 25° C.

Per cent in "saturated" air: 26 at 25° C.

Density of "saturated" air: 1.81 (air = 1) at 25° C.

Solubility in water: 4.2 ml./1000 ml. water at 22° C.

Miscible with ethyl alcohol and ether

Volatility: about 1 g./l. air at 20° C.; 2.5 times less volatile than ether<sup>15</sup>

1 mg./l.  $\approx$  204.8 p.p.m. and 1 p.p.m.  $\approx$  4.88 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (300-400 p.p.m.): 28.1-37.4 ml.

#### 4. Physiological Response in Animals

See Tables 13 and 14.

#### 5. Effects on Man

See Table 15.

TABLE 13  
*Physiological Response to Various Concentrations of Chloroform—Animals*<sup>15</sup>

Animal	Concentration		Response
	mg./l.	p.p.m.	
Guinea pig	80-100	16,384-20,480	Fatal limiting concentration
Rabbit	60	12,288	Fatal limiting concentration
Mouse	20-40	4,096-8,192	Fatal limiting concentration
	20	4,096	Deep narcosis in 1/2 hr.; recovery
	15	3,072	Slight narcosis in 1 hr
	12	2,458	No effect in 2 hr.

<sup>15</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1934.



TABLE 14

*Toxic Effects in Guinea Pigs from Inhalation of Chloroform (Quoted from Nuckolls, 1933)*<sup>11</sup>

Concentration		Symptoms
mg./l.	p.p.m.	
97.6-107.4	20,000-22,000	Progressive depression; death of 3 animals after 45-, 60-, and 120-min. exposures
34.26-43.9	7,000-9,000	Primary irritation, progressive depression, and slow recovery after 2-hr. exposure
<i>In the Presence of a Burning Gas Flame</i>		
107.4	22,000	Severe irritation; death of 3 animals after 5-, 18-, and 30-min. exposures
43.9	9,000	Severe irritation; no fatalities after 30-min. exposure

TABLE 15

*Physiological Response to Various Concentrations of Chloroform—Man*<sup>12</sup>

Concentration		Response
mg./l.	p.p.m.	
70-80	14,336-16,384	Narcotic limiting concentration
20	4096	Vomiting, sensation of fainting
7.2	1475	Dizziness and salivation after a few minutes
5	1024	Dizziness, intracranial pressure and nausea after 7 min.
5	1024	Definite aftereffects; fatigue and headache still felt hours later
1.9	389	Endured for 30 min. without complaint
1-1.5	205-307	Lowest amount that can be detected by smell

**6. Suggested Maximum Practical Working Level**

300-400 p.p.m.

**7. Odor**

Ethereal odor, sweet taste.

**BROMOFORM (Tribromomethane)****1. Source**

Bromoform,  $\text{CHBr}_3$ , is prepared by heating acetone or ethyl alcohol with bromine and alkali hydroxide, and recovery by distillation.<sup>14</sup>

**2. Uses and Industrial Exposures**

Medicine, intermediate in organic synthesis, geological assaying.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 252.77

Specific gravity: 2.8779 at 25°/4° C.

Melting point: 7.7° C.

Boiling point: 149.3 to 149.55° C.

Vapor density: 8.7 (air = 1)

Refractive index: 1.5980 at 19° C.

Solubility in water: 3.19 g./l. water at 30° C.

Soluble in benzene, petroleum ether, and oils

Miscible with ethyl alcohol, ether, and chloroform

1 mg./l.  $\approx$  96.7 p.p.m. and 1 p.p.m.  $\approx$  10.34 mg./cu.m. at 25° C., 760 mm.

<sup>14</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

**4. Physiological Response**

See Table 16.

**TABLE 16. Physiological Response to Vapors of Bromoform—Dogs<sup>14</sup>**

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
580	29,000	1 hr.	Deep narcosis in 8 min.; death after 1 hr.
		0.5 hr.	Deep narcosis; recovery on next day
		1 hr.	Repeated in 5 days caused deep narcosis in 20 min., which persisted until death, on sixth day

**5. Permissible Concentration**

There are not sufficient available data to warrant the choice of a permissible concentration.

**6. Odor**

Chloroformlike odor, sweet taste.

**IODOFORM (Tri-iodomethane)****1. Source**

Iodoform,  $\text{CHI}_3$ , may be prepared either by heating acetone or methyl alcohol with iodine in the presence of an alkali or alkaline carbonate or electrolytically by passing a current through a solution containing potassium iodide, alcohol, and sodium carbonate.<sup>14</sup>

**2. Uses and Industrial Exposures**

Medicine.

**3. Pertinent Chemical and Physical Properties**

Physical state: yellow hexagonal crystals or powder

Molecular weight: 393.78

Specific gravity: 4.08<sup>14</sup>

Melting point: 121° C.

Boiling point: sublimes; explodes at 210° C.<sup>15</sup>

Vapor density: 13.6 (air = 1)

Refractive index: 1.800<sup>15</sup>

Solubility in water: 0.01 part/100 parts water at 25° C.<sup>17</sup>

Solubility in ethyl alcohol: 1 g./66 ml. ethyl alcohol at 25° C.

Solubility in ethyl ether: 1 part/5.4 parts cold ether

Solubility in chloroform: 1 g./10 ml. chloroform at 25° C.

1 mg./l.  $\approx$  62.1 p.p.m. and 1 p.p.m.  $\approx$  16.1 mg./cu.m. at 25° C., 760 mm.

**4. Odor**

Penetrating, characteristic.

<sup>14</sup> *Handbook of Chemistry and Physics*. 28th ed., Chemical Rubber Pub. Co., Cleveland, 1944.

<sup>15</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

<sup>17</sup> W. F. von Oettingen, *J. Ind. Hyg. Toxicol.*, 19, 349 (1937).

TABLE 17  
*Physiological Response to Various Concentrations of Carbon Tetrachloride—Animals*<sup>17</sup>

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Rabbit	445	71,255	25 min.	Light narcosis
	240	38,160	1 hr. 25 min.	Light narcosis
	152	24,168	2 hr. 10 min.	Light narcosis
Guinea pig	125.8–	20,000–	5 min.	Semiconsciousness, tremors, slow recovery
	144.7	23,000	30 min.	All animals unconscious after 25 min., twitchings, slow respiration; slow recovery
			60 min.	Unconscious, respiration barely perceptible, 2 of 3 animals died after 10 min.
			120 min.	Death of all animals
Rabbit	110	17,490	3 hr.	Light narcosis
	90	14,310	4 <sup>3</sup> / <sub>4</sub> hr.	Light narcosis
	77	12,243	6 <sup>1</sup> / <sub>2</sub> –8 hr.	Depression after 30 min. and light narcosis after 6 <sup>3</sup> / <sub>4</sub> hr.
Guinea pig	69.2	11,000	5 min.	Distinct irritation, respiratory difficulties
			30 min.	Progressive inco-ordination, labored respiration, spasmodic twitchings
			60 min.	Depression, labored breathing, slow recovery
		120 min.	Respiratory distress, slow recovery	
Rabbit	60	9,540	6 <sup>1</sup> / <sub>2</sub> –8 hr.	Closing of eyes, salivation, convulsive movements and trembling
Guinea pig	44–	7,000–	5 min.	Moderate irritation
	56.6	9,000	30 min.	Spasmodic twitchings of legs; slow recovery
			60 min.	Semiconsciousness, labored breathing; slow recovery
		120 min.	Spasmodic tremors of whole body; slow recovery	
Rabbit	40	6,360	6 <sup>1</sup> / <sub>2</sub> –8 hr.	Same symptoms, as with 60 mg./l.; somewhat less pronounced
	20	3,180	6 <sup>1</sup> / <sub>2</sub> –8 hr.	Slightly narcotic
	5–10	1,295– 1,590	6 <sup>1</sup> / <sub>2</sub> –8 hr.	Lack of appetite, otherwise little effect
<i>In Presence of an Open Gas Flame</i>				
Guinea pigs	132.1	21,000		All animals died within 30 min. from pulmonary edema
	50.3	8,000		All animals died within 30 min.

TABLE 18. *Toxicity of Carbon Tetrachloride with Repeated and Prolonged Exposure*<sup>17</sup>

Animal	Concentration		Daily exposure, hr.	Repetition, days	Symptoms
	mg./l.	p.p.m.			
Rabbits	8–10	1,272–1,590	8	0	Normal first day but died subsequently from bronchitis and pneumonia
2 cats	5–10	795–1590	8	14	No pathological symptoms
1 cat	5–10	795–1590	8	27	No pathological symptoms
1 cat	4.9	779	8	0	Death after 12 hr.
1 cat	4.9	779	8	10	Loss of appetite and weight; death

**CARBON TETRACHLORIDE (Tetrachloromethane)****1. Source**

Carbon tetrachloride,  $\text{CCl}_4$ , may be prepared by the interaction of carbon bisulfide and chlorine in the presence of a catalyst.<sup>14</sup>

**2. Uses and Industrial Exposures**

One of the most important solvents of the chlorinated hydrocarbon group; degreasing agent, cleaning agent, fire-extinguishing agent; metal cleaning and polishing; lacquers; rubberizing fabrics.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless, noninflammable liquid	Per cent in "saturated" air: 15 at 25° C.
Molecular weight: 153.84	Density of "saturated" air: 1.64 (air = 1) at 25° C.
Specific gravity: 1.58472 at 25°/4° C.	Solubility in water: 0.080 g./100 g. water at 20° C.
Melting point: -22 to -22.6° C.	Miscible with alcohol, ether, chloroform, benzene, and most of the fixed and volatile oils
Boiling point: 76.71 to 76.75° C.	
Vapor density: 5.3 (air = 1)	
Vapor pressure: 114 mm. Hg at 25° C.	
Refractive index: 1.45732 at 25° C.	

1 mg./l.  $\approx$  159 p.p.m. and 1 p.p.m.  $\approx$  6.29 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (50-100 p.p.m.): 5.56-11.1 ml.

**4. Physiological Response in Animals**

See Tables 17 and 18.

**5. Effects on Man**

See Table 19.

TABLE 19

*Physiological Response to Various Concentrations of Carbon Tetrachloride—Man*<sup>17</sup>

Concentration		Response
mg./l.	p.p.m.	
400-500	64,000-80,000	Exposure for 1/2-1 hr., immediately or later fatal <sup>a</sup>
150-200	24,000-32,000	Exposure for 1/2-1 hr., dangerous to life <sup>a</sup>
60- 80	10,000-13,000	Exposure for 1/2-1 hr., without immediate or later consequence <sup>a</sup>
10	1,600	Effective with exposure for several hours <sup>a</sup>
320	50,000	Exposure for 5-10 min. fatal <sup>b</sup>
160	25,000	Exposure for 1/2-1 hr. dangerous <sup>b</sup>
60	10,000	Exposure for 1/2-1 hr. tolerated <sup>b</sup>
	>100 p.p.m.	Constant exposure dangerous <sup>c</sup>

<sup>a</sup> Quoted from Lehmann-Hess.

<sup>b</sup> Quoted from Flury.

<sup>c</sup> Quoted from Davis.

**6. Maximum Allowable Concentration**

50-100 p.p.m. The widely accepted value for the maximum allowable concentration is 100 p.p.m. However, recent data from both human and animal

experiment sources show evidence of minor toxic effects at exposures between 50 and 100 p.p.m. While no clearly demonstrable, irreversible or permanent injury has been shown associated with exposures less than 100 p.p.m., it would seem desirable to keep the permissible concentration at the lower figure until further investigation has indicated the proper value.

### 7. *Odor and Warning Properties*

Ethereal sweetish odor may be considered a warning property to the extent that atmospheric concentrations readily detected by odor are too high for prolonged daily exposure.

## CARBON TETRABROMIDE (Tetrabromomethane)

### 1. *Uses and Industrial Exposures*

To date carbon tetrabromide,  $\text{CBr}_4$ , has not been of industrial importance and exposures of men have not been reported.

### 2. *Pertinent Chemical and Physical Properties*

Physical state: monoclinic crystals	Vapor density: 11.44 (air = 1)
Molecular weight: 331.67	Refractive index: 1.59998 at 99.5° C. <sup>26</sup>
Specific gravity: 3.42 <sup>27</sup>	Insoluble in water
Melting point: $\alpha$ 48.4 C., $\beta$ 90.1 C. <sup>27</sup>	Soluble in ethyl alcohol, ether, and chloroform
Boiling point: 189.5° C.	

1 mg./l.  $\approx$  73.7 p.p.m. and 1 p.p.m.  $\approx$  13.56 mg./cu.m. at 25° C., 760 mm.

## MONOFLUOROTRICHLOROMETHANE (Trichlorofluoromethane)

### 1. *Uses and Industrial Exposures*

Monofluorotrichloromethane,  $\text{CCl}_3\text{F}$ , is the refrigerant known as Freon 11.

### 2. *Pertinent Chemical and Physical Properties*

Physical state: nonflammable, colorless gas at 25° C.	Boiling point: 24.9° C.
Molecular weight: 137.38	Vapor density: 4.7 (air = 1)
Specific gravity: 1.4944 at 17.2° C.	Refractive index: 1.3865 at 18.5° C.
Melting point: -111° C. <sup>28</sup>	Insoluble in water
	Soluble in ethyl alcohol and ether <sup>28</sup>

1 mg./l.  $\approx$  178 p.p.m. and 1 p.p.m.  $\approx$  5.61 mg./cu.m. at 25° C., 760 mm.

### 3. *Permissible Limits*

None have been established. Economic factors have kept exposures well below physiological limits. Possible decomposition products should be considered.

### 4. *Odor and Warning Properties*

Odorless at concentrations of less than 20 per cent by volume in air. At concentrations higher than 20 per cent by volume the odor is very mild and somewhat ethereal, similar to carbon tetrachloride. In all concentrations it is nonirritating to eyes, nose, throat, lungs, and skin. It must be kept in mind that all halogenated compounds may form toxic, irritant, and corrosive gases when in contact with a free flame or red-hot surfaces.

**DICHLORODIFLUOROMETHANE****1. Uses and Industrial Exposures**

Dichlorodifluoromethane,  $\text{CCl}_2\text{F}_2$ , is the refrigerant known as Freon 12.

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless nonflammable gas      Vapor density: 4.1 (air = 1)  
 Molecular weight: 120.92      Insoluble in water  
 Melting point:  $-160^\circ \text{C.}^{18}$       Soluble in ethyl alcohol and ether<sup>18</sup>  
 Boiling point:  $-28^\circ \text{C.}^{18}$

1 mg./l.  $\approx$  202.4 p.p.m. and 1 p.p.m.  $\approx$  4.94 mg./cu.m. at  $25^\circ \text{C.}$ , 760 mm.

**3. Physiological Response**

See Table 20.

TABLE 20

*Physiological Response to Various Concentrations of Dichlorodifluoromethane—Animals<sup>18, 19</sup>*

Animal	Concentration		Response
	mg./l.	p.p.m.	
Cat	3458	700,000	Necessary to produce tremors
Guinea pig	1408-1502	285,000-304,000	Nervousness, tremors and retching movements after 2 hr.
	988	200,000	No toxic effects up to 2-hr. exposure

**ETHYL CHLORIDE (Chloroethane)****1. Source**

Ethyl chloride,  $\text{C}_2\text{H}_5\text{Cl}$ , is a by-product in the manufacture of chloral. It can also be prepared by passing hydrogen chloride into a solution of zinc chloride and ethyl alcohol.<sup>20</sup>

**2. Uses and Industrial Exposures**

Local anesthetic; refrigerant; solvent and intermediate in the manufacture of other organic compounds.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless gas      Boiling point:  $13.1^\circ \text{C.}$   
 Molecular weight: 64.52      Vapor density: 2.23 (air = 1)  
 Specific gravity: 0.91708 at  $6^\circ/6^\circ \text{C.}$       Very slightly soluble in water  
 Melting point:  $-141.6^\circ \text{C.}$       Soluble in ethyl alcohol and ether

1 mg./l.  $\approx$  378.9 p.p.m. and 1 p.p.m.  $\approx$  2.64 mg./cu.m. at  $25^\circ$  760 mm.

**4. Physiological Response in Animals**

See Tables 21 and 22.

<sup>18</sup> M. B. Jacobs, *The Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

<sup>19</sup> C. Brenner, *J. Pharmacol.*, 59, 176 (1937).

<sup>20</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

TABLE 21

*Physiological Response to Various Concentrations of Ethyl Chloride—Guinea Pigs*<sup>21</sup>

Concentration		Response
mg./l.	p.p.m.	
612.5- 626.2	232,000- 241,000	In 30 sec. to 1 min. caused complete loss of equilibrium, side position running movements and scratching. Animals were completely unconscious after 5-min. and died after 8-min. exposure
403.9 374.9 335.3	153,000 142,000 127,000	After 1 min. caused complete loss of equilibrium, side position, running movements and scratching. After 15-20 min. depression set in and the respiration became shallow
403.9 335.3	153,000 127,000	The animals died after 30-40 min. exposure Animals died after 65-90 min. exposure
240.2 229.7 221.8 211.2 200.6	91,000 87,000 84,000 80,000 76,000	In 2 min. slight unsteadiness, running movements, and struggling. After 25-30 min. beginning depression. After exposure for 130 min. there was shaking in one, and after 270 min. several guinea pigs showed râles over the lungs but were not completely relaxed
240.2 229.7 221.8	91,000 87,000 84,000	One out of six animals died after 30-min. exposure All animals died within less than 1 day when exposed for 270 min. None of the animals died after exposure for 10 min.
211.2 200.6	80,000 76,000	All animals died several days after an exposure for 90 min.
134.6	51,000	One animal died 2 days after 40 min. exposure.
134.6 105.6	51,000 40,000	After 3 min. slightly unsteady; 22 min. moderately unsteady; 40 min. very unsteady. Respiration first became labored and later rapid and shallow
105.6	40,000	None died with exposure for 90, 122, and 270 min. Some died subsequently on exposure for 540 min.
52.8	20,000	No other symptoms than slight unsteadiness. No exposure up to 540 min. was fatal
26.4	10,000	No distinct symptoms up to 810-min. exposure

TABLE 22

*Toxicity of Ethyl Chloride*<sup>17</sup>

Minimum fatal dose		Maximum tolerated dose	
mg./l.	p.p.m.	mg./l.	p.p.m.
150-200 (narcotic dose).....	56,835-75,780	140.....	53,046

**5. Effects on Man**

See Table 23.

<sup>21</sup> R. R. Sayers, W. P. Yant, B. H. Thomas, and L. B. Berger, [response to methyl bromide, methyl chloride, ethyl bromide, and ethyl chloride], *U.S. Pub. Health Bull. No. 186* (1929).

TABLE 23  
Narcotic Concentrations in Man<sup>22</sup>

Concentration		Effects
mg./l.	p.p.m.	
105.6	40,000	After two inhalations stupor, irritation of the eyes, stomach cramps
88.7	33,600	After 30 sec. quickly increasing toxic effect
66	25,000	Lack of co-ordination
52.8	20,000	After four inhalations dizziness and slight abdominal cramps
50.4	19,000	Weak analgesia after 12 min.
34.3	13,000	Slight symptoms of poisoning

**6. Suggested Maximum Practical Working Level**

5000 p.p.m.

**7. Inflammability**

Inflammable within the range of 4.00 to 14.80 per cent by volume in air (see Chapter Thirteen).

**8. Odor**

Ethereal odor, burning sweet taste.

**ETHYL BROMIDE (Bromoethane)**

**1. Source**

Ethyl bromide,  $C_2H_5Br$ , is prepared by adding red phosphorus to absolute ethyl alcohol, then adding bromine slowly to the mixture, which is then distilled.<sup>20</sup>

**2. Uses and Industrial Exposures**

Organic synthesis; medicine (anesthetic); refrigerant.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Refractive index: 1.42405 at 20° C.
Molecular weight: 108.98	Per cent in "saturated" air: 62 at 25° C.
Specific gravity: 1.4505 at 25°/4° C.	Density of "saturated" air: 2.7 (air = 1) at 25° C.
Melting point: -115.5° C.	Solubility in water: 0.914 g. /100 g. water at 20° C.
Boiling point: 38.3 to 38.4° C.	Soluble in ethyl alcohol and ether
Vapor density: 3.76 (air = 1)	
Vapor pressure: 470 (approx.) mm. Hg at 25° C. <sup>23a</sup>	

1 mg./l.  $\approx$  224.3 p.p.m. and 1 p.p.m.  $\approx$  4.46 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

See Tables 24 and 25.

**5. Suggested Maximum Practical Working Level**

500 p.p.m.

<sup>22</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1934.

<sup>23</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.



TABLE 24  
*Physiological Response to Various Concentrations of Ethyl Bromide—Animals<sup>21,22</sup>*

Animal	Concentration		Duration of exposure	Response		
	mg./l.	p.p.m.				
Guinea pig	802.8	180,000	30 sec.-1 min.	Unable to stand; struggling and scratching; convulsive respiration; semiconscious with occasional convulsions; became unconscious without relaxation		
	624.4	140,000				
	588.7	132,000				
	446.0	100,000				
	802.8	180,000				
Guinea pig	446	100,000	16 min.	Fatal		
			19 min.	Fatal		
			28 min.	Fatal		
			89 min.	Fatal		
Rat	280	63,000	30 min.	Narcosis after 15 min.; fatal after 40 min.		
Mouse	240	60,500	5 min.	Narcosis in 1 min.; fatal		
Guinea pig	223-	50,000-	5-10 min.	Unsteadiness followed by inability to stand		
	267.6	60,000				
Guinea pig	223	50,000	95 min.	Quiet; convulsive respiration		
			Rabbit	200	45,000	1 hr.
Mouse	130	29,000	30 min.	Side position 3-10 min.; some recovered, some died 2 days later		
Rat	120	27,000	30 min.	Narcosis after 10 min.; fatal in 3-12 hr.		
Rabbit	120	27,000	90 min.+1 hr.	Incomplete narcosis; fatal after 1 day		
Guinea pig	97.04	24,000	3-7 min.	Unsteadiness, dizziness		
			10 min.	No deaths		
			13 min.	Side position		
			19 min.	Very weak		
			30 min.	3 out of 4 died in course of 3 days		
			270 min.	Fatal within 18 hr.		
Mouse	94	21,000	30 min.	Side position in 21-25 min.; recovered		
			90 min.	Fatal after 1 day		
Rat	80	18,000	60 min.	No narcosis; fatal after 1 day		
Rabbit	80	18,000	60 min.	No narcosis; fatal after 1 day		
Mouse	65	14,500	75 min.	Side position; fatal 3 days after exposure		
Guinea pig	53.5	12,000	90 min.	No symptoms		
			270 min.	Became weak		
			55 min.	No deaths		
			90 min.	1 died 3 days later		
			270 min.	All died within 18 hr. after exposure		
Guinea pig	45.5	10,200	30 min.	1 died		
			Rabbit	40	9,000	1 hr.
Guinea pig	29-	6,500-	270 min.	All died within 3 days		
			29.9	6,700	480 min.	1 animal died
			540 min.	Weakness; all died within 12 hr.		
			630-810 min.	All died during exposure		
Mouse	15	3,350	5 hr.	Death 10-hr. after exposure		
Guinea pig	14.3	3,200	270-540 min.	No symptoms		
			540 min.	All died within 1-5 days		
Mouse	13	2,900	5 hr.	Survived		

TABLE 25  
*Toxicity of Ethyl Bromide*<sup>24</sup>

Minimum lethal dose		Maximum tolerated dose	
mg./l.	p.p.m.	mg./l.	p.p.m.
15.2.....	3509	13.1.....	2938

### 6. *Inflammability*

Inflammable within the range of 6.70 to 11.30 per cent by volume in air (see Chapter Thirteen).

### 7. *Odor*

Ethereal.

## ETHYL IODIDE (Iodoethane)

### 1. *Source*

Ethyl iodide,  $C_2H_5I$ , can be produced by digesting red phosphorus with absolute ethyl alcohol, after which iodine is added. The mixture is heated under a reflux condenser and finally distilled.

### 2. *Uses and Industrial Exposures*

Anesthetic; organic synthesis.

### 3. *Pertinent Chemical and Physical Properties*

Physical state: colorless liquid  
 Molecular weight: 155.98  
 Specific gravity: 1.9292 at 20°/4° C.  
 Melting point: -110.6° C.  
 Boiling point: 72.3° C.  
 Vapor density: 5.4 (air = 1)  
 Vapor pressure: 130 (approx.) mm. Hg at 25° C.<sup>24</sup>

Refractive index: 1.5076 at 25° C.  
 Per cent in "saturated" air: 17.0 at 25° C.  
 Density of "saturated" air: 1.9 (air = 1) at 25° C.  
 Solubility in water: 0.391 g./100 g. water at 22.5° C.  
 Soluble in ethyl alcohol and ether; miscible with chloroform, benzene, methyl alcohol

1 mg./l.  $\approx$  156.7 p.p.m. and 1 p.p.m.  $\approx$  6.38 mg./cu.m. at 25° C., 760 mm.

### 4. *Physiological Response*

See Tables 26 and 27.

### 5. *Permissible Limit*

No limit has been proposed.

### 6. *Odor and Warning Properties*

Ethereal odor, inadequate warning properties.

<sup>24</sup> W. F. von Oettingen, *J. Ind. Hyg. Toxicol.*, 19, 349 (1937).

TABLE 26  
*Physiological Response to Various Concentrations of Ethyl Iodide—Mice*<sup>23</sup>

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
1.87	290	3 hr.	Fatal
0.94	150	24 hr.	Fatal
0.75	120	?	Tolerated

TABLE 27  
*Toxicity of Ethyl Iodide*<sup>24</sup>

Minimum lethal dose		Maximum tolerated dose	
mg./l.	p.p.m.	mg./l.	p.p.m.
0.9	141	0.74	115.7

## ETHYLENE DICHLORIDE (Ethylene Chloride; 1,2-Dichloroethane)

### 1. Source

Ethylene dichloride,  $\text{CH}_2\text{ClCH}_2\text{Cl}$ , is prepared by the action of chlorine on ethylene with subsequent distillation.<sup>20</sup>

### 2. Uses and Industrial Exposures

Solvent for fats, resins, rubber; solvent mixtures for cellulose esters and ethers; fumigants; dry-cleaning solvent mixtures; paint, varnish and finish removers; wetting agents; organic synthesis.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid  
 Molecular weight: 96.97  
 Specific gravity: 1.2529 at 20°/4° C.  
 Melting point: -36° C.  
 Boiling point: 83.5 to 84.1° C.  
 Vapor density: 3.34 (air = 1)  
 Vapor pressure: 78 (approx.) mm. Hg at 25° C.<sup>19a</sup>  
 Refractive index: 1.4451 at 20° C.

Per cent in "saturated" air: 10.3 at 25° C.  
 Density of "saturated" air: 1.2 (air = 1) at 25° C.  
 Solubility in water: 0.865 g./100 g. water at 25° C.  
 Soluble in ethyl alcohol and ether; miscible with benzene, toluene, and acetone  
 Volatility: 4.1 times less volatile than ether<sup>22</sup>

1 mg./l.  $\approx$  252 p.p.m. and 1 p.p.m.  $\approx$  3.97 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (100 p.p.m.): 9.1 ml.

### 4. Physiological Response

See Tables 28 and 29.

TABLE 28  
*Physiological Response to Various Concentrations of Ethylene Dichloride—Animals<sup>24,25</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Guinea pig	238.2	60,000	30 min.	Irritation of the eyes, vertigo, static and motor ataxia, twitching movements, semiconsciousness and death
			5 min.	No serious pathologic changes
Mouse	114	28,728	15 min.	Side position after 4 min.; dying, killed next day
Guinea pig	67.5	17,000	10 min.	No serious pathologic changes
Mouse	57	13,364	36 min.	Death during exposure
Guinea pig	39.7	10,000	15-20 min.	Irritation of the eyes, vertigo, static and motor ataxia, twitching movements
Mouse	23	5,796	54 min.	Side position after 40 min.; fatal after 1 day
			70 min.	Side position after 28 min.; death during exposure
Guinea pig	15.9	4,000	30 min.	No serious pathologic changes
Mouse	11.5	2,898		Death after 1 day
Guinea pig	7.9	2,000	120 min.	No serious pathologic changes
	4.8	1,200	8 hr.	No apparent symptoms. No deaths
	4.4	1,100	480 min.	No serious pathologic changes

TABLE 29  
*Summary of Pathologic Changes in Exposures to Various Concentrations of Ethylene Dichloride—Guinea Pigs<sup>24</sup>*

Concentration	Response
397-794	Fatal in a few minutes
15.9-23.8	Dangerous to life in 30 to 60 min.
13.8	Maximum concentration tolerated for 60 min. without serious disturbances
3.97	Maximum concentration producing but slight symptoms or no disturbance after several hours

##### 5. Maximum Allowable Concentration

100 p.p.m.

##### 6. Inflammability

Flash point: 56° F.

Inflammable within the range of 6.20 to 15.90 per cent by volume in air (see Chapter Thirteen).

<sup>24</sup> R. R. Sayers, W. P. Yant, C. P. Waite, and F. A. Patty, *U.S. Pub. Health Repts.* 45, 225 (1930).

**7. Odor and Warning Properties**

Chloroformlike odor, slightly irritating to the eyes and nose at 1000 p.p.m. but no irritation and little odor at 100 p.p.m.

**ETHYLENE DIBROMIDE (Ethylene Bromide; 1,2-Dibromoethane)****1. Source**

Ethylene dibromide,  $\text{CH}_2\text{BrCH}_2\text{Br}$ , is prepared by the action of bromine on ethylene gas.<sup>20</sup>

**2. Uses and Industrial Exposures**

Medicine; solvent for fats, oils, waxes, gums, resins, celluloid; ethyl gasoline; lubricating gasolines; waterproofing preparations; organic synthesis.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 187.88

Specific gravity: 2.1620 at 25°/4° C.

Melting point: 9.5° C.

Boiling point: 131.3° C.

Vapor density: 6.5 (air = 1)

Vapor pressure: 11.5 (approx.) mm. Hg at 25° C.<sup>21</sup>

Refractive index: 1.5380 at 20° C.

Percent in "saturated" air: 1.5 at 25° C.

Density of "saturated" air: 1.1 (air = 1) at 25° C.

Solubility in water: 1 part/250 parts water

Soluble in ethyl alcohol and miscible with ether, toluene, chloroform, benzene, and carbon tetrachloride

1 mg./l.  $\approx$  131.6 p.p.m. and 1 p.p.m.  $\approx$  7.61 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

*Acute effects* (see Table 30).

*Chronic effects* (see Table 31).

TABLE 30  
*Physiological Response to Various Concentrations of Ethylene Bromide—Animals.*  
*Acute Poisoning*<sup>23</sup>

Animal	Concentration		Response
	mg./l.	p.p.m.	
Mouse	66	8600	50-min. exposure: fatal in 1-2 days
Guinea pig	66	8600	50-min. exposure; fatal in 1-2 days. Tolerated a 10-min. exposure
Dog	44	5700	Salivation, respiratory difficulty, vomiting; fatal after 12 hr.
Cat	25	3300	Fatal after 3 <sup>3</sup> / <sub>4</sub> hr.
Dog	22	2900	After 1-hr. exposure some respiratory difficulty, turbidity of cornea, loss of weight; fatal after 6 wk.
Cat	4.1	520	Fatal after 12 hr.
	2.1	270	Tolerated a 4-hr. exposure

<sup>23</sup>S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, 38, 320 (1946).

**TABLE 31**  
*Physiological Response to Various Concentrations of Ethylene Bromide—Animals.*  
*Chronic Poisoning<sup>23</sup>*

Animal	Concentration		Response
	mg./l.	p.p.m.	
Guinea pig	21	2700	Tolerated daily 15-min. exposure for 6 days
Cat	1.1-2.3	140-300	Daily 4-hr. exposures fatal in 6 days; no evidence of cumulative effect
Rabbit	0.76	100	0.5-hr. exposures for 7 days—loss of appetite and weight; fatal after 4-22 days
Cat	0.76	100	0.5-hr. exposures for 7 days fatal
Rabbit	0.53	70	4-hr. exposures on alternate days tolerated for 40 days
Cat	0.53	70	4-hr. exposures on alternate days fatal after 14 days
Rabbit	0.38	50	4-hr. exposures on alternate days fatal after 7 days
Cat	0.08-0.25	10-30	Tolerated daily 4-hr. exposures for 3 weeks

### 5. Odor

Sweetish, resembling chloroform.

## ETHYLIDENE CHLORIDE (1,1-Dichloroethane)

### 1. Source

Ethylidene chloride,  $\text{CH}_3\text{CHCl}_2$ , may be produced by the action of phosphorus pentachloride on acetaldehyde.<sup>27</sup>

### 2. Uses and Industrial Exposures

Formerly used as inhalation anesthetic.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid	Refractive index: 1.41655 at 20° C.
Molecular weight: 98.97	Per cent in "saturated" air: 30 at 25° C.
Specific gravity: 1.16010 at 30°/4° C.	Density of "saturated" air: 1.72 (air = 1) at 25° C.
Melting point: -101.5° C.	Solubility in water: 0.56 g./100 g. water at 25° C.
Boiling point: 57.25° C.	Soluble in ethyl alcohol and ether <sup>28</sup>
Vapor density: 3.44 (air = 1)	
Vapor pressure: 230 (approx.) mm. Hg at 25° C. <sup>28</sup>	

1 mg./l.  $\approx$  247.1 p.p.m. and 1 p.p.m.  $\approx$  4.05 mg./cu.m. at 25° C. 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (200 p.p.m.): 19.7 ml.

<sup>27</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

<sup>28</sup> *Handbook of Chemistry and Physics*. 28th ed., Chemical Rubber Pub. Co., Cleveland, 1944.

**4. Physiological Response**

See Table 32.

TABLE 32  
*Narcotic and Toxic Properties of Ethylidene Chloride—Mice*  
*(quoted from Müller, 1925)<sup>24</sup>*

Concentration		Side position after (minutes)	Removal after (minutes)	Death after (days)
mg./l.	p.p.m.			
41	10,127	19	120	2
41	10,127	18	90	5
36.5	9,015	67	120	2
36.5	9,015	41	120	2
32	8,904	82	123	2
22	5,434	—	120	2

**5. Suggested Maximum Practical Working Level**

200 p.p.m.

**6. Odor**

Chloroformlike odor.

**1,1,1-TRICHLOROETHANE ( $\alpha$ -Trichloroethane, Methyl Chloroform)****1. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 133.42

Specific gravity: 1.3249 at 26°/4° C.

Boiling point: 74.1° C.

Vapor density: 4.6 (air = 1)

Vapor pressure: 130 mm. Hg at 25° C.

Refractive index: 1.43765 at 21° C.<sup>25</sup>

Per cent in "saturated" air: 17 at 25° C.

Density of "saturated" air: 1.6 (air = 1)  
at 25° C.Insoluble in water; miscible with ethyl  
alcohol and ether<sup>26</sup>1 mg./l.  $\approx$  183.3 p.p.m. and 1 p.p.m.  $\approx$  5.45 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working concentration (100 p.p.m.): 11.6 ml.

**2. Physiological Response**Narcotic concentrations of 1,1,1-trichloroethane ( $\text{CH}_2\text{CCl}_3$ ) in mice are given in Table 33.

TABLE 33  
*Narcotic Concentrations of 1,1,1-Trichloroethane in Mice<sup>29</sup>*

Concentration		Response
mg./l.	p.p.m.	
65	11,915	Smallest fatal concentration
45	8,249	Complete narcosis

**3. Suggested Maximum Practical Working Level**

100 p.p.m.

**1,1,2-TRICHLOROETHANE ( $\beta$ -Trichloroethane, Vinyl Trichloride)****1. Uses and Industrial Exposures**

Solvent for fats, oils, waxes, resins; organic synthesis.

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Vapor density: 4.6 (air = 1)

Molecular weight: 133.42

Refractive index: 1.4711

Specific gravity: 1.443 at 20°/4° C.

Insoluble in water; miscible with ethyl alcohol and ether<sup>30</sup>

Melting point: -36.7° C.

Boiling point: 113.65° C.

1 mg./l.  $\approx$  183.3 p.p.m. and 1 p.p.m.  $\approx$  5.45 mg./cu.m. at 25° C., 760 mm.**3. Physiological Response**Narcotic concentrations of 1,1,2-trichloroethane ( $\text{CH}_2\text{ClCHCl}_2$ ) in mice are given in Table 34. The response of animals is given in Table 35.

TABLE 34  
Narcotic Concentrations of 1,1,2-Trichloroethane in Mice<sup>30</sup>

Concentration		Response
mg./l.	p.p.m.	
60	10,998	Smallest fatal concentration
15	2,750	Complete narcosis

TABLE 35  
Physiological Response to Various Concentrations of 1,1,2-Trichloroethane—Animals<sup>30</sup>

Concentration		Disturbances to equilibrium after min.	Prostration after min.	Slight narcosis after min.	Deep narcosis after min.
mg./l.	p.p.m.				
81.8	14,800	1	2.5	4	6
50.1	9,100	2	7	10	18
34.5	6,200	6	28	36	37
13.1	2,400	24	50	150	264

**1,1,2,2-TETRACHLOROETHANE (Acetylene Tetrachloride)****1. Source**Tetrachloroethane ( $\text{CHCl}_2\text{CHCl}_2$ ) is prepared by the interaction of acetylene and chlorine, and subsequent distillation.<sup>30</sup>**2. Uses and Industrial Exposures**

Solvent; cleansing and degreasing metals; paint removers, varnishes, lacquers, photographic film; resins and waxes; extraction of oils and fats; organic synthesis.

<sup>30</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.



**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 167.86

Specific gravity: 1.5869 at 25°/4° C.

Melting point: -42.5° C.

Boiling point: 146.30° C.

Vapor density: 5.79 (air = 1)

Vapor pressure: 6 mm. Hg at 25° C.<sup>21</sup>Refractive index: 1.4918 at 25° C.<sup>20</sup>

Per cent in "saturated" air: 0.79 at 25° C.

Density of "saturated" air: 1.04 (air = 1) at 25° C.

Very slightly soluble in water

Miscible with alcohol and ether at 25° C.

1 mg./l.  $\approx$  145.5 p.p.m. and 1 p.p.m.  $\approx$  6.87 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (10 p.p.m.): 12 ml.

**4. Physiological Response in Animals**

See Table 36.

**5. Effects on Man**

See Table 37.

TABLE 36  
*Physiological Response to Various Concentrations of Tetrachloroethane—Animals<sup>22</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Cat	57	8294	30 min.	Light narcosis
			45 min.	Deep narcosis
Mouse	43	6257	20 min.	Side position after 9 min.
			34	4947
Cat	16	2328	2 hr.	Light narcosis
			3 hr.	Deep narcosis
Mouse	14	2037	94 min.	Side position after 16 min.
Cat	9.6	1496.8	3 hr.	Light narcosis
			3 <sup>3</sup> / <sub>4</sub> hr.	Deep narcosis
Mouse	7.5	1091	120 min.	Side position after 20 min.
Cat	5.7	829	4 <sup>1</sup> / <sub>2</sub> hr.	Light narcosis
			5 <sup>1</sup> / <sub>4</sub> hr.	Deep narcosis
Mouse	4.3	626	120 min.	Side position after 80 min.

TABLE 37  
*Physiological Response to Various Concentrations of Tetrachloroethane—Man<sup>23</sup>*

Concentration	Duration of exposure	Response
2.3	3 min.	Dizziness, increasing fatigue
2.3	10 min.	Flexing of the knees
1.8	5 min.	Dizziness and irritation of the mucous membranes
1.0	10 min.	Dizziness
1.0	12 min.	Irritation of the mucous membranes
1.0	20 min.	Fatigue
0.02	—	Smallest concentration perceptible by odor

<sup>20</sup> *The Condensed Chemical Dictionary*, 3rd ed., Reinhold, New York, 1942.<sup>21</sup> M. B. Jacobs, *The Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.<sup>22</sup> W. F. von Oettingen, *J. Ind. Hyg. Toxicology*, 19, 349 (1937).

**6. Maximum Allowable Concentration**

10 p.p.m.

**7. Odor**

Chloroformlike.

**1,1,2,2-TETRABROMOETHANE (Acetylene Tetrabromide)****1. Source**

Tetrabromoethane ( $\text{CHBr}_2\text{CHBr}_2$ ) is prepared by the action of bromine and acetylene.<sup>30</sup>

**2. Uses and Industrial Exposures**

In microscopy; solvent for fats, oils, waxes; separating minerals by density.

**3. Pertinent Chemical and Physical Properties**

Physical state: yellowish liquid

Molecular weight: 345.70

Specific gravity: 2.9536 at 25°/4° C.

Melting point: 0.13° C.

Boiling point: 239–242° C.<sup>30</sup>

Vapor density: 11.92 (air = 1)

Refractive index: 1.637951 at 20° C.

Solubility in water: 0.0651 g./100 g. water at 30° C.<sup>30</sup>Miscible with ethyl alcohol, ether, chloroform<sup>30</sup>

1 mg./l.  $\approx$  70.7 p.p.m. and 1 p.p.m.  $\approx$  14.14 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

See Table 38.

TABLE 38

*Physiological Response to Various Concentrations of Tetrabromoethane—Dogs<sup>37</sup>*

Concentration		Response
mg./l.	p.p.m.	
300	21,000	An exposure for 50 min. caused narcosis after 1/2 hr. Repeated in a day caused death after 24 hr.
36	2,560	Shortness of breath, vomiting, increasing ataxia and finally death after 5 days
18	1,280	
9	640	

**5. Odor**

Similar to camphor and chloroform.

**PENTACHLOROETHANE****1. Source**

Pentachloroethane ( $\text{CHCl}_2\text{CCl}_3$ ) may be prepared by the chlorination of tetrachloroethane, or trichloroethylene, or ethyl chloride.<sup>30</sup>

**2. Uses and Industrial Exposures**

Solvent for vegetable, mineral, and essential oils, gums, resins, cellulose esters; organic synthesis; soil sterilization.

**3. Pertinent Physical and Chemical Properties**

Physical state: colorless liquid	Refractive index: 1.503 at 24° C.
Molecular weight: 202.31	Per cent in "saturated" air: 0.45 at 25° C.
Specific gravity: 1.6712 at 25°/4° C.	Density of "saturated" air: 1.03 (air = 1) at 25° C.
Melting point: -22° C.	Insoluble in water
Boiling point: 161.95° C.	Miscible with ethyl alcohol and acetone
Vapor density: 6.98 (air = 1)	Soluble in ethyl ether
Vapor pressure: 3.4 mm. Hg at 25° C.	

1 mg./l.  $\approx$  120.78 p.p.m. and 1 p.p.m.  $\approx$  8.27 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

*Acute effects.* See Table 39.

TABLE 39

*Physiological Response to Various Concentrations of Pentachloroethane—Animals<sup>28</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Cat	70	8456	47 min.	Light narcosis
			67 min.	Deep narcosis
	60	7248	52 min.	Light narcosis
			70 min.	Deep narcosis
	50	6040	56 min.	Light narcosis
80 min.			Deep narcosis	
40	4832	64 min.	Light narcosis	
		90 min.	Deep narcosis	
Mouse	35	4235		Lowest fatal concentration
Cat	30	3624	70 min.	Light narcosis
			2 hr. and 40 min.	Deep narcosis
Mouse	25	3025		Deep narcosis
Cat	18	2174	3 hr. and 30 min.	Light narcosis
			4 hr.	Deep narcosis
Mouse	7.5	908		Slight narcosis

*Chronic effects.* 1 mg./l. (121 p.p.m.) for 8-9 hours daily for 23 days produced no serious poisoning symptoms in two cats.<sup>29</sup>

**5. Odor**

Chloroformlike.

**HEXACHLOROETHANE (Perchloroethane, Carbon Hexachloride)****1. Source**

Hexachloroethane ( $\text{CCl}_2\text{CCl}_2$ ) is produced by the action of sunlight on chlorine and ethyl and ethylene chlorides.<sup>30</sup>

**2. Uses and Industrial Exposures**

Organic synthesis; retarding agent in fermentation; antiseptic; camphor substitute in celluloid manufacture; rubber accelerator.

**3. Pertinent Chemical and Physical Properties**

Physical state: rhombic crystals  
 Molecular weight: 236.76  
 Specific gravity: 2.019 at 20°/4° C.<sup>24</sup>  
 Melting point: 186.85° C.; sublimes  
 Vapor density: 8.16 (air = 1)  
 Vapor pressure: 1.7 mm. Hg at 40° C.

Per cent in "saturated" air: 0.22 at 40° C.  
 Density of "saturated" air: 1.02 (air = 1)  
 at 40° C.  
 Insoluble in water  
 Very soluble in ethyl alcohol and ether<sup>24</sup>.

1 mg./l.  $\approx$  103.3 p.p.m. and 1 p.p.m.  $\approx$  9.68 mg./cu.m. at 25° C., 760 mm.

**4. Odor**

Camphorlike.

**DICHLOROTETRAFLUOROETHANE (1,2-Dichloro-1,1,2,2-tetrafluoroethane)****1. Source**

Dichlorotetrafluoroethane (CClF<sub>2</sub>CClF<sub>2</sub>) is formed by fluorination of hexachloroethane at high pressure.

**2. Uses and Industrial Exposures**

Refrigerant—"Freon 114."

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless gas  
 Molecular weight: 170.93  
 Boiling point: 3.6° C.  
 Vapor density: 5.9 (air = 1)

Refractive index: 1.3092 at 0° C.<sup>24</sup>  
 Insoluble in water  
 Soluble in ethyl alcohol and ether

1 mg./l.  $\approx$  143.1 p.p.m. and 1 p.p.m.  $\approx$  6.99 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

See Table 40.

TABLE 40

*Physiological Response to Various Concentrations of Dichlorotetrafluoroethane—Guinea Pigs*  
 (Quoted from Nuckolls, 1933)<sup>23</sup>

Concentration		Response
mg./l.	p.p.m.	
279.6-327.8	40,000-47,000	Distinct irritation, irregular respiration, rapid recovery after 2-hr. exposure
139.8-174.7	20,000-25,000	Distinct irritation, increased respiration, rapid recovery after 2-hr. exposure
62.9- 83.9	9,000-12,000	Slight irritation, immediate recovery after 2 hr.-exposure
<i>In the Presence of an Open Gas Flame</i>		
174.7	25,000	Severe irritation, death after 15-min. exposure
69.9	10,000	Severe irritation, death after 15-min. exposure

<sup>23</sup> Dogs exposed 8 hours per day for 21 consecutive days to 14 to 15 per cent by volume dichlorotetrafluoroethane vapor in air experienced tremors and convulsions during the exposure and a temporary shift to the left in the blood picture, but no deaths or gross pathology resulted; 20 per cent by volume proved fatal after a few daily 8-hour exposures.<sup>23</sup>

<sup>24</sup> W. P. Yant, H. H. Schrenk, and F. A. Patty, *U. S. Bur. Mines Repts. Investigations No. 3185* (1932).

<sup>25</sup> *Handbook of Chemistry and Physics*. 28th ed., Chemical Rubber Pub. Co., Cleveland, 1944.

**5. Odor**

Sweet, chloroformlike.

**MONOCHLOROETHYLENE (Vinyl Chloride, Chloroethylene, Chloroethene)****1. Uses and Industrial Exposures**

Monochloroethylene ( $\text{H}_2\text{C}:\text{CHCl}$ ) is used in organic synthesis; plastics manufacture; refrigerant.

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless gas

Vapor density: 2.16 (air = 1)

Molecular weight: 62.50

Slightly soluble in water

Freezing point:  $-159.7^\circ\text{C}$ .

Soluble in ethyl alcohol; very soluble in

Boiling point:  $-13.9^\circ\text{C}$ .

ether

1 mg./l.  $\approx$  391.0 p.p.m. and 1 p.p.m.  $\approx$  2.56 mg./cu.m. at  $25^\circ\text{C}$ ., 760 mm.

Liquid volume which if volatilized and distributed equally would give a concentration in 1000 cu.ft. at  $25^\circ\text{C}$ . equal to the suggested maximum practical working level (500 p.p.m.): 39.4 ml.

**3. Physiological Response**

*Acute effects* (see Tables 41 and 42).

TABLE 41  
*Acute Effects of Exposure to Monochloroethylene—Guinea Pigs<sup>26</sup>*

Concentration		Effects
mg./l.	p.p.m.	
512–1024	200,000–400,000	Kills in a very short time
256	100,000	Dangerous to life in 30 to 60 min.
128	50,000	Marked symptoms in 30 to 60 min.
25.6	10,000	Maximum amount for several hours with but slight or no symptoms
12.8	5,000	Maximum amount for several hours without serious disturbances

TABLE 42  
*Physiological Response to Various Concentrations of Monochloroethylene—Guinea Pigs<sup>26</sup>*

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
1024	400,000	15 sec.	Side position
		10–20 min.	Death
384–640	150,000–250,000	1 min.	Side position
		16–20 min.	Deep narcosis
256	100,000	18–55 min.	Death
		2 min.	Side position
128	50,000	60 min.	Deep narcosis
		120–360 min.	Slow shallow respiration. No deaths
25.6	10,000	50 min.	Deep narcosis
		360 min.	Slow shallow respiration. No deaths
		480 min.	No unsteadiness or other signs of narcosis

<sup>26</sup> F. A. Patty, W. P. Yant, and C. P. Waite, *U.S. Pub. Health Repts.*, 45, 1963 (1930).

**4. Suggested Maximum Practical Working Level**

500 p.p.m.

**5. Inflammability**

Inflammable within the range of 4.00 to 21.70 per cent by volume in air (see Chapter Thirteen).

**6. Odor and Warning Properties**

Weak odor; does not possess adequate warning properties of odor or irritation.

**1,2-DICHLOROETHYLENE (Acetylene Dichloride, 1,2-Dichloroethene)****1. Source**

Dichloroethylene ( $\text{CHCl:CHCl}$ ) is made by the partial chlorination of acetylene.<sup>30</sup>

**2. Uses and Industrial Exposures**

Solvent and extractor for fats and oils; dye extraction; perfumes; lacquers; rubber; organic synthesis.

**3a. Pertinent Chemical and Physical Properties of the "cis" Form**

Physical state: colorless liquid

Molecular weight: 96.95

Specific gravity: 1.2743 at 25°/4° C.

Melting point: -80.5° C.<sup>34</sup>

Boiling point: 60.25° C.

Vapor density: 3.34 (air = 1)

Vapor pressure: 320 mm. Hg at 25° C.

Refractive index: 1.44366 at 24.6° C.

Per cent in "saturated" air: 42 at 25° C.

Density of "saturated" air: 2.0 (air = 1) at 25° C.

Solubility in water: 8 ml. in 1 liter at room temperature

Miscible with ethyl alcohol and ether<sup>34</sup>

1 mg./l.  $\approx$  252.1 p.p.m. and 1 p.p.m.  $\approx$  3.97 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (200 p.p.m.): 17.7 ml.

**3b. Pertinent Chemical and Physical Properties of the "trans" Form**

Physical state: colorless liquid

Molecular weight: 96.95

Specific gravity: 1.2489 at 25°/4° C.

Melting point: -50.0° C.

Boiling point: 48.35° C.

Vapor density: 3.34 (air = 1)

Vapor pressure: 210 mm. Hg at 25° C.<sup>35</sup>

Refractive index: 1.44234 at 20.1° C.

Per cent in "saturated" air: 27.6 at 25° C.

Density of "saturated" air: 1.65 (air = 1) at 25° C.

Solubility in water: 8 ml. in 1 liter at room temperature

Miscible with ethyl alcohol and ether

1 mg./l.  $\approx$  252.1 p.p.m. and 1 p.p.m.  $\approx$  3.97 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (200 p.p.m.): 18.0 ml.

**4. Physiological Response in Animals**

See Table 43.

**5. Effects on Man**

See Table 44.

<sup>30</sup> D. H. Killeffer, *Ind. Eng. Chem.*, 30, 477, 565 (1938).

TABLE 43  
*Physiological Response to Various Concentrations of Dichloroethylene—Animals*<sup>27, 28</sup>

Animal	Concentration		Response
	mg./l.	p.p.m.	
Guinea pig	155	39,000	Death
Mouse	91	23,000	Prostration after 4 min.; death in less than 38 min.
Guinea pig	79.4– 104.3	20,000– 25,000	Deep narcosis and cramps after 2 hr.
Mouse	76	19,000	Death
Cat	72	18,000	Slight narcosis
Mouse	46	11,596	Side position in 16 min.
	39	9,770	Narcosis
	34	8,500	Prostration after 23 min.

TABLE 44  
*Physiological Response to Various Concentrations of trans-Dichloroethylene—Man*<sup>27</sup>

Concentration	Symptoms	
		mg./l.
6.8–8.8	1,700–2,200	In 5 min., dizziness, intracranial pressure, sleepiness
3.3	830	After 30 min. no unpleasant symptoms
1.1	280	Perceptible by odor

#### 6. Maximum Practical Working Level

200 p.p.m.

#### 7. Odor and Warning Properties

Chloroformlike odor, sweetish; inadequate warning.

## TRICHLOROETHYLENE

### 1. Source

Trichloroethylene ( $\text{CHCl}:\text{CCl}_2$ ) may be prepared either from tetrachloroethane by treatment with lime or alkali in the presence of water, followed by steam distillation; or from ethylene by chlorination followed by fractional distillation.<sup>30</sup>

### 2. Uses and Industrial Exposures

Degreasing of metals; industrial solvent; extraction of fats and oils, resins; solvent for tar and pitch, rubber; insecticide and dry cleaner.

<sup>27</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

<sup>28</sup> W. F. von Oettingen, *J. Ind. Hyg. Toxicology*, 19, 349 (1937).

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid  
 Molecular weight: 131.4  
 Specific gravity: 1.4649 at 20°/4° C.  
 Melting point: -83° C.  
 Boiling point: 86.95° C.  
 Vapor density: 4.54 (air = 1)  
 Vapor pressure: 70 (approx.) mm. Hg at 25° C.\*

Refractive index: 1.4777 at 19.8° C.  
 Per cent in "saturated" air: 9.2 at 25° C.  
 Density of "saturated" air: 1.33 (air = 1) at 25° C.  
 Solubility in water: 1.8 ml./l. water  
 Soluble in ethyl alcohol  
 Miscible with all common organic solvents

1 mg./l.  $\approx$  186 p.p.m. and 1 p.p.m.  $\approx$  5.37 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (200 p.p.m.): 20.8 ml.

**4. Physiological Response in Animals**

See Table 45.

**5. Effects on Man**

See Table 46.

TABLE 45

*Physiological Response to Various Concentrations of Trichloroethylene—Animals<sup>27,28</sup>*

Animal	Concentration		Duration of exposure	Side position (min.)	Response
	mg./l.	p.p.m.			
Cat	230	42,500	0.66 hr.	5	Light narcosis 15 min.; deep narcosis 40 min.
Mouse	165	30,000	10-20 min.	2 <sup>1</sup> / <sub>2</sub> -3	Death after 10-20 min.
Cat	147	27,000	1.75 hr.	10	Light narcosis 55 min.; deep narcosis 1 <sup>3</sup> / <sub>4</sub> hr.
Guinea pig	146	27,000	11-31 min.	—	Death
Mouse	60	11,000	2-3 min.	3	Recovery after 10 min.
Guinea pig	60	11,000	20 min.	20	Recovery after 1 hr.
Rabbit	60	11,000	20 min.	20	Recovery after 3 hr.
Mouse	40-50	7,400-9,300			Death after 2 hr.
Cat	45	8,300	5 hr.	20	Light narcosis 3 hr.; deep narcosis 5 hr.
	42	7,800	—	—	Death in 1 hr.
Guinea pig	30	5,500	30 min.	30	Recovery after 1 hr.
Rabbit	30	5,500	30 min.	<30	Recovery after 1 hr.
Mouse	30	5,500	12 <sup>1</sup> / <sub>2</sub> min.	8-11	Recovery in 15 min.
Cat	25	4,600	7 hr.	30	Light narcosis 7 hr.; deep narcosis
	22	4,100	—	—	Death after 2 <sup>1</sup> / <sub>2</sub> hr.

TABLE 46

*Physiological Response to Various Concentrations of Trichloroethylene—Man<sup>27</sup>*

Concentration	Response	
		mg./l.
6.9	1280	After 6 min. irritation of the mucous membranes, dizziness, severe headache, fatigue
1.5-2.0	280-360	Can be endured for 30 min.
0.9	160	Tolerated for 30 min. without effect

**6. Maximum Allowable Concentration**

200 p.p.m.

\* S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, 38, 320 (1946).



**7. Odor and Warning Properties**

Chloroformlike odor easily noticeable by most persons below 200 p.p.m.

**TETRACHLOROETHYLENE (Perchloroethylene)****1. Source**

Tetrachloroethylene ( $\text{CCl}_2\text{CCl}_2$ ) is prepared by treating pentachloroethane with alkali.<sup>30</sup>

**2. Uses and Industrial Exposures**

Organic preparations; solvent; metal degreaser; dry cleaner; pharmaceuticals.

**3. Pertinent Physical and Chemical Properties**

Physical state: colorless liquid

Molecular weight: 165.85

Specific gravity: 1.6226 at 20°/4° C.

Melting point: -23.5° C.

Boiling point: 121.1° C.

Vapor density: 5.7 (air = 1)

Vapor pressure: 23 mm. Hg at 25° C.

Refractive index: 1.50547 at 20° C.

Per cent in "saturated" air: 2.6 at 25° C.

Density of "saturated" air: 1.1 (air = 1) at 25° C.

Insoluble in water

Miscible with most common organic solvents

1 mg./l.  $\approx$  147.5 p.p.m. and 1 p.p.m.  $\approx$  6.78 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (200 p.p.m.): 23.7 ml.

**4. Physiological Response**

See Table 47.

TABLE 47

*Physiological Response to Various Concentrations of Tetrachloroethylene—Animals*<sup>37, 38</sup>

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Cat	235	34,662	23 min.	Light narcosis
			40 min.	Deep narcosis
	200	29,500	40 min.	Light narcosis
			74 min.	Deep narcosis
	140	20,650	72 min.	Light narcosis
2 hr.	Deep narcosis			
112	16,200	2½ hr.	Not fatal	
		100	14,750	1½ hr.
		3 hr.	Deep narcosis	
Dog	62	9,000		Narcotic concentration
Cat	60	8,850	3 hr.	Light narcosis
			4¼ hr.	Deep narcosis
Mouse	40	6,000		Death
Rat	40	6,000	6 hr.	Death
Cat	35	5,162	4¼ hr.	Light narcosis
			5¼ hr.	Deep narcosis
Mouse	25	3,700	20 min.	Prostration
			30 min.	No reflexes. Death
	20	3,000		Narcosis and loss of reflexes
	15	2,200		Prostration

**5. Maximum Allowable Concentration**

200 p.p.m.

**6. Odor and Warning Properties**

Ethereal odor, moderately strong and offensive to some persons below 200 p.p.m.

**PROPYL CHLORIDE (1-Chloropropane)****1. Source**

Propyl chloride ( $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$ ) is prepared by the action of hydrogen chloride on propyl alcohol.<sup>30</sup>

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 78.54

Specific gravity: 0.8910 at 20°/4° C.

Boiling point: 46.4° C.

Freezing point: -122.8° C.

Vapor density: 2.71 (air = 1)

Vapor pressure: 360 (approx.) mm. Hg at 25° C.<sup>30</sup>

Refractive index: 1.38838 at 20° C.

Per cent in "saturated" air: 47 at 25° C.

Density of "saturated" air: 1.8 (air = 1) at 25° C.

Solubility in water: 0.272 g./100 g. water at 20° C.

Miscible with ethyl alcohol and ether

1 mg./l.  $\approx$  310.8 p.p.m. and 1 p.p.m.  $\approx$  3.21 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (500 p.p.m.): 51.1 ml.

**3. Physiological Response**

See Table 48.

TABLE 48

*Physiological Response to Various Concentrations of Propyl Chloride—Mice<sup>40</sup>*

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
163	50,000	1 hr.	Side position after 2-3 min. Some died 1 hr. to 4 days later; some survived 10 days
122	38,000	1-2 hr.	Side position after 7 min.; survived 6 days
81	25,000	1-2 hr.	Side position after 20-60 min.; survived 2-3 days
24	7,500	2 hr.	Survived 3 days

**4. Suggested Maximum Practical Working Level**

500 p.p.m.

**PROPYL BROMIDE (1-Bromopropane)****1. Source**

Propyl bromide ( $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$ ) is prepared by the action of bromine and red phosphorus on propyl alcohol.<sup>80</sup>

<sup>40</sup>F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Refractive index: 1.43411 at 20° C.
Molecular weight: 123.0	Per cent in "saturated" air: 17.8 at 25° C.
Specific gravity: 1.3539 at 20°/4° C.	Density of "saturated" air: 1.6 (air = 1) at 25° C.
Melting point: -109.85° C.	Solubility in water: 0.245 g./100 g. water at 20° C.
Boiling point: 71.0° C.	Miscible with ethyl alcohol and ether
Vapor density: 4.25 (air = 1)	
Vapor pressure: 135 (approx.) mm. Hg at 25° C. <sup>29</sup>	

1 mg./l.  $\approx$  198.8 p.p.m. and 1 p.p.m.  $\approx$  5.03 mg./cu.m. at 25° C., 760 mm.

**3. Physiological Response**

See Table 49.

TABLE 49  
*Physiological Response to Various Concentrations of Propyl Bromide—Mice<sup>40</sup>*

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
86	17,000	26 min.	Side position in 26 min.; death after 1 day
50	10,000	36 min.	Side position in 36 min.; death after 1 day
37	7,300	80 min.	Survived 5 days

**PROPYLENE DICHLORIDE (1,2-Dichloropropane)**
**1. Source**

Propylene dichloride ( $\text{CH}_3\text{CHClCH}_2\text{Cl}$ ) is prepared by the action of chlorine on propylene.<sup>30</sup>

**2. Uses and Industrial Exposures**

Solvent for fats, oils, waxes, gums and resins; solvent mixtures for cellulose esters and ethers; organic synthesis; dry cleaning fluids; metal degreasing agents; fumigant.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Vapor pressure: 48 (approx.) mm. Hg at 25° C. <sup>30</sup>
Molecular weight: 112.99	Refractive index: 1.4068 at 20° C.
Specific gravity: 1.1593 at 20°/20° C.	Per cent in "saturated" air: 6.3 at 25° C.
Freezing point: -80° C.	Density of "saturated" air: 1.2 at 25° C.
Boiling point: 95.9° C.	Insoluble in water
Vapor density: 3.9 (air = 1)	Miscible with most common solvents

1 mg./l.  $\approx$  216.4 p.p.m. and 1 p.p.m.  $\approx$  4.62 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (100 p.p.m.): 11.3 ml.

**4. Maximum Allowable Concentration**

100 p.p.m.

**5. Inflammability**

Inflammable within the range of 3.40 to 14.50 per cent by volume in air (see Chapter Thirteen).

**6. Odor**

Chloroformlike.

**TRICHLOROPROPANE (1,2,3-Trichloropropane)****1. Source**

Trichloropropane ( $\text{CH}_2\text{ClCHClCH}_2\text{Cl}$ ) is prepared by direct chlorination of propane at temperatures of 130–250° C. and high pressures. Of the resulting mixture of crude dichloropropanes, 8 per cent is trichloropropane, which is separated by distillation.

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Vapor pressure: 4 (approx.) mm. Hg at 25° C. <sup>39</sup>
Molecular weight: 147.44	Per cent in "saturated" air: 0.52 at 25° C.
Specific gravity: 1.394 at 20°/4° C.; 1.417 at 15°/4° C. <sup>41</sup>	Density of "saturated" air: 1.02 (air = 1) at 25° C.
Freezing point: -14.7° C.	Insoluble in water
Boiling point: 156.85° C.	Soluble in ethyl alcohol and ether <sup>41</sup>
Vapor density: 5.09 (air = 1)	
1 mg./l. $\approx$ 165.8 p.p.m. and 1 p.p.m. $\approx$ 6.02 mg./cu.m. at 25° C., 760 mm.	

**DICHLOROETHYL ETHER [1-Chloro-2-( $\beta$ -chloroethoxy)ethane]****1. Source**

Dichloroethyl ether,  $(\text{CH}_2\text{ClCH}_2)_2\text{O}$ , is made by the chlorination of ethyl ether.<sup>42</sup>

**2. Uses and Industrial Exposures**

Dewaxing agent for lubricating oils; solvent for special lacquers, resins, and oils; degreasing agent; wetting agent and penetrant; organic synthesis.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Refractive index: 1.457 at 20° C.
Molecular weight: 143.02	Per cent in "saturated" air: 0.18 at 25° C.
Specific gravity: 1.222 at 20°/4° C.	Density of "saturated" air: 1.01 (air = 1) at 25° C.
Melting point: -51.7° C.	Insoluble in water
Boiling point: 178° C.	Soluble in ethyl alcohol and ether
Vapor density: 4.9 (air = 1)	
Vapor pressure: 1.4 mm. Hg at 25° C. <sup>43</sup>	

1 mg./l.  $\approx$  170.98 p.p.m. and 1 p.p.m.  $\approx$  5.85 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (15 p.p.m.): 2.1 ml.

<sup>41</sup> *Handbook of Chemistry and Physics*. 28th ed., Chemical Rubber Pub. Co., Cleveland, 1944.

<sup>42</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

**4. Physiological Response in Animals**

See Tables 50 and 51.

**5. Effects on Man**

See Table 52.

TABLE 50  
*Physiological Response to Various Concentrations of Dichloroethyl Ether—Guinea Pigs<sup>43</sup>*

Concentration		Duration of exposure, min.	Response
mg./l.	p.p.m.		
5.85	1000	—	Nasal and eye irritation immediately
		90	Respiratory disturbance
		180–300	Side position, dyspnea, gasping respiration
		230–330	Death
3.2	550	—	Nasal and eye irritation immediately
		180	Respiratory disturbance
		240–480	Side position
		360–500	Death
1.52	260	1	Nasal and eye irritation
		310	Respiratory disturbance
		445–600	Side position
		450–740	Death
0.61	105	2	Nasal and eye irritation
		810	Lacrimation not observed
		450	Respiratory disturbance
		525–810	Side position; death of 4 animals within 250 min. after exposure
0.205	35	3–10	Nasal and eye irritation
		810	No other symptoms observed; no deaths

TABLE 51  
*Summary of Acute Effects of Dichloroethyl Ether on Guinea Pigs<sup>43</sup>*

Concentration		Effect
mg./l.	p.p.m.	
2.93–5.85	500–1000	Dangerous to life in 30 to 60 min.
0.59–1.18	100–200	Maximum amount for 60 min. without serious disturbances
0.205	35	Slight symptoms after several hours, or maximum amount without serious disturbances

TABLE 52  
*Physiological Response to Various Concentrations of Dichloroethyl Ether—Man<sup>43</sup>*

Concentration		Effect
mg./l.	p.p.m.	
3.2–5.85	550–1000	On brief exposure, very irritating to the eyes and nasal passages; atmosphere considered intolerable
1.52	260	Similar in effect; atmosphere not considered intolerable
0.59	100	Slightly nauseating odor; slightly irritating
0.205	35	Easily noticeable odor, only slightly offensive, and practically free from irritation

<sup>43</sup> H. H. Schrenk, F. A. Patty, and W. P. Yant, *U.S. Pub. Health Repts.*, 48, 1389 (1933).

**6. Maximum Allowable Concentration**

15 p.p.m.

**7. Inflammability**

Inflammable; flash point 131° F. by closed-cup method.

**8. Odor and Warning Properties**

Pungent, irritating. Definite properties of odor, as well as eye, nose, and throat irritation, in concentrations that are dangerous in an exposure of one hour or less.

**CHLOROPRENE (2-Chloro-1,3-butadiene)****1. Source**

Chloroprene ( $\text{CH}_2\text{:CHCCl:CH}_2$ ) is prepared by passing monovinyl acetylene into a cold aqueous solution containing hydrogen chloride and cuprous chloride catalyst. The reaction may also be carried out in the vapor phase.

**2. Uses and Industrial Exposures**

In chemical industries, the starting material for the synthetic rubber, DuPrene.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 88.54

Specific gravity: 0.9583 at 20°/20° C.

Boiling point: 59.4° C.

Vapor density: 3.0 (air = 1)

Vapor pressure: 230 mm. Hg at 25° C.

Refractive index: 1.4583 at 20° C.

Per cent in "saturated" air: 30.2 at 25° C.

Density of "saturated" air: 1.6 (air = 1) at 25° C.

Very slightly soluble in water

Miscible with ethyl alcohol and ether

1 mg./l.  $\approx$  277 p.p.m. and 1 p.p.m.  $\approx$  3.62 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

See Table 53.

TABLE 53

*Physiological Response to Various Concentrations of Chloroprene—Mice.  
Minimal Fatal Concentration on Inhalation for One Hour*<sup>44</sup>

Concentration		Fatalities, %
mg./l.	p.p.m.	
33	9121.2	100
13	3593.2	100
11	3040.4	100
7	1934.8	100
5	1382.0	100
4.4	1105.7	100
3	829.2	100
1	277.0	None

1 mg./l. (277 p.p.m.)—considered to be dangerous<sup>44</sup>

0.3 mg./l. (83 p.p.m.)—with continued exposure may cause toxic effects

<sup>44</sup> W. F. von Oettingen, W. C. Hueper, W. Deichmann-Gruebler, and F. H. Wiley, *J. Ind. Hyg. Toxicol.*, 18, 240 (1936).

**5. Odor**  
Pungent.

**ALLYL CHLORIDE (3-Chloropropene)**

**1. Source**

Allyl chloride ( $\text{CH}_2\text{ClCH}:\text{CH}_2$ ) is prepared in the laboratory by treating allyl alcohol with hydrochloric acid and zinc chloride. It is prepared commercially by the high-temperature chlorination of propene.

**2. Uses and Industrial Exposures**

Chemical intermediate; manufacture of synthetic perfumes.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Refractive index: 1.41538 at 20° C.
Molecular weight: 76.53	Per cent in "saturated" air: 46 at 25° C.
Specific gravity: 0.9379 at 20°/4° C.	Density of "saturated" air: 1.75 (air = 1) at 25° C.
Freezing point: -136.4° C.	Insoluble in water
Boiling point: 45.7° C.	Miscible with ethyl alcohol, ether, and chloroform
Vapor density: 2.64 (air = 1)	
Vapor pressure: 350 (approx.) mm. Hg at 25° C. <sup>26</sup>	

1 mg./l.  $\approx$  319.9 p.p.m. and 1 p.p.m.  $\approx$  3.13 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

See Table 54.

TABLE 54  
*Physiological Response to Various Concentrations of Allyl Chloride—Animals<sup>26</sup>*

Concentration		Response	
mg./l.	p.p.m.	Rat	Guinea pig
100	29,300	Eye and nose irritation, unconscious after 1 hr.; 100% fatality after an exposure of less than 30 min.	
50	14,500	Irritation of eyes and nose, drowsiness, weakness, instability, labored breathing. All deaths occurred within 24 hr. 100% fatality after an exposure of less than 75 min.	Similar symptoms; 100% fatality after an exposure of less than 45 min.
20	5,800	Eye and nose irritation. Fatal within 24 hr. 100% fatality after an exposure of less than 120 min.	
10	2,900	Slight eye and nose irritation within few minutes. Fatal during exposure. 100% fatality after an exposure of less than 180 min.	Similar symptoms; did not produce unconsciousness. Majority died after exposure. 100% fatality after an exposure of less than 120 min.
1	290	Drowsiness and unsteadiness after a 4-hr. exposure Eye irritation and unconsciousness after 6 hr. exposure. Fatal within 24 hr. 100% fatality after an exposure of less than 480 min.	Similar symptoms after 4-hr. exposure Similar symptoms after 6-hr. exposure. Fatal within 24 hr. 100% fatality after an exposure of less than 240 min.

<sup>26</sup>E. M. Adams, H. C. Spencer, and D. D. Irish, *J. Ind. Hyg. Toxicol.*, **22**, 79 (1940).

**5. Odor**

Unpleasant.

**ALLYL BROMIDE (3-Bromopropene)****1. Source**

Allyl bromide ( $\text{CH}_2\text{BrCH}:\text{CH}_2$ ) is prepared by the action of bromine and phosphorus upon allyl alcohol.

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 120.99

Specific gravity: 1.3980 at 20°/4° C.

Freezing point: -119.4° C.

Boiling point: 70.0° ± 0.15° C.

Vapor pressure: 140 (approx.) mm. Hg at 25° C.\*

Refractive index: 1.46545 at 20° C.

Per cent in "saturated" air: 18 at 25° C.

Density of "saturated" air: 1.57 (air = 1) at 25° C.

Insoluble in water

Soluble in chloroform and carbon tetrachloride

Miscible with ethyl alcohol and ether

1 mg./l. ⇌ 202.1 p.p.m. and 1 p.p.m. ⇌ 4.95 mg./cu.m. at 25° C., 760 mm.

**3. Odor**

Unpleasant, penetrating.

**CHLOROBENZENE (Monochlorobenzene, Chlorobenzol)****1. Source**

Chlorobenzene ( $\text{C}_6\text{H}_5\text{Cl}$ ) is prepared by passing dry chlorine into benzene to which a small aluminum-mercury couple is added as a carrier. Action is stopped when the additional weight corresponds to the replacement of one hydrogen atom by one of chlorine. The liquid is neutralized with caustic soda, dehydrated over calcium chloride and finally recovered by distillation.

Chlorobenzene is also produced when chlorine is passed into benzene in the presence of molybdenum chloride.

**2. Uses and Industrial Exposures**

Solvent for cellulose acetate, artificial resins, oils, and fats; component of lacquers, of fast drying inks; a dry cleaning agent; organic synthesis.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 112.56

Specific gravity: 1.1066 at 20°/4° C.

Melting point: -44.9° C.

Boiling point: 132.0° C.

Vapor density: 3.9 (air = 1)

Vapor pressure: 11.5 mm. Hg at 25° C.

Refractive index: 1.5216 at 25° C.

Per cent in "saturated" air: 1.5 at 25° C.

Density of "saturated" air: 1.04 (air = 1) at 25° C.

Insoluble in water

Very readily soluble in ethyl alcohol, ether and chloroform

Volatility: slight, 12.5 times less than ether\*\*

\* K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.



1 mg./l.  $\approx$  217.2 p.p.m. and 1 p.p.m.  $\approx$  4.60 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (75 p.p.m.): 8.9 ml.

#### 4. Physiological Response

See Table 55.

TABLE 55  
*Physiological Response to Various Concentrations of Chlorobenzene—Cats<sup>47</sup>*

Concentration		Response
mg./l.	p.p.m.	
37	8000	Severe narcosis after 1/2 hr.; death 2 hr. after removal from exposure
17	3700	Death after 7 hr.
11-13	2400-2900	Unsteadiness after about 1 hr.; tremor; twitching; if removed within 7 hr. no severe injury
5.5	1200	Definite narcotic symptoms
1-3	220-660	Tolerated for one hour

#### 5. Maximum Allowable Concentration

75 p.p.m.

#### 6. Inflammability

Inflammable within the range of 1.35 to 7.05 per cent by volume in air (see Chapter Thirteen).

#### 7. Odor

Pleasant, almondlike.

### ***o*-DICHLOROBENZENE (1,2-Dichlorobenzene)**

#### 1. Source

Dichlorobenzene (C<sub>6</sub>H<sub>4</sub>Cl<sub>2</sub>) is prepared by the further chlorination of monochlorobenzene.<sup>48</sup>

#### 2. Uses and Industrial Exposures

Solvent for oxides of nonferrous metals, gums, fats, oils, waxes, sulfur, organic sulfur derivatives, resins; paints, varnishes, lacquers; paint and varnish removers; metal polishes; polishing and cleaning compounds; organic synthesis; fumigant; disinfectant and general insecticide; in removal of sulfur from illuminating gas.

#### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid	Refractive index: 1.5476 at 25° C.
Molecular weight: 147.01	Per cent in "saturated" air: 0.18 at 40° C.
Specific gravity: 1.2973 at 25°/4° C.	Density of "saturated" air: 1.01 (air = 1) at 40° C.
Melting point: -17.5° C.	Insoluble in water
Boiling point: 179.2° C.	Soluble in ethyl alcohol and ether
Vapor density: 5.07 (air = 1)	Miscible with most organic solvents
Vapor pressure: 1.4 mm. Hg at 40° C.	

<sup>47</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

<sup>48</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

1 mg./l.  $\approx$  166.3 p.p.m. and 1 p.p.m.  $\approx$  6.01 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (75 p.p.m.): 9.8 ml.

#### 4. *Physiological Response*

Lethal concentration for guinea pigs after 20 hours was 0.1 per cent.<sup>49</sup>

Lethal concentration in air: 2.5 times that of carbon tetrachloride.<sup>49</sup>

#### 5. *Maximum Allowable Concentration*

75 p.p.m.

#### 6. *Inflammability*

Inflammable; flash point by closed-cup method, 81° F.

#### 7. *Odor*

Pleasant aromatic.

### *m*-DICHLOROBENZENE (1,3-Dichlorobenzene)

#### 1. *Pertinent Chemical and Physical Properties*

Physical state: colorless liquid

Boiling point: 172° C. (766 mm.)

Molecular weight: 147.01

Refractive index: 1.5457 at 20.9° C.

Specific gravity: 1.2799 at 25°/4° C.

Insoluble in water

Melting point: -24.8° C.<sup>51</sup>

Soluble in ethyl alcohol and ether

### *p*-DICHLOROBENZENE (1,4-Dichlorobenzene)

#### 1. *Uses and Industrial Exposures*

Insecticide; germicide; deodorant; dyes; intermediates; mothproofing compositions.

#### 2. *Pertinent Chemical and Physical Properties*

Physical state: colorless or white crystals

Refractive index: 1.52104 at 80.3° C.

Molecular weight: 147.01

Insoluble in water

Specific gravity: 1.526 at 21.5° C.

Soluble in ethyl alcohol, ether and chloroform

Melting point: 54° C.

Boiling point: 174.5° C.

#### 3. *Inflammability*

Inflammable; flash point 153° F., closed-cup method.

#### 4. *Odor*

Penetrating.

### BENZYL CHLORIDE ( $\alpha$ -Chlorotoluene)

#### 1. *Source*

Benzyl chloride ( $C_6H_5CH_2Cl$ ) is prepared by passing chlorine over boiling toluene until it has increased 38 per cent in weight. The product is washed with water and separated by fractional distillation.<sup>48</sup>

\* Ethel Browning, *Toxicity of Industrial Organic Solvents*. H.M. Stationery Office, London, 1937.

**2. Uses and Industrial Exposures**

Dyes; intermediates; benzyl compounds; synthetic tannins; perfumery; pharmaceuticals; synthetic resins.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Vapor pressure: 1 mm. Hg at 25° C. <sup>80</sup>
Molecular weight: 126.58	Per cent in "saturated" air: 0.13 at 25° C.
Specific gravity: 1.100 at 25°/4° C.	Density of "saturated" air: 1.04 (air = 1)
Melting point: -43.2° C.	at 25° C.
Boiling point: 179.3° C.	Insoluble in water
Refractive index: 1.5414 at 15.4° C.	Soluble in ethyl alcohol and ether
Vapor density: 4.37 (air = 1)	

1 mg./l.  $\approx$  193.13 p.p.m. and 1 p.p.m.  $\approx$  5.17 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response in Animals**

*Acute effects.* See Table 56.

*Subacute effects.* See Table 57.

**5. Effects on Man**

See Table 58.

TABLE 56

*Physiological Response to Various Concentrations of Benzyl Chloride—Animals<sup>47</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Cat	24	4600	1/2 hr.	Fatal, after apparent recovery, on 21st day
	11.5	2200	6 1/2 hr.	Complete paralysis of the extremities; unconscious after 3 1/2 hr.; fatal after 6 1/2 hr.
	7-18	1400-3500	8 hr.	Fatal immediately after completion of experiment
	From 5 on	1000	About 2 hr.	Besides general irritation, some signs of paralysis
	2	400	7 1/2 hr.	Immediate irritation; after 1 hr. became accustomed; on the next day coughing, sneezing, turbidity of the cornea; death after 2-3 days due to pulmonary edema
Dog	1.9	370	8 hr.	Fatal
Cat	0.9	170	8 hr.	Extremely irritating; dangerous to life; after-effects
	0.5	100	8 hr.	Extremely irritating
	0.2	40	8 hr.	Slight irritation

TABLE 57

*Subacute Poisoning with Benzyl Chloride—Animals<sup>47</sup>*

Concentration		Duration of exposure	Response	
mg./l.	p.p.m.		Cat	Guinea pig
0.48	93	8 hr. daily for 6 days	Increasing inflammation of the conjunctiva and respiratory tract. Fatal to some	Very little irritation; redness of mucous membranes first noticed on 6th day

<sup>80</sup> D. H. Killeffer, *Ind. Eng. Chem.*, 30, 477, 565 (1938).

TABLE 58  
*Physiological Response to Various Concentrations of Benzyl Chloride—Man*<sup>47</sup>

Concentration		Effect
mg./l.	p.p.m.	
1	190	Considered injurious to the respiratory tract
0.16	31	Extremely irritating to the eyes; less irritating to the nose; the effect did not last long
0.085	16	Normal person cannot tolerate for longer than 1 min.

### 6. Odor and Warning Properties

Very strong odor; produces tears even in concentrations below 16 p.p.m.

## BENZYL BROMIDE (*α*-Bromotoluene)

### 1. Source

Benzyl bromide ( $C_6H_5CH_2Br$ ) may be produced either by the bromination of toluene or by the interaction of benzyl alcohol and hydrobromic acid.<sup>48</sup>

### 2. Uses and Industrial Exposures

Military poison gas ("Cyclite"); organic synthesis; making foaming and frothing agents; yeast antiseptic.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid	Vapor pressure: 2.0 mm. Hg at 20° C. <sup>49</sup>
Molecular weight: 171.04	Per cent in "saturated" air: 0.26 at 20° C.
Specific gravity: 1.4380 at 22°/0° C.	Density of "saturated" air: 1.01 (air = 1) at 20° C.
Melting point: -4.0° C. <sup>51</sup>	Insoluble in water
Boiling point: 201° C.	Soluble in ethyl alcohol and ether
Freezing point: -3.9° C.	Volatility: 2.4 mg./l. at 20° C. <sup>52</sup>
Vapor density: 5.90 (air = 1)	

1 mg./l.  $\approx$  142.97 p.p.m. and 1 p.p.m.  $\approx$  6.99 mg./cu.m. at 25° C., 760 mm.

### 4. Physiological Response in Animals

*Cats.* Benzyl bromide, 0.2 mg./l. (29 p.p.m.) was lethal to cats after 3 days.<sup>47</sup>

### 5. Effects on Man

See Table 59.

TABLE 59  
*Physiological Response to Various Concentrations of Benzyl Bromide—Man*<sup>47,52</sup>

Concentration		Response
mg./l.	p.p.m.	
4.50	643.5	Lethal concentration for 10-min. exposure
0.05-0.06	7-8	At 1 min., concentration intolerable for man
0.0035	0.5	After few seconds of exposure individuals incapacitated because of eye irritation

<sup>47</sup> *Handbook of Chemistry and Physics*. 28th ed., Chemical Rubber Pub. Co., Cleveland, 1944.

<sup>48</sup> A. M. Prentiss, *Chemicals in War*. McGraw-Hill, New York, 1937.

**6. Odor**

Pleasant aromatic odor resembling watercress.

**ETHYLENE CHLOROHYDRIN (2-Chloroethanol)****1. Source**

Ethylene chlorohydrin ( $\text{CH}_2\text{ClCH}_2\text{OH}$ ) is produced by the action of hypochlorous acid on ethylene.<sup>48</sup>

**2. Uses and Industrial Exposures**

Solvent for cellulose acetate, resins, wax lacquers; cleaning and dyeing industry; organic synthesis.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 80.52

Specific gravity: 1.2019 at 20°/4° C.

Melting point: -69° C.<sup>51</sup>

Boiling point: 127.9° C.

Freezing point: -67.5° C.

Vapor density: 2.78 (air = 1)

Vapor pressure: 8.5 mm. Hg at 25° C.<sup>52</sup>

Refractive index: 1.4421 at 20° C.

Per cent in "saturated" air: 1.1 at 25° C.

Density of "saturated" air: 1.02 (air = 1) at 25° C.

Soluble in ethyl alcohol and ether

Miscible with water

1 mg./l.  $\approx$  304 p.p.m. and 1 p.p.m.  $\approx$  3.29 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

See Table 60.

TABLE 60

*Physiological Response to Various Concentrations of Ethylene Chlorohydrin—Animals<sup>48</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Guinea pig	18.0	5500	15 min.	Apathy; death within 30 hr.
Cat	4.5	1370	Repeated exposures	Severe symptoms, chiefly related to nervous system; death 3 hr. after end of experiment
Guinea pig	3.6	1100		Lowest concentration that would be fatal after 1-hr. inhalation
Cat	2.5	760	3 hr. daily for 4 days	Fatal on 4th day

**5. Inflammability**

Inflammable; flash point 140° F. by closed-cup method (see Chapter Thirteen).

**6. Odor**

Faint ethereal odor.



## CHAPTER TWENTY-SIX

# The Alcohols

J. F. TREON, Jr.

### METHYL ALCOHOL

#### 1. Uses and Industrial Exposure

Methyl alcohol ( $\text{CH}_3\text{OH}$ ), methanol, has been known also as carbinol, Columbian spirit, wood alcohol, and wood spirit. It is used extensively as an industrial solvent, in the lacquer industry, in the preparation of celluloid, films, plastics, textile soaps, wood stains, artificial leather, and nonshatterable glass. It is used in enamels, stains, dyes for straw hats, paint and varnish removers, cleaning and dewaxing preparations, embalming fluids, and antifreeze mixtures. It is also used as an intermediate and as an extracting medium in organic synthesis.<sup>1</sup> Seventy-two occupations that offer exposure to methyl alcohol have been reported by the United States Department of Labor.

Industrial injuries or fatalities have been reported from the inhalation of high concentrations of methyl alcohol by persons engaged in varnishing beer vats,<sup>2</sup> varnishing metal,<sup>3</sup> varnishing the engine room of a submarine,<sup>4</sup> shellacking lead pencils,<sup>5</sup> shellacking hogsheads,<sup>6</sup> coloring cloth and other articles in solutions of dyes in methyl alcohol,<sup>7,8,9</sup> stiffening hats,<sup>10,11</sup> and manufacturing shoes.<sup>12</sup>

The concentration of methyl alcohol was 22 to 25 p.p.m.<sup>13</sup> in well-ventilated

<sup>1</sup> I. Mellan, *Industrial Solvents*. Reinhold, New York, 1939, p. 202.

<sup>2</sup> C. A. Wood, *J. Am. Med. Assoc.*, 59, 1962 (1912).

<sup>3</sup> E. Browning, *Med. Research Council Ind. Health Research Board, Rept. No. 80*, H. M. Stationery Office (1937).

<sup>4</sup> S. L. Ziegler, *J. Am. Med. Assoc.*, 77, 1160 (1921).

<sup>5</sup> *N. Y. State Dept. of Labor Bull. No. 86* (1917).

<sup>6</sup> A. B. Hale, *J. Am. Med. Assoc.*, 37, 1447 (1901), *ibid.*, 1450.

<sup>7</sup> A. Hamilton, *Industrial Poisons in the United States*. Macmillan, New York, 1925, p. 427.

<sup>8</sup> *Natl. Research Council of Canada. Bull. No. 15*, 20 (1930).

<sup>9</sup> J. M. Robinson, *J. Am. Med. Assoc.*, 70, 148 (1918).

<sup>10</sup> C. Baskerville, "Wood Alcohol: A report on Chemistry, Technology, and Pharmacology of and the Legislation Pertaining to Methyl Alcohol." *Second report, N. Y. State Factory Investigating Commission, 1913*, Appendix VI, Vol. 2, p. 917.

<sup>11</sup> F. Buller and C. A. Wood, *J. Am. Med. Assoc.*, 43, 1117 (1904).

<sup>12</sup> E. R. Hayhurst, *Occupational Survey of Ohio*, 1915.

<sup>13</sup> L. Greenburg, M. R. Mayers, L. J. Goldwater, and W. J. Burke, *J. Ind. Hyg. Toxicol.*, 20, 148 (1938).

rooms in which a mixture of methyl alcohol and acetone was employed to impregnate fused collars. At a distance of 6 ft. from the site at which artificial flowers were being dipped, there was 200 p.p.m. of methyl alcohol in the air. Vapors were also noticeable at a distance of 75 ft. from the point of dipping and drying.<sup>5</sup> Concentrations of 50 to 6000 p.p.m. of methyl alcohol in workrooms have been reported.<sup>8</sup> On the assumption that there was one change of air per hour, Loewy<sup>14</sup> estimated the concentrations of methyl alcohol in various workrooms in which violins, artificial flowers, shoes, and hats were being processed, through calculations based on the volume of the rooms and the quantities of alcohol vaporized therein. He arrived at values of less than 50 p.p.m. in seven rooms, 50 to 100 p.p.m. in five rooms, and 265 to 622 p.p.m. in four rooms.

In the manufacture of photographic film, methyl alcohol is kept essentially within a closed system, but, during the loading of mixers and the changing of filters, Sterner<sup>14a</sup> found concentrations of methyl alcohol ranging from 200 to several thousand p.p.m., the latter values occurring for only short periods of time. The daily average of the concentrations to which operators were exposed was probably between 400 and 500 p.p.m. Sterner believes these latter values would not ordinarily result in any serious effect or even moderate discomfort, since numbers of men known by him to have been exposed to such conditions while handling millions of gallons of this solvent failed to show any evidences of methyl alcohol intoxication. Concentrations of methyl alcohol ranging from 165 to 635 p.p.m. were found in four plants employing duplicating machines,<sup>14b</sup> while the concentration in a fifth plant varied between 40 and 50 p.p.m.

## 2. Physical Properties

Methyl alcohol is a clear, colorless, inflammable, hygroscopic, volatile fluid, entirely miscible with water, alcohols, ketones, esters, and halogenated hydrocarbons, and partially miscible with benzene.<sup>1</sup> Fats and oils are only slightly dissolved by methyl alcohol. The compound has the following physical properties: molecular weight, 32.042<sup>15</sup>; specific gravity 0.792 at 20°/4° C.<sup>1</sup>; melting point, -97.8°<sup>16</sup>; boiling point, 64.5°<sup>16</sup>; refractive index, 1.329 at 20°<sup>1</sup>; vapor pressure, 96.0 mm. Hg at 20°<sup>1</sup>; vapor pressure, 160 mm. Hg at 30°<sup>1</sup>; (125 mm. Hg at 25°, calculated). The vapor density is 1.11 (air = 1). "Saturated" air contains 21.05 per cent methyl alcohol by volume at 30° C. and has a density of 1.02 (air = 1).

1 mg./l.  $\approx$  764 p.p.m. and 1 p.p.m.  $\approx$  1.31 mg./cu.m. at 25° C., 760 mm.

## 3. Determination in the Atmosphere

The Denigès<sup>17</sup> test, which is the basis for most accepted methods for the determination of methyl alcohol in air, is based upon the oxidation of methyl

<sup>14</sup> A. Loewy, *Vierteljahrsschr. gerichtl. Med.*, 48, Suppl., 93 (1914).

<sup>14a</sup> J. H. Sterner, *personal communication*.

<sup>14b</sup> A. E. Goss and G. H. Vance, *Ind. Hyg. Newsletter*, 8, No. 9, 15 (1948).

<sup>15</sup> "Atomic Weights, 1941," (International) *J. Am. Chem. Soc.*, 63, No. 3 (1941).

<sup>16</sup> *International Critical Tables of Numerical Data, Physics, Chemistry, and Technology* Vol. I. McGraw-Hill, New York, 1926, p. 177.

<sup>17</sup> E. Denigès, *Compt. rend.*, 150, 832 (1910).



alcohol by potassium permanganate to formaldehyde and the subsequent measurement of the color produced with fuchsin in sulfurous acid (Schiff's reagent). The sensitivity and precision of this test were increased by Chapin<sup>18</sup> who employed Elvove's<sup>19</sup> modification of Schiff's reagent. Chapin's method can be used in the presence of ethyl alcohol. Wright<sup>20</sup> found rosaniline a better coupling agent than fuchsin because it is quite stable and more sensitive than fuchsin.

By absorbing methyl alcohol from the air in a bubbler containing water and subsequently employing fuchsin, concentrations as low as 5 p.p.m.<sup>21</sup> can be detected, while 30 p.p.m. can be determined quantitatively. Jephcott<sup>21</sup> found the development of color was dependent upon the reaction of the medium. Rosaniline was employed by Ackerbauer,<sup>22</sup> who used a series of scrubbers to eliminate chlorine, sulfur dioxide, formic acid, and acetic acid from air containing them while the air was flowing at the rate of 1 liter every 25 minutes for 5 or 10 liters. He claimed that the error of determination of concentrations as low as 6 p.p.m. of methyl alcohol in the presence of formaldehyde was not more than 5 per cent.

The following interfering substances have been eliminated by suitable chemical methods followed by distillation: formaldehyde, terpenes, phenol, carbohydrates,<sup>18</sup> pectin,<sup>20</sup> and glycerol.<sup>18,20</sup> Chapin<sup>18</sup> found amyl alcohol, acetone, formic acid, and acetic acid are not apt to interfere.

#### 4. Determination in Tissues and Blood

A method based upon the colorimetric measurement, at 585  $m\mu$ , of dichromate reduced to trivalent chromium by methyl alcohol, has been used by Hine *et al.*<sup>22a</sup> to determine methyl alcohol in blood tissues and expired air. The colorimetric measurement of the diffuse violet color produced by the reaction products of methanol, permanganate, and manganese dioxide with chromotropic acid, are the basis of a method by Ozburn<sup>22b</sup> for the determination of methyl alcohol in blood and body fluids.

#### 5. Physiological Response

*Animal symptomatology.* Exposure of animals to concentrations of methyl alcohol in air may induce the following signs of intoxication: increased rate of respiration, a state of nervous depression followed by excitation, irritation of the mucous membranes, ataxia, partial paralysis, agony, prostration, deep narcosis, convulsions, decrease in rectal temperature, loss in weight, and death due to respiratory failure. The narcotic effect of methyl alcohol is weaker than that of ethyl alcohol, but the toxic effect from accumulated doses of methyl alcohol, owing to slow elimination, is greater than that of ethyl alcohol. There is not a

<sup>18</sup> R. M. Chapin, *Ind. Eng. Chem.*, **13**, 543 (1921).

<sup>19</sup> E. Elvove, *Ind. Eng. Chem.*, **9**, 295 (1917).

<sup>20</sup> L. O. Wright, *Ind. Eng. Chem.*, **19**, 750 (1927).

<sup>21</sup> C. M. Jephcott, *Analyst*, **60**, 588 (1935).

<sup>22</sup> C. F. Ackerbauer and R. J. Lebowich, *J. Lab. Clin. Med.*, **28**, 372 (1942).

<sup>22a</sup> C. N. Hine, T. E. Shea, Jr., and W. R. Oldsford, *Federation Proc.*, **6**, 338 (1947).

<sup>22b</sup> E. T. Ozburn, *U.S. Naval Med. Bull.*, **46**, 1170 (1946).

TABLE 1  
*Physiological Effects upon Animals of the Inhalation of Methyl Alcohol*

Animal	Concentration		Duration of exposure	Signs of intoxication	Outcome	Investigator
	p.p.m.	mg./l.				
Cat	132,000	173	5-5.5 hr.	Narcosis	Died	Witte <sup>21</sup>
	65,700	86	4.5 hr.	On side	50% died	"
	33,600	44	6 hr.	Inco-ordination	50% died	"
	18,300	24	6 hr.	None, but salivation	Survived	"
	72,600	95	54 hr.	Narcosis	Died	Weese <sup>22</sup>
	72,600	95	28 hr.	Narcosis	Died	"
	54,000	70.7	54 hr.	Narcosis	Died	"
	48,000	62.8	24 hr.	Narcosis	Survived	"
	10,000	13.1	230 hr.	Ataxia	Survived	"
	152,800	200	94 min.	Narcosis		Mashbitz <i>et al.</i> <sup>23</sup>
101,600	133	91 min.	Narcosis		"	
91,700	120	95 min.	Narcosis		"	
76,400	100	89 min.	Narcosis		"	
61,100	80	134 min.	Narcosis		"	
45,800	60	153 min.	Narcosis		"	
30,600	40	190 min.	Narcosis		"	
173,000	227	—	—	Died	Bachem <sup>24</sup>	
139,000	182	—	Highest concentration endurable	—	"	
Rat	60,000	78.5	2.5 hr.	Narcosis, convulsions	—	Loewy and von der Heide <sup>27</sup>
	31,600	41.4	18-20 hr.	—	Died	"
	22,500	29.5	8 hr.	Narcosis	—	"
	13,000	17	24 hr.	Prostration	—	"
	8,800	11.5	8 hr.	Lethargy	—	"
	4,800	6.3	8 hr.	None	—	"
	3,000	4	8 hr.	None	—	"
	50,000	65.4	1 hr.	Drowsiness	Survived	Müller <sup>25</sup>

Animal	Concentration		Duration of exposure	Signs of intoxication	Outcome	Investigator
	p.p.m.	mg./l.				
Dog	37,000	48.4	8 hr.	Prostration, inco-ordination	—	Loewy and von der Heide <sup>27</sup>
	13,700	17.9	4 hr.	None	—	"
	2,000	2.6	24 hr.	None	—	"
	10,000	13.1	3 min. 8 times each day at hourly intervals for 100 days	None	Survived	Sayers <i>et al.</i> <sup>28</sup>
Dogs and pups	450-500	0.59-0.65	8 hr. a day 7 days a week for 379 days	None	Survived	Sayers <i>et al.</i> <sup>28a</sup>
Monkey, rabbit, rat	40,000	52.4	4 hr.	Illness	Death	McCord <sup>29</sup>
	40,000	52.4	1 hr. daily	—	Delayed death	"
	10,000	13.1	18 hr. daily	—	Death	"
	10,000	13.1	7 hr. daily for several weeks	—	Delayed death	"
	1,000	1.3	41 hr.	—	Death	"

very wide difference between the concentration necessary to produce narcosis and that which is lethal. Temporary or permanent visual disturbances and blindness may result from repeated exposure to intermediate concentrations. Numerous investigators have shown that the toxicity of methyl alcohol is due to its inherent properties or to those of its metabolites and not to some contaminating substance.

The minimum lethal concentration of methyl alcohol in the air breathed by different animals over short periods of time varies widely with the species and according to the investigator (Table 1). The highest value is that reported by Bachem,<sup>23</sup> who found that mice tolerated 139,000 p.p.m., but died if exposed for an unstated period of time to 173,000 p.p.m. Mice exposed to air containing 48,000 p.p.m. for 3.5 to 4 hours daily up to a cumulative total of 24 hours were in a state of narcosis, but survived, whereas they succumbed in coma when correspondingly exposed for 54 hours to air containing 54,000 p.p.m.<sup>25</sup> Cats survived a 6-hour exposure to 18,300 p.p.m. without any signs of intoxication other than an initial salivation, but when exposed for 6 hours to 33,600 p.p.m. they suffered incoordination and 50 per cent died.<sup>24</sup> Rats became drowsy when exposed for 1 hour to 49,700 p.p.m., but survived without any aftereffect<sup>30</sup>; they died when exposed for 18 to 20 hours to a concentration of 31,600 p.p.m.<sup>27</sup> The lowest fatal concentration for animals was reported by McCord<sup>29</sup> in relation to monkeys, some of which died after a few 18-hour exposures on successive days to the concentration of 1000 p.p.m. Tyson and Schoenberg<sup>31</sup> also found the monkey more susceptible than the guinea pig, rabbit, or dog. It is not surprising that such divergent results have been reported if one recognizes such experimental variables as the different means employed for vaporizing the liquid, the differences in the methods of exposing the animals (some of the inhalation chambers had inadequate air exchange), the qualitative and quantitative variability of the analytical procedures for the determination of the actual concentrations in the air breathed by the animals, and the variations in the age and state of health of the experimental animals. However, despite the variability of the recorded data, it seems

<sup>23</sup> C. Bachem, *Arch. exptl. Path. Pharmacol.*, **122**, 69 (1927).

<sup>24</sup> R. Witte, *Dissertation*, Würzburg, 1931.

<sup>25</sup> H. Weese, *Arch. exptl. Path. Pharmacol.*, **135**, 118 (1928).

<sup>27</sup> L. M. Mashbitz, R. M. Sklianskaya, and F. M. Urievea, *J. Ind. Hyg. Toxicol.*, **18**, 117 (1936).

<sup>29</sup> A. Loewy and R. von der Heide, *Biochem. Z.*, **65**, 230 (1914).

<sup>30</sup> R. Müller (cited in Loewy and von der Heide), *Z. angew. Chem.*, **23**, 351 (1910).

<sup>31</sup> R. R. Sayers, W. P. Yant, H. H. Schrenk, J. Chornyak, S. J. Pearce, F. A. Patty, and J. G. Linn, *J. Ind. Hyg. Toxicol.*, **26**, 255 (1944).

<sup>32</sup> R. R. Sayers, W. P. Yant, H. H. Schrenk, J. Chornyak, S. J. Pearce, F. A. Patty, and J. G. Linn, *U.S. Bur. Mines Repts. Investigations No. 3617* (1942).

<sup>29</sup> C. P. McCord, *Ind. Eng. Chem.*, **23**, 931 (1931).

<sup>30</sup> K. B. Lehmann and F. Flury, *Tozikologie und Hygiene der technischen Lösungsmittel*. Springer, Berlin, 1938, p. 149.

<sup>31</sup> H. H. Tyson and M. J. Schoenberg, *Arch. Ophthalmol.*, **44**, 275 (1915).

probable that it would be dangerous for men to be exposed to the vapors of methyl alcohol in concentrations of the order of 30,000 to 50,000 p.p.m. for as much as 30 to 60 minutes.

A valuable experiment conducted upon dogs for 379 consecutive days by Sayers and his associates<sup>28a</sup> has revealed that repeated exposure of this animal to 450 or 500 p.p.m. for 8 hours daily is innocuous. Following preliminary observation, the dogs were exposed to a vapor-air concentration maintained within the stated limits as demonstrated analytically by the method of Chapin. The animals showed no unusual behavior, impairment of vision, or loss of weight, and all survived. Ophthalmoscopic examinations disclosed no remarkable abnormalities. There were no significant changes in the formed elements or the chemical constituents of the blood of the animals, nor were there gross or microscopic abnormalities in their tissue at necropsy. The concentration of methyl alcohol in the blood of these dogs at the end of an 8-hour exposure generally varied between 10 and 15 mg. per 100 milliliters of blood, but occasional concentrations as high as 52 mg. were found.

A second report by Sayers and his associates,<sup>28</sup> who exposed two dogs to 10,000 p.p.m. for about 3 minutes in each of 8 periods per day at hourly intervals on 100 consecutive days, reveals no noteworthy effects attributable to methyl alcohol poisoning. Median values of 6.5 mg. and 14 mg. per 100 milliliters, respectively, were obtained for the methyl alcohol concentration in the blood of these two animals.

*Pathology in animals.* The following pathological changes found in the tissues of animals exposed to inhalation of methyl alcohol are quite similar to those observed in animals following ingestion of this compound. In the eyes of the dog Tyson and Schoenberg<sup>32</sup> found hyperemia of choroid, edema of the ocular tissue with early signs of degeneration of the ganglionic cells of the retina and nerve fibers. Scott and his associates<sup>33</sup> also found that the vessels of the choroid of poisoned animals were markedly congested, the entire retina was edematous, and the ganglion cells were degenerated. Occasionally there were degenerative changes and fibrosis of the optic nerve. Although Weese<sup>25</sup> observed degenerative alterations in retinae of mice, he did not attribute them to the effects of methyl alcohol.

Petechial hemorrhages in the lungs of dogs were seen by Tyson and Schoenberg.<sup>32</sup> Lehmann and Flury<sup>30</sup> reported the occurrence of pulmonary edema. Rabbits developed patchy bronchopneumonia,<sup>34</sup> and the lungs of poisoned mice were extensively so involved, if they survived for 24 hours, according to Weese.<sup>25</sup> In cases of milder poisoning, Scott and associates<sup>33</sup> found edema, congestion, and desquamation of alveolar epithelium, and in more advanced cases there was terminal pneumonic consolidation.

<sup>28</sup> H. H. Tyson and M. J. Schoenberg, *J. Am. Med. Assoc.*, 63, 915 (1914).

<sup>28</sup> E. Scott, M. K. Helz, and C. P. McCord, *Am. J. Clin. Path.*, 3, 311 (1933).

<sup>34</sup> A. A. Eisenberg, *Am. J. Pub. Health*, 7, 765 (1917).

The only pathological change found by Tyson and Schoenberg<sup>32</sup> in the livers of monkeys, dogs, and rabbits was a slight darkness (congestion). The livers of the poisoned rabbits were increased in size, friable and involved in an albuminous degeneration (cloudy swelling), fatty degeneration, with also an increased amount of connective tissue in those of animals subjected to repeated exposures or examined some time after exposure had been terminated.<sup>34</sup> The cell nuclei of the liver of mice were unaltered, but Weese<sup>25</sup> found mild fatty infiltration of the liver parenchyma. Lehmann and Flury<sup>30</sup> reported the occurrence of mild fatty infiltration of the liver as the consequence of brief, severe exposure and more severe fatty changes in association with prolonged or frequently repeated exposures. Scott and associates<sup>33</sup> found in the livers of rats, monkeys, and rabbits parenchymatous degeneration with focal necroses.

In the kidney Tyson and Schoenberg<sup>32</sup> found only dark purple congestion. Albuminous and fatty degeneration are reported by Eisenberg.<sup>34</sup> Damage to the kidneys of mice, characterized principally by fatty infiltration, was described by Weese.<sup>25</sup> Parenchymatous degeneration of the epithelium lining of the convoluted tubules was seen by Scott and associates.<sup>33</sup> Fatty infiltration of the kidney following brief high exposures and more severe fatty changes in repeated exposures were reported by Lehmann and Flury.<sup>30</sup>

No alteration in the hearts of mice was observed by Weese.<sup>25</sup> Cardiac dilatation with vascular engorgement was reported by Lehmann and Flury. The muscle was dark and the cavities were empty when examined by Tyson and Schoenberg.<sup>32</sup> Eisenberg<sup>34</sup> noted fatty degeneration of the heart muscle with occasional fragmentation and segmentation of the muscle cells. Edema, granular degeneration, and, in some instances, necrosis of heart muscle fibers were described by Scott and associates.<sup>33</sup>

Degenerative injuries of the central nervous system have been described by Lehmann and Flury.<sup>30</sup> The meninges of dogs showed marked congestion according to Tyson and Schoenberg.<sup>32</sup> In the rabbit, disintegration of nerve cells of the cerebrum, with actual atrophy and diffuse fibrosis, was described by Eisenberg.<sup>34</sup> Pathological changes in the central nervous system were manifested by capillary congestion, edema, and patchy degeneration in the neurons.<sup>33</sup> The cellular degeneration occurred more often in the spinal cord than in the brain.

Hyperplasia of the lymph nodes was reported by Scott and coworkers.<sup>33</sup> The spleen was a dark indigo blue.<sup>32</sup> Pin-point hemorrhages and congestion of the gastric mucosa were believed by Tyson and Schoenberg<sup>32</sup> to be characteristic of poisoning from the inhalation of methyl alcohol.

#### **6. Absorption, Distribution, and Excretion**

The distribution of methyl alcohol within the tissues of dogs exposed to 4000 and 15,000 p.p.m. in air over periods ranging from 12 hours to 5 days was found to be rapid.<sup>35</sup> The quantities found in the various tissues were correlated

<sup>35</sup> W. P. Yant and H. H. Schrenk, *J. Ind. Hyg. Toxicol.*, 19, 337 (1937).

to their water content; although the differences were not great, the highest concentrations were found in the blood, eye fluid, bile, and urine, and the lowest in the bone marrow and fatty tissue.

Loewy and von der Heide<sup>27</sup> showed that the lipoid solubility of methyl alcohol is slight and that fat rats absorb less proportionally than the lean. The entire carcasses of rats exposed for 8 hours to 4500, 8500, or 22,500 p.p.m. contained 0.65, 2.0, and 4.3 g. of methanol per kilogram of body weight, respectively.

One to seven milligrams of methyl alcohol per gram of blood (100 to 700 mg. per 100 milliliters) was found by Haggard and Greenberg<sup>36</sup> in the blood of rats following oral administration of 4 g. of methyl alcohol per kilogram of body weight. Seventy per cent of the methyl alcohol lost by the animals was eliminated in the expired air. The amount eliminated in unit time was determined by the concentration in the blood and the volume of the pulmonary ventilation. This was demonstrated by the exponential curve that resulted when the concentration of methyl alcohol in the blood was plotted against the time elapsing after the administration of methyl alcohol, under varying conditions of pulmonary ventilation. The rate of elimination of methyl alcohol from the blood was increased when pulmonary ventilation was increased by carbon dioxide or 2,4-dinitrophenol. (Newman and Tainter<sup>37</sup> have shown that the increased elimination of methyl alcohol from the blood, following intramuscular injection of dinitrophenol, is due to pulmonary ventilation and not to oxidation, by the simple expedient of determining the rate of methyl alcohol elimination on the part of dogs so injected, under conditions of enforced rebreathing of the expired air, as compared with free breathing of ordinary atmosphere.)

The extent of the oxidation of methyl alcohol to formaldehyde or formic acid, and the role that these substances play in determining the toxicity of methyl alcohol have not been too well established. However, there is evidence in support of their occurrence as metabolic products. Although it has been established that formaldehyde can remain intact for but a short time because of its reaction with proteins, Keeser<sup>38</sup> found it present for a short time in vitreous humor, spinal fluid, and abdominal fluids of rabbits poisoned by methyl alcohol. Keeser<sup>39</sup> also showed that methyl alcohol was oxidized *in vitro* by the freshly prepared vitreous humor of calves, but that hexamethylenetetramine could be formed if ammonium carbonate were present, and the resulting amount of formaldehyde were materially decreased. The evidence is somewhat stronger for the formation of formic acid. Following inhalation of vapors of methyl alcohol by dogs, Tyson and Schoenberg<sup>32</sup> found an increase in the electroconductivity of blood due to an increase in H-ion content which was substantiated by alkaline titration. The excretion of formic acid for several days following administration

<sup>27</sup> H. W. Haggard and L. A. Greenberg, *J. Pharmacol.*, 66, 479 (1939).

<sup>37</sup> H. W. Newman and M. L. Tainter, *J. Pharmacol.*, 57, 67 (1936).

<sup>38</sup> E. Keeser, *Deut. med. Wochschr.*, 57, 398 (1931).

<sup>39</sup> E. Keeser, *Arch. exptl. Path. Pharmacol.*, 160, 687 (1931).

of methyl alcohol was observed by Pohl<sup>40</sup> and Hunt.<sup>41</sup> Formic acid was excreted in the urine of rabbits during inhalation of methyl alcohol, according to Bachem.<sup>23</sup> A few milligrams of formate were found in the blood, muscle, kidney, and lung of a 7-kg. animal by Pohl<sup>40</sup> on the day following the administration of 25 ml. of methyl alcohol. These findings indicate there is very little storage of formate ion in the body. Bastrup<sup>41a</sup> found that rabbits that had been given a single oral dose of methyl alcohol (2 to 10 g. per kilogram of body weight) excreted 0.1 to 1.1 per cent of it as formate and 13 to 20 per cent of it as methyl alcohol in the urine within 47 to 143 hours. Dogs, however, excreted in the urine 5 to 15 per cent of an oral dose of methyl alcohol (1 to 2 g. per kilogram) as formate and 5 to 8 per cent as unchanged methyl alcohol.

When kept in prolonged contact with the skin, liquid methyl alcohol induces a moderate feeling of local warmth, slight local hyperemia, and eventually a dryness and brittleness of the involved skin.<sup>30</sup> Apparently, methyl alcohol can penetrate the skin in sufficient quantity to cause fatal intoxication, although the available information on this point is somewhat inadequate and is certainly inconclusive with respect to the dosage required. McCord<sup>29</sup> is authority for the statement that the application of 0.5 ml. per kilogram of body weight upon the skin of a monkey produced illness and death, but the details of the experiment are not given and the means by which inhalation of vapor was prevented were not described. Yant and his associates<sup>42</sup> drenched the entire bodies of unshaven dogs for several hours in such a manner as to eliminate any inhalation of the vapor. According to Schrenk<sup>43</sup> the unpublished data for these experiments reveal, from the amount of methyl alcohol in the blood, that as far as dogs are concerned the possibility of poisoning by this method was not great and certainly was very much less than from inhalation. Ocular disturbances and blindness in man have been reported by Campbell<sup>44</sup> and Woods<sup>45</sup> from repeated rubbing of the skin with methyl alcohol under conditions that did not prevent inhalation of the vapor. As may be seen, the available evidence as to the magnitude of the hazard from the percutaneous absorption is somewhat inadequate, but such as it is, it suggests that prolonged or frequently repeated exposure by this means should be avoided.

### 7. Effects upon Man

From the time of Buller and Wood<sup>11</sup> in 1904 until the present time, numerous cases of blindness and death due to the drinking of a few ounces of methyl alcohol have been reported. The recent articles of Jacobson and his associates,<sup>46</sup>

<sup>40</sup> J. Pohl, *Arch. exptl. Path. Pharmacol.*, **31**, 281 (1893).

<sup>41</sup> R. Hunt, *Bull. Johns Hopkins Hosp.*, **13**, 213 (1902).

<sup>41a</sup> J. T. Bastrup, *Acta pharmacol.*, **3**, 303 (1947).

<sup>42</sup> W. P. Yant, H. H. Schrenk, and R. R. Sayers, *Ind. Eng. Chem.*, **23**, 551 (1931).

<sup>43</sup> H. H. Schrenk, *personal communication*.

<sup>44</sup> J. A. Campbell, *J. Ophth. Otol. Laryng.*, **21**, 756 (1915).

<sup>45</sup> H. Woods, *J. Am. Med. Assoc.*, **60**, 1762 (1913).

<sup>46</sup> B. M. Jacobson, H. K. Russell, J. J. Grimm, and E. C. Fox, *U.S. Naval Med. Bull.*, **44**, 1099 (1945).



Kaplan and Levreault,<sup>47</sup> and Voegtlin and Watts<sup>48</sup> record 24 deaths from drinking methyl alcohol. In acute cases, the use of intravenous injection of sodium bicarbonate or sodium lactate and glucose in physiological saline has been recommended by Johnstone,<sup>49</sup> Jacobson and others,<sup>46</sup> and Voegtlin.<sup>48</sup> These investigators have also recommended the use of emetics, a high fluid intake, cardiac and respiratory stimulants, and oxygen or artificial respiration. Chew *et al.*<sup>50</sup> and Røe<sup>50a</sup> have also recommended the alkali treatment for methyl alcohol poisoning but disagree on the efficacy of the use of ethyl alcohol for poisoning from methyl alcohol. Suprunov<sup>50b</sup> has recommended the administration of vitamin C and thiamine in cases of poisoning by methyl alcohol, since he found a reduced amount of these vitamins in the tissues of rabbits following subcutaneous injections of sublethal amounts of methyl alcohol.

Although the individual response of man to methyl alcohol may vary considerably, industrial exposures are not very hazardous if concentrations are maintained within the upper limit of 200 p.p.m. by proper ventilation. Under varying conditions of severity and duration of exposure to the vapor of methyl alcohol, the signs of intoxication may include: irritation of all the mucous membranes, headache, roaring in the ears, tiredness, insomnia, nystagmus, trembling, vertigo, unsteady gait, dyspnea, nausea, vomiting, colic, constipation, dilated pupils, clouded vision, diplopia, blindness, itching of the skin, eczema, and dermatitis.<sup>4,9,10,14,51</sup>

General physical, ocular, and hematological examinations by Greenburg and his associates<sup>13</sup> of 19 workers who had been repeatedly exposed to 22 to 25 p.p.m. of methyl alcohol and 40 to 45 p.p.m. of acetone revealed no significant abnormalities. Likewise, a survey by Yant and associates<sup>42</sup> of 36 men employed in the manufacture of methyl alcohol and of 24 drivers of trucks using methyl alcohol as an antifreeze disclosed no harmful effects. The latter group of investigators found the concentration of methyl alcohol to be higher in the urine and blood in the evening than in the morning, but the amounts were all less than those found in the urine and blood of dogs poisoned by the inhalation of methyl alcohol.

*Human pathology.* Examination by Province *et al.*<sup>51a</sup> of the tissues of five persons fatally poisoned by the ingestion of methyl alcohol disclosed the occurrence of catarrhal gastritis, acute enteritis, focal necrosis of the liver with infiltration by polymorphonuclear leucocytes, pulmonary edema, and early degeneration

<sup>47</sup> A. Kaplan and G. V. Leveault, *U.S. Naval Med. Bull.*, 44, 1107 (1945).

<sup>48</sup> W. L. Voegtlin and C. E. Watts, *U.S. Naval Med. Bull.*, 41, 1715 (1943).

<sup>49</sup> R. T. Johnstone, *Occupational Diseases*. Saunders, Philadelphia, 1941, p. 169.

<sup>50</sup> W. B. Chew, E. H. Berger, O. A. Brines, and M. J. Capron, *J. Am. Med. Assoc.*, 130, 61 (1946).

<sup>50a</sup> O. Røe, *Acta Med. Scand.*, 126, 182, 253 (1946); *Chem. Abstracts*, 41, 2805 (1947).

<sup>50b</sup> A. T. Suprunov, *Farmakol. i Toxikol.*, 9, 49 (1946); *Chem. Abstracts*, 41, 3221 (1947).

<sup>51</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

<sup>51a</sup> W. D. Province, R. A. Kritzler, and F. P. Calhoun, *Bull. U.S. Army Med. Dept.*, 6, 114 (1946).

of the neurons of the brain. Chew *et al.*<sup>50</sup> at necropsy of five other cases found cerebral edema, hypostatic pulmonary congestion, fatty infiltration of the liver, and passive congestion of all organs. On examining eleven similar cases Tønning<sup>51b</sup> found superficial necrosis of the stomach accompanied by mucous distensions of epithelial cells, parenchymatous degeneration of the liver, engorgement of the pulmonary vessels, edema and hyperemia of the brain accompanied by occasional punctate hemorrhages and accumulation of brown pigment in the neurons, and irregular staining of the ganglion cells of the retina accompanied by eccentric nuclei, fraying, vacuolation and autolysis. Necrosis of the pancreas of a woman succumbing from ingestion of methyl alcohol was the most characteristic finding of Branch.<sup>51c</sup>

### 8. Suggested Maximum Concentration

The American Standards Association<sup>52</sup> has adopted 200 parts of methyl alcohol per million parts of air by volume (0.26 mg. per liter at 25° C. and 760 mm.) as the maximum allowable concentration for exposures not exceeding a total of 8 hours daily. 200 p.p.m. is the maximum allowable concentration adopted by most states, but Kentucky and Maryland have accepted the value of 100 p.p.m., and Minnesota the value of 300 p.p.m.

### 9. Inflammability

The flash point of methyl alcohol is 52° F. and the ignition temperature is 878°.<sup>53</sup> The lower and upper explosive limits are, respectively, 6.72 and 36.50 per cent by volume<sup>54</sup> (see Chapter Thirteen).

### 10. Odor and Warning Properties

Methyl alcohol does not have suitable warning odor or irritating properties except at high concentrations. Witte<sup>24</sup> found an initial salivation by cats when exposed to 18,300 p.p.m. (24 mg. per liter). It becomes unendurable in concentrations of 50,000 p.p.m. (65 mg. per liter).<sup>30</sup>

## ETHYL ALCOHOL

### 1. Uses and Industrial Exposure

Ethyl alcohol (C<sub>2</sub>H<sub>5</sub>OH), ethanol, is also called alcohol, grain alcohol, ethyl hydrate, spirit, spirit of wine, and cologne spirits. Among the most important of the three hundred uses of ethyl alcohol listed by Mellan<sup>55</sup> are its use in perfumes, flavoring extracts, drugs, cosmetics, soaps, cleaning solutions, emulsions, anti-freeze mixtures, lacquers, plastics, photographic film, rayon, smokeless powder,

<sup>50</sup> D. J. Tønning, *Nova Scotia Med. Bull.*, 24, 1 (1945).

<sup>51c</sup> A. Branch, *Can. Med. Assoc. J.*, 51, 428 (1944).

<sup>52</sup> American Standards Assoc., "Allowable concentration of methanol," Z37.14-1944.

<sup>53</sup> N. J. Thompson, *Ind. Eng. Chem.*, 21, 134 (1929).

<sup>54</sup> G. W. Jones, *Chem. Revs.*, 22, 1 (1938).

<sup>55</sup> I. Mellan, *Industrial Solvents*. Reinhold, New York, 1939, p. 205.

and esters. It has been used for fuel in some countries. Numerous denaturants for ethyl alcohol have been listed by Zangger.<sup>56</sup>

On the assumption that there was one change of air per hour in workrooms in which violins, artificial flowers, shoes, and hats were being processed, Loewy<sup>57</sup> estimated the prevailing concentrations of ethyl alcohol in the air through calculations based on the volume of the rooms and the quantities of alcohol vaporized therein. He arrived at values of 200 to 1000 p.p.m. in six rooms, 1000 to 5000 p.p.m. in seven rooms, and more than 5000 p.p.m. in three rooms.

## 2. Physical Properties

Ethyl alcohol is a colorless, inflammable, volatile liquid miscible in all proportions with water and most organic solvents. It has the following physical properties: molecular weight, 46.068<sup>58</sup>; specific gravity, 0.78506 at 25°/4° C.<sup>59</sup>; melting point, -114.4°<sup>55</sup>; boiling point, 78.4°<sup>55</sup>; refractive index, 1.3633 at 15°<sup>55</sup>; and vapor pressure, 50 mm. Hg at 25°.<sup>59</sup> The vapor density is 1.59 (air = 1). "Saturated" air contains 6.58 per cent ethyl alcohol vapor by volume at 25° C. and has a density of 1.04 (air = 1).

1 mg./l.  $\approx$  532 p.p.m. and 1 p.p.m.  $\approx$  1.88 mg./cu.m. at 25° C., 760 mm.

## 3. Determination in the Atmosphere

Although no method for the determination of ethyl alcohol has been generally adopted, there are several satisfactory but nonspecific methods available. Jacobs<sup>60</sup> states that ethyl alcohol in the air can be determined by measurement of the specific gravity of its aqueous solution if the sample is bubbled through water until the latter contains more than 0.1 per cent alcohol by volume. The immersion refractometer can be employed if more than 0.5 per cent by volume of alcohol is present in water. Haggard and Greenberg<sup>61</sup> determined the amount of alcohol in air by passing it over iodine pentoxide and measuring the liberated iodine by titration with sodium sulfite. Hydriodic acid, which is also liberated by the pentoxide, is reacted with iodate to liberate additional iodine which is also determined by titration with sodium sulfite.

The oxidation of alcohol to acetic acid by potassium bichromate according to the procedure of Nicloux<sup>62</sup> has been applied to the determination of alcohol in blood and animal tissues and should be applicable to the determination of alcohol in air. After distillation of the acetic acid formed by this reaction, Gettler and

<sup>56</sup> H. Zangger, *Arch. Gewerbepath. Gewerbehyg.*, **2**, 205 (1931).

<sup>57</sup> A. Loewy and R. von der Heide, *Biochem. Z.*, **56**, 125 (1918).

<sup>58</sup> "Atomic Weights (International), 1941," *J. Am. Chem. Soc.*, **63**, No. 3 (1941).

<sup>59</sup> *International Critical Tables of Numerical Data, Physics, Chemistry, and Technology*, Vol. III. McGraw-Hill, New York, 1928, p. 27.

<sup>60</sup> M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941, p. 482.

<sup>61</sup> H. W. Haggard and L. A. Greenberg, *J. Pharmacol.*, **52**, 137 (1934).

<sup>62</sup> M. Nicloux, *Compt. rend. soc. biol.*, **3**, 841 (1896).

Tiber<sup>63</sup> titrated it with 0.05 *N* alkali using phenolphthalein. The quantity of bichromate consumed in the Nicloux reaction was determined iodometrically by McNally,<sup>64</sup> or measured by employing methyl orange to determine when an excess of ferrous sulfate was present.<sup>65</sup>

Ethyl alcohol can be determined in the presence of methyl alcohol by the use of alkaline and acid permanganate.<sup>66</sup> Ethyl alcohol has been determined in the presence of other alcohols by oxidation of the alcohols to fatty acids which are subsequently determined by partition between isopropyl ether and water.<sup>67</sup> Acetone can be destroyed in the presence of ethyl alcohol by paraformaldehyde.<sup>68</sup>

#### 4. Determination in Tissues and Blood

Most methods for the determination of ethyl alcohol in tissues or blood are based upon measurement of the quantity of dichromate used up in oxidizing the alcohol. Ferrous sulfate has been employed by some investigators to titrate the excess dichromate. Harger<sup>65</sup> employed methyl orange as an indicator and Chaikelis and Floersheim<sup>68a</sup> used congo red. Rochat<sup>68b</sup> removed the excess dichromate with Mohr's salt and subsequently titrated with permanganate. McNally and Coleman<sup>68c</sup> titrated the excess dichromate with sodium thiosulfate in the presence of potassium iodide. Gingras and Gaudry<sup>68d</sup> based their procedure upon the measurement, at 600 m $\mu$ , of the green-colored chromic sulfate. Henry *et al.*<sup>68e</sup> oxidized the alcohol to acetaldehyde with dichromate, subsequently determining the aldehyde colorimetrically by its reaction with *p*-hydroxydiphenyl.

#### 5. Physiological Response

*Animal symptomatology.* Animals exposed to ethyl alcohol in air may manifest the following signs of intoxication: slight irritation of the mucous membranes, excitation followed by ataxia, drowsiness, prostration, narcosis, twitching, general paralysis, dyspnea, and occasionally death associated with respiratory failure. Ethyl alcohol has a stronger narcotic effect than methyl alcohol. Although the actual concentration of ethyl alcohol found in the tissues of fatally poisoned animals is less than that of methyl alcohol under corresponding circumstances, the much more rapid oxidation, and hence the slower accumulation of ethyl alcohol in the body, renders ethyl alcohol much less hazardous than methyl

<sup>63</sup> A. O. Gettler and A. Tiber, *Arch. Path. Lab. Med.*, **3**, 218 (1927).

<sup>64</sup> W. D. McNally, *Toxicology*. Industrial Medicine, Chicago, 1937, p. 648.

<sup>65</sup> R. N. Harger, *J. Lab. Clin. Med.*, **20**, 746 (1935).

<sup>66</sup> Hepter, *Z. Nahr.-Genussm.*, **26**, 342 (1913).

<sup>67</sup> C. H. Werkman and O. L. Osburn, *Ind. Eng. Chem., Anal. Ed.*, **3**, 387 (1931).

<sup>68</sup> R. D. Stanley, *J. Assoc. Official Agr. Chem.*, **22**, 594 (1939).

<sup>68a</sup> A. S. Chaikelis and R. D. Floersheim, *Am. J. Clin. Path. (Tech. Suppl.)*, **10**, 180 (1946); *Biol. Abstracts*, **21**, 5367 (1947).

<sup>68b</sup> J. Rochat, *Helv. Chim. Acta*, **29**, 819 (1946); *Analyst*, **72**, 450 (1947).

<sup>68c</sup> W. D. McNally and H. M. Coleman, *J. Lab. Clin. Med.*, **29**, 429 (1944); *Chem. Abstracts*, **38**, 5858 (1944).

<sup>68d</sup> R. Gingras and R. Gaudry, *Laval Med.*, **9**, 661 (1944); *Chem. Abstracts*, **39**, 954 (1945).

<sup>68e</sup> R. J. Henry, C. F. Kirkwood, S. Berkman, R. D. Housewright, and J. J. Henry, *J. Lab. Clin. Med.*, **33**, 241 (1948).

alcohol. Ethyl alcohol is oxidized to carbon dioxide and water, but small amounts of the unoxidized material remain in the blood and are excreted in the urine and expired air for several hours after exposure. Westerfield and associates<sup>69</sup> have shown the transitory presence of acetaldehyde in the oxidation of ethyl alcohol by the body. As in the case of methyl alcohol, there is no difference in the toxicity of natural and synthetic ethyl alcohol.

The physiological effects of the inhalation of ethyl alcohol in various concentrations in air by various animal species are given in Table 2. Dogs subjected to alcohol vapors for 42 minutes showed no signs of intoxication other than slight staggering.<sup>70</sup> The mouse is able to tolerate 23,000 to 25,000 p.p.m.,<sup>71-73</sup> but dies when exposed for a short time to 29,000 p.p.m.<sup>71,72</sup> Guinea pigs survived exposure to 13,300 p.p.m. but succumbed when the concentration was 21,900 p.p.m.<sup>74</sup> Loewy and von der Heide<sup>74</sup> showed that the survival time of rats, which were more susceptible than guinea pigs, was roughly proportional to the duration of exposure, being 6.5, 10-15, and 22 hours in relation to concentrations of 44,000, 22,000, and 12,700 p.p.m., respectively. Rats died when exposed for several days to saturated vapors of ethyl alcohol, according to Macht.<sup>76</sup> Smyth and Smyth<sup>75</sup> exposed guinea pigs for 4 hours per day six days a week on 64 exposure days without any untoward effects.

*Animal pathology.* Weese<sup>73</sup> reports that reversible fatty infiltration of the liver occurs following repeated exposure to high concentrations. Mertens<sup>77</sup> exposed rabbits to air saturated with alcoholic vapors for periods ranging from 25 to 365 days and thereby induced cirrhosis of the liver as a common lesion. Petri<sup>78</sup> found hemorrhagic perivascular infiltrates in the tissues of animals subjected to high dosage.

*Human pathology.* Petri<sup>78</sup> records that Fahr listed the following as the most commonly encountered lesions resulting from prolonged ingestion of toxic quantities of alcohol: fatty infiltration of the liver and heart muscle, chronic leptomeningitis, and chronic gastritis. Brezina,<sup>79</sup> without much proof, accepts certain cardiac disturbances as effects of the inhalation of the vapors of warm alcohol.

<sup>69</sup> W. W. Westerfield, E. Stotz, and R. L. Berg, *J. Biol. Chem.*, 149, 237 (1943).

<sup>70</sup> Gréchant and E. Quinquaud, *Compt. rend. soc. biol.*, 5, 426 (1883).

<sup>71</sup> C. Bachem, *Arch. exptl. Path. Pharmacol.*, 122, 69 (1927).

<sup>72</sup> K. B. Lehmann and F. Flury, *Tozikologie und Hygiene der technischen Lösungsmittel*. Springer, Berlin, 1938, p. 152.

<sup>73</sup> H. Weese, *Arch. exptl. Path. Pharmacol.*, 135, 118 (1928).

<sup>74</sup> A. Loewy and R. von der Heide, *Biochem. Z.*, 86, 125 (1918).

<sup>75</sup> H. F. Smyth and H. F. Smyth, Jr., *J. Ind. Hyg.*, 10, 261 (1928).

<sup>76</sup> D. I. Macht, *J. Pharmacol.*, 16, 1 (1920).

<sup>77</sup> H. Mertens, *Arch. intern. pharmacodynamie*, 2, 127 (1896).

<sup>78</sup> E. Petri, in F. Henke and O. Lubarsch, *Handbuch der speziellen pathologischen Anatomie und Histologie*, Vol. X. Springer, Berlin, 1930, p. 276.

<sup>79</sup> E. Brezina, *Internationale Übersicht über Gewerbekrankheiten*. Springer, Berlin, 1929, p. 83.

TABLE 2  
*Physiological Effects upon Animals of the Inhalation of Ethyl Alcohol*

Animal	Concentration		Duration of exposure, hr.	Signs of intoxication	Outcome	Investigator
	p.p.m.	mg./l.				
Mouse	29,370	55.2	Short (?)	—	Died	Bachem <sup>23</sup>
	22,980	43.2	"	Tolerated	Survived	"
	31,900	70.0	0.33	Ataxia	—	Lehmann and Flury <sup>72</sup>
	29,300	55.0	7.0	Narcosis	Died	"
	23,940	45.0	1.25	Narcosis	—	"
	13,300	25.0	1.33	Ataxia	—	"
	25,000	48.1	125 over several days	Narcosis	Survived	Weese <sup>25</sup>
	16,700	31.4	24 over several days	Narcosis	Survived	"
	8,350	15.7	29 X 7.2	Ataxia	Survived	"
	45,000	84.6	3.75	Inco-ordination	—	Loewy and von der Heide <sup>57</sup>
Guinea pig	44,000	82.7	7.5	Deep narcosis	—	"
	50,170	94.3	10.2	Deep narcosis	Died	"
	19,260	36.2	3.75	None	—	"
	20,000	37.6	6.5	Inco-ordination	—	"
	21,900	41.2	9.8	Deep narcosis	Died	"
	9,080	17.1	5.25	None	—	"
	12,850	24.2	8.75	Inco-ordination	—	"
	13,300	25.0	24.0	Light narcosis	—	"
	6,400	12.0	8.0	None	Survived	"
	3,000 <sup>c</sup>	5.6	64 X 4	None	Survived	Smyth and Smyth <sup>75</sup>

Animal	Concentration		Duration of exposure, hr.	Signs of intoxication	Outcome	Investigator
	p.p.m.	mg./l.				
Rat	45,000	84.6	3.75	Deep narcosis	—	Loewy and von der Heide <sup>67</sup>
	44,000	82.7	6.5	Deep narcosis	Died	"
	19,260	36.2	2.0	Light narcosis	—	"
	21,960	41.2	9.8	Deep narcosis	Died	"
	18,200	34.2	1.0	Excitation	—	"
	18,200	34.2	1.75	Inco-ordination	—	"
	22,800	42.9	8.0	Deep narcosis	—	"
	22,100	41.5	15.0	Deep narcosis	Died	"
	10,750	20.2	0.5	None	—	"
	10,750	20.2	2.0	Inco-ordination	—	"
	12,400	23.3	8.5	Deep narcosis	—	"
	12,700	23.8	21.75	Deep narcosis	Died	"
	5,660	10.6	1.75	Inco-ordination	—	"
	6,400	12.3	12.0	Light narcosis	Survived	"
	3,260	6.1	6.0	None	—	"
	3,260	6.1	8.0	Drowsiness	—	"
	4,580	8.6	21.13	Ataxia	Survived	"

<sup>67</sup> This was volatilized from alcohol containing 0.5 per cent benzene.

### 6. Absorption and Excretion by Animals

Loewy and von der Heide<sup>74</sup> found that a state of diminished excitability on the part of rats exposed to the vapors of alcohol was associated with the presence in their carcasses of concentrations of alcohol ranging from 0.16 to 0.27 g. per kilogram of their total weight. Corresponding concentrations of 1 g. per kilogram were associated with the induction of a state of narcosis, and concentrations ranging from 3.1 to 5.8 g. per kilogram were found in the bodies of fatally poisoned animals. Guinea pigs, which are more resistant than rats, are severely intoxicated but may survive in spite of the presence of concentrations of alcohol within the latter range. Rats and guinea pigs oxidized 66.5 to 98.9 per cent of the absorbed alcohol<sup>74</sup> when exposed for about 2 hours to air containing 27,600 to 41,400 p.p.m. of ethyl alcohol. Chickens exposed by Carpenter<sup>80</sup> to alcohol vapors for 2 to 29 hours usually had the highest concentration in the blood, although occasionally higher concentrations were found in the brain. The lowest concentrations of alcohol were found in the fat. According to Carpenter,<sup>80</sup> when the concentration of alcohol in the blood of chickens was more than 2.5 g. per kilogram, or when that in the whole body was more than 1.7 g. per kilogram, the animals showed signs of abnormal behavior. Concentrations of 3.7 to 5.6 g. per kilogram of body weight proved fatal. The concentration of alcohol in the blood of dogs was found to be about 60 per cent higher than that in the body as a whole.<sup>81</sup> This percentage is in excellent agreement with that of Carpenter. The concentration of alcohol in the blood of dogs breathing an undetermined concentration of alcohol rose from 0.8 g. per kilogram of blood after 2 hours to 4.0 after 6 hours.

Following the ingestion by dogs of 3.3 g. of alcohol per kilogram of body weight, Haggard and Greenberg<sup>81a</sup> found that the concentration of alcohol in the urine in relation to that in the arterial blood corresponded closely to the relative solubility *in vitro* of alcohol in urine and blood (1.14 to 1). These observations were interpreted as suggesting that alcohol passes through the kidneys by simple diffusion. During the period of absorption from the gastroenteric tract, the concentration of ethyl alcohol found in a peripheral vein (femoral) was somewhat lower than that in the arterial blood. The same investigators found that during a 16-hour period following ingestion of alcohol by dogs, 2.1 to 4.3 per cent of the total alcohol ingested was eliminated by the kidneys, the rate of elimination within this range being a function of the concurrent urinary volume. The ratio of the concentration of ethyl alcohol in the arterial blood to that in the alveolar air was found to be 1142 to 1 in correspondence with the distribution of alcohol *in vitro* in the media involved. The total amount eliminated by dogs in the expired air in a period of 8 hours following ingestion of 4 g. per kilogram amounted to 4 per cent of the total amount ingested.

<sup>74</sup> T. M. Carpenter, *J. Pharmacol.*, **37**, 217 (1929).

<sup>81</sup> H. W. Haggard and L. A. Greenberg, *J. Pharmacol.*, **52**, 167 (1934).

<sup>81a</sup> H. W. Haggard and L. A. Greenberg, *J. Pharmacol.*, **52**, 150 (1934).



In a further article, Haggard and Greenberg<sup>81</sup> have shown that, as in the case of methyl alcohol, the rate of oxidation of ethyl alcohol is proportional to the amount of alcohol present in the body. This was demonstrated by finding a uniform hourly decrease of 17.6 per cent of the alcohol present in the arterial blood. Elimination in the expired air was increased slightly by the increased ventilation induced by administration of carbon dioxide.

Eggleston and Smith<sup>81b</sup> observed a depression of chloride excretion in the urine of man during a period of diuresis following the ingestion of ethyl alcohol. Lolli *et al.*<sup>81c</sup> suggested that the water lost in diuresis was insufficient in quantity to account for thirst following alcohol intoxication. They suggested that there is a redistribution of intracellular to extracellular water in the body, since rats given ethyl alcohol by mouth or injection showed an increase in extracellular water.

Ethyl alcohol penetrates the skin of animals, but not at a rate sufficient to induce serious effects. Deichmann<sup>82</sup> found values of 0.13 and 0.04 mg. of alcohol, respectively, per 100 milliliters of blood, at 0.5- and 1-hour intervals following one application of 35 ml. per kilogram of body weight upon the belly of a rabbit protected against inhalation of the vapor. Boughton<sup>83</sup> made 187 daily applications of 10 drops of 50 per cent solution of ethyl alcohol upon the facial skin of rats without injury to the skin, hair, and eyes other than temporary irritation.

Newman and Lehman<sup>84</sup> demonstrated that dogs habituated to drinking alcohol showed better neuromuscular co-ordination under the influence of a given concentration of alcohol in the blood than did control dogs. Furthermore, since the brains of habituated rats contained a slightly higher concentration of alcohol than did those of control rats under corresponding condition of dosage, these investigators<sup>84</sup> believe that acquired tolerance in animals is primarily an adaptation of the cells of the central nervous system.

### 7. Effects upon Man

The well-known effects of chronic alcoholism from the excessive use of alcoholic beverages are not matters of concern in relation to occupational hazards, except to the extent that they may influence the effects of exposure to other substances and environmental conditions. In any case, they do not enter into the present discussion.

The following nonindustrial cases of idiosyncrasy of children to alcohol vapors have been reported: vomiting, unconsciousness, and nystagmus by James<sup>85</sup>; narcosis by Kalt<sup>86</sup>; and death by Leschke.<sup>87</sup>

Although ethyl alcohol is relatively innocuous if proper ventilation is main-

<sup>81b</sup> M. G. Eggleston and I. G. Smith, *J. Physiol.*, 104, 435 (1946).

<sup>81c</sup> G. Lolli, M. Rubin, and L. A. Greenberg, *Quart. J. Studies Alc.*, 5, 5 (1944).

<sup>82</sup> W. Deichmann, *personal communication*.

<sup>83</sup> L. L. Boughton, *J. Am. Pharm. Assoc., Sci. Ed.*, 33, 111 (1944).

<sup>84</sup> H. W. Newman and A. J. Lehman, *J. Pharmacol.*, 62, 301 (1938).

<sup>85</sup> V. C. James, *Brit. Med. J.*, 1, 539 (1931).

<sup>86</sup> A. Kalt, *Schweizer Korresp.*, 1906 (p. 725).

<sup>87</sup> E. Leschke, *Munch. med. Wochschr.*, 79, 751 (1932).

tained, prolonged exposures to too high a concentration may produce: irritation of the mucous membrane, irritation of the upper respiratory tract, headache, nervousness, dizziness, tremors, fatigue, nausea, and narcosis.<sup>74,88,89</sup> The effects of ethyl alcohol upon the power of concentration and alertness should be remembered in relation to the prevention of industrial accidents. Lehmann and Flury<sup>72</sup> are authority for the statement that intoxication has been seen among human beings subjected to inhalation of the vapors of hot alcohol.

In terms of symptomatology in relation to dosage, there is no doubt that a tolerance is acquired after repeated exposure to alcohol. However, no proof has been submitted of physiological adaptation in man in terms of metabolic changes or of resistance to cellular injuries. Loewy and von der Heide<sup>74</sup> (Table 3) have

TABLE 3  
*Symptoms Induced in Man by Inhalation of Ethyl Alcohol*

Average concentration		Duration of exposure, min.	Symptoms
mg./l.	p.p.m.		
A. Subject Unaccustomed to Alcohol			
2.59	1380	39	None after 28 min.; after 33 min. headache and slight numbness
6.28	3340	100	Sensation of warmth and coldness, nasal irritation, headache, numbness
16.62	8840	64	Initial intolerable odor and difficulty in breathing, soon overcome, conjunctival and nasal irritation, feeling of warmth, headache, drowsiness, fatigue
B. Subject Accustomed to Alcohol			
9.45	5030	120	Slight headache after 20 min.
11.50	6120	120	Odor intense, slight pressure in left temple
13.14	6990	109	Headache, conjunctival irritation, feeling of warmth, drowsiness, fatigue

shown that the symptoms are less severe and the time required to produce them is greater in subjects accustomed to alcohol than in those unaccustomed to it. A subject unaccustomed to alcohol complained of headache after 33 minutes in an atmosphere of 1380 p.p.m. of ethyl alcohol; a feeling of warmth after 11 minutes, and numbness after 50 minutes of exposure to 3340 p.p.m.; intense stinging of eyes and drowsiness after 10 minutes, and a feeling as of intracranial pressure, numbness, and drowsiness after 29 minutes of exposure to a concentration of 8840 p.p.m. Subjects accustomed to alcohol exhibited only slight headache after 20 minutes of exposure to 5030 p.p.m.; occasional sensations of intracranial pressure after 120 minutes of exposure to 6120 p.p.m; and a feeling of warmth and drowsiness after 90 minutes when subjected to 6990 p.p.m. of ethyl alcohol in the air.

<sup>88</sup> F. Koelsch, *Zentr. Gewerbehyg. Unfallverhüt.*, 9, 203 (1921).

<sup>89</sup> E. Roth in R. Abel, *Handb. der prakt. Hygiene*, p. 232.

Determination of the content of ethyl alcohol in the blood, spinal fluid, urine, or even the breath is useful in determining the amount absorbed, when such data are considered in conjunction with accurate information on the time and duration of the exposure. Although there is considerable variation among individuals and in the same individual at different times, as well as some divergence in the data of various authorities, the clinical effects shown in Table 4 are commonly associated with the indicated concentrations in the blood.<sup>72</sup>

TABLE 4  
*Effects of Ethyl Alcohol in the Blood*

Effect	Alcohol concentration in Blood, %
Beginning of uncertainty .....	0.06-0.08
Slow comprehension .....	0.10
Stupor .....	0.12-0.15
Drunkenness .....	0.16
Severe intoxication .....	0.2-0.4
Death .....	0.4-0.5

### 8. Suggested Maximum Concentration

Lehmann and Flury<sup>72</sup> have suggested that 1060 parts of ethyl alcohol per million parts of air by volume (2.0 mg. per liter at 25° C. and 760 mm. Hg) be considered the highest permissible concentration. Loewy and von der Heide<sup>74</sup> believe that the alcoholic vapor in workrooms should be less than 2500 p.p.m. (4.7 mg. per liter) and preferably less than 1000 p.p.m. Smyth and Smyth<sup>75</sup> accept repeated exposure to 3000 p.p.m. (5.7 mg. per liter) as safe. The Union of Soviet Socialist Republics has recommended 250 p.p.m. (0.47 mg. per liter), as has also the Kentucky State Department of Health. The Industrial Accident Commission of California, the Florida Industrial Commission, and the New York State Department of Labor have adopted the concentration of 1000 p.p.m. (1.88 mg. per liter).

### 9. Inflammability

The flash points of 95 per cent alcohol and absolute alcohol are 65° F. and 57° F., respectively,<sup>55</sup> and the ignition temperature of 95 per cent alcohol is 738° F. (392° C.).<sup>90</sup> The lower and upper explosive limits of alcohol are, respectively, 3.28 and 18.95 per cent by volume in air<sup>91</sup> (see Chapter Thirteen).

### 10. Odor and Warning Properties

Concentrations of 6000 to 9000 p.p.m. have an intense odor and may be practically intolerable at first, but one becomes acclimated to them after a short time. Concentrations of this order of magnitude, however, should not be permitted.

<sup>90</sup> N. J. Thompson, *Ind. Eng. Chem.*, **21**, 134 (1929).

<sup>91</sup> G. W. Jones, *Chem. Revs.*, **22**, 1 (1933).

## *n*-PROPYL ALCOHOL

### 1. Uses and Industrial Exposure

*n*-Propyl alcohol, (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>OH), 1-propanol, although not used as extensively as certain other alcohols, may be used as a solvent for castor, croton, linseed, and other oils; natural and synthetic resins; and certain cellulose ethers.<sup>94</sup>

### 2. Physical Properties

*n*-Propyl alcohol is a colorless, inflammable, volatile liquid with an odor that has some resemblance to that of fusel oil. It is miscible with water, alcohol, and ether. It has the following physical properties: molecular weight, 60.0940<sup>92</sup>; specific gravity, 0.804 at 20°/4° C.<sup>93</sup>; melting point, -127°; boiling point, 97.4°<sup>93</sup>; and vapor pressure, 20.8 mm. Hg at 25°.<sup>94</sup> The vapor density is 2.08 (air = 1). "Saturated" air contains 2.7 per cent *n*-propyl alcohol vapor by volume at 25° C. and has a density of 1.03 (air = 1).

1 mg./l.  $\approx$  408 p.p.m. and 1 p.p.m.  $\approx$  2.45 mg./cu.m. at 25° C., 760 mm.

### 3. Physiological Response

*Animal symptomatology.* Animals exposed to vapors of *n*-propyl alcohol may manifest the following signs of intoxication: irritation of the mucous membrane, ataxia, lethargy, prostration, narcosis, and death. Weese<sup>95</sup> found that mice survived when they were exposed intermittently to the narcotic vapor of 7874 p.p.m. in air (19.3 mg. per liter) for a total period of 95 hours, but died if exposed for 160 minutes to 13,120 p.p.m. (32.2 mg. per liter) or for 120 minutes to 19,680 p.p.m. (48.2 mg. per liter).

Groups of mice (two in each) were exposed by Starrek<sup>96</sup> for decreasing lengths of time (480, 240, 135, 120, 90, and 60 minutes) to increasing concentrations of *n*-propyl alcohol in the atmosphere [3250 p.p.m. (8 mg. per liter), 4100 p.p.m. (10 mg. per liter), 8150 p.p.m. (20 mg. per liter), 12,250 p.p.m. (30 mg. per liter), 16,300 p.p.m. (40 mg. per liter), and 24,500 p.p.m. (60 mg. per liter)]. The length of time required for the appearance of ataxia, prostration, and deep narcosis was inversely proportional to the concentration to which the mice were exposed. Ataxia appeared in 10 to 14 minutes at 24,500 p.p.m. and in 90 to 120 minutes at 3250 p.p.m. Prostration was evident in 19 to 23 minutes at the former concentration and in 165 to 180 minutes at the latter. Deep narcosis was manifest in 60 minutes at 24,500 p.p.m. and in 240 minutes at 4100 p.p.m. Only one of twelve mice that showed signs of intoxication died. Mice exposed for 480 minutes to 2050 p.p.m. (5 mg. per liter) showed no reaction.

<sup>92</sup> "Atomic Weights (International) 1941," *J. Am. Chem. Soc.*, 63, No. 3 (1941).

<sup>93</sup> Beilstein, *Handbuch der organischen Chemie*. 4th ed., Vol. I, Springer, Berlin, 1918, p. 350.

<sup>94</sup> I. Mellan, *Industrial Solvents*. Reinhold, New York, 1939, pp. 215, 216.

<sup>95</sup> H. Weese, *Arch. exper. Path. Pharmacol.*, 135, 118 (1928)

<sup>96</sup> E. Starrek, *Dissertation, Würzburg*, 1938.

#### 4. Absorption and Excretion

*n*-Propyl alcohol was found in the blood of a dog for 275 minutes following the oral administration of 16.1 g. of this alcohol. Acetone, derived from isopropyl alcohol, was found in the blood of a dog for 540 minutes following the oral administration of 15.8 g. of isopropyl alcohol. Hence, *n*-propyl alcohol is oxidized and eliminated faster than isopropyl alcohol.<sup>97</sup> Basing his opinion upon the concentrations in the blood, the same investigator<sup>97</sup> concluded that *n*-propyl alcohol was oxidized and eliminated from the dog considerably more rapidly than was ethyl alcohol. Rabbits given *n*-propyl alcohol by the intravenous route also oxidized it more rapidly than ethyl alcohol.<sup>98</sup>

#### 5. Inflammability

*n*-Propyl alcohol vapor is inflammable within the range of 2.15 to 13.50 per cent by volume in air. The flash point of *n*-propyl alcohol is 59° F. (15.0° C.) and the ignition temperature is 822° F. (see Chapter Thirteen).

### ISOPROPYL ALCOHOL

#### 1. Uses and Industrial Exposure

Isopropyl alcohol,  $(\text{CH}_3)_2\text{CHOH}$ , is also known as isopropanol, 2-propanol, *sec*-propyl alcohol, dimethylcarbinol, Perspirit, Petrohol, or Avantine. It is used as a solvent in perfumes, cosmetics, pharmaceuticals, and lacquers. Isopropyl alcohol is used in extraction processes and as a preservative and dehydrating agent.<sup>94</sup> It has been used in the "fused collar" industry.<sup>99</sup> Recently it has gained widespread use as a rubbing alcohol. However, it should not be taken internally.

Isopropyl alcohol does not constitute an industrial hazard; no deleterious effects have been reported as a result of its industrial use, except for a case of encephalopathy<sup>99</sup> which followed exposure to a mixed solvent containing isopropyl alcohol. It is probable that an associated solvent was responsible for the reported injury.<sup>100</sup>

#### 2. Physical Properties

Isopropyl alcohol is a water-white stable liquid with an odor similar to that of ethyl alcohol. Its physical properties are: molecular weight, 60.0940<sup>92</sup>; specific gravity, 0.7874 at 20°/20° C.<sup>94</sup>; melting point, -85.8°<sup>94</sup>; boiling point, 82.4°<sup>94</sup>; refractive index, 1.3776 at 20°<sup>94</sup>; vapor pressure, 44.0 mm. Hg at 25°<sup>94</sup>. The vapor density is 2.08 (air = 1). "Saturated" air contains 5.79 per cent isopropyl alcohol vapor by volume at 25° C. and has a density of 1.06 (air = 1). Essential and other oils, alkaloids, gums, shellac, sandarac, rosin, mastic, copals, and some

<sup>92</sup> M. Neymark, *Skand. Arch. Physiol.*, 78, 242 (1938).

<sup>93</sup> S. M. Berggren, *Skand. Arch. Physiol.*, 78, 249 (1938).

<sup>94</sup> D. E. Donley, *J. Ind. Hyg. Toxicol.*, 18, 571 (1936).

<sup>100</sup> C. E. Parsons and M. E. M. Parsons, *J. Ind. Hyg. Toxicol.*, 20, 124 (1938).

synthetic resins are dissolved by it.<sup>94</sup> Isopropyl alcohol is miscible with water and most organic solvents.

1 mg./l.  $\approx$  407 p.p.m. and 1 p.p.m.  $\approx$  2.45 mg./cu.m. at 25° C., 760 mm.

### 3. Determination in the Atmosphere

Isopropyl alcohol that has been collected in water may be oxidized to acetone by chromic acid, and the acetone subsequently measured iodimetrically.<sup>101</sup> The use of sodium nitroprusside for determining the acetone seems feasible.<sup>102</sup> After absorbing isopropyl alcohol on silica gel, Hahn<sup>103</sup> recovered it by steam distillation, converted it to isopropyl nitrite, and subsequently titrated the liberated nitrous acid according to the procedure of Knipping and Ponndorf.<sup>104</sup>

### 4. Physiological Response

*Animal symptomatology.* Isopropyl alcohol in large amounts is more toxic<sup>105</sup> and more narcotic<sup>95,106</sup> than ethyl alcohol, but less so than *n*-propyl alcohol.<sup>107</sup> There is apparently little or no accumulation in the body. On the basis of symptomatology<sup>108-110</sup> and concentration of alcohol in the blood,<sup>109</sup> there is some evidence that a slight tolerance is acquired.

Animals subjected to vapor of isopropyl alcohol have manifested the following signs of intoxication: irritation of the mucous membranes, ataxia, prostration, deep narcosis, and death.

Rats were unaffected except for slight intoxication when exposed by Macht<sup>107,111</sup> intermittently over a period of a week (total number of hours of exposure not given) to air apparently saturated with vapor of isopropyl alcohol. Mice subjected by Weese<sup>95</sup> to 10,900 p.p.m. isopropyl alcohol in air (26.8 mg. per liter) for about 4 hours per day until they had accumulated 123 hours of exposure were narcotized but survived. Mice died if exposed to 12,800 p.p.m. (31.4 mg. per liter) for 200 minutes or 19,200 p.p.m. (47.1 mg. per liter) for 160 minutes. The difference between the results of Macht and Weese would hardly seem explainable in terms of the varying susceptibility of the two animal species. Until more conclusive evidence is available, it is wise to assume that high concentrations may be dangerous.

The length of time required for the development of ataxia, prostration, and deep narcosis on the part of mice exposed by Starrek<sup>96</sup> to vapors of isopropyl

<sup>101</sup> M. B. Jacobs, *The Analytical Chemistry of Industrial Poisons, Hazards and Solvents*. Interscience, New York, 1941, p. 487.

<sup>102</sup> G. Kleyer, *Pharm. Ztg.*, **72**, 1262 (1927).

<sup>103</sup> E. Hahn, *Biochem. Z.*, **292**, 148 (1937).

<sup>104</sup> H. W. Knipping and W. Ponndorf, *Z. physiol. Chem.*, **160**, 25 (1926).

<sup>105</sup> A. J. Lehman and H. F. Chase, *J. Lab. Clin. Med.*, **29**, 561 (1944).

<sup>106</sup> A. J. Lehman, H. Schwerma, and E. Rickards, *J. Pharmacol.*, **82**, 196 (1944).

<sup>107</sup> D. I. Macht, *J. Pharmacol.*, **16**, 1 (1920).

<sup>108</sup> H. C. Fuller and O. B. Hunter, *J. Lab. Clin. Med.*, **12**, 326 (1927).

<sup>109</sup> A. J. Lehman, H. Schwerma, and E. Rickards, *J. Pharmacol.*, **85**, 61 (1945).

<sup>110</sup> J. Pohl, *Biochem. Z.*, **127**, 66 (1921).

<sup>111</sup> D. I. Macht, *Arch. intern. pharmacodynamie*, **26**, 285 (1922).

alcohol was inversely proportional to the concentration. Ataxia was manifest in 12 to 26 minutes at 24,500 p.p.m. (60 mg. per liter), but it occurred with progressively decreasing rapidity at concentrations of 16,300 p.p.m. (40 mg. per liter), 12,250 p.p.m. (30 mg. per liter), 8150 p.p.m. (20 mg. per liter), and 4100 p.p.m. (10 mg. per liter), until at 3250 p.p.m. (8 mg. per liter) 180 to 195 minutes were required. Prostration appeared in 37 to 46 minutes at 24,500 p.p.m. and in 340 to 350 minutes at 3250 p.p.m. The onset of deep narcosis ranged from 100 minutes at 24,500 p.p.m. to 460 minutes at 3250 p.p.m. Only one of twelve mice exposed in these experiments succumbed. Mice exposed for 480 minutes to 2050 p.p.m. (5 mg. per liter) gave no evidence of reaction.

*Animal pathology.* Reversible fatty changes in the livers of mice, following repeated inhalation of isopropyl alcohol, have been reported by Weese.<sup>95</sup> No gross or microscopic abnormalities of the brain, pituitary, lung, heart, liver, spleen, kidneys, or adrenals of rats given 0.5 to 10.0 per cent of isopropyl alcohol in their drinking water for 27 weeks were observed by Lehman and Chase.<sup>105</sup>

#### 5. Absorption and Excretion by Animals and Man

Numerous investigators have found acetone in the urine of men and animals following oral administration of isopropyl alcohol. According to Fuller and Hunter,<sup>108</sup> small amounts of acetone were found in the urine of men 2 to 4 days after the last of three doses of 20 or 30 ml. of 50 per cent aqueous isopropyl alcohol, one dose per day for three successive days having been given. Acetone was found by Kemal<sup>112</sup> in the urine of men after ingestion of 0.1 g. of isopropyl alcohol. This investigator found a relatively small quantity of acetone, as compared with the amount of isopropyl alcohol, in the urine of men for 24 hours and 48 hours, respectively, following the ingestion of 5 or 10 g. of isopropyl alcohol. Morris and Lightbody<sup>113</sup> gave 6 ml. of isopropyl alcohol per kilogram of body weight by mouth to each of six rabbits, and found acetone in the urine of five of them during the following 72 hours, but none thereafter. Kemal<sup>114</sup> gave a progressively increasing daily dose of isopropyl alcohol (5 to 90 ml.) by stomach tube to three dogs. From the thirteenth day on, when doses of 65 ml. or more of isopropyl alcohol were given, 48 to 71 mg. of acetone and 119 to 148 mg. of isopropyl alcohol, per 100 milliliters of urine, were found in daily volumes of urine ranging from 1070 to 2250 ml. A method for the determination of both isopropyl alcohol and acetone in the urine has been described by Cook and Smith.<sup>115</sup> The isopropyl alcohol of one aliquot is oxidized to acetone and the total acetone weighed as the mercuric sulfate complex of Denigès. In another aliquot, the original acetone present is distilled into hydroxylamine hydrochloride and the resulting hydrochloric acid titrated using methyl orange as an indicator.

In the experiments of Lehman and associates,<sup>109</sup> this alcohol was metabo-

<sup>108</sup> H. Kemal, *Biochem. Z.*, **187**, 461 (1927).

<sup>109</sup> H. J. Morris and H. D. Lightbody, *J. Ind. Hyg. Toxicol.*, **20**, 428 (1938).

<sup>110</sup> H. Kemal, *Z. physiol. Chem.*, **246**, 59 (1937).

<sup>115</sup> C. A. Cook and A. H. Smith, *J. Biol. Chem.*, **85**, 251 (1929).

lized more slowly than was ethyl alcohol at two levels of concentration by cats, rabbits, and pigeons, but in dogs the rate of disappearance of isopropyl alcohol from the blood was more rapid than that of ethyl alcohol when the concentrations were high and slower when they were low. The rate of decrease of isopropyl alcohol in the blood of dogs for a period of 4 to 24 hours following intravenous infusion of isopropyl alcohol (0.64 to 3.84 ml. per kilogram) or oral administration (0.93 to 3.75 ml. per kilogram) has been found to vary with the concentration of alcohol in the blood.<sup>106</sup>

Acetone and isopropyl alcohol have been found in the expired air of animals and man following intake of isopropyl alcohol. In a period of 12 hours following the oral administration of 2.37 g. of isopropyl alcohol to rabbits, 0.251 g. of acetone (equivalent to 0.258 g. isopropyl alcohol) and 0.0281 g. of isopropyl alcohol were found by Pohl<sup>110</sup> in the expelled air. These amounted to 10.9 and 1.2 per cent, respectively, of that administered. The administration of adrenaline, histamine, or oxyphenylethylamine to dogs did not alter significantly the rate of their oxidation of isopropyl alcohol.<sup>110</sup> For a period of a few hours following the ingestion of 720 mg. of aqueous isopropyl alcohol by man, Hahn<sup>103</sup> found the expired air contained isopropyl alcohol and acetone.

The distribution of isopropyl alcohol and acetone in the tissues of dogs 4 hours after the oral administration of 90 ml. of isopropyl alcohol was determined by Kemal.<sup>114</sup> (These dogs had been given progressively increasing amounts of the alcohol for the previous 59 days.) In general, the concentrations of isopropyl alcohol found in the tissues and body fluids decreased in the following order: brain, urine, heart, kidney, and blood. The relationship of the concentrations of acetone in the tissues and urine was not as clearly defined as that of isopropyl alcohol. Except in the blood, where the value for acetone approached that for isopropyl alcohol, the concentration of isopropyl alcohol in the tissues and urine was about twice that for acetone.

By measuring the electric current necessary to induce clonic convulsions in rabbits, rats, and cats, Chu *et al.*<sup>115a</sup> found that isopropyl alcohol had anticonvulsant properties. These authors measured the increase in acetone in the blood and concluded that it paralleled the anticonvulsant action.

Single or repeated applications of isopropyl alcohol upon the skin of rats, rabbits, dogs, or human beings induced no untoward effects.<sup>111,116,117</sup>

## 6. Inflammability

The flash point of isopropyl alcohol is 53° F. and the ignition temperature is 853° F. The lower limit of inflammability is 2.02 per cent by volume in air (see Chapter Thirteen).

<sup>115a</sup> N. Chu, R. L. Driver, and P. J. Hanzlik, *J. Pharmacol.*, **92**, 291 (1948).

<sup>116</sup> H. Boruttau, *Deut. med. Wochschr.*, **47**, 747 (1921).

<sup>117</sup> L. L. Boughton, *J. Am. Pharm. Assoc., Sci. Ed.*, **33**, 111 (1944).



### 7. Suggested Maximum Concentration

A value of 400 p.p.m. has been suggested by Cook<sup>118</sup> as a maximum allowable concentration of the vapor of isopropyl alcohol in air. Although isopropyl alcohol is more toxic than ethyl alcohol, its vapor pressure is less, so it should be but little more hazardous in industrial use than ethyl alcohol.

### 8. Warning Properties

Mild irritation of the eyes, nose, and throat was induced in human subjects exposed by Nelson and associates<sup>119</sup> for 3 to 5 minutes to 400 p.p.m. of isopropyl alcohol. Although the effects of exposure to 800 p.p.m. were not severe, most subjects found the atmosphere objectionable. From the viewpoint of comfort, these subjects found 200 p.p.m. to be the highest concentration acceptable for an 8-hour exposure.

## *n*-BUTYL ALCOHOL

### 1. Uses and Industrial Exposure

*n*-Butyl alcohol ( $C_2H_5CH_2CH_2OH$ ), 1-butanol, is also called butyl hydroxide, propylcarbinol, butyric alcohol, or hydroxybutane. It is used as a detergent, defrother, penetrant, denaturant, and to enhance the solvent powers of other solvents.<sup>120</sup> The production, or in some cases use, of the following substances may offer exposure to *n*-butyl alcohol: artificial leather, butyl esters, rubber cement, dyes, fruit essences, lacquers, motion picture and photographic films, raincoats, perfumes, pyroxylin plastics, rayon, safety glass, shellac, varnish, and waterproofed cloth.<sup>120-123</sup>

Concentrations of 5 to 100 p.p.m. of butyl alcohol in the air in 6 plants manufacturing raincoats and waterproofed cloths for sleeping pads have been reported by Tabershaw and his associates.<sup>122</sup>

### 2. Physical Properties

*n*-Butyl alcohol is a water-white, combustible liquid with a pungent odor somewhat like that of fusel oil. It is miscible with most organic solvents. At 25° C. butyl alcohol is soluble in water to the extent of 8.9 per cent by volume and water is soluble in butyl alcohol to the extent of 17.1 per cent by volume.<sup>120</sup> *n*-Butyl alcohol has the following physical properties: molecular weight, 74.120<sup>124</sup>; specific gravity, 0.8108 at 20°/20° C.<sup>120</sup>; melting point, -89.8°<sup>120</sup>; boiling point, 117.7°<sup>120</sup>; refractive index, 1.3974 at 25°<sup>120</sup>; vapor pressure, 6.5 mm. Hg at

<sup>118</sup> W. A. Cook, *Ind. Med.*, 14, 936 (1945).

<sup>119</sup> K. W. Nelson, J. F. Ege, Jr., M. Ross, L. E. Woodman, and L. Silverman, *J. Ind. Hyg. Toxicol.*, 25, 282 (1943).

<sup>120</sup> I. Mellan, *Industrial Solvents*. Reinhold, New York, 1939, pp. 229, 236.

<sup>121</sup> D. G. Cogan and W. M. Grant, *Arch. Ophthalmol.*, 33, 106 (1945).

<sup>122</sup> I. R. Tabershaw, J. P. Fahy, and J. B. Skinner, *J. Ind. Hyg. Toxicol.*, 26, 323 (1944).

<sup>123</sup> U.S. Dept. Labor, *Bur. Labor Statistics Bull.* No. 41, 38 (1942).

<sup>124</sup> "Atomic Weights (International), 1941," *J. Am. Chem. Soc.*, 63, No. 3 (1941).

25°. <sup>120</sup> The vapor density is 2.56 (air = 1). "Saturated" air contains 0.86 per cent *n*-butyl alcohol vapor by volume at 25° C. and has a density of 1.01 (air = 1). 1 mg./l.  $\approx$  330 p.p.m. and 1 p.p.m.  $\approx$  3.03 mg./cu.m. at 25° C., 760 mm.

### 3. Determination in the Atmosphere

No specific analytical method is available, but under circumstances involving the presence of *n*-butyl alcohol alone, its oxidation by chromic acid may be measured quantitatively. The determination of *n*-butyl alcohol in the presence of acetone and ethyl alcohol in an aqueous solution is described by Christensen and Fulmer.<sup>125</sup> In measuring industrial air concentrations, Tabershaw and his associates<sup>122</sup> employed the method of Ficklen<sup>126</sup> which measures iodimetrically the amount of chromate necessary to oxidize *n*-butyl alcohol to butyric acid. This is similar to a method referred to previously, in the case of ethyl alcohol. Hoch<sup>126a</sup> employed a commercial type of equipment (M-6 Vaportester, Davis Emergency Equipment Co.) for determining the concentration of butyl alcohol in air.

### 4. Physiological Response

*Animal symptomatology.* Animals exposed to *n*-butyl alcohol in the air may manifest the following signs of intoxication: restlessness, irritation of mucous membranes, ataxia, prostration, and narcosis. Following absorption of sufficient quantities death, associated with respiratory failure, occurs. At high concentrations, *n*-butyl alcohol is more narcotic than is *n*-propyl alcohol<sup>127,128</sup> but slightly less so than is *sec*-butyl alcohol.<sup>127</sup>

Two rabbits exposed by Gardner<sup>129</sup> to unstated varying concentrations of *n*-butyl alcohol in the air for an unstated length of time per day on each of 55 days out of a total period of 71 days, showed no signs of intoxication other than an increased restlessness, some slight irritation of the mucous membranes, a mild anemia, and a terminal leucocytosis. Guinea pigs exposed to 100 p.p.m. butyl alcohol in the atmosphere (0.303 mg. per liter) for 4 hours per day on 64 days (1 day per week omitted) gained in weight but exhibited some decrease in the number of red blood cells and a relative and absolute lymphocytosis.<sup>130</sup> According to Weese,<sup>128</sup> mice subjected to 130 hours of total exposure (unstated number of hours per day for several days) to the concentration of 8000 p.p.m. (24.3 mg. per liter of air) were narcotized repeatedly but gained in weight and survived.

<sup>125</sup> L. M. Christensen and E. I. Fulmer, *Ind. Eng. Chem., Anal. Ed.*, 7, 180 (1935).

<sup>126</sup> J. B. Ficklen, *Manual of Industrial Health Hazards*. Service to Industry, West Hartford, Connecticut, 1940, p. 50.

<sup>126a</sup> S. M. Hoch, *personal communication*.

<sup>127</sup> E. Starrek, *Dissertation*, Würzburg, 1938.

<sup>128</sup> H. Weese, *Arch. exptl. Path. Pharmacol.*, 135, 118 (1928).

<sup>129</sup> H. A. Gardner, *Paint Mfrs. Assoc. U.S. Tech. Circ.* No. 250, 89 (1925).

<sup>130</sup> H. F. Smyth and H. F. Smyth, Jr., *J. Ind. Hyg.*, 10, 261 (1928).

However, the mice died when they were exposed for 260 minutes to 10,700 p.p.m.\* (32.4 mg. per liter, supersaturated) or for 200 minutes to 16,040 p.p.m.\* (48.6 mg. per liter).

Several groups of mice were each exposed by Starrek<sup>127</sup> to one of a series of concentrations of *n*-butyl alcohol in the air: 6600 p.p.m. (20 mg. per liter), 9900 p.p.m.\* (30 mg. per liter), 13,200 p.p.m.\* (40 mg. per liter), 16,500 p.p.m.\* (50 mg. per liter), or 19,800 p.p.m.\* (60 mg. per liter), for a period of time which decreased as the concentration was increased, being 190, 95, 75, 58, and 45 minutes, respectively. The length of time required for the onset of ataxia, prostration, or narcosis varied inversely with the concentration of the alcohol. Thus ataxia appeared in 7 to 9 minutes at 19,800 p.p.m. and 55 to 80 minutes at 6600 p.p.m.; prostration in 14 to 17 minutes at 19,800 p.p.m. and in 88 to 150 minutes at 6600 p.p.m.; deep narcosis in 45 minutes at the former concentration and in 190 minutes at the latter. Three of the eight mice exposed to 9900 p.p.m. or more died, while no evidence of intoxication could be discerned in any of the animals exposed to 3300 p.p.m. (10 mg. per liter) or 1650 p.p.m. (5 mg. per liter) for 420 minutes.

*Animal pathology.* Gardner<sup>129</sup> reported that a mild bronchial irritation, associated with some enlargement of bronchial lymph nodes, was the only demonstrable lesion resulting from the prolonged exposure of rabbits to air containing the vapors of this alcohol. Smyth and Smyth<sup>130</sup> found hemorrhagic areas in the lungs, early degenerative lesions in the livers, and cortical and tubular degeneration in the kidneys of exposed guinea pigs. Weese<sup>128</sup> described reversible fatty changes in the livers of mice.

##### 5. Absorption and Excretion by Animals

*n*-Butyl alcohol is oxidized more rapidly than is ethyl alcohol in the tissues of the rabbit.<sup>131</sup> According to Sander,<sup>132</sup> cited by von Oettingen,<sup>133</sup> *n*-butyl alcohol is absorbed through the skin of animals, but whether this is of any practical significance is not apparent.

##### 6. Effects upon Man

*n*-Butyl alcohol is potentially more toxic than any of the lower homologs, but the practical hazards associated with its industrial production and use (at ordinary temperatures) are appreciably diminished by its relatively low volatility. Exposure of human beings to vapors of this alcohol may induce the following symptoms: irritation of the nose, throat, and eyes; the formation of trans-

\* Vapor pressure data indicate that 8600 p.p.m. is the highest vapor concentration to be obtained under ordinary conditions, 25° C. and 760 mm. Hg.

<sup>131</sup> S. M. Berggren, *Skand. Arch. Physiol.*, 78, 249 (1938).

<sup>132</sup> F. Sander, *Inaugural Dissertation*, Köln, 1933; cited by W. F. von Oettingen, *U.S. Pub. Health Bull.* No. 281, 123 (1943).

<sup>133</sup> W. F. von Oettingen, *U.S. Pub. Health Bull.* No. 281, 123 (1943).

lucent vacuoles in the superficial layers of the cornea; headache; vertigo; and drowsiness.<sup>121,132,134</sup> Contact dermatitis, involving the fingers and hands, also may occur.

Twenty-eight of thirty-four women employed in a plant in which raincoats were being manufactured, were found to have from 10 to 1000 vacuoles in the corneal epithelium, in association with pain, itching, swelling, and epiphora, but only occasional redness. These signs were more severe upon awakening in the morning than during the day.<sup>121</sup> The significance of a reported case of injury to the liver following exposure to a mixed solvent containing *n*-butyl alcohol is quite questionable in relation to this compound.<sup>135</sup>

Hoch<sup>126a</sup> reports that, in the manufacture of vitamins, *n*-butyl alcohol, as well as *sec*- and isobutyl alcohol, have been employed in variable quantities without giving rise to any evidence of systemic intoxication. However, he calls attention to the fact that all of these alcohols have irritating properties which serve as a warning of their presence in the atmosphere.

#### 7. Maximum Permissible Concentration

Lehmann and Flury,<sup>136</sup> as well as Tabershaw and his associates,<sup>122</sup> regard one hundred parts of butyl alcohol per million parts of air by volume (0.33 mg. per liter) as the maximum allowable concentration for prolonged exposure. The concentration of 200 p.p.m. (0.66 mg. per liter) is suggested in the *Manual of Industrial Hygiene*<sup>137</sup> sponsored by the United States Public Health Service. This latter value has also been adopted by the states of California, New York, and Oregon. A value of 100 p.p.m. has been recommended by the states of Kansas, Kentucky, Ohio, South Carolina, Utah, and Washington, while a value of 50 p.p.m. has been adopted by the states of Florida and Massachusetts.

#### 8. Inflammability

The flash point of *n*-butyl alcohol is 100° F. and the ignition temperature is 653° (345° C.).<sup>138</sup> The lower limit of inflammability is 1.70 per cent by volume<sup>139</sup> (see Chapter Thirteen).

#### 9. Odor and Warning Properties

Mild irritation of the nose, throat, and eyes of human subjects is caused by 3 to 5 minutes of exposure to 25 p.p.m. of *n*-butyl alcohol.<sup>119</sup> Exposure to 50 p.p.m. was objectionable, producing pronounced irritation of the throat in all subjects and mild headache in some instances. From the standpoint of comfort, Nelson *et al.*<sup>119</sup> have considered that the highest concentration that is likely to

<sup>124</sup> E. Krüger, *Arch. Gewerbepath. Gewerbehyg.*, **3**, 798 (1932).

<sup>126</sup> G. E. C. Burger and B. H. Stockmann, *Zentr. Gewerbehyg. Unfallverhüt.*, **9**, 29 (1932).

<sup>136</sup> K. B. Lehmann and F. Flury, *Toxikologie und Hygiene der technischen Lösungsmittel*. Springer, Berlin, 1938, p. 157.

<sup>137</sup> U. S. Public Health Service, National Institute of Health, W. M. Gafafer, Ed., *Manual of Industrial Hygiene*. Saunders, Philadelphia, 1943, p. 264.

<sup>138</sup> N. J. Thompson, *Ind. Eng. Chem.*, **21**, 134 (1929).

<sup>139</sup> G. W. Jones, *Chem. Revs.*, **22**, 1 (1938).

be found enduring over periods of 8 hours is somewhat less than 25 p.p.m. According to Tabershaw *et al.*<sup>122</sup> exposure to concentrations in excess of 50 p.p.m. is associated with irritation of the eyes.

## **sec-BUTYL ALCOHOL**

### **1. Uses**

*sec*-Butyl alcohol ( $C_2H_5CHOHCH_3$ ), 2-butanol, or methylethyl carbinol, although not used extensively, finds some use as a solvent and thinner in lacquers and as an intermediate in the manufacture of secondary butyl esters and ketones.<sup>120</sup> Smith<sup>140</sup> reports its possible use for the separation of wax from paraffin-base crudes. Its use as a motor fuel has been suggested.<sup>141</sup>

### **2. Physical Properties**

*sec*-Butyl alcohol is a water-white, inflammable liquid with a choking odor.<sup>120</sup> It is soluble in 8 parts of water by weight at 20° C. (but not in the presence of alkaline carbonate),<sup>142</sup> and is miscible with benzene, alcohol, or ether. The compound has the following physical properties: molecular weight, 74.120<sup>124</sup>; specific gravity, 0.808 at 20°/4° C.<sup>142</sup>; melting point, -114.7; boiling point, 99.5°<sup>143</sup>; refractive index,  $n_D^{22}$ , 1.39236<sup>143</sup>; vapor pressure, 31 mm. Hg at 32.2°.<sup>144</sup> The vapor density is 2.56 (air = 1). "Saturated" air contains 4.08 per cent *sec*-butyl alcohol vapor by volume at 32.2° C. and has a density of 1.06 (air = 1).

1 mg./l.  $\approx$  330 p.p.m. and 1 p.p.m.  $\approx$  3.03 mg./cu.m. at 25° C., 760 mm.

### **3. Determination in the Atmosphere**

The nonspecific determination of the ethylenic hydrocarbon by bromination following dehydration of the alcohol has been reported by Grane and associates.<sup>145</sup>

### **4. Physiological Response**

*Animal symptomatology.* The signs of intoxication in animals exposed to vapors of *sec*-butyl alcohol in the air are similar to those induced by *n*-butyl alcohol. The vapor of *sec*-butyl alcohol is slightly more narcotic<sup>127,128</sup> and lethal<sup>128</sup> than *n*-butyl alcohol. Based upon the effects of intraperitoneal injections into mice, Butler and Dickison<sup>146</sup> found the optically isomeric *sec*-butyl alcohols were equal in anesthetic activity. Mice subjected repeatedly by Weese<sup>128</sup> to the concentration of 5330 p.p.m. (16.2 mg. per liter) *sec*-butyl alcohol for a total of 117 hours were narcotized, but survived. Concentrations of 10,670 p.p.m. (32.3 mg.

<sup>140</sup> H. M. Smith, *U.S. Bur. Mines Repts. Investigations No. 2822* (1927).

<sup>141</sup> J. Hooton, U.S. Patent, 2,240,040, *Chem. Abstracts*, 35, 4940 (1941).

<sup>142</sup> Beilstein, *Handbuch der organischen Chemie*, 4th ed., Vol. I, Springer, Berlin, 1918, p. 371.

<sup>143</sup> Beilstein, *Handbuch der organischen Chemie*, Suppl. to 4th ed., Vol. I, Springer, Berlin, 1928, p. 188.

<sup>144</sup> M. J. Copley, E. Ginsberg, G. F. Zellhoefer, and C. S. Marvel, *J. Am. Chem. Soc.*, 63, 254 (1941).

<sup>145</sup> O. Grane, B. Löfström, and R. Winbladh, *Ing. Vetenskaps Akad., Handl.*, No. 147, (1938).

<sup>146</sup> T. C. Butler and H. L. Dickison, *J. Pharmacol.*, 69, 225 (1940).

per liter) for 225 minutes and 16,000 p.p.m. (48.5 mg. per liter) for 160 minutes were fatal for mice.<sup>128</sup>

Groups of mice (2 in each) were exposed by Starrek<sup>127</sup> for decreasing lengths of time (300, 190, 75, 60, 45, and 40 minutes) to increasing concentrations of *sec*-butyl alcohol in the air: 3300 p.p.m. (10 mg. per liter), 6600 p.p.m. (20 mg. per liter), 9900 p.p.m. (30 mg. per liter), 13,200 p.p.m. (40 mg. per liter), 16,500 p.p.m. (50 mg. per liter), and 19,800 p.p.m. (60 mg. per liter). As in the case of other alcohols used by Starrek, the duration of exposure necessary to induce ataxia, prostration, or deep narcosis was inversely proportional to the concentration. Thus at 3330 p.p.m., ataxia, prostration, and narcosis became evident in 51 to 100 minutes, 120 to 180 minutes, and 300 minutes, respectively; whereas at 19,800 p.p.m. these signs appeared in 7 to 8 minutes, 12 to 20 minutes, and 40 minutes, respectively. No deaths occurred among any of these twelve mice. No signs of intoxication were observed in mice exposed for 420 minutes to 1650 p.p.m. (5 mg. per liter).

### 5. Inflammability

The ignition temperatures of *sec*-butyl alcohol in air and oxygen are respectively 777° F. (414° C.) and 710° F. (377° C.).<sup>147</sup> The flash point is 70° F.

## ISOBUTYL ALCOHOL

### 1. Uses

Isobutyl alcohol,  $(\text{CH}_3)_2\text{CHCH}_2\text{OH}$ , known also as 2-methyl-1-propanol, or isopropylcarbinol, is used to a small extent in the lacquer industry.<sup>147a</sup> Its use as an intermediate in organic syntheses of dyes and other chemicals, and as a solvent in fruit essences, perfumes, and paint removers has been reported.<sup>148</sup>

### 2. Physical Properties

Isobutyl alcohol is an inflammable, water-white liquid with a slightly choking odor. Isobutyl alcohol is soluble in 10 parts of water by weight at 20° C., while water is soluble in 5.8 parts of isobutyl alcohol by weight at 25°.<sup>149</sup> This alcohol is miscible with ethyl alcohol and diethyl ether. Isobutyl alcohol has the following physical properties: molecular weight, 74.120<sup>150</sup>; specific gravity, 0.803 at 20°<sup>149</sup>; melting point, -108°<sup>151</sup>; boiling point, 107.3°<sup>151</sup>; refractive index, 1.397 at 20°<sup>152</sup>; vapor pressure, 12.2 mm. Hg at 25° C.<sup>152</sup> The vapor density is 2.56 (air = 1). "Saturated" air contains 1.61 per cent isobutyl alcohol vapor by volume at 25° C. and has a density of 1.03 (air = 1).

1 mg./l.  $\approx$  330 p.p.m. and 1 p.p.m.  $\approx$  3.03 mg./cu.m. at 25° C., 760 mm.

<sup>147</sup> W. J. Huff, *U.S. Bur. Mines Repts. Investigations* No. 3669 (1942).

<sup>147a</sup> H. H. Weber and W. Koch, *Chem.-Ztg.*, 57, 73 (1933).

<sup>148</sup> L. Schwartz and L. Tulipan, *A Textbook of Occupational Diseases of the Skin*. Lea & Febiger, Philadelphia, 1939, p. 717.

<sup>149</sup> A. K. Doolittle, *Ind. Eng. Chem.*, 27, 1169 (1935).

<sup>150</sup> "Atomic Weights (International), 1941," *J. Am. Chem. Soc.*, 63, No. 3 (1941).

<sup>151</sup> *International Critical Tables of Numerical Data, Physics, Chemistry, and Technology*. Vol. I, McGraw-Hill, New York, 1926, p. 189.

<sup>152</sup> I. Mellan, *Industrial Solvents*. Reinhold, New York, 1939, pp. 226, 236.

### 3. Determination in the Atmosphere

Although the reactions are not specific for isobutyl alcohol, the oxidation of isobutyl alcohol by chromic acid to the aldehyde and the subsequent reaction of the latter with *o*-nitrobenzaldehyde may serve as a means of detecting isobutyl alcohol qualitatively.<sup>153</sup>

### 4. Physiological Response

*Animal symptomatology.* Like the other alcohols, isobutyl alcohol is primarily narcotic in action. It is somewhat less lethal when inhaled in high concentrations than is normal or *sec*-butyl alcohol.<sup>128</sup> Weese<sup>128</sup> subjected mice to a concentration of 2125 p.p.m. (6.44 mg. per liter) for 223 hours in a series of intermittent exposures, each of which was of 9.25 hours' duration, without any untoward effects. Mice were narcotized repeatedly in a series of intermittent exposures totaling 136 hours at 6400 p.p.m. (19.3 mg. per liter), but survived. Exposure of mice to concentrations of 10,600 p.p.m. (32.2 mg. per liter) for 300 minutes, and 15,950 p.p.m. (48.3 mg. per liter) for 250 minutes, resulted in fatal poisoning.

*Effects upon man.* Slight erythema and hyperemia, without the formation of wheals, were observed by Oettel<sup>154</sup> following the application of isobutyl alcohol to the skin of man. According to Schwartz and Tulipan,<sup>148</sup> isobutyl alcohol may be a skin irritant.

### 5. Inflammability

The flash point of isobutyl alcohol is 82° F. (27.7° C.) and the ignition temperature is 813° F. (434° C.).<sup>155</sup> The lower limit of inflammability of this alcohol is 1.68 per cent by volume in air<sup>156</sup> (see Chapter Thirteen).

## **tert-BUTYL ALCOHOL**

### 1. Uses

*tert*-Butyl alcohol, (CH<sub>3</sub>)<sub>3</sub>COH, known also as trimethylcarbinol, and 2-methyl-2-propanol, has but little use in industry. According to Schwartz and Tulipan,<sup>157</sup> it is used for intermediates, fruit essences, cellulose esters, plastics, and lacquers.

### 2. Physical Properties

*tert*-Butyl alcohol is a colorless inflammable liquid, soluble in water, alcohol, or ether. *tert*-Butyl alcohol has the following physical properties: molecular weight, 74.120<sup>150</sup>; specific gravity 0.783 at 25°/25° C.<sup>152</sup>; melting point, 25.5°<sup>151</sup>;

<sup>153</sup> H. H. Weber and W. Koch, *Chem. Ztg.*, 57, 73 (1933).

<sup>154</sup> H. Oettel, *Arch. exper. Path. Pharmacol.*, 183, 641 (1936).

<sup>155</sup> N. J. Thompson, *Ind. Eng. Chem.*, 21, 134 (1929).

<sup>156</sup> G. W. Jones, *Chem. Revs.*, 22, 1 (1938).

<sup>157</sup> L. Schwartz and L. Tulipan, *A Textbook of Occupational Diseases of the Skin*. Lea & Febiger, Philadelphia, 1939, p. 717.

boiling point, 82.8<sup>o151</sup>; refractive index,  $n_D^{20}$ , 1.387<sup>151</sup>; vapor pressure, 42.0 mm. Hg at 25<sup>o</sup>.<sup>152</sup> The vapor density is 2.56 (air = 1). "Saturated" air contains 5.53 per cent *tert*-butyl alcohol vapor by volume at 25<sup>o</sup> C. and has a density of 1.09 (air = 1).

1 mg./l.  $\approx$  330 p.p.m. and 1 p.p.m.  $\approx$  3.03 mg./cu.m. at 25<sup>o</sup> C., 760 mm.

### 3. Determination in the Atmosphere

Although no specific method is available for the determination of *tert*-butyl alcohol in the air, the possibility of developing a method from known color reactions seems feasible. Several alcohols including *tert*-butyl give color reactions with aldehydes, i.e., anisaldehyde, furfural, piperonal, salicylaldehyde, sucrose, vanillin, and cinnamaldehyde in the presence of sulfuric acid.<sup>158</sup>

### 4. Physiological Response

*Animal symptomatology.* The signs of intoxication on the part of animals exposed to vapors of *tert*-butyl alcohol are similar to those induced by the other butyl alcohols. It has a stronger narcotic action upon mice than has normal or isobutyl alcohol.<sup>159</sup>

*Effects upon man.* Oettel<sup>154</sup> observed no reaction other than slight erythema and hyperemia following the application of *tert*-butyl alcohol to human skin. Schwartz and Tulipan<sup>157</sup> are authority for the statement that it may be a skin irritant.

### 5. Inflammability

The flash point of *tert*-butyl alcohol is 52<sup>o</sup> F. The ignition temperatures of this alcohol in air and oxygen are, respectively, 892<sup>o</sup> F. (478<sup>o</sup> C.) and 860<sup>o</sup> F. (460<sup>o</sup> C.).<sup>160</sup> The lower limit of inflammability at 25<sup>o</sup> C. is 2.35 per cent by volume; the upper limit of inflammability at 55<sup>o</sup> is 8 per cent by volume<sup>160</sup> (see Chapter Thirteen).

## AMYL ALCOHOLS

### 1. Uses and Industrial Exposure

There are eight structural isomers of amyl alcohol. There are four primary amyl alcohols: (a) 1-pentanol, *n*-amyl alcohol, *n*-butylcarbinol, or pentan-1-ol; (b) 2-methyl-1-butanol, primary active amyl alcohol, *sec*-butylcarbinol, methyl-ethylcarbinol, or 2-methyl-butan-1-ol; (c) 3-methyl-1-butanol, isoamyl alcohol, primary isobutylcarbinol, 2-methylbutan-4-ol, or 3-methylbutan-1-ol; and (d) 2,2-dimethyl-1-propanol, *tert*-butylcarbinol, or neopentyl alcohol. There are three secondary amyl alcohols: (a) 2-pentanol, secondary active amyl alcohol, methyl-propylcarbinol, 1-methyl-1-butanol, or pentan-2-ol; (b) 3-pentanol, diethylcarbinol, 1-ethyl-1-propanol, or pentan-3-ol; and (c) 3-methyl-2-butanol, methyl-

<sup>154</sup> L. Ekkert, *Pharm. Zentralhalle*, 69, 289 (1928).

<sup>156</sup> H. Weese, *Arch. exper. Path. Pharmacol.*, 135, 118 (1928).

<sup>160</sup> W. J. Huff, *U.S. Bur. Mines, Repts. Investigations* No. 3669 (1942).



isopropylcarbinol, *sec*-isoamyl alcohol, 2-methyl-3-butanol, or 3-methylbutan-2-ol. There is one tertiary amyl alcohol, known as 2-methyl-2-butanol, *tert*-amyl alcohol, amylene hydrate, dimethylethylcarbinol, or 2-methylbutan-2-ol. The names most commonly used are given in Table 5.

Three of these, i.e., 2-methyl-1-butanol, 2-pentanol, and 3-methyl-2-butanol, possess an asymmetric carbon atom; hence each may exist as two optical isomers in addition to the optically inactive form. 2-Methyl-1-butanol is formed from the fermentation of an optically active substance; it exists in commerce largely as the *d*-amyl alcohol. Fusel oil is essentially 1 part of the active form of 2-methyl-1-butanol (*d*-amyl alcohol) and 7 parts of 3-methyl-1-butanol (isoamyl alcohol) with small amounts of pyridine, furfurals, and esters.<sup>152,161</sup>

"Pentanol" is a mixture of several amyl alcohols.<sup>162</sup> A commercial product containing about 80 per cent of 2-pentanol and 20 per cent of 3-pentanol is marketed as "*sec*-amyl alcohol."<sup>162</sup> In the past the handling and use of fusel oil have been the principal means of industrial exposure to amyl alcohols.

Amyl alcohols are used in the manufacture of lacquer, chemicals, rubber, plastics, dyes, fruit essences, and explosives.<sup>152,163-165</sup> The United States Department of Labor lists twenty occupations that offer exposure to amyl alcohol.<sup>165</sup>

## 2. Physical and Chemical Properties

Except for 2,2-dimethyl-1-propanol, which is a crystalline solid, the amyl alcohols when purified are colorless liquids with a mild odor. They are solvents for camphor, alkaloids, natural and synthetic resins, iodine, phosphorus, sulfur, benzyl abietate, copal ester, ester gum, etc.<sup>152</sup> They are miscible with organic solvents but are only slightly soluble in water. The physical properties are shown in Table 5. The molecular weight is 88.146.<sup>166</sup>

1 mg./l.  $\approx$  278 p.p.m. and 1 p.p.m.  $\approx$  3.60 mg./cu.m. at 25° C., 760 mm.

## 3. Determination in the Air

Amyl alcohol might be determined by either of two nonspecific methods employed for the determination of fusel oil in distilled spirits: (a) oxidation by chromic acid or (b) measurement of the color produced from coupling with various aldehydes in the presence of sulfuric acid.

Titration of valeric acid, distilled from a reaction mixture with sulfuric acid,

<sup>161</sup> F. C. Whitmore, *Organic Chemistry*. Van Nostrand, New York, 1937, p. 125.

<sup>162</sup> L. F. Fieser and M. Fieser, *Organic Chemistry*. Heath, Boston, 1944, p. 124.

<sup>163</sup> L. Carozzi, *Occupation and Health*, International Labor Office, Geneva, 1930, p. 115.

<sup>164</sup> E. B. Ley and F. J. Vintinner, *The Toxicology and Prevention of Industrial Disease*. 3rd ed., U.S. War Dept. Eighth Service Command, 1944, p. 13.

<sup>165</sup> U.S. Dept. Labor, *Bur. Labor Statistics Bull.* No. 41, 33 (1942).

<sup>166</sup> "Atomic Weights (International), 1941," *J. Am. Chem. Soc.*, 63, No. 3 (1941).

<sup>167</sup> *International Critical Tables of Numerical Data, Physics, Chemistry, and Technology*. Vol. I, McGraw-Hill, New York, 1926, p. 193.

<sup>168</sup> Beilstein, *Handbuch der organischen Chemie*. 4th ed. Vol. I, Springer, Berlin, 1918, p. 383.

<sup>169</sup> J. Timmermans and Mme. Hennault-Roland, *J. chim. phys.*, 29, 529 (1932).

<sup>169a</sup> A. K. Doolittle, *Ind. Eng. Chem.*, 27, 1169 (1935).

TABLE 5. *Physical Properties of Amyl Alcohols*

Isomer	Formula	Specific gravity	Melting point, °C.	Boiling point, °C.	Refractive index, $n_D$	Vapor pressure, mm. Hg.	Solubility of alcohol in water
Primary Alcohols							
1-Pentanol	$\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OH}$	0.817 at 20°/20° <sup>167</sup>	-78.5 <sup>167</sup>	137.9 <sup>167</sup>	1.414 at 13° <sup>167</sup>		Slightly soluble
2-Methyl-1-butanol	$\text{CH}_3-\text{CH}_2-\text{CH}-\text{CH}_2-\text{OH}$   $\text{CH}_3$	0.816 at 20°/4° <sup>167</sup>		128 <sup>167</sup>		3.4 at 25° <sup>163</sup>	3.6% at 30°
3-Methyl-1-butanol	$\text{CH}_3$ $\text{HC}-\text{CH}_2-\text{CH}_2-\text{OH}$   $\text{CH}_3$	0.812 <sup>167</sup>	-117.2 <sup>167</sup>	130.5 <sup>167</sup>	1.4075 at 20° <sup>167</sup>		In 50 parts $\text{H}_2\text{O}$ at 13° <sup>168</sup>
2,2-Dimethyl-1-propanol	$\text{CH}_3$ $\text{CH}_2-\text{C}-\text{CH}_2-\text{OH}$   $\text{CH}_3$		53 <sup>167</sup>	114 <sup>167</sup>			Slightly soluble
Secondary Alcohols							
2-Pentanol	$\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}-\text{OH}$   $\text{CH}_3$	0.809 <sup>167</sup>		119.5 <sup>167</sup>	1.4972 at 20° <sup>167</sup>		In 6 volumes $\text{H}_2\text{O}$ <sup>168</sup>
3-Pentanol	$\text{CH}_3-\text{CH}_2-\text{CH}-\text{CH}_2-\text{CH}_3$   $\text{OH}$	0.815 at 25°/4° <sup>167</sup>		115.6 <sup>167</sup>	1.410 at 20° <sup>167</sup>	12 at 30° <sup>168a</sup>	5.5% at 30°
3-Methyl-2-butanol	$\text{CH}_3-\text{CH}-\text{CH}-\text{CH}_3$   $\text{CH}_3$   $\text{OH}$	0.819 <sup>167</sup>		114 <sup>167</sup>			2.8% at 30°
Tertiary Alcohol							
2-Methyl-2-butanol	$\text{CH}_3$ $\text{CH}_3-\text{CH}_2-\text{C}-\text{OH}$   $\text{CH}_3$	0.809 at 20°/4° <sup>167</sup>	-11.9 <sup>167</sup>	101.8 <sup>167</sup>	1.406 at 20° <sup>167</sup>		In 8 parts $\text{H}_2\text{O}$ <sup>168</sup>

and chromate was employed by Allen and Chattaway,<sup>170</sup> and is given in the AOAC *Methods*.<sup>171</sup> Furfural,<sup>172</sup> salicylaldehyde,<sup>173,174</sup> benzaldehyde, *p*-dimethylaminobenzaldehyde, and vanillin,<sup>174</sup> in the presence of sulfuric acid, have been utilized for distilled spirits. Korenman<sup>175</sup> used furfural to determine the amount of amyl alcohol in the air. Quantities of the order of 0.6 to 2.0 mg. in 3.5 liters of air were determined with an error of  $\pm 10$  per cent.

#### 4. Physiological Response

*Animal symptomatology.* Animals have not been exposed experimentally to the vapors of any of the amyl alcohols but most investigators have found that amyl alcohol administered otherwise is more narcotic and lethal than the lower homologs. Baer<sup>176</sup> and Munch and Schwartz<sup>177</sup> compared amyl alcohol with the lower homologs by their oral administration to rabbits and found the latter less toxic. Joffroy and Serveaux<sup>178</sup> and Lehman and Newman<sup>179</sup> obtained similar results following intravenous administration of alcohols to rabbits; and Macht<sup>180</sup> arrived at the same conclusion from corresponding experiments upon cats. Intraperitoneal injections of the alcohols into rats, by Lendle,<sup>181</sup> likewise showed that amyl alcohol was more toxic than the lower homologs.

According to Munch and Schwartz<sup>177</sup> the narcotic action of a series of amyl alcohols, in the case of rabbits, decreases in the following order: 2-pentanol (a secondary alcohol), 2-methyl-2-butanol (a tertiary alcohol) and 3-methyl-1-butanol (a primary alcohol); the toxicity of the same three isomers decreases in the following order<sup>177</sup>: tertiary, secondary, and primary. Lendle<sup>181</sup> confirmed the latter results in his experiments on rats, reporting upon the toxicity of three alcohols in decreasing order: 2-methyl-2-butanol (tertiary), 2-pentanol (secondary), and 1-pentanol (primary). Starrek<sup>182</sup> found 1-pentanol (*n*-amyl) less toxic than 3-methyl-1-butanol (isoamyl)—both primary alcohols—when administered subcutaneously.

Strauss<sup>183</sup> reported the occurrence of liver injury in the rabbit following repeated oral administration of amyl alcohol.

<sup>170</sup> A. H. Allen and W. Chattaway, *Analyst*, 16, 102 (1891).

<sup>171</sup> *Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists*. 5th ed., Assoc. Official Agr. Chem., 1940, p. 175.

<sup>172</sup> H. P. Basset, *Ind. Eng. Chem.*, 2, 339 (1910).

<sup>173</sup> A. Komarowsky, *Chem. Ztg.* 27, 1086 (1903).

<sup>174</sup> W. B. D. Penniman, D. C. Smith, and E. I. Lawshe, *Ind. Eng. Chem., Anal. Ed.*, 9, 91 (1937).

<sup>175</sup> I. M. Korenman, *Arch. Hyg.*, 109, 108 (1932).

<sup>176</sup> G. Baer, *Arch. Anat. Physiol., Physiol. Abt.*, 233 (1898).

<sup>177</sup> J. C. Munch and E. W. Schwartz, *J. Lab. Clin. Med.*, 10, 985 (1925).

<sup>178</sup> A. Joffroy and R. Serveaux, *Arch. med. exptl. anat. path.*, 7, 569 (1895).

<sup>179</sup> A. J. Lehman and H. W. Newman, *J. Pharmacol.*, 61, 103 (1937).

<sup>180</sup> D. I. Macht, *J. Pharmacol.*, 16, 1 (1920).

<sup>181</sup> L. Lendle, *Arch. exptl. Path. Pharmacol.*, 132, 214 (1928).

<sup>182</sup> E. Starrek, *Dissertation, Würzburg*, 1938.

<sup>183</sup> Strauss, *Compt. rend. soc. biol.*, 4, 54 (1887).

### 5. Absorption and Excretion by Animals

Apparently dogs and cats exhale more unchanged amyl alcohol than do rabbits or rats. A dog weighing 11 kg., when injected subcutaneously with a dose of 0.1 ml. of 2-methyl-2-butanol (*tert*-amyl alcohol) exhaled 65 per cent of it within 5.75 hours. Another dog given a slightly larger dose of the same alcohol intravenously exhaled 52 per cent within 6 hours.<sup>184</sup> Cats also exhaled a large quantity unchanged.<sup>184</sup> When rabbits were injected intravenously with two levels of dosage, one approximately the same as that given to dogs and the other half as much, they exhaled, in the first instance, 21 per cent of the alcohol in unchanged form within 4 hours, and in the second, 22 per cent within 3 hours. Over a period of 3 hours a dog eliminated 55 per cent, whereas a rabbit expelled 17 per cent. A rat given 1 g. per kilogram of the same isomer eliminated 26.4 per cent unchanged in the expired air within 50 hours.<sup>185</sup>

Following oral administration of a primary alcohol (3-methyl-1-butanol), a secondary alcohol (2-pentanol), and the tertiary alcohol (2-methyl-2-butanol) to rabbits, small amounts of conjugated glucuronic acid were found in the urine.<sup>186,187</sup> Dogs excreted less glucuronic acid than rabbits following administration of the secondary alcohol, and none at all when given the tertiary alcohol.<sup>186,187</sup>

TABLE 6  
*Excretion of Amyl Alcohols by Rats in Per Cent of Total Given*

Compound	In expired air	In urine	Total excreted
Primary Alcohols			
1-Pentanol	0.88	0.29	1.2
2-Methyl-1-butanol	5.6	2.0	7.6
3-Methyl-1-butanol	0.86	0.22	1.1
3-Methyl-1-butanol (levo form)	0.97	0.27	1.2
Secondary Alcohols			
2-Pentanol	6.2 (42.3) <sup>a</sup>	1.3 (2.4) <sup>a</sup>	52.2
3-Pentanol	0.3 (51.2) <sup>a</sup>	0.1 (4.7) <sup>a</sup>	56.3
3-Methyl-2-butanol	8.3 (49.1) <sup>a</sup>	2.9 (2.5) <sup>a</sup>	62.8
Tertiary Alcohol			
2-Methyl-2-butanol	26.4	8.9	35.3

<sup>a</sup> Ketone excreted.

The rate of elimination (or oxidation) of the amyl alcohols from the body decreases in the following order: primary, secondary, tertiary. Haggard and his associates<sup>188</sup> gave each of the structural isomers except 2,2-dimethyl-1-propanol, and also the levo form of 2-methyl-1-butanol, in the dose of 1 g. per kilogram

<sup>184</sup> J. Pohl, *Arch. expil. Path. Pharmacol. Suppl.*, 427 (1908).

<sup>185</sup> H. W. Haggard, D. P. Miller, and L. A. Greenberg, *J. Ind. Hyg. Toxicol.*, 27, 1 (1945).

<sup>186</sup> O. Neubauer, *Arch. expil. Path. Pharmacol.*, 46, 133 (1901).

<sup>187</sup> H. Thierfelder and J. V. Mering, *Z. physiol. Chem.*, 9, 511 (1885).

to rats, intraperitoneally. These alcohols disappeared from the blood following their administration, after the following intervals of time: primary, 3.5 to 9 hours; secondary, 13 to 16 hours; and tertiary, 50 hours. The concentrations (milligrams per cent) found in the blood 1 hour after administration were as follows: primary, 14 to 55; secondary, 51 to 65; and tertiary, 12.5. Unlike the large amounts of unchanged tertiary alcohol exhaled by dogs, Pohl<sup>184</sup> found only traces of alcohol in the expired air of a dog following the intravenous administration of 2-methyl-1-butanol, a primary alcohol.

Guggenheim and Löffler<sup>188</sup> found that isovaleric acid was formed during the perfusion of the rabbit liver with isoamyl alcohol. Haggard and his associates<sup>185</sup> showed the transitory presence of small amounts of valeraldehydes in the blood following the administration of the primary alcohols. They believe the aldehyde is oxidized to valeric acid. The secondary alcohols were oxidized to the ketones, which were present in the blood in measurable quantities. The ketones were present about twice as long as the secondary alcohols. No volatile metabolites were found following the administration of *tert*-amyl alcohol. The conversion of alcohol to aldehyde is dependent upon the action of the liver, since in partially hepatectomized animals this conversion was largely inhibited. Although there was a definite decrease in the conversion of secondary amyl alcohols to ketone in partially hepatectomized mice, the inhibition was not nearly as great as in the case of the primary alcohol.

Haggard *et al.*<sup>185</sup> also found the following concentrations (milligram per cent) of the respective alcohols present in jugular blood at the time of death of mice from respiratory failure: 1-pentanol, 76; 2-methyl-1-butanol, 110; levo form of 2-methyl-1-butanol, 76; 3-methyl-1-butanol, 76; 2-pentanol, 86; 3-pentanol, 87; 3-methyl-2-butanol, 90; and 2-methyl-2-butanol, 191.

From the increasing amounts of 2-methyl-2-butanol (tertiary) required to narcotize a dog in successive experiments, evidence of habituation (tolerance) was obtained.<sup>189</sup> Similar observations upon a rabbit yielded no such evidence.<sup>189</sup>

Mice were narcotized by immersion in dilute aqueous solutions of amyl alcohol under conditions that prevented ingestion and inhalation of the alcohol.<sup>190</sup>

### 6. Effects upon Man

Without regard to any specific isomer most investigators have found that the inhalation of amyl alcohol vapors by man caused marked irritation of the eyes and respiratory tract, headache, and vertigo<sup>163-165, 191-195</sup>; dyspnea, and

<sup>186</sup> M. Guggenheim and W. Löffler, *Biochem. Z.*, **72**, 325 (1916).

<sup>188</sup> J. Biberfeld, *Biochem. Z.*, **92**, 198 (1918).

<sup>190</sup> Schwenkenbecher, *Arch. Anat. Physiol., Physiol. Abt.*, 121 (1904).

<sup>191</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931, p. 352.

<sup>193</sup> *Natl. Research Council Can. Bull.* No. 15, 21 (1930).

<sup>195</sup> K. W. Nelson, J. F. Ege, Jr., M. Ross, L. E. Woodman, and L. Silverman, *J. Ind. Hyg. Toxicol.*, **25**, 282 (1943).

<sup>194</sup> L. Resnick, *Eye Hazards in Industry*. Columbia Univ. Press, New York, 1941, p. 251.

<sup>196</sup> F. P. Underhill, *Toxicology*. 2nd ed., Blakiston, Philadelphia, 1928, p. 212.

cough<sup>191,194,196</sup>; nausea, vomiting, and diarrhea.<sup>164,165,191,196,197</sup> Double vision, deafness, delirium, and occasionally fatal poisoning, preceded by severe nervous symptoms, have been ascribed by Flury and Zernik<sup>191</sup> and by Eyquem,<sup>196</sup> to the effects of the absorption of amyl alcohol. Coma, glycosuria, and sometimes methemoglobinemia are represented by Fuchter<sup>198</sup> and Underhill<sup>195</sup> as characteristic of amyl alcohol intoxication.

A few cases of industrial poisoning appear to have been caused by amyl alcohol, although in each reported instance some other solvent was present to becloud the issue. A neurasthenic brewery manager who inhaled the vapors (primary active amyl and isoamyl) from fermentation vats, exhibited psychic stimulation, insomnia, and chromatopsia.<sup>197</sup> Eyquem<sup>196</sup> reported the following symptoms among workers engaged in producing smokeless powder: cough, irritation of the eyes, colic, diarrhea, vomiting, palpitation of the heart, nervous symptoms, headache, vertigo, disturbances of vision, forgetfulness, insomnia, somnolence, and weakness. One fatal case occurred. Although other alcohols and ether were employed, the signs increased as the use of amyl alcohol (probably fusel oil) increased. Two fatal cases from the use of a lacquer containing amyl alcohol and probably tetrachloroethane, for coating the inside surface of a tank, were reported by Zangger.<sup>199</sup> A lacquerer exposed to amyl alcohol and amyl acetate had digestive symptoms and secondary anemia, according to Baader.<sup>200</sup>

An increase of urobilin in the urine of lacquer sprayers exposed to a solvent containing amyl and butyl alcohols, amyl and butyl acetates, and acetone was reported by Burger and Stockmann.<sup>201</sup>

Nonindustrial cases of poisoning from drinking fusel oil, characterized by coma, glycosuria, and methemoglobinuria, were seen by Fuchter.<sup>198</sup> A patient died following an enema of 35 g. of amylene hydrate (Jacobi and Speer,<sup>202</sup> cited by Lewin<sup>197</sup>). Anker<sup>203</sup> reported the recovery of a woman who intentionally drank about 27 g. of amylene hydrate. Recovery was preceded by coma, dyspnea, irregular pulse, and dilation then contraction of the pupils.

No effects upon the nerves of the skin of men, and no local wheal formation, erythema, or hyperemia were observed by Oettel<sup>204</sup> following the application of all isomers except 1-pentanol. Schwartz and Tulipan<sup>205</sup> state that isoamyl, normal, secondary, and tertiary amyl alcohols may be irritating to the skin.

<sup>196</sup> Eyquem, *Ann. hyg. publ. méd. légale*, 3, 71 (1905).

<sup>197</sup> L. Lewin, *Gifte und Vergiftungen*. Stülke, Berlin, 1929, p. 407.

<sup>198</sup> T. B. Fuchter, *Am. Med.*, 2, 210 (1901).

<sup>199</sup> H. Zangger, *Arch. Gewerbepath. Gewerbehyg.*, 4, 117 (1933).

<sup>200</sup> E. Baader, *Verhandl. deut. Ges. inn. Med.*, 45, 318 (1933).

<sup>201</sup> G. E. C. Burger and B. H. Stockmann, *Zentr. Gewerbehyg. Unfallverhüt.*, 9, 29 (1932).

<sup>202</sup> W. Jacobi and E. Speer, *Therap. Halbmonatsh.*, 34, 445 (1920).

<sup>203</sup> M. Anker, *Therap. Monatsh.*, 6, 623 (1892).

<sup>204</sup> H. Oettel, *Arch. exper. Path. Pharmacol.*, 183, 641 (1936).

<sup>205</sup> L. Schwartz and L. Tulipan, *Occupational Diseases of the Skin*. Lea & Febiger, Philadelphia, 1939, p. 716.

### 7. Suggested Maximum Concentration

The highest permissible concentration of amyl alcohol in the air of work-rooms, according to Lehmann and Flury,<sup>206</sup> is 50 p.p.m. (0.18 mg. per liter). The Eighth Service Command, United States War Department,<sup>164</sup> recommended 400 p.p.m. (1.44 mg. per liter) as the maximum allowable concentration. Two hundred parts per million (0.72 mg. per liter) of 3-methyl-1-butanol (isoamyl alcohol) have been recommended by the California Industrial Accident Commission and the New York State Department of Labor. The Utah Department of Health suggests 55.6 p.p.m. (0.20 mg. per liter) (cited by Cook<sup>207</sup>), while 100 p.p.m. (0.36 mg. per liter) is accepted as the standard in the state of Florida.

### 8. Inflammability

The available data upon the flash points, limits of inflammability, and ignition temperatures for the various isomers of amyl alcohol are given in Table 7 (see Chapter Thirteen).

TABLE 7  
*Inflammability of Amyl Alcohols*

Isomer	Common alcohol name	Flash point, °F.	Lower limit of inflammability, vol. %	Ignition temperature, °C.
Primary Alcohols				
1-Pentanol	Primary amyl	100 <sup>208</sup>	1.19 <sup>209</sup>	391 <sup>208</sup>
2-Methyl-1-butanol	Primary active amyl			
3-Methyl-1-butanol	Isoamyl	114 <sup>208</sup>	1.2 <sup>209</sup>	343 <sup>208</sup>
2,2-Dimethyl-1-propanol	<i>tert</i> -Butylcarbinol			
Secondary Alcohols				
2-Pentanol	Secondary active amyl	94 <sup>208</sup>		343 <sup>208</sup>
3-Pentanol	Diethylcarbinol			
3-Methyl-2-butanol	<i>sec</i> -Isoamyl	102.9 <sup>208</sup>		
Tertiary Alcohol				
2-Methyl-2-butanol	<i>tert</i> -Amyl	67 <sup>208</sup>		

### 9. Warning Properties

According to Nelson *et al.*,<sup>103</sup> the following concentrations of 3-methyl-1-butanol (isoamyl alcohol) caused irritation of the respective mucous membranes of the majority of persons subjected to exposure for a few minutes: eyes, 150 p.p.m. (0.54 mg. per liter); nose, 150 p.p.m.; and throat, 100 p.p.m. (0.36 mg. per liter). From the standpoint of comfort these subjects agreed that the highest concentration for an 8-hour exposure should be less than 100 p.p.m.

<sup>206</sup> K. B. Lehmann and F. Flury, *Toxikologie und Hygiene der technischen Lösungsmittel*, Springer, Berlin, 1938, pp. 185, 248.

<sup>207</sup> W. A. Cook, *Ind. Med.*, 14, 936 (1945).

<sup>208</sup> Committee on Flammable Liquids, *Fire Hazard Properties*, Natl. Fire Protect. Assoc., Boston, 1941, pp. 6, 17.

<sup>209</sup> G. W. Jones, *Chem. Revs.* 22, 1 (1938).

## METHYLISOBUTYLCARBINOL

### 1. Uses

Methylisobutylcarbinol,  $\text{CH}_3\text{CHOHCH}_2\text{CH}(\text{CH}_3)_2$ , which is a hexyl alcohol, is also known as methyl amyl alcohol or 4-methyl-2-pentanol. It is used as a solvent in lacquers and in organic syntheses.<sup>210</sup>

### 2. Physical Properties

Methylisobutylcarbinol is a colorless, stable liquid. The compound has the following physical properties: molecular weight, 102.172<sup>211</sup>; specific gravity, 0.8034, at 25°/4° C.<sup>212</sup>; boiling point, 131.6–131.8°<sup>212</sup>; refractive index, 1.4089 at 25°<sup>210</sup>; vapor pressure, 3.52 mm. Hg at 20°.<sup>210</sup> The vapor density is 3.53 (air = 1). "Saturated" air contains 0.46 per cent methylisobutylcarbinol vapor by volume at 20° C. and has a density of 1.01 (air = 1). At 25° C. this alcohol is soluble in water to the extent of 1.64 per cent by weight<sup>212</sup> and water is soluble in the alcohol to the extent of 6.39 per cent by weight.<sup>210</sup> It is miscible with most of the commonly used organic solvents and is a solvent for oils, fats, waxes, resins, camphor, blown oils, and dyes.

1 mg./l. in air  $\approx$  239.3 p.p.m. and 1 p.p.m.  $\approx$  4.17 mg./cu.m. at 25° C., 760 mm.

There is no specific method for the determination of methylisobutylcarbinol in air. No data on its physiological effects are available.

### 3. Inflammability

The flash point of methylisobutylcarbinol is 45.6° C.<sup>210</sup>

## DIACETONE ALCOHOL

### 1. Uses

Diacetone alcohol,  $(\text{CH}_3)_2\text{COHCH}_2\text{COCH}_3$ , is also known as diacetone, diacetonol alcohol, 4-hydroxy-4-methyl-2-pentanone, dimethylacetonolcarbinol, Pyranton A, Deo, and Alco. This compound is used in cellulose-ester lacquers and coating compositions for papers and textiles, in the manufacture of artificial silk and leather, in celluloid cements, nonaqueous stains and dyeing mixtures, in the extraction of resins and waxes, in cleaning metals, in preservatives for animal tissues and for wood, and in antifreeze and hydraulic-compression fluids.<sup>210</sup>

### 2. Physical Properties

Diacetone alcohol is an inflammable liquid with a mintlike odor,<sup>210</sup> and, when pure, is colorless. It has the following physical properties: molecular weight, 116.156<sup>211</sup>; specific gravity, 0.9306 at 25°/4° C.<sup>210</sup>; melting point, -54 to -57°; boiling point, 164 to 166°<sup>210,213</sup>; refractive index, 1.42416 at 20°<sup>210</sup>; vapor pres-

<sup>210</sup> I. Mellan, *Industrial Solvents*. Reinhold, New York, 1939, pp. 62, 240, 246, 293.

<sup>211</sup> "Atomic Weights (International), 1941," *J. Am. Chem. Soc.*, 63, No. 3 (1941).

<sup>212</sup> P. M. Ginnings and R. Webb, *J. Am. Chem. Soc.*, 60, 1388 (1938).

<sup>213</sup> D. C. Walton, E. F. Kehr, and A. S. Lovenhart, *J. Pharmacol.*, 33, 175 (1928).



sure, 1.5 mm. Hg at 25°. <sup>214</sup> The vapor density is 4.01 (air = 1). "Saturated" air contains 0.2 per cent diacetone alcohol vapor by volume at 25° C. and has a density of 1.01 (air = 1). Diacetone alcohol is miscible with distilled water in all proportions without turbidity, <sup>210</sup> as well as with ethyl alcohol and diethyl ether. <sup>218</sup>

1 mg./l. in air  $\approx$  210.5 p.p.m. and 1 p.p.m.  $\approx$  4.75 mg./cu.m. at 25° C., 760 mm.

### 3. Determination in the Atmosphere

Diacetone alcohol may be differentiated qualitatively from acetone, since with 2,4-dinitrophenylhydrazine the former gives a red, and the latter a yellow, precipitate. <sup>218</sup>

### 4. Physiological Response

*Animal symptomatology.* Walton and his associates <sup>213</sup> observed that intravenous injections of diacetone alcohol into mice induced narcosis more rapidly than acetone, and that diacetone alcohol was about twice as toxic as acetone. Following intravenous, intramuscular, or oral administration to rabbits, diacetone alcohol depressed the respiration markedly, decreased the blood pressure, induced narcosis, and caused death by respiratory failure. <sup>213</sup> The progressive decrease in the blood pressure of dogs injected repeatedly with diacetone alcohol, noted by these investigators, led them to believe that increased susceptibility had resulted from the repetition of the injections.

Mice, rats, rabbits, and cats subjected for 20 minutes to inhalation of air containing 2100 p.p.m. (10 mg. per liter) of diacetone alcohol vapors, manifested restlessness, symptoms of irritation, coryza, symptoms of excitation, then sleepiness (unpublished work of E. Gross, cited by Lehmann and Flury <sup>208</sup>).

Keith <sup>215</sup> observed a temporary decrease in the hemoglobin content and numbers of erythrocytes in the peripheral blood of rats for 1 to 4 days following the oral administration of a sublethal dose of diacetone alcohol.

*Animal pathology.* Walton *et al.* <sup>213</sup> have reported one case of acute kidney damage among several rabbits. Gross, cited by Lehmann and Flury, <sup>208</sup> also found damage in the kidneys of exposed rabbits. Keith <sup>215</sup> described hepatic lesions, following the oral administration of a sublethal dose to rats, characterized by vacuolization and granulation of the parenchymal cells, which reached the maximum stage in about 24 hours.

### 5. Inflammability

The flash point of pure diacetone alcohol is 131° F. <sup>208</sup> The technical grade, which may contain as much as 15 per cent acetone, has a flash point of 40° to 57° F. <sup>208</sup>

<sup>214</sup> G. S. Gardner, *Ind. Eng. Chem.*, **32**, 226 (1940).

<sup>215</sup> H. M. Keith, *Arch. Path.*, **13**, 707 (1932).

## BENZYL ALCOHOL

### 1. Uses

Benzyl alcohol, ( $C_6H_5CH_2OH$ ), known also as phenylcarbinol or phenylmethanol, is widely used as a high boiling solvent and plasticizer. It is employed in making lacquers containing mixed cellulose derivatives,<sup>210</sup> in the manufacture of films, as a solvent in paint and varnish removers, and as a medium for grinding and suspending lacquer pigments.<sup>210</sup> It has been used in the manufacture of carbon paper.<sup>216</sup> Its use for the separation of flavin from phosphorylated flavin has been suggested.<sup>217</sup> Benzyl alcohol has been used as a local anesthetic.<sup>218,219</sup>

### 2. Physical Properties

Benzyl alcohol is a colorless liquid with a faint odor. About 4 parts of benzyl alcohol are soluble with difficulty in 100 parts of water.<sup>220</sup> This compound has the following physical properties: molecular weight, 108.134<sup>221</sup>; specific gravity, 1.04151 at 25° C.<sup>222</sup>; melting point, -15.3°<sup>222</sup>; boiling point, 205.5°<sup>222</sup>; refractive index  $n_D^{25}$ , 1.54259<sup>222</sup>; vapor pressure, 0.15 mm. Hg at 25°.<sup>210</sup> The vapor density is 3.73 (air = 1). "Saturated" air contains 0.02 per cent of benzyl alcohol vapor by volume at 25° C. and has a density of 1.00 (air = 1). Benzyl alcohol is miscible with most cellulose-ester solvents, aromatic hydrocarbons, and oils.<sup>210</sup> Benzyl alcohol will dissolve alkyl-, benzyl-, nitro-, and acetylcelluloses, benzyl abietate, copal esters, cumar resins, ester gum, linnoxyn, glyptal resins, mastics, and sulfur.<sup>210</sup>

1 mg./l. in air  $\approx$  226.1 and 1 p.p.m.  $\approx$  4.42 mg./cu.m. at 25° C., 760 mm.

### 3. Determination in the Atmosphere

Callaway and Reznick<sup>220</sup> determined the amount of benzyl alcohol in an aqueous solution by measuring the refractive index, or by measuring the amount of benzoic acid resulting from oxidation with a saturated potassium permanganate solution. A paper by Mohler and Hämmerle<sup>223</sup> describes a method in which benzyl alcohol in bitter-almond water was determined by means of its absorption spectrum in the ultraviolet region. They report results within the limits of an error of 5 per cent. The maxima at 267, 264, 258, and 252  $m\mu$  are recommended for quantitative estimation. This method should be adaptable to air analysis.

### 4. Physiological Response

*Animal symptomatology.* In a comparison of the lethal doses of various

<sup>216</sup> E. Starrek, *Dissertation, Würzburg* (1938).

<sup>217</sup> A. Emmerie, *Nature*, 141, 416 (1938).

<sup>218</sup> L. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*. Macmillan, New York, 1941, p. 303.

<sup>219</sup> D. I. Macht, *J. Pharmacol.*, 11, 263, 419 (1918).

<sup>220</sup> J. Callaway, Jr., and S. Reznick, *J. Assoc. Official Agr. Chem.*, 16, 285 (1933).

<sup>221</sup> "Atomic Weights (International), 1941," *J. Am. Chem. Soc.*, 63, No. 3 (1941).

<sup>222</sup> J. Timmermans and Mme. Hennault-Roland, *J. chim. phys.*, 32, 501 (1935).

<sup>223</sup> H. Mohler and W. Hämmerle, *Z. anal. Chem.*, 122, 202 (1941); *Chem. Abstracts*, 36, 4970 (1942).

alcohols injected subcutaneously into mice, Starrek<sup>216</sup> indicated that benzyl alcohol is 2.5 to 3 times as toxic as *n*-butyl or isopropyl alcohol. Poisoned mice suffered respiratory stimulation, respiratory and muscular paralysis, convulsions, and narcosis. Macht<sup>219</sup> also observed convulsions when lethal doses were injected into small animals, and reported the occurrence of a decrease in the blood pressure of animals following various modes of injection. Gruber<sup>224</sup> observed a decrease in the arterial blood pressure of rabbits, cats, and dogs following intravenous injection of benzyl alcohol, but failed to find such decrease in the case of dogs following the oral administration of 0.1 to 1.0 ml. per kilogram of body weight. Doses of 0.2 ml. per kilogram, or more, administered to dogs by stomach tube induced emesis and defecation. This was apparently due to irritation of the gastric mucosa, since no such effects resulted from smaller doses given by this route or from the injection of larger doses.<sup>224</sup> Diuresis, more pronounced in the rabbit than in the dog, resulted from the administration of benzyl alcohol by various means.<sup>225</sup> The blood sugar of fasting animals was increased somewhat by prolonged administration of benzyl alcohol.<sup>226</sup> The administration of benzyl alcohol stimulated the rate of elimination of an injected pigment by the liver.<sup>226</sup> Macht<sup>219</sup> believed death was caused by paralysis of the respiratory center, but Gruber<sup>224</sup> believed that cardiac paralysis might precede that of the respiratory center.

*Animal pathology.* The injection of 5 or 10 per cent benzyl alcohol in oil of sweet almond in the region of the auditory meatus of cats caused temporary degeneration of the small facial nerves.<sup>227</sup> Local necrosis of tissue following the accidental injection of pure benzyl alcohol in preparation for a circumcision has been described by Macht.<sup>228</sup>

### 5. Absorption and Excretion

The animal (and human) organism readily oxidizes benzyl alcohol to benzoic acid, which, after conjugating with glycine, is rapidly eliminated as hippuric acid in the urine. Rabbits, given 1 g. of benzyl alcohol subcutaneously, eliminated 300 to 400 mg. of hippuric acid within the following 24 hours.<sup>229</sup> Within 6 hours after the oral administration of 0.40 g. of benzyl alcohol per kilogram of body weight, rabbits eliminated 65.7 per cent of the dose as hippuric acid in the urine.<sup>230</sup> Within 6 hours after taking 1.5 g. of benzyl alcohol orally, human subjects eliminated 75 to 85 per cent of the dose in the urine as hippuric acid.<sup>231</sup>

<sup>216</sup> C. M. Gruber, *J. Lab. Clin. Med.*, 9, 15, 92 (1923).

<sup>219</sup> C. M. Gruber, *J. Lab. Clin. Med.*, 10, 284 (1924).

<sup>224</sup> I. Hosino, *Zikken Syokakibyogaku (Exptl. Gastroenterol.)*, 15, 117 (1940); *Japan. J. Med. Sci., II. Biochem.*, 4, No. 4, Abstracts (in English), 104 (1941).

<sup>227</sup> D. Duncan and W. H. Jarvis, *Anesthesiology*, 4, 465 (1943).

<sup>228</sup> D. I. Macht, *J. Pharmacol. Proc.*, 13, 509 (1919).

<sup>229</sup> J. A. Stekol, *J. Biol. Chem.*, 128, 199 (1939).

<sup>230</sup> S. L. Diack and H. B. Lewis, *J. Biol. Chem.*, 77, 89 (1928).

<sup>231</sup> I. Snapper, A. Grünbaum, and S. Sturkop, *Biochem. Z.*, 155, 163 (1925).

### 6. Effects upon Man

Seven cases of illness in association with the use of a lacquer containing 5 per cent benzene, 10 per cent benzyl alcohol, acetone, denatured alcohol, butyl tartrate, and cellulose acetate, were reported by de Gaulejac and Dervillée.<sup>232</sup> It was believed that benzene (which was present in the air in a poorly ventilated room to the extent of 0.3 mg. per liter) and benzyl alcohol were the chief causes of the violent headaches, vertigo, nausea, gastric pains, vomiting, diarrhea, and loss of weight. These signs of intoxication, which appeared after 1½ to 2 months of exposure, disappeared upon removal from the lacquer exposure.

### 7. Inflammability

The flash point of benzyl alcohol is 213° F. and the ignition temperature is 802° F.

## CYCLOHEXANOL

### 1. Uses

Cyclohexanol,  $\text{H}_2\text{C}(\text{CH}_2)_4\text{CHOH}$ , hexahydrophenol, is also sold under the names Hexalin, Anol, Hydralin, and Adronol. It is used in the production of plastics, lacquers, nylon polishes, printing inks, soaps, and insecticides. Cyclohexanol is used as a blending agent for solutions of nitrocellulose and rubber, and for lacquers containing cellulose derivatives and resins.<sup>233</sup> It is used in the textile, leather, and silk industries.<sup>233</sup>

### 2. Physical Properties

Cyclohexanol is a colorless, slightly volatile liquid having a menthol-like odor. The compound has the following physical properties: molecular weight, 100.156<sup>221</sup>; specific gravity, 0.944 at 26°/4° C.<sup>234</sup>; melting point, 25.2°<sup>235</sup>; boiling point, 160.7<sup>235</sup>; refractive index, 1.464 at 25°<sup>234</sup>; vapor pressure, 2.5 mm. Hg (extrapolated) at 30°, 3.5 mm. Hg at 34°.<sup>236</sup> The vapor density is 3.46 (air = 1). "Saturated" air contains 0.33 per cent cyclohexanol vapor by volume at 30° C. and has a density of 1.01 (air = 1). At 20° C. it is soluble in water to the extent of 4 to 5 per cent. The addition of a small amount of soap promotes much further aqueous solution. It is miscible in all proportions with most aliphatic, aromatic, hydrogenated, and chlorinated solvents, and is a good solvent for most fats, oils, and some natural and synthetic resins.

1 mg./l. of air  $\approx$  244.1 p.p.m. and 1 p.p.m.  $\approx$  4.10 mg./cu.m. at 25° C., 760 mm.

<sup>232</sup> R. de Gaulejac and P. Dervillée, *Ann. méd. légale criminol. police sci.*, 18, 146 (1938).

<sup>233</sup> I. Mellan, *Industrial Solvents*. Reinhold, New York, 1939, p. 246.

<sup>234</sup> The Barrett Division of Allied Chemical and Dye Corporation, *personal communication*.

<sup>235</sup> J. F. Treon, W. E. Crutchfield, Jr., and K. V. Kitzmiller, *J. Ind. Hyg. Toxicol.*, 25, 199 (1943).

<sup>236</sup> G. S. Gardner and J. E. Brewer, *Ind. Eng. Chem.*, 29, 179 (1937).

### 3. Determination in the Atmosphere

The concentration of cyclohexanol in the air may be determined colorimetrically by measuring the intensity of the straw color produced by the reaction with catechol and concentrated sulfuric acid.<sup>237</sup> The error of analysis of an aqueous solution of cyclohexanol containing no other alcohol is  $\pm 0.009$  mg. in the range of 0.05 to 0.25 mg.

### 4. Physiological Response

*Animal symptomatology.* Pohl<sup>238</sup> was unable to observe any effects when a dog was exposed to air saturated with cyclohexanol for 10 minutes per day on 7 successive days. However, exposure of animals to sufficiently high concentrations of cyclohexanol in air for 6 hours per day, 5 days per week (see Table 8) induces

TABLE 8  
*Physiological Response of Animals Subjected to Vapors of Cyclohexanol*

Number of animals exposed	Concentration		Duration of exposure, hr.	Percentage mortality	Signs of intoxication
	mg./l.	p.p.m.			
4 rabbits	4.93	1229	150	50	Narcosis, lethargy, inco-ordination, conjunctival congestion and irritation, salivation
4 rabbits	4.00	997	330	50	Narcosis, lethargy, conjunctival congestion and irritation, lacrimation, salivation, few convulsive movements
1 monkey	2.78	693	300	0	Lethargy, conjunctival irritation
4 rabbits	1.09	272	300	0	Slight conjunctival irritation
4 rabbits	0.58	145	300	0	None

an intoxication characterized by conjunctival congestion and irritation, lacrimation, salivation, lethargy, inco-ordination, narcosis, and mild convulsions.<sup>237</sup> Under suitable conditions this intoxication may terminate in death. Unlike benzene, this compound, when absorbed by experimental animals over considerable periods of time, has shown no tendency to bring about injury to the cellular elements of the peripheral blood.<sup>237</sup> A transient decrease in the blood pressure of rabbits was observed by Sato<sup>239</sup> following the intravenous injection of this compound.

*Animal pathology.* The oral administrations of lethal doses of cyclohexanol (2.6 g. or more per kilogram of body weight) to rabbits caused severe vascular damage and extreme toxic effects with massive coagulation necrosis of myocardium, lung, liver, kidney, and brain. Animals which survived somewhat smaller doses developed toxic degenerative lesions and vascular damage of much lesser degree. The changes observed following the cutaneous application of cyclohexanol were very similar in general to those caused by oral administration, and so afforded corroborative evidence of the absorption of the compound through the skin.<sup>235</sup>

<sup>237</sup> J. F. Treon, W. E. Crutchfield, Jr., and K. V. Kitzmiller, *J. Ind. Hyg. Toxicol.*, **26**, 323 (1943).

<sup>238</sup> J. Pohl, *Zentr. Gewerbehyg. Unfallverhüt.*, **12**, 91 (1925).

<sup>239</sup> K. Sato, *Japan. J. Med. Sci. IV, Pharmacol., Trans. Abstracts*, **3**, No. 1, 1 (1928).

Toxic degenerative changes were found in the brain, heart, liver, and kidneys of rabbits exposed repeatedly to concentrations of cyclohexanol in air ranging from 997 to 1229 p.p.m. (4.00 to 4.93 mg. per liter). Similar but less severe changes were seen in the myocardium, liver, and kidneys of rabbits exposed to vapors of this compound at the concentration of 272 p.p.m. in air (1.09 mg. per liter). Rabbits exposed to a concentration of 145 p.p.m. (0.58 mg. per liter) suffered little or no injury, slight degenerative changes being barely demonstrable in the liver and kidneys.<sup>237</sup>

### 5. Absorption and Excretion

When applied upon the intact skin of rabbits in single large doses, cyclohexanol induced tremors, narcosis, hypothermia, and death.<sup>235</sup> The application of 10 ml. of cyclohexanol upon the intact skin of a rabbit for 1 hour on each of 10 successive days induced narcosis, tremors, athetoid movements, and hypothermia, together with necrosis, exudative ulceration, and thickening of the skin in the area of contact.<sup>235</sup> A number of animals subjected to these applications were fatally poisoned. Only temporary erythema and superficial sloughing of the skin of rabbits occurred when an ointment consisting of potassium oleate and cyclohexanol, up to 15 per cent by weight, was applied in 5-g. portions for 1 hour per day over a period of 15 days.<sup>235</sup>

Pohl<sup>238</sup> found glucuronic acid in the urine of a dog following the oral administration of cyclohexanol. Following oral administration of cyclohexanol to rabbits, this compound is excreted in the urine in conjugation with sulfuric and glucuronic acids.<sup>235,240</sup> Similar results were obtained when animals were subjected to repeated inhalation of the compound.<sup>237</sup> In general, the increased elimination of conjugated sulfates could be correlated with the increase in the concentration of cyclohexanol in the air.<sup>237</sup> On the other hand, rabbits exposed to the lowest concentration used, 145 p.p.m. cyclohexanol in the air, showed no increase in the conjugation of urinary sulfates but excreted five times the normal amount of glucuronic acid.<sup>237</sup>

Di Prisco<sup>241</sup> found a decrease of 1 to 2 per cent in the reduced glutathione of the blood of rabbits subjected to the inhalation of vapors of cyclohexanol for 10 to 15 minutes upon alternate days over a period of 21 days.

### 6. Effects upon Man

Browning<sup>242</sup> has reported one case of suspected intoxication, characterized by vomiting, coated tongue, and slight tremors, in a worker engaged in spraying leather with a preparation which contained butyl acetate and cyclohexanol. The evidence in this case was not adequate to convict cyclohexanol as the offending agent. On the other hand, it is apparent that headache and conjunctival irritation have resulted from prolonged exposure to excessive concentrations.

<sup>240</sup> Y. Sasaki, *Acta Schol. Med. Univ. Imp. Kioto*, 1, 413 (1917).

<sup>241</sup> L. Di Prisco, *Minerva med.*, II, 423 (1932).

<sup>242</sup> E. Browning, *Toxicity of Industrial Organic Solvents*. H. M. Stationery Office, London, 1937, pp. 304, 306.

### 7. Suggested Maximum Permissible Concentration

The results of animal experimentation cannot be applied without considerable reservation to conditions of human exposure to this or any other toxic or irritant compound, but for practical purposes it is suggested that the concentration of 100 p.p.m. cyclohexanol in air, equivalent to 0.41 mg. per liter at 25° C. and 760 mm. Hg pressure, may be employed, tentatively, as the maximum allowable concentration for 8 hours of daily exposure.<sup>237,243</sup> Some attempt at a margin of safety is involved in the proposal but, despite this fact, careful medical supervision of exposed industrial workmen will be required to establish the facts with respect to human safety and comfort.

### 8. Warning Properties and Inflammability

Irritation of the eyes, nose, and throat was induced in human subjects exposed by Nelson *et al.*<sup>244</sup> for 3 to 5 minutes to 100 p.p.m. of cyclohexanol. The majority of these subjects believed that the highest permissible concentration for an 8-hour exposure, from the standpoint of comfort, should be less than 100 p.p.m. At the concentration of 272 p.p.m., which produced irritation of the eyes and nose in rabbits, the odor of the compound was recognized at once by human subjects.

The flash point of cyclohexanol is 154° F.

## METHYLCYCLOHEXANOL

### 1. Uses

Methylcyclohexanol, (CH<sub>3</sub>C<sub>6</sub>H<sub>10</sub>OH), hexahydroresol, methylhexalin, or hexahydromethylphenol, is also sold under the names methyl Adronol, methyl Anol, and Sextol. In general usage methylcyclohexanol and cyclohexanol are interchangeable. Methylcyclohexanol is probably not quite as satisfactory as cyclohexanol as a solvent nor as a stabilizer of emulsions, but it may have preference over cyclohexanol in soaps and preparations for dry cleaning and degreasing.<sup>234</sup>

### 2. Physical Properties

Methylcyclohexanol is a colorless, slightly volatile liquid having an odor suggesting that of menthol, but more harsh and woody. Methylcyclohexanol has the following physical properties: molecular weight, 114.182<sup>245</sup>; specific gravity, 0.913 at 25°/15.5° C.<sup>234</sup>; melting point, -47°<sup>246</sup>; boiling point, 173.0-175.3<sup>234</sup>; vapor pressure, 1.5 mm. Hg at 30°.<sup>234</sup> The vapor density is 3.94 (air = 1). "Saturated" air contains 0.20 per cent methylcyclohexanol vapor by volume at 30° C. and has a density of 1.01 (air = 1). At 20° C. it is soluble in water to the extent of 3 to 4 per cent. It is miscible with the common solvents, plasticizers,

<sup>243</sup> W. A. Cook, *Ind. Med.*, 14, 936 (1945).

<sup>244</sup> K. W. Nelson, J. F. Ege, Jr., M. Ross, L. E. Woodman, and L. Silverman, *J. Ind. Hyg. Toxicol.*, 25, 282 (1943).

<sup>245</sup> "Atomic Weights (International), 1941," *J. Am. Chem. Soc.*, 63, No. 3 (1941).

<sup>246</sup> Markownikow, *J. Russ. Phys.-Chem. Soc.*, 32, 304 (1900).

and gum solutions, and is a solvent for oils, fats, waxes, gums, and resins. There are three structural isomers of this compound (ortho, meta, and para), each of which may occur as cis and trans geometric isomers. The commercial product is composed essentially of a mixture of hydrogenated *m*- and *p*-cresols.

1 mg./l. of air  $\approx$  214.2 p.p.m. and 1 p.p.m.  $\approx$  4.67 mg./cu.m. at 25° C., 760 mm.

### 3. Determination in the Atmosphere

The concentration of methylcyclohexanol in air may be determined colorimetrically by measuring the intensity of the straw color produced by the reaction with catechol and sulfuric acid.<sup>237</sup> The error of analysis of an aqueous solution of methylcyclohexanol containing no other alcohol is  $\pm 0.009$  mg. in the range of 0.05 to 0.25 mg.

### 4. Physiological Response

*Animal symptomatology.* According to Pohl<sup>238</sup> there were no signs of intoxication in a dog exposed for 10 minutes daily on 7 consecutive days to air saturated with methylcyclohexanol. However, in other investigations of the compound, rabbits, subjected to 503 p.p.m. methylcyclohexanol in air for 6 hours per day 5 days per week over a total of 10 weeks, developed salivation, conjunctival congestion and irritation, and lethargy.<sup>237</sup> Corresponding conditions of exposure to lower concentrations (121 and 232 p.p.m.) resulted in no observed effects. No evidence of specific or general change in the cellular elements of the peripheral blood of animals, exposed repeatedly to any of these concentrations, was found.<sup>237</sup> On the basis of the comparative results of the intraperitoneal injection of the three isomeric forms into mice, Fillipi<sup>247</sup> concluded that *o*-methylcyclohexanol is more toxic than the other two isomers.

*Animal pathology.* The oral administration of lethal doses of methylcyclohexanol to rabbits (2.0 g. or more per kilogram of body weight) induced severe acute toxic parenchymal and vascular changes in the heart, liver, and kidneys, and toxic vascular damage in the lungs. As a general rule, these lesions were accompanied by cerebral edema and congestion. Diffuse degenerative changes in the liver were the only histopathological evidences of intoxication in the case of animals given sublethal oral doses of the compound.<sup>235</sup>

Comparable toxic lesions were found in the tissues of animals subjected to inhalation of the vapors in air and to percutaneous absorption of methylcyclohexanol. The severity of the toxic changes varied with the severity of the experimental conditions, assuming borderline or questionable significance (when compared with the incidental variations in the histological pattern in the tissues of control animals) in the case of rabbits exposed to the least concentration of methylcyclohexanol in air (121 p.p.m., 0.56 mg. per liter).<sup>237</sup>

### 5. Absorption and Excretion

The application of large doses of methylcyclohexanol upon the intact skin

<sup>247</sup> E. Fillipi, *Arch. Jarmacol. sper.*, 18, 178 (1914)



of rabbits induced fatal poisoning characterized by tremors, narcosis, and hypothermia.<sup>235</sup> The application of 10 ml. of methylcyclohexanol upon the intact skin of a rabbit for 1 hour on each of 6 successive days resulted fatally. At various stages of the experiment, weakness, tremors, deep anesthesia, and local petechiae, gross hemorrhage, and thickening of the skin were seen.<sup>235</sup> The application upon the intact skin of rabbits of 5 g. portions of a mixture of methylcyclohexanol (up to 15 per cent by weight) in potassium oleate, for 1 hour per day over a period of 15 days, produced only temporary erythema and superficial sloughing of the skin.

Glucuronic acid has been found in the urine of a dog following the oral administration of methylcyclohexanol<sup>238</sup>; in the case of rabbits, under similar conditions of administration, conjugation of the compound or a metabolite with both glucuronic and sulfuric acids has been demonstrated by analysis of the urine.<sup>235</sup> Some conjugation product with sulfuric acid was found also in the urine of animals exposed to 232 and 503 p.p.m. methylcyclohexanol in air.<sup>237</sup> The rate of excretion of glucuronic acid in the urine of rabbits is correlated directly with the concentration of methylcyclohexanol in the air to which they have been subjected.<sup>237</sup> Twice the normal quantity of glucuronic acid was found in the urine of rabbits subjected to 121 p.p.m. methylcyclohexanol in the air.

#### **6. Effects upon Man**

Headache and irritation of the ocular and upper respiratory membranes may result from prolonged exposure to excessive concentrations of the vapor of methylcyclohexanol in air.

After examining several workers who had been exposed to a cellulose solvent containing methylcyclohexanol, Browning<sup>242</sup> concluded that a few of them had slightly but significantly diminished total numbers of leucocytes in the peripheral blood streams, while one had a slight relative lymphocytosis.

#### **7. Suggested Maximum Permissible Concentration**

In view of the information obtained by animal experimentation, it is suggested that the concentration of the vapors of methylcyclohexanol in the atmosphere of industrial workrooms should not be permitted to exceed 75 p.p.m. (0.35 mg. per liter at 25° C. and 760 mm. Hg pressure). Careful medical supervision of workmen under these conditions will serve to establish the necessary facts in relation to human safety and comfort. On the basis of corresponding considerations Cook<sup>243</sup> has tentatively suggested the concentration of 100 p.p.m. as the maximum to be permitted.

#### **8. Warning Properties and Inflammability**

Methylcyclohexanol vapor in air can be detected and recognized by its odor, when present to the extent of 500 p.p.m., a concentration capable of causing upper respiratory irritations.

The flash point of methylcyclohexanol is 154° F.



## CHAPTER TWENTY-SEVEN

# Organic Acids

JAMES H. STERNER, M.D.

### I. GENERAL CONSIDERATIONS

#### A. SYMPTOMS IN ANIMALS

The lower members of the mono- and dicarboxylic acid series are strong primary irritants, and in sufficient concentration produce corrosion of skin and mucous membranes. In exposure to the vapors of formic and acetic acids, the discomfort effect is such that animals will escape if possible, and the irritation will be limited to the eyes and upper respiratory tract. If the animal is prevented from escaping from a high concentration exposure, the bronchi, bronchioles, and alveoli may be involved, with the acute chemical pneumonia ranging from edema to a hemorrhagic exudate of massive degree. Irritation of the eyes is evidenced as conjunctivitis of varying degree, and corneal edema, desquamation, and ulceration, with the associated lachrimation, photophobia, and pain. Formic acid is more irritant than acetic acid.

Oxalic acid, in concentrated solutions, produces marked irritation and even gangrene of the skin. Inhalation of oxalic acid takes place only as a dust, or mist in which the water droplet carries the dissolved acid. There may be marked irritation of the respiratory tract epithelium, usually of the upper portions.

The inhalation of formic and acetic acid vapors does not produce systemic intoxication as a result of absorption of these compounds, since the local irritant action will cause death before the very considerable amount of these easily metabolized acids required to disturb metabolic functions is absorbed. With oxalic acid, however, systemic intoxication may occur after ingestion or inhalation of the acid, with central nervous system involvement indicated by convulsions followed by paralysis.

#### B. GROSS PATHOLOGY IN ANIMALS

The inhalation of formic or acetic acid produces severe corrosion of the mucous membranes and pulmonary epithelium. Secondary effects in the animal body are nonspecific and are the result of the hemorrhagic pneumonia due to the irritant action of the chemicals. With oxalic acid, however, nephritis may result, with an accompanying deposition of calcium oxalate crystals in the kidney.

Formic and acetic acids may produce severe burns similar to those of the mineral acids. Concentrated oxalic acid solutions have a local caustic effect on the skin and mucous membranes and may produce gangrene.

#### C. ABSORPTION AND EXCRETION

In lower concentrations both formic and acetic acids should be readily absorbed through the pulmonary epithelium. It is likely that oxalates taken into the lungs as dust or mist are readily absorbed. Absorption of these acids takes place readily through the gastrointestinal tract. Acetic acid is easily oxidized to carbon dioxide and water. Formic acid is less readily oxidized than acetic so that following the intake of appreciable amounts a considerable proportion (up to two thirds) appears unchanged in the urine. With smaller doses the oxidation is almost complete. The oxalates are very resistant to oxidation and are mostly excreted unchanged through the kidney. The blood normally contains small amounts of formates, acetates, and oxalates.

#### D. MODE OF ACTION

The organic acids are strong primary irritants, with the vapors of formic and acetic acids producing local injury to the respiratory tract. The inhalation of oxalic acid as a dust or mist may produce severe systemic poisoning in addition to a moderate degree of local action on the mucous membranes of the respiratory tract. While oxalate ions do precipitate calcium *in vitro* and *in vivo*, it is doubtful if this is the most significant of the toxic effects. Glycogenolysis of rat liver slices is interfered with by oxalates—an amount of oxalate sufficient to bind only a tenth of the calcium present causing complete arrest of this function, although a decrease of calcium by 30 per cent does not interfere with glycogenolysis in the absence of oxalate.

#### E. PHYSIOLOGICAL RESPONSE IN MAN

In industrial exposures, systemic poisoning from formic and acetic acids has not been reported. At the lower and tolerable levels of exposure, the amounts of acid absorbed are readily oxidized; at higher concentrations, the discomfort is usually sufficient to force the individual out of the highly contaminated area. If an individual is trapped in a high concentration, the effects are those of severe local irritation—on the eyes, skin, and respiratory tract, with death resulting from an acute chemical pneumonia—edema, exudate, and hemorrhage.

Burns of the skin and irritation of the eyes and upper respiratory tract may occur with considerable frequency where large amounts of the acids are handled with inadequate precautions and ventilation. Usually, the inflammatory reaction of the eyes—conjunctivitis and corneal edema with the accompanying lacrimation, photophobia, and pain—is a limiting factor in exposures to lower concentrations, occurring before the development of appreciable respiratory tract inflammation.

The rare occupational intoxication cases reported as due to oxalic acid have occurred following the inhalation of dust or mist from concentrated oxalic acid solution, with loss of weight, pulmonary irritation, irritability, and paralysis.

Oxalic acid is a primary irritant and on ingestion will cause corrosion of the mucous membranes of the digestive tract; on skin contact, burns and, in severe cases, gangrene.

#### F. DETERMINATION IN THE ATMOSPHERE

The organic acids in the atmosphere may be collected by scrubbing a measured volume of air through a measured amount of standard alkali solution. It has been recommended to titrate the excess alkali with 0.01 *N* sulfuric acid, using a suitable indicator such as phenolphthalein or thymol blue. Carbon dioxide, which interferes, may be driven out of the nearly neutral solution by rapidly heating it to the boiling point. Care in neutralization must be exercised in order to avoid loss of acetic acid.

Formic acid and oxalic acid also may be determined by the reduction of potassium permanganate.<sup>1</sup>

## II. SPECIFIC COMPOUNDS

### ACETIC ACID

#### 1. Source

Acetic acid ( $\text{CH}_3\text{COOH}$ ) can be made by the oxidation and fermentation of dilute alcoholic liquors, by the dry distillation of wood, synthetically from acetylene, or more commonly now by the catalytic oxidation of ethanol.

#### 2. Uses and Industrial Exposures

Manufacture of various acetates, dyes, intermediates, cellulose acetate, artificial leather, lead whites, pharmaceuticals, phenol condensation products; medicine; textile printing; solvent; acetate rayon.

#### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid	Refractive index: 1.3721 at 20° C.
Molecular weight: 60.05	Percentage in "saturated" air: 2 at 25° C.
Specific gravity: 1.0499 at 20°/4° C.	Density of "saturated" air: 1.02 (air = 1) at 25° C.
Melting point: 16.6° C.	Insoluble in carbon disulfide
Boiling point: 118.5° C.	Miscible with water, ethyl alcohol, ether
Vapor pressure: 15 (approx.) mm. Hg at 25° C. <sup>2</sup>	

1 mg./l.  $\approx$  408 p.p.m. and 1 p.p.m.  $\approx$  2.554 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (10 p.p.m.): 0.69 ml.

<sup>1</sup> M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

<sup>2</sup> S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, 38, 320 (1946).

**4. Physiological Response**

*Animals.* See Table 1.

*Symptoms in man.*<sup>3</sup> 2–3 mg./l., 800–1200 p.p.m., causes trouble immediately and cannot be tolerated for longer than 3 min.

TABLE 1

*Physiological Response to Various Concentrations of Acetic Acid—Animals*<sup>3</sup>

Concentration		Response
mg./l.	p.p.m.	
47–86	19,000–35,000	Some hyperemia of the mucous membranes of the trachea; tolerated without any severe symptoms
30–36	12,000–14,500	Irritation of mucous membranes of the nose

**5. Maximum Allowable Concentration**

10 p.p.m.

**6. Limits of Inflammability**

Lower limit: 4.05 per cent by volume in air (see Chapter Thirteen).

**7. Odor**

Pungent.

**FORMIC ACID****1. Source**

Formic acid (HCOOH) is prepared by the distillation of sodium formate with sulfuric acid.

**2. Uses and Industrial Exposures**

Chemical manufacture (formates, organic esters, oxalic acid, allyl alcohol); dyeing and finishing of textiles; electroplating; food preservative; wine fermentation; the production of cellulose formate; rubber coagulant; leather.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 46.03

Specific gravity: 1.214 at 20°/4° C.

Melting point: 8.35° C.

Boiling point: 100.7° C.

Vapor pressure: 43 (approx.) mm. Hg at 25° C.<sup>3</sup>

Refractive index: 1.3719 at 20° C.

Percentage in "saturated" air: 5.6 at 25° C.

Density of "saturated" air: 1.03 (air = 1) at 25° C.

Miscible with water, ethyl alcohol, ether, chloroform

1 mg./l.  $\approx$  535.6 p.p.m. and 1 p.p.m.  $\approx$  1.891 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (10 p.p.m.): 0.44 ml.

**4. Suggested Maximum Working Level**

10 p.p.m.

<sup>3</sup>F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

**5. Odor**

Penetrating.

**OXALIC ACID****1. Source**

Oxalic acid,  $(\text{COOH})_2 \cdot 2\text{H}_2\text{O}$ , is produced by passing carbon monoxide under pressure into a hot concentrated solution of sodium hydroxide with subsequent conversion of the sodium formate thus formed into the oxalate, followed by the conversion of the latter into the acid. It may also be prepared from sawdust treated with dilute acids or alkalis: this yields a solution containing oxalic acid or alkali oxalate.<sup>4</sup>

**2. Uses and Industrial Exposures**

Dyestuffs; intermediates; bleaching straw; textile industries; tanning; analytical reagent; chemicals.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless monoclinic prisms

Molecular weight: 126.07

Specific gravity: 1.653 at 18.5°/4° C.

Melting point: 101.5° C. (187° C. anhydrous)

Boiling point: sublimes at 150° C.

Soluble in water

Solubility in ethyl alcohol: 23.23 g./100 ml. alcohol at 15° C.

Solubility in ethyl ether: 1.47 g. hyd. or 23.59 g. anhyd. in 100 ml. ether at 15° C.

**4. Odor**

None.

<sup>4</sup> *The Condensed Chemical Dictionary*, 3rd ed., Reinhold, New York, 1942.





## CHAPTER TWENTY-EIGHT

# The Esters

JAMES H. STERNER, M.D.

### I. Esters of Aliphatic Acids

#### A. GENERAL CONSIDERATIONS

The simpler aliphatic esters are among the least toxic of the organic solvents. Each is a combination of an alcohol and an organic acid, and on hydrolysis or saponification these corresponding moieties are liberated.

In general, an ester is less toxic than the corresponding acid or alcohol. Many of the members, however, possess a considerable volatility so that in spite of their relatively low toxicity there may be produced harmful concentrations at room temperature if there is an appreciable solvent surface area exposed.

#### *1. Symptoms in Animals*

The simpler aliphatic esters are characterized by a slight to moderate narcotic action and a degree of irritation ranging from slight to marked. The narcotic action is usually accompanied by considerable central nervous system excitation and the narcosis is likely to be of short duration with residual nervous system symptoms persisting after the narcotic effect has disappeared. Irritation of the upper respiratory tract and lungs may be marked with certain members of the series—sufficiently so that it serves as a warning when the subject is first exposed to the toxic concentration. However, these substances do produce a considerable fatigue of the olfactory sense so that the warning value of the ester is effective only on initial exposure.

The formates are the least toxic of the simpler compounds with the toxicity increasing slightly in the other members of the series from the acetates through the propionates to the butyrates. Within each series the toxicity and narcotic action increase with the molecular weight and the boiling point, with the exception of the methyl derivatives. Within the formates and the acetates the methyl compound is more toxic and more irritating but less narcotic than the corresponding ethyl compound.

A typical syndrome in animals is as follows: With the less irritant compound little effect is noted on exposure to relatively high concentrations for some

minutes. Then respiration is at first deepened but finally becomes shallow and irregular with the onset of narcosis: this is usually quite marked after narcosis has continued for some time, when there may be generalized convulsive seizures. With the more irritating compounds such as methyl formate and methyl acetate, the animal responds by nose rubbing, sniffing, and sneezing; and lacrimation and salivation may be marked.

The benzyl derivatives are less volatile but are narcotic, irritating, and somewhat more toxic than the aliphatic compounds. For example, exposure to benzyl acetate vapors results in marked irritation to the mucous membranes and eyes, with considerable salivation and nasal secretion. At concentrations producing marked irritation the narcotic action is slight or absent although certain species exhibit a narcoticlike effect, with loss of consciousness usually preceding death.

The lactates are only slightly volatile and apparently more narcotic but less irritating than the lower series of aliphatic esters.

A comparison of the narcotic activity with that of the common anesthetics will aid in evaluating this property. The lower acetates have a weaker narcotic effect than has chloroform, with *n*-propyl and *n*-butyl acetates about equal to ethyl ether. All of these acetates are more narcotic than is pentane.

The chronic effects of the simpler aliphatic esters are relatively slight. Even at concentrations approximating half the narcotic level, repeated exposures for many days may produce little evidence of injury. At higher concentrations the animals may lose weight, become hyperirritable, and develop symptoms of sub-acute or chronic irritation of the eyes and respiratory tract.

## 2. Gross Pathology in Animals

The chief findings at autopsy following death from exposure to the esters are those of irritation of the upper respiratory tract and lungs. These vary from mild hyperemia and edema to marked congestion with petechial hemorrhages and massive edema. Following exposure to very high concentrations, acute congestion of the brain, lungs, liver, and kidneys has been observed.

After repeated exposures to lower concentrations sufficient to cause loss of weight, autopsy on sacrificing the animals reveals little other than the mild to moderate inflammation of the eyes and respiratory tract, with some investigators reporting the finding of a moderately fatty liver and hyperemia of the kidneys.

## 3. Absorption and Excretion in Man

The simpler aliphatic esters are readily absorbed through the lungs. There is some absorption through the skin, but this relation has not been clearly defined. The esters are quite soluble in the plasma and are distributed quickly throughout the body.

In spite of the relatively high water solubility, the esters are not stored for long in the body. Excretion occurs partly through the lung and partly through

the kidney. Hydrolysis, with oxidation of the corresponding alcohol and acid, accounts for an appreciable amount of the absorbed ester.

#### 4. *Effects on Man*

The simpler aliphatic esters are among the least toxic of the organic solvents. In industrial exposures fatalities are extremely rare—occurring only in instances where high concentrations are encountered, as in the painting of the inside of a tank. The information as to the effect of the esters is usually confused by the fact that industrial exposures are rarely to a single compound, but rather to a mixture of solvents—esters, alcohols, hydrocarbons, etc. In the past, it frequently was the custom to attribute the toxicity of a mixture of solvents to the ester component: a conclusion not justified by consideration of its biologic properties when studied in a pure state.

Like the other animal species, man on exposure to the vapors of the simpler esters exhibits symptoms of eye and respiratory tract irritation, and on further exposure, of narcosis. Conjunctivitis may become rather marked. The eye irritation may cumulate so that the conjunctival edema and hyperemia, the corneal dryness and even superficial ulceration, and symptoms of photophobia and lacrimation may not develop until the latter part of the work week, and then usually disappear over the week end. The respiratory tract symptoms are those of mild irritation—hyperactive cough reflex, throat irritation, substernal burning or discomfort—and usually disappear shortly after exposure has terminated.

Gastrointestinal disturbances—loss of appetite, nausea, eructations, “dyspepsia”—have been reported in association with ester vapor exposures, but other classes of solvents present in the exposure render the value of the observation questionable.

There is no satisfactory evidence that the simpler aliphatic esters have any appreciable effect on the hematologic system.

#### 5. *Determination in the Atmosphere*

The esters may be determined by some of the general methods described in Chapter Eight, such as adsorption and weighing, the interferometer, combustion devices, and condensation. They may also be collected by any suitable means, for instance in a partially evacuated bottle, dissolved and refluxed with an excess of standard alkali, and the excess titrated with 0.1 *N* sulfuric acid.<sup>1</sup>

### B. SPECIFIC COMPOUNDS

#### METHYL FORMATE

##### 1. *Source*

Methyl formate ( $\text{HCOOCH}_3$ ) is prepared by heating methyl alcohol with sodium formate and hydrochloric acid, with subsequent distillation.<sup>2</sup>

<sup>1</sup> F. A. Patty, W. P. Yant, and H. H. Schrenk, *U.S. Pub. Health Repts.*, 51, 811 (1936).

<sup>2</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

### 2. Uses and Industrial Exposures

Organic synthesis; cellulose acetate solvent; making military poison gases; fumigant; larvicides.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless, inflammable liquid  
 Molecular weight: 60.05  
 Specific gravity: 0.9631 at 25° C.  
 Melting point: -100.4° C.  
 Boiling point: 31.5° C.  
 Vapor density: 2.07 (air = 1)  
 Vapor pressure: 600 mm. Hg at 25.8° C.

Refractive index: 1.3415 at 25° C.  
 Per cent in saturated air: 79 at 25.8° C.  
 Density of "saturated" air: 1.83 (air = 1) at 25.8° C.  
 Soluble in water, alcohol, and ether\*  
 Flash point: -2° F.

1 mg./l.  $\approx$  408 p.p.m. and 1 p.p.m.  $\approx$  2.554 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (400 p.p.m.): 29.8 ml.

### 4. Physiological Response

*Animals.* See Tables 1 and 2.

*Man.* See Table 3.

TABLE 1  
 Physiological Response to Various Concentrations of Methyl Formate—Animals<sup>4,5</sup>

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Guinea pig	127.7	50,000	1-2 min.	Nasal irritation
			2-3 min.	Eye irritation, lacrimation
			10-20 min.	Inco-ordination
			15-20 min.	Slow deep respiration
			20-25 min.	Narcosis
			25-35 min.	Death
	63.9	25,000	2 min.	Nasal irritation
			2-3 min.	Eye irritation, lacrimation
			20-40 min.	Slow, deep respiration
			30-40 min.	Inco-ordination
			40-50 min.	Narcosis
			50-72 min.	Death
25	10,000	2 min.	Nasal irritation	
		2-3 min.	Eye irritation, lacrimation	
		20 min.	Eye and nose irritation	
		75-120 min.	Slow, deep respiration	
		120-135 min.	Inco-ordination	
		120-150 min.	Narcosis	
Cat			150-175 min.	Death
			80 min.	Prostration
			90 min.	Ataxia
			2-3 hr.	Pulmonary edema, death
Guinea pig	8.9	3,500	3 min.	Nasal irritation
			3-10 min.	Eye irritation
			480 min.	No deaths
	3.8	1,500	5 min.	Nasal irritation
			480 min.	No further symptoms
				No deaths

\* I. Mellan, *Industrial Solvents*. Reinhold, New York, 1939.

<sup>4</sup> H. H. Schrenk, W. P. Yant, J. Chornyak, and F. A. Patty, *U.S. Pub. Health Repts.*, 61, 1329 (1936).

<sup>5</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

TABLE 2

*Summary: Physiological Response to Various Concentrations of Methyl Formate—Guinea Pig<sup>a</sup>*

Concentration		Response
mg./l.	p.p.m.	
127.7	50,000	Death in 20–30 min.
38–63.8	15,000–25,000	Danger to life in 30–60 min.
12.8	5000	Maximum amount for 60 min. without serious disturbances
3.8–5.1	1500–2000	Maximum amount for several hours without serious disturbances

TABLE 3

*Physiological Response to Methyl Formate—Man<sup>a</sup>*

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
3.8	1500	1 min.	Noticing of pleasant ethereal odor; no nasal or eye irritation; no other signs or symptoms

**5. Suggested Maximum Practical Working Level**400 p.p.m.<sup>6</sup>**6. Inflammability**

Inflammable within the range of 5.05 to 22.7 per cent by volume in air (see Chapter Thirteen).

**7. Odor and Warning Properties**

Penetrating, ethereal odor. While the odor of methyl formate is distinct and noticeable in concentrations that are relatively safe from the standpoint of producing acute poisoning, owing to its pleasant nature and the occurrence of olfactory fatigue it is doubtful whether the odor of methyl formate will serve as an effective warning of harmful conditions of exposure.<sup>4</sup>

**ETHYL FORMATE****1. Source**

Ethyl formate ( $\text{HCOOC}_2\text{H}_5$ ) is prepared by heating ethyl alcohol with formic acid in the presence of sulfuric acid.<sup>2</sup>

**2. Uses and Industrial Exposures**

Solvent for cellulose nitrate and acetate; acetone substitute; fumigant and larvicide; synthetic flavors; synthetic resins; medicine.

**3. Pertinent Chemical and Physical Properties**

Physical state: volatile liquid  
 Molecular weight: 74.08  
 Specific gravity: 0.9236 at 25°/4° C.  
 Melting point: -78.9° C.  
 Boiling point: 54.1° C.  
 Vapor density: 2.56 (air = 1)  
 Vapor pressure: 200 mm. Hg at 20.6° C.<sup>7</sup>  
 Refractive index: 1.3575 at 25° C.

Per cent in "saturated" air: 16.2 at 20.6° C.  
 Density of "saturated" air: 1.25 (air = 1) at 20.6° C.  
 Solubility in water: 1 part in 9 parts water at 18° C.  
 Soluble in ethyl alcohol and ether<sup>7</sup>  
 Miscible with benzene<sup>7</sup>  
 Flash point: -4° F.

<sup>a</sup> W. A. Cook, *Ind. Med.*, 14, 936 (1945).<sup>7</sup> *Handbook of Chemistry and Physics*. 28th ed., Chemical Rubber Publishing, Cleveland, 1944.

1 mg./l.  $\approx$  329.7 p.p.m. and 1 p.p.m.  $\approx$  3.03 mg./cu.in. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (400 p.p.m.): 37.6. ml.

#### 4. Physiological Response

*Animals.* See Table 4.

*Man.* See Table 5.

TABLE 4  
*Physiological Response to Various Concentrations of Ethyl Formate—Animals<sup>a,b</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Mouse	32	10,000	20 min.	Eye irritation, difficult breathing
Cat	32	10,000	20 min.	Some irritation
			80 min.	Some irritation; after 75 min. side position; death 90 min. after inhalation
Dog	32	10,000	3 hr.	Slight irritation; vomiting; recovery
			4 hr.	Similar symptoms; death from pulmonary edema
Mouse	16	5,000	20 min.	Eye irritation, difficult breathing
Cat	16	5,000	20 min.	Eye irritation, salivation

TABLE 5  
*Physiological Response to Vapors of Ethyl Formate—Man<sup>a</sup>*

Concentration	Response
32 mg./l.—10,000 p.p.m.	Slight irritation of the eyes, quickly increasing irritation of the nose, continuing even after 4 hr.

#### 5. Suggested Maximum Practical Working Level

400 p.p.m.

#### 6. Inflammability

Inflammable within the range of 2.75 to 16.40 per cent by volume in air (see Chapter Thirteen).

#### 7. Odor

Pleasant.

### *n*-PROPYL FORMATE

#### 1. Pertinent Chemical and Physical Properties of *n*-Propyl Formate, HCOO(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>

Physical state: colorless liquid

Molecular weight: 88.10

Specific gravity: 0.9058 at 20°/4° C.

Freezing point: -92.9° C.

Boiling point: 81.2 ± 0.1° C.

Vapor density: 3.04 (air = 1)

Vapor pressure: 85 mm. Hg at 25° C.<sup>a</sup>

Refractive index: 1.3771 at 20° C.<sup>a</sup>

Per cent in "saturated" air: 11.1 at 25° C.

Soluble in water, ethyl alcohol, ether

Miscible with methyl alcohol, benzene

Flash point: 27° F. (see Chapter Thirteen)

<sup>a</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

<sup>b</sup> *The Merck Index*. 5th ed., Rahway, New Jersey, 1940.

1 mg./l.  $\approx$  277.7 p.p.m. and 1 p.p.m.  $\approx$  3.60 mg./cu.m. at 25° C., 760 mm.

### 2. Suggested Maximum Practical Working Level

400 p.p.m.

### 3. Odor

Pleasant.

## *n*-BUTYL FORMATE

### 1. Uses and Industrial Exposures

*n*-Butyl formate,  $\text{HCOO}(\text{CH}_2)_3\text{CH}_3$ , is used as a solvent for nitrocellulose, some types of cellulose acetate, many cellulose ethers, and many natural and synthetic resins. It is also used in the preparation of lacquers and perfumes and in organic synthesis (intermediate).

### 2. Pertinent Chemical and Physical Properties

Physical state: colorless liquid	Refractive index: 1.3874 at 25° C.
Molecular weight: 102.13	Per cent in "saturated" air: 3.9 at 25° C.
Specific gravity: 0.8885 at 20°/4° C.	Density of "saturated" air: 1.09 (air = 1) at 25° C.
Melting point: -90.0° C. <sup>7</sup>	Soluble in water
Boiling point: 106.8 $\pm$ 0.05° C.	Miscible with ethyl alcohol and ether <sup>7</sup>
Vapor density: 3.5 (air = 1)	Flash point: 64° F.
Vapor pressure: 30 mm. Hg at 25° C. <sup>8</sup>	

1 mg./l.  $\approx$  239.4 p.p.m. and 1 p.p.m.  $\approx$  4.17 mg./cu.m. at 25° C., 760 mm.

### 3. Physiological Response

*Animals.* See Table 6.

*Man.* See Table 7.

TABLE 6  
*Physiological Response to Vapors of n-Butyl Formate—Animals<sup>6</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Cat	43.5	10,000	20 min.	Continuous eye irritation, salivation, stupor
			45 min.	At first irritation; side position after 15 min.; recovery
			60 min.	Deep narcosis; death 70 min. after start of experiment
Dog	43.5	10,000	60 min.	Some irritation, vomiting, vertigo; side position after 40 min.; recovery

TABLE 7  
*Physiological Response to Vapors of n-Butyl Formate—Man<sup>8</sup>*

Concentration	Response
43.5 mg./l.—10,000 p.p.m.	Strong irritation of the eyes, compelled to close eyelids, unbearable even after a few inhalations

### 4. Suggested Maximum Practical Working Level

400 p.p.m.

**n-AMYL FORMATE****1. Uses and Industrial Exposures**

*n*-Amyl formate ( $\text{HCOOC}_5\text{H}_{11}$ ) is used as a solvent for cellulose esters and resins, in solvent mixtures, in films and coatings, in celluloid substitutes, and in the artificial leather industry.

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Refractive index: 1.3992 at 20° C.
Molecular weight: 116.16	Per cent in "saturated" air: 1.3 at 25° C.
Specific gravity: 0.8853 at 20°/4° C.	Density of "saturated" air: 1.04 (air = 1) at 25° C.
Freezing point: -73.5° C.	Slightly soluble in water
Boiling point: 132.1 ± 0.02° C.	Miscible with ethyl alcohol and ether <sup>7</sup>
Vapor density: 4.0 (air = 1)	Flash point: 79° F. <sup>11</sup>
Vapor pressure: 9.6 (approx.) mm. Hg at 25° C. <sup>10</sup>	

1 mg./l.  $\approx$  210.5 p.p.m. and 1 p.p.m.  $\approx$  4.74 mg./cu.m. at 25° C., 760 mm.

**3. Suggested Maximum Practical Working Level**

400 p.p.m.

**4. Odor**

Penetrating odor, less pronounced than that of amyl acetate.

**BENZYL FORMATE****1. Uses and Industrial Exposures**

Benzyl formate ( $\text{HCOOCH}_2\text{C}_6\text{H}_5$ ) is used as a solvent for nitrocellulose, acetylcellulose, and some cellulose ethers, gums, and resins.

**2. Pertinent Chemical and Physical Properties**

Physical state: aromatic liquid	Vapor density: 4.7 (air = 1)
Molecular weight: 136.14	Insoluble in water <sup>7</sup>
Specific gravity: 1.081 at 23° C.	Soluble in ethyl alcohol <sup>7</sup>
Boiling point: 202-203° C. at 747 mm.	Miscible with ethyl ether <sup>7</sup>

1 mg./l.  $\approx$  179.6 p.p.m. and 1 p.p.m.  $\approx$  5.56 mg./cu.m. at 25° C., 760 mm.

**3. Odor**

Pleasant, fruity.

**METHYL ACETATE****1. Source**

Methyl acetate ( $\text{CH}_3\text{COOCH}_3$ ) is prepared by heating methyl alcohol and acetic acid in the presence of sulfuric acid, and distilling.<sup>12</sup>

<sup>10</sup> S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, **38**, 320 (1946).

<sup>11</sup> E. Browning, *Toxicity of Industrial Organic Solvents*. H. M. Stationery Office, London, 1937.

<sup>12</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.



**2. Uses and Industrial Exposures**

Solvent; extracts; perfumery; artificial leather; plastics; solvent for nitro-cellulose and acetylcellulose, cellulose esters; paints, varnishes, and lacquers.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Per cent in "saturated" air: 31 at 25° C.
Molecular weight: 74.08	Density of "saturated" air: 1.48 (air = 1) at 25° C.
Specific gravity: 0.9272 at 20°/4° C.	Solubility in water: 1 part in 3 parts of water
Melting point: -98.7° C.	Soluble in ethyl alcohol and ether
Boiling point: 57° C.	Miscible with benzene
Vapor density: 2.55 (air = 1)	Flash point: 14° F.
Vapor pressure: 235 (approx.) mm. Hg at 25° C. <sup>10</sup>	Volatility: 2.2 times as volatile as ether <sup>11</sup>
Refractive index: 1.3594 at 25° C.	

1 mg./l.  $\approx$  329.7 p.p.m. and 1 p.p.m.  $\approx$  3.03 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (400 p.p.m.): 36.8 ml.

**4. Physiological Response**

*Acute effects in animals.* See Table 8.

*Chronic effects in animals.* See Table 9.

*Human exposure.* See Table 10.

TABLE 8

*Physiological Response to Various Concentrations of Methyl Acetate—Animals*<sup>11,13,14</sup>

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Cat	95	31,000	—	Lethal dose
	65	21,730	2-3 hr.	Fatal limiting concentration
Mouse	63	21,000	—	Lethal dose
Cat	56	19,000	—	Narcotic dose
	Mouse	32	10,000	—
		32	10,000	20 min.
Cat	32	10,000	20 min.	Decreasing eye irritation
			22 hr.	At first irritation; part side position; after a few hours, stupor
Dog	32	10,000	22 hr.	Salivation and persistent eye irritation
Mouse	16	5,000	20 min.	No noticeable effect
Cat	16	5,000	20 min.	Eye irritation, salivation

<sup>11</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

<sup>14</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

TABLE 9  
*Physiological Response of Cats upon Prolonged Exposure to Methyl Acetate*<sup>14</sup>

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
20	6590	8 days, 6 hr. per day	Great loss of weight, severe exhaustion followed by slow recovery

TABLE 10  
*Physiological Response to Vapors of Methyl Acetate—Man*<sup>14,15</sup>

Concentration	Response
32 mg./l.—10,000 p.p.m.	Irritation of the eyes, nose, and throat; odor unpleasant, taste remains for some time

### 5. Suggested Maximum Practical Working Level

400 p.p.m.

### 6. Inflammability

Inflammable within the range of 3.15 to 15.60 per cent by volume in air (see Chapter Thirteen).

### 7. Odor

Pleasant, ethereal.

## ETHYL ACETATE

### 1. Source

Ethyl acetate ( $\text{CH}_3\text{COOC}_2\text{H}_5$ ) is prepared by heating acetic acid and ethyl alcohol in the presence of sulfuric acid and distilling.<sup>12</sup>

### 2. Uses and Industrial Exposures

Medicine; solvent; organic synthesis; flavoring; perfumery; artificial fruit essences; artificial leather; nitrocellulose varnishes, lacquers, and dopes; nitrocellulose plastics; pharmaceuticals; rayon.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless inflammable liquid	Density of "saturated" air: 1.02 (air = 1) at 25° C.
Molecular weight: 88.10	Slightly soluble in water
Specific gravity: 0.901 at 20°/4° C.	Soluble in ethyl alcohol, ether, chloroform, and carbon tetrachloride
Melting point: -82.4° C.	Flash point: 28° F.
Boiling point: 77.06 ± 0.030° C.	Volatility: about one third as volatile as ether <sup>15</sup>
Vapor density: 3.04 (air = 1)	
Vapor pressure: 100 mm. Hg at 25° C. <sup>16</sup>	
Refractive index: 1.3695 at 25° C.	
Per cent in "saturated" air: 1.3 at 25° C.	

<sup>15</sup> E. Browning, *Toxicity of Industrial Organic Solvents*. H. M. Stationery Office, London, 1937.

<sup>16</sup> D. H. Killeffer, *Ind. Eng. Chem.*, 30, 477 (1938).

1 mg./l.  $\approx$  277.7 p.p.m. and 1 p.p.m.  $\approx$  3.60 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (600 p.p.m.): 68.25 ml.

#### 4. Physiological Response

*Acute effects.* See Table 11.

*Chronic effects.* See Table 12.

TABLE 11  
*Physiological Response to Various Concentrations of Ethyl Acetate—Animals<sup>11,14</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Mouse	72	20,000	$\frac{3}{4}$ hr.	Side position after $\frac{3}{4}$ hr.; death of 1 animal, survival of 1; conjunctival clouding
Cat	43	12,000	—	Narcotic concentration
Mouse	36	10,000	$\frac{3}{4}$ hr.	Side position after $\frac{3}{4}$ hr. Survival of 2 of 4 animals; death of 1 animal at end of the experiment; death of 1 a day later; clouding of conjunctiva
	31	8,600	—	Lethal dose
	18	5,000	3-4 hr.	Side position after 3-4 hr.; clouding of conjunctiva; recovery
	7	2,000	17 hr.	Only nasal and eye irritation; dyspnea

TABLE 12  
*Effects of Repeated Exposures to Ethyl Acetate—Guinea Pig<sup>11,13</sup>*

Concentration	Duration of exposure	Response
15-16	6 hr. daily for 7 days	Irritation of the mucous membranes; no definite narcotic symptoms; aftereffects: loss of appetite and weight, fatigue
7	65 exposure periods	No ill effects

#### 5. Suggested Maximum Practical Working Level

600 p.p.m.

#### 6. Inflammability

Inflammable within the range of 2.18 to 11.40 per cent by volume of air (see Chapter Thirteen).

#### 7. Odor

Pleasant.

### *n*-PROPYL ACETATE

#### 1. Source

*n*-Propyl acetate ( $\text{CH}_3\text{COOC}_3\text{H}_7$ ) is produced from the interaction of *n*-propyl alcohol and acetic acid in the presence of sulfuric acid.<sup>12</sup>

### 2. Uses and Industrial Exposures

Flavoring agents; perfumery; solvent for nitrocellulose and a wide range of cellulose derivatives, natural and synthetic resins; lacquers; plastics; organic synthesis.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid

Molecular weight: 102.13

Specific gravity: 0.8884 at 20°/4° C.

Melting point: -92.5° C.

Boiling point: 101.6° C.

Vapor density: 3.5 (air = 1)

Vapor pressure: 35 mm. Hg at 25° C.<sup>10</sup>

Refractive index: 1.3828 at 25° C.

Per cent in "saturated" air: 4.2 at 25° C.

Density of "saturated" air: 1.11 (air = 1) at 25° C.

Solubility in water: 1 part in 49 parts water at 22° C.

Soluble in ethyl alcohol

Miscible with ethyl ether, benzene, acetone

Flash point: 58° F.

1 mg./l.  $\approx$  239.5 p.p.m. and 1 p.p.m.  $\approx$  4.17 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to suggested maximum practical working level (500 p.p.m.): 66.7 ml.

### 4. Physiological Response

See Table 13.

TABLE 13  
*Physiological Response to Various Concentrations of n-Propyl Acetate—Cat<sup>14</sup>  
Flowing Gas Mixture*

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
102	24,500	30 min.	Prostration after 5-16 min.; deep narcosis 13-18 min.; death of 1 after 4 days
38	7,400	5½ hr.	Stupor after ½-¾ hr.; prostration after 4½ hr., deep narcosis after 4-5¼ hr.; death of 1 after 5½ hr.
22	5,300	6 hr. daily for 5 days	Only slight eye irritation and salivation

### 5. Suggested Maximum Practical Working Level

500 p.p.m.

### 6. Odor

Pleasant.

## ISOPROPYL ACETATE

### 1. Source

Isopropyl acetate,  $\text{CH}_3\text{COOCH}(\text{CH}_3)_2$ , is prepared by reacting isopropyl alcohol with acetic acid in the presence of catalysts.<sup>12</sup>

### 2. Uses and Industrial Exposures

Solvent for nitrocellulose, fats, oils, waxes, gums, natural and synthetic resins;

artificial leather; artificial silk; dopes; films; lacquers; plastics; synthetic perfumes; organic synthesis.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid	Per cent in "saturated" air: 9.6 at 25° C.
Molecular weight: 102.13	Density of "saturated" air: 1.24 (air = 1) at 25° C.
Specific gravity: 0.8732 at 18°/4° C.	Solubility in water: 3.09 g. in 100 ml. at 20° C.
Freezing point: -73.4° C.	Miscible with ethyl alcohol, ether, methyl alcohol
Boiling point: 88.85 ± 0.15° C.	Flash point: 40° F.
Vapor density: 3.5 (air = 1)	
Vapor pressure: 73 (approx.) mm. Hg at 25° C. <sup>10</sup>	
Refractive index: 1.3740 at 25° C.	

1 mg./l.  $\approx$  239.5 p.p.m. and 1 p.p.m.  $\approx$  4.17 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to suggested maximum practical working level (500 p.p.m.): 68.0 ml.

### 4. Suggested Maximum Working Level

500 p.p.m.

## *n*-BUTYL ACETATE

### 1. Source

*n*-Butyl acetate (CH<sub>3</sub>COOC<sub>4</sub>H<sub>9</sub>) can be prepared by the esterification and then distillation after contact of *n*-butyl alcohol with acetic acid in the presence of a catalyst such as sulfuric acid.<sup>12</sup>

### 2. Uses and Industrial Exposures

Solvent in production of lacquers, lacquer enamels; solvent for nitrocellulose; in manufacture of artificial leather; perfumes; flavoring extracts; solvent for natural gums and synthetic resins.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless, inflammable liquid	Density of "saturated" air: 1.06 (air = 1) at 25° C.
Molecular weight: 116.16	Solubility: 1 part in 100 parts water at 22° C.
Specific gravity: 0.8824 at 18°/4° C.	Miscible with ethyl alcohol and ether
Boiling point: 124.8-126.5° C.	Flash point: 84° F.
Vapor density: 4.0 (air = 1)	Volatility: 90-100 mg./l. air at 25° C. <sup>13</sup>
Vapor pressure: 15 mm. Hg at 25° C.	
Refractive index: 1.3914 at 25° C.	
Per cent in "saturated" air: 1.97 at 25° C.	

1 mg./l.  $\approx$  210.5 p.p.m. and 1 p.p.m.  $\approx$  4.75 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to suggested maximum practical working level (400 p.p.m.): 61.0 ml.

### 4. Physiological Response

*Animals.* See Tables 14, 15, and 16.

*Man.* See Table 17.

TABLE 14

*Physiological Response to Various Concentrations of n-Butyl Acetate—Animals<sup>13, 14, 17</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Guinea pig	66.5	14,000	—	Nasal and eye irritation immediately
			1 min.	Lacrimation
			2-4 min.	Inco-ordination
			15-30 min.	Narcosis
			190 min.	Dyspnea, gasping
			240 min.	Death
Dog	50	10,000	24 hr.	Giddiness after 25 min.; death of 1 animal immediately; recovery of 1 within 24 hr.
Cat	50	10,000	24 hr.	Weak narcosis
Dog	34	7,200	24 hr.	Toleration without apparent effects
Guinea pig	33	7,000	—	Eye and nasal irritation immediately
			5 min.	Lacrimation
Cat	33	7,000	6 hr.	Narcotic limiting concentration
Guinea pig	33	7,000	420 min.	Inco-ordination
			700 min.	Narcosis
			810 min.	No further symptoms; no deaths
Mouse	30	6,300	6 hr.	Narcotic limiting concentration
Guinea pig	15.7	3,300	5 min.	Eye irritation
			810 min.	No further symptoms; no deaths

TABLE 15

*Physiological Response to Repeated Exposures to n-Butyl Acetate—Animals<sup>13, 18</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Cat	14.5-20.0	3100-4200	6 days for 6 hr. daily	Definite habituation to irritation of the mucous membranes; fatigue, slight decrease in weight
Guinea pig	4.3	900	65 exposures	Fatigue only symptom
	2.4	500	36 3-hr. exposures	Early depression and some renal changes

TABLE 16

*Summary: Physiological Response to Various Concentrations of n-Butyl Acetate—Guinea Pig<sup>17</sup>*

	Concentration		Response
	mg./l.	p.p.m.	
50-66.5	10,000-14,000		Danger to life after several hours
33	7,000		Maximum amount for 1 hr. without serious disturbance
15	3,300		Maximum amount for several hours with but slight or no symptoms

<sup>17</sup> R. R. Sayers, H. H. Schrenk, and F. A. Patty, *U.S. Pub. Health Repts.*, 51, 1229 (1936).<sup>18</sup> E. Browning, *Toxicity of Industrial Organic Solvents*. H. M. Stationery Office, London, 1937.

TABLE 17

*Physiological Response to Various Concentrations of n-Butyl Acetate—Man*<sup>17</sup>

Concentration		Response
mg./l.	p.p.m.	
66.5	14,000	On exposure for short time, atmosphere found extremely disagreeable because of strong odor and irritation to eyes and nasal passages
33	7,000	
15.7	3,300	

**5. Suggested Maximum Practical Working Level**

500 p.p.m.

**6. Odor**

Sweet fruity.

**sec-BUTYL ACETATE****1. Source**

sec-Butyl acetate,  $\text{CH}_3\text{COOCH}(\text{CH}_3)\text{C}_2\text{H}_5$ , is produced by the esterification of sec-butyl alcohol.<sup>19</sup>

**2. Uses and Industrial Exposures**

Solvent for nitrocellulose; lacquers; thinners; nail enamels; celluloid products; artificial leather; leather finishes; plastic wood; washable wallpaper.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 116.16

Specific gravity: 0.8701 at 20°/4° C.

Boiling point: 112.2° C.

Vapor density: 4.0 (air = 1)

Vapor pressure: 24 (approx.) mm. Hg at 25° C.<sup>20</sup>

Refractive index: 1.3840 at 25° C.

Per cent in "saturated" air 3.2 at 25° C.

Density of "saturated" air: 1.09 (air = 1) at 25° C.

Solubility in water: 3 per cent

Soluble in ethyl alcohol and ether<sup>19</sup>Flash point: 66° F.<sup>19</sup>1 mg./l.  $\approx$  210.5 p.p.m. and 1 p.p.m.  $\approx$  4.75 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (400 p.p.m.): 61.8 ml.

**4. Suggested Maximum Practical Working Level**

400 p.p.m.

**5. Odor**

Fruity.

**ISOBUTYL ACETATE****1. Source**

Isobutyl acetate,  $\text{CH}_3\text{COOCH}_2\text{CH}(\text{CH}_3)_2$ , is prepared by reacting isobutyl alcohol with acetic acid in the presence of catalysts.<sup>19</sup>

<sup>19</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

**2. Uses and Industrial Exposures**

Solvent for nitrocellulose and some gums and resins.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Per cent in "saturated" air: 2.6 at 25° C.
Molecular weight: 116.16	Density of "saturated" air: 1.08 (air = 1) at 25° C.
Specific gravity: 0.8747 at 20°/4° C.	Soluble in alcohols, ether, and hydrocarbons <sup>19</sup>
Freezing point: -93.85° C.	Immiscible with water <sup>20</sup>
Boiling point: 117.2° C.	Flash point: 71.6° F.
Vapor density: 4.0 (air = 1)	Volatility: about one eighth that of ethyl ether
Vapor pressure: 20 (approx.) mm. Hg at 25° C. <sup>20</sup>	
Refractive index: 1.3880 at 25° C.	

1 mg./l.  $\approx$  210.5 p.p.m. and 1 p.p.m.  $\approx$  4.75 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (400 p.p.m.): 61.1 ml.

**4. Suggested Maximum Practical Working Level**

400 p.p.m.

**5. Odor**

Mild, pleasant.

**n-AMYL ACETATE****1. Source**

The amyl acetates ( $\text{CH}_3\text{COOC}_5\text{H}_{11}$ ) are made by the acetylation of the alcohols obtained from fusel oil or those made synthetically from the olefin fractions of gasoline.<sup>21</sup>

**2. Uses and Industrial Exposures**

One of the best solvents for cellulose nitrate; solvent for celluloid, camphor, formaldehyde, synthetics, resins, waxes. Used in the manufacture of lacquers, in textile industry for printing and dry-dyeing of fabrics, in leather industry, in manufacture of artificial glass, in preparation of artificial fruit flavors.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Refractive index: 1.4031 at 20° C.
Molecular weight: 130.18	Per cent in saturated" air: 0.66 at 25° C.
Specific gravity: 0.8756 at 20°/4° C.	Density of "saturated" air: 1.02 (air = 1) at 25° C.
Melting point: -70.8° C.	Very slightly soluble in water
Boiling point: 148.8° C.	Soluble in alcohol and ether
Vapor density: 4.5 (air = 1)	Flash point: 77° F.
Vapor pressure: 5 (approx.) mm. Hg at 25° C. <sup>20</sup>	

1 mg./l.  $\approx$  187.8 p.p.m. and 1 p.p.m.  $\approx$  5.32 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (400 p.p.m.): 68.6 ml.

**4. Maximum Allowable Concentration**

400 p.p.m.

<sup>19</sup> S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, **33**, 320 (1946).

<sup>21</sup> I. Mellan, *Industrial Solvents*. Reinhold, New York, 1939.



**5. Odor**

Bananalike or pearlike.

**sec-AMYL ACETATE****1. Source**

sec-Amyl acetate,  $\text{CH}_3\text{COOCH}(\text{CH}_3)\text{C}_3\text{H}_7$ , is prepared by the esterification of sec-amyl alcohol and acetic acid.<sup>19</sup>

**2. Uses and Industrial Exposures**

Solvent for nitrocellulose and ethylcellulose; celluloid products; cements; coated paper; lacquers; enamels; patent leather; plastic wood; washable wall-paper.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 130.18

Boiling point: 133.5° C.

Vapor density: 4.5 (air = 1)

Vapor pressure: 9.3 (approx.) mm. Hg at 25° C.<sup>20</sup>

Per cent in "saturated" air: 1.2 at 25° C.

Density of "saturated" air: 1.04 (air = 1) at 25° C.

1 mg./l.  $\approx$  187.8 p.p.m. and 1 p.p.m.  $\approx$  5.32 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

*Animals.* See Tables 18 and 19.

*Man* See Table 20.

TABLE 18. *Physiological Response to Various Concentrations of sec-Amyl Acetate—Guinea Pig*<sup>21</sup>

Concentration			Response
mg./l.	p.p.m.		
53.2	10,000	—	Eye and nose irritation almost immediately
		1 min.	Lacrimation
		4 min.	Inco-ordination
		20 min.	Narcosis
		165 min.	Slow, shallow respiration
		300 min.	Death
48.9	9,200*	—	Eye and nose irritation almost immediately
		1 min.	Lacrimation
		6 min.	Inco-ordination
		20 min.	Narcosis
		180 min.	Slow, shallow respiration
		435 min.	Death
26.6	5,000	1 min.	Eye and nose irritation
		5 min.	Lacrimation
		90 min.	Inco-ordination
		300-540 min.	Narcosis
		720 min.	Slow, shallow respiration
		810 min.	No deaths
10.6	2,000	1 min.	Nasal irritation
		1-30 min.	Eye irritation
		810 min.	No further symptoms; no deaths

\* Refined sec-amyl acetate. All other concentrations prepared with commercial sec-amyl acetate.

<sup>21</sup> F. A. Patty, W. P. Yant, and H. H. Schrenk, *U.S. Pub. Health Repts.*, 51, 811 (1936).

TABLE 19

*Summary: Physiological Response to Various Concentrations of sec-Amyl Acetate—Guinea Pig<sup>22</sup>*

Concentration		Response
mg./l.	p.p.m.	
26.6–53.2	5,000–10,000	Danger to life after several hours
26.6	5,000	Maximum amount for 60 min. without serious disturbances
10.6	2,000	Maximum amount for several hours with but slight or no symptom

TABLE 20

*Physiological Response to Various Concentrations of sec-Amyl Acetate—Man<sup>22</sup>*

Concentration		Response
mg./l.	p.p.m.	
26.6–53.2	5,000–10,000	Atmosphere found extremely disagreeable on short exposure because of strong odor and irritation to eyes and nasal passages
10.6	2,000	Unpleasant; no marked symptoms

### 5. Maximum Allowable Concentration

400 p.p.m.

### 6. Odor

Bananalike or pearlike.

## ISOAMYL ACETATE

### 1. Pertinent Chemical and Physical Properties of Isoamyl Acetate, $\text{CH}_3\text{COO}(\text{CH}_2)_4\text{CH}(\text{CH}_3)_2$

Physical state: colorless liquid

Molecular weight: 130.18

Specific gravity: 0.8664 at 25°/4° C.

Boiling point: 142.1° C.

Vapor density: 4.5 (air = 1)

Vapor pressure: 6 (approx.) mm. Hg at 25° C.<sup>23</sup>

Refractive index: 1.4003 at 20° C.

Per cent in "saturated" air: 0.79 at 25° C.

Density of "saturated" air: 1.03 (air = 1) at 25° C.

Very slightly soluble in water

Soluble in alcohol and ether

1 mg./l.  $\approx$  187.8 p.p.m. and 1 p.p.m.  $\approx$  5.32 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (400 p.p.m.): 69.6 ml.

### 2. Physiological Response

*Acute effects in animals.* See Table 21.

*Chronic effects in animals.* See Table 22.

*Effects on man.* See Table 23.

TABLE 21  
*Physiological Response to Various Concentrations of Isoamyl Acetate—Animals*<sup>22-25</sup>

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Cat	40	7200	24 hr.	Slight disturbances of co-ordination, giddiness, delayed death after 16 or 24 days from bronchopneumonia
Dog	38	7200	—	No noticeable effects
Rabbit	35	7000	—	No fatalities
Dog	27	5076	1 hr.	Nasal irritation; drowsiness
Cat	24	4512	1/2 hr.	Complete loss of reflexes
Mouse	22	4136	20 min.	No noticeable effect
	21	4000	20 min.	Irritation of mucous membranes
Cat	21	4000	20 min.	Irritation of mucous membranes
Guinea pig	4.8	900	—	No effect

TABLE 22  
*Physiological Response to Chronic Exposure to Isoamyl Acetate—Cat*<sup>24,25</sup>

Concentration	Duration of exposure	Response	
			mg./l.
10	1,900	8 hr. daily for 6 days	Habituation to irritation, coughing, inflammation of the upper and lower respiratory passages, fatigue, loss of weight
5.3, 2.7	1,000, 500	36 3-hr. and 10 2-3-hr. exposures	No evidence of harm

TABLE 23  
*Physiological Response to Isoamyl Acetate—Man*<sup>23</sup>

Concentration	Duration of exposure	Response
5 mg./l.—950 p.p.m.	1/2 hr.	Headache, fatigue, pressure in chest, irritation of the conjunctiva and the mucous membranes of the nose and throat

### 3. Maximum Allowable Concentration

400 p.p.m.

### 4. Odor

Pleasant bananalike or pearlike odor in low concentrations but disagreeable in high concentrations.

<sup>22</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

<sup>24</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

<sup>25</sup> E. Browning, *Toxicity of Industrial Organic Solvents*. His Majesty's Stationery Office, London, 1937.

**sec-HEXYL ACETATE****1. Uses and Industrial Exposures**

sec-Hexyl acetate,  $\text{CH}_3\text{COOCH}(\text{CH}_3)\text{C}_4\text{H}_9$ , is used as a solvent for cellulose nitrate and most gums; used in lacquer industry.

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 144.21

Specific gravity: 0.863 at 20°/4° C.<sup>25</sup>

Boiling point: 146–156° C.<sup>25</sup>

Vapor density: 5.0 (air = 1)

Solubility in water: 0.1 per cent soluble at 25° C.<sup>25</sup>

1 mg./l.  $\approx$  169.5 p.p.m. and 1 p.p.m.  $\approx$  5.89 mg./cu.m. at 25° C., 760 mm.

**3. Odor**

Characteristic odor, more pleasant than those of the normal esters.

**BENZYL ACETATE****1. Source**

Benzyl acetate ( $\text{CH}_3\text{COOCH}_2\text{C}_6\text{H}_5$ ) is prepared by treating benzyl chloride with acetate of soda in various solvents or by esterification of benzyl alcohol with acetic anhydride or acetic acid.<sup>26</sup>

**2. Uses and Industrial Exposures**

Essential ingredient of artificial jasmine and many other flowery perfumes; soap perfume; in some flavors; high boiling solvent for cellulose acetate and nitrate, natural and synthetic resins; oils; lacquers; dopes; polishes; printing inks; varnish removers.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid

Molecular weight: 150.17

Specific gravity: 1.03814 at 22.5° C.

Melting point: -51.5° C.<sup>27</sup>

Boiling point: 216° C. at 762 mm. Hg

Vapor density: 5.2 (air = 1)

Vapor pressure: 1.9 mm. Hg at 60° C.<sup>28</sup>

Refractive index: 1.5227 at 22.5° C.

Per cent in "saturated" air: 0.25 at 60° C.

Density of "saturated" air: 1.01 (air = 1) at 60° C.

Very slightly soluble in water<sup>27</sup>

Soluble in ethyl alcohol and ether

Flash point: 216° F.

1 mg./l.  $\approx$  162.8 p.p.m. and 1 p.p.m.  $\approx$  6.13 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

See Tables 24 and 25.

<sup>25</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

<sup>27</sup> *Handbook of Chemistry and Physics*. 28th ed., Chemical Rubber Publishing, Cleveland, 1944.

<sup>28</sup> D. H. Killefer, *Ind. Eng. Chem.*, 30, 565 (1938).

TABLE 24  
*Physiological Response to Various Concentrations of Benzyl Acetate—Animals*<sup>24, 25</sup>

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Rabbit, guinea pig	10	1600	2 hr.	Serious irritation, restlessness, lacrimation, salivation; no narcotic symptoms; no aftereffects
Cat	10	1600	10 hr.	No narcosis
Mouse	10	1600	10 hr.	Condition like narcosis
	1.3	210	9-17 hr.	Prostration, loss of reflexes; narcotic dose
	0.5	80	47-90 hr.	Narcotic dose

TABLE 25  
*Chronic Poisoning with Benzyl Acetate—Cat*<sup>24</sup>

Concentration	Duration of exposure	Response
1.1-1.5 (flowing gas mixture)	180-240 7 <sup>1</sup> / <sub>2</sub> -10 hr. daily for 7 days	Irritation of mucous membranes at first, then habituation to irritation, trembling, definite narcotic symptoms

### 5. Odor

Pleasant odor, suggestive of jasmine.

## *n*-BUTYL PROPIONATE

### 1. Source

*n*-Butyl propionate,  $C_2H_5COO(CH_2)_3CH_3$ , is prepared by the esterification of propionic acid and *n*-butyl alcohol with sulfuric acid as a catalyst.<sup>26</sup>

### 2. Uses and Industrial Exposures

Solvent for nitrocellulose; retarder in lacquer thinner; lacquers.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid

Molecular weight: 130.08

Specific gravity: 0.8818 at 15°/4° C.

Freezing point: -89.55° C.

Boiling point: 146.8° C.

Vapor density: 4.5 (air = 1)

Vapor pressure: 5.3 (approx.) mm. Hg at 25° C.<sup>27</sup>

Per cent in "saturated" air: 0.7 at 25° C.

Density of "saturated" air: 1.02 (air = 1) at 25° C.

Refractive index: 1.4038 at 15° C.

Very slightly soluble in water

Soluble in alcohol and ether<sup>28</sup>

Miscible with all coal-tar and petroleum distillates<sup>29</sup>

Flash point: 90° F.

1 mg./l.  $\approx$  188 p.p.m. and 1 p.p.m.  $\approx$  5.32 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum working level (400 p.p.m.): 68.5 ml.

### 4. Suggested Maximum Practical Working Level

400 p.p.m.

<sup>26</sup> S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, **38**, 320 (1946).

**5. Odor**

Applelike.

***n*-AMYL PROPIONATE****1. Source**

*n*-Amyl propionate,  $C_2H_5COO(CH_2)_4CH_3$ , is produced by reacting amyl alcohol with propionic acid in the presence of sulfuric acid as a catalyst, followed by neutralization, drying, and distillation.<sup>26</sup>

**2. Uses and Industrial Exposures**

Solvent for nitrocellulose, certain resins; lacquers.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Refractive index: 1.4096 at 15° C.
Molecular weight: 144.21	Per cent in "saturated" air: 0.26 at 25° C.
Specific gravity: 0.8761 at 15°/4° C.	Density of "saturated" air: 1.01 (air = 1) at 25° C.
Freezing point: -73.1° C.	Insoluble in water <sup>27</sup>
Boiling point: 168.65° C.	Miscible with most organic solvents <sup>28</sup>
Vapor density: 5.0 (air = 1)	Flash point: 106° F.
Vapor pressure: 2 (approx.) mm. Hg. at 25° C. <sup>29</sup>	

1 mg./l.  $\approx$  169.6 p.p.m. and 1 p.p.m.  $\approx$  5.89 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (400 p.p.m.): 76.4 ml.

**4. Suggested Maximum Practical Working Level**

400 p.p.m.

**5. Odor**

Milder and more applelike than amyl acetate.

***n*-BUTYL BUTYRATE****1. Uses and Industrial Exposures**

*n*-Butyl butyrate,  $C_3H_7COO(CH_2)_3CH_3$ , is used as a solvent for cellulose nitrate and some gums and resins. It is also used in the lacquer industry where slower evaporation than that of amyl acetate is required.

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Refractive index: 1.4045 at 25° C.
Molecular weight: 144.21	Per cent in "saturated" air: 0.29 at 25° C.
Specific gravity: 0.8712 at 15°/4° C.	Density of "saturated" air: 1.01 (air = 1) at 25° C.
Freezing point: -91.5° C.	Slightly soluble in water <sup>27</sup>
Boiling point: 166.6 $\pm$ 0.01° C.	Soluble in ethyl alcohol and ether <sup>27</sup>
Vapor density: 5.0 (air = 1)	Flash point: 124° F. <sup>29</sup>
Vapor pressure: 2.2 (approx.) mm. Hg at 25° C. <sup>29</sup>	

<sup>29</sup>I. Mellan, *Industrial Solvents*. Reinhold, New York, 1939.

1 mg./l.  $\approx$  169.6 p.p.m. and 1 p.p.m.  $\approx$  5.89 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (400 p.p.m.): 76.8 ml.

**3. Suggested Maximum Practical Working Level**

400 p.p.m.

**4. Odor**

Applelike.

## ETHYL HYDROXY ISOBUTYRATE

**1. Uses and Industrial Exposures**

Ethyl hydroxy isobutyrate,  $(\text{CH}_3)_2\text{C}(\text{OH})\text{COOH}_2\text{CH}_3$ , is used as a solvent for nitrocellulose and cellulose acetate and in solvent mixtures for cellulose ethers.

**2. Pertinent Chemical and Physical Properties**

Physical state: water-white stable liquid<sup>20</sup>

Boiling range: 142–146° C.

Molecular weight: 121.16

Vapor density: 4.2 (air = 1)

Specific gravity: 0.978–0.986 at 20° C.

1 mg./l.  $\approx$  201.8 p.p.m. and 1 p.p.m.  $\approx$  4.95 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (200 p.p.m.): 28.9 ml.

**3. Suggested Maximum Practical Working Level**

200 p.p.m.

**4. Odor**

Mild, pleasant.

## ETHYL LACTATE

**1. Source**

Ethyl lactate,  $\text{CH}_3\text{CH}(\text{OH})\text{COOC}_2\text{H}_5$ , is prepared by the esterification of lactic acid with ethyl alcohol. It may also be made synthetically by combining acetaldehyde with hydrocyanic acid to form acetaldehyde cyanohydrin, which is converted into ethyl lactate by treatment with ethyl alcohol and an inorganic acid such as hydrochloric acid.<sup>26</sup>

**2. Uses and Industrial Exposures**

Solvent for nitrocellulose, cellulose acetate, many cellulose ethers, resins; lacquers; paints; enamels; varnishes; emollient; gelatinant; stencil sheets; safety glass.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Density of "saturated" air: 1.01 (air = 1) at 25° C.
Molecular weight: 118.13	Soluble in water: <sup>77</sup>
Specific gravity: 1.0299 at 20°/4° C.	Very soluble in ethyl alcohol and ether <sup>78</sup>
Boiling point: 154.5° C.	Miscible with ketones, esters, hydrocarbons, oils <sup>79</sup>
Vapor density: 4.06 (air = 1)	Flash point: (approx.) 129° F. <sup>80</sup>
Vapor pressure: 3.7 (approx.) mm. Hg at 25° C. <sup>81</sup>	
Per cent in "saturated" air: 0.49 at 25° C.	

1 mg./l.  $\approx$  207 p.p.m. and 1 p.p.m.  $\approx$  4.87 mg./ cu.m. at 25° C., 760 mm.

**4. Odor**

Mild.

**BUTYL LACTATE****1. Uses and Industrial Exposures**

Butyl lactate,  $\text{CH}_3\text{CH}(\text{OH})\text{COO}(\text{CH}_2)_3\text{CH}_3$ , is used as a solvent for nitrocellulose, ethylcellulose, oils, dyes, natural gums and many synthetic resins. It is also used in lacquers, varnishes, inks, perfumes, and dry-cleaning fluids, and as an intermediate.

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid when pure; technical product brownish <sup>80</sup>	Density of "saturated" air: 1.0 (air = 1) at 20° C.
Molecular weight: 146.18	Solubility in water: 3.4 per cent by vol. at 25° C. <sup>80</sup>
Specific gravity: 0.9803 at 22°/4° C.	Soluble in ethyl alcohol and ether <sup>82</sup>
Melting point: -43° C. <sup>80</sup>	Miscible with many lacquer solvents, diluents, oils <sup>83</sup>
Boiling range: 155-195° C. <sup>81</sup>	Flash point: 160° F. <sup>80</sup>
Vapor density: 5.04 (air = 1)	No significant vapor exposure at "room" temperatures
Vapor pressure: 0.4 mm. Hg at 20° C. <sup>80</sup>	
Refractive index: 1.42162 at 20° C. <sup>80</sup>	
Per cent in "saturated" air: 0.05 at 20° C.	

1 mg./l.  $\approx$  167.3 p.p.m. and 1 p.p.m.  $\approx$  5.97 mg./cu. m. at 25° C., 760 mm.

**3. Physiological Response**

See Table 26.

**4. Odor**

Mild.

**AMYL LACTATE****1. Uses and Industrial Exposures**

Amyl lactate,  $\text{CH}_3\text{CH}(\text{OH})\text{COO}(\text{CH}_2)_4\text{CH}_3$ , is used as a solvent for cellulose nitrate, some gums and resins. It is also used in the lacquer industry, chiefly in the nitrocellulose brushing lacquers when it is desirable to prolong the drying period.

<sup>80</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

<sup>81</sup> *Handbook of Chemistry and Physics*. 28th ed., Chemical Rubber Publishing, Cleveland, 1944.



TABLE 26

*Physiological Response to Subcutaneous Injections of Butyl Lactate—White Mice*<sup>21</sup>

Injection, mg./g. body wt.	Response
12.....	After 10 min., dyspnea, paralysis of the hind extremities, prostration After 25 min., loss of reflexes After 220 min., death
11.....	After 8 min., giddiness After 1 hr., prostration; definite aftereffects After 24 hr., death
10.....	After 10 min., giddiness, dyspnea After 18 min., prostration; no aftereffects Recovery
5.....	No symptoms

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Miscible with alcohols, esters, ketones, hydrocarbons <sup>20</sup>
Molecular weight: 160.21	Immiscible with water <sup>24</sup>
Specific gravity: 0.960 at 20° C. <sup>23</sup>	Flash point: 175° F. <sup>23</sup>
Boiling point: about 210° C. <sup>24</sup>	No significant vapor exposure at "room" temperatures
Vapor density: 5.5 (air = 1)	

1 mg./l.  $\approx$  152.6 p.p.m. and 1 p.p.m.  $\approx$  6.54 mg./cu.m. at 25° C., 760 mm.

**3. Odor**

Brandylike.

**II. Esters of Aromatic and Inorganic Acids****METHYL BENZOATE****1. Source**

Methyl benzoate ( $C_6H_5COOCH_3$ ) can be prepared by heating methyl alcohol and benzoic acid in the presence of sulfuric acid or by passing dry hydrogen chloride through a solution of benzoic acid in methyl alcohol. It also occurs naturally in oils of clove, ylang ylang, tuberose.<sup>33</sup>

**2. Uses and Industrial Exposures**

Perfumery; solvent for cellulose esters and ethers, resins, rubber.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless, oily liquid	Insoluble in water
Molecular weight: 136.14	Soluble in ethyl alcohol and ether
Specific gravity: 1.08714 at 25°/25° C.	Miscible with alcohols, ethers, ketones, and esters <sup>20</sup>
Melting point: -12.3° C.	No significant vapor exposure at "room" temperatures
Boiling point: 199.55° C.	
Vapor density: 4.7 (air = 1)	
Refractive index: 1.5144 at 18.7° C.	

<sup>23</sup> *The Condensed Chemical Dictionary*, 3rd ed., Reinhold, New York, 1942.

<sup>24</sup> E. Browning, *Toxicity of Industrial Organic Solvents*. H. M. Stationery Office, London, 1937.

1 mg./l.  $\approx$  179.6 p.p.m. and 1 p.p.m.  $\approx$  5.56 mg./cu.m. at 25° C., 760 mm.

#### 4. Odor

Fragrant.

### ETHYL BENZOATE

#### 1. Source

Ethyl benzoate ( $C_6H_5COOC_2H_5$ ) can be made by heating ethyl alcohol and benzoic acid in the presence of sulfuric acid.<sup>33</sup>

#### 2. Uses and Industrial Exposures

Flavoring extracts; perfumery; solvent mixtures; lacquers; solvent for many cellulose derivatives and natural and synthetic resins.

#### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid

Molecular weight: 150.17

Specific gravity: 1.0509 at 15°/4° C.

Melting point: -34° C.

Boiling point: 212.9° C.

Vapor density: 5.2 (air = 1)

Refractive index: 1.50104 at 20° C.

Slightly soluble in hot water.<sup>33</sup>

Soluble in alcohol and ether.<sup>33</sup>

No significant vapor exposure at "room" temperatures

1 mg./l.  $\approx$  162.8 p.p.m. and 1 p.p.m.  $\approx$  6.13 mg./cu.m. at 25° C., 760 mm.

#### 4. Odor

Pleasant.

### THE CARBONATES

No experimental work has been reported on the effect of the alkyl carbonates. There are no reported cases of industrial intoxication due to these compounds. These esters are slightly irritant to the eyes and respiratory tract and probably have a toxicity comparable to that of the acetate esters.

### DIMETHYL CARBONATE

#### 1. Source

Dimethyl carbonate,  $(CH_3)_2CO_3$ , is formed by the interaction of phosgene and methyl alcohol.<sup>33</sup>

#### 2. Uses and Industrial Exposures

Solvent for nitrocellulose; lacquer industry.

#### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid

Molecular weight: 90.08

Specific gravity: 1.0694 at 20°/4° C.<sup>33</sup>

Melting point: 0.5° C.<sup>33</sup>

Boiling point: 90.5° C.<sup>33</sup>

Vapor density: 3.1 (air = 1)

Vapor pressure: 56 (approx.) mm. Hg at 25° C.<sup>33</sup>

Refractive index: 1.3687 at 20° C.<sup>33</sup>

Per cent in "saturated" air: 7.4 at 25° C.

Density of "saturated" air: 1.15 (air = 1) at 25° C.

Insoluble in water.<sup>33</sup>

Soluble in ethyl alcohol and ether.<sup>33</sup>

<sup>33</sup> S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, **38**, 320 (1946).

1 mg./l.  $\approx$  271.8 p.p.m. and 1 p.p.m.  $\approx$  3.68 mg./cu.m. at 25° C., 760 mm.

## DIETHYL CARBONATE

### 1. Source

Diethyl carbonate,  $(C_2H_5)_2CO_3$ , cannot be made by the usual esterification process, as carbonic acid is not reactive with ethyl alcohol. The successive steps in its manufacture are:

Reacting chlorine and carbon monoxide to produce phosgene  
 Reacting phosgene with ethyl alcohol to make ethyl chlorocarbonate  
 Reacting ethyl chlorocarbonate with anhydrous ethyl alcohol to produce diethyl carbonate

After the above steps the crude diethyl carbonate is neutralized and redistilled.<sup>33</sup>

### 2. Uses and Industrial Exposures

Solvent for nitrocellulose, cellulose ethers, many synthetic and natural resins; radio tube cathode fixing lacquers.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid	Per cent in "saturated" air: 1.8 at 25° C.
Molecular weight: 118.13	Density of "saturated" air: 1.05 (air = 1) at 25° C.
Specific gravity: 0.9752 at 20°/4° C.	Insoluble in water <sup>32</sup>
Freezing point: -43° C.	Miscible with alcohols, ketones, esters, aromatic hydrocarbons, some aliphatic solvents <sup>33</sup>
Boiling point: 126.8° C.	Flash point: (approx.) 89° F. <sup>33</sup>
Vapor density: 4.1 (air = 1)	
Vapor pressure: 14 (approx.) mm. Hg at 25° C. <sup>33</sup>	
Refractive index: 1.3852 at 20° C.	

1 mg./l.  $\approx$  207 p.p.m. and 1 p.p.m.  $\approx$  4.83 mg./cu.m. at 25° C., 760 mm.

### 4. Odor

Weak, ethereal.

## n-PROPYL CARBONATE

### 1. Pertinent Chemical and Physical Properties of n-Propyl Carbonate, $(C_3H_7)_2CO_3$

Physical state: colorless liquid	Per cent in "saturated" air: 0.43 at 25° C.
Molecular weight: 146.18	Density of "saturated" air: 1.02 (air = 1) at 25° C.
Specific gravity: 0.9411 at 20°/4° C. <sup>33</sup>	Very slightly soluble in water <sup>32</sup>
Boiling point: 168.2° C. <sup>33</sup>	Miscible with ethyl alcohol and ether <sup>33</sup>
Vapor density: 5.05 (air = 1)	No significant vapor exposure at "room" temperatures
Vapor pressure: 3.3 (approx.) mm. Hg at 25° C. <sup>33</sup>	

1 mg./l.  $\approx$  167.3 p.p.m. and 1 p.p.m.  $\approx$  5.97 mg./cu.m. at 25° C., 760 mm.

<sup>33</sup> I. Mellan, *Industrial Solvents*. Reinhold, New York, 1939.

**ISOPROPYL CARBONATE****1. Uses and Industrial Exposures**

Isopropyl carbonate,  $[\text{CH}(\text{CH}_3)_2]_2\text{CO}_3$ , is used in the lacquer industry.

**2. Pertinent Chemical and Physical Properties**

Physical state: liquid	Vapor pressure: 5.1 (approx.) mm. Hg at 25° C. <sup>m</sup>
Molecular weight: 146.18	Per cent in "saturated" air: 0.67 at 25° C.
Specific gravity: 0.921 at 20°/4° C. <sup>m</sup>	Density of "saturated" air: 1.03 (air = 1) at 25° C.
Boiling point: 147.2° C. <sup>m</sup>	
Vapor density: 5.05 (air = 1)	
1 mg./l. $\approx$ 167.3 p.p.m. and 1 p.p.m. $\approx$ 5.97 mg./cu.m. at 25° C., 760 mm.	

**n-BUTYL CARBONATE****1. Uses and Industrial Exposures**

n-Butyl carbonate,  $(\text{C}_4\text{H}_9)_2\text{CO}_3$ , is used in the lacquer industry.

**2. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Insoluble in water <sup>m</sup>
Molecular weight: 174.24	Soluble in ethyl alcohol and ether <sup>m</sup>
Specific gravity: 0.9244 at 20°/4° C. <sup>m</sup>	No significant vapor exposure at "room" temperatures
Boiling point: 207.5° C. <sup>m</sup>	
Vapor density: 6.0 (air = 1)	
1 mg./l. $\approx$ 140.3 p.p.m. and 1 p.p.m. $\approx$ 7.12 mg./cu.m. at 25° C., 760 mm.	

**ISOBUTYL CARBONATE****1. Uses and Industrial Exposures**

Isobutyl carbonate,  $[\text{CH}_2\text{CH}(\text{CH}_3)_2]_2\text{CO}_3$ , is used in the lacquer industry.

**2. Pertinent Chemical and Physical Properties**

Physical state: liquid	Insoluble in water <sup>m</sup>
Molecular weight: 174.24	Miscible with ethyl alcohol and ether <sup>m</sup>
Specific gravity: 0.919 at 15°/4° C. <sup>m</sup>	No significant vapor exposure at "room" temperatures
Boiling point: 190.3° C. <sup>m</sup>	
Vapor density: 6.0 (air = 1)	
1 mg./l. $\approx$ 140.3 p.p.m. and 1 p.p.m. $\approx$ 7.12 mg./cu.m. at 25° C., 760 mm.	

**ISOAMYL CARBONATE****1. Uses and Industrial Exposures**

Isoamyl carbonate,  $[(\text{CH}_2)_2\text{CH}(\text{CH}_3)_2]_2\text{CO}_3$ , is used in the lacquer industry.

**2. Pertinent Chemical and Physical Properties**

Physical state: liquid	Vapor density: 7.0 (air = 1)
Molecular weight: 202.29	No significant vapor exposure at "room" temperatures
Specific gravity: 0.912 at 15°/4° C. <sup>m</sup>	
Boiling point: 228.7° C. <sup>m</sup>	
1 mg./l. $\approx$ 120.8 p.p.m. and 1 p.p.m. $\approx$ 8.27 mg./cu.m. at 25° C., 760 mm.	

<sup>m</sup> *Handbook of Chemistry and Physics*, 28th ed., Chemical Rubber Publishing, Cleveland, 1944.

## THE PHTHALATES

The phthalate esters have a very low volatility and in industrial situations, except under unusual circumstances, offer no hazard from toxicity. They are only moderately toxic substances even when administered parenterally.

*1. Symptoms in Animals*

Animals exposed to high-concentration mists of dimethyl phthalate exhibited moderate irritation of the respiratory tract, weakness, and paralysis, and some of them died. With diethyl phthalate mist the respiratory tract irritation was observed, but narcosis did not occur on a single inhalation. Following repeated exposures to a relatively high concentration of mist, the irritative symptoms disappeared, but anorexia, exhaustion, loss of weight, and apathy were observed. On autopsy, fatty degeneration of the liver and nephritis were found. The inhalation of a mist of dibutyl phthalate resulted chiefly in local irritation to the eyes and respiratory tract.

The relative toxicity in mice, by parenteral injection, of several of these compounds is as follows: phthalic acid, 1; sodium phthalate, 4; dimethyl phthalate, 5; dibutyl phthalate, 10; 2-dioctanol phthalate, 84.

*2. Effects on Man*

No cases of human industrial intoxication to the phthalate esters have been reported. At room temperature there is little or no hazard from the volatilization of these compounds. Precautions should be observed, however, if the material is volatilized by heat or dispersed by spraying.

**DIMETHYL *o*-PHTHALATE****1. Source**

Dimethyl *o*-phthalate,  $C_6H_4(COOCH_3)_2$ , is prepared by the standard esterifying reaction between methyl alcohol and phthalic anhydride, followed by steps of isolation and purification.<sup>38</sup>

**2. Uses and Industrial Exposures**

Plasticizer for nitrocellulose and cellulose acetate, resins, rubber; lacquers; plastics; coating agents; safety glass; molding powders.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless liquid	Vapor pressure: 1.9 mm. Hg at 110° C., <sup>39</sup>
Molecular weight: 194.18	less than 0.1 mm. Hg at 25° C. <sup>38,39</sup>
Specific gravity: 1.1905 at 20.7°/4° C.	Very slightly soluble in water <sup>38</sup>
Boiling point: 282° C.	Miscible with common organic solvents <sup>38</sup>
Refractive index: 1.515–1.516 at 20.7° C.	Flash point: 270° F. <sup>38</sup>

1 mg./l.  $\approx$  125.9 p.p.m. and 1 p.p.m.  $\approx$  7.94 mg./cu.m. at 25° C., 760 mm.

<sup>38</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

<sup>39</sup> D. H. Killeffer, *Ind. Eng. Chem.*, **30**, 565 (1938).

#### 4. Physiological Response

See Tables 27 and 28.

TABLE 27  
*Physiological Response to Various Concentrations of Dimethyl Phthalate—Cat<sup>40</sup>*

Concentration <sup>a</sup>		Response
mg./l.	p.p.m.	
10	1259	Fatigue, stupor, vomiting; recovery of 1 animal, death of 1 animal
2	251.8	Strong irritation of the mucous membranes, salivation, restlessness; no narcosis

<sup>a</sup> Flowing gas mixture. In view of the vapor tension of dimethyl phthalate of less than 0.1 mm. Hg at 25° C., it would not be possible to produce vapor-air mixtures of more than about 130 p.p.m. at this temperature; therefore the concentration figures in this table must be regarded with reserve.

TABLE 28  
*Physiological Response to Oral and Parenteral Administration of Dimethyl Phthalate<sup>40</sup>*

Animal	Dose, g./kg.	Route	Response
Mouse <sup>a</sup>	6	Injection	After 30 min., apathy, exhaustion; after 40 min., serious dyspnea and cyanosis; after 7 hr., prostration; death on average within 20 hr.
	1-4	Oral	No effects
Dog	0.7-1.4	Oral	No effects
Guinea pig	0.5	Subcut.	No effects

<sup>a</sup> The LD<sub>50</sub> for mice by intraperitoneal injection is 2.4 ml. per kilogram body weight.<sup>41</sup>

#### 5. Odor

Practically none.

### DIETHYL *o*-PHTHALATE (Ethyl Phthalate)

#### 1. Source

Diethyl *o*-phthalate, C<sub>8</sub>H<sub>4</sub>(COOC<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, is produced by reaction of phthalic anhydride with ethyl alcohol, followed by careful purification.<sup>38</sup>

#### 2. Uses and Industrial Exposures

Solvent for nitrocellulose, cellulose acetate; plasticizer; wetting agent; perfume fixative; insecticidal sprays; camphor substitute; plastics.

#### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid	Solubility in water: 0.04 g. in 100 ml. water at 25° C. <sup>37</sup>
Molecular weight: 222.23	Miscible with alcohols, ketones, esters, aromatic hydrocarbons; partly miscible with aliphatic solvents <sup>39</sup>
Specific gravity: 1.1175 at 20°/4° C.	Flash point: 284° F. <sup>40</sup>
Melting point: -40.5° C. <sup>38</sup>	
Boiling point: 298-299° C.	
Vapor pressure: 2.7 mm. Hg at 130° C. <sup>42</sup>	
Refractive index: 1.5019 at 20° C. <sup>39</sup>	

<sup>40</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

<sup>41</sup> H. C. Hodge, M. R. Goldstein, and M. Wrightington, *Proc. Soc. Exptl. Biol. Med.*, 49, 471 (1942).

1 mg./l.  $\approx$  110 p.p.m. and 1 p.p.m.  $\approx$  9.08 mg./cu.m. at 25° C., 760 mm.

#### 4. Physiological Response

See Tables 29 and 30.

TABLE 29  
*Physiological Response to Various Concentrations of Diethyl Phthalate—Cat<sup>40</sup>*

Concentration <sup>a</sup>		Duration of exposure	Response
mg./l.	p.p.m.		
10	1100	5 hr.	Irritation of the mucous membranes of the eyes and respiratory tract; no narcosis; rapid recovery
3.7	407	6 hr. daily for 7 days	Irritation, conjunctivitis, narcosis, fatigue, vomiting; aftereffects—apathy, loss of appetite, decrease in weight; slow recovery

<sup>a</sup> These concentrations are not in keeping with vapor pressure data. See Table 27 footnote

TABLE 30  
*Physiological Response to Oral and Parenteral Administration of Diethyl Phthalate<sup>40</sup>*

Animal	Dose, g./kg.	Route	Response
Rabbit	>5.0	Subcut.	Fatal dose
Guinea pig	0.56	Subcut.	No effect
Dog	0.4-0.8	Oral	No effect
Rabbit	0.1	Intrav.	Death after few minutes
	0.05	Intrav.	Paralysis of the hind legs

#### 5. Odor

Odorless with bitter disagreeable taste.

### DIBUTYL *o*-PHTHALATE (Butyl Phthalate)

#### 1. Source

Dibutyl *o*-phthalate, C<sub>6</sub>H<sub>4</sub>(COOC<sub>4</sub>H<sub>9</sub>)<sub>2</sub>, is prepared by reacting *n*-butyl alcohol with phthalic anhydride followed by purification, which results in a product unusually free from odor and color.<sup>38</sup>

#### 2. Uses and Industrial Exposures

Plasticizer in nitrocellulose lacquers and in pyroxylin plastics; solvent for perfume oils; perfume fixative; textile lubricating agent; safety glass; leather dopes; insecticides; printing inks; resin solvent.

#### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid

Molecular weight: 278.34

Specific gravity: 1.047-1.049 at 20°/20° C.<sup>43</sup>

Boiling point: 340° C.

Vapor pressure: 1.3 mm. Hg at 160° C.<sup>39</sup>

Refractive index: 1.48885 at 20° C.<sup>44</sup>

Very slightly soluble in water<sup>38</sup>

Miscible with the common organic solvents<sup>38</sup>

Flash point: 316-345° F.<sup>45</sup>

1 mg./l.  $\approx$  87.8 p.p.m. and 1 p.p.m.  $\approx$  11.38 mg./cu.m. at 25° C., 760 mm.

<sup>38</sup>S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, **38**, 320 (1946).

<sup>45</sup>I. Mellan, *Industrial Solvents*. Reinhold, New York, 1939.

#### 4. Physiological Response

See Table 31.

TABLE 31. *Physiological Response to Vapors of Dibutyl Phthalate—Cat*<sup>40</sup>

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
1	87.8	5½ hr. 3½ hr.	Irritation of the mucous membranes, salivation, and restlessness Fatigue; no aftereffect; quick recovery

LD<sub>50</sub> dose for mice by intraperitoneal injection was found to be 5.5 ml./kg. body weight.<sup>41</sup>

#### 5. Odor

None.

### TRI-*o*-CRESYL PHOSPHATE (*o*-Tolyl Phosphate)

Tri-*o*-cresyl phosphate,  $(\text{CH}_3\text{C}_6\text{H}_4)_3\text{PO}_4$ , has an appreciable toxicity, but its low vapor pressure markedly limits its hazard in industrial exposures.

Information about its toxic effects comes chiefly from the cases of accidental ingestion of the compound. While the human lethal dose is approximately 1 g. per kilogram of body weight, or about 75 g. for an adult man, the amount required to produce serious paralysis is only 0.5 to 2.0 g. In the chicken, repeated doses over a period of days, ineffective individually, will cause paralysis if the total dosage approaches the single minimum paralyzing dose.

The effects in animals following the ingestion of tri-*o*-cresyl phosphate are delayed—frequently for several days. Then a moderate hyperexcitability develops, but not convulsions. The gait becomes spastic and a generalized tremor of the entire musculature develops. This passes into a flaccid paralysis, and, in severe cases, impaired heart action, shallow respirations, and death. Sublethal doses produce nervous system effects, which may clear after weeks or months.

*Effects on man.* No industrial intoxications have been reported. The spraying of tri-*o*-cresyl phosphate or volatilization by heat should be carefully controlled. Appreciable absorption of the compound through the intact skin has been demonstrated.

*Determination.* For methods of detection and determination see Jacobs.<sup>44</sup>

#### 1. Uses and Industrial Exposures

Solvent for nitrocellulose, resins; plasticizer for nitrocellulose; lacquers; dopes.

#### 2. Pertinent Chemical and Physical Properties

Physical state: colorless liquid

Molecular weight: 368.36

Specific gravity: 1.170–1.180 at 20° C.<sup>45</sup>

Boiling point: 410° C.

Refractive index: 1.554–1.556 at 25° C.<sup>45</sup>

Insoluble in water

Readily soluble in ethyl alcohol and ether

Flash point: 446° F.<sup>46</sup>

<sup>44</sup> M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. 2nd ed., Interscience, New York, 1949.



3. *Physiological Response*

See Table 32.

TABLE 32

*Physiological Response to Oral and Parenteral Administration of Tri-o-cresyl Phosphate—Animals<sup>45,46</sup>*

Animal	Dose, g./kg.	Route	Response
Rat	30-15	Subcut.	No effects
	10-7	Oral	No effects
Mouse	3.3	Intraper.	LD <sub>50</sub>
Cat	1.18	Subcut.	Death in 6 days
Dog	1.18	Subcut.	Minimum effective dose
Chicken	1.18	Oral	Severe paralysis; death on 15th day
Rat	1.0	Intrav.	No effects in 4; death of 5 within a few minutes with pulmonary edema
Cat	0.78	Subcut.	Paralysis after 15 days; death in 4 mo.
Guinea pig	0.6	Oral	Death in 2 days
Cat	0.59	Subcut.	Paralysis after 13 days; death after 18 days
Rat	0.5	Intrav.	No effect in 6; death of 3 within a few minutes with pulmonary edema
Cat	0.47	Subcut.	Paralysis after 12 days; death
Chicken	0.47	Oral	Death of 1; death of 2 on 20th day
Rat	0.25	Intrav.	No effects
Chicken	0.24	Oral	All developed moderate to severe paralysis, followed by dyspnea and death in most cases
		Intrav.	Death of all
Cat	0.24	Subcut. or intrav.	Minimum effective dose
Guinea pig	0.2	Oral	Death in 5 days
Chicken	0.12	Intrav.	Death
		Oral	Marked paralysis in 5, slight in 1; death of 1 in 6 days; recovery of 5, apparently, in from 2-3 mo.
Rabbit	0.1	Oral	MLD
Guinea pig	0.1	Oral	Death in 14 days
Rabbit	0.075	Intrav.	MLD
Chicken	0.059	Oral	Slight ataxia with apparent recovery in 2; no effect in 1
		Intrav.	Paralysis and dyspnea in all; death of all
Rabbit	0.050	Oral and intrav.	Minimum toxic dose
Chicken	0.020	Oral	No effect
		Intrav.	No effect in 2 mo.

<sup>45</sup> M. I. Smith, E. W. Engel, and E. F. Stohlman, Further Studies on the Pharmacology of Certain Phenol Esters with Special Reference to the Relation of Chemical Constitution and Physiologic Action. *Natl. Inst. Health Bull.* No. 160 (1932).

<sup>46</sup> H. Hodge and J. Sterner, *J. Pharmacol.*, 79, 225 (1943).

## TRIPHENYL PHOSPHATE

Triphenyl phosphate,  $\text{PO}(\text{OC}_6\text{H}_5)_3$ , a solid at room temperature, has an extremely low vapor pressure.

*Symptoms in animals.* No experimental work has been done on dust inhalation. Following parenteral administration in cats, triphenyl phosphate produces degenerative changes of the peripheral and central nervous system, somewhat similar to those produced by tri-*o*-cresyl phosphate. Certain species of animals affected by tri-*o*-cresyl phosphate show an apparent, marked resistance to triphenyl phosphate, the rabbit and the chicken for example. The effect on the cat, however, is comparable to that produced by tri-*o*-cresyl phosphate.

*Effect on man.* No occupational intoxication has been reported from the use of this material.

### 1. Source

Phenol and phosphorus oxychloride are boiled in the presence of a little zinc chloride until no more hydrogen chloride is given off. The product is shaken with caustic soda solution, filtered, and the residue dissolved in ether. The ethereal solution is dehydrated and the ether evaporated.<sup>47</sup>

### 2. Uses and Industrial Exposures

Solvent and plasticizer for nitrocellulose; coating compositions; lacquers; plastics; etc.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless, odorless, noninflammable, crystalline solid<sup>47</sup>  
 Molecular weight: 326.28  
 Specific gravity: 1.268 at 60° C.<sup>47</sup>  
 Melting point: 48.5° C.<sup>47</sup>

Boiling point: 245° C. at 11 mm.<sup>47</sup>  
 Insoluble in water<sup>48</sup>  
 Solubility in alcohol: 155 parts in 100 parts alcohol at 25° C.<sup>48</sup>  
 Very soluble in ether<sup>48</sup>

### 4. Physiological Response

See Table 33.

### 5. Odor

None.

## DIMETHYL SULFATE

Dimethyl sulfate,  $(\text{CH}_3)_2\text{SO}_4$ , is an extremely toxic material.

*Symptoms in animals.* It acts as a severe local or topical irritant and after absorption produces serious injury to kidneys, liver, and heart. The immediate irritation may be relatively slight, so that little initial discomfort may result from an exposure to vapors which may cause death. After a latent period

<sup>47</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

<sup>48</sup> N. A. Lange, *Handbook of Chemistry*. Handbook Publishers, Sandusky, Ohio, 1944.

TABLE 33

*Physical Response to Oral and Parenteral Administration of Triphenyl Phosphate—Animals<sup>40,44</sup>*

Animal	Dose, g./kg.	Route	Response
Rabbit	3	Oral	Death of 1 in 7 days; survival of 3 with no ill effects
	3	Intramus.	Survived
Chicken	0.5-2.0	Oral	No effects
Rabbit	1	Intramus.	No ill effects noted
	1	Repeated subcut.	Fatal
Cat	1.0	Intramus.	Tremors and hyperexcitability on the 2nd day; death on 3rd day
Rabbit	0.1-1.0	Repeated oral	Kidney irritation
Cat	0.8	Intramus.	Prostration and general muscular weakness with fine tremors of the muscles of the anterior extremities on second day; death
	0.5	Intramus.	Prostration and general muscular weakness on the sixth day; death
	0.4	Intramus.	Slight hyperexcitability on the 4th day. General muscular paresis on the 5th day; death on the 7th
	0.3	Intramus.	General muscular weakness and tremors of head muscle on the 5th day; generalized flaccid paralysis and labored respiration on the 6th day; death on the 7th day
	0.2	Intramus.	Paresis of hind legs on 10th day; generalized paresis on 12th day; labored respiration and coarse tremors on 14th day; killed
Rabbit	0.1-0.2	Intraper.	No noticeable effects
Cat	0.1	Intramus.	No effects noted in 9 days; accidental death on 10th day

—similar to that seen in phosgene intoxication—acute inflammation of the eyes, nose, mouth, and respiratory tract may develop, rapidly becoming severe. Clouding of the cornea, marked edema and hemorrhages of the respiratory mucous membrane, and massive hemorrhagic pulmonary edema may result in death.

The symptoms—salivation, lacrimation, cough, dyspnea—of respiratory tract irritation are followed in varying rapidity by weakness, coma, death—the result of systemic action.

The liquid or vapors of dimethyl sulfate cause severe blistering and corrosion of the skin, and absorption of appreciable quantities through the skin may result in severe systemic poisoning.

*Gross pathology in animals—cause of death.* The earlier fatalities are usually due to a massive pulmonary edema, with the systemic-absorption effects sometimes an important contributory factor. If death does not occur in the first day or two, a secondary pneumonia or hemorrhages and edema of the kidney, liver, and heart may result in a delayed fatality. With a lesser exposure and severe respiratory-tract and systemic injuries, recovery may be very prolonged, weeks or even months.

*Mode of action.* Dimethyl sulfate is readily hydrolyzed in water to sulfuric acid and methyl alcohol. The undecomposed molecule interferes, at very low concentrations, with vital cellular oxidation-reduction systems.

**Effects on man.** The action on man is very similar to that in other animal species. Numerous cases of intoxication occurred when the material was used as a war gas in World War I. Industrial intoxications have been reported from several sources. Exposures, with the initial symptoms only moderate irritation to the eyes and respiratory tract, may result in serious or even fatal effects after a few hours. The vapors may not irritate the skin at first, but the liquid produces an immediate, severe burn.

Following inhalation of the vapors, inflammation of the eyes and respiratory tract may vary from mild congestion to severe corrosive lesions. In the lung, massive and hemorrhagic pulmonary edema may result in death in a few hours. The trachea and bronchi may show membranous lesions similar to those seen in diphtheria. Cases surviving the first few days may succumb to the secondary pneumonia and the degenerative toxic action of the absorbed poison in the liver, kidneys, and heart.

Lesser exposures may result in bronchitis and tracheitis which persist for some weeks. Following the slow healing of corrosive skin lesions, local analgesia may last for a long time.

**Determination in the atmosphere.** Dimethyl sulfate may be determined by scrubbing the atmosphere through dilute alkali and precipitating the sulfate with barium.<sup>44</sup>

#### 1. Source

Dimethyl sulfate is prepared by adding fuming sulfuric acid to methyl alcohol and distilling *in vacuo*.<sup>47</sup>

#### 2. Uses and Industrial Exposures

Methylating agent for amines and phenols; military poison gas (known in Germany as "D-Stoff").

#### 3. Pertinent Chemical and Physical Properties

Physical state: colorless oily liquid  
 Molecular weight: 126.13  
 Specific gravity: 1.3322 at 20°/4° C.  
 Melting point: -26.8° C.  
 Boiling point: 188.5° C.  
 Vapor density: 4.35 (air = 1)  
 Refractive index: 1.3855 at 25° C.

Solubility in water: 28 g. in 100 ml. water at 18° C.  
 Soluble in ethyl alcohol and ether  
 Insoluble in fatty oils<sup>48</sup>  
 Miscible with aromatic hydrocarbons  
 Volatility: about 3.3 mg./l. at 20° C.<sup>49</sup>

1 mg./l.  $\approx$  193.8 p.p.m. and 1 p.p.m.  $\approx$  5.15 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (1 p.p.m.): 0.11 ml.

#### 4. Physiological Response

See Table 34.

\* K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

TABLE 34  
*Physiological Response to Various Concentrations of Dimethyl Sulfate—Animals*<sup>50</sup>

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Guinea pig	10.7	2000	--	Death
Cat	0.9	175	11 min.	Death after several days
	0.4	78	11 min.	Death after 1½ wk.
Monkey	0.132	25.5	40 min.	Death after 3 days
Cat	0.1	19.5	11 min.	Death after 1½ wk.
Monkey	0.066	12.8	20 min.	Extremely ill after 6 hr.; recovery in 4 wk.

### 5. Suggested Maximum Practical Working Level

1 p.p.m.<sup>51</sup>

### 6. Odor and Warning Properties

Lack of odor and warning signs as well as the latency period without symptoms make dimethyl sulfate a very dangerous material with which to work.<sup>49</sup>

## DIETHYL SULFATE

### 1. Source

Diethyl sulfate,  $(C_2H_5)_2SO_4$ , is produced by the action of fuming sulfuric acid on ethyl alcohol.<sup>47</sup>

### 2. Uses and Industrial Exposures

Ethylating agent in organic synthesis.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless oily liquid	Vapor pressure: 0.1 mm. Hg at 20° C. <sup>47</sup>
Molecular weight: 154.18	Refractive index: 1.4010 at 18° C.
Specific gravity: 1.1723 at 25°/4° C.	Insoluble in water <sup>47</sup>
Melting point: -24.5° C.	Soluble in ethyl alcohol and ether <sup>47</sup>
Boiling point: 208° C. <sup>47</sup>	Flash point: 250° F. <sup>47</sup>

1 mg./l.  $\approx$  158.6 p.p.m. and 1 p.p.m.  $\approx$  6.30 mg./cu.m. at 25° C., 760 mm.

### 4. Odor and Warning Properties

Faint, ethereal odor; not a warning property.

## METHYL SILICATE (Tetramethyl Orthosilicate)

### 1. Uses and Industrial Exposures

Methyl silicate,  $Si(OCH_3)_4$ , is used in the ceramic industry for closing pores, in coating concrete cement, for coating metal surfaces, and as a bonding agent in paints and lacquers.

<sup>50</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

<sup>51</sup> W. A. Cook, *Ind. Med.*, 14, 936 (1945).

### 2. Physical and Chemical Properties

Physical state: liquid  
 Molecular weight: 152.2  
 Density: 1.0232 at 20° C.

Boiling point: 25–27° C. at 12 mm.  
 Refractive index: 1.3683 at 20° C.

1 mg./l.  $\approx$  160.7 p.p.m. and 1 p.p.m.  $\approx$  6.22 mg./cu.m. at 25° C., 760 mm.

### 3. Physiological Response

*Gross pathology in animals.* The administration of methyl silicate to animals resulted in death within a few hours to a few days. Injury to the kidney usually occurred regardless of the mode of administration. In less severe cases degeneration of the convoluted tubules was found, with complete degeneration of the organ in the more severe cases. Pulmonary edema also occurred in those animals who had received intravenous injections.

It has been reported that exposure to methyl silicate vapor under certain conditions of humidity, or to the liquid, may cause a necrosis of the cornea cells of the eye, which progresses long after exposure, is destructive and resistant to treatment, and may even lead to permanent blindness.<sup>52</sup>

The material was found to be more toxic than either ethyl silicate or silicic acid in animals similarly treated.

*Mode of action.* Methyl silicate hydrolyzes in the body to form silicic acid, and it is probable that the injury is largely due to the action of this material.

*Minimum lethal dose.* See Table 35.

TABLE 35  
*Toxicity of Methyl Silicate—Animals<sup>53</sup>*

MLD <sub>50</sub> (ml./100 g. body wt.)	Route	Animal
0.07	Oral	Rat
0.01	Intrav.	Rabbit
0.01	Intraper.	Rat and guinea pig

## ETHYL SILICATE (Tetraethyl Orthosilicate)

### 1. Uses and Industrial Exposures

Ethyl silicate,  $\text{Si}(\text{OC}_2\text{H}_5)_4$ , is used as a preservative for stone, brick, concrete, and plaster. It is used in weatherproof and acidproof mortar and cements, refractory bricks, other molded objects; heat-resistant paints; chemical-resistant paints; protective coatings for industrial buildings and castings; lacquers; and as a bonding agent.

<sup>52</sup> *Chem. Age.*, 55, 208 (1946).

<sup>53</sup> W. G. Fredrick, *personal communication*.

TABLE 36

*Physiological Response of Animals after Various Exposures (Time in Minutes) to Various Concentrations of Ethyl Silicate<sup>54</sup>*

Concentration		Maximum exposure	Nasal and eye irritation	Lacrimation	Tremors	Respiratory difficulty	Narcosis	First death	Half or more dead
mg./l.	p.p.m.								
Air of 70% Humidity									
26.1	3070	30	Immed.	15	—	—	—	—	—
21.5	2530	240	Immed.	30	60	90	100	120	240
16.8	1970	300	Immed.	90	95	120	140	180	240
9.0	1115	480	Immed.	120	120	180	200	240	480
6.0	700	360	—	—	—	—	300	360	—
3.4	395	480	—	—	—	—	—	—	—
Dry Air									
14.8	1740	420	Immed.	5	10	10	15	15	30
10.0	1170	480	Immed.	10	120	120	100	120	180
4.7	550	480	—	—	360	—	420	480	—

TABLE 37

*Summary: Acute Effects of Exposure of Guinea Pigs to Ethyl Silicate Vapors in Air of Normal (70%) Humidity<sup>51</sup>*

Concentration		Effects
mg./l.	p.p.m.	
17	2000	Maximum amount for 60 min. without serious disturbance
4.3	500	Maximum amount for several hours without serious disturbance

TABLE 38

*Physiological Response to Various Concentrations of Ethyl Silicate—Rat<sup>56</sup>*

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
9-20	1557-2348	4 hr.	Death within 5 days
1.4	164.3	8 hr. daily for 17 days	Survived but did not obtain weight increases equal to their controls

TABLE 39

*Physiological Response to Injections of Ethyl Silicate—Animals<sup>56</sup>*

Animal	Concn., ml./100 g. body wt.	Mode	Response
Rat	0.6	Intraper.	Death within 60 min.
	0.09-0.35	Subcut.	Survival of 5 longer than 4 days
	0.06-0.56	Intraper.	Death of all but 1 within 3 days
	0.06-0.25	Intraper.	Death of all within 4 days
	0.06	Intraper.	MLD
	0.02-0.04	Intraper.	Survival
Rabbit	0.02	Intrav.	Death in some instances within 5 min.; MLD

### 2. Pertinent Chemical and Physical Properties

Physical state: colorless liquid	Density of "saturated" air: 1.01 (air = 1)
Molecular weight: 208.2	at 25° C.
Specific gravity: 0.9356 at 20°/20° C. <sup>54</sup>	Hydrolyzes in water to form silicic acid <sup>54</sup>
Boiling point: 168.2 C. <sup>54</sup>	Soluble in ethyl alcohol <sup>54</sup>
Vapor density: 7.2 (air = 1)	Miscible with ether <sup>55</sup>
Vapor pressure: 1.47 mm. Hg at 25° C. <sup>54</sup>	Flash point: 125° F. <sup>54</sup>
Per cent in "saturated" air: 0.19 at 25° C.	

1 mg./l.  $\approx$  117.4 p.p.m. and 1 p.p.m.  $\approx$  8.51 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (100 p.p.m.): 25.8 ml.

### 3. Physiological Response

*Symptoms in animals.* The symptoms developed by animals exposed to high concentrations of ethyl silicate are those of irritation of the eyes and respiratory tract, with later evidences of toxic absorption. The initial lacrimation and respiratory difficulty, evidenced by nose rubbing, are followed by tremors, weakness, narcosis, paralysis, and death. Because of the relatively low vapor pressure, the highest concentration obtained at room temperature was not fatal on 30 minutes' exposure. See Tables 36-39.

*Gross pathology in animals.* Widely distributed petechial hemorrhages in the lungs were the most prominent finding in the animals killed by an exposure, with pulmonary edema and, in some cases, lobular pneumonia. The kidney effects were delayed, with softening, and a pale grayish brown discoloration. Splenic congestion was an inconstant finding.

*Cause of death.* Death rarely occurred during an exposure. The usual course, even when narcosis was observed during exposure, included at least a partial return to apparently normal activity, then regression and death in 2 or 3 days. Pulmonary edema and secondary pneumonia apparently accounted for some fatalities, while in other cases nephritis appears to have been the primary cause.

*Mode of action.* Ethyl silicate hydrolyzes readily in aqueous media, with the toxic action possibly due in part to the colloidal silica formed. Since the lesions do not closely parallel those due experimentally to colloidal silica, this effect does not fully explain the toxic mechanism.

*Effects on man.* No industrial intoxications from ethyl silicate have been reported. The relatively low vapor pressure of the compound at room temperature makes improbable a hazardous concentration, unless in an inclosed space with spraying or atomizing application. The stinging of the eyes and nose at 700 p.p.m. should serve as warning to limit exposure at such concentrations to a few minutes. See Table 40.

*Determination in the atmosphere.* The general methods for solvent vapors

<sup>54</sup> H. F. Smyth and J. Seaton, *J. Ind. Hyg. Toxicol.*, **22**, 233 (1940).

<sup>55</sup> M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

<sup>56</sup> J. A. Kasper, C. P. McCord, and W. G. Fredrick, *Ind. Med.*, **6**, 660 (1937).



as described in Chapter Eight are applicable to the determination of methyl and ethyl silicates. No specific methods have been proposed.

TABLE 40  
*Physiological Response to Various Concentrations of Ethyl Silicate—Man<sup>54</sup>*

Concentration		Effects
mg./l.	p.p.m.	
25.5	3000	Extremely irritating to eyes and nose
10.2	1200	Stings eyes and nose and produces tears
6.0	700	Mildly stings eyes and nose
2.1	250	Makes eyes and nose tingle slightly
0.7	85	Can be detected by odor

**4. Suggested Maximum Practical Working Level**

100 p.p.m.<sup>51</sup>

**5. Odor and Warning Properties**

Sharp, though esterlike odor, irritant to eyes and nose at 700 p.p.m. Threshold of irritation 250 p.p.m. Threshold of odor 85 p.p.m.<sup>54</sup>



## CHAPTER TWENTY-NINE

# The Aldehydes

JAMES H. STERNER, M.D.

### I. GENERAL CONSIDERATIONS

The strong primary-irritant effect of the aldehydes usually overshadows the moderate anesthetic action. The lower members of the series, which are more water soluble, produce irritation to the upper portion of the respiratory tract, with the higher, more fat-soluble compounds affecting more the bronchi and lung. The addition of a halogen atom markedly increases the irritant action, but adding three chlorine atoms, as in chloral hydrate, decreases the irritant effect, while greatly enhancing the narcotic activity. The unsaturated compounds are more irritant and more toxic than the saturated; for example acrolein (propenal,  $\text{CH}_2\text{:CHCHO}$ ) as compared with propionaldehyde (propanal,  $\text{CH}_3\text{CH}_2\text{CHO}$ ). The aromatic aldehydes, for example benzaldehyde, as with the higher aliphatic aldehydes, are less volatile and less toxic.

#### A. SYMPTOMS IN ANIMALS

With exposure to low concentrations of formaldehyde in the air, animals exhibit sneezing, coughing, salivation, irritation of the eyes, slowed respiration, and loss of appetite. As the concentration is increased, the symptoms of severe pulmonary involvement are encountered, with death occurring in a few minutes at very high concentrations—the result of the extremely irritant, almost corrosive action. With acetaldehyde the irritative action is slightly less marked, the narcotic effect more prominent, with stimulation followed by depression and paralysis of respiration, signs of the relatively increased narcosis. With acrolein the irritation of the respiratory tract is marked, and pulmonary edema is regularly produced by the higher concentrations. The irritative action on the respiratory tract caused by furfural is less than with either acrolein or formaldehyde, and the signs of central nervous system involvement—side position, convulsions, disturbances of co-ordination, and finally paralysis—may develop, in some species, before the local irritative pulmonary effects cause death.

#### B. GROSS PATHOLOGY AND CAUSE OF DEATH IN ANIMALS

Following the inhalation of high concentrations of formaldehyde, the whole respiratory tract is edematous with scattered hemorrhagic areas. The lung may

show a marked pulmonary edema with multiple hemorrhages and exudate. The effects are somewhat less marked than with the acid gases but death is due, in these acute cases, to the functional injury to the respiratory tract. These effects are somewhat less marked with acetaldehyde but essentially of the same character. With acrolein and the monohalogenated aldehydes the acute irritant effects on the respiratory tract may approach in intensity those of the acid gases. With furfural the irritant activity is less acute but in most instances death is due to the injury to the respiratory tract with evidences of absorptive changes of less importance.

#### C. ABSORPTION AND EXCRETION IN MAN

The aldehydes are quite readily absorbed through the pulmonary epithelium. In the body, unless very large doses are given, practically all of the absorbed formaldehyde is oxidized to formic acid. Small amounts may be excreted in the urine.

#### D. MODE OF ACTION

The toxic effects of the aldehydes are dependent upon several of their properties. The aldehydes, particularly formaldehyde, form a complex with protein in certain concentrations. The result is apparently a denaturation of the protein and precipitation. In other instances, the complex is a reversible one.

In addition, the aldehydes are potent reducing agents, themselves being oxidized into acid during the reaction. In this capacity they undoubtedly interfere with enzyme systems in the body although this effect has not been adequately defined.

A third and important action is that of producing specific sensitization, particularly of the skin. The formaldehyde apparently acts as an antigen to produce a formaldehyde-protein antibody. After sensitization has been developed, further exposure to relatively small amounts may result in irritation. Of the total number of individuals exposed to formaldehyde, the percentage developing sensitization is not very great, but individual cases may show a severe degree of reaction. The cutaneous sensitization is much more marked with the lower members of the series and absent or of very low order with the aromatic aldehydes. Sensitization of the pulmonary tract has been reported, with asthma of varying severity, but is rare. The cutaneous manifestations include eczematoid dermatitis (ectodermal tissue) and urticaria (mesodermal tissue).

#### E. PHYSIOLOGICAL RESPONSE IN MAN

The primary irritant action of the aldehydes is the most prominent of the actions on man. The eyes and mucous membranes of the respiratory tract are irritated by moderate concentrations. With higher concentrations from which the individual cannot escape, pulmonary edema may result. Repeated exposures to

moderate concentrations may produce bronchitis and tracheitis. In rare instances, sensitization of the pulmonary tissue may result in asthma. The more severe effects are not common in industrial experience.

Strong concentrations on the skin or mucous membranes may result in hardening and roughening of the skin or even in a superficial necrosis. Sensitization of the skin is not uncommon with an eczematoid dermatitis or urticaria, sometimes of severe degree.

With concentrations at the threshold level of irritation, approximately 10 to 15 p.p.m., there is no evidence of systemic effects or of severe local irritative action. At somewhat higher levels the subacute or chronic irritation of the respiratory tract may be disturbing, but there is no evidence of systemic involvement even at levels in which the irritation is marked.

## F. DETERMINATION IN THE ATMOSPHERE

Formaldehyde may be collected in a standard impinger using 1.25 per cent potassium hydroxide and determined colorimetrically or polarographically<sup>1</sup> or it may be collected in 1 per cent sodium or potassium bisulfite solution and titrated with iodine.<sup>2</sup> This latter method may be used for other aldehydes including acrolein. In the case of acrolein the sample after collection is adjusted with iodine in a neutral solution, and titrated with iodine after release of bisulfite from the aldehyde by proper adjustment of the alkalinity through the addition of sodium bicarbonate or carbonate. The polarograph may also be used in determining acetaldehyde.<sup>3</sup> Furfural may be determined colorimetrically by the aniline acetate method.<sup>4</sup>

## II. SPECIFIC COMPOUNDS

### FORMALDEHYDE

#### 1. Source

Formaldehyde (HCHO) is prepared by passing the vapors of methanol through a heated copper or platinum gauze with subsequent absorption in water.<sup>5</sup>

#### 2. Uses and Industrial Exposures

In making synthetic resins; as a deodorizer, bactericide, and preservative; in dye manufacture; leather, rubber, and textile industries; waterproofing and reducing agent.

<sup>1</sup> E. C. Barnes and H. W. Speicher, *J. Ind. Hyg. Toxicol.*, **24**, 10 (1942).

<sup>2</sup> F. H. Goldman and H. Yagoda, *Ind. Eng. Chem., Anal. Ed.*, **15**, 377 (1943).

<sup>3</sup> P. J. Elving and E. Ratner, *Ind. Eng. Chem., Anal. Ed.*, **18**, 176 (1946).

<sup>4</sup> I. J. Duncan, *Ind. Eng. Chem., Anal. Ed.*, **15**, 162 (1943).

<sup>5</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless gas (appears on market as an aqueous solution, "formalin," containing 40 g. per 100 ml.) at 20° C.  
 Melting point: -92° C.  
 Boiling point: -21° C.  
 Molecular weight: 30.03 Soluble in water, ethyl alcohol, and ethyl ether  
 Specific gravity of "formalin": 1.079-1.081  
 1 mg./l.  $\approx$  814 p.p.m. and 1 p.p.m.  $\approx$  1.227 mg./cu.m. at 25° C., 760 mm.  
 Liquid volume of "formalin" at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the maximum allowable concentration (10 p.p.m.): 0.8 ml.

**4. Physiological Response**

See Table 1.

TABLE 1  
*Physiological Response to Various Concentrations of Formaldehyde—Cat<sup>6</sup>*

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
8.0	6500	3½ hr.	Death
6.0	4900	3 hr.	Edema and hemorrhage of the lungs, emphysema, later inflammatory processes in the lungs; burning of the conjunctiva; death after a few hours
2.0	1600	4 hr.	Edema and hemorrhage of the lungs, emphysema, later inflammatory processes in the lungs; usually death
0.8	650	8 hr.	Edema and hemorrhage of the lungs, emphysema, later inflammatory processes in the lungs; usually death
0.8	650	4 hr.	Irritation of the mucous membranes; recovery after a few days
Up to 0.25	200	3½ hr.	Quick recovery without injury

**5. Maximum Allowable Concentration**

10 p.p.m.

**6. Inflammability**

Lower explosive limit, about 1.3 per cent.<sup>7</sup>

**7. Odor and Warning Properties**

Pungent, penetrating odor, moderate eye irritation.

**ACETALDEHYDE****1. Source**

Acetaldehyde (CH<sub>3</sub>CHO) is produced (a) from "first runnings" of alcohol stills by fractionation in a special still; (b) by passing alcohol vapor over platinum black; (c) by synthesis from acetylene gas.<sup>5</sup>

**2. Uses and Industrial Exposures**

Manufacture of chemicals, dyes, intermediates; yeast albumin; phenol con-

<sup>5</sup>F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

<sup>7</sup>M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

densation products; synthetic rubber; disinfectants; hardening dry gelatin films for photography; perfumes; drugs; synthetic resins; plastics; medicine.

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid at 20° C.	Percentage in "saturated" air: 98 at 20° C.
Molecular weight: 44.05	Density of "saturated" air: 1.5 (air = 1) at 20° C.
Specific gravity: 0.7834 at 18°/4° C.	Soluble in water, ethyl alcohol, ether, and chloroform
Melting point: -123.45° C.	Miscible with benzene, gasoline, toluene, xylene <sup>5</sup>
Boiling point: 20.8° C.	Flash point: -17° F.
Vapor pressure: 740 mm. Hg at 20° C. <sup>5</sup>	
Refractive index: 1.3316 at 20° C. <sup>5</sup>	

1 mg./l.  $\approx$  555.4 p.p.m. and 1 p.p.m.  $\approx$  1.80 mg./cu.m. at 25° C., 760 mm.

### 4. Physiological Response

See Table 2.

TABLE 2  
*Physiological Response to Various Concentrations of Acetaldehyde—Cat<sup>6</sup>*

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
About 20	11,000	1-2 hr.	Excitation then depression; finally death from respiratory paralysis
3-7	1,700-3,900	1-4 hr.	Severe irritation; recovery after days; weak narcosis
2	1,100	3 hr.	Severe temporary irritation of the mucous membranes
0.5	280	7 hr.	No noticeable effects

### 5. Inflammability

Inflammable within the range of 3.97 to 57.0 per cent by volume in air (see Chapter Thirteen).

### 6. Odor

Pungent, fruity.

## ACROLEIN (Propenal, Acrylaldehyde)

### 1. Source

Acrolein ( $\text{CH}_2\text{CHCHO}$ ) may be prepared by (a) the oxidation of allyl alcohol, (b) the distillation of fats, and (c) heating glycerol with potassium bisulfate.<sup>5</sup>

### 2. Uses and Industrial Exposures

Manufacture of artificial resins; organic synthesis; military poison gas; making colloidal osmium, rhodium, ruthenium; refrigerating boxes; water and sewage disinfection.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless to yellowish liquid (inflammable)	Vapor pressure: 260 (approx.) mm. Hg at 25° C. <sup>6</sup>
Molecular weight: 56.06	Refractive index: 1.39975 at 20° C.
Specific gravity: 0.8269 at 20° C.	Percentage in "saturated" air: 34 at 25° C.
Freezing point: -87.7° C.	Density of "saturated" air: 1.31 (air = 1) at 25° C.
Boiling point: 52.1° C.	Soluble in water, ethyl alcohol, and ether

1 mg./l.  $\approx$  436.5 p.p.m. and 1 p.p.m.  $\approx$  2.29 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (0.5 p.p.m.): 0.04 ml.

**4. Physiological Response**

*Animals.* See Table 3.

*Man.* See Table 4.

TABLE 3  
*Physiological Response to Various Concentrations of Acrolein—Animals<sup>6,7</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Cat	2	870	2 $\frac{1}{2}$ hr.	Death during experiment
	1.5	650	2 $\frac{1}{4}$ hr.	Death after 18 hr.
Mouse	0.3-0.4	133-178	10 min.	60% fatalities
Cat	0.2	87	2 $\frac{1}{2}$ hr.	Severe pulmonary irritation
	0.04	17.5	4 hr.	Very irritant; several days necessary for recovery
	0.025	11	Up to 9 hr.	Salivation, lacrimation, nasal irritation, gradual light narcosis
Mouse	0.0229	10	A few min.	Lethal for most animals
	0.0075	3.3	Several hr.	Tolerated without serious symptoms

TABLE 4  
*Physiological Response to Various Concentrations of Acrolein—Man<sup>7,8</sup>*

Concentration	Duration of exposure	Response
0.35	10 min.	Death
0.05		Intolerable
0.013	20 sec.	Painful eye and nose irritation
	1 min.	Practically intolerable
0.007		Lacrimation and nasal irritation
0.0023	2-3 min.	Eye and nose irritation
	4 min.	Moderate eye irritation with lacrimation
	5 min.	Painful and practically intolerable
0.0006	5 min.	Moderate irritation

<sup>6</sup> S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, **38**, 320 (1946).

<sup>7</sup> A. M. Prentiss, *Chemicals in War*. McGraw-Hill, New York, 1937.



**5. Suggested Maximum Practical Working Level**0.5 p.p.m.<sup>10</sup>**6. Odor and Warning Properties**

Disagreeable, choking odor; eye and nose irritation.

**FURAL (2-Furaldehyde, Furfural)****1. Source**Fural (C<sub>4</sub>H<sub>3</sub>OCHO) is obtained from oat hulls by steam-acid digestion.<sup>5</sup>**2. Uses and Industrial Exposures**

Solvent refining of lubricating oils, rosin, and other organic materials; solvent for nitrocellulose, cellulose acetate, shoe dyes, many types of synthetic resins; wetting agent; preparation of synthetic resins; weed killer; fungicide; furfural derivatives; bituminous road construction.

**3. Pertinent Chemical and Physical Properties**

Physical state: colorless oil, changes to brown upon standing

Molecular weight: 96.08

Specific gravity: 1.1598 at 20°/4° C.<sup>5</sup>

Melting point: -36.5° C.

Boiling point: 161.7° C.

Vapor pressure: 2.2 (approx.) mm. Hg at 25° C.<sup>5</sup>

Refractive index: 1.52345 at 25° C.

Percentage in "saturated" air: 0.29 at 25° C.

Density of "saturated" air: 1.01 (air = 1) at 25° C.

Solubility in water: 8.3% at 20° C.<sup>5</sup>

Soluble in ethyl alcohol, ether, and benzene

Flash point: 140° F. (see Chapter Thirteen)

1 mg./l.  $\approx$  254.8 p.p.m. and 1 p.p.m.  $\approx$  3.93 mg./cu.m. at 25° C., 760 mm.**4. Physiological Response**

See Tables 5 and 6.

TABLE 5  
*Physiological Response to Various Concentrations of Fural—Animals<sup>6</sup>*

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Rat	11	2800		Death during experiment (pulmonary edema)
Rabbit, guinea pig	11	2800	30 min.	Marked irritation
Cat	11	2800	30 min.	Side position; serious aftereffects with cramps, dyspnea; death after 3 days from pulmonary edema
Rabbit, guinea pig	1.1	280	1 hr.	Slight irritation to the mucous membranes (salivation and lacrimation)

<sup>10</sup> W. A. Cook, *Ind. Med.*, 14, 936 (1945).

TABLE 6  
*Physiological Response to Oral and Parenteral Administration of Fural*<sup>11</sup>

Animal	Dose, g./kg.	Mode	Response
Rabbit	1.0	Oral	Fatal
	0.75	Oral	Not fatal
Dog	0.65	Oral	Fatal
Cat	0.5	Subcut.	Fatal
Dog	0.25	Intrav.	Fatal
Rabbit	0.24	Subcut.	Fatal

### 5. Inflammability

Lower inflammable limit: 2.10 per cent by volume in air (see Chapter Thirteen).

### 6. Odor and Warning Properties

Penetrating odor, somewhat similar to benzaldehyde.

<sup>11</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

## CHAPTER THIRTY

# The Ketones

FRANK A. PATTY

### 1. Source

Acetone was the only ketone used to any extent commercially until recent years when catalytic processes have been developed to produce other ketones at prices which permit wide commercial application. Acetone remains a well-known and widely used solvent. It was formerly derived chiefly from the destructive distillation of wood, and the distillation of calcium acetate. Newer methods for the manufacture of ketones include synthesis from acetylene, the fermentation of corn products through the agency of cultured bacteria, and the catalytic oxidation of secondary alcohols.

### 2. Industrial Exposures

The possibilities of industrial exposures to ketones for the following workers have been recognized: acetylene workers; artificial leather makers; automobile body and fender finishers; rubber and plastic cement workers; cellulose acetate or nitrate workers; chloroform and iodoform makers; dental-supply workers; drug and patent medicine manufacturers; fused-collar makers; dye makers and dyers; makers of electrical fixtures; explosives workers; hemp, jute, and linen machine operators; methyl alcohol manufacturers; oil and fat extractors; paraffin workers; workmen removing old paint; photographic workers; raincoat makers; rubber workers; shoe manufacturers and repairers; spotters and dry cleaners; varnish, lacquer, paint, and airplane dope workers.

### 3. Physical and Chemical Properties

Table 1 gives the physical properties and other pertinent data for twelve of the most common ketones.

### 4. Determination in the Atmosphere

*Chemical methods.* The preferred chemical method of analysis consists of sampling in a partly evacuated bottle followed by titration with iodine, as described by Jacobs,<sup>1</sup> after Patty, Yant, and Schrenk.<sup>2</sup> 1 ml. 0.1 *N* iodine  $\approx$

<sup>1</sup> M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

<sup>2</sup> F. A. Patty, W. P. Yant, and H. H. Schrenk, *U.S. Pub. Health Repts.*, 50, 1217 (1935).



Compound	Acetone (di-methyl ketone)	2-Butanone (methyl ethyl ketone)	2-Pentanone (methyl n-propyl ketone)	2-Hexanone (methyl n-butyl ketone)	Hexone (methyl isobutyl n-butyl ketone)	2-Heptanone (methyl n-amyl ketone)	1-Octanone (methyl n-hexyl ketone)	Mesityl oxide (methyl isobutenyl ketone)	Isophorone (methyl cyclohexanone)	Acetyl acetone (2,5-hexanedione)	Cyclohexanone	Methylcyclohexanone (meta and para mixture)
Wt. % sol. in water	Miscible	25.37	5.51	1.64	1.91	0.43	0.09	2.9	1.2	M	8-9	2-3
Partition coefficients	0.16	1.7	9.04	18.3	24.0	26.9	30.5	4.7	—	0.05	10.4	—
Suggested max. practical working concn., p.p.m.	600	300	200	150	150	100	75	25-50	20-40	100	125	150
Its attendant warning properties	Odor 1-2 Fruity, pleasant Irrit. 0-1	Odor 2-3 St. disagreeable Irrit. 1-2	Odor 3 Irrit. 1-2	Odor 3 Irrit. 2	Odor 3	Odor 3	Odor 3	Odor 2	Odor 2	—	Odor 1-2	Odor 1-2
Flash point, °F.	0	30	60	95	73	120	155	90	205	185	93	118
Inflammable limits/g	2.55-12.86	1.81-9.50	1.55-8.15	1.22-8.00	1.35-7.60	—	—	—	—	—	—	—
p.p.m. ∞ 1 mg./l.	422	340	284	244	244	214	191	249	177	214	249	218
mg./cu.m. ∞ 1 p.p.m.	2.37	2.94	3.52	4.10	4.10	4.67	5.24	4.02	5.65	4.67	4.02	4.58

\* At 25°/4° unless otherwise noted.  
 † Saturated with vapor at 760 mm. Air = 1.  
 ‡ At 760 mm.  
 § Volume per cent.  
 M = miscible.

\* Cottonseed oil/water.  
 † See Chapter Thirteen.

approximately 0.4 ml. ketone vapor or 40 p.p.m. in a 10-liter sample. The sensitivity is thus dependent upon the size of the sample that can be obtained. Reducing or oxidizing materials interfere. The method is not suitable for cycloketones. Standardized against commercial ketones of high purity, 1 ml. 0.1 *N* iodine has been found equivalent to 0.967 mg. acetone; 1.12 mg. butanone; 1.35 mg. pentanone; 1.54 mg. hexanone; 1.60 mg. hexone; 1.76 mg. heptanone; 2.02 mg. octanone; 2.03 mg. acetyl acetone; and 1.62 mg. mesityl oxide.

The Morasco<sup>3</sup> method as described by Jacobs<sup>1</sup> is less sensitive but it can be used for any of the ketones. In using this method 1 mole of ketone requires for its equivalent 1 mole of NaOH.

*Physical methods.* By interferometer (page 204). The refractivity of 1 per cent vapor in air ( $U \Delta R \times 10^6$ ) of acetone is 7.6, butanone 10.2, pentanone 13.1, hexanone 16.1, hexone 16.6, heptanone 19.0, octanone 21.9, mesityl oxide 16.3, isophorone 19.2, cyclohexanone 13.7, and methylcyclohexanone 16.3. The atmosphere should be sampled direct and not filtered through soda lime or drying agents because if a drying train is used part of the sample may be lost due to absorption of the ketones by the filtering agents. Other physical methods are applicable.

### 5. Physiological Response

The aliphatic ketones have a relatively low order of toxicity. Even though the ketones are widely used reports of serious industrial poisonings are rare and there have been no reports of fatalities.

*Symptoms produced in guinea pigs.* In the order of their occurrence the symptoms produced in guinea pigs by exposure to ketones in general were eye and nasal irritation, lacrimation, inco-ordination, narcosis, and death. Table 2 indicates the lowest concentration at which each of three significant symptoms occurred either during or following an 8-hour exposure. Table 3 summarizes the acute effects of exposure of guinea pigs to vapors of eight ketones. The increase in toxicity with length of carbon chain in the aliphatic series is apparent. This is in keeping with the observations of Winterstein<sup>4</sup> and others.

*Gross pathology in guinea pigs.* The gross pathology exhibited by guinea pigs narcotized by, or dying from, a single exposure to an aliphatic ketone was slight to marked congestion of brain, lungs, liver, and kidneys. Pathology was absent in animals killed four days following exposure. Temporary corneal opacity was noted in several of the severe exposures. Smyth, Seaton, and Fischer<sup>5</sup> found that animals killed by exposure to volatile heads of isophorone evidenced severe kidney and lung injury while the same type of mesityl oxide exposure caused only congestion and cloudy swelling of the kidneys and some congestion of the lungs.

*Absorption and excretion in man.* The absorption of the ketones may be explained largely on the basis of their solubility in water. Acetone being miscible

<sup>3</sup> M. Morasco, *Ind. Eng. Chem.*, 18, 701 (1926).

<sup>4</sup> H. Winterstein, *Die Narkose*. 2nd ed., Springer, Berlin, 1926.

<sup>5</sup> H. F. Smyth, Jr., J. Seaton, and L. Fischer, *J. Ind. Hyg. Toxicol.*, 24, 46 (1942).

with water is readily absorbed through the lungs, and to some extent by all mucous surfaces, and distributed by the blood stream throughout the body. Kagan<sup>6</sup> found that a man breathing an estimated concentration of 22 mg. per liter (9300 p.p.m.) for 5 minutes absorbed 71 per cent of the inhaled acetone; two men breathing 11 mg. per liter (4650 p.p.m.) for 15 minutes absorbed 76 and 77 per cent; while 23 to 29 per cent was carried out with the expired air. Since the alveolar air during these short exposures would be expected to be relatively exhausted of acetone, due to its great solubility in blood and body fluids, the per cent of acetone found in the exhaled breath should be a measure of the physiological dead space in the respiratory tract. The average figure for this space as given by Best and Taylor<sup>7</sup> is 24 per cent and may vary for individuals and for depth of respiration. Kagan's percentage of acetone expired agrees satisfactorily with Best's figure for dead-air space and we may thus conclude that essentially all the acetone actually reaching the effective area of the lungs was absorbed, as would be expected. Those ketones less soluble in water are naturally less readily absorbed.

A portion of the aliphatic ketones is metabolized, the remainder being excreted unchanged in the exhaled breath and in the urine. Ketones in small amounts appear normally in the blood and urine. Depending upon diet, endocrine balance, and other factors they may accumulate to a considerable extent. Wick, Sherrill, and MacKay<sup>8</sup> report maximum amounts as high as 200 mg. per liter in the blood of human subjects after 4 days of fasting.

Briggs and Schaffer<sup>9</sup> found that the coefficient of distribution of acetone between alveolar air and blood or water was 1:333, expressed in mg. per liter. Thus a workman breathing the suggested maximum limit of 600 p.p.m. (1.4 mg. per liter) acetone in air would reach equilibrium when he had attained a blood concentration of approximately 0.5 g. per liter. Since the body is about 70 per cent water, if this relation holds true in the tissues throughout the body there would be an accumulation of approximately 26 g. in the entire body, for a man of average weight. After this level of saturation was reached, the only acetone absorbed would be to replace any amount metabolized or excreted and sufficient to equilibrate water consumed. That this equilibrium is never actually reached even after several days of continuous exposure has been demonstrated by Haggard, Greenberg, and Turner,<sup>10</sup> who found the value 330 for the coefficient of distribution. These investigators have shown that when men are exposed to moderate amounts of acetone vapor for 8 hours daily with 16 hours away from exposure, the residual amount at the end of the 16-hour period is so small that

<sup>6</sup> E. Kagan, *Arch. Hyg.*, 94, 41 (1924).

<sup>7</sup> C. H. Best and N. B. Taylor, *The Physiological Basis of Medical Practice*. 3rd ed., William & Wilkins, Baltimore, 1943.

<sup>8</sup> A. N. Wick, J. W. Sherrill, and E. M. MacKay, *Proc. Soc. Exptl. Biol. Med.*, 45, 437 (1940).

<sup>9</sup> A. P. Briggs and P. A. Schaffer, *J. Biol. Chem.*, 48, 413 (1921).

<sup>10</sup> H. W. Haggard, L. A. Greenberg, and J. M. Turner, *J. Ind. Hyg. Toxicol.*, 26, 133 (1944).

TABLE 2. Acute Exposure to Ketones. Symptoms Produced in Guinea Pigs and the Lowest Concentration at Which They Occurred during or following an Eight-Hour Exposure<sup>a</sup>

Symptom	Concentration, per cent by volume in air, for									
	Acetone	Butanone	Pentanone	Hexanone	Heptanone	Octanone	Mesityl oxide	Acetyl acetone	Cyclohexanone	Methylcyclohexanone
Irritation.....	1	0.6	0.4	0.1	0.1	0.15	0.13	0.04	0.03 <sup>b</sup>	0.05 <sup>b</sup>
Narcosis.....	2.3	1.5	0.6	0.5	0.4	0.2	0.13	•	0.31 <sup>b</sup>	b, <sup>c</sup>
Death.....	4.0	2	0.9	0.7	0.8	0.5	•	•	0.4 <sup>d</sup>	b, <sup>e</sup>

<sup>a</sup> The values given in this table are approximate and in several instances are estimated from graphs presented in the original reports.

<sup>b</sup> Repeated 6-hour daily exposures of rabbits.

<sup>c</sup> Not determined.

<sup>d</sup> Half of the animals exposed died 6 hours following exposure.

<sup>e</sup> Did not occur in maximum concentration attained at 25° C. and 760 mm. (0.13 per cent octanone, 0.04 per cent acetyl acetone, 0.18 per cent methylcyclohexanone.)

TABLE 3. Acute Effects of Exposure of Guinea Pigs to Vapors of Ketones

Effects	Concentration, per cent by volume in air, for									
	Acetone	Butanone	Pentanone	Hexanone	Heptanone	Octanone	Mesityl oxide			
Dangerous to life in 30 to 60 min.	<sup>a</sup>	5-10	3-5	1-2	2	•	0.5-1			
Dangerous to life in 4 to 8 hr.	4	1.3-1.8	0.9-1.2	0.5-0.7	0.7	•	0.2			
Maximum amount for 1 hr. without serious disturbance	3	1	0.5	0.3	0.3	0.2	0.13			
Maximum amount for 8 hr. without serious disturbance	1	0.3	0.2	0.15	0.2	0.15	0.02			

<sup>a</sup> Not determined.

<sup>b</sup> Not produced in the highest concentration obtained in a closed chamber by extended recirculation of air over wicks wet with the solvent (0.48 per cent heptanone, 0.13 per cent octanone).



the accumulation over a period of days is only slightly more than at the end of the first 8 hours, which was on the order of 20 to 30 per cent of the equilibrium figure. A man exercising moderately for 8 hours while inhaling an atmosphere containing 2100 p.p.m. acetone accumulated 330 mg. acetone per liter of blood and exhibited no distinct symptoms.

It appears likely that analysis of the blood or urine of exposed persons at the end of the exposure day and week would be helpful indications of the extent of exposure and maximum absorption. Samples of blood or urine taken for the purpose of establishing the absorption of ketones should be taken as soon as possible after termination of exposure and the time elapsed between the termination of exposure and sampling should be noted and reckoned with.

Working with animals exposed to cyclohexanone and methylcyclohexanone, Treon, Crutchfield, and Kitzmiller<sup>11</sup> found in the urine a decrease in the ratio of inorganic to total sulfates as well as a marked increase in glucuronic acid. They suggest that, if a like condition exists in man, the measurement of glucuronic acid excretion and urine sulfate ratio would constitute useful measures of industrial exposure to these ketones.

*Action of ketones and cause of death in animals.* The ketones are irritant to the eyes, nose, and throat; and they are narcotics. With the exception of isophorone, which Smyth found to be a kidney poison, and possibly mesityl oxide and the cycloketones, animals dying from the effects of exposure to ketones apparently die as a result of narcotic action. Indications are that the cycloketones produce a general vascular injury.

Haggard<sup>10</sup> found that inco-ordination (intoxication) occurs at a level of 1 to 2 g. per liter of blood, loss of righting reflex at about 3 g. per liter, loss of corneal reflex at 5 g. per liter, while deaths were frequent above 9 g. per liter, when rats were the experimental animals. Kagan<sup>6</sup> quotes Albertoni as finding 1 g. acetone per kilo of blood of dogs to be without effect, 5 g. causing narcosis, and 8 g. death.

With the aliphatic ketones, death was apparently due to a state of progressing narcosis and any irritation of the respiratory center was of secondary importance. Death did not occur after removal from exposure, except in isolated instances, even though in many animals narcosis continued for several hours. This would seem to indicate that the concentration of ketone in the blood and tissues is of more significance in causing death than is the time factor. More data on blood and urine concentrations corresponding to symptoms, including death, from exposure to ketones other than acetone, would be of considerable interest.

At autopsy of guinea pigs dying from the effects of repeated exposures to mesityl oxide for periods of 8 hours, Smyth<sup>5</sup> found congestion of kidneys, occasional congestion of liver, and slight congestion of the lungs; and concluded that injury was largely due to anesthetic action on circulation and respiration. How-

<sup>11</sup> J. F. Treon, W. E. Crutchfield, and K. V. Kitzmiller, *J. Ind. Hyg. Toxicol.*, 25, 323 (1943).

ever, Specht, Miller, Valaer, and Sayers,<sup>12</sup> from experiments with guinea pigs in which all animals exposed died either during or following exposure, concluded that mesityl oxide induces changes other than those resulting in narcosis. Vapor concentrations to which these guinea pigs were exposed included 1.0 per cent for 0.5, 1, and 3.5 hours; 0.5 per cent for 4, 5, and 7 hours; and 0.23 per cent for 6, 7, and 8 hours. Smyth also found that isophorone severely injured the lungs and kidneys of guinea pigs and rats and that death resulting from repeated exposures was apparently due to such injuries. He considers 25 p.p.m. isophorone and 50 p.p.m. mesityl oxide to be safe for repeated 8-hour daily exposures, producing no pathology in animals.

Treon,<sup>11</sup> using rabbits and monkeys, found that cyclohexanone and methylcyclohexanone were similar in action, with the methylated compound being slightly less toxic. Both produced liver and kidney damage after repeated daily 6-hour exposures. Some deaths occurred within 50 exposures to 3082 p.p.m. cyclohexanone (12.12 mg. per liter) while none occurred with the highest concentration of methyl cyclohexanone obtained, 1822 p.p.m. (8.2 mg. per liter). 190 p.p.m. cyclohexanone in 50 exposures of 6 hours each produced only the slightest indication of damage to kidney and liver. 182 p.p.m. methylcyclohexanone produced no detectable toxic reactions or microscopic changes after 50 exposures of 6 hours each and was judged safe for rabbits.

*Effects on man.* Sack<sup>13</sup> cited a case of acetone poisoning in which a workman using acetone for cleaning became seriously ill and was taken unconscious to the hospital, where he recovered after a brief illness. The concentration in the air was not stated. Nausea and salivation were severe. The blood sugar was high (140 mg. per cent) and on the morning of the second day blood acetone was determined to be 18 mg. per cent (0.18 gm. per liter). On the basis of 1:333 coefficient of distribution this would correspond at equilibrium with a concentration of only 0.54 mg. per liter or 228 p.p.m. acetone in the air. Two facts, however, place the atmospheric concentration to which this man had been exposed much higher: the duration of exposure was not sufficient to establish equilibrium, and elimination was well under way when the sample of blood was taken.

Upon investigating the cause of illness of two employees in a raincoat plant<sup>14</sup> it was found that 82 women were applying ketone-thinned waterproofing cements to seams, in a single large room and with only inadequate, natural ventilation. Two of the women had become ill and unconscious, and were hospitalized. No significant findings were reported and blood acetone was not determined. Both patients recovered rapidly and left the hospital with no apparent sequelae. Several other workers complained of headache and nausea. Analysis of the workroom air by the author revealed an average general room-air concentration of

<sup>12</sup> H. Specht, J. W. Miller, P. J. Valaer, and R. R. Sayers, *Natl. Inst. Health Bull.* No. 176 (1940).

<sup>13</sup> G. Sack, *Arch. Gewerbepath. Gewerbehyg.*, 10, 80 (1940).

<sup>14</sup> A. R. Smith and M. R. Mayers, *N. Y. State Labor Dept. Ind. Bull.*, 23, 5, 174 (1944).

550 p.p.m. methyl ethyl ketone and 450 p.p.m. acetone. Transient breathing-zone samples as high as 1850 p.p.m. methyl ethyl ketone and 1530 p.p.m. acetone were found. This condition had been in effect for a period of months, during which time the daily exposure of workers averaged 9 hours.

Before leaving the subject of effects on man, it should be pointed out that data on mixtures of vapors are lacking and even narcotics sometimes have an abnormal effect when acquired in combination with other materials. For example, the adverse effect of alcohol on persons exposed to many toxic materials, such as carbon tetrachloride, benzene, and aniline, has been recorded by many investigators.

#### **6. Maximum Permissible Limits**

With the exception of acetone, and possibly butanone, little is known about the effects upon man of prolonged exposures to ketones, and therefore the definite setting of maximum safe concentrations cannot be done. However, a guide or bench mark which, for want of a better term, may be designated as a suggested maximum practical working level, has been given for each of the twelve ketones in Table 1.

Possibly the figures given could be exceeded safely; it is very unlikely that injury will occur at these levels; and at the same time they are practical from the standpoint of engineering control.

#### **7. Inflammability**

All the ketones are inflammable and acetone, butanone, pentanone, and hexone offer explosion hazards at or below ordinary room temperatures. The remaining ketones are not sufficiently volatile to produce inflammable vapor-air mixtures except at temperatures above 90° F.

#### **8. Odor and Warning Properties**

With the exception of acetone, the odors of the ketones are distinct and the irritating effects are noticeable at the levels considered acceptable for prolonged exposures. However, it is not unusual to find workmen in atmospheres above these levels, indicating that the moderate warning properties are not heeded. Concentrations in the inflammable range are very irritant, and should be sufficiently so to attract the immediate attention of anyone entering such an atmosphere.



## Ethers, Glycols, and Glycol Ethers

FRANK A. PATTY

### ETHYL ETHER

Ether ( $C_2H_5OC_2H_5$ ), ethyl ether, ethoxyethane, diethyl ether, has a number of industrial applications, in which it may be used for extraction or other solvent usage. Exposures have been described in connection with the manufacture of smokeless powder, collodion, and pyroxylin plastics. It is widely used as an anesthetic.

#### 1. *Physical and Chemical Properties*

Ethyl ether is a colorless liquid having a molecular weight of 74.12, and a density of 0.7135 at  $20^\circ/4^\circ$  C. Its melting point is from  $-116.3^\circ$  to  $-123.3^\circ$  and it boils at  $34.6^\circ$ . The refractive index is 1.3497 at  $25^\circ$  C. Its solubility in water at  $20^\circ$  is 7.5 g. per 100 milliliters and it is miscible with most organic solvents. Its vapor pressure at  $25^\circ$  C. is equal to 537 mm. Hg, corresponding to a possible concentration of 70.8 per cent in "saturated" air at that temperature. The pure vapor is 2.5 times as dense as air, and the "saturated" vapor-air mixture is 2.1 times as dense as air. This is one of the most dense vapor-air mixtures encountered, and is notorious for its tendency to flow or "crawl" along tables, floors, or low spots for considerable distances from its place of origin, and then catch fire from some distant, unconsidered ignition source.

1 mg./l.  $\approx$  330 p.p.m. and 1 p.p.m.  $\approx$  3.03 mg./cu.m. at  $25^\circ$  C., 760 mm.

#### 2. *Determination in the Atmosphere*

For industrial hygiene purposes, ether may be determined satisfactorily by means of the gas interferometer, by adsorption on charcoal or silica gel and weighing, or by means of a combustible gas indicator.

#### 3. *Physiological Response*

The inhalation of 3.5 per cent by volume ether in air causes loss of consciousness within 30 to 40 minutes, and concentrations above 7.5 per cent are dangerous to life. Concentrations of ether above the lower narcotic range are mildly irritant, but the only effect of industrial concern is that of its narcotic action. Some persons

are reputed to be abnormally susceptible to the narcotic effects of ether. This may be a psychological condition and, if encountered, the most satisfactory control is removal from possible exposure. Ether is relatively inert to metabolic processes and is largely eliminated in the expired air.

Ether does not present an occupational disease exposure, but rather an accident hazard from the possibility of narcosis, as well as a danger of fire and explosion.

#### 4. *Permissible Limit*

Ether has a characteristic "operating-room" odor that is objectionable to some persons, possibly by association. Odors are important, but cannot be accepted as the ruling criterion for permissible concentrations in workrooms. Figures of 165, 400, and 500 p.p.m. have been proposed as acceptable limits; and industrial exposures of 1000 to 2000 p.p.m. are not unusual. The coefficient of distribution<sup>1</sup> of ether between alveolar air and the circulating blood is 1 : 15, and 500 p.p.m. ether in room air could cause a maximum blood concentration of about 0.022 g. of ether per liter of blood, or a total absorption of approximately 1.6 g. of ether in a man of average weight (see page 185). This amount is believed to be not sufficient to cause dizziness or injurious effects, and since it is quite safe from the fire and explosion viewpoint, and practical from the standpoint of engineering control, it appears to be a logical choice for a maximum permissible limit.

#### 5. *Warning Properties and Fire and Explosion Hazards*

The warning properties of ether are not a suitable safeguard against excessive exposures. The fire and explosion hazards are extraordinary due to the low flash point,  $-49^{\circ}$  F., the wide inflammable range, 1.85 to 36.50 per cent by volume vapor in air, and the relatively high density, 2.1, of "saturated" vapor-air mixtures. The normal ignition temperature of ether is  $379^{\circ}$  F. Ether may develop peroxides upon standing and exposure to light: these peroxides increase the ignition hazard.

## ISOPROPYL ETHER

Isopropyl ether,  $(\text{CH}_3)_2\text{CHOCH}(\text{CH}_3)_2$ , 2-isopropoxypropane, diisopropyl ether, has been offered as a motor fuel, especially for blending with gasoline. It also has solvent properties similar to those of ethyl ether.

#### 1. *Physical and Chemical Properties*

Isopropyl ether is a colorless liquid with a molecular weight of 102.17, specific gravity of 0.7258 at  $20^{\circ}/4^{\circ}$  C., melting point  $-60^{\circ}$ , boiling point  $67.5^{\circ}$ , refractive index 1.3680 at  $20^{\circ}$ , and a vapor pressure equal to 158 mm. Hg at  $20^{\circ}$ , corresponding to a "saturated" air concentration of 20.8 per cent vapor by volume. The density of the vapor is 3.5 times that of air, and the density of "saturated" air at  $20^{\circ}$  C. is 1.53 times that of air.

1 mg./l.  $\approx$  239 p.p.m. and 1 p.p.m.  $\approx$  4.18 mg./cu.m. at  $25^{\circ}$  C., 760 mm.

<sup>1</sup> Y. Henderson and H. W. Haggard, *Noxious Gases*. 2nd ed., Reinhold, New York, 1943.

## 2. Determination in the Atmosphere

The vapor in air may be determined satisfactorily by physical methods, such as the interferometer, or adsorption and weighing, or by the combustible gas indicator.

## 3. Physiological Response

As in the case of ethyl ether, isopropyl ether does not present a considerable occupational disease exposure, even though its toxicity is considered<sup>2</sup> to be 1.5 to 2 times that of ethyl ether. The oral lethal dose for rabbits is 7 to 9 ml. per kilogram. Three per cent vapor in air produced incomplete anesthesia in rabbits and in a monkey, and is considered dangerous to life for prolonged exposures. One per cent vapor in air can be tolerated for 20 daily 1-hour exposures without evident ill effects other than slight intoxication.

## 4. Permissible Limit

No permissible limit for prolonged exposure has been proposed; but, in view of its properties and relation to ethyl ether, a tentative figure on the order of 400 p.p.m. seems a logical choice at present, even though no injurious effects are indicated at levels somewhat above this. Further investigation with exposure of persons may indicate even this amount to be inconsistent with optimum work and well-being.

## 5. Warning Properties and Fire Hazards

The odor, which is similar to that of diethyl ether, but stronger, and yet resembles camphor, is not an adequate warning to prevent exposure to excessive vapor-air concentrations. The flash point by the closed-cup method is  $-6.7^{\circ}$  F., and the lower inflammable limit is between 1.5 and 2 per cent by volume vapor in air. As in the case of ethyl ether, peroxides, which may have developed upon standing and exposure to light, increase the dangers of ignition and explosion.

# ETHYLENE OXIDE

## 1. Physical and Chemical Properties

Ethylene oxide ( $\text{CH}_2\text{OCH}_2$ ), 1,2-epoxyethane, is a colorless, irritant gas used chiefly in chemical synthesis, and in fumigation. It is applicable to the fumigation of food products. Its molecular weight is 44.05, density as a gas is about 1.5 times that of air, and as a liquid is 0.887 at  $7^{\circ}/4^{\circ}$  C. It melts at  $-111.3^{\circ}$  and boils at  $10.7^{\circ}$ . It combines with all compounds having a labile hydrogen atom such as water, alcohols, ammonia, and organic acids.

1 mg./l.  $\approx$  556 p.p.m. and 1 p.p.m.  $\approx$  1.80 mg./cu.m. at  $25^{\circ}$  C., 760 mm.

## 2. Determination in the Atmosphere

Ethylene oxide may be determined by adsorption, by means of a gas inter-

<sup>2</sup> W. Machle, E. W. Scott, and J. Treon, *J. Ind. Hyg. Toxicol.*, 21, 72 (1939).

ferometer, or a combustible gas indicator, but will not pass through drying agents such as calcium chloride. It can also be determined by scrubbing through a measured quantity of standard 2 *N* hydrochloric acid, followed by an alkali trap to capture escaping hydrogen chloride which must be accounted for: 1 mole of ethylene oxide combines with 1 mole of hydrogen chloride to form glycol chlorohydrin, after which the excess hydrogen chloride in the mixture is titrated, cold, with strong standard barium hydroxide. None of these methods are entirely satisfactory for low gas-air concentrations (below 100 p.p.m.). Lubatti<sup>3</sup> recommends scrubbing through 0.1 *N* sulfuric acid containing 50 per cent magnesium bromide and titrating with 0.1 *N* sodium hydroxide, using bromocresol green indicator. Spectrometric methods should prove to be useful.

### 3. Physiological Response

*Acute effects.* Ethylene oxide is an irritant in relatively low concentrations, and a vesicant in high concentrations, and contact of the skin with the concentrated gas for a relatively short time causes blistering. With acute exposures of guinea pigs, ethylene oxide was found to be primarily an irritant to the lungs, respiratory passages, and the eyes and, also, a poison to protoplasm, with evidence of gross pathology in the kidneys. The effects of various concentrations for single continuous exposures<sup>4</sup> have been tabulated as shown in Table 1.

TABLE 1  
*Acute Exposures of Guinea Pigs to Ethylene Oxide*

Response and time	Ethylene oxide, per cent by volume in air
Death in a few minutes.....	5-10
Danger to life in 30 to 60 min.....	0.3-0.6
Maximum amount for 60 min. without serious disturbance.....	0.3
Slight symptoms after several hours.....	0.025

A frothy exudate was noted in animals exposed to concentrations ranging from 0.3 to 1.4 per cent vapor in air. Dyspnea and gasping usually preceded death. Narcosis observed in most of the animals exposed to concentrations ranging from 0.7 to 8.5 per cent may have been due in part at least to anoxia resulting from constriction and obstruction of the bronchioles and alveolar ducts. The principal gross pathological change observed was marked irritation of the entire respiratory system. Flury<sup>5</sup> observed opacity of the cornea of guinea pigs in some instances. This finding has also been observed to occur with a number of other toxic gases and vapors. He also suggests that delayed effects may be due to the metabolic products, such as aldehydes or, less likely, oxalic acid. The acute effects and fatality resulting from a single continuous exposure to ethylene oxide-air mixtures, as found by various investigators, are summarized in Table 2.

<sup>3</sup> O. F. Lubatti, *J. Soc. Chem. Ind.*, 63, 133 (1944).

<sup>4</sup> C. P. Waite, F. A. Patty, and W. P. Yant, *U.S. Pub. Health Repts.*, 45, 1832 (1930).

<sup>5</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.



With the exception of the first experiment cited in this table, the results are all in satisfactory accord. They indicate that cats are more susceptible to poisoning by ethylene oxide than are most of the animals commonly used for inhalation experiments. This has been found to be the case with some other materials, also, and has been attributed to the greater activity of cats in attempting to escape from the exposure atmosphere. These results indicate that for most

TABLE 2  
*Summary of Acute Response of Animals to Exposure to Ethylene Oxide*

P.p.m. by vol. in air	Time, hr.	Animal	Response	Ref. No.
250-280	2	Cat	Death within 24 hr.	6
	8	Guinea pig	Slight respiratory changes; no deaths	4
	38	Cat	Death within 24 hr.	5
	48	Guinea pig	Occasional death	5
560-600	7	Guinea pig, cat, and dog	No deaths	5
	8	Guinea pig	Occasional death	4
	22	Guinea pig and cat	Death during or following exposure	5
	22	Rabbit, dog	No deaths	5
1100	5	Rat, guinea pig, and rabbit	Moderate injury, no deaths	5
	5	Cat, dog	Serious injury, few deaths	5
	8	Guinea pig, dog, and rabbit	Slight injury, no deaths	5
	8	Rat, cat	Death within 24 hr.	5
1300	3	Guinea pig	Serious irritation, no deaths	4
	8	Guinea pig	Majority died in one to 8 days	4
2200	1½	Cat	Injurious, no deaths	5
	3	Cat	Death within 24 hr.	5
	4	Guinea pig	Injurious, few deaths	5
	4	Rabbit	Injurious, no deaths	5
	4	Cat, dog	Death within 24 hr.	5
3000	1	Guinea pig	No deaths	4
	3	Guinea pig	Death of majority within 1 to 8 days	4
	8	Guinea pig	Death of majority within 24 hr.	4
5000	1	Guinea pig	Death in 1 to 8 days	6
7000	½	Guinea pig	No evidence of injury	4
	1	Guinea pig	Death of majority within 1 to 8 days	4
	2½	Guinea pig	Death within 24 hr.	4
14,000	10 min.	Guinea pig	No evidence of injury	4
	20 min.	Guinea pig	Majority died in 1 to 8 days	4
	60 min.	Guinea pig	Death within 24 hr.	4
51,000-64,000	5 min.	Guinea pig	Majority died in 1 to 8 days	4
	10 min.	Guinea pig	Death within 24 hr.	4

animals 250 p.p.m. or less can be tolerated with reasonable safety for a single exposure of not more than 8 hours; twice that concentration may cause an occasional fatality; while concentrations of 1100 to 1300 p.p.m. frequently prove fatal following an exposure of 4 to 8 hours.

*Chronic effects.* Koelsch and Lederer,<sup>6</sup> using cats for experimental animals, determined the chronic effects of ethylene oxide, as given in Table 3.

<sup>6</sup> Koelsch and Lederer as quoted by F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

A dog exposed to 100 p.p.m. 1 hour daily for 11 days, 1 hour twice a day for 4 days, then to 200 p.p.m.  $1\frac{1}{2}$  hour twice a day for 2 days, and once on the last day, died on the 21st day.

These results, in view of the apparently greater susceptibility of cats, are not inconsistent with the results of acute exposures; but they indicate that either the injurious effects of daily irritation are additive or, more likely, that ethylene oxide and its metabolic products are additive and act as systemic poisons in repeated, daily exposures. A factor that has an important bearing on prolonged inhalation exposures to ethylene oxide is its great tenacity for water.

TABLE 3  
*Response of Cats to Prolonged Repeated Exposure to Ethylene Oxide*

P.p.m.	Extent of Exposure	Response
50	18 daily 3-hr. exposures followed by	Paralysis on the 19th day
100	2 daily 3-hr. exposures, and 1 day of $1\frac{1}{2}$ -hr. exposure	Death on 22nd day
100	18 1-hr. exposures in 21 days	Death after 21st day
200	2 $1\frac{1}{2}$ -hr. exposures and 1 1-hr. exposure in 4 days	Death on 5th day

Having combined with water, it does not have an appreciable vapor pressure so, unlike most other vapors and gases, practically all the gas reaching the lungs is completely absorbed, and practically none is exhaled. There is no reversible equilibrium and the only limitations to absorption are the concentration in the air and the volume of inspired air. It may also be pointed out that when ethylene oxide combines with water, glycol and, later, diethylene glycol are formed. The toxicity of diethylene glycol was demonstrated in 1937 when it was used as a vehicle for "Elixir of Sulfanilamide" and many deaths resulted. Although the exact mechanics of the poisonous action of the glycol products is yet to be proved, serious kidney damage and uremia are consistent findings, as is also necrosis of the liver. The pattern for the more toxic glycols<sup>7</sup> is similar: a selective action on the convoluted tubules of the kidneys, with an abnormal accumulation of fluid in the cellular tissue, causes obstruction within the kidney, complete suppression of urine, and death, apparently from uremia.

#### 4. Permissible Limits

It seems inadvisable for workmen to be exposed to more than 250 p.p.m. ethylene oxide for even a single, brief period, and for repeated exposures throughout the working day a concentration on the order of one tenth that amount might well be used as a tentative control standard pending additional, enlightening information. It is obviously essential that industrial processes employing ethylene oxide have effective, gastight enclosures.

<sup>7</sup> E. P. Laug, H. O. Calvery, H. J. Morris, and G. Woodard, *J. Ind. Hyg. Toxicol.*, **21**, 173 (1939).

### 5. *Inflammability and Warning Properties*

Ethylene oxide-air mixtures are inflammable within the range of 3 to 80 per cent ethylene oxide by volume. Violent explosions<sup>8</sup> have occurred as a result of unexpected reactions of ethylene oxide with mercaptans, and with an alcohol. Although the gas is irritant, it has only moderate warning properties in concentrations considered safe for a brief, single exposure, and entirely inadequate warning in amounts that may be harmful for prolonged exposure.

## DIOXANE

### 1. *Physical and Chemical Properties*

1,4-Dioxane ( $\overbrace{\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2}^{\text{p-dioxane}}$ ) *p*-dioxane, diethylene dioxide, is a colorless liquid with a faint, inoffensive odor in low concentrations. It has wide application as a solvent in the manufacture of lacquers, plastics, varnishes, paints, as well as paint and varnish removers. It dissolves cellulose acetate, ethyl- and benzylcellulose, oil-soluble dyes, and many fats, greases, waxes, and resins. It is not only miscible with most vegetable and mineral oils and organic solvents, but also miscible with water. The molecular weight is 88.10, density 1.0353 at 20°/4° C., melting point 11.7°, boiling point 101.5°, and  $n_D$  1.4232 at 20°. Dioxane forms a constant boiling mixture with water, containing 81.6 per cent dioxane and boiling at 87.8° C. at a pressure of 760 mm. Hg. Dioxane has a vapor pressure of 36 mm. at 25° C. corresponding to a "saturated" air concentration of 4.75 per cent. The density of the vapor is approximately three times that of air, and the density of the "saturated" vapor-air mixture is 1.1 times that of air.

1 mg./l.  $\approx$  278 p.p.m. and 1 p.p.m.  $\approx$  3.6 mg./cu.m. at 25° C., 760 mm.

### 2. *Determination in the Atmosphere*

No very satisfactory chemical method for determining a low concentration of dioxane vapor in the air has been developed. It can be determined by means of the interferometer, adsorption, or the combustible gas indicator. The infrared spectrometer and possibly the ultraviolet spectrophotometer should offer acceptable means of evaluation.

### 3. *Physiological Response*

*Acute effects.* The acute effects of dioxane by inhalation indicate a relatively low order of toxicity. Several investigators, with various species of animals, and by the various modes of dosage such as inhalation, ingestion, and intravenous or subcutaneous injection, have shown that dioxane, though relatively moderate in its toxic effects, can cause injury and death. Although there are variations with different species of animals, the results are of a similar order of magnitude and those obtained with guinea pigs<sup>9</sup> may be accepted as representative.

<sup>8</sup> D. P. Meigs, *Chem. Eng. News*, 20, 1318 (1942).

<sup>9</sup> W. P. Yant, H. H. Schrenk, C. P. Waite, and F. A. Patty, *U.S. Pub. Health Repts.*, 45, 2023 (1930) (Reprint 1407).

TABLE 4  
*Acute Effects of Exposure of Guinea Pigs to Dioxane Vapor in Air*

Exposure time and effects	Concentration, per cent by volume
Death within a few minutes.....	a
Danger to life within 1 hr.....	a
Danger to life within 3 to 8 hr.....	1.5-3.0
Maximum amount for 1 hr. without marked effect.....	0.5
Maximum amount for several hours with but slight effect.....	0.2-0.3

\* Not produced by 3.0 per cent, the highest concentration obtained by extended recirculation of air over wicks wet with dioxane.

A concentration of 3 per cent for periods up to 9 hours caused the following symptoms in the order given: nasal and eye irritation; retching movements or marked expiratory effort consisting of spasmodic contraction of the abdominal wall while the head was lifted and mouth open; narcosis; and concurrently, respiratory changes such as dyspnea, shallow rapid respiration, gasping, then shallow slow respiration; and death. A concentration of 1 per cent produced only evidence of irritation and retching, while concentrations below 1 per cent led to no symptoms other than nose and eye irritation throughout an 8-hour exposure.

With man, the inhalation of a concentration of 0.1 per cent by volume in air causes no discomfort. There is a quite inoffensive, mild odor and a slight sensation of warmth in the nose and throat similar to, but less than, that experienced from the inhalation of a corresponding concentration of ethyl alcohol. The effects gradually lessen with time. Inhalation exposure to somewhat higher concentrations causes, among men,<sup>10,11</sup> eye and nasopharynx irritation with coughing, but this tends to disappear with continued exposure and symptoms of drowsiness, vertigo, headache, and moderate gastric symptoms such as anorexia, nausea, and vomiting appear. With termination of the acute exposure at this stage recovery is complete. Continued inhalation is associated with more severe gastric symptoms, pain and tenderness of the abdomen and lumbar regions. This may develop into the subacute stage.

*Subacute effects.* Where the exposure was continued past the stages outlined under acute exposure, poisoning resulted in acute hemorrhagic nephritis with suppression of urine, uremia, coma, and death.<sup>10</sup> Liver necrosis,<sup>12</sup> a consistent finding in subacute dioxane poisoning, is thought to be compatible with recovery.

Liver damage and, more especially, kidney damage from the glycols and their derivatives (including dioxane) have been reported<sup>7</sup> by many investigators as a result of experiments with animals.

<sup>10</sup> *Annual Report of the Chief Inspector of Factories and Workshops for the Year 1933.* London, 1934, p. 66.

<sup>11</sup> H. H. Schrenk and W. P. Yant, *J. Ind. Hyg. Toxicol.*, 18, 448 (1936).

<sup>12</sup> H. Barber, "Hemorrhagic Nephritis and Necrosis of the Liver from Dioxane Poisoning," *Guys Hosp. Repts.*, 84, 267 (1934).

*Chronic effects.* There is little evidence of chronic poisoning among persons exposed to the vapors of dioxane, but there was a definite increase of leucocytes,<sup>12</sup> particularly the neutrophiles.

#### 4. *Absorption and Excretion*

Absorption of dioxane in industry is chiefly by inhalation, though it may result from ingestion, and has been demonstrated to result to some extent from skin absorption.<sup>13</sup>

#### 5. *Permissible Limit*

No permissible limit has been established for either brief or prolonged exposures. In view of the extent of our present knowledge, 1000 p.p.m. may be suggested as a relatively safe concentration for a single exposure not exceeding  $\frac{1}{2}$  hour. A maximum safe amount for prolonged exposure cannot well be approximated. From the engineering viewpoint there appears little reason to condone concentrations of more than 200 p.p.m. in workroom atmospheres, even though no evidence of serious harm to animals or men has ever been demonstrated to result from repeated 8-hour exposures to several times this amount. When dealing with a solvent of established, harmful potentialities the margin of safety should be broad until such a time as convincing evidence is presented to show that higher concentrations are safe.

#### 6. *Warning Properties and Inflammability*

Concentrations of 200 p.p.m. dioxane have practically no warning properties other than a characteristic, but faint and inoffensive, odor. Upon entering 1000 p.p.m. there is an initial sense of warmth in the upper respiratory passages, with little or no irritation, and an easily noticeable, inoffensive odor. Even at higher concentrations the initial irritation to eyes and respiratory passages is transitory, and the warning properties cannot be considered adequate to prevent exposure.

Dioxane vapor-air mixtures within the range of 1.97 to 22.25 per cent dioxane by volume are inflammable (see Chapter Thirteen).

## ETHYLENE GLYCOL

### 1. *Physical and Chemical Properties*

Ethylene glycol ( $\text{CH}_2\text{OHCH}_2\text{OH}$ ), 1,2-ethanediol, glycol, is a colorless, syrupy liquid, molecular weight 62.07, with a refractive index of 1.4274 at 20°, density 1.1155 at 20°/4° C., melting point of -17.4°, boiling point of 197.2°. It is miscible with water and alcohol and is extremely hygroscopic, absorbing approximately twice its weight of water from the air at room temperature and 100 per cent relative humidity. It forms azeotropes with many organic compounds. Its low vapor pressure, equal to 0.12 mm. Hg at 20° C., limits its air concentration to less than 160 p.p.m. even in enclosed and unventilated spaces

<sup>12</sup> A. Fairley, E. C. Linton, and A. H. Ford Moore, *J. Hyg.*, 34, 486 (1934).

at that temperature, so that from a practical viewpoint harmful inhalation exposures are not to be expected unless elevated temperatures or atomization are involved.

1 mg./l.  $\approx$  365 p.p.m. and 1 p.p.m.  $\approx$  2.74 mg./cu.m. at 25° C., 760 mm.

It is used as a solvent, coolant, antifreeze, and in the preparation of various glycol products including the explosive, glycol dinitrate.

## 2. Determination in the Atmosphere

The interferometer is not satisfactory for the determination of low concentrations of vapors having low refractivity, such as the glycols. Combustion methods, likewise, are not sufficiently sensitive in most instances. The Nicloux method for ethyl alcohol has been used successfully for some glycol ethers,<sup>14</sup> and should be applicable to all glycols as well; but, like most of the other methods, it is not specific. Spectrometric methods may be used to advantage: infrared<sup>15</sup> absorption has been applied; and ultraviolet absorption, which can be made very conveniently, should be applicable (see page 208). It may also be determined by oxidation with periodate to formaldehyde and titrated with iodine<sup>16</sup> or determined polarographically.<sup>17</sup>

## 3. Physiological Response

Ethylene glycol perhaps can be accepted as representative of the group of glycol products among which, with the possible exception of propylene glycol, there is a common pharmacological action. The more toxic glycols appear to have a selective, injurious action upon the kidneys that results in urine retention and uremia; necrosis of the liver is of secondary importance; and depressant effects upon the central nervous system are of still less import. Some of these vapors in relatively high concentrations are moderate lung irritants. In acute exposures, death may result quickly from narcotic or irritant effects, but delayed deaths are frequently, if not always, associated with damage to the kidneys. This has been described<sup>7</sup> as a selective action on the convoluted tubules of the kidneys with an abnormal accumulation of fluid in the cellular tissue causing obstruction within the kidney, complete suppression of urine, and death, apparently from uremia. Many oxalate crystals were found in the renal tubules of men who died after drinking glycol solution.<sup>18,19</sup> Calcium oxalate crystals were also found in the brain. Degeneration of the brain was thought to be the cause of death.

*Acute effects.* Oral administration has indicated that the order of relative toxicity,<sup>7</sup> from lowest to highest on a weight per kilogram basis, of single doses of some of the glycols is: propylene glycol, diethylene glycol, ethylene glycol, di-

<sup>14</sup> H. W. Werner and J. L. Mitchell, *Ind. Eng. Chem., Anal. Ed.*, 15, 375 (1943).

<sup>15</sup> C. Z. Nawrocki, F. S. Brackett, and H. W. Werner, *J. Ind. Hyg. Toxicol.*, 26, 193 (1944).

<sup>16</sup> R. C. Reinke and E. N. Luce, *Ind. Eng. Chem.*, 18, 244 (1946).

<sup>17</sup> B. Warshowsky and P. J. Elving, *Ind. Eng. Chem.*, 18, 253 (1946).

<sup>18</sup> G. Milles, *Arch. Pathol.*, 41, 631 (1946).

<sup>19</sup> C. A. Pons and R. P. Custer, *Am. J. Med. Sci.*, 211, 544 (1946).

ethylene glycol monoethyl ether, dioxane, and ethylene glycol monoethyl ether (Cellosolve). The  $LD_{50}$  for mice, rats, and guinea pigs range from about 19 to 24 ml. per kilogram for propylene glycol down to 2.8 to 4.3 ml. for Cellosolve; and the average  $LD_{50}$  for the three species, for each of the six glycols listed, follow: 21.3, 15.4, 8.7, 5.3, 4.9, and 3.5 ml. per kilogram, respectively.

That the magnitude of the highest possible dose of ethylene glycol vapor by inhalation in an 8-hour day is of an insignificant order is evident. "Saturated" air at normal room temperature contains slightly over 0.5 ml. of liquid glycol per cubic meter of air, and if a man absorbed all the vapor from 10 cu.m. of saturated air (a rather unlikely circumstance) his dose would be only 5 or 6 ml. There have been several instances recorded where single doses of 15 to 50 ml. have been swallowed by men, with no ill effects. Ethylene glycol does not irritate the skin nor is it absorbed through the skin in toxic amounts. The only instances of acute poisoning recorded are from the drinking of glycol solutions.

*Chronic effects.* Mice and rats exposed to 0.35 to 0.4 g. per cubic meter (approximately 150 p.p.m.) 8 hours per day, 5 days per week, for 16 weeks, evidenced no ill effects or pathology that could be attributed to glycol.<sup>20</sup> A few of the animals died from what was believed to be an infection, but their internal organs were in a healthy condition. As a result of this experiment and a general knowledge of the glycols, the conclusion was reached that concentrations of 0.3 g. per cubic meter, 110 p.p.m., would have no toxic effects on either animals or men even with repeated daily exposures of 8 hours a day extending over a period of 3 1/2 months. This concentration is probably the highest that would be encountered as a vapor at normal room temperature. Again, it should be pointed out that fogs, mists, or sprays of this or any other material offer exposures in excess of vapor pressure limitations, and may present a situation that is harmful even for single exposures.

#### 4. Inflammability

The flash point of ethylene glycol by the closed-cup method is 232° F. (see Chapter Thirteen) but it must always be remembered that regardless of how high the flash point of an inflammable solvent may be, atomized particles (mists) of it can be inflammable at ordinary room temperatures.

## PROPYLENE GLYCOL

Propylene glycol ( $CH_3CHOHCH_2OH$ ), 1,2-propanediol, methyl ethylene glycol, is a colorless, almost odorless liquid similar to ethylene glycol. Its molecular weight is 76.09, its specific gravity is 1.0381 at 20°/4° C., the boiling point is 188.2°, and  $n_D$  at 27° is 1.4293. The vapor pressure equals 0.18 mm. Hg at 20° C. corresponding to a concentration in "saturated" air of about 235 p.p.m. It is miscible with water, alcohol, and many organic solvents. It is used chiefly as a

<sup>20</sup> F. H. Wiley, W. C. Hueper, and W. F. von Oettingen, *J. Ind. Hyg. Toxicol.*, 18, 123 (1936).

solvent, to some extent as a noncorrosive antifreeze agent for refrigeration systems, and in organic synthesis.

1 mg./l.  $\approx$  322 p.p.m. and 1 p.p.m.  $\approx$  3.11 mg./cu.m. at 25° C., 760 mm.

The toxicity of propylene glycol, as determined by feeding experiments,<sup>21</sup> and by intramuscular injections,<sup>22</sup> is moderate and less than that of ethylene glycol, and its metabolic products are less toxic than those of other glycols. Acceptance of propylene glycol in *New and Non-Official Remedies*<sup>23a</sup> may be cited as evidence of its low order of toxicity. It is considered comparable to glycerin when taken by mouth. There are no records of poisonings from industrial exposures, and it is believed that the vapors do not offer a harmful exposure at ordinary environmental temperatures. Inhalation of propylene glycol mists should be avoided until the harmlessness of their effects has been established with animals.

The flash point of propylene glycol by the closed-cup method is 207° F. The range of inflammable vapor-air mixtures is from 2.62 to 12.55 per cent propylene glycol by volume (see Chapter Thirteen).

## DIETHYLENE GLYCOL

Diethylene glycol,  $O(CH_2CH_2OH)_2$ , 2,2-oxydiethanol, 2,2'-dihydroxyethyl ether, is a colorless, essentially odorless, syrupy liquid with a molecular weight of 106.12, a density of 1.1177 at 20°/4° C., melting point -10.45°, boiling point 244.8°, and a refractive index of 1.446 at 25°. Its vapor pressure, which equals 0.01 mm. Hg at 20° C., corresponds to only 13 p.p.m. in "saturated" vapor-air mixtures at 20° and atmospheric pressure of 760 mm. Hg. Diethylene glycol is miscible with water, alcohol, and many other solvents. Its high affinity for water makes it useful both as a moistening and softening agent, and as a drying agent. It is also used in chemical manufacture and as an antifreeze.

1 mg./l.  $\approx$  230.5 p.p.m. and 1 p.p.m.  $\approx$  4.35 mg./cu.m. at 25° C., 760 mm.

The vapor pressure of diethylene glycol is so low as to make poisoning by vapor inhalation extremely unlikely. As with the other glycols, there is no danger of skin absorption and little danger of skin irritation. It is moderately toxic by ingestion and was the cause of nearly 100 deaths when it was used in a pharmaceutical preparation termed "Elixir of Sulfanilamide." The pathology caused by diethylene glycol, like that from many other glycol compounds, is primarily injury to the kidneys, accompanied by liver damage (see under Glycol).

There is little reason to expect harmful industrial exposures unless fogs or mists of the compound are inhaled for prolonged periods. Such fogs or mists may also be inflammable. The flash point by the closed-cup method is 255° F. (see Chapter Thirteen).

<sup>21</sup> M. A. Seidenfeld and P. J. Hanzlik, *J. Pharmacol.*, 44, 109 (1932).

<sup>22</sup> H. A. Braun and G. F. Cartland, *J. Am. Pharm. Assoc.*, 25, 746 (1936).

<sup>23a</sup> *New and Non-Official Remedies*. Am. Med. Assoc., Chicago, 1942.



## TRIETHYLENE GLYCOL

Triethylene glycol,  $(\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH})_2$ , 2,2'-ethylene dioxidiethanol, is a colorless, practically odorless liquid with a molecular weight 150.17, and a density of 1.1254 at 20°/20° C. Its melting point is -5° and boiling point is 287.3°. It has a vapor pressure at 20° of less than 0.01 mm. Hg. It is very hygroscopic, and is used for much the same purposes as diethylene glycol. It is used in making resins and plasticizers, as a heat transfer medium, and as a dehydrating agent for the atmosphere in air-conditioning equipment. It has been promoted as an agent for air sterilization.

1 mg./l.  $\approx$  163 p.p.m. and 1 p.p.m.  $\approx$  6.14 mg./cu.m. at 25° C., 760 mm.

The liquid is not harmful to the skin, and harmful vapor inhalation exposures do not occur. Fogs or mists of triethylene glycol can offer harmful inhalation exposures or fire hazards. The concentration of fog that would be permissible has not been established. The flash point by the closed-cup method is 313° F. and the inflammable range of concentrations of the heated vapors in air is 0.89 to 9.20 per cent by volume (see Chapter Thirteen).

## ETHYLENE GLYCOL MONOMETHYL ETHER

Ethylene glycol monomethyl ether ( $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$ ), methyl Cellosolve, 2-methoxyethanol, is a colorless volatile solvent for cellulose acetate and most natural resins, with some solvent action for nitrocellulose. It is used as an ingredient of thinners for cellulose acetate lacquers and dopes, and as a sealer for transparent wrapping materials. It gained some notoriety in New York State in connection with its use in the manufacture of "fused" collars.<sup>23</sup>

### 1. Physical and Chemical Properties

Methyl Cellosolve, molecular weight 76.09, is the most volatile of the glycol ethers. It boils at 124.3° C. and has a vapor pressure at 20° variously reported as equaling from 7.0 to 10.2 mm. Hg (0.93 to 1.34 per cent in "saturated" air). Werner<sup>24</sup> reports a concentration of 31.6 mg. per liter as being a "saturation concentration under ordinary conditions of temperature and pressure," but does not further define the conditions. This corresponds (if at 25° C., 760 mm.) to a concentration of 1.018 per cent by volume or 7.75 mm. Hg partial pressure. The density of the liquid is 0.9605 at 20°/4° C. The vapor is 2.6 times as heavy as air, while the relative density of the "saturated" vapor-air mixture at 20° C. is 1.02 or essentially the same as air. Methyl Cellosolve is miscible with water and very soluble in most organic solvents. The refractive index is 1.40150 at 20° C. and 1.4004 at 26°.

1 mg./l.  $\approx$  322 p.p.m. and 1 p.p.m.  $\approx$  3.11 mg./cu.m. at 25° C., 760 mm.

<sup>23</sup> L. Greenburg, M. R. Mayers, L. J. Goldwater, W. J. Burke, and S. Moskowitz, *J. Ind. Hyg. Toxicol.*, **20**, 134 (1938).

<sup>24</sup> H. W. Werner, J. L. Mitchell, J. W. Miller, and W. F. von Oettingen, *J. Ind. Hyg. Toxicol.*, **25**, 157 (1943).

## 2. Determination in the Atmosphere

Determination of methyl Cellosolve vapor in air may be made by adsorption and weighing, or by means of the interferometer (see page 204), but more satisfactorily by reaction with potassium dichromate in sulfuric acid, a modification of the Nieloux method for ethyl alcohol.<sup>25,26</sup>

## 3. Physiological Response

*Acute effects.* Methyl Cellosolve is toxic to man and animals, and the symptoms and pathology resulting from its inhalation or ingestion are similar to those common to poisoning by any of the glycols. Single exposures of mice for 7 hours to the glycol ethers individually indicated that the minimum lethal concentrations (50 per cent of the exposed animals died within 3 weeks after exposure) of the monoalkyl ethers of ethylene glycol are: methyl 1480 p.p.m., ethyl 1820 p.p.m., *n*-propyl 1530 p.p.m., isopropyl 1930 p.p.m., and butyl 700 p.p.m. Pathology was observed in the lungs, kidneys, liver, and spleen. Lehmann and Flury<sup>27</sup> reported deaths among guinea pigs 2 to 14 days following exposure to 9300 p.p.m. methyl Cellosolve for 3 hours. Death was due to pneumonia and kidney injury. Inhalation of more than 3200 p.p.m. for a 7-hour period caused the death of all experimental animals.

Methyl Cellosolve is both a moderate irritant and a systemic poison. It is a weak narcotic.

*Chronic effects.* The inhalation<sup>27</sup> of 800 p.p.m. methyl Cellosolve 8 hours per day caused the death of guinea pigs in 9 to 12 days, the illness of two rabbits in 15 days, the death of one in 4 days, and no evident ill effects in a mouse. Similar inhalation experiments with 1600 p.p.m. for 8 hours per day resulted in the death of most animals within 2 to 10 days. Pulmonary irritation and kidney damage were common findings.

Dogs exposed to 750 p.p.m.<sup>28</sup> methyl Cellosolve 7 hours daily, 5 days a week for 12 weeks, evidenced a decrease in hemoglobin and red cells, and a shift to the left of the white cells. There was some indication of liver damage, a slight increase in blood urea, but no evidence of kidney damage or of bone marrow injury. There was an increase in the number of calcium oxalate crystals in the urine. Return to normal after termination of exposure was dependent upon the severity of the anemia.

Greenburg and others<sup>28</sup> reported two poisonings among a group of workers engaged in the manufacture of fused collars, which they attributed to prolonged exposure to methyl Cellosolve. The methyl Cellosolve vapor is known to have

<sup>25</sup> H. W. Werner and J. L. Mitchell, *Ind. Eng. Chem., Anal. Ed.*, 15, 375 (1943).

<sup>26</sup> H. B. Elkins, E. D. Storlazzi, and J. W. Hammond, *J. Ind. Hyg. Toxicol.*, 24, 229 (1942).

<sup>27</sup> K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

<sup>28</sup> H. W. Werner, J. L. Mitchell, J. W. Miller, and W. F. von Oettingen, *J. Ind. Hyg. Toxicol.*, 25, 409 (1943).

been accompanied by approximately three times its volume of ethyl alcohol vapor and one fifth its volume of methyl alcohol, as well as insignificant amounts of ethyl acetate and petroleum naphtha. They found that the two workmen most seriously poisoned were severely anemic, and the other exposed workmen had abnormal blood pictures. The concentration of the combined vapors causing these effects is believed to have been very high, but it could not be determined satisfactorily because improvements had been made in the exhaust system following the evidence of intoxication, and preceding sampling. A sample of general room air taken after the improvement in ventilation was found to have 25 p.p.m. methyl Cellosolve, and these investigators proposed this amount as a maximum permissible limit.

#### 4. *Permissible Concentration, Warning Properties, and Inflammability*

Cook<sup>29</sup> has proposed a maximum allowable concentration of 100 p.p.m. and this concentration appears to be a logical figure for engineering control until further information concerning effects, or their absence, can be coupled with data on the concentrations actually inhaled. Methyl Cellosolve is inflammable and its flash point by the closed-cup method is 107° F. (see Chapter Thirteen). Warning properties of this solvent are of no significance.

## ETHYLENE GLYCOL MONOETHYL ETHER

Ethylene glycol monoethyl ether ( $C_2H_5OCH_2CH_2OH$ ), Cellosolve, 2-ethoxyethanol, is used as a colorless, liquid solvent for nitrocellulose in lacquers, dopes, and their thinners.

#### 1. *Physical and Chemical Properties*

Cellosolve has a molecular weight of 90.12, specific gravity of 0.9311 at 20°/4° C., boiling point of 135.1°, a refractive index of 1.4042 at 24°, and a vapor pressure of 3.8 at 20°. The vapor is approximately three times as heavy as air, but the "saturated" vapor-air mixture at 20° C. (0.5 per cent by volume) has a density of 1.01 relative to air, or essentially the same as that of air. Cellosolve is miscible with water, alcohol, and ether.

1 mg./l.  $\approx$  272 p.p.m. and 1 p.p.m.  $\approx$  3.68 mg./cu.m. at 25° C., 760 mm.

#### 2. *Determination in the Atmosphere*

Vapors of Cellosolve in the air may be determined in the same ways as those of methyl Cellosolve.

#### 3. *Physiological Response*

*Acute effects.* The relative toxicities of the monoalkyl ethers of ethylene glycol<sup>24</sup> (compared on a molecular basis, such as parts per million) were found to increase with increasing molecular weight except for methyl Cellosolve. This

<sup>29</sup> W. A. Cook, *Ind. Med.*, 14, 936 (1945).

compound appeared to be slightly more toxic than the ethyl derivative and, being somewhat more volatile, it also offers more of an exposure problem.

The acute response of guinea pigs<sup>30</sup> to Cellosolve vapor in air is summarized in Table 5. The symptoms exhibited were inactivity, weakness, dyspnea, and death.

TABLE 5  
*Acute Response of Guinea Pigs to Cellosolve Vapor*

Cellosolve, p.p.m.	Exposure, hours	Response
6000	1	No symptoms, no deaths
	4	No symptoms, slight injury, no deaths
	8	Inactive, 1 of 6 died 48 hr. later
	24	Of 6 animals, 4 died on test, 1 was killed for autopsy, and 1 died 3 hr. later
3000	4	No symptoms, pathology, or deaths
	8	No symptoms, slight injury, no deaths
	16	1 of 6 animals died within 8 days
1000	16	1 of 6 animals died within 8 days
	24	1 of 6 animals died within 8 days
500	16	No symptoms, no injury, no deaths
	24	No symptoms, no injury, no deaths

Cellosolve is a mild irritant to mucous membranes. Guinea pigs dying from the effects of exposure to its vapors evidenced, principally, congestion and edema of the lungs, small hemorrhagic areas in the stomach, and a hyperpnea or congestion of the kidneys.

*Chronic effects.* Lehmann and Flury<sup>27</sup> report that the majority of animals exposed to Cellosolve 8 hours per day, repeatedly, died after 4 to 12 exposures. Cats were most susceptible, dying 2 days after 4 or 5 days of exposure; one of two mice died after 9 exposures, but the other survived 12 exposures without evident effects; two rabbits survived 12 exposures, one dying 7 days later; while two guinea pigs survived 12 exposures without evidence of injury.

Browning<sup>31</sup> reported a case of industrial poisoning.

Dogs exposed to 840 p.p.m. Cellosolve<sup>28</sup> 7 hours daily, 5 days a week for 12 weeks, evidenced a slight decrease in hemoglobin and red cells, a shift to the left of white cells, slight liver damage, a small but definite increase in blood urea, but no evidence of kidney damage or of bone marrow injury. There was an increase in the number of calcium oxalate crystals in the urine. The time required for return to normal after termination of exposure was dependent upon the severity of the anemia. The effects were similar to those resulting from exposure to 750 p.p.m. methyl Cellosolve. Rats exposed to 370 p.p.m. Cellosolve vapor<sup>32</sup> 7 hours

<sup>30</sup> C. P. Waite, F. A. Patty, and W. P. Yant, *U.S. Pub. Health Repts.*, 45, 1459 (1930).

<sup>31</sup> E. Browning, *Toxicology of Industrial Solvents*. Med. Research Council, Ind. Health Research Board, London, 1937.

<sup>32</sup> H. W. Werner, C. Z. Nawrocki, J. L. Mitchell, J. W. Miller, and W. F. von Oettingen, *J. Ind. Hyg. Toxicol.*, 25, 374 (1943).

daily, 5 days a week for 5 weeks, gave some evidence of adverse effects upon the blood cells.

#### 4. *Permissible Limit*

The toxicity of Cellosolve and its effects are similar to those of methyl Cellosolve, possibly less severe. When dealing with vapors having a recognized, insidious action, such as some of the glycols have upon the kidneys, a reasonable factor of safety should be required. Until evidence is submitted to indicate a more logical figure, a permissible limit of 100 p.p.m. is suggested. This is practicable: Cellosolve with its lower vapor pressure presents less of an engineering control problem than methyl Cellosolve.

#### 5. *Warning Properties and Inflammability*

The highest concentration of Cellosolve vapor that occurs at ordinary environmental temperatures and pressures is disagreeably odoriferous but only moderately irritant; concentrations in the range of permissibility for prolonged exposure have no irritant effects, and the faint odor is not offensive to most persons.

Cellosolve is inflammable, and its flash point by the closed-cup method is 104° F. (see Chapter Thirteen).

## ETHYLENE GLYCOL MONOBUTYL ETHER

### 1. *Physical and Chemical Properties*

Ethylene glycol monobutyl ether ( $C_4H_9OCH_2CH_2OH$ ), 2-butoxyethanol, butyl Cellosolve, is a colorless liquid with a molecular weight of 118.17, a density of 0.9027 at 20°/4° C., boiling point 170.6°, and  $n_D$  1.4177 at 26°. The density of the vapor is 4, compared with that of air as 1, but the vapor pressure equal to 0.6 mm. Hg at 20° C. limits the amount in "saturated" air at that temperature to 790 p.p.m., and the density of such a vapor-air mixture is essentially the same as that of air. Its solvent properties are similar to those of the other glycol ethers, and its use in lacquers permits the concomitant use of petroleum distillates in the lacquers and in their thinners. Butyl Cellosolve is used in detergent solutions to dissolve the soap and to promote emulsification. It is also used with phosphoric acid in metal cleaners to prepare sheet metal for lacquering and enameling. No specific methods for its determination have been developed (see Ethylene Glycol).

1 mg./l.  $\approx$  207 p.p.m. and 1 p.p.m.  $\approx$  4.84 mg./cu.m. at 25° C., 760 mm.

### 2. *Physiological Response*

Butyl Cellosolve produces the same toxic effects as the other three glycol ethers described, and is the most toxic of the group. Rats exposed to concentrations of 135 p.p.m. and 320 p.p.m. butyl Cellosolve 7 hours per day, 5 days a week for 5 weeks, evidenced small, but measurable, effects on the cellular elements of the blood.<sup>32</sup> One milliliter per kilogram of body weight given to rabbits by

mouth caused their death,<sup>33</sup> with acute inflammation of the kidneys. The inhalation of 520 p.p.m., 2.5 mg. per liter, 8 hours per day for 8 to 12 days, caused the death of cats, rabbits, and guinea pigs, but had no evident, adverse effects upon mice. Kidney inflammation was present in all animals that died.

### 3. *Permissible Limit, Warning Properties, and Inflammability*

The data are too few to establish a definite permissible limit for butyl Cellosolve, but since its toxicity is apparently greater than those of the other Cellosolves, its concentration in the air for daily 8-hour exposures should be less than 100 p.p.m., a condition that poses no engineering hardship in view of the low vapor pressure of the solvent. It may be pointed out, also, that when any water-soluble solvent is mixed with water its vapor pressure is reduced in relation to the amount of water in the solution.

Butyl Cellosolve has a rancid odor that is not agreeable, but does not serve as a satisfactory warning of harmful concentrations. Butyl Cellosolve is inflammable and its flash point by the closed-cup method is 141° F. (see Chapter Thirteen).

## ETHYLENE GLYCOL DIETHYL ETHER

### 1. *Physical and Chemical Properties*

Ethylene glycol diethyl ether ( $C_2H_5OCH_2CH_2OC_2H_5$ ), diethyl Cellosolve, is a colorless, volatile liquid the vapors of which are irritating to the eyes and to nasal membranes. Its molecular weight is 118.17, its density is 0.8424 at 20°/20° C., its boiling point is 121.4°, and its vapor pressure equals 9.4 mm. Hg at 20°, which corresponds to a vapor concentration in "saturated" air at 20° of 1.24 per cent by volume. The density of the vapor itself is 4.1 times that of air, and the density of the "saturated" vapor-air mixture at 20° C. is 1.04 times that of air. Diethyl Cellosolve is soluble in water to the extent of 21 per cent by weight. As a solvent in colloidal systems of limited water solubility it permits water dilution.

1 mg./l.  $\approx$  207 p.p.m. and 1 p.p.m.  $\approx$  4.84 mg./cu.m. at 25° C., 760 mm.

### 2. *Physiological Response*

*Acute effects.* Diethyl Cellosolve vapor is irritant, narcotic, and a kidney poison.<sup>33</sup> The inhalation of 1 per cent for 1 hour caused irritation of mucous membranes and a suggestion of narcosis. Cats were more sensitive than were rabbits, guinea pigs, or dogs. All recovered from the exposure. A cat fed 1 ml. per kilogram on 4 occasions died about 30 to 40 hours after the last dose. A guinea pig that received 7 subcutaneous injections of  $\frac{1}{2}$  ml. per kilogram became ill and lost weight, but subsequently recovered. Injections of 1 ml. per kilogram given in a similar manner caused temporary narcosis after the fourth injection, pros-

\* K. B. Lehmann and F. Flury, *Toxicology and Hygiene of Industrial Solvents*. Trans. by E. King and H. F. Smyth, Jr., Williams & Wilkins, Baltimore, 1943.

tration and death with nephritis following the seventh. There are no data on exposures of man.

*Chronic effects.* Twelve daily 8-hour inhalation exposures of mice, guinea pigs, a rabbit, and two cats to 500 p.p.m. diethyl Cellosolve resulted in the death of the rabbit and the cats, but no evident injury to the mice and guinea pigs. This would seem to indicate that diethyl Cellosolve is somewhat more toxic than either methyl Cellosolve or ethyl Cellosolve, and that its effects are similar.

### 3. *Permissible Limit, Warning Properties, and Inflammability*

There are not sufficient data upon which to base a suggestion for a permissible limit, but the indications are that such a limit probably should be somewhat less than 100 p.p.m. Diethyl Cellosolve does not have suitable warning properties for avoiding exposure. It presents an explosion hazard since its flash point by the closed-cup method is 95° F.

## DIETHYLENE GLYCOL MONOETHYL ETHER

### 1. *Properties and Physiological Response*

Diethylene glycol monoethyl ether ( $C_2H_5OCH_2CH_2OCH_2CH_2OH$ ), Carbitol, is a colorless liquid with a molecular weight of 134.17, a density of 0.9902 at 20°/4° C., boiling point of 201.9°, and  $n_D$  of 1.4240 at 26°. It has solvent properties similar to those of butyl Cellosolve and its lower vapor pressure, which is equal to 0.2 mm. Hg at 20° C., limits its concentration in the air at that temperature to 260 p.p.m., which does not constitute an acute toxicity exposure. This has been verified by the author by exposure of guinea pigs<sup>34</sup> to "saturated" air at about 25° C. for periods up to 24 hours without evidence of injury. Feeding experiments indicate that Carbitol is a kidney poison, and that its acute toxicity is less than that of butyl Cellosolve and of the same order as that of Cellosolve and diethyl Cellosolve, but possibly less. As far as chronic poisoning from vapor inhalation is concerned, however, the danger in general plant atmosphere is remote because of the low vapor pressure. Concentrations approaching the saturation point were not injurious to guinea pigs, rabbits, cats, and mice<sup>33</sup> in inhalation experiments lasting as long as 12 days. Where fogs, mists, or sprays are encountered, or elevated temperatures in absence of any general ventilation, a serious exposure may result.

1 mg./l.  $\approx$  182.2 p.p.m. and 1 p.p.m.  $\approx$  5.49 mg./cu.m. at 25° C., 760 mm.

### 2. *Permissible Limit*

A vapor limit, in view of the low vapor pressure and the difficulty of attaining or even closely approaching "saturated" air, hardly seems necessary. The scanty available information, however, suggests that vapor concentrations on the order of 100 p.p.m. might be tentatively acceptable until additional data are available.

\* Unpublished work conducted at the United States Bureau of Mines.

### **3. *Warning Properties and Inflammability***

Carbitol vapor has little odor and no irritant properties. The flash point of the liquid is about 210° F., and when dispersed as a spray or mist it can form inflammable mixtures with air.

## **ACETATES OF THE GLYCOLS AND OF THE GLYCOL ETHERS**

The acetates of the glycols and of the glycol ethers are good solvents for cellulose, nitrocellulose, and resins, and are used in lacquers, enamels, and thinners, as well as varnish removers. They evaporate relatively slowly, and in lacquers they offer some protection against "blushing." Information on their toxicity<sup>33</sup> is sketchy, but it indicates that, on a volume (p.p.m.) basis, the acetates have a toxicity similar to that of the corresponding glycols and glycol ethers. The acetates are perhaps slightly more narcotic and irritant. All of those investigated cause kidney damage. Since their vapor pressures are less than those of the glycols and glycol ethers, the vapor exposures are correspondingly easier to control. However, it is important when dealing with such compounds that not only the vapor exposures be considered for control, but also the mist or spray exposures. All of these acetates are inflammable at elevated temperatures or when suspended in air as particulate matter.



# Aliphatic Nitro, Diazo, and Amino Compounds

JAMES H. STERNER, M.D.

## I. General Considerations

### A. SYMPTOMS IN ANIMALS

The nitroparaffins—nitromethane, nitroethane, nitropropane, and nitrobutane—by inhalation act primarily as moderate irritants. An initial restlessness and apparent discomfort with signs of irritation of the respiratory tract is followed by conjunctival irritation, increased salivation, and occasional audible râles. In later stages twitching and jerking movements are sometimes followed by generalized convulsions. Anesthetic effects are light, although in general the animals that were anesthetized died later. Nitroethane is apparently more irritating to the mucous membranes than is nitromethane although the latter, on inhalation, produces more severe central nervous system involvement.

The addition of one or more chlorine atoms to a nitroparaffin increases the irritating properties, with the degree of irritation paralleling the increase in chlorine atoms. With the monochloronitroparaffins the irritating effect is moderate, with sneezing, coughing, increased lacrimation, and nasal secretion, but it reaches a severe degree with trichloronitromethane, chloropicrin. The symptoms are those of respiratory-tract irritation with no general narcosis and no marked central nervous system symptoms. Continued exposure to higher concentrations of the chlorinated nitroparaffins results in severe injury to the upper respiratory tract and lungs.

### B. GROSS PATHOLOGY IN ANIMALS

Generalized vascular and cerebral congestion was found in fatal cases. Following the inhalation of high concentrations, pulmonary congestion with edema was noted, somewhat more with nitroethane and nitropropane, but never sufficient to be the primary cause of death. Cerebral congestion was found regularly, particularly following inhalation of nitromethane and nitroethane where, in fatal cases, it was frequently accompanied by marked cerebral edema and, in one case, small pial hemorrhages. Hepatic injury of some degree was present in all

fatal cases, with edema, cloudy swelling, and occasionally necrosis. In the guinea pigs, the degree of hepatic injury was proportional to the increase in molecular weight of the nitroparaffins. Edema of the kidneys, myocardium, and other tissues was moderate.

The irritant effects of the chlorinated nitroparaffins on the upper respiratory tract and lungs is considerably greater than that of the simple nitroparaffins, and the pulmonary edema and hemorrhage resemble somewhat those produced by the acid gases. The monochloronitroparaffins are not markedly irritating to the skin, but the dichloro and, particularly, the trichloro compounds are marked skin irritants. With higher concentration exposures to the dichloro compounds, severe injury of the heart muscle with acute myocardial degeneration, focal hemorrhages, cellular infiltration and exudate of the lungs, and generalized vascular injury were noted. The hepatic injury was less marked than expected, with diffuse toxic changes noted. Kidney damage consisted of edema with occasional capsular necrosis and tubular degeneration. These effects were less marked with the monochloro compounds.

#### C. ABSORPTION AND EXCRETION

The nitroparaffins are absorbed through the lung with considerable ease and rapidity and the increase in toxicity, corresponding to the increase in molecular weight, is more marked when these compounds are acquired by the inhalation route than when by ingestion. This is probably due to the differences in solubility and the slower absorption through the gastrointestinal tract of the higher molecular weight compounds. Nitroethane, the compound more completely studied, is excreted and metabolized by the rabbit and rat at a fairly rapid rate, with doses as large as 1 g. being completely eliminated and destroyed in 30 hours. Appreciable quantities are eliminated through the lung regardless of the route of administration. Attempts to demonstrate the absorption of the nitroparaffins through the skin gave no evidence of systemic injury in any of the animals.

Absorption through the skin of the chlorinated substituted compounds was not appreciable.

#### D. MODE OF ACTION AND CAUSE OF DEATH

The initial effect following inhalation of the mononitroparaffins is that of moderate irritation of the upper respiratory tract and eyes. The secondary effects, resulting from absorption and distribution of the materials in the body, are those of central nervous system irritation with narcotic effects being relatively minor. In exposure to lower but still effective concentrations, a general toxic action with loss of weight and reduction in erythrocytes and hemoglobin occurred, but recovery was prompt following cessation of exposure. The effect on blood pressure and respiration is relatively slight, very much less than that of the nitrates or sodium nitrite. Concentrations considerably below the narcotic

concentrations are lethal; hence narcosis cannot be used as a warning. The nitro-paraffins are partially oxidized in the body with the corresponding aldehyde and nitrite being identified in relatively large amounts.

### E. PHYSIOLOGICAL RESPONSE IN MAN

Scant published reports indicate only slight irritation to the eyes and upper respiratory tract from short exposures to the simple mononitroparaffins. The addition of one chlorine atom increases somewhat the irritant properties. No instances of occupational intoxication or injury have been reported.

There is considerable human experience with the toxic effect of trichloro-nitromethane (chloropicrin) since this material was used as a war gas in World War I. Chloropicrin produces severe lacrimation, sneezing, coughing, nausea, vomiting, colic, and diarrhea. Continued exposure, or even short exposure to high concentrations, results in severe injury to the respiratory tract with acute pulmonary edema, hemorrhages, and exudate similar to, but generally less severe than, that produced by phosgene. Occupational intoxication has not been reported.

### F. DETERMINATION OF THE NITROPARAFFINS

Any of the nitroparaffins in the air may be determined with an interferometer. Nitromethane can be determined by means of the color developed when it is heated with vanillin in ammoniacal solution.<sup>1</sup> The other mononitroparaffins can be collected in sodium hydroxide solution, acidified with hydrochloric acid, and determined by means of a red color developed with ferric chloride.<sup>2</sup> The chlorinated nitroparaffins likewise can be determined by colorimetric procedures: those of Machle *et al.*,<sup>3</sup> or Yagoda,<sup>4</sup> or Yagoda and Goldman.<sup>5</sup>

## II. Specific Compounds

### NITROMETHANE

#### 1. Source

Nitromethane ( $\text{CH}_3\text{NO}_2$ ) is produced by nitration of methane.

#### 2. Uses and Industrial Exposures

Solvent for nitrocellulose, cellulose acetate, cellulose acetopropionate, cellulose acetobutyrate, vinyl, alkyd, and many other resins, waxes, fats, and dye-stuffs. Chemical synthesis.

<sup>1</sup> W. Machle, E. W. Scott, and J. Treon, *J. Ind. Hyg. Toxicol.*, **22**, 315 (1940).

<sup>2</sup> E. W. Scott and J. F. Treon, *Ind. Eng. Chem., Anal. Ed.*, **12**, 189 (1940).

<sup>3</sup> W. Machle, E. W. Scott, J. F. Treon, F. F. Heyroth, and K. V. Kitzmille, *J. Ind. Hyg. Toxicol.*, **27**, 95 (1945).

<sup>4</sup> H. Yagoda, *Ind. Eng. Chem., Anal. Ed.*, **15**, 27 (1943).

<sup>5</sup> H. Yagoda and F. H. Goldman, *J. Ind. Hyg. Toxicol.*, **25**, 440 (1943).

### 3. Pertinent Chemical and Physical Properties

Physical state: colorless liquid	Percentage in "saturated" air: 5. at 25° C.
Molecular weight: 61.04	Density of "saturated" air: 1.06 (air = 1) at 25° C.
Specific gravity: 1.139 at 20°/20° C. <sup>a</sup>	Solubility in water: 9.5 ml./100 ml. at 20° C. <sup>a</sup>
Melting point: -28.5° C. <sup>a</sup>	Soluble in ethyl alcohol, ether, and carbon tetrachloride
Boiling point: 100.76°-100.86° C.	Flash point: 95° F. <sup>a</sup>
Vapor density: 2.1 (air = 1)	
Vapor pressure: 38 mm. Hg at 25° C. <sup>1</sup>	
Refractive index: 1.38133 at 21.6° C.	

1 mg./l.  $\approx$  400.7 p.p.m. and 1 p.p.m.  $\approx$  2.495 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (200 p.p.m.): 12.4 ml.

### 4. Physiological Response

*Acute effects.* See Table 1.

TABLE 1  
*Physiological Response to Various Concentrations of Nitromethane—Animals.<sup>1</sup> Two Rabbits and Two Guinea Pigs Exposed in Each Experiment*

Concentration		Duration of exposure	Fatalities		
mg./l.	p.p.m.		Rabbit <sup>a</sup>	Guinea pig	Monkey
124.8	50,000	1 hr.	Pronounced nervous system symptoms		
			Two	Two	—
74.9	30,000	2 hr.	Two	Two	—
			Pronounced nervous system symptoms after 1 hr.		
		1 hr.	None	Two	—
		30 min.	None	One	—
		15 min.	None	None	—
56.1	22,500	1 hr.	None	One	—
25.0	10,000	6 hr.	No signs of central nervous system symptoms during first 5 hr.		
			Two	Two	—
		3 hr.	None	Two	—
		1 hr.	None	None	—
12.5	5,000	6 hr.	One	One	—
		3 hr.	None	One	—
6.3	2,500	12 hr.	Two	One	—
2.5	1,000	30 hr.		Two	—
		48 hr.	None exposed	—	Fatal to single animal exposed
1.3	500	140 hr.	None	None	Not fatal to single animal exposed

<sup>a</sup> The lethal dose for rabbits by oral administration is 0.75-1.00 g. per kilogram.<sup>1</sup>

<sup>1</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

**5. Suggested Maximum Practical Working Level**200 p.p.m.<sup>7</sup>**6. Odor and Warning Properties**

The odors of the nitroparaffins are moderately strong and in relatively low concentrations are disagreeable to most observers. At 200 p.p.m. these warning properties are not dependable.

**DINITROMETHANE****1. Pertinent Chemical and Physical Properties**Formula:  $\text{CH}_2(\text{NO}_2)_2$ Melting point:  $< -15^\circ \text{C.}^8$ Physical state: liquid<sup>a</sup>Boiling point:  $100^\circ \text{C.}$  (decomposes)<sup>a</sup>

Molecular weight: 106.04

Soluble in water<sup>a</sup>1 mg./l.  $\approx$  230.7 p.p.m. and 1 p.p.m.  $\approx$  4.34 mg./cu.m. at  $25^\circ \text{C.}$ , 760 mm.**TRINITROMETHANE****1. Pertinent Chemical and Physical Properties**Formula:  $\text{CH}(\text{NO}_2)_3$ Melting point:  $15^\circ \text{C.}$  (explodes)<sup>a</sup>Physical state: colorless crystals<sup>a</sup>Boiling point:  $45-47^\circ \text{C.}$  (at 22 mm.)<sup>a</sup>

Molecular weight: 151.04

Soluble in water<sup>a</sup>1 mg./l.  $\approx$  161.9 p.p.m. and 1 p.p.m.  $\approx$  6.18 mg./cu.m. at  $25^\circ \text{C.}$ , 760 mm.**TETRANITROMETHANE****1. Source**

Nitration of methane

**2. Industrial Exposures**

During manufacture of TNT.

**3. Pertinent Chemical and Physical Properties**Formula:  $\text{C}(\text{NO}_2)_4$ Vapor pressure: 13 (approx.) mm. Hg at  $25^\circ \text{C.}^{8a}$ Physical state: colorless liquid<sup>a</sup>

Molecular weight: 196.04

Refractive index: 1.43976 at  $16.9^\circ \text{C.}$ Specific gravity: 1.650 at  $13^\circ/4^\circ \text{C.}^8$ Per cent in "saturated" air: 1.7 at  $25^\circ \text{C.}$ Melting point:  $13^\circ \text{C.}^8$ Density of "saturated" air: 1.09 (air = 1) at  $25^\circ \text{C.}$ Boiling point:  $125.7^\circ \text{C.}^8$ Insoluble in water<sup>a</sup>

Vapor density: 6.8 (air = 1)

Very soluble in alcohol and ether<sup>a</sup>1 mg./l.  $\approx$  124.7 p.p.m. and 1 p.p.m.  $\approx$  8.02 mg./cu.m. at  $25^\circ \text{C.}$ , 760 mm.**4. Physiological Response**

Acute effects. See Table 2.

<sup>7</sup> W. A. Cook, *Ind. Med.*, 14, 936 (1945).<sup>8a</sup> S. B. Lippincott and M. M. Lyman, *Ind. Eng. Chem.*, 38, 320 (1946).<sup>a</sup> N. A. Lange, *Handbook of Chemistry*, 5th ed., Handbook Publishers, Sandusky, Ohio, 1944.

TABLE 2  
*Physiological Response to Various Concentrations of Tetranitromethane—Cat<sup>9</sup>*

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
0.8	100	20 min.	Death in 1 hr.
0.08	10	20 min.	Death after 10 days

### 5. Odor

Pungent.

## NITROETHANE

### 1. Source

Nitration of ethane.

### 2. Uses and Industrial Exposures

Solvent for organic esters of cellulose, especially cellulose acetate; vinyl, alkyd, and many other resins; waxes, fats, and dyestuffs. Chemical synthesis.

### 3. Pertinent Chemical and Physical Properties

Formula:  $\text{CH}_3\text{CH}_2\text{NO}_2$

Physical state: colorless liquid

Molecular weight: 75.07

Specific gravity: 1.052 at 20°/20° C.<sup>6</sup>

Melting point: -50° C.

Boiling point: 114° C.

Vapor density: 2.6 (air = 1)

Vapor pressure: 25 mm. Hg at 25° C.<sup>1</sup>

Refractive index: 1.39007 at 24.3° C.

Percentage in "saturated" air: 3.3 at 25° C. (calculated)

Density of "saturated" air: 1.05 (air = 1) at 25° C.

Solubility in water: 4.5 ml. in 100 ml. water at 20° C.<sup>6</sup>

Soluble in chloroform<sup>10</sup>

Miscible with ethyl alcohol and ether

Flash point: 82° F.<sup>6</sup>

1 mg./l.  $\approx$  325.7 p.p.m. and 1 p.p.m.  $\approx$  3.07 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (200 p.p.m.): 16.6 ml.

### 4. Physiological Response

Acute effects. See Table 3.

### 5. Suggested Maximum Practical Working Level

200 p.p.m.<sup>7</sup>

### 6. Odor

Pleasant odor, intensity of 3 at 1000 p.p.m.

<sup>6</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

<sup>10</sup> *Handbook of Chemistry and Physics*. 28th ed., Chemical Rubber Publishing, Cleveland.

TABLE 3  
*Physiological Response to Various Concentrations of Nitroethane—Animals.<sup>1</sup> Two Rabbits and Two Guinea Pigs Exposed in Each Experiment*

Concentration		Duration of exposure	Fatalities		
mg./l.	p.p.m.		Rabbit <sup>a</sup>	Guinea pig	Monkey
92.1	30,000	75 min.	Stupor, narcosis, and light general anesthesia		
			Two	Two	—
		1 hr.	One	One	—
		30 min.	One	None	—
76.8	25,000	2 hr.	Two	None	—
30.7	10,000	3 hr.	Stupor, narcosis, and light general anesthesia		
			Two	One	—
		1 hr.	One	None	—
15.4	5,000	3 hr.	Two	None	—
		2 hr.	One	None	—
7.7	2,500	3 hr.	None	None	—
3.1	1,000	12 hr.	One	None	—
			Stupor, narcosis, light general anesthesia; symptoms disappeared rapidly		
		6 hr.	None	None	—
1.5	500	30 hr.	None	None exposed	—
		140 hr.	None	None	Not fatal to single exposed animal

<sup>a</sup>The lethal dose for rabbits by oral administration is 0.50–0.75 g. per kilogram.<sup>1</sup>

## DINITROETHANE (1,1-Dinitroethane)

### 1. Pertinent Chemical and Physical Properties

Formula:  $\text{CH}_3\text{CH}(\text{NO}_2)_2$

Boiling point: 185–186° C.<sup>8</sup>

Physical state: liquid<sup>8</sup>

Solubility in water: very slightly soluble<sup>8</sup>

Molecular weight: 120.07

Soluble in alcohol and ether<sup>8</sup>

Specific gravity: 1.350 at 23.5°/23.5° C.<sup>8</sup>

1 mg./l.  $\approx$  203.7 p.p.m. and 1 p.p.m.  $\approx$  4.91 mg./cu.m. at 25° C., 760 mm.

## TRINITROETHANE (1,1,1-Trinitroethane)

### 1. Pertinent Chemical and Physical Properties

Formula:  $\text{CH}_3\text{C}(\text{NO}_2)_3$

Melting point: 56° C.<sup>8</sup>

Physical state: crystal<sup>8</sup>

Solubility in water: very slightly soluble<sup>8</sup>

Molecular weight: 165.07

Soluble in alcohol and ether<sup>8</sup>

1 mg./l.  $\approx$  148.2 p.p.m. and 1 p.p.m.  $\approx$  6.75 mg./cu.m. at 25° C., 760 mm.

## 1-NITROPROPANE

### 1. Source

Nitration of propane.

### 2. Uses and Industrial Exposures

Solvent for organic esters of cellulose; vinyl, alkyd, and many other resins; waxes, fats and dyestuffs. Chemical synthesis.

### 3. Pertinent Chemical and Physical Properties

Formula:  $\text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2$

Physical state: colorless liquid

Molecular weight: 89.09

Specific gravity: 1.003 at 20°/20° C.<sup>1</sup>

Boiling point: 131.5° C.

Vapor density: 3.1 (air = 1)

Vapor pressure: 13 mm. Hg at 25° C.<sup>1</sup>

Refractive index: 1.40027 at 24.3° C.

Percentage in "saturated" air: 1.7 at 25° C.

Density of "saturated" air: 1.04 (air = 1) at 25° C.

Solubility in water: 9.5 ml. in 100 ml. at 20° C.<sup>1</sup>

Miscible with ethyl alcohol and ether

Flash point: 93° F.<sup>1</sup>

1 mg./l.  $\approx$  274.7 p.p.m. and 1 p.p.m.  $\approx$  3.64 mg./cu.m. at 25° C., 760 mm.

Liquid volume at 25° C. which if volatilized and distributed equally would give a concentration in 1000 cu.ft. equal to the suggested maximum practical working level (100 p.p.m.): 10.2 ml.

### 4. Physiological Response

Acute effects (see Tables 4 and 5).

TABLE 4

*Physiological Response to Various Concentrations of 1-Nitropropane—Animals.<sup>1</sup> Two Rabbits and Two Guinea Pigs Exposed in Each Experiment*

Concentration		Duration of exposure	Fatalities	
mg./l.	p.p.m.		Rabbit	Guinea pig
36.4	10,000	3 hr.	Two	Two
		1 hr.	None	One
18.2	5,000	3 hr.	Two	Two

TABLE 5

*Lethal Dose—Rabbit<sup>1</sup>*

Compound	Dose, g./kg.	Route
1-Nitropropane	0.25–0.50	Oral
2-Nitropropane	0.50–0.75	Oral

### 5. Suggested Maximum Practical Working Level

100 p.p.m.



**6. Odor and Warning Properties**

At 1000 p.p.m. sweet, nitro compound odor, intensity of 4. Eye irritation, intensity 3. Slight lacrimation.

**2-NITROPROPANE****1. Source**

Nitration of propane.

**2. Uses and Industrial Exposures**

Solvent for organic esters of cellulose; vinyl, alkyd, and many other resins; waxes, fats and dyestuffs. Chemical synthesis.

**3. Pertinent Chemical and Physical Properties**

Formula: $\text{CH}_3\text{CH}(\text{NO}_2)\text{CH}_3$	Refractive index: 1.3941 at 20° C. <sup>11</sup>
Physical state: colorless liquid	Percentage in "saturated" air: 2.6 at 25° C.
Molecular weight: 89.09	Density of "saturated" air: 1.05 (air = 1) at 25° C.
Specific gravity: 0.992 at 20°/20° C. <sup>11</sup>	Solubility in water: 1.7 ml. in 100 ml. at 20° C. <sup>11</sup>
Boiling point: 120° C.	Flash point: 75° F. <sup>11</sup>
Vapor density: 3.1 (air = 1)	
Vapor pressure: 20 mm. Hg at 25° C. <sup>12</sup>	
1 mg./l. $\approx$ 274.7 p.p.m. and 1 p.p.m. $\approx$ 3.64 mg./cu.m. at 25° C., 760 mm.	

**1,1-DINITROPROPANE****1. Pertinent Chemical and Physical Properties**

Formula: $\text{C}_3\text{H}_5\text{CH}(\text{NO}_2)_2$	Specific gravity: 1.258 at 22° C. <sup>8</sup>
Physical state: acidic oil <sup>8</sup>	Boiling point: 189° C. <sup>8</sup>
Molecular weight: 134.09	Solubility in water: soluble in alkaline <sup>8</sup>
1 mg./l. $\approx$ 182.4 p.p.m. and 1 p.p.m. $\approx$ 5.48 mg./cu.m. at 25° C., 760 mm.	

**2,2-DINITROPROPANE****1. Pertinent Chemical and Physical Properties**

Formula: $(\text{CH}_3)_2\text{C}(\text{NO}_2)_2$	Boiling point: 185.5° C. <sup>8</sup>
Physical state: crystal <sup>8</sup>	Very slightly soluble in water <sup>8</sup>
Molecular weight: 134.09	Insoluble in alkaline alcohol <sup>8</sup>
Melting point: 53° C. <sup>8</sup>	
1 mg./l. $\approx$ 182.4 p.p.m. and 1 p.p.m. $\approx$ 5.48 mg./cu.m. at 25° C., 760 mm.	

**1-NITROBUTANE****1. Source**

Nitration of butane.

**2. Uses and Industrial Exposures**

Solvent for organic esters of cellulose, especially cellulose acetate.

<sup>11</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

<sup>12</sup> W. Machle, E. W. Scott, and J. Treon, *J. Ind. Hyg. Toxicol.*, **22**, 315 (1940).

**3. Pertinent Chemical and Physical Properties**

Formula: $C_2H_5NO_2$	Refractive index: 1.41044 at 20° C. <sup>13</sup>
Physical state: liquid	Percentage in "saturated" air: 0.66 at 25° C.
Molecular weight: 103.12	Density of "saturated" air: 1.02 (air = 1) at 25° C.
Specific gravity: 0.9774 at 15.56°/15.56° C. <sup>13</sup>	Solubility in water: 0.5 ml. in 100 ml. <sup>13</sup>
Boiling point: 151° C.	Miscible with ethyl alcohol and ether <sup>10</sup>
Vapor density: 3.6 (air = 1)	
Vapor pressure: 5 mm. Hg at 25° C. <sup>13</sup>	

1 mg./l.  $\approx$  237 p.p.m. and 1 p.p.m.  $\approx$  4.21 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response in Animals**

The lethal dose for rabbits by oral administration is 0.50–0.75 g. per kilogram.<sup>12</sup>

**2-NITROBUTANE****1. Source**

Nitration of butane.

**2. Uses and Industrial Exposures**

Solvent for organic esters of cellulose, especially cellulose acetate.

**3. Pertinent Chemical and Physical Properties**

Formula: $CH_3CH(NO_2)C_2H_5$	Vapor pressure: 8 mm. Hg at 25° C. <sup>12</sup>
Physical state: liquid	Refractive index: 1.40480 at 20° C. <sup>12</sup>
Molecular weight: 103.12	Percentage in "saturated" air: 1.05 at 25° C.
Specific gravity: 0.9728 at 15.56°/15.56° C. <sup>12</sup>	Density of "saturated" air: 1.03 (air = 1) at 25° C.
Boiling point: 139° C.	Solubility in water: 0.9 ml. in 100 ml. <sup>12</sup>
Vapor density: 3.6 (air = 1)	

1 mg./l.  $\approx$  237 p.p.m. and 1 p.p.m.  $\approx$  4.21 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response in Animals**

The lethal dose for rabbits by oral administration is 0.50–0.75 g. per kilogram.<sup>12</sup>

**1-CHLORO-1-NITROETHANE****1. Pertinent Chemical and Physical Properties**

Formula: $CH_3CHCl(NO_2)$	Refractive index: 1.4264 at 20° C. <sup>13</sup>
Physical state: colorless liquid	Percentage in "saturated" air: 1.6 at 25° C.
Molecular weight: 109.5 <sup>13</sup>	Density of "saturated" air: 1.04 (air = 1) at 25° C.
Specific gravity: 1.2860 at 20°/20° C. <sup>13</sup>	Solubility in water: 0.4 ml. in 100 ml. at 20° C. <sup>13</sup>
Boiling point: 127.5° C. <sup>13</sup>	
Vapor density: 3.8 (air = 1)	
Vapor pressure: 11.9 mm. Hg at 25° C. <sup>13</sup>	

1 mg./l.  $\approx$  223.3 p.p.m. and 1 p.p.m.  $\approx$  4.48 mg./cu.m. at 25° C., 760 mm.

**2. Physiological Response**

The lethal oral dose for rabbits lies between 0.10 and 0.15 g. per kilogram body weight.<sup>13</sup>

<sup>13</sup> W. Machle, E. W. Scott, J. F. Treon, F. F. Heyroth, and K. V. Kitzmiller, *J. Ind. Hyg. Toxicol.*, **27**, 95 (1945).

**1,1-DICHLORO-1-NITROETHANE****1. Pertinent Chemical and Physical Properties**Formula:  $\text{CH}_3\text{CCl}_2(\text{NO}_2)$ 

Physical state: liquid

Molecular weight: 143.9<sup>18</sup>Specific gravity: 1.4271 at 20°/20° C.<sup>18</sup>

Boiling point: 124° C.

Vapor density: 5.0 (air = 1)

Vapor pressure: 16 mm. Hg at 25° C.<sup>18</sup>Refractive index: 1.444 at 20° C.<sup>18</sup>

Percentage in "saturated" air: 2.1 at 25° C.

Density of "saturated" air: 1.08 (air = 1) at 25° C.

Solubility in water: 0.25 ml. in 100 ml. water at 20° C.<sup>18</sup>1 mg./l.  $\approx$  169.9 p.p.m. and 1 p.p.m.  $\approx$  5.89 mg./cu.m. at 25° C., 760 mm.**2. Physiological Response***Acute effects.* See Table 6.

TABLE 6  
*Physiological Response to Various Concentrations of 1,1-Dichloro-1-nitroethane—Animals.<sup>18</sup> Two Rabbits and Two Guinea Pigs Exposed in Each Experiment*

Concentration		Duration of exposure	Fatalities	
mg./l.	p.p.m.		Rabbit <sup>a</sup>	Guinea pig
90	15,291	75 min.	Two	Two
57.7	9,803	10 min. & 30 min.	Two	Two
28.9	4,910	30 min.	Two	Two
		10 min.	Two	None
14.4	2,446	135 min.	Two	Two
		40 min.	Two	None
5.8	985	210 min.	Two	One
		60 min.	One	None
		30 min.	One	One
5.0	850	10 min.	None	None
3.5	594.6	300 min.	Two	Two
		150 min.	One	None
2.0	339.8	30 min.	None	None
1.5	254.8	60 min.	None	None
1.0	169.9	120 min.	One	One
		30 min.	None	None
0.7	118.9	60 min.	None	None
0.58	100	360 min.	Two	Two
0.35	60	120 min.	None	None
0.3	52	1,125 min.	Two	None
0.2	34	240 min.	None	None
0.14	25	12,240 min.	None	None
		1,125 min.	None	None

<sup>a</sup>The lethal dose of 1,1-dichloro-1-nitroethane for rabbits is between 0.15 and 0.20 g. per kilogram.<sup>18</sup>

**1-CHLORO-1-NITROPROPANE****1. Pertinent Chemical and Physical Properties**Formula:  $\text{CH}_2\text{CH}_2\text{CHCl}(\text{NO}_2)^{12}$ 

Physical state: liquid

Molecular weight: 123.5<sup>12</sup>Specific gravity: 1.209 at 20°/20° C.<sup>12</sup>Boiling point: 139.5°–143.3° C.<sup>12</sup>

Vapor density: 4.3 (air = 1)

Vapor pressure: 5.8 mm. Hg at 25° C.<sup>12</sup>Refractive index: 1.4302 at 20° C.<sup>12</sup>

Percentage in "saturated" air: 0.76 at 25° C.

Density of "saturated" air: 1.03 (air = 1) at 25° C.

Solubility in water: 0.5 ml. in 100 ml. water at 20° C.<sup>12</sup>1 mg./l.  $\approx$  198 p.p.m. and 1 p.p.m.  $\approx$  5.05 mg./cu.m. at 25° C., 760 mm.**2. Physiological Response***Acute effects.* See Table 7.

TABLE 7

*Physiological Response to Various Concentrations of 1-Chloro-1-nitropropane—Animals.<sup>13</sup> Two Rabbits and Two Guinea Pigs Exposed in Each Experiment*

Concentration		Duration of exposure	Fatalities	
mg./l.	p.p.m.		Rabbit <sup>a</sup>	Guinea pig
32	6336	30 min.	None	One
28	5544	60 min.	One	None
25	4950	60 min.	Two	One
24	4752	30 min.	One	None
19	3800	30 min.	None	None
18	3564	120 min.	Two	Two
13	2574	120 min.	Two	None
12	2376	30 min.	One	None
11	2178	60 min.	None	One
5.9	1168	120 min.	One	None
5.4	1069	60 min.	None	None
3.5	693	120 min.	None	None
2.0	396	360 min.	One	None

<sup>a</sup> The lethal oral dose of 1-chloro-1-nitropropane for rabbits is between 0.05 and 0.10 g. per kilogram.<sup>13</sup>**2-CHLORO-2-NITROPROPANE****1. Pertinent Chemical and Physical Properties**Formula:  $\text{CH}_2\text{CHCl}(\text{NO}_2)\text{CH}_2$ 

Physical state: liquid

Molecular weight: 123.5

Specific gravity: 1.1973 at 20°/20° C.<sup>12</sup>Boiling point: 133.6° C.<sup>12</sup>

Vapor density: 4.3 (air = 1)

Vapor pressure: 8.5 mm. Hg at 25° C.

Refractive index: 1.4258 at 20° C.<sup>12</sup>

Percentage in "saturated" air: 1.1 at 25° C.

Density of "saturated" air: 1.03 (air = 1) at 25° C.

Solubility in water: 0.5 ml. in 100 ml. water at 20° C.<sup>12</sup>1 mg./l.  $\approx$  198 p.p.m. and 1 p.p.m.  $\approx$  5.05 mg./cu.m. at 25° C., 760 mm.

**2. Physiological Response**

The lethal oral dose for rabbits lies between 0.50 and 0.75 g. per kilogram.<sup>15</sup>

**TRICHLORONITROMETHANE (Chloropicrin)****1. Source**

Trichloronitromethane is prepared by the action of picric acid on calcium hypochlorite or by nitration of chlorinated hydrocarbons.<sup>15</sup>

**2. Uses and Industrial Exposures**

War gas ("Aquinite" in France, "Klop" in Germany, and "PS" in the United States); organic synthesis, dyestuffs; fumigant preparations; fungicides; insecticides; rat exterminator.

**3. Pertinent Chemical and Physical Properties**

Formula: $\text{CCl}_3\text{NO}_2$	Percentage in "saturated" air: 2.2 at 20° C.
Physical state: colorless liquid	Density of "saturated" air: 1.1 (air = 1) at 20° C.
Molecular weight: 164.39	Solubility in water: 0.1621 g. in 100 ml. water at 25° C.
Specific gravity: 1.6511 at 22.8°/4° C.	Soluble in ethyl alcohol
Melting point: -69.2° C.	Slightly soluble in ethyl ether <sup>15</sup>
Boiling point: 112° C.	Miscible with benzene
Vapor density: 5.7 (air = 1)	
Vapor pressure: 16.91 mm. Hg at 20° C. <sup>15</sup>	
Refractive index: 1.46075 at 22.8° C.	

1 mg./l.  $\approx$  148.8 p.p.m. and 1 p.p.m.  $\approx$  6.72 mg./cu.m. at 25° C., 760 mm.

**4. Physiological Response**

See Tables 8 and 9.

TABLE 8

*Physiological Response to Various Concentrations of Trichloronitromethane—Animals*<sup>16</sup>

Animal	Concentration		Duration of exposure	Response
	mg./l.	p.p.m.		
Dog	1.05	155	12 min.	Became ill
	0.8-0.95	117-140	30 min.	Death of 43% of the animals; survival of remainder
Mouse	0.85	125	15 min.	Death in 3 hr. to 1 day
Cat	0.51	76	25 min.	Death usually in 1 day
Mouse	0.34	50	15 min.	Death after 10 days
Dog	0.32	48	15 min.	Tolerated
Cat	0.32	48	20 min.	Death after 8-12 days
	0.26	38	21 min.	Survived 7 days
Mouse	0.17	25	15 min.	Tolerated

<sup>15</sup> *The Condensed Chemical Dictionary*. 3rd ed., Reinhold, New York, 1942.

<sup>16</sup> F. Flury and F. Zernik, *Schädliche Gase*. Springer, Berlin, 1931.

TABLE 9. *Physiological Response to Various Concentrations of Trichloronitromethane—Man*<sup>16,17</sup>

Concentration		Duration of exposure	Response
mg./l.	p.p.m.		
2.0	297.6	10 min.	Lethal concentration
0.8	119.0	30 min.	Lethal concentration
0.1	15.0	1 min.	Intolerable
0.050	7.5	10 min.	Intolerable
0.009	1.3	—	Lowest irritant concentration
0.0073	1.1	—	Odor detectable
0.002-0.025	0.3-3.7	3-30 sec.	Closing of eyelids according to individual sensitivity

### 5. *Odor and Warning Properties*

Pungent odor; violently irritating effect on eyes and mucous membranes.

## DIAZOMETHANE

### 1. *Source*

Made from nitroso methyl urethan.

### 2. *Uses and Industrial Exposures*

Methylating agent used in chemical synthesis.

### 3. *Pertinent Chemical and Physical Properties*

Formula:  $\text{CH}_2\text{N}_2$

Physical state: yellow gas

Molecular weight: 42.04

Freezing point:  $-145^\circ \text{C}$ .

Boiling point:  $-24^\circ \text{C}$ .

Density of gas: 1.45 (air = 1)

Decomposes in water

Soluble in ethyl alcohol and ether

1 mg./l.  $\approx$  581.5 p.p.m. and 1 p.p.m.  $\approx$  1.72 mg./cu.m. at  $25^\circ \text{C}$ ., 760 mm.

### 4. *Physiological Response*

*Acute effects.* Diazomethane produces severe irritation of the whole respiratory tract and of the central nervous system, indicating system absorption. In experimental animals following inhalation the lungs show hemorrhages and edema. In man there is marked irritation of the skin and of the mucous membranes, especially of the eyes. Dyspnea, chest discomfort, and bronchial catarrh are encountered. After more intense exposure, severe injury of the lungs may result with associated symptoms of dull pain in the ears, headache, weakness, and collapse. A 10-minute exposure of cats<sup>16</sup> to a concentration of 175 p.p.m. (0.3 mg. per liter) proved fatal within three days from hemorrhage and edema of the lungs.

### 5. *Odor and Warning Properties*

None in lower toxic range.

<sup>16</sup> A. M. Prentiss, *Chemicals in War*. McGraw-Hill, New York, 1937.

## ALIPHATIC AMINES

### I. General Considerations

*Action and properties.* The aliphatic amines are strongly alkaline in character and if they are inhaled they produce moderate to severe irritation of the upper respiratory tract and lungs. The toxicity increases with the length of the carbon chain. Of the isomeric amines the one possessing the longest carbon chain has the highest toxicity. The aliphatic diamines are more toxic than the monoamines.

There are no reports of occupational injury from the inhalation of the alkyl amines.

*Determination in the atmosphere.* The aliphatic amines may be determined by a procedure similar to the Kjeldahl method<sup>18</sup> or they may be estimated by a colorimetric procedure employing anhydrobisindandione (bindone).<sup>19</sup> This latter method can also be made to apply to nitro compounds after reduction with zinc and acetic acid.

### II. Specific Compounds

#### METHYLAMINE (Aminomethane)

##### 1. Uses and Industrial Exposures

Tanning; dyestuffs; liquid methylamine is an especially good solvent for many organic compounds; synthetic products; also used in the treatment of cellulose acetate rayon to improve its affinity for direct cotton dyes.

##### 2. Pertinent Chemical and Physical Properties

Formula:  $\text{CH}_3\text{NH}_2$

Physical state: inflammable gas

Molecular weight: 31.06

Specific gravity: 0.699 at  $-10.8^\circ/15^\circ \text{C.}$ <sup>18</sup>

Technical grade supplied as 30% solution in water

Freezing point:  $-92.5^\circ \text{C.}$

Boiling point:  $-6.0^\circ$  to  $-5.5^\circ \text{C.}$  (768 mm.)

Density of gas: 1.080 (air = 1)

Soluble in water, ethyl alcohol, and ether

Flash point (30% solution):  $32.5^\circ \text{F.}$ <sup>18</sup>

1 mg./l.  $\approx$  788 p.p.m. and 1 p.p.m.  $\approx$  1.271 mg./cu.m. at  $25^\circ \text{C.}$ , 760 mm.

##### 3. Odor

Strong, ammoniacal.

#### ETHYLAMINE (Aminoethane)

##### 1. Uses and Industrial Exposures

Preparation of dyestuff intermediates.

<sup>18</sup> A. W. Rawlston and C. W. Hoerr, *Ind. Eng. Chem., Anal. Ed.*, 16, 459 (1944).

<sup>19</sup> G. Vanags, *Z. anal. Chem.*, 126, 21 (1943).

**2. Pertinent Chemical and Physical Properties**

Formula: $\text{CH}_3\text{CH}_2\text{NH}_2$	Melting point: $-83.8^\circ \text{C}$ .
Physical state: gas at $25^\circ \text{C}$ ., supplied in commerce as 70% solution in water	Boiling point: $16.6^\circ \text{C}$ .
Molecular weight: 45.08	Density of gas: 1.55 (air = 1)
Specific gravity: 0.6892 at $15^\circ/15^\circ \text{C}$ .	Miscible with water, alcohol, and ether
	Flash point: below $0^\circ \text{F}$ . <sup>15</sup> (70% solution)
1 mg./l. $\approx$ 542 p.p.m. and 1 p.p.m. $\approx$ 1.843 mg./cu.m. at $25^\circ \text{C}$ ., 760 mm.	

**3. Odor and Warning Properties**

Odor of ammonia, burning taste.

**PROPYLAMINE (1-Aminopropane)****1. Pertinent Chemical and Physical Properties**

Formula: $\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2$	Vapor pressure: 397 mm. Hg at $32.2^\circ \text{C}$ . <sup>21</sup>
Physical state: colorless liquid	Refractive index: 1.39006 at $16.6^\circ \text{C}$ . <sup>20</sup>
Molecular weight: 59.11	Percentage in "saturated" air: 52 at $32.2^\circ \text{C}$ .
Specific gravity: 0.714	Density of "saturated" air: 1.54 (air = 1) at $32.2^\circ \text{C}$ .
Freezing point: $-83.0^\circ \text{C}$ .	Miscible with water, alcohol, and ether
Boiling point: $47.8^\circ \text{C}$ .	Flash point: less than $20^\circ \text{F}$ . <sup>15</sup>
Density of vapor: 2.04 (air = 1)	
1 mg./l. $\approx$ 413 p.p.m. and 1 p.p.m. $\approx$ 2.418 mg./cu.m. at $25^\circ \text{C}$ ., 760 mm.	

**n-BUTYLAMINE (1-Aminobutane)****1. Uses and Industrial Exposures**

Pharmaceuticals, dyestuff, rubber chemicals, emulsifying agents, desizing agents for textiles, butylated acid amides and other analogous nitrogen-containing organic compounds.

**2. Pertinent Chemical and Physical Properties**

Formula: $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$	Refractive index: 1.401 at $20^\circ \text{C}$ . <sup>20</sup>
Physical state: colorless liquid	Percentage in "saturated" air: 13.8 at $32.2^\circ \text{C}$ .
Molecular weight: 73.14	Density of "saturated" air: 1.21 (air = 1) at $32.2^\circ \text{C}$ .
Specific gravity: 0.7401 at $20^\circ \text{C}$ .	Miscible with water, alcohol, and ether
Melting point: $-50.5^\circ \text{C}$ . <sup>20</sup>	Flash point: less than $40^\circ \text{F}$ . <sup>15</sup>
Boiling point: $77.8^\circ \text{C}$ . (760.4 mm.)	
Vapor density: 2.5 (air = 1)	
Vapor pressure: 105 mm. Hg at $32.2^\circ \text{C}$ . <sup>21</sup>	
1 mg./l. $\approx$ 334 p.p.m. and 1 p.p.m. $\approx$ 3.00 mg./cu.m. at $25^\circ \text{C}$ ., 760 mm.	

**3. Odor**

Ammonia-like.

<sup>20</sup> *Handbook of Chemistry and Physics*. 28th ed., Chemical Rubber Publishing, Cleveland, 1944.

<sup>21</sup> M. J. Copley, E. Ginsberg, G. F. Zellhoefer, and C. S. Marvel, *J. Am. Chem. Soc.*, **63**, 254 (1941).



**sec-BUTYLAMINE (2-Aminobutane)****1. Pertinent Chemical and Physical Properties**

Formula: $\text{CH}_3\text{CHNH}_2\text{C}_2\text{H}_5$	Vapor pressure: 287.5 mm. Hg at 32.2° C. <sup>21</sup>
Physical state: colorless liquid	Refractive index: 1.39501 at 16.7° C. <sup>20</sup>
Molecular weight: 73.14	Percentage in "saturated" air: 38 at 32.2° C.
Specific gravity: 0.724 at 20°/4° C. <sup>20</sup>	Density of "saturated" air: 1.58 (air = 1) at 32.2° C.
Melting point: -104.5° C. <sup>20</sup>	Miscible with water, alcohol, and ether <sup>20</sup>
Boiling point: 62° to 69° C. <sup>18</sup>	Flash point: below 20° F. <sup>18</sup>
Vapor density: 2.5 (air = 1)	

1 mg./l.  $\approx$  334 p.p.m. and 1 p.p.m.  $\approx$  3.00 mg./cu.m. at 25° C., 760 mm.

**tert-BUTYLAMINE (Trimethylaminomethane)****1. Pertinent Chemical and Physical Properties**

Formula: $(\text{CH}_3)_3\text{CNH}_2$	Boiling point: 46.4° C. <sup>20</sup>
Physical state: colorless liquid	Vapor density: 2.5 (air = 1)
Molecular weight: 73.14	Refractive index: 1.37940 at 18° C. <sup>20</sup>
Specific gravity: 0.696 at 20°/4° C. <sup>20</sup>	Miscible with water, alcohol, and ether <sup>20</sup>
Melting point: -67.5° C. <sup>20</sup>	

1 mg./l.  $\approx$  334 p.p.m. and 1 p.p.m.  $\approx$  3.00 mg./cu.m. at 25° C., 760 mm.



## Nitro and Amino Compounds of the Aromatic Series

DONALD O. HAMBLIN, M.D.

### I. General Considerations

Nitro and amino derivatives of the aromatic series constitute a large and varied group of compounds of great commercial importance. These are widely used in the production of intermediates, preliminary to the synthesis of "coal tar" or "aniline dyes," pharmaceuticals, and of accelerators and antioxidants for the rubber industry. Likewise, several intermediates are classed as fur "dyes," although they actually are not dyestuffs because they have no tinctorial value in their unoxidized form. In addition, these compounds find more limited uses in the production of paints, varnishes, shoe polishes, perfumes, fungicides, plastics, and synthetic resins.

All of this series is, of course, characterized chemically by the substitution of the amino ( $\text{NH}_2$ ) radical or of a nitro ( $\text{NO}_2$ ) radical for a hydrogen atom in the benzene ring or in one of its homologs. The naphthalene and anthracene rings may be regarded chemically as analogs of benzene. The nitro or amino radicals may be substituted in these rings almost at will in any position in the ring, along with the halogens (most frequently chlorine) and certain of the alkyl radicals, chiefly the methyl and ethyl groups ( $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ). There is possible, therefore, an almost endless permutation and combination of substitution products.

These compounds are, for the most part, similar in chemical properties and, likewise, in pharmacological or toxicological effects. These effects are, of course, modified to a greater or lesser degree by the substituted radicals. The entire series, therefore, lends itself well to a discussion of characteristic toxic properties common to most of them. It should be emphasized that the nitro and amino derivatives of benzene and its homologs and analogs differ quite markedly toxicologically from their parent compounds (i.e., benzene, toluene, xylene, naphthalene, etc.).

#### A. MODES OF ABSORPTION

The simplest of these series of compounds and those that are most typical toxicologically are aniline and mononitrobenzene (oil of mirbane). From these

basic compounds and their homologs stem long and interesting series. It was pointed out above that the substitution of various radicals and atoms in the ring modifies the toxic properties in varying degrees. It should be borne in mind, in addition, that the physical properties of these compounds markedly influence the magnitude of hazard to the exposed worker. The vapor pressure or volatility of a given compound in particular determines to what extent there is a hazard by absorption through the respiratory tract. Similarly, the fat-solvent properties of a compound largely determine its hazard as to absorption through the skin. In general, those compounds that are soluble in the common organic solvents, such as alcohol, ether, chloroform, and so forth, are fat-soluble or fat-solvent and insoluble in water. Such compounds penetrate the intact skin readily. Conversely, compounds that are water-soluble and insoluble in organic solvents usually do not penetrate the skin appreciably.

Therefore, compound A, with a high vapor-pressure curve and highly fat-soluble, may be much more of a hazard to exposed workmen than compound B, even though B, if administered directly by the oral route or parenterally, is of a much higher order of systemic toxicity.

#### B. TOXICOLOGY

The toxicology of some of these compounds is fairly well understood. About others, we are still more or less ignorant. The manufacture of these compounds in this country for the most part dates back only to World War I, when our supply from Germany was abruptly cut off. For a good many years, therefore, our knowledge of the toxicology of these compounds was based upon Old World literature. However, as time has elapsed and our experience with them has increased, ample opportunity has been afforded for intelligent observations in this country. It has become increasingly evident that the earlier literature is in many instances inaccurate, incomplete, and often misleading. Quite understandably, many of the early American writers in this field leaned heavily upon this early literature, so that these erroneous observations and conclusions have frequently been perpetuated even by present-day writers.

The absorption of either aniline or nitrobenzene (MNB), which characterize these series, results primarily in the formation of methemoglobin as the outstanding pharmacological effect. Of the two, nitrobenzene is said to be on the order of fifty times as toxic as aniline. Both of these intermediates are fat solvents and fat-soluble, so they readily penetrate the intact skin. Their vapors are, of course, readily absorbed through the respiratory tract. The vapor-pressure curve of nitrobenzene is appreciably higher than that of aniline and this increased volatility undoubtedly contributes to its reputedly higher toxicity than that of aniline in this type of exposure: probably much in the way that benzene is more hazardous in industrial operating conditions than is toluene.

Methemoglobinemia is insidious in its onset. Before hygienic regulations were enforced strictly, it was not uncommon for workmen to be sent to the

Medical Department because their foreman or a fellow worker had observed that their lips were blue. These patients were completely unaware of their condition, usually felt very well, and would complain vigorously that there was nothing wrong with them. It would be very startling to them when they were asked to look into a mirror. Frequently such individuals would deny exposure of any consequence to either aniline or nitrobenzene, but further examination or questioning would disclose that they had picked up a leather or cotton glove contaminated with aniline, or that "they had got a little on their leather shoes" during the course of the day without being aware of it.

Most textbooks, even some of the more recent ones, have perpetuated a picture of aniline and nitrobenzene poisoning that has not been borne out by clinical observations in this country. We quote from one of these texts (Hamilton<sup>1</sup>):

"In a light case of poisoning with a nitro or amino compound, the symptoms are at first those of anoxemia because, so it is generally believed, the formation of methemoglobin brings about a condition of internal asphyxia. The symptoms are typical of the latter—a flushed face, pressure in the head, which increases to a violent throbbing headache, with dizziness, weakness in the knees, and more or less dyspnea. In severe cases, the face is deeply cyanosed, the lips, tongue and ears are purple; there is nausea, sometimes vomiting, a complaint of cramps in the abdomen, a staggering gait, and extreme weakness."

In our experience and in that of other observers,<sup>2-4</sup> the onset of methemoglobinemia is either symptomless or accompanied by an euphoria. Certainly, nearly all of our patients, even though they appeared markedly cyanotic, for the first hour or so insisted that they felt unusually well. This is perhaps not surprising, since it is a rather typical effect of acetanilide to which these aromatic compounds are pharmacologically similar. Methemoglobin, as contrasted with hemoglobin or oxyhemoglobin, presumably holds oxygen so tightly bound that it is not available to tissue. Therefore, as methemoglobinemia increases in concentration, tissue anoxia is to be expected. Darling and Roughton<sup>5</sup> and others believe that:

"some further action besides the lowering of the O<sub>2</sub> carrying power of the blood is . . . indicated. In the case of methemoglobinemia, this has been thought to be due entirely to the direct effect of the methemoglobin producing agent on the tissues, e.g., vaso-dilatation in the case of nitrites."

They further state:

"Although 20 to 30 per cent methemoglobin should be tolerated well by normal individuals, just as is 20 to 30 per cent CO-hemoglobin, more than that would be likely to lead to

<sup>1</sup> A. Hamilton, *Industrial Toxicology*. Harper, New York, 1934, p. 170.

<sup>2</sup> E. E. Evans, Medical Superintendent, Dyeworks, E. I. du Pont de Nemours & Co., Deepwater Point, N. J., *personal communication*.

<sup>3</sup> J. Foulger, Director of Haskell Laboratory, E. I. du Pont de Nemours & Co., Wilmington, Del., *personal communication*.

<sup>4</sup> A. F. Mangelsdorff, Chief Physician, Calco Chemical Division of American Cyanamid Co., Bound Brook, N. J., *personal communication*.

<sup>5</sup> R. C. Darling and F. J. Roughton, *J. Physiol.*, 187, 56 (1942).

serious tissue anoxemia quite independently of any direct toxic action of the methemoglobin producing agent on the tissues."

While this may hold for the effect of sodium nitrite, in our experience, as will be brought out later, the average individual tolerates concentrations of methemoglobin higher than 30 per cent when the causative agent is aniline or another compound of this series. It is true that as methemoglobinemia increases in intensity severe headaches may develop. These are transiently relieved by the inhalation of oxygen or oxygen-carbon dioxide mixtures. Such inhalations, however, appear to have no appreciable influence on decreasing the methemoglobin content of the blood. In our experience, such patients have not felt sick or even experienced severe headaches until their methemoglobin content has approached 40 per cent of the available hemoglobin. Within rather widely variable limits, however, cyanosis is usually grossly recognizable when the methemoglobin concentration reaches from 10 to 15 per cent. We have never observed nausea or abdominal cramps or any other gastrointestinal signs or symptoms so frequently described in the older literature, even with a methemoglobinemia exceeding 70 per cent. As methemoglobin increases in concentration to above 50 per cent, there are increasing complaints of headaches and some rise in pulse rate, and finally, elevations in respiratory rate. Except for this violent headache and a sense of weakness, in a large series of cases little else in the way of symptoms has been observed.

The older literature likewise has perpetuated<sup>6</sup> some observations with regard to blood changes that we have not been able to confirm. One of these changes frequently reported is that early spectroscopic examination of the blood will reveal methemoglobin absorption bands, but as cyanosis deepens these bands can no longer be demonstrated. Hamilton<sup>1</sup> writes as follows:

Curschmann, Lehmann,<sup>7</sup> and Mohr<sup>8</sup> say that methemoglobin is formed early in the course of intoxication and probably the destruction of red blood cells is coincident with it. The red-blood-cell count and the hemoglobin fall, the blood becomes chocolate-colored and thicker, and the spectroscope shows the lines of methemoglobin. However, the latter finding is disputed by some (see Price-Jones and Boycott<sup>9</sup>) and even Curschmann says that methemoglobin disappears very rapidly and usually by the time cyanosis is fully developed it can no longer be demonstrated.

It has been demonstrated to our satisfaction in a long series, however, that quite to the contrary, and as would be expected, the severity of the clinical picture remains throughout directly proportionate to the concentration of methemoglobin present.<sup>10</sup> In other words, we have consistently found that as methemoglobinemia increases the patient becomes sicker; as it decreases, he is better.

<sup>6</sup>R. T. Johnstone, *Occupational Diseases*. Saunders, Philadelphia, 1941, p. 142.

<sup>7</sup>K. B. Lehmann, *Kurzes Lehrbuch der Arbeits- und Gewerbehygiene*. Leipzig, 1919.

<sup>8</sup>L. Mohr, *Deut. med. Wochschr.*, 28, 73 (1902).

<sup>9</sup>Price-Jones and Boycott, *Guy's Hosp. Repts.*, 63, 309 (1901).

<sup>10</sup>D. O. Hamblin and A. F. Mangelsdorff, *J. Ind. Hyg. Toxicol.*, 20, 523 (1938).

These observations have been made with the assistance of a highly accurate and sensitive spectrophotometer, the Pinceo Recording Electrospectrophotometer. When this delicate and costly instrument is not available, other instruments, such as the Evelyn Photoelectric Colorimeter, will yield sufficiently accurate results to be of great value in methemoglobin determinations. This method of methemoglobin determination was described by Evelyn and Malloy.<sup>11</sup>

Contrary to statements in the early literature, we find evidence that the methemoglobin to hemoglobin phase is a readily reversible reaction. Providing the patient has no further sources of absorption of the offending compound, i.e., nitrobenzene or aniline, as a rule reversion from methemoglobin to hemoglobin is complete within 24 to 48 hours.

The literature on this subject states that<sup>12</sup> "sulfhemoglobinemia is also frequently observed in aniline poisoning." However, with the very accurate Pinceo Recording Spectrophotometer we have never obtained curves that suggest any alteration in the hemoglobin except methemoglobin. Likewise, in our series we have never found any evidence that hemolysis plays a prominent role in poisoning from this group of compounds. We frequently have observed an initial rise in red-blood-cell count, for example, from 4,500,000 to 5,500,000 in the first two or three hours, possibly due to a mobilization in response to anoxic stimuli. There is also a definite increase in hemoglobin. Frequently a rise from 90 to 120 per cent has been observed. However, we have had previous blood counts and hemoglobin recordings as a basis of comparison in nearly every instance, and we have found these values to return to approximately the previously established level within 24 hours. Also, we have not been able to demonstrate urobilin or urobilinogen in the urine during acute phases of poisoning or thereafter. The urine does become darker, but it would appear to be a reasonable assumption that this change is due to the presence of *p*-aminophenol, which darkens rapidly as it oxidizes and which can be demonstrated to be present in the urine of patients suffering from poisoning from aniline and mononitrobenzene.

Much of the confusion with regard to "aniline poisoning" apparently arose primarily from two causes. First, the spectroscopy of methemoglobin reported by many earlier observers was unquestionably inaccurate in many instances. Second, different species of experimental animals exhibit wide differences in their resistance to methemoglobin formation. For example, it has been clearly demonstrated that the herbivores, such as guinea pigs and rabbits, are exceedingly resistant to methemoglobin formation, and apparently metabolize aniline and kindred compounds entirely differently from carnivores. Lester<sup>13</sup> has demonstrated that the rabbit and monkey form virtually no methemoglobin with acetanilide. In order of sensitivity to methemoglobin formation he found that

<sup>11</sup> K. A. Evelyn and H. T. Malloy, *J. Biol. Chem.*, **126**, 655 (1938).

<sup>12</sup> W. F. von Oettingen, "The Aromatic Amino and Nitro Compounds, Their Toxicity and Potential Dangers," *U.S. Pub. Health Bull.* No. 271 (1941).

<sup>13</sup> D. Lester, *J. Pharmacol.*, **77**, 154 (1943).

man is slightly more than half as sensitive as the cat, the dog is half as sensitive as man, and the sensitivity of the rat is one sixth that of the dog. Heubner<sup>14</sup> earlier had reported his inability to form methemoglobin in herbivores. Yet with all this being true, many observations on the pharmacology of this group were based on work with the guinea pig.<sup>15</sup> Quite inexplicably, a group of workers in the University of Michigan Laboratories reported<sup>16</sup> that the administration of aniline caused no methemoglobin to be formed in the dog and rabbits, but reported instead a wide range of cardiac arrhythmias which they demonstrated by electrocardiographic tracings. It is little wonder that there has been considerable confusion in comprehending the changes that take place in man when poisoned by a compound of the aromatic nitro and amino series.

Some accurate and helpful observations were made, however, by some of the earlier German workers in this field, particularly as to the chemistry of the metabolism (catabolism) of these compounds. Heubner<sup>14</sup> reported that aniline by oxidation and nitrobenzene by reduction were within the body converted to *p*-aminophenol. It was also suggested that an intermediate and highly reactive compound, phenylhydroxylamine, was part of this reaction. This appears consistent with more recent observations. Clark *et al.*<sup>17</sup> postulate that this conversion to *p*-aminophenol accounts for the lag in the clinical appearance of methemoglobinemia following the absorption of aniline et cetera. Likewise, methemoglobinemia from the administration of *p*-aminophenol is much more transient: the reversion of methemoglobin to hemoglobin occurs much more rapidly than with aniline. So, while *p*-aminophenol is itself a powerful methemoglobin former, the conversion of aniline to this compound in the body is actually a detoxification, because of the speed with which reversion to hemoglobin occurs. *p*-Aminophenol conjugated with the sulfate radical is easily demonstrable in the urine of man following absorption of aniline and nitrobenzene. This, perhaps, explains the cycle whereby most severe poisonings with these compounds have completely cleared within 24 hours.

Clark *et al.*<sup>18</sup> have made further valuable contributions to the understanding of aniline poisoning through their studies of the oxygen tension of arterial blood. In view of the marked decrease of available hemoglobin and the resultant tissue anoxia, it has been difficult to understand why there were not more marked compensatory accelerations of the pulse and respiratory rates and changes in blood pressure. He suggests that, while there is a marked deficiency of available oxygen in venous blood, the equilibrium previously mentioned with the methemoglobin-forming agent and the hemoglobin-methemoglobin system does not sufficiently disturb the oxygen tension of arterial blood to set in motion compensatory re-

<sup>14</sup> W. Heubner, *Arch. exptl. Path. Pharmacol.*, 72, 240 (1913).

<sup>15</sup> H. F. Smyth, *J. Ind. Hyg.*, 13, 87 (1931).

<sup>16</sup> A. G. Young, C. W. Muehlberger, and W. J. Meek, *J. Pharmacol.*, 27, 101 (1926).

<sup>17</sup> B. B. Clark, E. J. Van Loon, and R. W. Morrissey, *J. Ind. Hyg. Toxicol.*, 25, 1 (1943).

<sup>18</sup> B. B. Clark, E. J. Van Loon, and W. L. Adams. *Am. J. Physiol.*, 139, 64 (1943).



sponses in the circulatory-respiratory centers. This would appear to indicate that the unconverted hemoglobin continues to function quite undisturbed as an oxygen carrier.

### C. TREATMENT

The treatment of acute aniline and nitrobenzene poisoning is satisfactory and simple. It consists mainly in keeping the patient at rest and warm in a comfortable bed, and having good ventilation. It is essential that every possible source of further absorption be eliminated completely. The entire body, including the hair and fingernails, should be thoroughly cleansed with soap and water. If any odor of aniline or nitrobenzene persists, this process should be repeated until the odor has completely disappeared. If other nitro-amino compounds in solid form constitute the exposure, such as dinitrobenzene or *p*-toluidine, the nasal passage should be repeatedly irrigated with normal saline solution in order to remove all possible traces. The old treatment, which was common during and for some time after World War I, was to walk the patient for long periods and to ply him with large quantities of milk. To walk a patient already suffering from anoxemia of a severe type is, of course, not very good therapy. However, even in former days, very few individuals died from such poisoning, although they had absorbed relatively large quantities. Death may ensue, however, and there is no question but that these patients are critically ill when the methemoglobin rises above 60 per cent, even individuals who had previously been in good health. Obviously, individuals who are suffering from anemia or cardiovascular or pulmonary pathology, which make for a lowered vital capacity, are greatly handicapped in overcoming such poisoning and, for this reason, should never be employed where such exposures are possible. It was suggested by Brooks<sup>19</sup> in 1935 in connection with her work on cyanide antidotes that intravenous glucose seemed to hasten the reversion of methemoglobin to hemoglobin. This appears to have been borne out in our experience and we have routinely administered 1000 or more milliliters of 5 per cent glucose solution intravenously to all individuals who have exhibited 40 per cent or more methemoglobin in their blood stream. Obviously, it is virtually impossible to establish satisfactory controls in such a series, but we do believe that the glucose appears to hasten recovery.

A few years ago, it was subsequently suggested by Wendel<sup>20</sup> that methylene blue, likewise, was of great value in bringing about the reversion of methemoglobin to hemoglobin. Since methylene blue is, in itself, a methemoglobin former, the rationale of its use in combating methemoglobinemia has remained rather obscure. This apparently contradictory form of therapy was explained as being pharmacologically justifiable on the basis that the dye reacts directly with hemoglobin to form methemoglobin and the reduced (leuco) form of methylene

<sup>19</sup> M. M. Brooks, *Am. J. Physiol.*, 114, 160 (1935).

<sup>20</sup> W. B. Wendel, *J. Clin. Investigation*, 18, 179 (1939).

blue formed by the reaction reacts with oxygen to regenerate methylene blue. Wendel states further that it is not equally clear how methylene blue accomplishes reduction of methemoglobin to hemoglobin. We quote:

"Since each molecule of dye injected effects conversion of many molecules of methemoglobin to hemoglobin, this reaction, too, is catalytic. Here, however, the catalysis is one of reduction, and leuco methylene blue would appear to be the effective reductant. Two possible sources of the leuco methylene blue in the body are reduction of methylene blue in the erythrocytes by enzyme systems present there and reduction of methylene blue in other tissues. Preliminary experiments suggest that the rate of formation of leuco methylene blue in the erythrocytes may not be sufficiently rapid to account for all the methemoglobin reduced. Thus, it would appear that leuco methylene blue formed in the more actively metabolizing tissues and returned as such to the erythrocytes may play a role in reducing methemoglobin to hemoglobin. Experiments designed to test this possibility are in progress."

Brooks<sup>21</sup> may have shed some light on this mechanism through her observation that the presence of glucose in the blood stream inhibits the formation of methemoglobin in experimental animals. She suggests, in other words, that variations in the glucose content may account for the wide species difference in resistance to the formation of methemoglobin. It also prompted her to suggest that the introduction intravenously of large amounts of glucose should be worth considering as a means of combating methemoglobinemia in man. From clinical observations only, we believe that her assumption may be justified. As we have stated previously, however, since it is impossible to establish satisfactory clinical controls in humans, this must remain as an assumption. Cox and Wendel,<sup>22</sup> on the other hand, in their work with dogs, have apparently demonstrated that glucose has no influence on the rate of reversion of methemoglobin to hemoglobin.

Crisler,<sup>23</sup> in 1935, working with pups and rats, concluded from his experiments that he "felt forced to join the ranks of those who deem methylene blue contraindicated in cases of carbon monoxide poisoning or any other condition in which the margin of safety of hemoglobin concentration has already been encroached upon."

Since then a few case reports have appeared in the literature, one of which we cite later, in which recovery from severe poisoning by one of the nitro-amino series has followed the administration of 1 per cent methylene blue intravenously. However, whether such recoveries occurred in spite of or because of such therapy is not clear. Certainly its use has not been widely adopted in industries which have had extensive experience with this type of poisoning.

However, in view of the recent work, carried out for the Chemical Warfare Service in connection with cyanide antidotes, by Gutman and Bodansky,<sup>24</sup> which completely confirms the observation of Wendel as to methylene blue, we may have to revise our thinking along these lines. They found that methemoglobi-

<sup>21</sup> M. M. Brooks, *Proc. Soc. Exptl. Biol. Med.*, **32**, 63 (1934).

<sup>22</sup> W. W. Cox and W. B. Wendel, *J. Biol. Chem.*, **143**, 331 (1942).

<sup>23</sup> George Crisler, *Am. J. Physiol.*, **110**, 580 (1935).

<sup>24</sup> H. Gutman and O. Bodansky, *personal communication*, 1946.

nemia of 50 per cent could be induced in dogs by the intravenous administration of 2.5 mg. per kilogram of body weight of *p*-aminopropiophenone (dissolved in propylene glycol). The peak of 50 per cent was reached in about 1 hour after injection and was reduced spontaneously to half this value in about 200 minutes. However, when 1 mg. per kilogram of body weight of methylene blue was injected at the time of the peak concentration, the decrease to half the peak value occurred in 30 to 40 minutes; the reversion was increased in rapidity five to six times by methylene blue.

Through personal communications,<sup>25</sup> we have learned of two or three cases in which it has been used with rather alarming results. At least the introduction of methylene blue into the venous blood is reported to have been very frightening since an already intense cyanosis was appreciably deepened immediately. The tinctorial value of this solution of a blue dye may possibly have added significantly to the cyanotic appearance. One of the case reports,<sup>26</sup> in which a severe methemoglobinemia following nitrobenzene poisoning was "promptly cured by the administration of methylene blue," states that methylene blue, however, was administered intravenously either with or followed by 600 ml. of 18 per cent glucose. In the conclusions, no consideration of the glucose administered is made and the recovery is attributed entirely to methylene blue.

Anoxic headaches are relieved transiently by oxygen inhalation. Apparently the residual available hemoglobin and the plasma carry sufficient oxygen to afford relief. It has been our custom to leave patients in an oxygen tent for a period of hours because they feel better, rather than because we have any evidence that the reversion of methemoglobin to hemoglobin is hastened thereby. Codeine is useful in the relief of headaches providing it is not pushed to the point that depresses respiration. We believe that acetanilide and this general group of analgesics are contraindicated because of their tendency to form methemoglobin. Alcohol in any form is absolutely contraindicated because of its marked synergistic effect in the presence of the methemoglobin formers. Alcohol, even to the extent of a glass of beer, will precipitate a dormant case into a clinical case of aniline poisoning. There is some evidence that, because of their fat-solvent characteristics, these compounds are stored to some extent in the body by lipid deposits. It is possible that alcohol serves to liberate these stores. At any rate, steady drinkers or heavy drinkers do not get along well when exposed to aniline and nitrobenzene and to similar compounds of this series.

The best guide to the progress of the patient is the quantitative determination of methemoglobin in samples of venous blood, which should be taken hourly or even more often if the patient's condition appears critical. It has been our experience that the rise and fall of methemoglobin is of much greater prognostic value than trying to estimate the degree of cyanosis from the patient's appearance. It is with great relief that we find a steadily falling curve of methemoglobin con-

<sup>25</sup> E. E. Evans, *personal communication*.

<sup>26</sup> J. R. Williams and F. E. Challis, *J. Lab. Clin. Med.*, 19, 166 (1933).

centrations in a critically ill patient. On the other hand, if after six to eight hours methemoglobin concentrations do not fall, one can be pretty certain that, from some source, the patient is absorbing further quantities of the offending compound. We have had several cases in which, through splashes involving large portions of the entire body, or through careless operating supervision, the methemoglobin has reached as high as 76 per cent. Although these cases have given us some anxious moments, all of them have recovered within 24 to 48 hours, virtually completely and uneventfully, following the simple measures of treatment just described.

Chronic aniline poisoning is probably nonexistent: cases reported as such represent, rather, recurrent subacute poisoning.

#### D. EQUILIBRIUM IN METHEMOGLOBIN

The concentration of methemoglobin, in our observation over a period of years, regardless of the intensity of the exposure and the amount of aniline absorbed, has never exceeded 76 per cent. Interestingly enough, Lester *et al.*<sup>27</sup> and Clark, Van Loon, and Morrissey,<sup>17</sup> working with experimental animals, have likewise been unable to obtain higher concentrations of methemoglobin than 75 per cent. Lester *et al.* worked with acetanilide, *p*-aminophenol,  $\beta$ -phenylhydroxylamine, and aniline chloride administered to rats. They found that a maximum methemoglobin level was obtained with each of these compounds, which could not be further increased by the administration of additional amounts of these methemoglobin formers. Since the maximum formation of methemoglobin occurred with one seventh of the lethal dose of  $\beta$ -phenylhydroxylamine and with half of that of *p*-aminophenol, it was concluded:

"The formation of methemoglobin plays no important part in the acute toxicity of  $\beta$ -phenylhydroxylamine and *p*-aminophenol. Indications are given that this fact applies also to aniline and acetanilide."

On the other hand, Clark *et al.*, following administration of aniline to dogs, concluded:

"The effects of acute aniline intoxication in the dog are reported. The most important action is the production of methemoglobinemia and thus indirectly the effects of oxygen deficiency on the various physiological systems."

They further state:

"Very large doses cause circulatory depression and cardiac arrhythmias."

In our experience with humans poisoned with aniline and nitrobenzene, the results and conclusions of Clark *et al.* appear to be borne out much more clearly than do the conclusions that Lester *et al.* draw from the administration of *p*-aminophenol and  $\beta$ -phenylhydroxylamine to rats. This discrepancy may, of course, be due to the species' differences in susceptibility or to the fact that the compounds employed, while similar to and possibly metabolites of aniline, are not aniline.

<sup>27</sup> D. Lester, L. A. Greenberg, and E. Shukovsky, *J. Pharmacol.*, 80, 78 (1944).

At any rate, the failure to obtain levels of methemoglobin higher than 75 per cent is explained by Heubner.<sup>28</sup> He states that an equilibrium between the oxidation reduction potentials of the *p*-aminophenol system and the methemoglobin system is reached. Clinically, this equilibrium is of the greatest importance since it accounts for the fact that methemoglobinemia apparently seldom reaches a concentration sufficient to kill by anoxia.

Gutman and Bodansky,<sup>24</sup> from their recent work not yet published, cast some doubt about the attainment of such an equilibrium at 76 per cent, at least in the case of *p*-aminopropiophenone. They have been able, by the intravenous administration of this compound to dogs, to obtain blood levels of 90 to 95 per cent methemoglobin with death ensuing from anoxia.

As has been stated previously, modification of the benzene and naphthalene rings by the substitution of various elements and radicals may appreciably alter the toxicological characteristics so that methemoglobin-forming properties are either reduced or increased.

#### E. VARIATIONS IN TOXICOLOGICAL EFFECTS

*Dinitrobenzene*, for example, even though it is a solid, is a methemoglobin former par excellence. While it has a comparatively low vapor pressure, it appears to be much more toxic than aniline and nitrobenzene. Comparable exposure to or absorption of this compound results in a more intense methemoglobinemia, which is much less readily reversible than that from an equivalent exposure to its parent compound, nitrobenzene. This is perhaps explained as suggested by Lipschitz<sup>29</sup> that, *in vitro*, blood may reduce dinitrobenzene to nitrosophenylhydroxylamine, with the further assumption that the body is unable to break down this compound further than nitroaniline, which, in itself, is highly toxic in addition to causing a more persistent methemoglobinemia than dinitrobenzene and may, following prolonged exposures, result in a toxic hepatitis which may occasionally progress into acute yellow atrophy.

*Dinitrochlorobenzene* has the outstanding characteristic of being an almost universal skin sensitizer. Repeated and minute contacts with this compound may produce anything from a few itching papular vesicles to a generalized exfoliative dermatitis.<sup>30</sup> As a hazard in its production, methemoglobinemia seems to be of little importance. In producing many tons of this compound, we recall no instances in which it has given rise to clinical cyanosis.

*Dinitrophenol* is rather aberrant in its behavior. This derivative is not important as a methemoglobin former, but profoundly affects metabolism. Absorption of this compound in toxic quantities leads to a marked elevation of the basal metabolic rate and rises in temperature to as high as 110° F., with perhaps

<sup>28</sup> W. H. Heubner and G. Schwedtko, *Arch. exptl. Path. Pharmacol.*, 184, 80 (1936).

<sup>29</sup> W. Lipschitz, *Z. physiol. Chem.*, 109, 189 (1920).

<sup>30</sup> K. Landsteiner, A. Rostenberg, and M. S. Sulzberger, *J. Investigative Dermatol.*, 2, 25 (1939).

additional nervous system effects. Likewise, liver damage and kidney damage have been reported, as well as destructive changes in the thyroid.<sup>31-35</sup> It will be recalled that, in 1933, 1,2,4-dinitrophenol<sup>36</sup> was advocated in this country as an agent for the easy treatment of obesity. It will be recalled how disastrously toxic this compound proved to be in many cases, not only in severe acute poisonings and deaths, but in a most unfortunate delayed effect, the formation of cataracts of the lens.<sup>37,38</sup>

*Aniline hydrochloride*, a simple addition product of aniline, ceases to be a hazard of significance commercially. It is a white, crystalline solid with a very low vapor pressure, which apparently is not readily absorbed through the intact skin, and which can be handled with impunity. It is, of course, toxic if administered either orally or parenterally and its effects are very similar to those of aniline. Precautions should be taken to prevent inhalation of its dusts.

*The addition products of this series*, usually the hydrochloride or the sulfate, like aniline hydrochloride, with few if any exceptions, behave similarly.

*m-Toluylenediamine and m-phenylenediamine*, reduction products of the highly toxic compounds, dinitrotoluene and dinitrobenzene, cease to be of any practical importance as industrial hazards since they are, when pure, colorless crystalline water-soluble compounds, which are not fat-soluble. Both compounds exhibit very low vapor pressures. Industrially, they have never, in so far as we are aware, given rise to methemoglobinemia nor to any other toxic effects more troublesome than a deep staining of the skin. However, when administered either orally or parenterally, both compounds are reported to be highly toxic.<sup>39</sup> In repeated small doses, it was found that toluylenediamine can be used to produce jaundice at will. The mechanism by which such damage is produced is summarized by Greene and Schaal,<sup>40</sup> who offer the following three explanations: (a) that the toluylenediamine icterus is caused by damage to the epithelium of the larger biliary ducts, resulting in passage of the bile into the lymph spaces, the thoracic duct, and the blood; (b) that it may be of hemolytic and hyperfunctional origin as indicated by the greater activity of Kupffer's cells; and (c) that biliary thrombi may be formed, blocking the central biliary ducts, causing a static icterus.

*p-Phenylenediamine* (known as Ursol in the fur-dyeing industry) also is

<sup>31</sup> H. Magne, A. Mayer, and L. Plantefol, *Ann. physiol. physicochim. biol.*, 7, 269 (1931).

<sup>32</sup> N. Alwall and G. Mansfeld, *Arch. expl. Path. Pharmacol.*, 135, 93 (1937).

<sup>33</sup> L. Lutz and G. Baume, *Compt. rend. soc. biol.*, 80, 483 (1917).

<sup>34</sup> M. L. Tainter, W. C. Cutting, Wood and Proescher, *Arch. Path.*, 18, 881 (1934).

<sup>35</sup> I. Peissakowitsch and P. Kostenko, *Arch. Gewerbepath. Gewerbehyg.*, 6, 160 (1935).

<sup>36</sup> M. L. Tainter, A. B. Stockton, and W. C. Cutting, *J. Am. Med. Assoc.*, 101, 1472 (1933).

<sup>37</sup> Warren D. Horner, R. B. Jones, and W. W. Boardman, *J. Am. Med. Assoc.*, 105, 108 (1935).

<sup>38</sup> W. W. Boardman, *J. Am. Med. Assoc.*, 105, 108 (1935).

<sup>39</sup> W. Gibbs and E. T. Reichert, *Arch. Anat. Physiol., Suppl.* 259, (1892); *Am. Chem. J.*, 16, 443 (1894).

<sup>40</sup> H. H. Greene and W. Schaal, *Beitr. path. Anat.*, 89, 61 (1932).

water-soluble and not appreciably soluble in fats, and is of little importance as a toxic hazard in industry. When pure, it is a colorless crystalline compound, but, when exposed to air and moisture, it is oxidized rather rapidly and progresses to red, brown, and finally black. It is widely employed in the dyeing of furs when a deep black is desired. Its oxidation may also be arrested at the brown or reddish stages, but such an arrest of oxidation is difficult to control. This compound, which is really an intermediate and not a dyestuff, has done more to bring "aniline dyes" as a whole into unmerited opprobrium than any other compound. In its intermediate stages of oxidation it frequently is a skin sensitizer and may produce contact dermatitis of varying intensities. Thus, carelessly dyed furs, which have not been completely oxidized and after-treated, have been the causes of litigation because of dermatoses of varying severity in sensitized wearers of furs. It is stated by Mayer<sup>41</sup> and others that the oxidation product which is the offender is quinonediimine. In addition, *p*-phenylenediamine has, in industrial exposures, caused a true allergenic bronchial asthma.<sup>42</sup> Systemic poisoning from industrial exposures to this compound is unknown, although it is reported as being highly toxic when administered orally or parenterally to experimental animals.

*p*-Aminophenol is very similar in its properties to *p*-phenylenediamine, both chemically and pharmacologically. It also finds considerable use as a fur dye, chiefly in obtaining varying shades of brown. It, likewise, may cause contact dermatitis in its various stages of oxidation and has also been reported as causing bronchial asthma.

TNT (*trinitrotoluene*), many millions of tons of which were produced during World Wars I and II—with the resultant exposure of many thousands of workers—is a highly toxic compound, but one which, like all others of the aromatic series, may be produced without injury to the exposed individuals if rigid hygienic measures are enforced. That it is perfectly feasible to manufacture TNT without harmful effects is illustrated by reports of Cone<sup>43</sup> and by reports of plant physicians whom I visited personally during the recent war. Because of poor hygiene, however, serious poisoning and fatalities unfortunately have occasionally occurred. These fatalities may, in some degree, be due to "idiosyncrasies," since exposures equal in duration and severity bring about wide variations in clinical responses. McConnell and Flinn<sup>44</sup> report for the United States Ordnance Department that, in the period of three and a half years during the past war, 22 fatalities occurred, which, however, is at a rate of only 3 fatalities per 100,000 operating employees, a record which speaks rather well for the program of hygiene enforced. In a series of 22 fatal cases, these writers report that 8 died of toxic hepatitis, 13 of aplastic anemia, and 1, who recovered partially from hepatitis,

<sup>41</sup> R. L. Mayer, *Arch. Dermatol. Syphilis*, 156, 331 (1928).

<sup>42</sup> H. Reichel, *Samml. Vergiftungsfällen*, 5, A21 (1934).

<sup>43</sup> T. E. Cone, Jr., *J. Ind. Hyg. Toxicol.*, 26, 260 (1944).

<sup>44</sup> W. J. McConnell and R. H. Flinn, *J. Ind. Hyg. Toxicol.*, 28, 76 (1946).

died from aplastic anemia or a combination of anemia and hepatitis. The number of cases of toxic jaundice and aplastic anemia who did not die is not known, but very few cases of aplastic anemia recovered from such poisoning. Hepatitis was observed to occur more frequently among the younger age group, the average age being thirty years; and aplastic anemia more frequently among the older age group, the average age being forty-five years. These writers report that, unfortunately, the early symptoms of poisoning are indefinite and not sufficiently marked to cause patients to report for medical aid until their condition has become advanced. Most of the employee groups were examined at from one- to two-month intervals during exposure. It is reported that the most significant findings in the laboratory were the elevation of the icterus index, a decrease in hemoglobin, or a low hematocrit. It is obvious, however, that by the time a significant elevation of icterus index has occurred liver damage of some severity has already occurred, which makes this a rather unsatisfactory test. In the Lake Ontario Ordnance Works we found that a prothrombin time (modified Quick Test) showed some promise of giving earlier indications of disturbed liver functions and believe that this is well worth trying. Sievers *et al.*,<sup>45</sup> in a case study of TNT workers in a bomb and shell loading plant, report no cases of severe TNT intoxication, but state that cyanosis was observed among 68 per cent of the men and 36 per cent of the women. They say that cyanosis was barely perceptible in the majority of subjects. They quote other authors<sup>46-48</sup> who have made similar observations in TNT workers, and further state that the cyanosis observed evidently was not due entirely to methemoglobinemia, and report that the highest concentration observed was 6 to 7 per cent. They conclude that no correlation was found to exist between the degree of cyanosis observed and the amount of methemoglobin found in the blood. We believe that these observations are open to question, as has been pointed out previously, and that rather the methods employed for the determination of methemoglobin were at fault. Also, as has been pointed out previously, in our experience with the nitro and amino series, 6 to 7 per cent methemoglobin, let alone 2 per cent methemoglobin, is not grossly detectable. Mild hypochromic anemia was frequently observed, as well as a slightly, but significantly, shortened coagulation time in exposed men. No positive urobilins or urobilinogens in urine were encountered. They concluded that the health of exposed workers could be satisfactorily controlled by accurate hemoglobin, Wintrobe cell volume and icterus index determinations once a month. These observers concluded that the administration of ascorbic acid at a rate of 100 mg. daily, or regular "shotgun" vitamin pills, had no recognizable value

<sup>45</sup> R. F. Sievers, A. H. Lawton, F. Shoog, P. A. Neal, and W. F. von Oettingen, "A Medical Study of the Effect of TNT on Workers in a Bomb and Shell Loading Plant," *U.S. Pub. Health Bull.* No. 291 (1945).

<sup>46</sup> C. Voegtlin, C. W. Hooper, and J. M. Johnson, "I. Trinitrotoluene Poisoning—its Nature, Diagnosis, and Prevention," *Hygienic Lab. Bull.* No. 126 (1920).

<sup>47</sup> P. N. Pantou, *Lancet*, 2, 77 (1917).

<sup>48</sup> T. J. Putnam and W. Herman, *J. Ind. Hyg.*, 1, 238 (1919).



either in the prevention or the therapy of TNT poisoning. With this we are in complete agreement.

*Tetryl (tetranitromonomethylaniline)*, an explosive (a booster), was manufactured by the millions of tons during both wars. As an industrial hazard, even though it contains four nitro groups, it is of very minor significance. Hatch and Probst<sup>49</sup> state that the consensus appears to be that systemic poisoning from this compound does not occur, although some earlier writers report the appearance of systemic effects, none of which, however, are severe. Tetryl, however, causes a high incidence of contact dermatitis and nasal irritation and epistaxis. One of the most troublesome effects of tetryl, of no toxic significance, is a yellow staining of the skin and hair, which cosmetically and psychologically disturbs many individuals.

#### F. MISCONCEPTIONS REGARDING CERTAIN AMINO COMPOUNDS

*$\beta$ -Naphthylamine and "aniline" tumors of the bladder.* "Aniline tumors of the bladder" is a misnomer inherited from German literature. The Germans, quite understandably, attributed the occurrence of bladder tumors, both malignant and benign, to aniline and numerous more or less related compounds. Their assumption came about because it was common practice in producing these intermediates to manufacture several of these compounds within the same shop or within a small area of the plant in which workmen were freely sent from job to job with a resultant mixed exposure. In this country, however, after many years of observation, it became apparent that aniline, which was produced in several plants on a large scale in isolated operations, i.e., free from a mixed exposure, never caused bladder tumors. However, bladder tumors were occurring in the dyestuff industry. Aniline had been eliminated, but there remained what were, for the most part, mixed exposures to a variety of other intermediates. For many years it was not clear as to whether one compound was the causative agent, or several. Thanks to the persistent and diligent studies of Evans,<sup>50</sup> Gehrman,<sup>51</sup> Wolfe,<sup>52</sup> Foulger,<sup>53</sup> and others, the suspect list was progressively narrowed down. It now appears that most probably  $\beta$ -naphthylamine alone is the intermediate that causes bladder tumors. These physicians, after years of study, have clearly demonstrated that with experimental animals, chiefly dogs, bladder tumors can be consistently produced by the prolonged administration of  $\beta$ -naphthylamine, which is, of course, identical with  $\alpha$ -naphthylamine, except for the position of the  $\text{NH}_2$  group.  $\alpha$ -Naphthylamine does not cause bladder tumors in experimental animals; this is likewise true of benzidine (see page 375). In spite of the fact that most of their researches have been published and are available to all those who are interested, we find that the *Journal of the American Medical Association*

<sup>49</sup> H. S. Hatch and E. W. Probst, *Ind. Med.*, 14, 189 (1945).

<sup>50</sup> E. E. Evans, *J. Urol.*, 38, 212 (1937).

<sup>51</sup> G. H. Gehrman, *J. Urol.*, 31, 126 (1934).

<sup>52</sup> H. D. Wolfe, *J. Urol.*, 38, 216 (1937).

<sup>53</sup> J. H. Foulger, *personal communication*, 1946.

printed an editorial in which "aniline dyes" were mentioned as among the agents causing bladder tumors. This editorial<sup>54</sup> entitled "Bladder Tumors and Urinary Carcinogens," discussed the various agents that were known or supposed to cause bladder tumors as follows:

The total number of aniline dye tumors of the bladder collected from the world's literature is over five hundred. . . . One argument sometimes advanced in attempts to minimize the importance of the aniline dyes as causes of bladder tumors is that they are not accompanied by an excessively great incidence of tumors higher in the urinary tract as might be expected if they were due to a substance being excreted by the kidney. This argument has lost its force since it has been shown by Hueper, Wiley, and Wolfe<sup>55</sup> that dogs fed or injected with  $\beta$ -naphthylamine develop tumors of the urinary bladder and not of the kidney, while Sempronj and Morelli<sup>56</sup> produced kidney tumors and no bladder tumors by the injection of  $\beta$ -anthraquinoline. Other dyes have also induced tumors of the bladder.<sup>57</sup> These experiments illustrate high biologic selectivity.

Thus, we find the careless use of the words "aniline dye tumors" perpetuated.  $\beta$ -Naphthylamine cannot, by any stretch of the imagination, be called an aniline dye. It is dubious whether any dye or, for that matter, any other dye intermediate gives rise to bladder tumors. The bulk of the evidence points directly to  $\beta$ -naphthylamine as being the sole causative agent.

In another editorial<sup>58</sup> in the *Journal of the American Medical Association*, in discussing environmental cancer, the term "aniline dye tumor" is no longer used, but among the causes of occupational cancer are noted "aromatic amino compounds (aniline, naphthylamine, benzidine)." This correction is certainly a step in the right direction, but you will note that aniline is still included as a causative agent. Aniline has been so definitely ruled out that this constitutes a further perpetuation of misinformation. Benzidine possibly still belongs on the suspect list, however.

As a matter of fact, finished dyes of the coal-tar series, which are derived for the most part from rather toxic intermediates, are not toxic compounds in the commonly accepted sense of the word. This, in so far as we are aware, holds with few exceptions. Occasionally, finished dyes prove to be sources of contact dermatitis of the true sensitization type but they are mild even in this respect. Bismark Brown and Orange Y and a few of the other azo colors, from time to time, are mild offenders. Chrysoidine and Chrysarobine, as is known, are extensively used in the alleviation of psoriasis. Scarlet red, a simple azo dye, is of value in stimulating the proliferation of epithelium. The only potentially grave offender of which we are aware is *o*-aminoazotoluene, listed in the color index as Butter

<sup>54</sup> Editorial, "Bladder Tumors and Urinary Carcinogens," *J. Am. Med. Assoc.*, 123, 37 (1943).

<sup>55</sup> W. C. Hueper, F. H. Wiley, and H. D. Wolfe, *J. Ind. Hyg. Toxicol.*, 20, 46 (1938).

<sup>56</sup> A. Sempronj and E. Morelli, *Am. J. Cancer*, 35, 534 (1939).

<sup>57</sup> W. C. Hueper, *Occupational Tumors and Allied Diseases*. C. C. Thomas, Springfield, Illinois, 1942, Chap. 5.

<sup>58</sup> Editorial, "Environmental Cancer," *J. Am. Med. Assoc.*, 126, 836 (Nov. 25, 1944).

Yellow Number 17. With this compound, cancer of the liver was produced in experimental animals. Fifteen of the synthetic dyestuffs have been certified as suitable for use in the coloring of foodstuffs and more than forty have been certified by the Federal Food and Drug Administration as being suitable for use in cosmetics. All of these are likewise regarded by the Food and Drug Administration as suitable for intravenous administration as coloring matter in various solutions. These have been selected because of their color values and not because they were less toxic than other dyes. There appears to be little question but that many more dyes, in fact nearly all of them, could be so certified if their coloring qualities were particularly desirable for such use.

### *Summary*

In man the characteristic effect of the absorption of nitro-amino compounds of the aromatic series is methemoglobinemia. This conversion of hemoglobin to methemoglobin is a readily reversible reaction. Deviations from this pattern vary from a high incidence of bladder tumors in the case of  $\beta$ -naphthylamine, profound metabolic disturbances including hyperpyrexia and hepatitis in the case of dinitrophenol, to relatively little systemic toxicity in the case of tetryl.

With proper plant hygiene all of the members of this series of compounds can be produced and handled without serious hazard to the workers. It is to be expected that an occasional accident, such as the breaking of a valve or pipe line or an overflow, may bring about an acute poisoning.

Preventive hygiene necessitates strict cleanliness in the work area, including its atmosphere, and meticulous personal cleanliness on the part of every individual employee. This can be brought about with the cooperation of an intelligent and sympathetic management in various ways:

(1) Engineering must be directed not only toward good yields and low production costs, but also toward protection of the worker from exposure.

(2) Where totally closed systems are not feasible, adequate ventilation at the source of exposure must be insisted upon.

(3) Daily changes of freshly laundered clothing must be provided for workers engaged in the production of these compounds and a shower bath must be compulsory at the end of each work period.

(4) Every individual employed in a hazardous area should pass through the medical department for inspection at the end of each shift, since the onset of acute methemoglobinemia is symptomless.

(5) Individuals showing the slightest gross evidence of cyanosis should be kept under observation until an accurate methemoglobin determination can be made and as much longer than that as appears necessary.

(6) Workmen should never be permitted to enter a vessel which has contained compounds of this series until a determination of the degree of atmospheric contamination has been quantitatively established by the plant hygienist.

(7) Workers exposed to these compounds should be given a complete physical examina-

tion, including hemoglobin determinations, red, white and differential counts, and complete urinalysis, every six months or oftener. In cases of TNT, dinitrobenzene, and dinitrophenol exposures, workers should be examined monthly and inspected daily.

(8) In exposures to  $\beta$ -naphthylamine, cystoscopic examination of the bladder mucosa should be performed every six to twelve months.

(9) Those suffering from cardiovascular or renal disease of significant severity or individuals suffering from lowered vital capacity for any reason should not be employed. Likewise, those suffering from blood dyscrasia, as well as chronic alcoholics, should never be employed in areas in which this series of compounds is produced.

#### G. DATA ON MISCELLANEOUS ANALOGS OF THE AROMATIC NITROAMINES

In section II there are described briefly the physical constants, uses, and toxicological effects of several compounds that characterize this series. These have been chosen because they are of commercial importance and because they serve to illustrate the wide variations not only in toxicological, but in physical properties. For a more complete list of compounds of this series, the interested reader is referred to a comprehensive and excellent review of the literature written by W. F. von Oettingen, Principal Industrial Toxicologist, United States Public Health Service.<sup>59</sup>

The physical constants listed for these compounds were obtained from various sources,<sup>60</sup> which are not always in agreement on these data. Solubility figures are in grams per 100 g. of solvent unless otherwise stated. The summaries of toxicological characteristics are based largely upon the writer's observations.

## II. Specific Compounds

### ***o*-AMINOPHENOL (*o*-Hydroxyaniline)**

Formula:  $\text{NH}_2\text{C}_6\text{H}_4\text{OH}$

Physical state: colorless rhombic needles or plates

Molecular weight: 109.12

Melting point: 173° C.

Boiling point: sublimes

Solubility: water—1.7 at 0° C.; alcohol—4.3 at 0°; ether—very soluble

Odor and warning properties: none

#### 1. Uses

Dye intermediate and fur and hair "dye."

<sup>59</sup> W. F. von Oettingen, *U.S. Pub. Health Bull.* No. 271 (1941).

<sup>60</sup> *Heilbron's Dictionary of Organic Compounds*, Oxford Univ. Press, London, 1934. *Lange's Handbook of Chemistry*, 3rd ed., Handbook Publishers, Sandusky, Ohio, 1939. *Factory Mutual Data Sheet*, No. 36.10, Assoc. Factory Mutual Fire Insurance Cos., Boston, 1940. *Handbook of Chemistry and Physics*, 28th ed., Chemical Rubber Publishing Co., Cleveland, 1944. Beilstein, *Handbuch der organischen Chemie*, Springer, Berlin. Acknowledgment is made to J. H. Sterner, M.D., Tennessee Eastman Corporation, and W. R. Bradley, American Cyanamid Co., for valuable aid in compiling these data, and to Mr. Bradley for collecting information on methods of air analyses.

**2. Toxicity**

Not readily absorbed through intact skin, but may prove to be a sensitizing agent with resultant contact dermatitis. Inhalation of dust should be avoided since, if inhaled in excessive amounts, it may cause methemoglobinemia. In rare instances, *o*- and *p*-aminophenol have caused a bronchial asthma.

***p*-AMINOPHENOL (*p*-Hydroxyaniline)**

Formula:  $\text{NH}_2\text{C}_6\text{H}_4\text{OH}$

Physical state: white leaflets

Molecular weight: 109.12

Melting point: 184° C.

Boiling point: sublimes

Solubility: water—1.1 at 0° C.; alcohol—4.5 at 0°; ether—slightly soluble

Odor and warning properties: none

**1. Uses**

Identical with *o*-aminophenol.

**2. Toxicity**

Identical with *o*-aminophenol.

***m*-AMINOPHENOL (*m*-Hydroxyaniline)**

Formula:  $\text{NH}_2\text{C}_6\text{H}_3\text{OH}$

Physical state: colorless prisms

Molecular weight: 109.12

Melting point: 122° C.

Solubility: water—2.6 at 0° C.; alcohol—very soluble; ether—very soluble

Odor and warning properties: none

**1. Uses**

Of little commercial importance. Used chiefly in the synthesis of dyes and occasionally as a fur "dye."

**2. Toxicity**

Similar to the ortho and para compounds.

**ANILINE (Aminobenzene, Phenylamine)**

Formula:  $\text{C}_6\text{H}_5\text{NH}_2$

Physical state: liquid

Molecular weight: 93.12

Density of liquid: 1.022 at 20°/4° C.

Melting point: -6.2° C.

Boiling point: 184.4° C.

Density of vapor: 3.22 (air = 1)

Vapor pressure: 15 mm. at 77° C.

Index of refraction: 1.5863 at 20° C.

Solubility: water—3.4 at 20° C.; alcohol—soluble; ether—soluble; benzene—soluble; chloroform—soluble; carbon tetrachloride—soluble;

Flash point: 168° F.

Autoignition temperature: 1418° F.

Maximum allowable concentration: 5 p.p.m.

Odor and warning properties: characteristic, peculiar odor and burning taste

**1. Uses**

Manufacture of dyestuffs, other dyestuff intermediates, rubber accelerators and antioxidants; also as an intermediate in the manufacture of pharmaceuticals, photographic developers, plastics and ion exchange resins.

**2. Toxicity**

See pages 988 to 998.

**BENZIDINE (4,4'-Diaminobiphenyl, *p,p'*-Bianiline)**

Formula:  $\text{NH}_2\text{C}_6\text{H}_4\text{C}_6\text{H}_4\text{NH}_2$

Physical state: white or slightly reddish crystals, powder, or leaflets

Molecular weight: 184.23

Density: 1.250 at 20°/4°

Melting point: 116.5° C.

Boiling point: 401.7° C.

Solubility: water—0.04 at 12° C., 0.94 at 100°; alcohol—soluble; ether—2.2

**1. Uses**

Synthesis of dyes and dye intermediates.

**2. Toxicity**

Of little importance as a methemoglobin former and of a low order of toxicity in industrial exposures. It remains on the suspect list as a possible cause of bladder tumors, although available information indicates that bladder tumors cannot be caused by administration of this compound to experimental animals as in the case of  $\beta$ -naphthylamine.

***p*-CHLOROANILINE (4-Chlorophenylamine)**

Formula:  $\text{ClC}_6\text{H}_4\text{NH}_2$

Physical state: rhombic prisms

Molecular weight: 127.57

Density: 1.427 at 19°/4° C.

Melting point: 70° C.

Boiling point: 231° C.

Solubility: water—soluble; alcohol—soluble; ether—soluble

Odor and warning properties: characteristic sweet odor

**1. Uses**

Synthesis of dyestuffs and other intermediates.

**2. Toxicity**

Absorbed through the intact skin and may cause methemoglobinemia. Less hazardous than aniline or mononitrobenzene in industrial exposures. Relatively low vapor pressure, but precaution should be taken to avoid inhalation of vapors.

***o*-CHLOROANILINE (2-Chlorophenylamine)**

Formula:  $\text{ClC}_6\text{H}_4\text{NH}_2$

Physical state: liquid

Molecular weight: 127.57

Density of liquid: 1.2125 at 20°/4° C.

Melting point (solid states):  $\alpha$ , 14° C.;  $\beta$ , 3.5°.

Boiling point: 208.8° C.

Index of refraction: 1.5895 at 20° C.

Solubility: water—insoluble; alcohol—miscible; ether—soluble

Odor and warning properties: characteristic sweet odor

**1. Uses**

Same as *p*-chloroaniline.

**2. Toxicity**

Absorbed through the intact skin, but according to Lehmann<sup>61</sup> methemoglobinemia does not follow its absorption but rather kidney and, to a lesser extent, liver damage may result. Relatively low vapor pressure, but precaution should be taken to avoid inhalation of vapors.

***m*-CHLOROANILINE (3-Chlorophenylamine)**

Formula:  $\text{ClC}_6\text{H}_4\text{NH}_2$

Physical state: liquid

Molecular weight: 127.57

Melting point:  $-10.4^\circ\text{C}$ .

Boiling point:  $229.8^\circ\text{C}$ .

Index of refraction: 1.59424 at  $20^\circ\text{C}$ .

Solubility: water—insoluble; alcohol—miscible; ether—soluble

Odor and warning properties: characteristic sweet odor

**1. Uses**

Same as *p*-chloroaniline.

**2. Toxicity**

Readily absorbed through the intact skin. May cause methemoglobinemia and possible liver and kidney damage. Relatively low vapor pressure, but precaution should be taken to avoid inhalation of vapors.

**4-CHLORO-1,2-DINITROBENZENE**

Formula:  $\text{C}_6\text{H}_3\text{Cl}(\text{NO}_2)_2$

Physical state: monoclinic prisms, needles

Molecular weight: 202.56

Melting point:  $\alpha$ ,  $36.3^\circ$ ;  $\beta$ ,  $37.1^\circ$ ;  $\gamma$ ,  $38.8^\circ$ ;  
 $\delta$ ,  $28^\circ\text{C}$ .

Boiling point:  $315^\circ\text{C}$ .

Solubility: water—insoluble; alcohol—soluble in hot, difficultly in cold; ether—soluble

**1. Uses**

Commercial chlorodinitrobenzene is usually a mixture of the six possible isomers, which are closely related chemically and physically to each other. The physical constants given above refer to 4-chloro-1,2-dinitrobenzene and illustrate general properties common to this series. It is used in the manufacture of dye-stuffs, other dye intermediates, and in the explosive roburite.

**2. Toxicity**

In industrial exposures it is of little importance as a systemic poison, although it is almost a universal sensitizer, causing contact dermatitis in from 60 to 80 per cent of individuals having even minute contact with it. This contact dermatitis may vary from a few itching, vesicular papules to a generalized exfoliative dermatitis.

<sup>61</sup> K. B. Lehmann, *Arch. Hyg. Bakt.*, 110, 12 (1933).

**3-CHLORO-1,2-DINITROBENZENE**

Formula:  $C_6H_3Cl(NO_2)_2$

Physical state: crystals from alcohol or ether

Molecular weight: 202.56

Melting point: 78° C.

Solubility: water—insoluble; alcohol—soluble; ether—soluble

Flash point: 382° F. (closed cup), 405° F. (open cup)

**1. Uses**

Identical with 4-chloro-1,2-dinitrobenzene.

**2. Toxicity**

Identical with 4-chloro-1,2-dinitrobenzene.

**2-CHLORO-1,3-DINITROBENZENE**

Formula:  $C_6H_3Cl(NO_2)_2$

Physical state: yellow needles from alcohol

Molecular weight: 202.56

Melting point: 88° C.

Boiling point: 315° C.

Index of refraction: 1.6867 at 16.5° C.

Solubility: water—insoluble; alcohol—soluble; ether—soluble

**1. Uses**

Identical with 4-chloro-1,2-dinitrobenzene.

**2. Toxicity**

Identical with 4-chloro-1,2-dinitrobenzene.

**2-CHLORO-1,4-DINITROBENZENE**

Formula:  $C_6H_3Cl(NO_2)_2$

Physical state: light yellow crystals

Molecular weight: 202.56

Melting point: 64° C.

Solubility: water—insoluble; alcohol—soluble; ether—soluble

**1. Uses**

Identical with 4-chloro-1,2-dinitrobenzene.

**2. Toxicity**

Identical with 4-chloro-1,2-dinitrobenzene.

**4-CHLORO-1,3-DINITROBENZENE**

Formula:  $C_6H_3Cl(NO_2)_2$

Physical state: crystals

Molecular weight: 202.56

Melting point:  $\alpha$ , 53.4°;  $\beta$ , 43° C.

Boiling point: 315° C. (762 mm.)

Solubility: water—insoluble; alcohol—readily soluble in hot, difficultly in cold; ether—soluble

**1. Uses**

Identical with 4-chloro-1,2-dinitrobenzene.

**2. Toxicity**

Identical with 4-chloro-1,2-dinitrobenzene.



**5-CHLORO-1,3-DINITROBENZENE**Formula:  $C_6H_3Cl(NO_2)_2$ 

Physical state: colorless needles

Molecular weight: 202.56

Melting point: 55° C.

Solubility: water—insoluble; alcohol—soluble; ether—soluble

**1. Uses**

Identical with 4-chloro-1,2-dinitrobenzene.

**2. Toxicity**

Identical with 4-chloro-1,2-dinitrobenzene.

**DIETHYLANILINE (*n*-Phenyldiethylamine)**Formula:  $C_8H_9N(C_2H_5)_2$ 

Physical state: colorless or yellow or brown inflammable oil

Molecular weight: 149.23

Density: 0.93507 at 20°/4° C.

Melting point: -38.8° C.

Boiling point: 215.5° C.

Index of refraction: 1.54105 at 22° C.

Solubility: water—1.44 at 12° C.; alcohol—soluble; ether—soluble

**1. Uses**

Dyestuffs, and in synthesis of other intermediates and pharmaceuticals.

**2. Toxicity**

Quantitatively less toxic than aniline, but very similar in its effects. It is readily absorbed through the intact skin and precautions must be taken to avoid inhalation of its vapors.

**DIMETHYLANILINE (*n*-Phenyldimethylamine)**Formula:  $C_8H_9N(CH_3)_2$ 

Physical state: yellow liquid

Molecular weight: 121.18

Density of liquid: 0.9557 at 20°/4° C.

Melting point: 2.5° C.

Boiling point: 192.5° C.

Density of vapor (air = 1): 4.17

Index of refraction: 1.55819 at 20° C.

Solubility: water—slightly soluble; alcohol—soluble; ether—soluble

Flash point: 145° F. (closed cup), 170° F. (open cup)

Autoignition temperature: 700° F.

Maximum allowable concentration: 5 p.p.m.

**1. Uses**

Synthesis of dyestuffs, other dyestuff intermediates, as a solvent, as an aid in methylation and as a reagent.

**2. Toxicity**

Same as diethylaniline.

***o*-DINITROBENZENE (1,2-Dinitrobenzene)**Formula:  $C_6H_4(NO_2)_2$ 

Physical state: colorless to yellow monoclinic plates

Molecular weight: 168.11

Density: 1.565 at 17°/4° C.

Melting point: 117–118° C.

Boiling point: 319° C. (773 mm.)

Vapor density: 5.79 (air = 1)

Solubility: water—0.01 (cold), 0.38 at 100° C.; alcohol—3.8 at 25°; chloroform—27.1 at 18°; benzene—5.0 at 18°; methyl alcohol—soluble

Flash point: 302° F. (closed cup)

**1. Uses**

Dinitrobenzene in the meta, para, and ortho isomers is of commercial importance and is usually manufactured as a mixture of the three isomers. It is used in the synthesis of dyestuffs, of other dyestuff intermediates, in explosives, and as a camphor substitute in celluloid production.

**2. Toxicity**

A powerful methemoglobin former and on prolonged exposure may lead to liver damage. It is readily absorbed through the intact skin and its vapors are highly toxic. It is reported to cause a secondary anemia on absorption, but this has not been a consistent finding during our observation over a period of years.

**p-DINITROBENZENE (1,4-Dinitrobenzene)**

Formula:  $C_6H_4(NO_2)_2$

Physical state: colorless to yellow monoclinic needles

Molecular weight: 168.11

Density: 1.625 at 20°/4° C.

Melting point: 173° C.

Boiling point: 299° C. (777 mm.)—sublimes

Solubility: water—0.18 at 100° C.; alcohol—0.4 at 20°; chloroform—1.82 at 18°; benzene—2.3 at 18°

Maximum allowable concentration: 5 p.p.m.

**1. Uses**

Identical with *o*-dinitrobenzene.

**2. Toxicity**

Identical with *o*-dinitrobenzene.

**m-DINITROBENZENE (1,3-Dinitrobenzene)**

Formula:  $C_6H_4(NO_2)_2$

Physical state: colorless to yellow rhombic needles or plates

Molecular weight: 168.11

Density: 1.571 at 0°/4° C.

Melting point: 89.57° C.

Boiling point: 302.8° C. (770 mm.)

Solubility: water—0.0469 at 15° C., 0.32 at 100°; alcohol—2.6 at 20°; ether—6.7 at 15°; benzene—soluble; toluene—soluble; chloroform—soluble; ethyl acetate—soluble

Flash point: 302° F. (closed cup)

Maximum allowable concentration: 5 p.p.m.

**1. Uses**

Identical with *o*-dinitrobenzene.

**2. Toxicity**

Identical with *o*-dinitrobenzene.

**2,3-DINITROPHENOL**

Formula:  $C_6H_3OH(NO_2)_2$

Physical state: yellow monoclinic prisms

Molecular weight: 184.11

Melting point: 144° C.

Solubility: water—slightly soluble; alcohol—very soluble in hot; ether—very soluble

**1. Uses**

The isomers of dinitrophenol are usually not separated but are prepared as mixtures; however, the mixtures or the individual isomers are so similar toxico-

logically and chemically that they need not be considered separately. They are used in the synthesis of dyestuffs, picric acid, and picramic acid. They are also used in the preservation of timber and in the manufacture of the photographic developer Amidol.

### 2. Toxicity

This highly toxic compound is readily absorbed through the intact skin; its vapors are absorbed through the respiratory tract. For details see preceding text on 1,2,4-dinitrophenol (page 997).

## 2,4-DINITROPHENOL

Formula:  $C_6H_3OH(NO_2)_2$

Physical state: yellow rhombic crystals or needles

Molecular weight: 184.11

Melting point: 114, 115° C.

Solubility: water—0.56 at 18° C., 4.3 at 100°; alcohol—3.9 at 19°; ether—3.065 at 15°; chloroform—soluble; benzene—soluble

Odor and warning properties: bitter taste

### 1. Uses

Identical with 2,3-dinitrophenol.

### 2. Toxicity

Identical with 2,3-dinitrophenol.

## 2,5-DINITROPHENOL

Formula:  $C_6H_3OH(NO_2)_2$

Physical state: yellow needles

Molecular weight: 184.11

Melting point: 104° C.

Solubility: water—slightly soluble; alcohol—soluble in hot; ether—easily soluble

### 1. Uses

Identical with 2,3-dinitrophenol.

### 2. Toxicity

Identical with 2,3-dinitrophenol.

## 2,6-DINITROPHENOL

Formula:  $C_6H_3OH(NO_2)_2$

Physical state: yellow rhombic crystals

Molecular weight: 184.11

Melting point: 63.5° C.

Solubility: water—slightly soluble in cold, more soluble in hot; alcohol—readily soluble in hot; ether—readily soluble; benzene—soluble

### 1. Uses

Identical with 2,3-dinitrophenol.

### 2. Toxicity

Identical with 2,3-dinitrophenol.

## 3,4-DINITROPHENOL

Formula:  $C_6H_3OH(NO_2)_2$

Physical state: colorless needles

Molecular weight: 184.11

Melting point: 134° C.

Solubility: alcohol—very soluble; ether—very soluble

**1. Uses**

Identical with 2,3-dinitrophenol.

**2. Toxicity**

Identical with 2,3-dinitrophenol.

**3,5-DINITROPHENOL**

Formula:  $C_6H_3OH(NO_2)_2$

Physical state: monoclinic prism

Molecular weight: 184.11

Melting point: 122–123° C.

Solubility: alcohol—very soluble; ether—very soluble; chloroform—soluble; benzene—soluble

**1. Uses**

Identical with 2,3-dinitrophenol.

**2. Toxicity**

Identical with 2,3-dinitrophenol.

**4,6-DINITRO-*o*-CRESOL (2-Methyl-4,6-dinitrophenol)**

Formula:  $C_6H_2(CH_3)OH(NO_2)_2$

Physical state: yellow prisms

Molecular weight: 198.13

Melting point: 85.8° C.

Solubility: water—slightly soluble; alcohol 10.82 at 15° C.; ether—very soluble; acetone—soluble

**1. Uses**

The two dinitrocresol isomers for which physical constants are presented are those of greatest commercial importance. Their uses are similar to those given for dinitrophenol.

**2. Toxicity**

Resembles dinitrophenol.

**2,6-DINITRO-*p*-CRESOL (4-Methyl-2,6-dinitrophenol)**

Formula:  $C_6H_2(CH_3)OH(NO_2)_2$

Physical state: long yellow prisms

Molecular weight: 198.13

Melting point: 81° C.

Solubility: water—slightly soluble; alcohol—soluble; ether—very soluble

**1. Uses**

Identical with 4,6-dinitro-*o*-cresol.

**2. Toxicity**

Identical with 4,6-dinitro-*o*-cresol.

**DIPHENYLAMINE (Phenylaniline)**

Formula:  $(C_6H_5)_2NH$

Physical state: colorless monoclinic leaflets

Molecular weight: 169.22

Density: 1.159 at 20°/4° C.

Melting point: 53° C.

Boiling point: 302° C.

Solubility: water—0.03 at 25° C.; alcohol—44; ether—very soluble; methyl alcohol—57.5

Odor and warning properties: floral odor

**1. Uses**

Synthesis of dyestuffs, other dyestuff intermediates, and explosives.

**2. Toxicity**

Similar to that of aniline but much less toxic and less readily absorbed through the skin and respiratory tract.

***α*-NAPHTHYLAMINE (1-Naphthylamine)**

Formula:  $C_{10}H_7NH_2$

Physical state: yellow rhombic needles

Molecular weight: 143.18

Density: 1.123 at 25°/25° C.

Melting point: 50° C.

Boiling point: 301° C.

Vapor density: 4.93 (air = 1)

Index of refraction: 1.6703 at 51.2° C.

Solubility: water—0.17; alcohol—very soluble; ether—very soluble

Flash point: 315° F. (closed cup)

**1. Uses**

Synthesis of dyestuffs and other dyestuff intermediates and as a developer for naphthol AS colors.

**2. Toxicity**

As an industrial hazard it is of little importance except that commercially it may contain up to 10 per cent *β*-naphthylamine. Because of this beta content, it may theoretically give rise to bladder tumors in prolonged exposures.

***β*-NAPHTHYLAMINE (2-Naphthylamine)**

Formula:  $C_{10}H_7NH_2$

Physical state: leaflet form

Molecular weight: 143.18

Density: 1.061 at 98°/4° C.

Melting point: 110.2° C.

Boiling point: 306.1° C.

Index of refraction: 1.64927 at 98.4° C.

Solubility: water—insoluble; alcohol—soluble; ether—soluble; benzene—soluble

**1. Uses**

Dyestuffs and other dyestuff intermediates.

**2. Toxicity**

Readily absorbed through the skin and respiratory tract. May cause mild methemoglobinemia but it is a highly dangerous compound because it causes bladder tumors which may occur following from one to twelve years' exposure.

***m*-NITROANILINE (1-Amino-3-nitrobenzene)**

Formula:  $NO_2C_6H_4NH_2$

Physical state: yellow rhombic needles

Molecular weight: 138.12

Density: 1.430 at 20°/4° C.

Melting point: 111.8° C.

Boiling point: 286° C.

Solubility: water—0.089 at 25° C.; alcohol—6.10 at 25°; ether—5.67 at 20°

Odor and warning properties: burning sweet taste

**1. Uses**

Synthesis of dyestuffs and other intermediates.

**2. Toxicity**

Powerful methemoglobin former with attendant hemolytic effect. May also on prolonged and excessive exposures cause liver damage. It is readily absorbed through the intact skin and its vapors are highly toxic as well.

**p-NITROANILINE (1-Amino-4-nitrobenzene)**

Formula:  $\text{NO}_2\text{C}_6\text{H}_4\text{NH}_2$

Physical state: yellow monoclinic needles

Molecular weight: 138.12

Density: 1.424 at 20°/4° C.

Melting point: 147.5° C.

Boiling point: 331.73° C.

Solubility: water—0.08 at 19° C. or 2.2 at 100° C.; alcohol—4.61 at 20°; ether—4.39 at 20°

**1. Uses**

Synthesis of dyestuffs and other intermediates.

**2. Toxicity**

Powerful methemoglobin former with attendant hemolytic effect. May also on prolonged and excessive exposures cause liver damage. It is readily absorbed through the intact skin and its vapors are highly toxic as well.

**o-NITROANILINE (1-Amino-2-nitrobenzene)**

Formula:  $\text{NO}_2\text{C}_6\text{H}_4\text{NH}_2$

Physical state: orange rhombic needles

Molecular weight: 138.12

Density: 1.442 at 20°/4° C.

Melting point: 71.5° C.

Boiling point: 284.11° C.

Solubility: water—0.126 at 25° C.; alcohol—15.8 at 15°, 27.87 at 25°; ether—very soluble

**1. Uses**

Of slight importance commercially. Used as a dye intermediate.

**2. Toxicity**

Practically identical with the meta and para isomers.

**NITROBENZENE (Oil of Mirbane)**

Formula:  $\text{C}_6\text{H}_5\text{NO}_2$

Physical state: liquid

Molecular weight: 123.11

Density: 1.19867 at 25°/4° C.

Melting point: 5.7° C.

Boiling point: 210.9° C.

Density of vapor: 4.1 (air = 1)

Index of refraction: 1.55291 at 20° C.

Solubility: water—0.19 at 20° C., 0.8 at 80°; alcohol—very soluble; ether—very soluble; benzene—soluble; oils—soluble

Flash point: 190° F. (closed cup)

Maximum allowable concentration: 5 p.p.m.

Odor and warning properties: oil of bitter almond odor

**1. Uses**

One of the most important and basic intermediates, widely used in the preparation of other intermediates and other organic syntheses. Also used to mask unpleasant odors because of its musklike smell.

**2. Toxicity**

A powerful methemoglobin former; in this respect probably more potent than aniline per unit of weight or vapor concentration. See preceding text for discussion.

***o*-NITROPHENOL**

Formula:  $\text{NO}_2\text{C}_6\text{H}_4\text{OH}$

Physical state: light yellow monoclinic needles or prisms

Molecular weight: 139.11

Density: 1.657 at 20° C.

Melting point: 45° C.

Boiling point: 214.5° C.

Solubility: water—0.21 at 20° C., 1.08 at 100°; alcohol—46.0 at 25°; ether—very soluble; alkali—soluble

Odor and warning properties: aromatic odor and sweet taste

**1. Uses**

Synthesis of dyestuffs and other intermediates.

**2. Toxicity**

Methemoglobin former, but less so than aniline and mononitrobenzene. May be absorbed through the intact skin and its vapors through the respiratory tract.

***m*-NITROPHENOL**

Formula:  $\text{NO}_2\text{C}_6\text{H}_4\text{OH}$

Physical state: colorless to yellow monoclinic form

Molecular weight: 139.11

Density: 1.485 at 20° C.

Melting point: 96° C.

Boiling point: 174° C., 70 mm.

Solubility: water—1.35 at 25° C., 13.3 at 90°; alcohol—195.0 at 25°; ether—very soluble; benzene—soluble; alkali—soluble

**1. Uses**

Identical with *o*-nitrophenol.

**2. Toxicity**

Identical with *o*-nitrophenol.

***p*-NITROPHENOL**

Formula:  $\text{NO}_2\text{C}_6\text{H}_4\text{OH}$

Physical state: colorless to yellowish monoclinic prisms

Molecular weight: 139.11

Density: 1.479 at 20° C.

Melting point: 114° C.

Boiling point: 279° C. (decomposes)

Solubility: water—1.6 at 25° C., 26.9 at 90°; alcohol—189.5 at 25°; ether—very soluble; chloroform—soluble

Odor and warning properties: odorless, taste sweetish, later burning

**1. Uses**

Identical with *o*-nitrophenol.

**2. Toxicity**

Identical with *o*-nitrophenol.

***o*-NITROTOLUENE**

Formula:  $\text{NO}_2\text{C}_6\text{H}_4\text{CH}_3$   
 Physical state: yellow liquid  
 Molecular weight: 137.13  
 Density: 1.163 at 20°/4° C.  
 Melting point:  $\alpha$ , 10.6° C.;  $\beta$ , 4.1°  
 Boiling point: 222.3° C.  
 Vapor pressure: 1.6 mm. at 60° C.

Index of refraction: 1.54739 at 20.4° C.  
 Percentage of vapor in "saturated" air: 0.21 at 60° C.  
 Solubility: water—0.0652 at 30° C.; alcohol—soluble; ether—soluble; benzene—soluble; chloroform—soluble

**1. Uses**

Synthesis of dyestuffs and other intermediates and explosives.

**2. Toxicity**

Methemoglobin former of an apparently low grade which is not important as an industrial hazard. May be absorbed through the intact skin and through the respiratory tract.

***p*-NITROTOLUENE**

Formula:  $\text{NO}_2\text{C}_6\text{H}_4\text{CH}_3$   
 Physical state: colorless rhombic needles  
 Molecular weight: 137.13  
 Density: 1.286 at 20° C.  
 Melting point: 51.3° C.  
 Boiling point: 238° C.  
 Density of vapor: 4.72 (air = 1)  
 Vapor pressure: 1.3 mm. at 65° C.

Index of refraction: 1.5346 at 62.5° C.  
 Percentage of vapor in "saturated" air: 0.17 at 65° C.  
 Solubility: water—0.0442 at 30° C.; alcohol—soluble; ether—very soluble; benzene—soluble  
 Flash point: 223° F. (closed cup)

**1. Uses**

Identical with *o*-nitrotoluene.

**2. Toxicity**

Identical with *o*-nitrotoluene.

***m*-NITROTOLUENE**

Formula:  $\text{NO}_2\text{C}_6\text{H}_4\text{CH}_3$   
 Physical state: liquid  
 Molecular weight: 137.13  
 Density: 1.157 at 20°/4° C.  
 Melting point: 15.5° C.  
 Boiling point: 231° C.  
 Vapor pressure: 1.0 mm. at 60° C.

Index of refraction: 1.5475 at 20° C.  
 Percentage of vapor in "saturated" air: 0.13 at 60° C.  
 Solubility: water—0.0498 at 30° C.; alcohol—soluble; ether—soluble; benzene—soluble

**1. Uses**

Identical with *o*-nitrotoluene.

**2. Toxicity**

Identical with *o*-nitrotoluene.



***p*-NITROSODIMETHYLANILINE**Formula:  $\text{NO}_2\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2$ 

Physical state: green triclinic crystals

Molecular weight: 150.18

Melting point: 85° C.

Solubility: water—insoluble; alcohol—soluble; ether—soluble

**1. Uses**

Synthesis of dyestuffs and as an accelerator in the vulcanization of rubber.

**2. Toxicity**

Apparently not a methemoglobin former, but is highly irritating to the skin both as a primary irritant and as a sensitizing agent.

***m*-PHENYLENEDIAMINE (1,3-Diaminobenzene)**Formula:  $\text{C}_6\text{H}_4(\text{NH}_2)_2$ 

Physical state: colorless rhombic needles

Molecular weight: 108.14

Density: 1.1389 at 5° C.; 1.107 at 58°

Melting point: 62.8° C.

Boiling point: 287° C.

Index of refraction: 1.63390 at 57.7° C.

Solubility: water—35.1 at 25° C.; alcohol—soluble; ether—soluble

**1. Uses**

Chiefly used in the synthesis of dyestuffs and of other dyestuff intermediates.

**2. Toxicity**

Industrially presents no recognized hazard.

***p*-PHENYLENEDIAMINE (1,4-Diaminobenzene)**Formula:  $\text{C}_6\text{H}_4(\text{NH}_2)_2$ 

Physical state: colorless monoclinic crystals

Molecular weight: 108.14

Melting point: 139.7° C.

Boiling point: 267° C.

Solubility: water—3.8 at 24° C., 669 at 107°; alcohol—soluble; ether—soluble; chloroform—soluble

**1. Uses**

Synthesis of dyestuffs and other intermediates and as a "fur dye."

**2. Toxicity**

Systemic toxicity in industrial exposures apparently is not recognizable. It, however, may cause contact dermatitis through sensitization and may cause bronchial asthma. Such asthma, of course, ceases promptly with complete withdrawal from exposure.

**TETRYL (Trinitrophenylmethylnitramine, *N*-Methyl-*N*-2,4,6-tetranitroaniline)**Formula:  $(\text{NO}_2)_3\text{C}_6\text{H}_2\text{N}(\text{NO}_2)\text{CH}_3$ 

Physical state: yellow monoclinic crystals

Molecular weight: 287.15

Density: 1.57 at 19° C.

Melting point: 130° C.

Boiling point: 187° C., explodes

Solubility: water—insoluble; alcohol—0.422 at 18° C.; ether—very soluble; benzene—soluble; acetic acid—soluble

Maximum allowable concentration: 1.5 mg./cu.m.

**1. Uses**

Explosive.

**2. Toxicity**

Systemic toxicity has never been recognized from this compound. Irritating to the mucous membranes of the upper respiratory tract.

**2,3,4-TRINITROTOLUENE ( $\beta$ )**Formula:  $C_6H_2CH_3(NO_2)_3$ 

Physical state: crystals

Molecular weight: 227.13

Melting point: 112° C., explodes at 290–310°

Solubility: water—insoluble; alcohol—slightly soluble; ether—slightly soluble

**1. Uses**

Explosive.

**2. Toxicity**

Of little importance as a methemoglobin former but may cause aplastic anemia and liver damage. For further details, see Section I.

**2,4,5-TRINITROTOLUENE ( $\gamma$ )**Formula:  $C_6H_2CH_3(NO_2)_3$ 

Physical state: pale yellow prisms

Molecular weight: 227.13

Melting point: 104° C.

Boiling point: 290° C. (decomposes), 288–293° (explodes)

Solubility: water—insoluble; alcohol—very slightly soluble in cold, much more readily in hot; ether—readily soluble; hot glacial acetic acid, benzene, acetone—soluble

Maximum allowable concentration: 1.5 mg./cu.m.

**1. Uses**

Identical with 2,3,4-trinitrotoluene.

**2. Toxicity**

Identical with 2,3,4-trinitrotoluene.

**2,4,6-TRINITROTOLUENE ( $\alpha$ , or TNT)**Formula:  $C_6H_2CH_3(NO_2)_3$ 

Physical state: monoclinic prisms, crystals (colorless)

Molecular weight: 227.13

Melting point: 80.35°, 81.1° C.

Boiling point: 240° C. (explodes)

Vapor pressure: 0.046 mm. (82° C.)

Solubility: water—0.02 at 15° C., 0.15 (hot);

alcohol—0.1 g. in 8 cc. at 18°; ether—0.1 g. in 4 cc. at 18°; chloroform—readily soluble, 0.1 g. in 0.4 cc.; carbon tetrachloride—0.1 g. in 7 cc. at 18°; benzene—readily soluble; toluene—readily soluble; acetone—readily soluble

Maximum allowable concentration: 1.5 mg./cu.m.

**1. Uses**

Identical with 2,3,4-trinitrotoluene.

**2. Toxicity**

Identical with 2,3,4-trinitrotoluene.

**2,3,5-TRINITROTOLUENE ( $\epsilon$ )**

Formula:  $C_6H_3CH_3(NO_2)_3$

Physical state: yellow rhombic crystals

Molecular weight: 227.13

Melting point: 97° C.

Boiling point: explodes at 333–337° C.

Solubility: alcohol—soluble; ether—insoluble

Maximum allowable concentration: 1.5 mg./cu.m.

**1. Uses**

Identical with 2,3,4-trinitrotoluene.

**2. Toxicity**

Identical with 2,3,4-trinitrotoluene.

**2,3,6-TRINITROTOLUENE**

Formula:  $C_6H_3CH_3(NO_2)_3$

Physical state: monoclinic needles (from alcohol)

Molecular weight: 227.13

Melting point: 111° C.

Boiling point: explodes at 327–335° C.

Solubility: alcohol—soluble in 9 parts boiling alcohol or 11 parts of cold

Maximum allowable concentration: 1.5 mg./cu.m.

**1. Uses**

Identical with 2,3,4-trinitrotoluene.

**2. Toxicity**

Identical with 2,3,4-trinitrotoluene.

**3,4,5-TRINITROTOLUENE**

Formula:  $C_6H_3CH_3(NO_2)_3$

Physical state: yellow-green monoclinic prisms or needles (alcohol)

Molecular weight: 227.13

Melting point: 132.0° C.

Boiling point: explodes 305–318° C.

Solubility: alcohol—100 parts 95% alcohol dissolves 1 part at 15° C.

Maximum allowable concentration: 1.5 mg./cu.m.

**1. Uses**

Same as other isomers.

**2. Toxicity**

Same as other isomers.

***p*-TOLUIDINE (*p*-Methylaniline)**

Formula:  $CH_3C_6H_4NH_2$

Physical state: leaflets

Molecular weight: 107.15

Melting point: 45° C.

Boiling point: 200.3° C.

Index of refraction: 1.55324 at 59.1° C.

Density: 1.046 at 20°/4° C., 0.973 at 50°/50°

Solubility: water—0.74 at 21° C.; alcohol—156 at 30° C.; ether—soluble

Odor and warning properties: aromatic, winelike odor; burning taste

**1. Uses**

Synthesis of dyestuffs and other intermediates and in the preparation of ion exchange resins.

**2. Toxicity**

Very similar to aniline, but in addition causes a transient hematuria which, in our experience, has been unaccompanied by any further signs of kidney damage and which is cleared completely upon removal from further exposure.

***o*-TOLUIDINE (*o*-Methylaniline)**

Formula:  $\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$

Physical state: colorless liquid

Molecular weight: 107.15

Density: 1.004 at 20°/4° C.

Melting point:  $\alpha$ , 24.4° C.;  $\beta$ , 16.3°

Boiling point: 199.84° C.

Index of refraction: 1.57276 at 20° C.

Solubility: water—1.5 at 25° C.; alcohol—soluble; ether—soluble

**1. Uses**

Same as *p*-toluidine.

**2. Toxicity**

Same as *p*-toluidine.

**III. Determination in the Atmosphere**

These compounds may exist in the air of industrial workplaces in the form of either dusts or vapors. Specific methods for air sampling or for analysis, however, appear in the literature for only a few of them. Studies of industrial environments where these substances may exist as a contaminant deal with trace quantities, so that techniques of efficient trapping and sensitive methods for analysis are required.

The dusts, of course, may be collected by impingement in a suitable vehicle, or may be electrically precipitated where there are no explosion hazards. The vapors may be trapped by scrubbing through weak acid solutions or specific solvents. Condensation employing dry ice and acetone and a condensing chamber of three or more bulbs is preferred. The condensate may then be dissolved in the solvent of choice. Methods employing the collection of aromatic nitro and amino compound vapors on silica gel or activated charcoal may not prove satisfactory.

The chemical analysis for many of these compounds, such as aniline, toluidine, phenylenediamine, the nitrobenzenes, the nitrotoluenes, picric acid, and other nitrophenols have been reviewed by Jacobs.<sup>62</sup> However, those chemical analytical methods that involve diazotization and coupling do not avoid the opportunity for side reactions and other interferences that reduce the accuracy. The official British<sup>63</sup> method for aniline depends on the formation of the hydrochlorite com-

<sup>62</sup> M. B. Jacobs, *Analytical Chemistry of Industrial Poisons, Hazards, and Solvents*. Interscience, New York, 1941.

<sup>63</sup> Dept. Sci. Ind. Research, "Methods for the Detection of Toxic Gases in Industry—Aniline Vapor," *Leaflet No. 11*. H. M. Stationery Office, London, 1939.

plex and a blue coloration following the addition of ammonia and phenol. Jacobs<sup>62</sup> lists a table on the "Colorimetric Detection of Certain Dyestuffs and Intermediates," which is an aid in identification.

TABLE 1  
*Ultraviolet Absorption<sup>a</sup>*

Compound	Solvent	<i>E</i> (1%, 1 cm.)	Wave length
<i>m</i> -Aminophenol	95% ethanol	204	285 m $\mu$
Aniline	Cyclohexane <sup>b</sup>	192	291
Aniline	Cyclohexane <sup>b</sup>	211	288
Aniline	Cyclohexane <sup>b</sup>	204	283.9
Aniline	Cyclohexane <sup>b</sup>	185	281
<i>o</i> -Dinitrobenzene	Cyclohexane <sup>b</sup>	388	250
<i>m</i> -Dinitrobenzene	95% ethanol	1025	233
<i>p</i> -Dinitrobenzene	95% ethanol	876	260
Diphenylamine	95% ethanol	137	284
<i>o</i> -Nitroaniline	95% ethanol	408	408-409
<i>o</i> -Nitroaniline	95% ethanol	390	278
<i>m</i> -Nitroaniline	95% ethanol	109	374-375
<i>p</i> -Nitroaniline	95% ethanol	151	374
<i>p</i> -Nitroaniline	95% ethanol	66	230
Nitrobenzene	Cyclohexane	753	253
<i>o</i> -Nitrophenol	95% ethanol	231	347
<i>o</i> -Nitrophenol	95% ethanol	446	273
<i>m</i> -Nitrophenol	95% ethanol	154	329
<i>m</i> -Nitrophenol	95% ethanol	444	270
<i>p</i> -Nitrophenol	95% ethanol	802	315
<i>p</i> -Nitrosodimethylaniline	95% ethanol	388	271.6
<i>p</i> -Nitrosodimethylaniline · HCl	95% ethanol	288	233
<i>m</i> -Phenylenediamine	95% ethanol + water	100	288
<i>p</i> -Phenylenediamine · HCl	95% ethanol	191	309
Sulfanilic acid	70% ethanol	225	247
<i>o</i> -Toluidine	Cyclohexane	209	281-289
<i>m</i> -Toluidine	Cyclohexane	172	286-294
<i>p</i> -Toluidine	Cyclohexane	563	294

Calculations for sensitivity: If it is assumed that the minimum detectable amount transmits 90% of the light, then:

$$\log I_0/I = \log (100/90) = 0.045$$

$$E (1\%, 1 \text{ cm.}) \text{ for } m\text{-dinitrobenzene} = 1025$$

$$0.045/1025 = 5 \times 10^{-6}\% = 0.5 \text{ p.p.m.}$$

$$E (1\%, 1 \text{ cm.}) \text{ for } m\text{-phenylenediamine} = 100$$

$$0.045/100 = 45 \times 10^{-6}\% = 4.5 \text{ p.p.m.}$$

<sup>a</sup> Unpublished data, Stamford Research Laboratories, American Cyanamid Co.

<sup>b</sup> Cyclohexane must be entirely free of impurities such as benzene.

Trinitrotoluene and tetryl can be satisfactorily collected and analyzed by the method of Goldman and Rushing.<sup>64</sup> The collecting solvent they employ is

<sup>64</sup> F. H. Goldman and D. E. Rushing, *J. Ind. Hyg. Toxicol.*, **26**, 164, 195 (1943).

diethylaminoethanol. Ficklen<sup>65</sup> has reported on methods for collecting and analyzing aniline, nitrobenzene, and toluidine.

The analysis of these compounds existing as vapors is greatly facilitated by the use of physical testing instruments. Instruments employing infrared and ultraviolet techniques, visible spectroscopy, and refractometric tools such as the interferometer are available. The indices of refraction of this group of compounds are sufficiently high to make possible determinations in air of concentrations between 5 and 20 p.p.m., making the interferometer a practical tool.

Spectrometric methods (see Chapter Eight) are also applicable; and trace analysis of aromatic nitro and amino vapors may be accomplished with ultraviolet absorption techniques. In collecting vapors, for application of this method, the solvents of choice are 95 per cent ethyl alcohol or, preferably, cyclohexane. Table 1 presents, for various compounds and solvents, the extinction coefficients for 1 per cent solutions by weight in a 1-cm. cell at the specified wave lengths. Assuming a conservative limit to be 10 per cent absorption for a 1-cm. cell, the range of sensitivities will for such solutions be between 0.5 and 4.5 p.p.m., barring any interferences and assuming Beer's law to be obeyed. A 10 per cent absorption is quite conservative as the sensitivity of most ultraviolet spectrometers is of the order of 0.5 to 1 per cent.

<sup>65</sup>J. B. Ficklen, *Manual of Industrial Health Hazards*. Science Press, Lancaster, Pa., 1940.

# Phenol and Phenolic Compounds

WILLIAM B. DEICHMANN

## PHENOL

### 1. *Physical and Chemical Properties*

Phenol or carboic acid,  $C_6H_5OH$ , occurs as a crystalline mass or in the form of hygroscopic translucent needle-shaped crystals having a distinct, aromatic, somewhat sickeningly sweet and acrid odor, and a sharp and burning taste. It has a molecular weight of 94.05, a specific gravity of 1.011 and a vapor pressure equivalent to 1 mm. Hg at  $44.8^\circ C$ . The compound deteriorates when exposed to light and air, taking on a reddish tint.

Phenol added to water forms a true solution ( $25^\circ C$ .) when present in concentrations up to about 8 per cent, and also in concentrations ranging from about 71 to 97 per cent, both in terms of weight-volume. The compound is soluble to more than 50 per cent in ethyl alcohol, chloroform, ethyl ether, ethyl acetate, toluene, glycerol, and olive oil. Its solubility in mineral oil is about 0.2 per cent ( $25^\circ C$ .), in petroleum ether 5.5 per cent ( $31^\circ$ ) and in rabbit fat 40 per cent ( $34^\circ$ ).<sup>1</sup> According to Pilcher and Sollmann,<sup>2</sup> one part of crystallized phenol dissolves in 8 to 9 parts of petroleum, 20 to 21 parts of gasoline, 23 to 24 parts of solid petrolatum, and 45 to 50 parts of liquid petrolatum.

### 2. *Preparation of Phenol in Industry*

Phenol is one of the many aromatic compounds present in coal tar. It is separated from other substances by fractional distillation ( $170^\circ$  to  $230^\circ C$ .) and by other methods of purification until "gray phenic acid" or a pure grade of phenol has been obtained. Synthetic processes developed for the production of phenol include its preparation by fusion of sodium benzene sulfonate with sodium hydroxide, and by hydrolysis of chlorobenzene.

### 3. *Uses of Phenol*

Phenol is used in the production or manufacture of a large variety of aromatic compounds. With rare exceptions, human exposure is limited to accidental contact of phenol with the skin or to inhalation of the vapor. Either may occur

<sup>1</sup> W. B. Deichmann, S. Witherup, and M. Christian, *unpublished observations*.

<sup>2</sup> J. D. Pilcher and T. Sollmann, *J. Pharmacol.*, 6, 377 (1914).

during the manufacture of phenol or during its use in the production of cresols, picric acid, explosives, fertilizers, bakelite, coke, illuminating gas, lamp black, paints, paint removers, rubber, asbestos goods, wood preservatives, synthetic resins, tannin, textiles, drugs, pharmaceutical preparations, and perfumes. Phenol also finds use in the petroleum, leather, paper goods, soap, toy, dye, and agricultural industries.

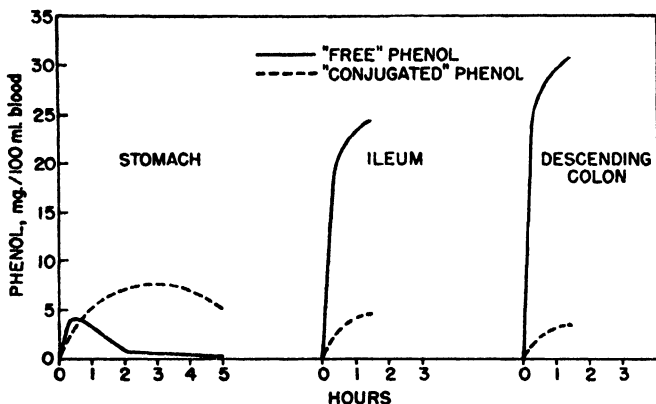


Fig. 1. Comparative rate of absorption of phenol from the stomach, ileum and descending colon of the rabbit.<sup>1</sup> 0.3 g. phenol per kilogram, as a 5 per cent aqueous solution, was placed into ligatured sections of the gastroenteric tract.

Following the introduction of the phenol spray by Lister in 1867, the compound became very popular and was used extensively for a number of years. Its medicinal uses are now limited chiefly to its application as an agent for relieving itching, as a disinfectant for septic wounds, as a cauterizing agent, as an insecticide, and as an agent in the treatment of some systemic disorders.<sup>2-12</sup>

#### 4. Absorption of Phenol

Phenol is readily absorbed through the intact skin and from the stomach, intestinal tract, uterus, intraperitoneal cavity, and subcutaneous tissues of man

<sup>1</sup> Bacelli, cited by H. C. Wood, Jr., *J. Am. Med. Assoc.*, **32**, 1249 (1899).

<sup>2</sup> U. Conforti, *Policlinico (Italy)*, No. 44, 1381 (1909).

<sup>3</sup> A. Ellinger, in A. Heffter, *Handbuch der experimentellen Pharmakologie*. Springer, Berlin, 1923.

<sup>4</sup> H. Herding, *Bull. méd.*, **53**, 281 (1939).

<sup>5</sup> R. Kobert, *Lehrbuch der Intoxikationen*. Ende, Stuttgart, 1906.

<sup>6</sup> L. Lewin, *Gifte und Vergiftungen*. Stilke, Berlin, 1929.

<sup>7</sup> B. Mistretta, *Policlinico, Rome, Sez. prat.*, **44**, 2287 (1937).

<sup>8</sup> A. Pisani, *Gazz. medica Lombarda*, **87**, 99 (1928).

<sup>9</sup> M. Sein, *Indian Med. Gaz.*, **74**, 270 (1939).

<sup>10</sup> C. Sironi, *Gazz. ospedali Clin.*, **51**, 395 (1930).

<sup>11</sup> H. Zangger, in F. Flury and H. Zangger, *Lehrbuch der Toxikologie*, Springer, Berlin, 1928; *Occupation and Health*, International Labor Office, Geneva, 1934.



and animals. Vapors of phenol are readily absorbed into the pulmonary circulation.

The rate of absorption of phenol through the skin of rabbits and consequently the degree of systemic poisoning induced by the experimental application of dilute and concentrated preparations of phenol in water, vegetable oils, alcohol, glycerol, and camphor depends primarily upon the skin area exposed and not upon the concentration in which it is applied (Deichmann *et al.*<sup>14</sup>). The degree of local damage varies with individual vehicles; it is greatest after application of a concentrated preparation. Observations which were made upon other experimental animals have furnished information as to the rate of absorption of phenol from different sections of the gastroenteric tract. According to Jackson,<sup>15</sup> absorption from the stomach is slow and of course is much influenced by the type and quantity of food in this organ. The rate of absorption from the intestine is very rapid at first, but later it becomes very much retarded.<sup>16,17</sup> Figure 1 represents the comparative rates of absorption of an aqueous preparation of phenol introduced into ligatured sections of the gastroenteric tract of rabbits starved for 48 hours prior to experimentation. Lethal concentrations of phenol in the blood readily resulted from absorption of phenol from the ileum and descending colon.<sup>1</sup>

### 5. Normal Metabolism of Phenol

Tyrosine and possibly other amino acids and related compounds are broken down by bacteria in the intestinal tract with the formation of *p*-cresol. This becomes oxidized to phenol and is carried by the blood to all the tissues.<sup>18-21</sup> At

<sup>14</sup> W. B. Deichmann and S. Witherup, *J. Pharmacol.*, **80**, 233 (1944).

<sup>15</sup> D. E. Jackson, *Experimental Pharmacology and Materia Medica*. Mosby, St. Louis, 1939.

<sup>15a</sup> S. S. Adams, *Arch. Pediatrics*, **11**, 825 (1894).

<sup>15b</sup> W. R. M. Turtle, and T. Dolan, *Lancet*, **2**, 1273 (1922).

<sup>15c</sup> S. E. Light, *Northwest Med.*, **30**, 232 (1931).

<sup>15d</sup> W. H. Brown, *Lancet*, **2**, 543 (1895).

<sup>15e</sup> R. Abrahams, *Pediatrics, N. Y.*, **9**, 241 (1900).

<sup>15f</sup> W. Gibson, *Queens Med. Quart.*, **10**, 113 (1905).

<sup>15g</sup> H. Wieland, *Therap. Halbmonatshefte*, **36**, 424 (1921).

<sup>15h</sup> V. Chlumsky, *Therap. Monatshefte*, **27**, 583 (1913).

<sup>15i</sup> E. Francis, *J. Am. Med. Assoc.*, **117**, 1973 (1941).

<sup>15j</sup> P. H. De Kruif, *Readers Digest*, May, 1942, p. 46.

<sup>15k</sup> H. O. Calvery, *J. Am. Med. Assoc.*, **119**, 366 (1942).

<sup>15l</sup> E. M. Satulsky and W. Halpern, *J. Med. Soc. New Jersey*, **40**, 137 (1943).

<sup>15m</sup> F. G. Miller, *Canad. Med. Assoc. J.*, **46**, FVE (1942).

<sup>16</sup> H. Nicolai, *Klin. Wochschr.*, **18**, 123 (1939); **20**, 80 (1941).

<sup>17</sup> T. Sollmann, P. J. Hanslik, and J. D. Filcher, *J. Pharmacol.*, **1**, 409 (1910).

<sup>18</sup> E. Baumann, *Arch. ges. Physiol.*, **13**, 285 (1876); *Z. physiol. Chem.*, **2**, 335 (1878-79); *ibid.*, **3**, 149, 250 (1879); *ibid.*, **6**, 183 (1882); *ibid.*, **10**, 123 (1886); *Arch. Anat. Physiol., Physiol. Abstracts*, 1879, 245.

<sup>19</sup> L. Brieger, *Z. physiol. Chem.*, **2**, 241 (1878-79); **3**, 134 (1879).

<sup>20</sup> F. Müller, *Berlin klin. Wochschr.*, **24**, 405, 433, 436 (1887).

<sup>21</sup> E. Salkowski, *Arch. path. Anat.*, **73**, 409 (1878); *Arch. ges. Physiol.*, **5**, 335 (1872); *Z. physiol. Chem.*, **7**, 161 (1882-83); **13**, 264 (1889).

least two mechanisms are involved in the metabolism of this endogenous phenol in the body: conjugation and oxidation appear to be of equal importance. Some

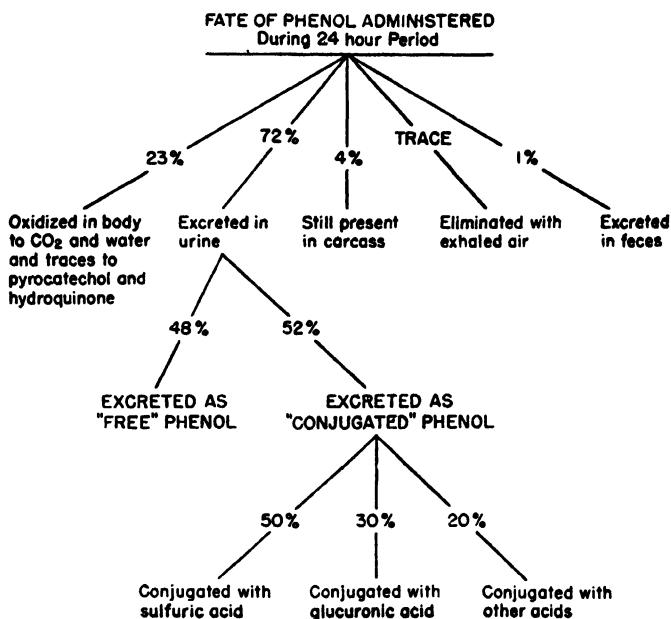


Fig. 2. Metabolism of phenol in a rabbit given a sublethal oral dose (0.3 g. per kilogram).<sup>24</sup>

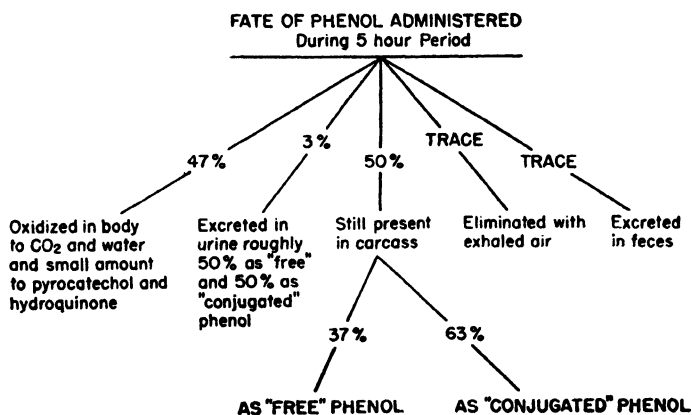


Fig. 3. Metabolism of phenol in a rabbit given a lethal oral dose (0.5 g. per kilogram).<sup>24</sup>

quantity is excreted unchanged or "free." Baumann<sup>18</sup> and other investigators of his period did much to elucidate the metabolism of this compound in the mammalian body.

Analyses carried out by means of a method for which a high degree of accuracy has been claimed have given the following concentrations of phenol in 100 g. or ml. of normal human body fluids or excretions<sup>22</sup>: blood, 0 to 0.08 mg. "free" and 0 to 0.08 mg. "conjugated" phenol; perspiration, 0.09 to 0.4 mg. "free" and 0.04 to 0.1 mg. "conjugated" phenol; saliva, 0.1 to 0.2 mg. "free" and 0.07 to 0.15 mg. "conjugated" phenol; feces, 1.9 to 4.2 mg. total phenol. The individual organs of two human beings who came to their death by accidental means, and who suffered no terminal or otherwise unusual exposure to phenol, contained not more than from 0 to 0.09 mg. "free" and from 0 to 0.56 mg. "conjugated" phenol. Twenty-four-hour urine specimens contained 0 to 3.8 mg. of "free" and 9.9 to 36.4 mg. "conjugated" phenol.<sup>22</sup> Normal tissues of rabbits and rats contain comparable concentrations. These animals excrete less phenol in their urine, but again, roughly 90 per cent of the phenol so excreted is conjugated.<sup>1,22</sup>

### 6. Metabolism in Cases of Poisoning

Various pathological conditions may induce a somewhat elevated formation or retention of phenol,<sup>7,19,23</sup> but the quantities observed under these conditions are much below, and can hardly be confused with, those encountered in cases of accidental or intentional phenol poisoning.

In cases of poisoning, the respective quantities of phenol disposed of by oxidation and by excretion, either as such or in conjugation, depend upon the rate at which "free" phenol enters the circulation. When this is low, the bulk of the phenol is conjugated and excreted in the urine within 24 hours, but when this is high and the amount absorbed is sufficient to kill, roughly half of such a dose of phenol is oxidized, while a similar amount is still present in the carcass at death. Figures 2 and 3, respectively, show graphically the fate of a lethal and a sublethal dose of phenol.<sup>18,24</sup> An explanation as to why and where phenol is conjugated in this manner may be found in the *in vitro* observations of Lipschitz, Bueding, de Meio, Arnolt, Darby, M. L. C. Bernheim, and F. Bernheim.<sup>25-28</sup>

### 7. Signs and Symptoms of Acute Poisoning by Phenol

Fatalities from poisoning by phenol have occurred more frequently in past decades than in recent years, although this compound and its various commercial preparations are still available to the public. Accidental poisoning has occurred in the home through the unintentional ingestion of phenol instead of some medicine or beverage.

<sup>22</sup> W. Deichmann and L. Schafer, *Am. J. Clin. Path.*, **12**, 129 (1942).

<sup>23</sup> E. Becher, S. Litzner, W. Täglic, and F. Doenecke, *Münch. med. Wochschr.*, **1676** (1925); **1656** (1927); *Klin. Wochschr.*, **147** (1926); *Z. klin. Med.*, **104**, 182, 195 (1926); *Z. physiol. Chem.*, **47**, 173 (1906).

<sup>24</sup> W. Deichmann, *Federation Proc.*, **2**, 77 (1943); *Arch. Biochem.*, **3**, 345 (1944).

<sup>25</sup> W. J. Darby, R. H. de Meio, M. L. C. Bernheim, and F. Bernheim, *J. Biol. Chem.*, **158**, 67 (1945).

<sup>26</sup> R. H. de Meio, *Arch. Biochem.*, **7**, 323 (1945).

<sup>27</sup> R. H. de Meio and R. I. Arnold, *J. Biol. Chem.*, **156**, 577 (1944); *J. Pharmacol.*, **84**, 64 (1945); *Rev. soc. argentina biol.*, **17**, 570 (1941); **18**, 158 (1942).

<sup>28</sup> W. L. Lipschitz and E. Bueding, *J. Biol. Chem.*, **129**, 333 (1939).

An oral dose of 1 g. of phenol may be lethal to man but there are also exceptional cases on record indicating that patients have survived the ingestion of 65 g. of pure phenol or 120 g. of the crude product. Roughly 50 per cent of all reported cases have terminated fatally.<sup>7,8</sup>

The swallowing of phenol causes intense burning of the mouth and throat followed by marked abdominal pain. The breath has the odor of phenol, the face is pale and usually covered with cold sweat, the pupils may be contracted or dilated, and cyanosis is usually marked. Collapse—manifested by muscular weakness and unconsciousness—occurs in many cases a few minutes after the poison is swallowed. The pulse is usually weak and slow, but occasionally it is racing. Respiration may be increased in rate in the early stage of poisoning, but later it decreases in both rate and magnitude. The temperature of the body may fluctuate above or below normal. Reflex activity is lost. General tremors or tonic-clonic convulsions or twitchings of isolated muscles of the face or limbs are occasionally observed, but they are never marked. Death usually results from respiratory failure.<sup>8,13,21,29-31</sup>

The signs and symptoms of systemic poisoning induced by the absorption of lethal concentrations of phenol through the skin are the same as those observed in cases of oral intoxication. The local effects include a tingling sensation followed by pain, anesthesia, and numbness. The epidermis may become soft and wrinkled and changed in color to white and later to yellow or brown. Deep erosions and necrosis may occur to such a degree as to require extensive excision or the amputation of an extremity. Similar local or systemic effects have also been noted after wrapping a limb or a finger for a day in a bandage soaked in a 1 or 2 per cent aqueous solution of phenol.<sup>5,7,8</sup> Adams reported in 1894<sup>15a</sup> the case of a 7-month-old boy whose body was covered almost completely with a poultice composed of 2.5 per cent phenol and stale bread for the purpose of "removing scales and crusts, and to allay itching." Severe signs of poisoning became apparent in 3 minutes. The child survived the acute intoxication but died later because of enterocolitis. In 1922, Turtle and Dolan<sup>15b</sup> cited the case of a patient who accidentally broke a bottle of dilute phenol that he was carrying in his pocket. The contents ran down his thighs. In these two instances, signs of systemic intoxication became apparent within 5 minutes. The toxemia was characterized by severe cyanosis, stertorous breathing with mucous vibrating in the larynx, vomiting, coma, abolition of reflexes, pin-point pupils, and lowering of body temperature.

Aqueous calamine zinc lotions containing 1 or 2 per cent phenol have enjoyed much popularity as agents to allay itching. The report by Light<sup>15c</sup> is of interest since it appears to be the only one of its type. A calamine and zinc lotion containing 1 per cent phenol was applied once a day to nearly the entire body of an 82-year-old woman. Shortly after the seventeenth application, she experienced

<sup>7</sup> T. Sollmann, *A Manual of Pharmacology*. Saunders, Philadelphia, 1927.

<sup>8</sup> F. P. Underhill, *Toxicology or the Effects of Poisons*. Blakiston, Philadelphia, 1928.

<sup>15</sup> A. R. Cushny, C. W. Edmunds, and J. A. Gunn, *Pharmacology and Therapeutics*. Lea & Febiger, Philadelphia, 1940.

weakness, dizziness, and collapse, followed by severe generalized clonic convulsions. She recovered from this intoxication, but since Dr. Light was not certain that phenol was the offending drug, he repeated the local applications, this time with a lanolin ointment containing 1 per cent phenol. After the seventh application, the patient showed tremors and convulsions lasting 40 minutes. After a rest period of about 4 weeks, 1 per cent phenol in calamine was applied again, once a day. After the fourth application, she showed convulsions and coma that lasted for 30 minutes. She died 3 $\frac{1}{2}$  months later of pneumonia. It is of interest in this connection that the first or the major signs of illness noted in experimental animals, and in humans who have repeatedly absorbed toxic but sublethal doses of phenol, are respiratory difficulties and pulmonary injury.

Brown<sup>15d</sup> described a severe acute intoxication that occurred in a three-year-old child whose scalp was treated accidentally with pure phenol instead of as directed, with a dilute solution. The mistake was discovered about 4 minutes after application of the material, when the child became unconscious. It recovered. A fatal case was reported by Abrahams.<sup>15e</sup> A nurse who had some pure phenol on her thumb and index finger accidentally touched the groin of a 7-day infant, leaving two sites from which absorption occurred. One was the size of a dime, the other as large as a dollar. Severe convulsions were observed within 5 minutes. The rectal temperature quickly rose to 105° F., while the body was covered with cold sweat. The pupils assumed pin-point size. Deep coma, cyanosis, and spasms of the facial musculature remained until death, which came 10 hours after the accident occurred. Gibson<sup>15f</sup> reported a fatal case in 1905, that of a 13-year-old girl who accidentally poured pure phenol over her scalp and cheeks. She died within 2 hours.

Concentrated mixtures of phenol and camphor were introduced in 1888 for the purpose of treating local areas of infection (Wieland<sup>15g</sup>). At room temperature the two compounds form an oily, colorless mixture which has the odor of its components, but primarily that of camphor. Preparations containing these two compounds in roughly equal gram molecular proportions were readily adopted since it was generally experienced that phenol, when associated with camphor, loses the greater part of its caustic effect, but maintains its analgesic and antiseptic action. About 1900, Chlumsky<sup>15h</sup> added a small volume of alcohol to the phenol-camphor mixture in order to reduce its viscosity. He adopted the following composition: camphor, 60 g.; phenol, 30 g.; alcohol, 10 g. Chlumsky's preparation and its anhydrous modifications became favorites among some doctors and dentists who used them for treating local areas of infection or for irrigating purulent wounds, abscesses, or joints. In 1941, Francis<sup>15i</sup> recommended a preparation containing 50 per cent each of phenol and camphor as a nonirritating mixture for the treatment of athlete's foot. His only precautionary remarks call attention to a breakdown of the preparation, with the consequent liberation of caustic phenol, should the phenol-camphor mixture be applied to wet skin. De Kruif's<sup>15j</sup> popularization of Francis' paper in *Readers Digest* resulted in

many requests to the medical and pharmacy professions for prescriptions and compoundings of this combination.

Calvery<sup>15k</sup> cited one case of local injury which resulted from self-medication with Francis' phenol-camphor mixture. The material was applied to a fairly large area of the leg near the ankle. A necrotic area developed at the site of application that required several weeks to heal. Hubler<sup>32</sup> reported a similar incident. A woman applied "Phenolene" for the treatment of "ringworm of the feet." At the time of admission to the hospital, one week after application of the 50 per cent phenol-camphor mixture, her feet were painfully swollen and there were numerous deep ulcerations between all of the toes. The patient was hospitalized for 13 days and totally disabled for 27 days. Seven similar cases came to the attention of Satulsky and Halpern.<sup>15l</sup> In each instance the difficulties arose because of self-medication. The chief complaints were burning and stinging. In one man, a lesion resulted from a single application of this phenol-camphor for the purpose of treating dermatophytosis. In another, phenol-camphor was applied for treatment of paronychia at the fourth finger and for "scaliness between the toes of both feet." The material was applied to each site once a day for a total of 7 days even though burning and stinging, lasting 4 to 5 hours, were experienced after each application. A fatality was reported by Miller<sup>15m</sup>. An 18-year-old lad obtained a phenol-camphor mixture, containing 70.7 per cent phenol, and had his housekeeper rub it over his right shoulder, scapular region, and parts of the trunk for treatment of ringworm. Since he complained of a burning sensation before the completion of the application, the housekeeper diluted part of this mixture with water and continued the application. The boy became dyspneic, collapsed, and died within a few minutes. Chemical analysis revealed the presence of phenol in all organs analyzed. Summarizing these and other observations it can be said that claims that the causticity is totally eliminated, in mixtures containing more than 30 per cent each of phenol and camphor, are exaggerations. The causticity remaining can be traced in part to an aqueous phenol phase, formed because of equilibration of the phenol between the phenol-camphor and the tissue fluids or perspiration, of which no wound or skin remains free for any length of time. Mixtures of phenol and camphor containing 30 per cent or a higher concentration of phenol should never be considered for self-medication. Their effectiveness in the treatment of dermatophytosis needs verification.

Dilute preparations of phenol and camphor also have been used for many years but only a single report of an adverse result has been found in the literature. Satulsky and Halpern<sup>15l</sup> reported the case of a white soldier who had treated himself for "crabs" by applying some of the contents of a one-ounce bottle labeled "Campho-Phenique" to the groin, pubic area, lower abdomen, and genitalia. The bottle was purchased in Panama. According to information obtained from the manufacturer, the concentration of phenol in this preparation may have been anywhere between  $16\frac{2}{3}$  and 4.75 per cent, since at about this time the concentration of phenol had been gradually reduced. A burning sensa-

<sup>32</sup> W. R. Hubler, *J. Am. Med. Assoc.*, 123, 990 (1943).

tion and pain were experienced within 2 hours after the application of the material. These symptoms increased in severity during the next few days. The man was in marked distress when admitted to the hospital. Examination revealed severe dermatitis. A subsequent patch test carried out with the same material induced severe burning in 30 minutes. The skin became extremely red and showed the beginning of vesiculation. Some of the material was then applied to the skin of the back and this time left uncovered. The effect was the same as that previously described. In order to determine whether this soldier represented a hypersensitive individual, some of the material was painted upon the upper arms of a nurse and the two authors. The results were much like those described.

Cronin and Brauer recently<sup>38a</sup> reported the death of a child due to phenol in Foille, which is essentially 2 per cent phenol in corn oil. It was applied to a dressing covering that part of the body (25 to 30 per cent) which had suffered first and second degree burns. The total volume applied over 2½ days was more than 7½ liters. The child died nearly 3 days after the accident occurred with signs and symptoms typical of systemic phenol intoxication.

Serious cases of intoxication have also been reported, after the application of about 0.3 to 1 per cent aqueous solutions of phenol to wounds, peritoneum or uterus.<sup>7,33-37</sup> Occasionally one encounters persons who possess a hypersensitivity to phenol and who may show marked symptoms of poisoning or severe dermatitis following absorption of very small doses.<sup>37a,37b</sup> According to Schwartz and Tulipan,<sup>38</sup> phenol causes about 20 per cent of the dermatitis (particularly in women) that occurs in the phenol resin industries.

The signs of illness induced by phenol in experimental animals, regardless of the mode of administration, resemble those observed in man. However, in man, phenol usually exerts (directly and indirectly) a predominant action upon the higher centers resulting in sudden collapse. In other mammals the predominant effects are exerted upon motor centers in the spinal cord inducing marked twitchings and severe convulsions. The dose necessary to induce poisoning varies with the species and is influenced by the method of administration, quantity and type of stomach contents, and by the solvent employed. As a rule, the survival time after the administration of a lethal dose is inversely proportional to the dose administered, ranging from 5 minutes to about three hours.<sup>14</sup> Occasionally death is delayed for several days when the compound is given (in a single dose) subcutaneously or upon the skin (Tables 1 and 2).

<sup>33</sup> C. W. Brown, *Lancet*, 1, 453 (1895).

<sup>34</sup> R. Abrahams, *Lancet*, 1, 1362 (1895).

<sup>35</sup> W. Gibson, *Queen's Med. Quart.*, 10, 133 (1905); *Mass. Repts.*, 138, 165 (1905).

<sup>36</sup> T. E. Harrington, *J. Am. Med. Assoc.*, 68, 1448 (1917).

<sup>37</sup> J. Gottlieb and E. Storey, *Maine Med. J.*, 27-28, 161 (1936-37).

<sup>37a</sup> S. E. Light, *Northwest Med.*, 30, 232 (1931).

<sup>37b</sup> R. de Blasio and M. Luca, *Rinascenza med.*, 13, 303 (1936).

<sup>38</sup> L. Schwartz and L. Tulipan, *Occupational Diseases of the Skin*. I. Philadelphia, 1939. (1910).

<sup>38a</sup> T. D. Cronin and R. O. Brauer, *J. Am. Med. Assoc.*, 139, 777 (1931).

TABLE 1  
*Toxicity of Two to Seven Per Cent Aqueous Solutions of Phenol for Adult Experimental Animals*

Animal	Route	Dose killing approx. 50% of animals, g./kg.	References
Mouse	Subcut.	0.3-0.35	Tollens, <sup>39</sup> Duplay and Cazin <sup>40</sup>
Rat	Subcut.	0.45	Deichmann and Witherup <sup>14</sup>
	Oral	0.53 <sup>a</sup>	" " "
	Cut.	2.5	" " "
Guinea pig	Subcut.	0.68	Duplay and Cazin <sup>40</sup>
Rabbit	Intrav.	0.18	Deichmann and Witherup <sup>14</sup>
	Subcut.	0.5-0.6	Tauber, <sup>41</sup> Tollens <sup>39</sup>
	Oral	0.6	Clarke and Brown <sup>42</sup>
	Oral	0.4-0.6	Deichmann and Witherup <sup>14</sup>
	Intraper.	0.5-0.6	" " "
Cat	Subcut.	0.09	Tollens <sup>39</sup>
	Oral	0.1	Macht <sup>43</sup>
Dog	Oral	0.5	"
Monkey	Toxicity is of similar order to that for rabbit		Smith, Elvove, and Frazier <sup>44</sup>

<sup>a</sup> LD<sub>50</sub>.

TABLE 2  
*Comparative Toxicity of Aqueous Preparations of Phenol in Different Concentrations\* Applied to the Abdominal Skin of Rabbits<sup>14</sup>*

Dose of 2 g./k., administered as	Number of rabbits used	Per cent of deaths
Emulsion: 10 g. phenol and 90 g. water	10	100
Emulsion: 25 g. phenol and 75 g. water	10	90
Emulsion: 50 g. phenol and 50 g. water	10	90
Solution: 75 g. phenol and 25 g. water	10	80
Solution: 90 g. phenol and 10 g. water	10	50
Solution: 95 g. phenol and 5 g. water	17	53
Melted phenol reagent heated to 40°C.	15	30

\* Standard dose for all concentrations = 2 g. phenol per kilogram of rabbit.

### 8. Chronic Poisoning by Phenol

In Lister's day,<sup>44a</sup> cases of chronic or subacute phenol poisoning were not uncommon among surgeons and their assistants, who were exposed regularly to phenol sprays. As Kobert<sup>7</sup> remarks, many of the doctors must have possessed great tolerance considering that they used, applied, and inhaled sprays of carbolic acid for years without illness or apparent discomfort. No doubt the inter-

<sup>39</sup> K. Tollens, *Arch. exptl. Path. Pharmacol.*, 52, 220 (1905).

<sup>40</sup> S. Duplay and M. Cazin, *Compt. rend.*, 112, 672 (1891).

<sup>41</sup> E. Tauber and S. Tauber, *Z. physiol. Chem.*, 2, 366 (1878-79); *Arch. exptl. Path. Pharmacol.*, 36, 197, 211 (1895).

<sup>42</sup> T. W. Clarke and E. D. Brown, *J. Am. Med. Assoc.*, 46, 782 (1906).

<sup>43</sup> Macht, *Bull. Johns Hopkins Hosp.*, 26, 98 (1915).

<sup>44</sup> Smith, E. Elvove, and W. H. Frazier, *U. S. Pub Health Repts.*, 45, 2509 (1930).

<sup>44a</sup> *Lancet*, 2, 95, 353, 668 (1867).

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mittent character of their exposure was a factor in their favor. Data which give us an insight into the quantities of phenol apparently tolerated by man were reported in 1881 by Falkson,<sup>45</sup> who stated that after inhaling these vapors for several hours his own urine contained phenol in amounts up to 2 g. per day, while the urine of patients who absorbed the compound from the inspired air as well as from the skin or from open wounds, contained up to 5 g. per day.

Chronic phenol poisoning occurs infrequently at present. It usually results from absorption of phenol by way of the respiratory tract or through the skin. According to Zangger,<sup>13</sup> the state of chronic poisoning in man is characterized by serious systemic disorders: digestive disturbances, including vomiting, difficulty of swallowing, ptyalism, diarrhea, and anorexia; nervous disorders, with headache, fainting, vertigo, and mental disturbances; and an eruption on the skin. The disease is usually fatal when there is extensive damage to the liver and kidneys. Prolonged cutaneous exposure to preparations of phenol may result in ochronosis.

Biebl<sup>46</sup> fed the compound to dogs and found that doses up to 0.4 g. administered twice weekly for 9 months were tolerated well; somewhat larger doses usually produced no signs of acute poisoning but they sometimes resulted in dyspnea and sudden death. Heller and Pursell<sup>47</sup> added phenol to the drinking water of rats for a prolonged period of time and concluded that concentrations lower than 10 g. per liter did not interfere with normal digestion, absorption, or other metabolic functions. Observations by other investigators<sup>48</sup> indicate that concentrations of 2 g. of phenol per liter and above retard the growth of rats and lessen their resistance to intercurrent diseases of the lungs. Bronchopneumonia was noted by Wachholz<sup>49</sup> who injected the compound subcutaneously in sublethal concentrations into cats. It appears from these and other reports<sup>5,13,50,51</sup> that the repeated absorption (from the gastroenteric tract or subcutaneous tissues) of toxic but sublethal doses of phenol affects the lungs with considerable frequency; also damages such other organs as the heart, liver, and genitourinary tract.

Only one group of investigators<sup>52</sup> appears to have studied the effects resulting from prolonged inhalation of low concentrations of phenol vapor. Inhalation by guinea pigs of vapors in concentrations ranging from 0.1 to 0.2 mg. of phenol per liter of air (30 to 60 p.p.m.) induced obvious distress and illness, with respiratory difficulties, loss of weight, and paralysis after 20 7-hour periods of exposure. Rabbits showed no signs of illness after 63 such periods of exposure.

<sup>45</sup> R. Falkson, *Arch. klin. Chir.*, 26, 204 (1881).

<sup>46</sup> M. Biebl, *Beitr. path. Anat.*, 84, 257 (1930); *Z. ges. exptl. Med.*, 87, 436 (1933); *ibid.*, 93, 515 (1934).

<sup>47</sup> V. G. Heller and L. Pursell, *J. Pharmacol.*, 63, 99 (1938).

<sup>48</sup> W. B. Deichmann and P. Oesper, *Ind. Med.*, 9, 296 (1940).

<sup>49</sup> L. Wachholz, *Deut. med. Wochschr.*, 1896, 146.

<sup>50</sup> Wandel, *Arch. exptl. Path. Pharmacol.*, 56, 161 (1907).

<sup>51</sup> W. Hesselbach, *Inaugural Dissertation*, Halle, 1890.

<sup>52</sup> W. B. Deichmann, K. V. Kitzmiller, and S. Witherup, *Am. J. Clin. Pat.* (1910).

but suffered extensive and progressive pulmonary inflammation and injury. Rats failed to show signs of illness or postmortem evidences of injury after 53 periods of exposure.

#### **9. Maximum Permissible Concentration**

The maximum permissible concentration of vapors of phenol in air has not been established, but it appears from observations of W. B. Deichmann, K. V. Kitzmiller, and S. Witherup that an attempt should be made to keep concentrations well below 30 parts per million. According to Irish, concentrations in air (and water) of 5 p.p.m. or less are detectable by most individuals (chlorophenols are detectable when present to about 1 part per hundred million). Beinhardt<sup>53</sup> indicates that concentrations of about 4 p.p.m. will impart a decided phenol taste to vegetables and fruits grown within a radius of more than a mile from a plant where such vapors escape.

#### **10. Prevention of Poisoning by Phenol**

The manufacture and use of phenol in industry need not be considered an industrial hazard as long as management installs effective safety measures and employees are instructed and supervised in the handling of this material. Since certain persons are extremely sensitive to phenol, it is well to question new employees as to any known susceptibility to this or to closely related materials. Those affected with hepatic or kidney diseases should not be employed for any length of time if such employment involves exposure to phenol. Even intermittent exposure to vapors of phenol may become quite dangerous, particularly when the material is handled at elevated temperatures. It should also not be overlooked that liquid phenol is combustible and that mixtures of air containing 3 to 10 per cent phenol are explosive.

Measures of safety should consider at least the following:

(a) Publication and distribution of a manual outlining individual steps to be followed in the manufacture, handling, loading, storage, transport, and unloading of phenol.

(b) Effective ventilation sufficient to reduce the concentration of phenol in air to a level that is not injurious to workmen.

(c) Proper disposal of phenol waste without overlooking either the comfort and health of the population living near the plant, or the possible pollution of streams and underground waters.

(d) Cleaning of tanks should not be attempted without proper gear: a rescue harness and life line, hose mask, boots, apron and gloves of rubber, and a "watcher" stationed at the entrance of the tank.

(e) Continuous vigilance on the part of the hygienist or physician for signs and symptoms of chronic, local, or systemic intoxication.

(f) For the removal of phenol accidentally spilled upon the skin, showers and other facilities adequate to supply, quickly and easily, a vertical *flood* of water. A first-aid station should be established for giving the promptest attention to any casualty. The recommendation to cover the skin by protective creams gives most workers a false sense of security and therefore, not be advocated.

### 11. Treatment of Phenol Poisoning

*Phenol spilled upon the skin is removed most efficiently by flooding the affected area with water in such a manner as to carry the phenol away from the body. To be effective, however, this must be done promptly, since otherwise time will have been given for absorption to occur.*

Experimental observations<sup>54,55</sup> have shown that the rate of absorption from the skin of animals depends primarily upon the size of the area involved, and upon the duration of contact. The concentration of the solution applied appears to be a less important factor. For this reason, if a preparation of phenol be spilled upon the skin, it is imperative that all parts of the body and clothing that have become wetted by the washings be flushed until all traces of phenol have been removed. It is best to undress under the shower and later don new garments. It is well to cover phenol burns with wet dressings, such as compresses of saturated sodium sulfate. Healing of the cutaneous burns of animals where local damage was induced by the application of concentrated phenol, the compound being removed subsequently by flushing with water, was not expedited by treatment with various vegetable oils or glycerol. Application of a solution of 50 per cent camphor in ethyl alcohol irritated the skin of rabbits and consequently retarded healing.

Speed is equally essential in the treatment of *oral poisoning*. If a patient is conscious and it is ascertained that by placing a finger far back into the throat he can easily be induced to vomit, 15 to 30 ml. of castor oil or some other vegetable oil may well be administered. If vomiting is not induced readily and promptly, gastric lavage should be initiated without delay, employing preferably an aqueous solution of 40 per cent of Bacto-Peptone or milk, or if these are not available, water. Washing should be continued employing 300 to 400 ml. of liquid at a time until the odor of phenol is no longer detectable.

After the stomach has been washed out, an oral dose of 15 to 50 ml. of castor or other vegetable oil may be administered to advantage. (Animal experiments have shown that phenol is less toxic when administered in castor oil than in other vegetable oils.<sup>55</sup> However, caution is in order in the face of serious alimentary damage, and it may be inadvisable to give a cathartic such as castor oil if much time has elapsed since the ingestion of the phenol. As Jackson<sup>56</sup> and others<sup>57,58</sup> have pointed out, oils retard the absorption of phenol and tend to reduce the local damage.

Symptomatic treatment consists primarily of the administration of circulatory stimulants. These may augment the systemic poisoning temporarily but they counteract stasis, and therefore tend to prevent thrombosis and necrosis. Trans-

<sup>54</sup> W. B. Deichmann and S. Witherup, *J. Pharmacol.*, **80**, 233 (1944).

<sup>55</sup> W. B. Deichmann, S. Witherup, and M. Christian, *unpublished observations*.

<sup>56</sup> D. E. Jackson, *Experimental Pharmacology and Materia Medica*. Mosby, St. Louis, 1939.

<sup>57</sup> R. Kobert, *Lehrbuch der Intoxikationen*. Enke, Stuttgart, 1906.

<sup>58</sup> T. Sollmann, P. J. Hanzlik, and J. D. Pilcher, *J. Pharmacol.*, **1**, 409 (1910).

fusions may also be indicated. In collapse, heat should be applied.

The treatment of *chronic phenol poisoning* is symptomatic after the patient has been removed from the site of exposure.

### 12. Factors Relating to Legal Aspect of Poisoning by Phenol

The gross appearance of the lesions is suggestive but not sufficiently specific to exclude all other substances. Microscopic examination of tissues that have had brief contact with phenol is likely to be entirely fruitless because of the excellent "fixing" properties of phenol solutions. Chemical analysis will provide positive or negative evidence in a case in which poisoning by phenol is suspected. Stomach contents (in oral poisoning) and blood and urine are best suited for analysis in the surviving patient. The relative concentrations of "free" and "conjugated" phenol will furnish useful information in relation to the prognosis. In fatal cases any tissue or excretion may be employed.

Analysis of tissues should be carried out as soon as feasible after death because glycolysis will alter the respective concentrations of "free" or "conjugated" phenol. Rising and Lynn<sup>59</sup> suggest ethyl alcohol as a preservative for samples of viscera containing phenol. These recommendations are supported by other observations,<sup>55</sup> which indicate that 10 to 15 per cent of phenol was lost during a period of 12 months when rat tissues (containing originally 25 mg. of phenol) were kept in ethyl alcohol, at 7° C., in paraffin-stoppered containers. Fifty per cent of the original content of phenol was lost from corresponding tissues, preserved under identical conditions except for the presence of alcohol. Embalming destroys the evidence of poisoning by phenol since fluids employed for this purpose contain this or very closely related compounds.

### 13. Chemical Analysis of Phenol

It cannot be overemphasized that in order to determine the phenol content of materials one must use analytical procedures that possess a high degree of specificity; obviously, the choice and application of a procedure should be in the hands of a competent chemist. Qualitative tests can be expected to give useful information only if it is realized that a positive test may also be induced by one or several of a large group of related compounds.<sup>60</sup>

Standard solutions for the quantitative determination of phenol may be prepared according to Messinger and Vortmann<sup>61</sup> or Folin and Denis.<sup>62</sup> Aqueous solutions of resorcinol<sup>63</sup> or  $\beta$ -naphthol<sup>64</sup> are also suitable as standards. These compounds have the advantage of being solids at room temperature and consequently they can be weighed directly; however, they must be compared with standard solutions of phenol by the specific analytical method to be employed in the estimation.

<sup>59</sup> L. W. Rising and E. V. Lynn, *J. Am. Pharm. Assoc.*, 21, 138 (1932).

<sup>60</sup> W. Deichmann and L. Schafer, *Am. J. Clin. Path.*, 12, 129 (1942).

<sup>61</sup> J. Messinger and Vortmann, *Ber.*, 22, 2313 (1889).

<sup>62</sup> O. Folin and W. Denis, *J. Biol. Chem.*, 22, 305, 309 (1915); 26, 507 (1916).

<sup>63</sup> S. R. Benedict and R. C. Theis, *J. Biol. Chem.*, 30, 95 (1918).

<sup>64</sup> C. Henningson, *Ind. Eng. Chem.*, 15, 406 (1923).

A critical review of analytical methods and their usefulness and limitations in estimating "free" and "conjugated" phenol in blood, organs, urine, saliva, feces, etc. was published in 1942.<sup>60</sup> In addition to the analytical procedures recommended therein, the reader is advised to consider also those that have appeared more recently by Schmidt,<sup>65</sup> Tucker,<sup>66</sup> Chirkov,<sup>67</sup> Baernstein,<sup>68</sup> and Lykken *et al.*<sup>69</sup>

The concentration of phenol in the atmosphere may be estimated by collecting a sample of contaminated air in an evacuated sampling flask and treating it with sodium hydroxide and a reagent giving a color that lends itself for comparison with suitable standard solutions. This principle is simple and is expected to give satisfactory results when other compounds reacting similarly are absent. Final analysis by means of a spectrophotometer will give more accurate and more specific information.<sup>52,60</sup>

## PYROCATECHOL

Pyrocatechol,  $C_6H_4(OH)_2$ , *o*-dihydroxybenzene, 1,2-benzenediol, pyrocatechin, also known as catechol, is a colorless crystalline solid (molecular weight of 110.11, specific gravity of 1.37) which melts at 104° C. and decomposes when heated to 240° or 245°. It dissolves readily in water, alcohol, and ether. The compound is used for various purposes, but particularly as an antioxidant<sup>70-72</sup> in the rubber, chemical, photographic, dye, fat,<sup>73</sup> and oil<sup>74</sup> industries. It is also employed in cosmetics<sup>75</sup> and in some pharmaceuticals.

Cases of industrial or accidental poisoning have been rare. Contact with the skin has been known to cause an eczematous dermatitis, while absorption through the skin in a few instances has resulted in symptoms of illness resembling closely those induced by phenol, except for certain central effects (convulsions) which were more marked.<sup>76</sup>

Phenol-like signs of illness are induced also in experimental animals given toxic or lethal doses. The repeated absorption of sublethal doses by animals may also induce methemoglobinemia, leucopenia, and anemia. Little is known about the metabolism of this compound, except that part of it is oxidized, and that another fraction conjugates in the body with hexuronic, sulfuric, and other acids.

<sup>60</sup> E. G. Schmidt, *J. Biol. Chem.*, **145**, 533 (1942); **150**, 69 (1943).

<sup>66</sup> I. W. Tucker, *J. Assoc. Official Agr. Chem.*, **25**, 779 (1942).

<sup>67</sup> S. K. Chirkov, *J. Appl. Chem. (U. S. S. R.)*, **17**, 31 (1944).

<sup>68</sup> H. D. Baernstein, *J. Biol. Chem.*, **161**, 685 (1945).

<sup>69</sup> L. Lykken, R. S. Treseder, and V. Zahn, *Ind. Eng. Chem.*, **18**, 103 (1946).

<sup>70</sup> J. Lavollay and J. L. Parrot, *Compt. rend.*, **215**, 496 (1942).

<sup>71</sup> S. Manskaya and Emelyanova, *Biokhimiya*, **5**, 432 (1940).

<sup>72</sup> G. T. Martin *et al.*, *Am. J. Physiol.*, **136**, 66 (1942).

<sup>73</sup> C. H. Lea, *J. Soc. Chem. Ind.*, **63**, 107 (1944).

<sup>74</sup> K. Biltz and W. Simon, *Monatschr. Textil-Ind.*, **56**, 195 (1941).

<sup>75</sup> *Cosmetics and Allied Preparations*. Bur. Investigation, Am. Med. Assoc., Chicago, Illinois, 1938.

<sup>76</sup> A. R. Cushny, C. W. Edmunds, and J. A. Gunn, *Pharmacology and Therapeutics*. Lea & Febiger, Philadelphia, 1940.

A small amount is excreted in the urine as "free" pyrocatechol. The "conjugated" fraction hydrolyzes easily in the urine<sup>68,77</sup> with the liberation of the "free" compound; this is oxidized with the formation of dark-colored substances that impart to the urine a "smoky" appearance (see also phenol poisoning).

Pyrocatechol is more toxic than phenol. The approximate lethal oral dosages (in grams per kilogram) for various experimental animals are: dog, 0.37<sup>78</sup>; rabbit, 0.27<sup>79</sup>; cat, 0.1; and guinea pig, 0.16.<sup>80</sup> Most rats and guinea pigs die when given a single subcutaneous injection of about 0.22 g. per kilogram, while the lethal intravenous dose for dogs is about 0.04 g. per kilogram.<sup>81</sup>

## RESORCINOL

Resorcinol,  $C_6H_4(OH)_2$ , *m*-dihydroxybenzene, also known as resorcin, occurs in colorless rhombic tablets and pyramids, which have a sweet taste. It has a molecular weight of 110.11, a specific gravity of 1.29, a melting point of 110° C., and boiling point of 276°. It has a vapor pressure of 20.1 mm. Hg at 25.1° corresponding to 2.64 per cent by volume in "saturated" air at that temperature. The compound is readily soluble in water, alcohol, glycerol, and ether.<sup>82</sup> It is used in tanning, in photography, and in the manufacture of explosives, dyes, cosmetics, organic chemicals, and antiseptics.<sup>83,84</sup> Recently it has also been suggested as an aerial bactericide.<sup>85,86</sup>

Resorcinol, in a suitable solvent, is readily absorbed through the human skin. The cutaneous application of solutions or salves<sup>87</sup> containing from 3 to 25 per cent of this compound may result in local hyperemia, itching, dermatitis, edema, and corrosion, associated with enlargement of regional lymph glands, as well as in serious systemic disorders such as restlessness, methemoglobinemia, cyanosis, convulsions, tachycardia, dyspnea, and death.<sup>76,88,89</sup>

Ingestion of resorcinol induces similar signs of systemic illness. Thus a child, after accidentally swallowing 4 g., complained of dizziness and somnolence. The ingestion of 8 g., in another case, induced an almost immediate hypothermia, fall in blood pressure, and decrease in the rate of respiration, with tremors, icterus, and hemoglobinuria. Recovery was noted 2 hours after the poisoning.<sup>88</sup> Other

<sup>77</sup> F. Vorsatz, *Collegium*, 424 (1942); *Chem. Abstracts*, 37, 6927 (1943).

<sup>78</sup> G. Colasanti and R. Moscatelli, *Boll. e atti accad. med. Roma* (1887-88).

<sup>79</sup> F. Heyroth and E. Largent, *personal communication*.

<sup>80</sup> A. Masing, *Inaugural Dissertation*, Dorpat, 1882.

<sup>81</sup> W. Gibbs and H. A. Hare, *Dubois Arch. Physiol.*, 1890, 352

<sup>82</sup> *Merck Index*, Merck, Rahway, N. J., 1940.

<sup>83</sup> P. A. Ark, *Phytopathology*, 30, 1 (1940).

<sup>84</sup> A. Laurie, *Agr. News Letter, Pub. Relations Dept.*, E. I. du Pont de Nemours & Co., 9, 22 (1941).

<sup>85</sup> C. C. Twort and A. H. Baker, *J. Hyg.*, 42, 266 (1942).

<sup>86</sup> A. E. Williamson and H. B. Gotaas, *Ind. Med.*, 11, 40 (1942).

<sup>87</sup> E. A. Strakosch, *Arch. Dermatol. Syphilol.*, 48, 384 (1943).

<sup>88</sup> L. Lewin, *Gifte und Vergiftungen*. Stilke, Berlin, 1929.

<sup>89</sup> L. Schwartz and L. Tulipan, *Occupational Diseases of the Skin*. Lea & Febiger, Philadelphia, 1939.

cases are on record in which similar doses had apparently no ill effects.<sup>90</sup> The compound is excreted in the urine, as are other phenols, in a free state and conjugated with hexuronic, sulfuric, or other acids. Analytical methods for the estimation of resorcinol<sup>91-93</sup> have not been adapted to its solution in body fluids. Because of the potential toxicity of this compound, it should be handled and employed with caution. Safe concentrations have not been established for its use as an aerial bactericide.

The approximate lethal oral dose of resorcinol, in aqueous solution, for rabbits is 0.75 g. per kilogram<sup>79</sup> and for rats and guinea pigs 0.37 g. per kilogram.<sup>94</sup> The signs of illness resemble those induced by phenol, except that the antipyretic action of resorcinol is more marked.

## HYDROQUINONE

Hydroquinone,  $C_6H_4(OH)_2$ , *p*-dihydroxybenzene, crystallizes from water in hexagonal prisms, which have a sweet taste. It has a molecular weight of 110.11, a specific gravity of 1.35, a melting point of 170° C., and a boiling point of 285°. The compound dissolves readily in hot water (7 per cent at 25° C.), alcohol, and ether. Its industrial uses are similar to those of pyrocatechol and resorcinol.<sup>95-105</sup>

When a sufficient concentration of hydroquinone is absorbed into the tissues of man, it causes signs and symptoms of illness resembling those induced by its ortho or meta isomer. Ingestion of 1 g. by an adult (smaller quantity by a child) may induce tinnitus, nausea, dizziness, a sensation of suffocation, an increased rate of respiration, vomiting, pallor, muscular twitchings, headache, dyspnea, cyanosis, delirium, and collapse. The urine is usually green or brownish-green in color and continues to darken on standing.<sup>88</sup> Fatal cases have been reported after ingestion of 5 to 12 g.<sup>106</sup> Certain "health teas" have been prepared from leaves of blueberry, red whortle berry, cranberry, or bear berry. Their ingestion should be avoided for the leaves may contain hydroquinone in a concentration (sometimes exceeding 1 per cent) capable of producing irritation of the intestinal mucosa and systemic poisoning.<sup>88</sup> Cases of dermatitis have resulted from

<sup>90</sup> V. Surbeck, *Deutsch. Arch. klin. Med.*, **32**, 515 (1883).

<sup>91</sup> F. M. Garfield, *J. Assoc. Official Agr. Chem.*, **25**, 897 (1942).

<sup>92</sup> A. O. Songina, *Chem. Abstracts*, **37**, 53 (1943).

<sup>93</sup> P. Torti, *Boll. chim.-farm.*, **81**, 28 (1942); *Chem. Abstracts*, **38**, 3220 (1944).

<sup>94</sup> L. Brieger, *Z. physiol. Chem.*, **2**, 241 (1878-79); **3**, 134 (1879).

<sup>95</sup> U. P. Basu, *Ann. Biochem. Exptl. Med.*, **1**, 165 (1941); *Chem. Abstracts*, **37**, 3559 (1943).

<sup>96</sup> C. Golumbic and H. A. Mattill, *J. Am. Chem. Soc.*, **63**, 1279 (1941).

<sup>97</sup> C. E. Hartt, *Chem. Abstracts*, **37**, 6150 (1943).

<sup>98</sup> H. A. Hollender and P. H. Tracy, *J. Dairy Sci.*, **25**, 249 (1942).

<sup>99</sup> A. Overman, *J. Biol. Chem.*, **142**, 441 (1942).

<sup>100</sup> W. T. Sumerford, A. B. Huff, and O. K. Coleman, *J. Am. Pharm. Assoc.*, **33**, 150 (1944).

<sup>101</sup> H. Süllmann, *Helv. Chim. Acta*, **26**, 1114 (1943).

<sup>102</sup> R. Waite, *J. Dairy Research*, **12**, 178 (1941).

<sup>103</sup> K. Weber, *Radiologica*, **1**, 223 (1937).

<sup>104</sup> A. Weissberger, D. S. Thomas, and J. E. LuValle, *J. Am. Chem. Soc.*, **65**, 1489 (1943).

<sup>105</sup> K. T. Williams, E. Bickoff, and B. Lowrimore, *Oil & Soap*, **21**, 161 (1944).

<sup>106</sup> I. Zedman and R. Deute, *Am. J. Med. Sci.*, **210**, 328 (1945).

skin contact with hydroquinone. Lapin<sup>107</sup> reports such findings after application of an "antiseptic oil" which apparently contained traces of hydroquinone as an antioxidant. Velhagen,<sup>108</sup> Sterner,<sup>109</sup> and others<sup>110</sup> have reported cases of keratitis and discoloration of the conjunctiva among men exposed to concentrations ranging from 10 to 30 mg. of vapor or dust of hydroquinone per cubic meter of air.

When absorbed to a sufficient concentration in the tissues of experimental animals, hydroquinone induces signs of illness which resemble in many respects those induced by phenol. In acute poisoning one may see an increased motor activity, hypersensitivity to external stimuli, hyperactive reflexes, dyspnea, and cyanosis; these signs are followed by marked clonic convulsions and later by complete exhaustion, hypothermia, paralysis, loss of reflexes, coma, and death. (Marked formation of methemoglobin occurs after death.) Subacute poisoning may be characterized by hemolytic icterus, anemia, leukocytosis, reticulocytosis, increased cell fragility, hypoglycemia, depigmentation of fur, and marked cachexia. Little is known about the metabolism of hydroquinone except that it appears to induce specific effects primarily after having become oxidized to the more toxic quinone.<sup>111-117</sup> (Hydroquinone will also oxidize to quinone when exposed to light or air.) Hydroquinone and quinone are partially excreted as such, and in conjugation with hexuronic, sulfuric, and other acids.

Hydroquinone is more toxic than phenol. The approximate lethal oral dosages of this compound in aqueous solution are 0.2 g. per kilogram for the rabbit,<sup>76</sup> and 0.08 g. per kilogram for the cat.<sup>118</sup> The lethal intravenous dose for the dog is about 0.09 g. per kilogram,<sup>119</sup> and the lethal subcutaneous dose for mice is about 0.16 g. per kilogram.<sup>111</sup>

In view of its potential toxicity, hydroquinone should be handled with caution. The inhalation of vapors, liberated particularly at elevated temperatures, must be avoided. Sterner<sup>109</sup> recommends that the concentration of dust of hydroquinone in air be kept below 5 mg. per cubic meter. Analysis of the blood or urine may serve to demonstrate the absorption of this compound.<sup>68,120-123</sup>

<sup>107</sup> J. H. Lapin, *Am. J. Diseases Children*, 63, 89 (1942).

<sup>108</sup> Velhagen, cited in L. Schwartz and L. Tulipan, *Occupational Diseases of the Skin*. Lea & Febiger, Philadelphia, 1939.

<sup>109</sup> J. H. Sterner, *personal communication*.

<sup>110</sup> A. I. Dashevskiy and F. F. Marmorshteyn, *Vestnik oftalmol.*, 19, Nos. 1-2, 50 (1941).

<sup>111</sup> S. Busatto, *Deut. Z. ges. gerichtl. Med.*, 31, 285 (1939); *Arch. antropol. criminale, psichiat. med. legale, Torino*, 60, 620 (1940).

<sup>112</sup> A. Ellinger, in A. Heffter, *Handbuch der experimentellen Pharmakologie*. Springer, Berlin, 1923.

<sup>113</sup> R. Honorato and R. E. Ortuzar, *Rev. med. aliment.*, 5, 223 (1943).

<sup>114</sup> Lahes, *Arch. exptl. Path. Pharmacol.*, 146, 44 (1929); 152, 111 (1930).

<sup>115</sup> P. Marquardt, *Arch. exptl. Path. Pharmacol.*, 201, 234 (1943).

<sup>116</sup> S. Sato and M. Ugai, *Okayama Igakkai-Zasshi*, 51, 829 (1939).

<sup>117</sup> E. N. Speranskaya-Stepanova, *J. Physiol. (U. S. S. R.)*, 29, 334 (1940).

<sup>118</sup> Oettel, *Arch. exptl. Path. Pharmacol.*, 153, 319 (1936).

<sup>119</sup> W. Gibbs and H. A. Hare, *Dubois Arch. Physiol.*, 1890, 352.

<sup>120</sup> W. Deichmann, *J. Lab. Clin. Med.*, 28, 770 (1943).

<sup>121</sup> E. Ergruwe, *Z. anal. Chem.*, 125, 241 (1943).

<sup>122</sup> J. G. Stott, *J. Soc. Motion Picture Engrs.*, 39, 37 (1942).

<sup>123</sup> J. F. Treon and W. Crutchfield, Jr., *Ind. Eng. Chem.*, 14, 119 (1942).



## QUINONE

Quinone,  $\text{OC}_6\text{H}_4\text{O}$ , *p*-, or 1,4-benzoquinone, occurs in large yellow monoclinic prisms. It has a molecular weight of 108.09, specific gravity of 1.32, and a melting point of  $115.7^\circ\text{C}$ . The compound (in the solid state) has a considerable vapor pressure and sublimates readily upon gentle heating. Quinone is soluble in hot water, alcohol, and ether; it is easily reduced to hydroquinone or quinhydrone. The compound has found wide application in the dye, textile, chemical, tanning, and cosmetic industries primarily because of its ability to transform certain nitrogen-containing compounds into a variety of colored substances.

Severe local damage to the skin and mucous membranes may occur following contact with solid quinone or solutions of quinone, or with vapors that may condense upon exposed parts (particularly upon moist surfaces) of the body during industrial use of quinone.

The local changes induced may include discoloration, severe irritation, erythema, swelling, and the formation of papules and vesicles. Prolonged contact may lead to necrosis. Vapors condensing upon the eyes are capable of inducing serious disturbances of vision.<sup>124-129</sup> According to Sterner, the injury usually extends through the entire layer of the conjunctiva and is characterized by a deposit of pigment. The staining, varying from a diffuse brown to globules of brownish-black, is located primarily in the zones extending from the canthi medially to the edge of the cornea. All layers of the cornea are involved in the injury, with a resultant discoloration that may be white and opaque or brownish-green and translucent. Ulceration of the cornea has resulted from one brief exposure to a high concentration of the vapor of quinone, as well as from repeated exposures to moderately high concentrations. Recovery occurs promptly and spontaneously, following discontinuation of exposure, and appears to be nearly complete. There were no systemic effects or changes in the composition of the blood and urine.<sup>109</sup> Analytical methods for the estimation of quinone have not been adapted to analysis of biological material.<sup>130-135</sup>

Control of the exposure is largely a matter of adequate ventilation. Sterner recommends that the concentration of quinone vapor in air be kept below 0.1

<sup>124</sup> A. Hamilton, *Industrial Poisons in the United States*. Macmillan, New York, 1925.

<sup>125</sup> W. C. Hueper, *Occupational Tumors and Allied Diseases*, C. C. Thomas, Springfield, Ill., 1942.

<sup>126</sup> R. L. Mayer, *Klin. Wochschr.*, 7, 1958 (1928); *Arch. Dermat. Syphilis*, 158, 266 (1929).

<sup>127</sup> L. Schwartz and L. Tulipan, *Occupational Diseases of the Skin*. Lea & Febiger, Philadelphia, 1939.

<sup>128</sup> N. Takizawa, *Proc. Imp. Acad. (Tokyo)*, 16, 309 (1940).

<sup>129</sup> R. P. White, *The Dermatogoses or Occupational Affections of the Skin*. 4th ed., Lewis, London, 1934.

<sup>130</sup> F. P. Dann, *Proc. Soc. Exptl. Biol. Med.*, 42, 663 (1939).

<sup>131</sup> L. Rosenthaler, *Pharm. Acta Helv.*, 14, 93 (1939).

<sup>132</sup> J. Rzymkowski, *Z. Elektrochem.*, 31, 371 (1925).

<sup>133</sup> E. Schulek and P. Rozsa, *Chem. Abstracts*, 35, 7993 (1941); 35, 5821 (1941).

<sup>134</sup> B. Singh and S. Singh, *J. Indian Chem. Soc.*, 16, 346 (1939); *Chem. Abstracts*, 34, 3204 (1940).

<sup>135</sup> N. R. Trenner and F. A. Baehler, *J. Biol. Chem.*, 137, 745 (1941).

p.p.m. (0.44 mg. per cubic meter). Comparison of this limit with Sterner's recommended level for hydroquinone dust in air (5 mg. per cubic meter) shows that quinone is considerably more toxic than hydroquinone. However, one circumstance making for a greater hazard from a dust such as hydroquinone is that the extent of eye injury depends largely upon the concentration of the compound in the fluids bathing the eye. The irritating vapors of quinone become diluted and washed away with the tears, while dust particles of hydroquinone are apt to remain for a longer period of time and in dissolving produce localized areas of high concentrations.

Cases of oral poisoning have apparently not been reported.<sup>112</sup> Absorption of large doses of quinone from the gastroenteric tract or subcutaneous tissues of animals induced local changes, crying, clonic convulsions, respiratory difficulties, drop of blood pressure, and death by paralysis of the medullary centers. Asphyxia appears to play an important role in the terminal picture, both because of pulmonary damage resulting from excretion of quinone into the alveoli and because of certain not too well-defined effects of quinone upon the hemoglobin.<sup>136</sup> The urine of severely poisoned animals may contain protein, blood, casts, and free or conjugated hydroquinone.

## PYROGALLOL

Pyrogallol,  $C_6H_3(OH)_3$ , 1,2,3-trihydroxybenzene, also known as pyrogallie acid or "Pyro," occurs as odorless, needle- or leaf-shaped crystals. It has a molecular weight of 126.11 and a specific gravity of 1.45. It melts at 133° C., decomposes at 293°, and boils at 309°. The compound is readily soluble in water, alcohol, and ether<sup>137</sup>; it is easily oxidized in alkaline solution (even by atmospheric oxygen) so that such a solution becomes a potent reducing agent. Its usefulness in various industries<sup>138-140</sup> is based primarily upon this property.

Human cases of poisoning have not been frequent. Cases reported in the older literature<sup>112</sup> include one man who ingested an aqueous solution containing 8 g. of pyrogallol and recovered after suffering an acute intoxication; another, who ingested 15 g. of this compound, died despite prompt vomiting. When applied upon the human skin in the form of a salve, it may cause discoloration, local irritation, eczema, or even death.<sup>141</sup> Repeated contact with the skin may cause sensitization.<sup>142</sup> The symptoms observed in cases of acute intoxication in man resemble closely the signs of illness displayed by experimental animals. These

<sup>136</sup> S. Liu, *Biochem. Z.*, 195, 248 (1928).

<sup>137</sup> *Merck Index*. Rahway, N. J., 1940.

<sup>138</sup> F. Bergel, *Chemistry & Industry*, 14, 127 (1944).

<sup>139</sup> W. W. Scheumann and J. H. Haslam, *Ind. Eng. Chem.*, 34, 485 (1942).

<sup>140</sup> K. Ziegler and P. Herte, *Ann.*, 551, 127 (1942).

<sup>141</sup> A. Neisser, *Z. klin. Med.*, 1, 88 (1880).

<sup>142</sup> E. Zurhelle and S. K. de Boer, *Arch. Dermat. Syphilis*, 183, 130 (1942).

are: vomiting, hypothermia, fine tremors, weakness, muscular inco-ordination, diarrhea, loss of reflexes, coma, and asphyxia.<sup>143</sup>

Because of its marked reducing action, pyrogallol has tremendous affinity for the oxygen of the blood. Heyroth and Largent<sup>144</sup> observed that the intravenous injection of 0.3 g. per kilogram into a rabbit provided a sufficient quantity of pyrogallol to unite with all of the oxygen of the blood, thereby causing the death of the animal. There was extensive destruction and fragmentation of the erythrocytes.

The urine of poisoned animals may contain casts, glucose, hemoglobin, met-hemoglobin, urobilin, and other compounds that cause discoloration. A fraction of the pyrogallol is excreted unchanged but a larger portion is first conjugated with hexuronic, sulfuric, or other acids.

Repeated absorption of toxic but sublethal concentrations into the tissues of animals has been found to cause severe anemia, icterus, nephritis, and uremia.

The approximate lethal dosages of pyrogallol in aqueous solution for various animal species, under varying conditions of administration, are as follows: 1.1 g. per kilogram administered orally to the rabbit,<sup>144</sup> 1.0 g. per kilogram administered subcutaneously to the rabbit or guinea pig,<sup>112</sup> 0.35 g. per kilogram administered subcutaneously to the dog or cat, and 0.09 g. per kilogram administered intravenously to the dog.<sup>145</sup>

*Phloroglucinol* (1,3,5-trihydroxybenzene) and *benzenetriol* (1,2,4-trihydroxybenzene) are of little industrial or hygienic importance.

## CRESOL

Crude cresol is a mixture of aromatic compounds containing about 20 per cent of *o*-cresol, 40 per cent of *m*-cresol, and 30 per cent of *p*-cresol. It is obtained by distilling "gray phenic acid" at a temperature within the ranges of about 180° to 205° C. Crude cresol has an odor much like that of phenol or creosote; it is nearly colorless when prepared, but turns brown on exposure to light or air. It dissolves freely in alcohols and alkalis but only slightly in water.

Cresylic acid,  $\text{CH}_3\text{C}_6\text{H}_4\text{OH}$  (pure cresol, cresol U.S.P., or tricresol), is a mixture of the three isomers freed from other compounds. It distills at temperatures ranging from 195° to 205° C. and has a specific gravity ranging from 1.030 to 1.038.

*o*-Cresol may be separated from the crude or purified mixture by repeated fractional distillation and crystallization or by double distillation *in vacuo*. *m*-Cresol and *p*-cresol are separated by treating the mixture with sulfuric acid; this yields crystallized disulfonic acid of *p*-cresol, and *p*-cresol on hydrolysis. The liquid fraction, when hydrolyzed with steam at 130° C., yields *m*-cresol, which may be further purified by double distillation *in vacuo*. Each of the cresols can

<sup>143</sup> L. Lewin, *Gifte und Vergiftungen*. Stilke, Berlin, 1929.

<sup>144</sup> F. Heyroth and E. Largent, *personal communication*.

<sup>145</sup> W. Gibbs and H. A. Hare, *Dubois Arch. Physiol.*, 1890, 352.

be prepared synthetically by diazotization of the specific toluidine or fusion of the corresponding toluene sulfonic acid with sodium hydroxide.

*o*-Cresol is a colorless crystalline compound. The molecular weight is 108.13 and the specific gravity, 1.051. The compound melts at between 30° and 31° C., boils at 191°, and has a vapor pressure equivalent to 1 mm. Hg at 36.6°. *m*-Cresol is a yellowish liquid. The molecular weight is 108.13 and the specific gravity, 1.042. It melts at between 11° and 12° C., boils at 202°, and has a vapor pressure equivalent to 1 mm. Hg at 55.9°. *p*-Cresol is a white, crystalline compound. The molecular weight is 108.13 and the specific gravity, 1.039. It melts at 37° C., boils at 202°, and has a vapor pressure equivalent to 1 mm. Hg at 55.7°. These compounds become discolored when exposed to light, and they all have phenol-like odors. They are readily soluble or miscible with organic solvents or vegetable oils. Their solubility (at 25° C.) in water is roughly 0.3, 1.5, and 1.0 per cent, and in mineral oil about 2.0, 2.5, and 0.7 per cent, respectively.

The cresols have found wide application in the synthetic resin, explosive, petroleum,<sup>146</sup> photographic, paint,<sup>147,148</sup> and agricultural industries.<sup>149,150</sup> They have been used for years as antiseptics, disinfectants,<sup>151-156</sup> and insecticides.<sup>157,158</sup>

Ortho-, meta-, and para-cresols are marketed individually ("practical grade," purity 98 or 99 per cent), or in a mixture as cresylic acid, or as crude cresol. Preparations containing cresols include: (a) Liquor Cresolis Saponatus (or Compositus) U.S.P., which is a clear 50 per cent solution of cresol U.S.P. in a mixture of linseed oil, sodium and potassium hydroxide and water; (b) Lysol, a proprietary preparation, which is essentially the same as Liquor Cresolis Saponatus, except that its composition is not constant, and it may be found to contain various coal-tar derivatives, acids, bases, or salts; (c) Carbolinum, the composition of which varies, usually containing naphthalene and pyridine and sometimes acridine and anthracene, in addition to cresols and phenol; (d) Saprol, a mixture of crude cresols dissolved in petroleum solvents, which upon addition of water yields a turbid solution; (e) Creoline, a water-soluble mixture, prepared by the addition of sulfuric acid to mixtures of cresol and phenol.

The fragmentary information available as to the normal metabolism and the rate of absorption, detoxication, and excretion of ortho-, meta-, or para-cresol

<sup>146</sup> T. Kennedy, *J. Inst. Petroleum Tech.*, 27, No. 207, 15 (1941).

<sup>147</sup> F. Moll, *Farben-Chem.*, 11, 101 (1940).

<sup>148</sup> G. H. Young, G. W. Gerhardt, W. K. Schneider, *Ind. Eng. Chem.*, 35, 432 (1943).

<sup>149</sup> M. Kondo and Y. Kasahara, *Ber. Ohara Inst. landw. Forsch. Japan*, 8, 325 (1941).

<sup>150</sup> T. Manley et al., *Report of the Research Com., West Va. Gladiolus Soc., Gladiolus Suppl.*, 6, No. 1, 10 (1942).

<sup>151</sup> A. Bos, *Tijdschr. Diergeneeskunde*, 70, 55 (1943).

<sup>152</sup> C. M. Brewer, *J. Assoc. Official Agr. Chem.*, 23, 557 (1940).

<sup>153</sup> H. J. Henk, *Deut. Parfüm. Ztg.*, 27, 120 (1941).

<sup>154</sup> G. Klust, *Chem. Zentr.*, 1, 2468 (1941).

<sup>155</sup> R. Puget, *Ann. hyg. publ., ind. sociale*, 18, 319 (1940).

<sup>156</sup> M. Waldhecker, *Münch. med. Wochschr.*, 88, 949 (1941).

<sup>157</sup> P. H. Berry, *Pharm. J.*, 148, 112 (1942).

<sup>158</sup> A. J. Salle and H. L. Guest, *Proc. Soc. Exptl. Biol. Med.*, 55, 26 (1944).

in cases of poisoning indicates that these compounds behave very much as does phenol in the mammalian organism<sup>159-162</sup> (see Table 3). The predominant signs of local and systemic intoxication by Lysol<sup>163</sup> and Carbolineum,<sup>164</sup> are also like those induced by phenol.<sup>148</sup> Suitable quantitative analytical methods<sup>165-169</sup> have not been readily available and consequently many cases of poisoning induced by Lysol<sup>170</sup> or the cresols have been reported as cases of phenol poisoning.<sup>171</sup> This is of little consequence from the point of view of industrial hygiene, since the treatment of poisoning and the precautions required for the safe handling and use of cresol and its various preparations are the same as those recommended in the case of phenol. The degree of systemic illness that may be induced by one of the commercial preparations depends primarily upon its content of cresol. Campbell<sup>172</sup> appears to have carried out the only recorded observations on the

TABLE 3  
*Approximate Lethal Dosages of Cresols for Experimental Animals*

Animal	Route	Dosage (g./kg.)			Reference
		<i>o</i> -Cresol	<i>m</i> -Cresol	<i>p</i> -Cresol	
Mouse	Subcut. (dil. aq. suspensions)	0.35	0.45	0.15	Tollens <sup>173</sup>
Rat	Oral (10% soln. in olive oil)	1.35 LD <sub>50</sub>	2.02 LD <sub>50</sub>	1.8 LD <sub>50</sub>	Deichmann and Witherup <sup>169</sup>
Rabbit	Intrav. (0.5% aq. soln.)	0.2	0.28	0.16	Deichmann and Witherup <sup>169</sup>
	Subcut. (dil. aq. suspensions)	0.45	0.5	0.3	Meili <sup>174</sup> , Tollens <sup>173</sup>
	Oral (10% soln. in olive oil)	0.8	1.1	1.1	Deichmann and Witherup <sup>169</sup>
Cat	Subcut. (20% aq. suspension)	0.06	0.15	0.08	Deichmann and Witherup <sup>169</sup>

effect upon animals (mice) of the inhalation of air saturated with vapors of cresylic acid. Single brief exposures did not seem to be harmful, while repeated exposures caused fatalities.

The disinfecting action of the cresols in relation to phenol is roughly 2.5 to 1, *m*-cresol being the most active of the three and *o*-cresol the least. Lysol, because of its greater penetrating power, compares with phenol in the ratio of about

<sup>159</sup> W. B. Deichmann and S. Witherup, *J. Pharmacol.*, **80**, 233 (1944).

<sup>160</sup> R. D. Embury *et al.*, *Trans. Am. Fisheries Soc.*, **70**, 304 (1940).

<sup>161</sup> M. Hunaki, *Mitt. med. Akad. Kioto*, **29**, 99 (1940).

<sup>162</sup> M. E. Klinger and J. F. Norton, *Ind. Hyg. Dig.*, **9**, 355 (1945).

<sup>163</sup> J. Hasenbach, *Zentr. Chir.*, **68**, 67 (1941).

<sup>164</sup> F. Beran, *Nachrbl. deut. Pflanzenschutzdienst*, **20**, 33 (1940).

<sup>165</sup> W. Bielenberg and L. Fischer, *Brennstoff-Chem.*, **22**, 278 (1941); *Oel Kohle Erdoel Teer*, **37**, 496 (1941).

<sup>166</sup> N. R. Campbell and D. H. Hey, *Nature*, **153**, 745 (1944).

<sup>167</sup> W. Deichmann, *Ind. Eng. Chem.*, **16**, 37 (1944).

<sup>168</sup> V. P. Maevskaya, *Zavodskaya Lab.*, **8**, 812 (1939).

<sup>169</sup> H. Mühmann, *Pharm. Acta Helv.*, **15**, 141 (1940).

<sup>170</sup> E. F. Koster, *Ohio State Med. J.*, **39**, 840 (1943).

<sup>171</sup> A. Ellinger, in A. Heffter, *Handbuch der experimentellen Pharmakologie*, Springer, Berlin, 1923.

<sup>172</sup> I. Campbell, *Soap Sanit. Chemicals*, **17**, No. 4, 103 (1941).

<sup>173</sup> K. Tollens, *Arch. experl. Path. Pharmacol.*, **52**, 220 (1905).

<sup>174</sup> Meili, *Dissertation*, Bern, 1891.

10 to 1. Certain acids, bases, or salts when present in the medium will further augment the disinfecting action; organic matter lowers it. Compounds that are used in the official disinfection of cars, boats, and stockyards must conform to a very definite standard of composition and solubility, which the United States Bureau of Animal Industry furnishes upon request.

## CREOSOTE

Creosote (creosotum, creosote oil, brick oil) is obtained by distillation (205–220° C.) of the tar obtained from beech and other woods, as well as from coal (200–250°). Recently creosote has also been prepared from the residue of olives.<sup>175</sup> That obtained from beechwood is composed almost entirely of guaiacol (C<sub>6</sub>H<sub>4</sub>OHCH<sub>3</sub>) and creosol (C<sub>6</sub>H<sub>3</sub>OHCH<sub>3</sub>OCH<sub>3</sub>), while creosote obtained from coal tar contains in addition to these, phenol, cresols, pyrol, pyridine, and other aromatic compounds. Purification of the crude preparation is accomplished by distillation and extraction with suitable oils.<sup>176,177</sup>

Purified creosote (specific gravity 1.07 to 1.08) is a yellowish or colorless inflammable oily liquid with a characteristic smoky odor. It is soluble in glycerol, benzene, and glacial acetic acid, slightly soluble in water (about 1 per cent at 25° C.), and miscible with alcohol, chloroform, ether, and oils.

Creosote has found application as an antiseptic,<sup>178</sup> disinfectant,<sup>179–186</sup> antipyretic, astringent, styptic and germicide, and as a therapeutic agent in certain internal disorders.<sup>187–190</sup> It is also used as a lubricant, as an agent for waterproofing, and as a constituent of fuel oil.<sup>191–195</sup>

Creosote is rapidly absorbed from the gastroenteric tract and through the skin. Fatalities have occurred among adults in from 14 to 36 hours after the ingestion of about 7 g. and among children within about the same length of time

<sup>175</sup> G. de B. Camps, *An. real. acad. farm.*, 2, 353 (1941).

<sup>176</sup> P. A. Bobrov, *Trans. Viatka Sci. Res. Inst.*, 2, 87 (1926); *Chem. Abstracts*, 22, 1434 (1928).

<sup>177</sup> G. P. Krivokhatskii, *Mitt. Kirov. forsttech. Akad. (U. S. S. R.)*, No. 54, 16 (1939).

<sup>178</sup> C. Richet and H. Cardot, *Compt. rend.*, 165, 491 (1917).

<sup>179</sup> E. F. Armstrong, *Chem. Abstracts*, 35, 8305 (1941).

<sup>180</sup> P. da R. Azevedo, *Anais. assoc. quim. Brasil*, 2, 97 (1943).

<sup>181</sup> R. L. Datta *et al.*, *Soap, Perfumery, Cosmetics*, 12, 583 (1939).

<sup>182</sup> W. E. Dove and S. W. Simmons, *J. Econ. Entomol.*, 35, 582 (1942).

<sup>183</sup> E. J. Fellows, *J. Pharmacol.*, 60, 178 (1937); 60, 183 (1937).

<sup>184</sup> E. J. Fellows, *Proc. Soc. Exptl. Biol. Med.*, 42, 103 (1939).

<sup>185</sup> M. S. Hudson and R. H. Baechler, *Proc. Am. Wood-Preservers Assoc.*, 74 (1940).

<sup>186</sup> C. J. Ramsburg, *Am. Inst. Mining, Metal Engrs. Contrib. No. 122* (1942).

<sup>187</sup> E. J. Fellows, *Am. J. Med. Sci.*, 197, 683 (1939).

<sup>188</sup> J. G. Samson and G. Limkako, *Philippine J. Sci.*, 23, 515 (1923).

<sup>189</sup> M. E. Stevens *et al.*, *Can. Med. Assoc. J.*, 48, 124 (1943).

<sup>190</sup> R. R. Wade, *Chem. Abstracts*, 19, 3316 (1925).

<sup>191</sup> E. B. Davies, *Fuel Econ. Rev.*, 21, 82 (1942).

<sup>192</sup> A. J. Gibbs-Smith, *Petroleum Times*, 47, 496 (1944).

<sup>193</sup> C. A. McDonnell and P. J. Tracy, *Brit. Patent 548,125* (1942).

<sup>194</sup> F. Newman, *Steam Engr.*, 12, 348 (1943).

<sup>195</sup> M. Stuart, *S. African Mining Eng. J.*, 42, 27 (1931).

after the ingestion of 1 to 2 g.<sup>143</sup> The symptoms of systemic illness included salivation, vomiting, respiratory difficulties, thready pulse, vertigo, headache, loss of pupillary reflex, hypothermia, cyanosis, and mild convulsions. The repeated absorption of therapeutic doses from the gastroenteric tract may induce signs of chronic intoxication, characterized by disturbances of vision and digestion (increased peristalsis and excretion of bloody feces). In isolated cases of "self-medication" hypertension<sup>196</sup> or general cardiovascular collapse<sup>148</sup> has been described. Creosote appears to be excreted in the urine mainly in conjugation with sulfuric, hexuronic, and other acids.<sup>184,187,197</sup> Oxidation also occurs with the formation of compounds that impart a "smoky" appearance to the urine. Traces are excreted by way of the lungs.

The signs of intoxication in the case of animals resemble those described above. The approximate lethal dosages of creosote when administered orally to various animal species are 0.1 g. per kilogram for the pigeon and 0.6 to 0.8 g. per kilogram for the rabbit, cat, or dog.<sup>143</sup> Cattle have been fatally poisoned by licking off creosote from treated telephone poles, the resultant lesions being those of intense irritation and congestion of the entire gastroenteric tract.<sup>198,199</sup>

Contact of creosote with the skin or condensation of vapors of creosote upon the skin or mucous membranes may induce an intense burning and itching together with local erythema, grayish-yellow to bronze pigmentation,<sup>200,201</sup> papular and vesicular eruptions, gangrene,<sup>202,203</sup> and in isolated instances cancer.<sup>204-209</sup> (An excellent review of this phase of the problem is given by Hueper.<sup>197</sup>) Heinz bodies have been noted<sup>210</sup> in the blood of a patient one year after his exposure to creosote. Jonas<sup>201</sup> and Goldenberg<sup>210</sup> made similar observations following percutaneous absorption of this preparation. Eye injuries include keratitis,<sup>211</sup> conjunctivitis, and abrasion of the cornea. According to Jonas permanent corneal scars result in about one third of such cases. Photosensitization has been reported by Schwartz and Tulipan<sup>207</sup> and severe systemic illness by Lewin.<sup>143</sup>

<sup>196</sup> S. K. Robinson, *Illinois Med. J.*, 74, 278 (1938).

<sup>197</sup> W. C. Hueper, *Occupational Tumors and Allied Diseases*. C. C. Thomas, Springfield, Ill., 1942.

<sup>198</sup> G. Hanlon, *Australian Vet. J.*, 14, 73 (1938).

<sup>199</sup> K. Kasai, *Chem. Abstracts*, 2, 2583 (1908).

<sup>200</sup> Hudelo *et al.*, *Bull. soc. franc. dermatol. syphilig.*, 34, 144 (1927).

<sup>201</sup> A. D. Jonas, *J. Ind. Hyg. Toxicol.*, 25, 418 (1943).

<sup>202</sup> G. Michel *et al.*, *Rev. méd. de l'est*, 63, 775 (1935).

<sup>203</sup> D. Schapiro, *Vrachebnoe Delo*, 11, 631 (1928).

<sup>204</sup> S. Cabot, N. Shear, and M. J. Shear, *Am. J. Path.*, 16, 301 (1940).

<sup>205</sup> M. Knallinsky, *Rev. argent. dermatosif.*, 23, 313 (1939).

<sup>206</sup> R. D. Sall *et al.*, *J. Natl. Cancer Inst.*, 1, 45 (1940).

<sup>207</sup> L. Schwartz and L. Tulipan, *Occupational Diseases of the Skin*. Lea & Febiger, Philadelphia, 1939.

<sup>208</sup> L. Schwartz, *Ind. Med.*, 11, 387 (1942).

<sup>209</sup> R. P. White, *The Dermatogoses or Occupational Affections of the Skin*. 4th ed., Lewis, London, 1934.

<sup>210</sup> E. Y. Goldenberg, *Vrachebnoe Delo*, 10-11, 663 (1939).

<sup>211</sup> G. T. Birdwood, *Brit. Med. J.*, 2, 18 (1938).

Injuries to the skin and eyes have occurred mainly among men engaged in dipping or in "pickling" and handling "sleepers," mine timbers, and woods for floors and other purposes. Jonas calls attention to burns induced by fine particles of wood dust freed during sawing of creosote-treated lumber. He observed that men with a fair skin were very sensitive, while colored workers demonstrated a remarkable resistance. The burns were reduced to a minimum on rainy days, probably because of the decreased dispersion of both the wood particles and creosote. Engels<sup>212</sup> considers that the use of creosote-treated timber in mines is inadvisable, both because of the fire hazard it involves and because of the contamination of the air.

Protective measures include adequate ventilation, use and frequent change of protective garments, wearing of goggles, application of a heavy layer of petroleum jelly<sup>201</sup> or lanolin-castor oil ointment upon the skin of the face, thorough cleansing of all parts of the body that have become exposed accidentally, and thorough washing of the face and hands after every working period. Jonas has recommended a preparation containing calcium salts, benzocain, sulfur, and a vegetable oil base for the treatment of creosote burns; for inflamed eyes, he has suggested washing with aqueous boric acid or, if pain is a factor, the application of Metaphen ophthalmic ointment. (Coal-tar ointments will intensify the local damage.<sup>203</sup>) Caution is in order when old creosote-treated lumber is handled or sawed for it retains a considerable portion of the oil for periods up to 25 or 30 years.<sup>213,214</sup> Analytical methods<sup>215-218</sup> for the estimation of creosote apparently have not been applied to analysis of biological material.

<sup>212</sup> W. Engels, *Chem. Ztg.*, 55, 285 (1931).

<sup>213</sup> N. A. Richardson, *Chemistry & Industry*, 1934, 710.

<sup>214</sup> H. von Schrenk, A. L. Kammerer, and H. Schmitz, *Proc. Am. Wood-Preservers Assoc.*, 167 (1936).

<sup>215</sup> H. Degner, *Chem. Abstracts*, 26, 801 (1932).

<sup>216</sup> L. Ekkert, *Pharm. Zentralhalle*, 73, 487 (1932); *ibid.*, 75, 49 (1934); *Chem. Abstracts*, 26, 5380 (1932); *ibid.*, 28, 1955 (1934).

<sup>217</sup> W. Franke, *Braunkohlenarch.*, No. 36, 1 (1932).

<sup>218</sup> K. L. Nilstead, *J. Assoc. Official Agr. Chem.*, 21, 543 (1938).



## Potential Exposures in Industry: Their Recognition and Control

FRANK A. PATTY and FRANCIS R. HOLDEN

This chapter endeavors to give significant information about some of the processes, occupations, or industries that are of hygienic interest. The listing is alphabetical and, where information is desired on an industry not listed, significant processes of the industry may be found elsewhere in the chapter.

### Abrasive Blasting

There are two types of abrasive-blasting equipment, the automatic and the manually operated. Either type may use sand, steel shot, or artificial abrasives.

Although the degree of potential health hazard is more severe when silica is employed, essentially all abrasive blasting requires adequate exhaust ventilation. The use of steel shot or an artificial abrasive on a casting coated with sand would produce a mixed dust containing free silica within the dangerous particle sizes (less than  $5 \mu$ ) and in amounts above the maximum allowable concentration for continuous exposure (5 million particles of free silica per cubic foot of air). Even when steel shot or artificial abrasives are used on clean metal surfaces, the amounts of dust produced are so great that exposure of men is undesirable.

In the inspection of automatic equipment air flow into the machine through all openings should be ascertained. The exhausted air should be cleaned by a dust collector that discharges the air outside the building at a point remote from windows or air intakes. The air from the dust collector should not be returned to the plant.

Abrasive-blasting helmets are required to protect workmen stationed within abrasive-blasting rooms. The helmet should be of a type approved by the United States Bureau of Mines and should be maintained adequately. The air flow into the helmet should be fixed at approximately 6 c.f.m. to ensure protection. Adjustment of the air flow should not be left to the discretion of the workman. The air supply must be clean and free from oil or carbon monoxide. Dust counts on air samples taken under the helmet while the worker is engaged in blasting should not exceed one million particles per cubic foot of air.

Good housekeeping is an essential feature of the proper operation of abrasive-blasting equipment. Piles of abrasive near the equipment should be avoided.

As a check on the effectiveness of exhaust ventilation, samples of air for dust-counting purposes should be collected in the breathing zone of operators of automatic blasting machines. If the air from the dust collector is returned to the workroom, it also should be checked by dust count. If counts exceed two or three million particles per cubic foot of air, equipment should be checked for leakage, unless there are obvious sources of dust from adjacent operations.

See also Casting Cleaning.

### *Wet-Sand Blasting*

A "vapor blast" consisting of sand, water, and air is sometimes used. Although the dust arising from such an operation does not compare in magnitude with that from an ordinary sandblast, nevertheless dust counts on the order of 100 million particles per cubic foot of air are common in the vicinity of the blast.

The operation must be conducted inside of exhaust enclosures and when the operators are stationed inside the enclosure they must wear supplied-air abrasive-blasting helmets. Openings to the booth must be protected from the direct blast. The volume of air exhausted from the booth must be sufficient to prevent escape of air, sand, or mist into the room and maintain an inward flow through all openings. If short open drainpipes are provided for the booths, they may become sources of excessive silica dust or mist, requiring control. The filling of sand hoppers and reservoirs also may necessitate control measures.

Where finely powdered quartz is used as the abrasive (microblast, micro-brasive blast, and so forth) housekeeping assumes greater importance because the major portion of the abrasive is of "air-float" or respirable size and may be swept from the floor into the air by drafts.

## **Abrasives Manufacture and Use**

### **1. Artificial Abrasives**

The raw materials for the manufacture of silicon carbide include sand, coke, salt, and sawdust, which are fused together in an electric-arc furnace and then broken up, washed, and classified by size. Carbon monoxide and smoke, or fume, arise in considerable quantity from the furnaces and necessitate exhaust ventilation, the extent of which can usually be adjusted satisfactorily by controlling the carbon monoxide. Aluminum oxide abrasives, Alundum and Aloxite, are similarly made by fusing bauxite, crushing the fused mass, then sizing the resulting particles. Bonding materials used with these abrasives are for the most part ceramics, artificial resins, and glue. Infrequently these resins may give rise to dermatitis. Ultraviolet and infrared radiations arising from the electric arcs offer exposures that should be considered. A lung malady named "Shaver's Disease," after discoverer Dr. C. G. Shaver,<sup>1</sup> is believed to result from exposure to silica<sup>1a</sup> and alumina fumes arising from bauxite furnaces.

<sup>1</sup> C. G. Shaver and A. R. Riddell, *J. Ind. Hyg. Toxicol.*, 29, 145 (1947).

<sup>1a</sup> C. M. Jephcott, J. H. Johnston, and G. R. Finlay, *ibid.*, 30, 145 (1948).

In the manufacture of abrasive wheels, abrasive paper, and abrasive cloth, there are numerous dust-producing operations such as crushing, grinding, sifting or screening, edging, facing, and shaving. Although the dusts of all these manufactured abrasives are considered to be of an inert character and of a nuisance nature, they are usually kept well below the frequently stated nuisance dust standard of fifty million particles per cubic foot of air, by light-field count. Whenever such dust concentrations exceed fifteen or twenty million particles per cubic foot, the dustiness becomes noticeable and therefore undesirable. A further incentive to control is the abrading action of such dusts on all bearings or moving parts of machinery in use.

The characteristics of the dusts, and their control, mentioned above in connection with the manufacture of wheels, paper, and cloth apply also to situations in which these products are being used. In the main, they can be applied, as well, to the manufacture and use of similar products made of garnet, pumice, and other naturally occurring mineral abrasives other than quartz sand and possibly tripoli.

## **2. Sand Abrasives**

Sand abrasives, wheels, disks, or paper, have been replaced almost entirely by artificial abrasives; but wherever sand-abrasive products are being made or used free silica dust concentrations should be maintained below 5 million particles per cubic foot of air. The use of water does not assure the control of a silica dust exposure. Mist containing finely divided silica may reach excessive concentrations. This is particularly true if the water is recirculated, allowing dust to accumulate in the water or other coolant. It has been observed that, where the humidity is low, the water evaporates from dust particles leaving them suspended in the air.

In the use of abrasive wheels the highest concentrations of dust arise from dry dressing of the wheels.

## **Acetylene Manufacture**

Acetylene is manufactured by the action of water on calcium carbide. The reaction is frequently automatically controlled in enclosed apparatus. The calcium carbide is made by fusing a mixture of lime and coke in an electric furnace. The danger of an explosion of acetylene is the greatest potential hazard in the industry. Some operations are dusty to the extent of polluting the atmosphere surrounding the plant, but such dust is not considered harmful to health. The operations disperse coke, lime, and carbide dusts, of which the lime and carbide dusts are caustic and therefore somewhat irritant to the skin and to the respiratory tract. Carbon monoxide is a by-product and the possibility of its presence in the atmosphere must be recognized. Excessive temperatures are prevalent near the furnaces. Crude acetylene frequently contains traces of ammonia, hydrogen sulfide, and phosphine, which are usually scrubbed out with caustic soda solution. In making tests in atmospheres containing acetylene, ignition

sources must be carefully avoided and combustible gas indicators should be used only when they are suitably protected by flash arresters.

When acetylene is to be confined in cylinders, acetone is used as an absorbent for it. The placing of asbestos or siliceous absorbents for the acetone in the cylinders frequently presents a dust problem. Cylinder reclaim involves a possible lead hazard, through grinding on painted surfaces, and exposure to toxic solvents in the use of paint removers.

## Acid Manufacture and Recovery

### 1. Hydrochloric Acid

Hydrochloric acid is made by absorbing hydrogen chloride gas in water, utilizing absorption towers or scrubbers of various designs. The hydrogen chloride may be a by-product of chlorination; or it may be obtained from a bisulfate retort, from burning hydrogen, methane, or water gas in chlorine, or from the decomposition of magnesium chloride in the presence of steam.

Some of the absorption systems have a high efficiency so that little hydrogen chloride gas escapes, while in others the tail gas escaping from the scrubber has sufficient hydrogen chloride in it to cause objectionable concentrations in the surrounding atmosphere. Where little personal attention is required, irritant levels of hydrogen chloride are sometimes condoned, particularly for brief exposures where gas masks are worn. Concentrations in the air can readily be controlled by means of passing the tail gas through one or more additional scrubbers and there seems no logical reason why amounts above 10 p.p.m. in the atmosphere should be tolerated.

### 2. Nitric Acid

Nitric acid manufacture is more hazardous than hydrochloric acid manufacture in that it requires more personal attention and the oxides of nitrogen have inadequate warning properties in low, toxic concentrations. Nitric acid may be made by heating sodium nitrate with sulfuric acid in retorts, distilling off the resultant nitric acid, and condensing it; by the electric-arc process in which atmospheric oxygen and nitrogen are combined directly to form nitric oxide; or by the ammonia-oxidation process wherein air or oxygen and ammonia are passed over a hot platinum catalyst to yield nitric oxide. Ammonia oxidation may be accomplished at either atmospheric pressure or at pressures up to 100 p.s.i. The concentration of ammonia must be maintained well below the lower inflammable limit (15.5 per cent in air; 14.8 per cent in oxygen) in order to avoid an explosion. In each case the NO oxidizes to NO<sub>2</sub> and is absorbed in water to yield nitric acid. The periodic sampling of nitric oxide may present an exposure hazard as does the escape of nitrogen dioxide, which may occur at cracks or at the joints in ceramic pipes. Breaking up nitrogen dioxide saturated sulfate cake residue from the retorts also may entail excessive exposure to nitrogen dioxide. Nitric oxide and nitrogen dioxide in the atmosphere should not be permitted to exceed a total of 25 p.p.m. The escape of ammonia from storage tanks or cylinders

at gage glasses, valves, or lines may present a catastrophe hazard of explosion or injury from the irritant action of ammonia on eyes, nose, throat, and lungs.

Nitric acid recovery plants, for the recovery and concentration of spent or weak nitric acid, frequently have atmospheres ranging from 5 to 50 p.p.m. nitrogen dioxide due to liquid or gas leaks at the cemented joints of ceramic pipes. Vent stacks from nitrogen dioxide scrubbers, unless well elevated, are frequent sources of excessive amounts of nitrogen dioxide.

### **3. Sulfuric Acid**

Sulfuric acid is made by either the chamber process or the contact process. In the chamber process sulfur or pyrite ore is burned to sulfur dioxide and this gas is mixed with water and oxides of nitrogen in lead chambers. A nitrosylsulfuric acid is formed, and this is passed through a Glover tower where a counter-current of hot gases removes the oxides of nitrogen, leaving sulfuric acid, up to 80 per cent, in water.

In the contact process sulfur dioxide, along with an excess of air, is passed through a catalyst such as vanadium, platinum, or chromium-tin. The  $\text{SO}_2$  is oxidized to  $\text{SO}_3$  with evolution of heat. The sulfur trioxide is absorbed in 80 per cent to 99 per cent sulfuric acid. When sulfur trioxide is absorbed, it is important that it not be allowed to come in contact with water vapor else a persistent fog of finely divided droplets of sulfuric acid is formed. Sulfuric acid of 98 to 99 per cent strength is said to be the most satisfactory absorbent, since concentrations below 98 per cent may fog and those above 99 per cent may permit sulfur trioxide to escape. Cottrell precipitators have been used successfully to prevent the escape of sulfur trioxide fog.

Both sulfur dioxide and sulfur trioxide are irritant. Recommended practice is to keep concentrations of sulfur dioxide below 10 p.p.m. and not to exceed 2 p.p.m. of sulfur trioxide. These concentrations are frequently exceeded around the ordinary plant and, if not too excessive, may be acceptable where men are not stationed in the contaminated area and where respiratory protection is provided for use when needed. Pyrites often contain arsenic which then contaminates the product and may present an arsine hazard where the sulfuric acid is used. Sulfur and pyrite dusts are considered as nuisance dusts.

### **Aircraft Manufacture, Maintenance, and Repair**

Aircraft manufacture embraces many operations that are common to other industries: thus, it may include various potentially harmful conditions. Outstanding among these are the fluoride exposures in magnesium foundry practice, as well as the solvent and paint exposures during the cleaning and painting of the fuselages, especially interiors. Fluoride exposure may cause nasal irritation, eye irritation, epistaxis, and possibly adverse systemic effects. Suggested maximum permissible limits range from 2 to 6 mg. total fluoride per cubic meter of air. The fluoride may exist as hydrogen fluoride gas, fluoride fume, dust, mist, or any combination of these. Good process ventilation is recommended for con-

trolling fluorides. Substitution of nontoxic materials, where applicable, is to be preferred.

Any work involving solvent exposure, such as in the application of de-icers, or the swabbing of solvents for cleaning purposes, can present a serious hazard unless factors, such as toxicity and volatility of the solvent, and amount and direction of air flow, are considered. Painting of large parts or entire planes requires a well-engineered spray room or booth. Painting of interior compartments requires individual air supply or exhaust and, frequently, effective respiratory protection.

For a discussion of additional exposures incidental to aircraft manufacture, maintenance, and repair see Abrasive Blasting, Aluminum and Magnesium Foundry, Anodizing, Degreasing, Doping, Electroplating, Engine Testing, Grinding and Polishing, Heat Treating, Chlorinated Oils and Waxes, Industrial X-Ray, Metalizing, Metal Cleaning, Quartz Crystal Cutting, Radium and Radium Dial Painting, Soldering, and Spray Painting.

### **Aluminum Manufacturing**

Aluminum is produced electrolytically from its oxide, bauxite. Since this raw material is not found associated with significant free silica, its handling does not entail a silicosis risk.

Aluminum oxide is dissolved in a bath of molten cryolite (the double fluoride of aluminum and sodium) in steel cells lined with carbon for electrolysis. Gases and fumes evolved from the cells include carbon monoxide, hydrogen fluoride, silicon tetrafluoride, aluminum fluoride, and cryolite. Gravity ventilation from the hot cells is generally employed to remove the contaminants. Most of the carbon monoxide is burned as it escapes from the cells. The fluoride, gas and fume, in modern aluminum plants is below concentrations harmful to health. Extensive programs of physical examinations at modern plants have shown no harmful effects that could be attributed to fluorides.

The principal problem requiring control is the accident hazard from hot metal and electricity. Heat exposure is also considerable. The manipulation of aluminum to prepare wire, sheets, bars, etc. results in no specific exposure harmful to health. Powdered aluminum employed in paints must be carefully handled because of the danger of dust explosions. Aluminum compounds have low toxicity and are not recognized as sources of industrial poisoning.

### **Ammonia Manufacture and Use**

Ammonia is a by-product of the distillation of coal. It is manufactured by the action of steam on cyanamide, and by the catalytic combination of nitrogen and hydrogen. It is extensively used in refrigeration, and in the manufacture of chemicals, such as fertilizers, nitric acid, explosives, plastics, and other materials. The workroom atmosphere should be so controlled that extended exposure to 100 p.p.m. does not occur. In the manufacture and use of compressed ammonia gas the prolonged exposure to low concentrations, up to 200 p.p.m., though undesirable, is not as much of a hazard as is the accidental exposure to much higher

concentrations. High concentrations may result from the failure of a valve, or line, or the breakage of a gage glass on a storage tank of the compressed gas. Canister gas masks approved by the United States Bureau of Mines should be provided for emergency use whenever compressed ammonia is used; and where the amounts involved are likely to produce mixtures of more than 3 per cent in the atmosphere, fresh-air hose masks or oxygen rebreathing apparatus should be provided. Fire and explosion hazards are significant. Ammonia escaping from a leak can be ignited readily and gas-air mixtures of 15.5 to 26.6 per cent ammonia are violently explosive.

### **Aniline Manufacture, Distillation, and Handling**

Aniline and dimethylaniline are hazardous liquids and exposed workmen should always be instructed how to recognize and avoid the dangers involved. Aniline manufacture by nitration of benzene and subsequent reduction of the nitrobenzene involves potential exposures to nitric acid, nitrogen oxides, benzene, and nitrobenzene, in addition to aniline itself. A chlorination process involves benzene, chlorine, and chlorobenzene exposures. Aniline, though only slightly volatile when used at room temperature, requires either local or good general ventilation; and when used at elevated temperatures, requires either very effective process ventilation, or enclosed processes and general ventilation. The dangers and likelihood of absorption of the aniline or nitrobenzene through the skin are even greater than those from inhalation of the vapors; and shoes, gloves, or any other articles of clothing that have come in contact with any visible amount of these materials should be discarded without delay and the skin should be thoroughly washed.

Even the small amount of aniline used in some formulas for waterproof ink offers exposure in the manufacture, storage, handling, and use of the ink. Poisoning has occurred due to skin contact with unlaundered cloth stamped with such inks. The maximum amount of aniline in air permissible for an 8-hour exposure is 5 p.p.m., and a few drops on the skin or clothing may cause poisoning. Aniline is especially dangerous on shoe soles, where it is likely to be overlooked and remain, to gradually soak through and be absorbed by the feet.

### **Anodizing**

Anodizing is an operation whereby a coating highly resistant to corrosion is formed upon a metal surface. It is accomplished in an electrolytic bath with the metal to be treated forming the anode. A resistant oxide film is formed in this way on aluminum and aluminum alloys. The bath may contain any of a number of materials, with dilute chromic acid and sulfuric acid electrolytes being common. Hydrogen evolved in the process may carry corrosive mists out of the tank unless the tank is correctly ventilated. A trained observer can recognize excessive chromic-acid or sulfuric-acid mists or sprays by nasal irritation. Where any uncertainty exists regarding an exposure, air analyses should be made and cor-

rective measures taken where indicated. It is the usual practice, however, to provide effective ventilation for all anodizing tanks. Permissible limits are discussed under the compounds concerned.

### **Armature Workers**

Lead "tinning" baths and lead pots, when small and equipped with temperature controls, may not present serious lead exposures. However, the larger operations, especially when no temperature control is in use, can offer serious exposures. Wherever there is any question of exposure, the operation should either be provided with mechanically induced air flow to remove or dilute the lead fumes before they can be inhaled, or else air or urine samples should be collected and analyzed for lead to establish whether ventilation is necessary.

Waterproof varnishes, especially those made from cashew nutshell liquid-formaldehyde resins, may cause dermatitis. This may result from contact with the wet varnish, from the varnish dust dispersed in grinding armatures, or from skin contact with dirty solvent baths for dipping and cleaning old armatures. The solvent bath should not be permitted to become badly contaminated and skin contact must be avoided. In the case of wet or dry varnish, good personal cleanliness is an effective preventive measure, and varnish dust should be controlled by process ventilation. Protective creams and clothing may be useful in some instances.

### **Art-Metal Casting**

Art-metal casts for displays, trophies, medals, and the like are usually cast from white metal or britannia metal, which are alloys of tin, antimony, and copper, often having some zinc and bismuth, occasionally lead, and possibly arsenic. The alloys are melted in pots, temperatures rarely exceeding 300° or 400° C. Burring, filing, belt "sanding," and buffing may be done and, unless controlled, significant exposures to mechanically generated metal dusts may result. At the temperatures ordinarily employed there is little likelihood of an exposure to metal fumes, however. Where uncertainties exist, exposures should be evaluated and, when found excessive, controlled. Other possible exposures in the industry involve plating baths and cyanide dips. Soldering operations are usually at low temperatures to avoid fusing the low-melting point alloys, and therefore are not conducive to the formation of metal fumes.

### **Asbestos Workers**

Dustiness around asbestos workers is frequently above the proposed standard of five million particles per cubic foot. Perhaps mining offers the greatest exposure to dust, and in fabrication plants the operations, listed in the probable, decreasing order of dustiness, are: screening, picking, stacking, and willowing in the preparation room; carding, dry weaving, spinning, twisting, winding, and warping. The sawing, filing, drilling, and grinding of brake linings is ordinarily well controlled. Grinding, mixing, and bagging asbestos cement and insulating



material, and the sawing or beveling of asbestos board, are dusty operations unless properly engineered. The asbestos content of these dusts frequently is not high but diatomaceous earth in considerable quantities may accompany it, thus complicating the exposure with free silica. It may be desirable in asbestos exposures to keep the dust count down to five million particles, or less, per cubic foot, but it has been neither practical nor possible to do this in all instances. The question can well be raised as to whether in the light of experience, especially in the mining industry, such rigid control is justified or necessary.

### **Asphalt (Mineral Pitch)**

The name "asphalt" applies to bitumen or to earth or rocks impregnated with bitumen and to a residue from certain petroleum, coal tar, lignite tar, etc. (artificial asphalt). It is a black solid formed in the earth from slow decomposition of organic matter. It is composed chiefly of hydrocarbons along with varying amounts of oxygen, nitrogen, and sulfur compounds.

Asphalt is used principally for water-excluding coatings upon roads, floors, or roofs. It is employed as a rust preventive in ducts, collectors, tanks, and so forth to protect metals from corrosive (acid) liquids and gases. For such application it is commonly dissolved in benzene.

Vapors and gases from heated asphalt are obnoxious and toxic, containing among other compounds some hydrogen sulfide. Dermatitis from contact with asphalt has been reported as common, with the entire body sometimes affected. Skin cancer has also been reported, but statistics are lacking. Some authorities attribute most of the poisoning, which has occurred from the use of asphalt, to the solvents employed with it (benzene, phenol, etc.).

Grinding operations and hot processes should have exhaust ventilation. Personal cleanliness is the heart of any program for preventing skin disease.

### **Automobile Manufacture**

The manufacture of automobiles has few operations that are peculiar to the industry. There are many exposures and potential exposures common to other industries.

These are discussed elsewhere under specific headings such as: Abrasive Blasting, Anodizing, Battery Manufacture, Electroplating, Foundry Operations, Forging and Iron Working, Garages, Grinding and Polishing, Heat Treating, Industrial X-Ray, Lead Workers, Metal Cleaning, Metalizing, Motor Testing, Painting and Decorating, Pickling, Plastics and Resins, Radio Manufacture and Repair, Welding, etc.

Body polishing by the use of tripoli polishing compounds is an operation more or less peculiar to the production of highly polished automobile bodies. No harmful effects have been associated with this operation. However, any dust arising from the polishing, and especially from compressed-air blowoff operations, and from the cleaning of the brushes should be controlled. There seems no logical excuse for condoning such dust in concentrations of more than ten million par-

ticles per cubic foot of air. Because of the large size of the automobile body and consequent hooding difficulties, in some instances it may be necessary to move large volumes of air and, in the interest of economy, employ filtration and recirculation of the air.

Another operation peculiar to the industry is that of filling seams with solder. This operation or, more likely, the subsequent operation of removing excess metal by disk grinding has caused lead absorption in years past. Disk grinding of leaded surfaces is now done in exhausted enclosures and respirators are used. Careful checks of atmospheric and blood or urinary lead concentrations should accompany these operations wherever exposures are suspected. Where the arsenic content of the solder is low—less than 1.0 per cent—the possibility of significant arsenic exposure is slight but, due to its greater volatility, arsenic should be considered. Arsine formed from the use of acid fluxes is apparently not enough for concern. Temperatures used in applying the lead are not sufficiently high to volatilize excessive amounts of lead, therefore canopy-type hoods are adequate, but the disk grinding operations require well-engineered ventilation to take care of the dust evolved. If the operation is enclosed in a booth, and only sufficient air exhausted to prevent the spread of dust to other areas of the plant, supplied-air helmets are necessary. Air exhausted from the disk grinding of leaded surfaces should be passed through a dust collector and on to the outside air.

Contact with oils, emulsions, and solvents, though not peculiar to automobile manufacture, is the most common exposure in the many machining operations that are involved in the making of an automobile.

A statistical study of about 400 cases of dermatitis indicated that where contact with the hands is frequent, mineral seal oil, containing an "improver," caused the highest incidence of dermatitis—on the order of 33 cases per hundred persons exposed per year—while cutting oils, such as are encountered by bar-machine, screw-machine, and other operators, caused the next highest incidence of dermatitis—on the order of 20 per hundred per year of operation—and emulsions, "soluble oils," were third with 10 per hundred per year.

Some of the inhibitors, antiseptics, and "improvers" occasionally used in each of these oils may make matters worse in that they may be themselves either primary irritants or sensitizers. Offensive agents have included nitrobenzene, nitrophenol, cresylic acid, some sulfur compounds, chlorine compounds, aromatic amines, and strong alkalies. Not all sulfur or chlorine additives, however, are objectionable.

It is important to remove metallic particles from recirculated oils, but sterilization or the addition of disinfectants to cutting oils does not appear to be desirable. In the case of emulsifiers or coolants, there appears to be less difficulty where they are discarded and replaced frequently. Elaborate systems for pasteurization have not proved advantageous. There are, however, many who claim that certain bactericidal agents can be added to retard the formation of offensive odors without causing any harmful effect.

The most successful measure for prevention of comedones and folliculitis is effective washing with correct cleaning agents. Unless prevented by supervision, solvents used for cleaning parts and machines will be used for cleaning hands, with definitely unfavorable results. Where low viscosity oils are encountered, some means such as impervious gloves or creams can be used to advantage to prevent defatting the skin or causing sensitization. Creams may have some use both before and following the work period. When the hands and arms frequently become covered with oil, clean waste or rags should be provided. The splash or spray of oils and emulsions, or dispersion of excessive oil fog or mist, should be controlled.

### **Battery Manufacture**

#### *Lead Storage Battery*

The manufacture of lead storage batteries involves lead exposures that necessitate continuous and competent industrial hygiene supervision. Mechanization, enclosed processes, and well-designed process ventilation have been advanced to the point where inhalation exposures can be held down to less than 0.5 mg. per cubic meter consistently, if the control program is vigilantly supervised. The industrial hygienist should be thoroughly familiar with the basic information in Chapter Twenty-One, and in *United States Public Health Bulletin* Number 262.<sup>2</sup>

There is little information to be gained by a few random breathing-zone samples. The sampling must be extensive enough to indicate the average, as well as the range, of the exposures. Of more practical interest than individual exposures is information on sources and extent of atmospheric contamination, so that it can be tied in with improved engineering control.

Casting or molding operations, if ventilated, ordinarily do not present an exposure control problem. Smelting and reclaim require well-engineered ventilation and rigid housekeeping. Oxide manufacture requires enclosed processes with well-designed ventilation control, as well as due regard for housekeeping. Maintenance or repair jobs in furnaces offer hazardous exposures and also present room contamination problems. Oxide mixing is ordinarily provided with a dust control system that properly ventilates each dust dispersion point, and spilled oxide is removed by a vacuum cleaning system. The operation of hand scooping and weighing presents more of a control problem. Respirators should be used only as a last resort where ventilation control is unsuccessful; but should always be used wherever the exposure exceeds the practical control limit established as a part of a particular control program.

From the time the lead oxide paste is applied to the plates, the control of the exposure becomes more difficult. The paste is applied wet either by hand or machine, and the application itself presents little difficulty, but as soon as the paste becomes dry it is easily dispersed into the air. This introduces a problem

<sup>2</sup> W. C. Dressen, T. I. Edwards, W. H. Reinhart, R. T. Page, S. H. Webster, D. W. Armstrong, and R. R. Sayers, *U.S. Pub. Health Bull.* No. 262 (1941).

wherever heat is applied, or the plates are cleaned, transferred, racked, stacked, trimmed, split, etc. Moreover, the wet paste, if it is allowed to fall on the floor or contaminate equipment, sooner or later becomes dry and adds to the exposure sources. Housekeeping is more than just a name in this control program. Work tables with grids provided with good exhaust have proved very effective in controlling dust dispersion, as well as floor contamination. The plates should be handled manually as little as possible. Ready-charged batteries, the plates of which are handled and shipped dry, ready for service as soon as the electrolyte is added, offer much more of a dust-control problem than plates handled and shipped wet.

Controlling lead exposures in storage battery manufacture is not a piecemeal problem, but one which requires: (1) competent engineering control; (2) pre-employment examinations; (3) periodic surveys of atmospheric contamination; (4) periodic blood examinations for stippled cells or basophilic aggregation, hemoglobin, and red cell counts of persons in potentially hazardous work places; (5) urinalyses for lead wherever excessive exposures are demonstrated or suspected; (6) education of employees about personal hygiene, good health practices, and safe working procedures; and (7) transfer of any affected person to a position of minimum exposure.

Experience in the battery industry has indicated that if atmospheric lead concentrations are kept below 0.5 mg. per cubic meter and the above outlined program is maintained, there is a reasonable assurance of the prevention of lead poisoning.<sup>2a</sup> This is not intended to discredit in any way the standard of 0.15 mg. per cubic meter, which has been established as a safe permissible limit, but merely to emphasize the importance of a well-balanced control program in one industry, which has demonstrated its merits over a period of several years.

The charging room atmosphere is necessarily subject to contamination by hydrogen and acid mist and, since battery grids often contain from 5 to 10 per cent antimony, production of stibine is at least theoretically possible. Haring and Compton<sup>8</sup> concluded that stibine is generated in perceptible quantities during overcharging. The amount is very small in relation to total battery gases but it increases with the age of the battery. Ventilation sufficient to dilute or remove the irritant acid mist in the battery gases, must be provided. Under normal conditions this will also control any other gases formed.

#### *Edison Cell*

The Edison or "iron nickel" cell uses a spongy iron anode and a compressed flake nickel cathode in a solution of 15 per cent caustic soda containing a small amount of lithium hydrate. Except for the corrosive action of caustic, no significant exposures accompanying the manufacture of the Edison cell have been recognized or described.

<sup>2a</sup> G. S. Winn and C. Shroyer, *J. Ind. Hyg. Toxicol.*, **29**, 351 (1947).

<sup>8</sup> H. E. Haring and K. G. Compton, *Trans. Electrochem. Soc.*, **68**, 283 (1935).

### *Dry Cells*

Dry cells are manufactured in many sizes and shapes. The positive pole is a carbon rod, while the negative pole is a sheet of zinc that serves as a container for the battery. A mixture of manganese dioxide, powdered graphite, and ammonium chloride made into a paste is used to pack around the positive center pole. The filled cell is then sealed on the top with a layer of hot pitch or sealing wax. The only significant exposures are to manganese dioxide dust generated from the handling and mixing of manganese dioxide.

The use of mercuric oxide in dry cells,<sup>4</sup> an innovation developed during the war, involves exposures to mercury dust and especially to mercury vapor. The exposures are not confined to the manufacturing process but may, under adverse conditions, result where the cells are used. The cells have been known to explode, when shorted, dispersing microscopic mercury droplets which readily disappear in crevices or in dusty places and continue to emit mercury vapor for an indefinite period.

### **Beer Vat Coating**

Steel vats or tanks about 8 feet in diameter and up to 30 or more feet in length are frequently used for the storage of beer. Various types of coating materials are used on the inside of these vats and the application of the coatings involves at least potentially hazardous exposures. Men enter each tank through a manhole to apply plastic coatings in solvent solution by spraying, or to apply waxes with the aid of gas torches.

In the spraying operation hose masks must be used for respiratory protection and, also, explosive atmospheres may be involved. Air sufficient to keep the vapor concentration well below the inflammable limit should be supplied at the bottom of one end of the tank and exhausted at the top of the other end, in order to provide effective vapor removal.

In the case of the waxes, where torches are employed, no personal respiratory protection is needed but ventilation must be provided to remove the excessively hot and oxygen-depleted atmosphere. This involves an air supply to the bottom of one end of the tank and an exhaust at the top of the other end of not less than 250 c.f.m. per torch. Portable ducts may be used to direct the air flow and the workman should hold the torch on the downstream side of him.

### **Bleaching**

The bleaching of textiles normally consists of oxidation or reduction reactions to remove color. Strong chemicals such as hypochlorites, formaldehyde, hydrosulfites, ozone, and peroxides may be used.

Mechanical ventilation is required for most processes as the lung irritants, chlorine, sulfur dioxide, and ozone are likely to be evolved. In some instances

<sup>4</sup> S. W. Gurney, *personal communication*.

control of high humidity, due to steam arising from heated vats, is desirable. Process ventilation is more effective, but general ventilation is frequently, and not always advantageously, employed. Suitable clothing for protection against irritant materials is necessary.

### **Brick and Tile Manufacture**

The appraisal of exposures in brick and tile manufacture is concerned principally with free silica. The mineralogical composition of air-borne dust must be ascertained with emphasis on the determination of quartz, tridymite, and cristobalite. Plant operations are generally dusty, releasing to the atmosphere various quantities of clays and shales.

Glazing operations may introduce a lead exposure, and other relatively minor hazards include exposures to excessive temperatures, sulfur dioxide, and carbon monoxide.

Dust appraisal calls for particle enumeration by the standard light-field counting procedure, and particle composition by petrography and x-ray diffraction (silica) and chemical analysis (lead).

### **Broom Manufacture**

In the manufacture of brooms, the brush or seed top of broom corn, after removal of the seed, is used. The scraping and trimming of the brush is done by machines and is a dusty operation unless control ventilation is applied. Bleaching and dyeing operations may require control depending upon the materials employed. The industrial hygienist should find out what materials are in use, know their toxicity and, if necessary, then devise measures to safeguard workmen. Broom handles are frequently lacquered by dipping them in an open vat or tank. Both the dipping and the subsequent drying operations evolve excessive lacquer-solvent vapors unless ventilation control is applied.

### **Carpentry**

Most of the operations in carpentry include accident hazards. Mechanical saws, planers, shapers, and other equipment require a safety program of high caliber, as does work from scaffolds.

Dermatitis and irritations of the upper respiratory tract occur among some workmen. Generally these reactions are due to allergenic substances, but some woods are known to contain irritants. Wood dusts do not cause characteristic, disabling lung disease, but dust control is advisable for dust-producing machines such as power saws in order to prevent fires or dust explosions.

Chemically coated nails are now used to produce strong joinings with the minimum number of nails. The chemical coatings in some cases cause a characteristic dermatitis on the hand used for holding the nails. Other parts of the body may be involved.

## Carroting

The carroting of fur by a mixture of mercuric nitrate and nitric acid has had mercury poisoning associated with it for two hundred years. The mixture is applied to the tips of the fur on processed rabbit pelts, either by hand or by a revolving brush, in order to improve the felting properties of the fur.

The skins are then dried below 140° F. to produce a white carrot or at 160° to 250° F. for a yellow carrot. The dried pelts may be stored for several months, or immediately sent to the brushing department. After the fur is brushed to smooth it, it is sheared and the skin is shredded. The separated fur is cleaned and sent to the hatting departments.

Bloomfield and DallaValle<sup>5</sup> reported average mercury exposures varying from 7.2 mg. per 10 cu. meters of air for shippers, to 0.6 mg. per 10 cu. meter of air for office workers, machinists, etc. They recommend: (1) segregation of skin-handling operations, (2) local exhaust ventilation for cutting, brushing, and blowing operations, (3) natural or mechanical ventilation to decrease exposures associated with piling and shipping, (4) removal of treated fur from workrooms as quickly as possible and storage in well-ventilated rooms, (5) good housekeeping and sanitation, and (6) arrangement of processes to increase efficiency of operation, with resulting decrease of mercury exposure.

Beal, McGregor, and Harvey<sup>6</sup> report that satisfactory carrot can be obtained by means of hydrolyzing acid-hydrogen peroxide mixtures. Oxidizing acids such as permanganic, iodic, chloric, and so forth may also be used with hydrolyzing acids such as sulfuric or phosphoric. The mixtures are controlled by Beal and McGregor patents. These carroting solutions usually contain chloric and sulfuric acids, or hydrogen peroxide with a hydrolyzing acid. It is claimed that the only hazards involved in the use of these carrots are those of corrosion. Adequate protection of the workers by gloves and guards, and exhaust ventilation capable of removing spray are necessary. It is also advisable to remove fumes evolved during the drying of carroted fur regardless of the type of carroting used. There are said to be no health hazards in any of the succeeding mechanical operations.

## Cement and Concrete

Cement is made from cement rock or a mixture of finely ground limestone, or other form of calcium carbonate, with clay, shale, slate, or blast furnace slags, rarely sandstone, and certain accelerators or retarders. The mixed powders are heated in a kiln, usually rotary, to about 1300° to 1400° C. The kilns are heated by fuel jets of powdered coal, gas, or oil. The cement rock rarely contains more than 6 or 8 per cent quartz; the finished product usually less than 1 per cent, though occasionally it may contain up to 6.5 per cent. The dusts are ordinarily

<sup>5</sup> J. J. Bloomfield and J. M. DallaValle, *Am. J. Pub. Health*, 27, 167 (1937).

<sup>6</sup> G. D. Beal, R. R. McGregor, and A. W. Harvey, *Chem. Eng. News*, 19, 1239 (1941).

classed as nuisance dusts but their concentration may exceed the most liberal ideas of permissible limits.

There are several dust-producing operations and they are amenable to control measures. Some of these sources are: stone quarrying, crushing, grinding, the rotary kiln, screens, bagging operations, and the loading and unloading of cars. Dust clouds, if uncontrolled, not only are conducive to undesirable working conditions but also constitute an atmospheric pollution nuisance in the community. Electrostatic precipitation as well as centrifugal collectors have been used successfully to remove the dust from the effluent air from kilns and silos, and the amount recovered is said sometimes to exceed 5 per cent of total raw materials. A method that has been successfully applied to the rotary kiln elsewhere (see Sand Refining) is to exhaust the hot kiln gases through baffled water-spray chambers and conduct the water flowing from the sprays through a settling basin from which the sludge may be recovered. The important factors in evaluating exposures are the degree of dust control and the free silica content of dust particles less than  $5 \mu$  in diameter. Lung injury from exposure to cement dust, however, has not been demonstrated and the most frequent, harmful result of exposure is that of skin irritation from the alkaline action of the cement. In the mixing and use of concrete, the irritant, alkaline action of the wet mixture is similar to that of the cement dust, and both warrant suitable control to prevent prolonged contact with the skin.

### **Chlorinated Waxes and Oils**

#### *Synthetic Chlorowaxes*

The synthetic chlorowaxes comprise a number of chlorinated hydrocarbons which are derivatives of naphthalene or diphenyl. Halowax is the trade name of one manufacturer for the chlorowaxes.

The damage that may occur from inhalation, ingestion, and skin absorption of the chlorowaxes will vary with the degree of chlorine saturation of the compounds. The amount of dermatitis and poisoning increases rapidly as the amount of chlorine in the waxes increases. The commonly accepted maximum permissible limit for atmospheric contamination with trichloronaphthalene is 100 mg. per 10 cubic meters of air; for the tetra- and pentachloronaphthalenes, it is placed at 10 mg. per 10 cubic meters of air. The majority of the chlorowaxes carrying amounts of chlorine in excess of those previously named are restricted to 5 mg. per 10 cubic meters of air.

Systemic poisoning from the chlorowaxes is generally characterized by damage to the liver. Serious exposure may produce acute yellow atrophy. The skin effects are commonly in the form of acne which is more widely distributed on the body than common acne.

Among the recommendations for the prevention of chlorowax poisoning are: (1) vapors and dust should be controlled by exhaust ventilation to prevent exposure to amounts of the compounds in excess of the safe limits mentioned above; (2) foremen and workers should be told of the toxicity of the materials



which they are handling and instructed to keep skin contacts with the material to a minimum; (3) pre-employment and periodical physical examinations should be given with special attention to the skin and to the liver, liver function tests being performed periodically; and (4) the best hygienic conditions should prevail, including the provision of clean work clothing, protective gloves, and protective creams. Those manufacturers who have had the most favorable results in preventing chlorowax poisoning have provided double locker rooms, one for street clothes and one for work clothes, with a shower room in between. The workers should be required to take a shower every day before leaving the factory; it is well to provide supervision to make certain that this practice is complied with.

Air analysis for the chlorowaxes is most commonly performed by passing the air over heated platinum in an electrically heated quartz tube; the waxes decompose and the effluent gas is scrubbed in a column of glass beads moistened with sodium carbonate; the chlorine is converted to sodium chloride which is recovered by washing the beads, and is usually determined nephelometrically. The impinger, using amyl acetate as the collecting medium, has also been employed for collection of samples; afterward the samples are burned, products of combustion collected and chlorides determined.

#### *Chlorinated Oils*

There are two general types of oils falling within this class: the first contains additive substances such as carbon tetrachloride to improve cutting properties; the second has chlorine combined in complex organic structure.

The chlorine additive agents may be recovered by distillation and are released from the oils in accordance with vapor pressure laws. The use of oil plus chlorinated hydrocarbon may be hazardous unless exhaust ventilation is provided. Nausea and malaise are common complaints of workers handling the mixtures. The haphazard methods used in preparing the mixtures tend to increase the danger. Commonly the chlorine compound is added in unknown proportion as an antidote for cutting difficulties. In some instances the mixture has been found to contain as much as 40 per cent carbon tetrachloride.

The chlorine in the second type of oil is firmly bound at lower temperatures; upon heating, little decomposition occurs below 200°; near and above 250° hydrogen chloride is evolved. It is known that temperatures in excess of 300° C. are produced locally from heavy cutting operations. This type of oil probably can be used safely for light precision machining.

Animal experimentation has shown that chlorine compounds in oils are readily absorbed through the intact skin, frequently causing liver damage. Dermatitis from chlorinated oils is also of common occurrence.

#### **Chlorine Manufacture**

Chlorine is manufactured by the electrolysis of brine, sodium hydroxide and hydrogen being simultaneously produced. It is not necessary here to emphasize the corrosive action of caustic soda or the inflammability of hydrogen, but it is

in order to point out the more obscure mercury vapor exposure that may accompany the use of the Castner, the Sorensen, the Krebs, or any other cell in which mercury is used. These cells can be used safely when the exposure possibilities of mercury are recognized and controlled. Wherever mercury is used in quantity, the potential exposure should be evaluated and controlled.

The toxicity of chlorine itself is well recognized; chlorine is no longer considered a desirable or beneficial addition to the atmosphere. It has warning properties that aid in its recognition and control.

### Compressed Air Work

Work in compressed air has been discussed extensively in Chapter Six. Discussion here will be limited to the use of helium-oxygen mixtures for the alleviation of "ear block." "Ear block," or more properly tubal or sinus block, occurs with considerable frequency during compression and decompression even when the working pressure is not more than one atmosphere above normal. The condition, which is similar to one encountered in rapid ascent or descent<sup>7</sup> in an airplane, is painful and may be accompanied by deafness, vertigo, tinnitus, and rupture of the eardrum. A mixture of 80 per cent helium and 20 per cent oxygen is administered by means of a face mask.<sup>8</sup> This is most effective when done in the man lock but may be accomplished in the first-aid room near the lock. The similar use of oxygen has been described under oxygen.

The principal objection to administering the gas in the lock is the difficulty of sterilization of facepieces. Only 1 to 3 minutes inhalation of the gaseous mixture is required, and the method is highly successful. A difficulty of the application of this method in the first-aid room prior to compression in the lock is that the lapse of time between inhalation of the gas and start of compression permits partial loss of the gas and its beneficial effect.

The use of the helium-oxygen mixture has been abused and it should never be administered by persons who have a lack of appreciation of sanitation. Medical supervision of personnel is required else persons with colds and respiratory infections that make them unsuited for compressed-air work are likely to take advantage of helium-oxygen inhalation as a means of getting through the lock.

### Cork and Linoleum Industry

The term "cork" is applied to a part of the bark of the cork oak, which is grown principally in southern Europe. There are no recognized hazards peculiar to stripping the bark from the trees.

The cork is graded according to quality and cut into various shapes for marketing. It is said that in some shaping operations about 35 per cent of the cork is converted to dust. Cork dust is of the nuisance variety except for the

<sup>7</sup> W. R. Lovelace, C. W. Mayo, and W. M. Boothby, *Proc. Staff Meetings Mayo Clinic*, 14, 91 (1939).

<sup>8</sup> J. W. Crosson, R. R. Jones, and R. R. Savers, *U. S. Pub. Health Repts.*, 55, 1487 (1940).

real danger of dust explosions. Attention should be directed to dust control and elimination, to housekeeping, and to the elimination of static electricity and other sources of ignition.

Linoleum is manufactured by impregnating a woven framework of hemp or jute with oxidized linseed oil combined with vegetable gums, rosin, cork, and pigments. Substitutes may be employed for linseed oil or for cork. Here again, dust explosions from cork or other fillers are the principal hazard. Acrolein and other obnoxious volatile organic vapors or gases are released from linseed oil during oxidation. Lead, manganese, arsenic, and mercury compounds are used in oxidizing the oils, and metal poisoning must be considered. Volatile solvents such as benzene, xylene, methyl alcohol, and turpentine may be encountered also.

### Cotton Industry

Some picker-room operations result in very high dust concentrations and the dust may cause acute inflammatory irritation of the nasal pharynx and bronchi. Fever and a bad cough are frequent symptoms. These conditions occur most commonly when low grade cotton is processed. The British<sup>9</sup> consider the respiratory response to be caused by histaminelike substances present in the fine dust. The dust is described as being ultramicroscopic,  $0.2 \mu$  and less.

Trice<sup>10</sup> recommends that carding machines be housed and provided with exhaust ventilation. Vacuum strippers and grinders are also recommended. It has been found that vacuum cleaning is valuable in reducing the dust load on machines. This prevents redistribution of the dust in the air.

Britten *et al.*<sup>11</sup> found dust to be of little consequence in cotton cloth plants which they investigated. High temperatures and humidities were found in southern mills but no definite effect on health was established.

Caminita, Schneiter, Kolb, and Neal<sup>12</sup> found a Gram-negative microorganism occurring in large numbers in low-grade stained cotton. The organism was responsible for acute illness which closely resembled "mill fever" reported among cotton-mill operators.

### Detinning Scrap and the Manufacture of Tin Tetrachloride

Tin scrap is pressed into bundles or bales of about one to two hundred pounds and detinned in large steel chambers. The scrap must be completely dry, and dry chlorine is admitted to the chlorination chamber at ordinary temperatures. The chlorine reacts with the tin, with evolution of heat, to produce liquid tin tetrachloride, which drips to the bottom of the reaction chamber and is removed through pipe lines for purification by distillation. The large quantities of chlorine

<sup>9</sup> C. Prausnitz, *Investigations on Respiratory Dust Disease in Operatives in the Cotton Industry*, H. M. Stationery Office, London, 1932.

<sup>10</sup> M. F. Trice, *Respiratory Disturbances Suffered by Cardroom Workers Attributed to Protein in Cotton Dust*. North Carolina State Board of Health, Sept., 1939.

<sup>11</sup> R. H. Britten *et al.*, *U.S. Pub. Health Bull.* No. 207 (1933).

<sup>12</sup> B. H. Caminita, R. Schneiter, R. W. Kolb, and P. A. Neal, *U.S. Pub. Health Repts.*, 68, 1165 (1943).

used necessitate emergency equipment for protection against both low and high concentrations of chlorine in the event of leaks or ruptures of connecting pipe lines. There are opportunities for exposure to chlorine, hydrochloric acid, and tin tetrachloride.

The operation of filling drums with tin tetrachloride and sealing them is accompanied by excessive exposures to tin tetrachloride and hydrogen chloride unless effective control, such as exhaust ventilation, is provided. "Sampling" of the stannic chloride from the reaction cylinder also may be accompanied by exposure to hydrogen chloride and stannic chloride. Tin tetrachloride, with a boiling point of 114.1° C., is quite volatile and in filling drums an essentially saturated vapor-air mixture is displaced from the drum into the room. Concentrations as high as 700 p.p.m. hydrogen chloride have been measured in the room near the drum during filling, when there was no ventilation. No permissible limit for tin tetrachloride has been established, but, since it readily hydrolyzes in the presence of moisture to form hydrochloric acid, it is logical to assume that its physiological effect would not be less than that of hydrogen chloride, and might be more severe in that some of it would tend to reach the alveoli before hydrolysis occurred. Although tin tetrachloride can be handled in iron or steel containers when dry, not so the moist vapor-air mixture: any fans, ducts, or enclosures for control of the vapors must either be replaced frequently or be constructed of material resistant to hydrochloric acid.

### Doping

Dope for airplane fabrics consists essentially of cellulose esters and volatile solvents. Since large surfaces are involved and the solvents evaporate readily, they contaminate the surrounding atmosphere during application and drying of the dope. Solvents in use today are chiefly alcohols, ketones, esters, and ethers, with moderate amounts of toluene. The dope is often applied in large rooms with only general ventilation. This requires a volume of air movement directly proportional to the amount of dope applied in order to dilute the vapors to acceptable levels. Where humidity-controlled or air-conditioned rooms are used for doping, ventilation is more of a problem. Recirculation through scrubbers has been successfully applied to the control of water-soluble solvent vapors where it was necessary to limit the discharge of air.

A permissible concentration of vapors in the workroom air must be decided upon by the industrial hygienist for each particular situation, based upon the known composition of the dope.

### Dye Manufacture and Use

Aniline dyes have an unwarrantedly bad reputation. In their manufacture, raw materials, intermediates, and by-products, such as ammonia, aliphatic amines, acids, sulfur dioxide, nitrogen dioxide, methyl alcohol and other solvents, aniline, *m*- and *p*-phenylenediamine, nitrosodiethylaniline, tolylenediamine, toluidine,

pyrogallol, quinone, benzidine, and phenylnaphthylamine, warrant careful attention and control to prevent inhalation exposures or skin contact.

The mixing, grinding, and packaging of dyes should be segregated and provided with engineering control measures that prevent objectionable air contamination. Because of the small particle size and the costliness of most dyes, exhaust ventilation must be sparingly applied or else a filter must be used to recover the product.

Drying ovens should be vented to the exterior. Vats evolving steam or hydrogen sulfide, formaldehyde, or other noxious gases should be provided with process ventilation designed to give satisfactory control; reliance should not be placed upon general ventilation alone. Alkalies, chromates, arsenic, some dyes, and most of the materials named above require effective control measures to avoid skin irritation or sensitization from direct contact.

### Electroplating

Electroplating is preceded by metal cleaning, which is described elsewhere. Chromium plating is the most common plating operation requiring good exhaust ventilation control. The recommended exhaust volume of 120 to 150 c.f.m. per square foot of tank surface (discussed in Chapter Ten) may vary considerably depending upon tank location and design, baffles, interfering air movements, current density, and plating efficiency. The plating solution may be conserved by keeping the surface of the solution 8 in. or more below the exhaust slot. A further, remarkable saving in plating solution can be accomplished by the use of a layer of inert small objects floated on the surface of the bath. About a 2-in. layer of plastic tubes or "chips,"  $\frac{1}{4} \times 1\frac{1}{2}$  in. floated on the surface of a small chromium plating bath, was found to reduce the chromic acid loss over 80 per cent and the exhaust volume requirements about 50 per cent. When used on conveyORIZED equipment the chips present a problem in that they tend to follow the conveyor leaving exposed surfaces at one end of the bath and accumulating at the other. "Chips" that tend to adhere to the work are unsatisfactory. Reduction of surface tension by addition of a suitable wetting agent to the plating bath also reduces loss of chromic acid.

Plating solutions containing arsenic require very effective exhaust ventilation. Cadmium plating and lead fluoroborate plating operations do not ordinarily present harmful exposures even though unventilated. Copper, zinc, and nickel acid plating operations seldom necessitate mechanical exhaust. Cyanide baths frequently require exhaust and alkaline plating baths sometimes evolve offensive amounts of alkali mists requiring exhaust measures. It is good practice to ventilate all hot baths in order to control excessive humidity and there is some merit in making it general practice to hood and ventilate *all* plating baths as a safeguard against any change in plating procedures that might cause harmful exposures; but such recommendations in many cases cannot be justified by air analyses.

It seems superfluous to say that cyanides should be kept locked and stored where they cannot cause a catastrophe from accidental contact with acids, but they still frequently are stored carelessly.

Ammonia from zinc cyanide plating operations may reach annoying levels, but it is doubtful if it ever exceeds permissible concentrations where the plating department has suitable general ventilation. Concentrations of 5 to 10 p.p.m. ammonia are easily recognized and therefore sometimes offensive to persons in adjacent departments. Methods of control include foam-producing agents as well as ventilation.

### **Fertilizer Manufacture**

The principal health hazard in the production of fertilizers occurs in the preparation of soluble phosphates. The raw material, fluoroapatite, is a calcium phosphate rock containing as much as 3 or 4 per cent of calcium fluoride. When phosphate rock is acidified to produce soluble phosphates, about half of the fluoride is evolved as silicon tetrafluoride and hydrofluoric acid. The tetrafluoride is produced by the reaction of hydrofluoric acid with silica present in the rock.

It is common practice to reclaim the valuable fluoride gases and to convert them into fluosilicates. Throughout the entire operation there are potential exposures to fluoride gases and dusts. The finished phosphates themselves normally contain about one half of the original fluoride, and are potentially dangerous. The extent of the fluoride exposure has not been exactly defined. There is some evidence that the fluoride exposures which occur in the manufacture of fertilizers, and of aluminum, do not produce damage when fluoride concentrations are twice the bench mark suggested by Williams<sup>13</sup> (3 p.p.m. of HF or 20 mg. of fluoride per 10 cubic meters of air).

The exposure should be evaluated by air analyses. One procedure is to collect fluoride dusts with an electrostatic precipitator and to determine gaseous fluoride in the cleaned air. It is also possible to determine dust with a precipitator, and both dust and gas by bubblers. The fluoride gas is then obtained by difference.

The preparation of mixed fertilizers is frequently accompanied by the release of quantities of dust. It is advisable to determine the extent of the exposures by dust-counting technique, and to limit the dust to fifty million particles per cubic foot of air. No health hazard is to be anticipated if this standard of permissibility for nuisance dust is met.

In some plants, phosphate fertilizers are treated with ammonia to provide available nitrogen. Ammonia gas in the air should not exceed 100 p.p.m.

### ***Roasting Phosphate Rock and the Manufacture of Superphosphate***

In this industry phosphate rock is fused in an electric furnace with carbon and silica or clay. The gases from this furnace, consisting of elemental phosphorus and carbon monoxide, pass to a condenser where the phosphorus is condensed to a liquid, and the carbon monoxide passes through to be recovered for fuel. The elemental phosphorus may either be collected as such, or vaporized with

<sup>13</sup> C. R. Williams, *J. Ind. Hyg. Toxicol.*, **24**, 277 (1942).

compressed air and burned to phosphorus pentoxide, which subsequently is absorbed in water to make phosphoric acid. Ground phosphate rock and phosphoric acid are in turn used to make superphosphate. Although the processes are carried out within a closed system, opportunities exist, especially during cleaning and repairing of the system, for exposures to elemental phosphorus, phosphorus oxides, carbon monoxide, and fluorides from calcium fluoride in the phosphate rock. The water that has been in contact with phosphorus is under suspicion as a source of exposure because it is thought to contain colloidal phosphorus. All potential exposures should be evaluated periodically.

See also Phosphorus.

### **Forging and Iron Working**

Exposure to high temperatures, sudden changes of temperature, and radiant energy present the principal health problems in forging and iron working.

Ventilation by means of air douches and man-cooling fans, protective asbestos clothing, and radiant-heat baffles are commonly used to alleviate the exposures. It is also of value to ventilate the building, as by means of roof ventilators which allow heated air to escape from the structure. Wherever excessive gas and smoke occur they should be removed by means of local exhaust ventilation.

Excessive infrared radiant energy is undesirable and it may damage the eyes of workers. Heat cataract may develop, depending upon the intensity of radiation, source (point or broad band), length of time exposed, and the age and health of the individual. The danger from radiant bodies multiplies rapidly as the size of the radiant body increases and as the temperature exceeds 2500° F. It has not been possible to set a safe limit based on our knowledge to date. Workers exposed to significantly intense radiation should wear approved protective lenses.

The use of salt in drinking water, or as tablets, is well recognized as a necessity in the prevention of heat disease. If tablets are used, however, care should be taken to make certain that the tablets dissolve readily and rapidly. Some salt tablets are so hard that they stay in the stomach for long periods of time. Cases of nausea following the use of salt tablets have been traced to their failure to dissolve.

Carbon monoxide also is an ever-present danger and excessive fumes and gases from furnaces should be vented outside the building at such a height as to produce adequate dispersion.

### **Foundry Operations**

The foundry environment varies not only with the kind of metal poured, such as steel, iron, brass, bronze, aluminum, or magnesium, but with industries, location, communities, experience and attitudes of management and labor, and other factors. All of these must be taken into consideration in evaluating and controlling the environment. The industry as a whole has been subjected to much criticism in recent years and its environment described as "hot, dusty, smoky,

unhealthful, and hazardous." Such a description may apply in isolated instances, but not to the industry; foundrymen are improving the environment and are not only desirous of learning of any possibly harmful conditions existing in their plants, but are ready to listen to any practical, positive means of controlling them. The manager or superintendent who thumps his chest and exhibits his robust physique as evidence that the environment in his foundry is beyond reproach may need to be reminded that the office worker's environment is somewhat different from that of the shakeout man. Foundry management in general not only is desirous of controlling exposures known to be harmful but also wants to clean up the plant atmosphere sufficiently to make it a desirable place in which to work.

How far to go in making recommendations for control is a matter to be left to the judgment of the responsible investigator. It is perhaps better to be satisfied, at first at least, with bringing only the more obviously harmful situations under immediate control and to leave the way open for progressive friendly relations, than it is to prescribe sufficient control to make a dirty, dusty place into a model of cleanliness throughout. A "clean up" plan which is too ambitious may be received with antagonism and is likely to be placed in the "permanent file." The foundry that had a part in producing the armor for the "Merrimac," for instance, is steeped in lore and tradition. Such older foundries could proudly point to the fact that in nearly one hundred years of operation, during which flasks have always been poured and upset in the general foundry area, no one has died on the job or, so far as is known, been a victim of silicosis. The management of such a foundry may not welcome with open arms all of the newfangled medical and engineering ideas advanced by some itinerant industrial hygienist. Here, suggestions for such changes as the installation of flush toilets, substitution of electrically operated hoists and trolleys to replace a system of belts and pulleys operated by water power for transporting ladles of molten metal, and the segregation and ventilation of floor shakeout operations possibly would be a logical start in improving the environment.

If the foundry happens to be staffed by hardy mountaineers they may prefer to wear nothing more than a pair of shorts in warm weather and they may scoff at any mention of protective clothing or at the idea of wearing respirators in dust clouds ranging upward of one or two hundred million particles per cubic foot of air. Management and employees alike may scorn the "sissy" ideas expressed by a tenderfoot hygienist, especially if he gives way to the urge to don a respirator while making his survey. The obviously hazardous situations should be attacked first and tactful education should start with the management.

One the other hand, if the foundry is more or less completely mechanized, has correctly exhausted, enclosed shakeouts, model core knockouts, dustless molding and core making, a tempered air supply, well-engineered and controlled sand-handling equipment, spacious, well-kept aisles and so on, and all that can be found wrong is that some smoke and fumes are escaping from the pouring



operation or the cooling sheds or tunnels and marring the freshly painted girders and walls, the method of approach will be somewhat different. But, even here, the hygienist has an opportunity to be of service to the management and workmen in helping them keep a showplace by advising how the escape of the smoke can be prevented or controlled.

The foundry survey is not merely a matter of collecting breathing-zone samples to evaluate exposures, but should include the location of sources of harmful or annoying exposures and the development of methods for control. The silica exposure has been overrated but is nevertheless the most important factor where dustiness is excessive (on the order of thirty million particles per cubic foot). Sea coal is perhaps the most offensive source of visible dirt and has been the cause of disastrous dust explosions: satisfactory substitutes are being sought and, in a limited degree, applied. Iron fumes may give rise to confusing x-ray photographs of the chest. Cold drafts should be corrected, especially where shake-out or core-knockout operations are located in front of an open window so that the operator is excessively heated in front with radiant heat while his back is chilled with the inrush of cold air.

The control of the foundry environment will be discussed by following the metal from melting to cleaning.

## I. IRON AND STEEL

### A. Melting

The *cupola* may be the source of carbon monoxide exposures and, if no dust control is employed on the stack, dust and iron fumes may be an objectionable source of atmospheric pollution in some neighborhoods, and may cause excessive deposits on the roof of the foundry. Automatic-spray dust arrestors with no fans have proved very satisfactory means of control.<sup>14</sup>

*Electric furnaces* may give rise to large amounts of iron oxide and various other fumes, such as silicon dioxide and manganese dioxide, depending upon the composition of the steel. Roof ventilation above the furnace is common practice, but local exhaust is more effective. Breathing-zone samples collected with the electrostatic precipitator should be evaluated for toxic fumes and dusts, as well as for free silica (possibly from ferrosilicon<sup>15</sup>). Gases such as nitrogen oxides should be considered also.

If tellurium or selenium is added to the molten metal, any fumes resulting should be controlled by ventilation.

### B. Mold and Core Making

Ordinarily there are not many potentially harmful operations involved in making molds and cores. Some points worth investigating, though, are the dusting of flint or silica flour, the spraying of liquid mixtures containing harmful solvents, chemicals, or silica particles, and the cutting or grinding of baked cores. Chills are sometimes sprayed with shellac or other adhesive material and dusted with sand. This may involve an exposure to solvent vapors and, where the sand contains fines, a dust exposure. Carbon tetrachloride, if used in

<sup>14</sup> A. H. Allen, *Foundry*, 73, 88 (Nov., 1945).

<sup>15</sup> T. Bruce, *J. Ind. Hyg. Toxicol.*, 19, 155 (1937).

molds, presents an exposure problem during the making of molds and a more difficult one at pouring stations due to decomposition products.

### *C. Pouring*

Smoke, gases, and vapors from the destructive distillation of sea coal mixed into the molding sand, and insignificant amounts of iron fume, arise from pouring operations, and for a considerable period after pouring. The gases, including carbon monoxide, escaping from the mold usually ignite spontaneously or are fired by a torch.

The heat, smoke, and fumes arising from this operation usually need no evaluation other than by the senses. The problem, which is chiefly of a nuisance nature rather than one of health, may involve mildly irritant aldehydes and much smoke that not only makes the atmosphere appear offensive but deposits black residues on all objects in the plant. Where the sand-conditioning process involves the addition of a solvent, this solvent may distill out of the mold at the instant of pouring and necessitate effective ventilation control. A properly constructed side-draft hood with the top extending out as far as possible over the flask and provided with an exhaust volume of 100 c.f.m. per square foot of face will remove most of the smoke, fog, or fume from a central pouring area. Up to more than twice this volume may be required to remove all contamination where conditions are not ideal.

Where flasks are poured on the floor, the general practice has been to provide high ceilings with air outlets as high as possible and inlets at or near floor level to provide dilution and directional general ventilation, either gravity or mechanical.

Cooling canopies or cooling tunnels, however, are desirable for removing smoke, fumes, and gases from the molds during cooling. Where mold conveyors are used, fairly close-fitting, heavy-gage metal tunnels from pouring station to shakeout, with 30- to 36-in. gravity ventilation stacks, have proved satisfactory if the make-up air supply is adequate. Tunnel air inlets, 8 to 18 in. high, are provided along the sides at floor level and, so long as the foundry is not airbound, smoke and gases can be controlled. Some tunnels have been constructed with removable side panels to permit ready access for maintenance purposes, but this almost invariably has resulted in some of the panels being removed and not replaced, with the result that the smoke pours out of this opening instead of being drawn to the gravity stack. The hinging of these panels might improve the situation, but a more positive method is to make the tunnel of solid welded construction. When necessary to provide an opening for maintenance, a cutting torch may be used and the plate replaced by welding as soon as the repair job is completed. Of course if sufficient mechanical exhaust ventilation is applied, rather than gravity stack ventilation, the results are more dependable, and a few missing panels may not seriously interfere with smoke removal. In cold weather a little fuel can be saved by supplying the cooling tunnel with make-up air from out-of-doors.

### *D. Shakeout*

#### *1. Enclosure*

The most effective control for shakeouts is the relatively complete enclosure with sufficient exhaust volume removed at the top to maintain an inflow of about 200 f.p.m. at all openings. The degree of enclosure will be limited by such factors as the kind and extent of mechanization for bringing in and upsetting flasks, size of flasks and castings, and manual or automatic castings discharge. This type of hood is limited to relatively small castings. The exhaust volume for such enclosures can be determined as 200 times the total area of openings in square feet, but must never be less than a minimum volume, which has been suggested by Kane<sup>16</sup> to be 200 c.f.m. per square foot of shakeout grate. This minimum volume is required to remove expanded air and steam.

<sup>16</sup>J. M. Kane, *Foundry*, 74, 86 (Feb.), 104 (Mar., 1946).

## 2. Side Hood

The side hood is applicable to castings of nearly any size. It should be parallel to and larger than the long side of the grate; and the top, which should be reinforced with a bumper, should extend as near as possible to the centerline of the grate. At times it may be expedient to place baffles or side shields at one or both ends of the hood to increase the effect of air flow over the grate. Many factors, such as cross drafts, ratio of sand to metal, temperature of casting, and hood location and design, influence the exhaust volume required (see Chapter Ten), but 400 to 500 c.f.m. per square foot of grate area is ordinarily required for satisfactory control. It is practically impossible to control shakeout dust if "man-cooler" fans or air-supply ducts are directed toward the shakeout hood.

## 3. Downdraft

Although downdraft has many appealing features, effective dust control is not one of the major points. Hot castings create intense, opposing updrafts, and the sand covers the effective grate area at the time and place at which a downward flow of air is most necessary. A good part of the air for the exhaust flows in at floor level and so offers no dust control. It is not practical to control by downdraft the upward surge of hot air and its heavy charge of fine dust particles rising directly above red-hot castings.

Such an arrangement has been applied successfully to the shakeout of cooled castings, with volumes as low as 200 c.f.m. per square foot of grate area. At the usual temperatures for shakeout of iron castings volumes of 500 to 600 c.f.m. per square foot of grate area frequently fail to control the dust, while the high-velocity air tends to aspirate the sand out through the exhaust system.

## E. Core Knockout

The side-hood arrangement with exhaust volume similar to that for the shakeout is the preferred method of control for the vibrating core knockout, but enclosures can be applied and, when the castings are not too hot, the floor grill is more applicable here than it is to the shakeout. A combination of side hood and downdraft is very effective.

The use of compressed-air jets to blow out the last of the core sand is objectionable in that it disperses excessive amounts of fine silica dust. Hydraulic methods of core removal are reputedly successful.

## F. Sand Handling and Conditioning

It is a very difficult job to clean up a foundry having mechanical shakeouts and sand-handling equipment but lacking enclosures and correct ventilation. The outstanding points of dust dispersion requiring enclosures and exhaust ventilation are: the shakeout hopper, transfer to return conveyor, transfer to elevator, transfer to and from other belt conveyors, sand screens, tailing pipes, sand mixers, and receiving ports on sand bins. Exhaust ducts must be designed for correct conveying velocities, yet each hood connection must have a low-velocity entrance into the duct in order to avoid picking up large-sized grains. Abrupt hood connections at or near dust-dispersing points waste sand, which may settle out in the exhaust duct. Sea coal, being relatively light and fine, is rapidly removed from the hot sand by the exhaust system and can be reclaimed from collectors in some instances. Its explosion properties should not be overlooked. Shakeout tunnels usually require general ventilation in addition to the control mentioned above, especially where hot sand is transported on an open belt. Depending upon the length and size of the tunnel, it may be practical to sweep the air the length of the tunnel by exhausting at one end, while in others a central exhaust, or a distributed supply along one side and exhaust along the other, may be necessary. In

any case there must be a controlled flow and displacement of air rather than dilution and mixing. Conditioning equipment and portable sand riddles that chop and discharge the sand by means of propellers, with sufficient force to throw the sand several feet, are dangerous sources of dust when used with relatively dry sand.

### *G. Casting Cleaning*

Blast cabinets, Wheelabrators, and tumbling mills must be maintained so that the relation between the area of openings and the volume of exhaust is in the proper balance to prevent the escape of dust into the room; and all unnecessary openings should be eliminated.

Blast rooms must be sufficiently tight to prevent the escape of larger particles through the velocity of their travel, either direct from the blast, or rebound from the work or walls. At the same time they should be provided with a sufficient volume of exhaust to prevent the escape of dust at crevices and to promote visibility. Where the room is large enough so that its ventilation with plant air involves significant heat loss, it may be supplied with some air from out-of-doors.

Air chisels for cleaning castings are frequently the source of excessive dustiness, and therefore dust respirators may be required unless a side or grill exhaust can be provided. Here again compressed-air jets, especially high-pressure ones, are objectionable for blowing off dust.

See also Abrasive Blasting.

### *H. Make-Up Air*

The necessity for make-up air has been discussed in Chapter Ten. In summer, if the air discharged by the cupolas and exhaust stacks is sufficiently clean, make-up air ordinarily comes through the open windows and doors, and so offers no problem. However, the use of air supplied through insulated ducts, or ducts below floor level, offers attractive cooling possibilities. With windows and doors closed, as in winter, there is necessity for a supply of air sufficient to keep the indoor-outdoor pressure essentially balanced if drafts and the other adverse effects associated with reduced interior pressure are to be avoided. In the average foundry there appears to be no point in supplying more air than is exhausted, and probably not as much air, for, depending on the type of construction, a variable and considerable volume of air filters in through the walls and cracks at relatively low pressure differential and velocity.

Various ideas for utilization of waste heat around the foundry in winter by delivering the make-up air through heat exchangers have some merit. Perhaps the most available sources of waste heat are furnace stacks, and casting-cooling conveyors. There are many places where cold air might be used to supply make-up air for process control without having it traverse working spaces, thus avoiding the heat loss from using tempered room air for this purpose. Examples are: shakeouts, cooling tunnels, tumbling mills, blast cabinets, and so on.

### *I. Layout*

It is not possible to have a clean foundry and satisfactory environmental control along with overcrowding. The establishment of good "housekeeping" must necessarily start with the provision of sufficient working space and aisles. Mechanization is an aid to any environmental control program. Conveyorized lines for mold and core preparation, pouring, cooling, and shakeout should be laid out with a view toward minimum-handling, co-ordinated flow of materials, and ample work space. Those operations that involve heavy lifting, or are stationed in a hot, smoky, or dusty atmosphere should be studied with a view toward simplification or mechanization to an extent that will provide satisfactory environmental conditions for each workman. Automatic pushoffs, vibrating core knockouts, and enclosures for shakeouts

and core knockouts that permit the operator to remain outside, are outstanding examples of mechanized means of improving the environment.

## II. BRASS AND BRONZE

Many of the problems previously discussed under the iron and steel foundry apply here. In addition, the melting and pouring operations usually necessitate mechanical ventilation control of zinc fumes, and this exposure must always be considered.

Where phosphor bronze is made by adding white phosphorus to the molten metal, strict safety precautions and good ventilation are necessary. Replacing the white phosphorus with a copper-phosphorus alloy or an ore containing phosphorus might well be given a trial.

If lead is used, the possibility of a lead exposure should be investigated.

## III. ALUMINUM

Sometimes chlorine gas is bubbled through aluminum in the melting furnace to volatilize impurities: control by ventilation is then necessary. Lateral-flow hoods with partial enclosures on the sides are effective, while conventional canopy hoods have not proved satisfactory. Carbon tetrachloride and mixtures containing it, if used in a similar manner, involve a greater potential exposure due not only to the vapors of carbon tetrachloride, but also to its possible decomposition with formation of phosgene gas.

Sometimes an alloy is made by adding about 0.3 per cent mercury to a mixture of molten zinc and aluminum in the melting crucible at about 1000° F. and pouring it at 900°. Since the boiling point of mercury is 674.4° F. this obviously presents a serious potential mercury exposure even though the mercury is introduced through a tube to the bottom of the crucible. The operation requires effective ventilation control, as well as care to avoid spillage.

Any other exposures are similar to those discussed under iron and steel foundries.

## IV. MAGNESIUM

The use of antioxidants, fluxes, or conditioning agents such as sulfur, sulfur dioxide, and fluorides makes it necessary to provide ventilation control for melting, pouring, and mold-cooling operations. Where fluorides are mixed with the molding sand or sprayed on cores, fluoride exposures must be considered and controlled at pouring, core spraying—especially when sprayed hot, shakeout, and core-knockout operations. Depending upon what fluorides are used, the air contamination may be gaseous (hydrogen fluoride), or particulate, or both.

Heat-treat ovens with a reducing atmosphere containing sulfur dioxide, usually on the order of 0.5 per cent, require mechanical ventilation for all openings, and the hoods and ducts must be designed to accommodate the escape of large volumes of the atmosphere when the oven doors are opened for loading and unloading.

Due to the use of a fine-grained sand, even those exposures attendant to the handling of the dry, raw sand must be well controlled.

## Galvanizing

Galvanizing is done by dipping cleaned metal into molten zinc. The iron must be cleaned by dilute acids, zinc chloride, molten caustic, abrasive blasting, or barrel tumbling before galvanizing.

Zinc is a physiologically inert element and it should not be considered an industrial poison.<sup>17</sup> As fume (finely divided zinc oxide) it does, however, cause metal-fume fever. This is a transient effect, which is unpleasant but which seldom

<sup>17</sup> H. Engel, *Occupation and Health*. International Labor Office, Geneva, 1934, p. 1285.

lasts longer than 24 hours. The fever may be caused by other metallic oxides. Aged fume (partially agglomerated) does not cause fever. The maximum allowable concentration for zinc fume is 15 mg. per cubic meter of air. Skin affections from zinc are uncommon but zinc chloride has been described by several investigators as a skin irritant.

The processes employed for cleaning iron surfaces should be examined carefully. Exposures to the splash of molten caustic, to acid vapors or mists, or to silica dust from abrasive blasting, may require control.

### Garages

The principal problem around garages is the exposure to carbon monoxide from exhaust gases. This problem is easily solved by the use of flexible exhaust duct connections for automobiles during test operations (see page 308). Unwarranted, and possibly unsafe, devices such as ozonators for "purifying" exhaust gases should not be relied upon because they have no beneficial effect upon carbon monoxide, the toxic constituent of exhaust gas. It is essential to provide sufficient general ventilation to dilute and remove exhaust gases generated by cars in motion, so as to keep the average concentration of carbon monoxide below 100 p.p.m. Brief and fleeting concentrations of carbon monoxide up to five times this amount are of no consequence.

The use of trichloroethylene and other solvents is discussed under Metal Cleaning. Spray painting when confined to touch-up work is not a serious problem; for more extensive operations see Spray Painting. When solder is applied to automobile bodies by the use of a torch for the purpose of filling dents or cracks, it does not cause a significant exposure to lead, but in a room where men work this solder should never be removed by a disk grinder without positive personal respiratory protection. Such disk grinding, unless done in a controlled and segregated area, contaminates the room with sufficient lead dust to present an exposure for an extended time after the actual operation has been finished. Rasping or scraping does not produce a significant amount of respirable dust, but does present a "housekeeping" problem.

The use of gasoline in open containers such as vats, pans, or buckets is hazardous and should be avoided. Sandblast cleaners for spark plugs, if operated for consistently prolonged periods, warrant checking for possible silica dust exposures and lead exposures.

### Glass Manufacture and Fabrication

The two main divisions of the glass manufacturing industry are flat glass and container glass. With the exception of certain specialty glasses, the ingredients are similar for each type. A typical formula contains dolomite, limestone or lime, feldspar, salt cake, sand, and soda ash. Minor constituents include arsenic, antimony, carbon, cobalt, rouge, and selenium.

The major proportion of each batch of ingredients is sand, which potentially

would seem to present a serious silicosis hazard. Actually, in most cases today washed sand is used, from which most of the "fines" have been removed. It is common to find that air-borne dust from the mixed batch will contain only from 1 to 5 per cent of free silica. Silicosis under modern conditions is rare.

However, with certain types of sand the methods of handling can present a silicosis hazard. The unloading of dry sand from boxcars either by power scoop or by shovel and wheelbarrow may produce dangerous quantities of fine silica dust. When wet washed sand is obtained in hopper cars and unloaded by gravity or, after drying, handled mechanically in a totally enclosed system (with exhaust ventilation) there is no harmful exposure.

The other major constituents of glass represent a nuisance dust problem rather than an exposure harmful to health. Their only detrimental effect upon health has been dermatitis where reasonable standards of cleanliness are neglected. The minor constituents have caused some harm to health, with arsenic being the principal offender. Perforation of the septum or severe skin effects were not uncommon in the past. Modern methods of handling have eliminated most of this trouble.

Glassmaker's cataract has been referred to in the literature<sup>18</sup> and is believed to result from exposure to high intensities of infrared. Statistics do not indicate the extent of the industrial hazard nor is there any recognized limitation on infrared tolerance.

Flat glass including plate glass and window glass has been made by two processes, the pot and the tank methods.

#### *Pot Process*

The older, or pot, process is now used principally for the manufacture of certain specialty or high-quality glasses, such as optical and mirror glass, or for structural glass. The tank method is used for window glass and most of the regular production plate glass.

The pots vary in size up to those capable of holding nearly two tons of ingredients, and their manufacture has been responsible for the greater portion of the silicosis which has come from glass manufacturing. The pots are made from a number of different types of clay combined with flint (silica) or silica flour. Pot manufacture was commonly a very dusty industry. It is only in the last 10 to 15 years that dust control has been practiced.

An investigation of the health hazards in pot houses should include x-ray diffraction studies of the various dusts with attention given to their possible content of the three forms of silica: quartz, cristobalite, and tridymite. Dusts that contain the modifications of quartz should be treated with unusual respect. There is evidence to indicate that the safe limit for cristobalite and tridymite should not exceed three million particles per cubic foot of air.

Pot glass is manufactured in furnaces that, because of waste heat, provide their own dust removal through gravity ventilation. Dust concentrations in the

<sup>18</sup> C. F. Kutscher, *Ind. Med.*, 15, 311 (1946).

breathing zone of workers in furnace halls are usually below five million particles per cubic foot of air.

Optical and structural glass may contain lead, manganese, and potassium dichromate. Close attention must be given to the handling of these and other toxic materials, particularly in the batch house.

#### *Tank Process*

Many of the latest glass tanks provide for enclosed, continuous feed of batch ingredients. This has been adopted mainly to prevent coarse dust from accumulating on the roof of the tank, where it interferes with heat transfer. Numerous dust counts made at the feed end of glass tanks show that typical dust concentrations are of the order of one to two million particles per cubic foot of air. This is true even with poorly designed feed systems. The heat of the tank provides effective updraft removal of the fine dust.

#### *Furnace and Tank Construction and Repair*

The stones, blocks, and bricks used in the construction of furnaces and tanks contain free silica in significant amounts. Silica brick contains tridymite as its principal constituent. When assaying the dust exposure, care should be taken to determine tridymite and cristobalite as well as quartz. Respirators are seldom worn by repairmen, because of the heat. Research is being conducted to provide practical means of ventilating both construction and repair processes.

#### *Mirror Manufacture*

The trend in mirror manufacture is toward the use of conveyor lines. The silver solution is fed automatically onto the cleaned glass and does not contaminate the air. Attention should be given to the type of silver solution used, as fulminating silver is liable to be produced by the action of ammonia on silver oxide. Unused solutions of this type should be discarded or the silver recovered (as by precipitation as silver chloride) at the end of the shift. Extensive contact of silver nitrate or its solutions with the skin should be avoided. Cyanides should never be used to remove silver stains from the skin.

The silvered glass, after it is washed and dried, is normally spray-painted. Ventilation is necessary to control the spray mist. Some mirrors are electrolytically plated with copper after being silvered. The solutions may cause dermatitis, but ventilation is not required.

Finished mirrors that are found to have flaws are desilvered with nitric acid. The acid is poured onto the coating, which after a short time can be removed by gentle rubbing with a wooden block. The acid mist and gases must be removed by ventilation.

In the grinding and polishing work on mirror glass, mostly wet processes and artificial abrasives are used. The glass is frequently given a final cleaning with pumice. The free silica content of the pumice should not exceed 5 per cent.



### *Grinding and Polishing*

Plate glass is ground by large revolving iron runners with sand or emery as the abrasive. The process is wet but air currents carry mist from the tables into the workroom. Air analysis is advisable in order to measure the exposure of the grinder men.

The polishing process uses revolving felt pads with rouge as the agent. No health hazard is present.

### *Glass Bending*

Many of the new shapes of glass used in store fronts, airplanes, and so forth are produced by bending the glass in furnaces and kilns. The larger plates are laid in finely ground burned fireclay which has been molded into the proper contours. The molds are often rebuilt for each heat.

For mass production the kiln process is used more frequently, and iron molds are replacing the older fireclay molds. Where fireclay is used, the composition of the air-borne dust should be determined, and the dust concentration measured. Because of the heat stored in the cars, the continuous kiln process provides ventilation by means of heated air, which rises, carrying the dust up with it and out of high, open windows.

### *Wareroom Operations*

The processes that are used in cutting glass in the wareroom produce some glass dust but the amounts are far below the nuisance level. The sand that forms the major constituent of glass batch is converted in the pot or tank to silicate—there is no free silica in glass. Some grinding is performed on edges of glass but the work is carried on wet or with exhaust ventilation.

### *Fiberglass*

In the manufacture, fabrication, or use of glass wool (spun glass), fiberglass, particles tend to disperse into the air and settle on the skin. Whenever the ends of glass fibers come in contact with the skin, irritation may result. Since moist surfaces tend to aggravate the condition, the use of protective clothing in warm weather is not always successful. Most workmen soon become "hardened." Process ventilation is the control method of choice where it is applicable. Frequent bathing with soap and water to remove the particles is the most successful personal control measure. Pulmonary irritation or injury from the inhalation of fiberglass has not been recognized in persons or demonstrated in animals.

### **Grain Handlers—Elevators**

The cost of grain dust explosions in the United States between 1916 and 1936 was: 320 persons killed, 750 injured, and \$35,000,000 in property damage

(calculated from insurance payments). The control of dust explosions is based upon: (1) prevention or control of dust, (2) elimination of sources of ignition, and (3) construction of buildings so as to minimize damage.

Concentrations of grain dust to be within the explosive range must be high, probably in excess of 15 g. per cubic meter of air: clouds of dust of this intensity are practically opaque. The greatest danger lies within enclosures where the grain is in motion, and in the accumulation of piles of dust on ledges, and so forth, whence it is can be dispersed as such a cloud.

Sources of ignition include open flames, static electricity, faulty electrical wiring and electrical equipment, and sparks from pieces of metal. Magnetic separators should be used to remove metal from the grain.

Explosions can be minimized or diverted into less harmful channels by means of lightweight roofs, special windows, and other vents. An inert gas, such as carbon dioxide, is sometimes employed to reduce the oxygen content of the atmosphere in storage bins below 12 per cent, the minimum amount that will permit an explosion.

Grain handlers find that irritation and discomfort occur when fine dust enters the respiratory tract. Flour and meal dusts may form ulcers in the mucous membranes of the nose. "Grain fevers" from the dust or from fungi have also been described. Allergic manifestations from grain dust proteins also occur. The mold, *aspergillus*, when taken into the lungs, can cause a condition that may be misinterpreted as silicosis or miliary tuberculosis.

The fumigation of grain to destroy weevils may entail exposure to chemicals such as: carbon tetrachloride, carbon disulfide, ethylene dichloride, chloropicrin, ethylene oxide, and hydrogen cyanide. Where seed corn is treated with an insecticide containing mercury<sup>19</sup> and cadmium, excessively harmful exposures may result.

"Grain itch" is common. It is caused by a parasite that infests the grain; cleanliness is the principal means of prevention.

### **Grinding, Buffing, and Polishing**

#### *Grinding*

The dust produced by grinding operations will be composed of the material being ground and the abrasive. Either or both may be dangerous to health or the dust may be solely of the nuisance variety. Dry grinding must have exhaust ventilation if the dust that is produced contains significant quantities of free silica, asbestos, or a toxic material. Exhaust ventilation should be used in all other cases where nuisance-dust concentrations exceed fifty million particles per cubic foot of air. In attempting to provide a clean environment, some companies now exhaust all fixed-position dry-grinding wheels that operate more than an hour daily.

When natural abrasives containing free silica are used, wheel dressing fre-

<sup>19</sup> H. F. Schulte, *J. Ind. Hyg. Toxicol.*, 28, 159 (1946).

quently causes the greater portion of the dust exposure. Attention should be directed to this operation, which occurs in both dry and wet grinding. It should be remembered also that even though the dust from grinding with artificial abrasives on iron is of the nuisance variety, it can be contaminated by sand adhering to the iron castings.

Wet-grinding operations produce less dust than dry, but with high-speed wheels dangerous spray may result. Under some conditions the moisture may vaporize leaving dust particles suspended in the atmosphere. The spray itself also is known to be hazardous under some conditions. With low-speed or moderate-speed wheels exhaust ventilation is normally unnecessary.

### *Buffing*

Buffing compounds may contain free silica or toxic materials. Some of the ingredients may irritate the skin. Any specific operation can be appraised by air analysis. Knowledge of the composition of the buffing compound is desirable, particularly if skin irritation has been suspected. Where irritants are known to be present and it is not practical to eliminate them, protective clothing—or possibly creams—may furnish control, but personal cleanliness is most important.

### *Polishing*

The most commonly used polishing agents, such as rouge or emery, are not harmful to health. If the operation is excessively dusty, exhaust ventilation is desirable.

## **Hat Manufacture**

The exposures to mercury attendant to working with carroted fur have been discussed under Carroting. In the manufacture of hats the mercury exposure problem can be solved by using fur that has not been treated with mercury, or by providing efficient exhaust ventilation as proposed by the United States Public Health Service.<sup>20</sup>

The mercury exposures include mercury vapor, mercury nitrate, and particulate mercury or its compounds; and they occur wherever the fur or felt is stored, agitated, subjected to hot water, steam, or drying operations. The average mercury vapor concentration found, in milligrams per cubic meter of air, was: fur storage, mixing, and blowing, 0.5; coning, 0.27; hardening, 0.25; starting, wetting down, and sizing, 0.21; and drying 0.49. The highest vapor-air concentration recorded was 15.0 mg. per cubic meter of air around kettle fur-dyeing operations at a temperature near the boiling point of water. The highest concentration that has been encountered by the author was in the drying room, which, at 100° F., was unventilated except for one small open window: the concentration was 3.3 mg. mercury vapor per cubic meter of air. The safe limit of

<sup>20</sup> P. A. Neal, R. H. Flinn, T. I. Edwards, W. H. Reinhart, J. W. Hough, J. M. Dalla-Valle, F. H. Goldman, D. W. Armstrong, A. S. Gray, A. L. Coleman, B. F. Postman, *U.S. Pub. Health Bull.* No. 263 (1941).

exposure is considered to be 0.1 mg. total mercury per cubic meter of air.

Many gas-fired appliances, some of which are not properly vented, make carbon monoxide a factor to be considered.

In the manufacture of straw hats, bleaching and cleaning operations involve the use of oxalic acid and sulfur. Lacquer-spraying operations involve the use of highly volatile, inflammable thinners and hats with a defective paint job are sometimes sponged off with the thinner. Any exposures or hazards accompanying the use of these materials should be investigated.

### Heat-Treating

There are many ways of heat-treating steel for hardening purposes: most common are controlled atmosphere furnaces and salt and metal baths.

Controlled atmospheres may consist of inert gas containing either carbon dioxide or carbon monoxide. Benzene ( $C_6H_6$ ) is used in one process. Special atmospheres for nitriding employ ammonia. When carbon monoxide (up to 20 per cent) is used, care must be exercised to prevent its escape into the workroom. The inert-gas producers should be checked for leakage when first used, and after any repairs, to make certain that all of the joints are tight. Good practice dictates the use of exhaust hoods above the furnaces and flame curtains at the openings. It must be ascertained that no explosive mixture is present when the furnaces are lighted. If an excess gas-producing capacity exists, as when only a portion of furnace capacity is used, the gas must be vented safely to the atmosphere outside the plant. Furnaces depending upon gravity stack ventilation should be watched for carbon monoxide leakage during the warm-up period.

Ventilation should be employed on nitriding furnaces when ammonia gas is used. As ammonia is explosive in the range of 15.5 to 26.6 per cent by volume in air, the tanks and lines containing liquid ammonia must be protected from breakage. The release of liquid ammonia could result in an explosive atmosphere coming in contact with one of the many open flames in the department.

It is common practice to provide exhaust ventilation for cyanide baths. This is not because of the production of cyanide fume. The fume consists essentially of sodium carbonate, which is somewhat irritant. Cyanides should be stored under lock and key away from acid carboys.

Nitrate baths are exhausted as a precaution against irritant gases. Care should be taken to prevent organic matter from coming in contact with the hot salt because the mixture might be explosive. Neutral salt baths also are frequently exhausted, principally to control the heat during hot weather and to remove vapors corrosive to metal parts.

Lead baths are frequently held at temperatures between 1000–1500° F. and therefore require exhaust ventilation.

Where sprinkler systems are used, canopies should be erected above all oil, salt, and metal baths to prevent water from cascading into them. Any workman adjacent to a hot bath when water struck it would be in grave danger.

Oil quench tanks are frequently ventilated to remove the irritating smoke which is evolved during their use. Some tanks have cooling coils to control the temperature of the oil and reduce any fire hazard as well as the tendency to produce smoke.

### Induction Furnaces

Converters used for the operation of some high-frequency induction furnaces contain upwards of 50 lb. of mercury in two iron pots, in which adjustable electrodes may be raised or lowered in relation to the pools of sealed-in mercury. This assembly may be sealed in with an iron, ceramic, or plastic cylinder, and cylinder heads. It may be in either two or three parts, with gaskets of rubber or other material to prevent the escape of hydrogen and mercury vapor. An atmosphere of hydrogen is maintained by allowing hydrogen gas to flow slowly through tubing from a cylinder of the compressed gas into the electrode chamber. The hydrogen escapes by bubbling slowly through a mercury trap that maintains the pressure at about  $1/2$  in. of Hg above atmospheric. When the furnace is being heated, the electrodes arc and the heat volatilizes the mercury within the electrode chamber. Any leaking hydrogen carries mercury vapor out with it. Leaks may result from the use of faulty gaskets, insecurely fastened heads, or from dispersion of vapor through rubber tubes used as connectors between the electrode chamber and the hydrogen escape trap. Exposures to mercury vapor and dust in the converter area, and especially those of maintenance men who service and clean the converter, should be evaluated and, where necessary, controlled. The dust deposited inside the cages surrounding some of these converters has been found to have a very high mercury content. Although the design of these converters has undergone many improvements since the exposure was first reported by Turner,<sup>21</sup> there are many installations in use today that warrant careful investigation and control if mercurialism is to be avoided.

### Industrial X-Ray

Industrial x-ray installations for the inspection of metal, and to some extent also x-ray diffraction apparatus, are serious potential exposure sources. The control is relatively simple and consists of complete shielding with lead or its equivalent to prevent the escape of rays in excess of 0.1 *r* per 8-hour day<sup>21a</sup> into any area where persons spend significant time. See table of equivalent shielding at front of this volume. Leakage rates of 0.1 *r* per hour should not be permitted in inhabited areas at any time. The ability of concrete or other surfaces to deflect x-rays at any angle must always be considered. Tests should be made with a suitable dosage meter, especially at cracks, joints, or suspected crevices and flaws in protective barriers, to detect any significant leakage. Ceilings and floors of x-ray rooms are frequently found to lack shielding. An instantaneous-

<sup>21</sup> J. A. Turner, *U.S. Pub. Health Repts.*, 39, 329 (1924).

<sup>21a</sup> American Standards Association War Standard Z54.1 (1946).

reading device calibrated for a full-scale reading of 1.0  $r$  per 8-hour day, to read in multiples of 0.01  $r$ , is perhaps more useful than an integrating instrument for the purpose of locating exposures, since this type gives a more prompt indication of intensity. This Geiger-tube type of instrument, however, unless properly shielded and grounded may be susceptible to radio and other high-frequency waves, which are air-borne or that may feed in over the power source. Judgment must be exercised in its use. A device calibrated for gamma radiation is not suitable for the measurement of stray x-rays. All measuring devices are energy dependent and should be calibrated against x-rays at the energy to be encountered. Ear-phones increase the sensitivity and usefulness of the instruments. The integrating device finds its greatest usefulness for the industrial hygienist in measuring the total amount of radiation over a given time at a fixed spot or in a fixed position on a person, or in calibrating the instantaneous reading device described above.

### Iron and Steel Industry

Iron ore, the life blood of the iron and steel industry, is received substantially free from silica: hence, there is no silicosis hazard at the blast furnaces. However, serious health hazards that may be present during the production of iron are carbon monoxide, hydrogen sulfide, and sulfur dioxide.

By-product coke plants produce many valuable chemicals, which must be carefully handled. Carbon monoxide, ammonia, benzene, carbon disulfide, and so forth, are potentially harmful. Most operations occur in totally enclosed systems so that the principal difficulty is unexpected leakage resulting in momentarily high concentrations. Plant maintenance, intelligent supervision, and thorough training are required to control the chemicals safely. Urine sulfate tests, air analyses, and red and white cell counts are valuable tools in the appraisal of benzene exposures.

Heat is a real problem in the iron and steel industry. Heat sickness is now controlled by means of extra salt, with glucose as an adjunct. The alternating heat and cold experienced in winter months is related to the high pneumonia rate found by the United States Public Health Service among iron and steel workers.

Iron and steel foundries have been discussed under Foundry Operations.

Open hearth operations expose men to carbon monoxide. Furnace repairs also present a silica hazard. Leaded steels were reported by Fehnel<sup>22</sup> to introduce a lead poisoning problem during pouring. Concentrations in crane cabs were as high as 88 mg. per 10 cubic meters of air. Special steels may contain nickel, chromium, ferromanganese, tungsten, and molybdenum. Fehnel reported that these metals were not found in the air near the furnace charger nor on the pouring platform. Fluorides may be encountered.

The production of tin plate involves exposure to acids while terneplate also involves lead. Zinc baths have been found contaminated with lead in amounts sufficient to constitute a hazard.

<sup>22</sup> J. W. Fehnel, *Ind. Med.*, 11, 358 (1942).

Iron and steel plants also may have plating operations, spray painting, welding, and so forth. Fehnel advises that attention be directed to maintenance shops, for the detection of other significant exposures.

See also Galvanizing, Heat-Treating, and Metal Cleaning.

### Lead Workers

The hazard present in exposures to lead and its compounds is now known to be dependent not only upon the air-borne concentration but also the form in which it is present. G. C. Harrold *et al.*<sup>23</sup> have shown that 1.5 mg. of lead per 10 cubic meters of air in lead chromate spraying operations is far less than a reasonable safety limit. Whether the explanation for this fact is low solubility as ascribed by Harrold or failure of the lead chromate to reach the lungs (particle size, etc.) is not known. However, the absence of specific data on the safety limits for most lead compounds makes it advisable to adhere to the maximum allowable concentration of 1.5 mg. per 10 cubic meters of air in most cases.

Molten lead does not produce significant quantities of vapor below 900° F. but lead oxide dross formed on the surface may be thrown into the air. Burning operations are well-known producers of dangerous concentrations. When lead is poured, agitated, or skimmed, the danger from oxides increases.

The appraisal of a lead hazard is best accomplished by a combination of air analysis with blood or urine determinations. Air samples should be collected with the electrostatic precipitator when fume is present, but dust is satisfactorily retained by the impinger. In evaluating the exposure of an individual the samples should be collected from the breathing zone. Respirator filter analysis, when properly supervised, affords a valuable adjunct to other sampling methods (see Chapter Twenty-One).

### Leather Industry

The leather industry has no typical, or outstanding, harmful exposures, but many common exposures that require recognition and control. In the tanning of leather there is first the matter of handling the raw hides and skins. One of the potential exposures is that of infection from contact with organisms such as anthrax. This was a serious problem in the past, especially with skins imported from anthrax-infested areas, but improved methods of treating imported hides have done much to bring the exposure under control. Anthrax is acquired usually by contact of the anthrax bacillus with wounds or abrasions, but the organism may be acquired by inhalation or ingestion. Persons working with raw hides or skins have greater need for medical supervision and inspection than do the average workers because the prevention and control of infections is primarily a medical problem.

<sup>23</sup> G. C. Harrold, S. F. Meek, G. R. Collins, and T. F. Markell, *J. Ind. Hyg. Toxicol.*, **26**, 47 (1944).

Soaking, unhairing, and pickling may involve, in addition to potential exposures to pathogenic organisms, exposures to sodium sulfide, hydrogen sulfide, sulfurous acid, arsenic sulfide, chlorine, 2-naphthol, *p*-nitrophenol, mercury compounds, dimethylamine, sodium cyanide, lime, formic acid, and ammonia.

The tanning process may involve exposures to chromates, chromic acid, alkalies such as trisodium phosphate and borax, oxalic acid, and formaldehyde.

In the finishing and cementing of leather almost any of the common solvents may be encountered. Any exposures should be sought out and evaluated. In the process of coating leather sides with a mixture of ethyl acetate and castor oil, after which the hides are hung in the room on racks to dry, very high atmospheric concentrations of ethyl acetate may result. It has been the authors' privilege to observe and measure concentrations of ethyl acetate ranging from 375 to 1500 p.p.m. in the breathing zone of such workmen. Although this condition had existed for several months no adverse symptoms or illnesses were observed. This is of interest as an indication of the relatively low toxicity of ethyl acetate.

Gas-heated shaping presses are a potential source of carbon monoxide. Various dyes and stains are likewise potentially harmful. Grinding, sanding, buffing, and polishing operations are dust producers requiring ventilation control. In the leather industry there is much opportunity for the correct application of control measures such as protective clothing, protective creams, segregation of processes, and exhaust ventilation.

### Lime

Protection of the eyes and of the skin presents the major environmental control problems in the production of calcium oxide or quick lime. The material is of small particle size and is very irritant to both mucous membranes and the moist skin. It combines with water, with evolution of heat, to form calcium hydroxide which is nearly as caustic as potassium hydroxide.

Air-slaked lime, which is more or less completely calcium carbonate, has mild causticity and usually it will attack mucous membranes only. If warm, it may cause dermatitis after prolonged exposure.

Quick lime rarely affects the lungs as its irritant action on the upper respiratory tract precludes the necessary exposure. It rapidly produces coughing and sneezing limiting further exposure.

Workmen at lime kilns may be exposed to dangerous quantities of gases: carbon monoxide, carbon dioxide, hydrogen sulfide, and arsine. Severe temperatures are also common.

Roessle and others have shown that among lime workers the mortality rate from tuberculosis is less than the average. Some cases of pneumonia among workers exposed to excessive dust concentrations have been described.

No maximum allowable concentration for dust exposure has been proposed.



However, dust control sufficient to prevent significant irritation of the nose, throat, and eyes is indicated.

### Mantle Manufacture

The manufacture of gas mantles, though not the thriving business it once was, still furnishes a means of obtaining excellent illumination from gas, kerosene, and gasoline lamps and lanterns as well as a means of livelihood for many people. No occupational diseases have been found peculiar to the industry. However, since thorium nitrate, a radioactive material, is used to impregnate the mantles, potential exposures to thorium-bearing dusts and thoron gas should be evaluated and controlled.

The Welsbach gas mantle is made by dipping a mantle woven of ramie fiber into an aqueous solution of nitrates—essentially 99 parts thorium nitrate and 1 part cerium nitrate. The mantle is dried, formed, burned to remove the fiber and leave the metal oxides, and coated with collodion to protect it during shipment. Mantle-soaking operations require ventilation to keep the thoron gas below the accepted concentration of  $10^{-11}$  curie per liter of air. In mantle-cutting or mantle-trimming operations and especially in reclaiming operations there is, besides the potential exposure to thoron gas, possibly a more serious exposure to thorium-bearing dusts. There are also insignificant amounts of cerium and beryllium involved. Any dust containing thorium should be controlled (see Chapter Nine).

In lamp manufacture, which often accompanies the mantle manufacture, there may be glazing operations, spray painting, glass etching, soldering, and silvering.

### Meat-Packing and Slaughter Industry

The environmental conditions common to the meat-packing industry include extreme dry radiant heat, extreme cold, sudden temperature changes, and high humidity with wet surroundings. Sickness frequency rates<sup>24</sup> indicate the highest rates in decreasing order to be in high humidity, sudden temperature change, and extreme cold. The occupations that had the highest frequencies were: cold-meat workers, among white females; and by-products workers, among Negro males. An excess of respiratory diseases was associated with the high frequency rates. Excessive rates for rheumatic diseases were also found. Material exposures associated with the highest rates were hides, glue, and entrails; digestive diseases were most in evidence in this last exposure.

Dermatitis occurs among meat handlers from contact with alkaline cleaning and dehairing baths and resinous dehairing agents; and also as a rash termed "hog itch"—among casing workers.

<sup>24</sup> H. P. Brinton, H. E. Seifert, and E. S. Frasier, *U.S. Pub. Health Repts.*, 54, 2196 (1939).

Brucellosis, which has a high incidence<sup>25</sup> in the packing industry, may result from eating partially cooked meat in process. Packing-house workers have been known to eat slices of freshly killed pork after partly cooking it in hot water baths or on steam radiators. Skin abrasions and cuts on the hands may be another contributing factor.

Ammonia refrigeration systems may develop leaks and so present a potential exposure harmful to health and a possible explosion hazard.

### Metal-Cleaning Processes

Metal cleaning covers a wide field; an adequate discussion of all its ramifications would require more space than can be allotted here.

The choice of a cleaning method is influenced by many factors, including: composition and structure of the parts to be cleaned, soil or dirt to be removed, and sequence of the cleaning operation. The preceding operation frequently determines the nature of the contaminant and hence the cleaning method, and the next following operation may regulate the degree of cleanliness required. The equipment available, its cost and operating expense, and, above all, the health and safety problems need be considered. Brief discussions of several different processes of metal cleaning follow.

#### I. ACID CLEANING

##### A. Pickling Tanks

Acids such as sulfuric, hydrochloric, phosphoric, sometimes with chromic or hydrofluoric, are used in water solutions and their splash hazard and corrosive action on skin, clothing, and machinery are well recognized. Bubbles of hydrogen rising from the bath carry an invisible acid mist the amount of which depends upon bath temperature, the acid, its concentration, the metal, its surface area, and whether or not the bath contains an inhibitor. Commercial organic inhibitors have varied, more or less secret compositions, but paper-mill waste, flour-mill waste, and flour (1 oz. per 15 gal.) have been used successfully. An inhibitor may work either as a protective film that clings to clean metal surfaces, slowing down the action on the metal more than on the oxide, or as a producer of foam that inhibits escape of mist; the former type has been more successful.

The nature and extent of ventilation control required depends on the rate of acid mist escape; where the exposure is a mild one the addition of an inhibitor may make process or slot ventilation unnecessary. Inhibitors should never be added to an automatically timed conveyorized job without adjustment because pickling action is slowed by most inhibitors.

The possibility of exposure to arsine or other metal hydrides, though not common, should not be overlooked: impure acids or the metal being cleaned can be the source of arsenic, phosphorus, selenium, antimony, and so forth.

A good point to remember is that atmospheric acid even below the physiological danger point may corrode intricate and costly metallic parts and increase the plant's general corrosion problems, particularly in humid atmospheres.

Hydrofluoric and chromic acids require good tank ventilation control and increased precautions to avoid skin contact.

<sup>25</sup> M. G. Levine, *J. Ind. Hyg. Toxicol.*, 25, 451 (1943).

### *B. Bright Dips*

Acid bright dips are usually mixtures of nitric and sulfuric acids employed to remove tarnish from copper and copper alloys. The extremely corrosive bath is frequently contained in a large crock. Brown nitrogen oxide gases are evolved from the bath and since these gases are very corrosive, as well as dangerously toxic, bright dip baths require more efficient hooding and exhausting than do most other metal-cleaning operations. Canopy hoods are not satisfactory. Hooding must be arranged so as to direct the gases away from the operator's face and prevent him from even momentarily inhaling the concentrated gas (see Chapter Ten).

### *C. Phosphoric Acid Cleaners*

Phosphoric acid solution in water is used alone or with the admixture of alcohols and ethers, including butyl Cellosolve, to remove light rust on steel in preparation for lacquering and enameling. It may be applied by dipping, swabbing, or brushing, and usually when sufficient water is employed the operation does not produce harmful gases, vapors, or mists that require control measures other than protection from splashing and contact with the dilute acid. If mists, fogs, or elevated temperatures are involved, ventilation control is necessary.

### *D. Ferric Sulfate Pickle*

Ferric sulfate pickling baths in themselves present no special problem. When the temperature involved is sufficient to produce steam it requires control measures, and if hydrofluoric or other acids are added they then become the problem for control.

### *E. Gas Pickling*

Gas pickling, utilizing 10 to 40 per cent hydrogen chloride at a temperature of about 1300° F., is used for the pickling of cold-rolled steel strip in preparation for galvanizing. The pickling atmosphere may be produced by burning a mixture of fuel gas, chlorine, and air and adding flue gas. This atmosphere is confined in a furnace through which the steel sheet passes. Any oil on the strip is burned off and the oxides are removed. It is proposed to apply this pickling method previous to the coating of steel with tin, aluminum, and lead, as well as to vitreous enameling and electroplating. Obviously, the pickling atmosphere must be effectively confined by suitable traps or reduced pressure, or else all points of escape must be provided with effective exhaust ventilation so as to maintain an atmosphere of less than 10 p.p.m. hydrogen chloride in working areas. It may be necessary to provide an exhaust hood to remove acid gas from the pickled metal after it leaves the pickling atmosphere.

## II. ALKALI CLEANING

Alkaline cleaners are used in soak tanks, dipping tanks, and power washers. Alkaline baths may contain caustic soda, soda ash, trisodium phosphate, sodium pyrophosphate, sodium hexametaphosphate, rosin, sodium resinsates and other soaps, wetting agents, and emulsifiers. Sometimes solvents such as *o*-dichlorobenzene, butyl Cellosolve, pine oil, or petroleum distillates are added. Clay is sometimes added as a scrubber.

In general, when alkaline baths contain no solvents other than water, and no electric current is employed, ventilation is not required for the control of alkali mists unless readily attacked metals such as aluminum and zinc are being cleaned. However, it is desirable to remove the steam from heated baths in order to avoid excessive humidity, which contributes to the corrosion of metals and the discomfort of workmen.

The splash hazard of an alkaline bath is mainly dependent on the temperature of the bath and its degree of alkalinity. Caustic soda, upon contact with body tissue, gelatinizes the tissue, forming soluble compounds, and may produce deep and painful destruction of tissue. Even weak alkalis soften the epidermis, emulsify the skin fats, and cause severe skin irritation. All soaps hydrolyze in water to produce free alkali. Trisodium phosphate is somewhat less caustic than caustic soda and is a better detergent. Its cleaning properties are improved by the addition of either tetrasodium pyrophosphate or sodium metasilicate, either of which is still less alkaline than trisodium phosphate.

Paint-stripping operations usually involve baths of a high degree of alkalinity. The operation lends itself well to a conveyORIZED machine.

### III. EMULSION CLEANERS

Emulsion cleaners containing kerosene are used in power washers and soak tanks. When used in soak tanks at room temperature no ventilation is required. When the cleaner is sprayed or used hot, the operation should be confined and ventilated.

Emulsion cleaners that contain cresylic acid, phenols, or halogenated hydrocarbons should be provided with ventilation to prevent vapor concentrations in excess of accepted permissible limits. Skin contact should be carefully avoided, impervious rubber gloves should be used, and the face should always be protected by a suitable shield.

### IV. CYANIDE BRIGHT DIP

Cyanide dip tanks are sometimes used for the removal of tarnish or light oxide films from brass and copper. They should be operated at temperatures below 140° F. and preferably should be ventilated. It is of the greatest importance that they be maintained well on the alkaline side and protected from the accidental addition or accumulation of acid, which might release potentially fatal concentrations of hydrogen cyanide. Overflow or drippings from the bath should not be permitted to mix with acid overflow and drippings, but should be promptly flushed into the sanitary sewer with plenty of water. Cyanide residues should not be dumped into the sewer but may be admitted very slowly, well diluted with water, providing the concentration does not exceed the limits set by official agencies.

### V. BURN OFF

In preparing for many types of painting operations, particularly sheet metal to be black-enameled, it is possible to replace other means of oil and grease removal with a burn-off operation. This is usually done in an oven heated with open gas burners to a temperature sufficient to ignite and burn any residual oil or grease film. No special problems are involved in venting the products of combustion to the exterior.

### VI. MOLTEN SALT BATHS

Molten salt baths for heat-treating have some incidental application to the cleaning of metal. For a discussion of this see Heat-treating.

### VII. MOLTEN CAUSTIC DESCALING BATHS

Molten caustic, either with or without an electric current, is used for cleaning and descaling alloy steel and cast iron. Its use is restricted to those metals and alloys that are not adversely affected by caustic soda at the temperatures employed, usually from 680° to 950° F., in some instances up to 1000°. The advantage claimed for this type of cleaning is a good bond, especially with cast iron, when coating it with lead, zinc, or solder of any kind, and in brazing and vitreous enameling. The method also cleans sand from castings.

Oxides such as those of chromium, nickel, and iron are removed by reduction and the metal is not attacked. Oils are burned off, graphite and carbon are removed, and sand is removed. The oxides and possibly some of the sand collect as sludge on a sludge pan in the bottom of the bath and must be removed periodically. The other contaminants either combine with the molten caustic, float on the surface of the bath, or are volatilized as vapor, smoke, or fume. One patented process employs an electric current through the molten caustic bath. In this electrolytic bath the current is reversed during the cleaning process, it being claimed that certain contaminants are oxidized while the work is in the anodic position and others reduced while it is in the cathodic position.

### *Sodium Hydride Descaling*

One variation of molten caustic cleaning is the sodium hydride descaling process, in which no current is used and sodium hydride is fed continually to the bath through the action of metallic sodium in order to obtain the scale reduction required. This bath is maintained at about 700° F. and metallic sodium bricks weighing 2½ to 5 lb. are added to the molten caustic by admitting them through a partially submerged generator box suspended along one side of the bath. An atmosphere of hydrogen, a mixture of hydrogen and nitrogen (cracked ammonia), or, in fact, any dry gas containing some hydrogen and at the same time free from oxygen, carbon monoxide, and carbon dioxide is maintained in this generator by letting the gas flow in at the bottom and out of a port at the top. The excess hydrogen is burned as it flows from the exit port and some is burned also at the charge hole in the top of the generator box during the time the sodium bricks are being added.

Obviously in either of these descaling processes there are the hazards connected with the use of a bath of molten caustic. The precautions practiced with alkali baths are in order and, in addition, protection from direct burns due to splashes from the hot alkali are important. Moisture entering the bath from any source, such as on or in the work being descaled, through leaks in the roof, leaks or condensation from overhead water pipes, splashes from a quench bath, and so forth, may be vaporized with an explosive violence that can throw particles of the molten caustic a considerable distance. It is necessary to have a remote-control hoist or crane to move the work, and safety shields or enclosures for the bath or for the operator are desirable as additional protection. Overhead water pipes, including automatic sprinkling systems, should be avoided. Safety practices required for handling metallic sodium must be enforced.

Contamination of the environment resulting from the caustic bath is ordinarily not excessive since the caustic is only slightly volatile at the temperature of the bath. Considerable heat arises from the hot bath. Where no electric current is used, and where general ventilation is good, the caustic bath may not require exhaust ventilation other than that necessary to remove any smoke or fumes resulting from the metal being descaled, but it is frequent practice to provide exhaust to remove the heat and any caustic that escapes into the air. The quench tank following the descaling tank requires good exhaust in order to control the steam and alkali mist. Complete enclosures with mechanical exhaust have the advantage of controlling the splash and splatter hazard, as well as any caustic-mist and heat exposures.

## VIII. SOLVENT DEGREASING

### *A. Cold-Dipping*

Cold-dipping is practiced to a certain extent for the cleaning of various objects including internal combustion engines and for the removal of carbon and resinous binders from

pistons. The solvents used may vary from a high-flash petroleum distillate to a mixture that includes aliphatic and aromatic chlorinated hydrocarbons, ketones, Cellosolves, creosote, and cresylic acid. No generalities regarding control can be made to apply satisfactorily except that no readily volatile or fast-drying solvent should be used in large, open containers without effective mechanical exhaust ventilation if workmen are to be exposed to its vapors for more than a few minutes a day. Skin contact with these materials should be avoided and a face shield should be used to protect the eyes and face. Covered soak tanks with an adjacent mechanically ventilated work table offer satisfactory vapor control.

Under certain conditions covered soak tanks may be used successfully without ventilation and if the tank has a water solution layer over the surface, that also serves to retard the escape of solvent vapors. Low volatility materials such as mineral spirits and kerosene usually present no inhalation exposure, but the subsequent widely practiced compressed air blow-off operation may produce an objectionable irritant mist unless controlled.

### *B. Solvents Applied by Brushing or Wiping*

When solvents are kept in a safety can or other suitable covered container and applied in small amounts by brushing or wiping, the inhalation hazard far exceeds any fire hazard; and where this kind of operation is found necessary it is better to use petroleum distillates, ketones, and esters rather than chlorinated hydrocarbons. If chlorinated hydrocarbons are found necessary to the operation, exhaust should be provided at the point of usage unless the solvent is applied very sparingly. Soldering and brazing operations are often said to require the use of carbon tetrachloride but in nearly all instances it has been found that where the right flux is used it makes little difference as to what solvent is used or whether any is used on the joint just before soldering.

Where work is conducted without ventilation in confined spaces such as small rooms, vats, tanks, and the like, volatile organic fluids should never be liberally applied by a swab or brush or used in a container that permits much surface contact of the air and liquid. If it is necessary to use volatile solvents in such situations fresh-air hose masks should be employed for personal respiratory protection and the explosion hazard must be reckoned with.

### *C. Petroleum Solvent Sprays*

Spraying with high-flash petroleum distillates such as oleum spirits, mineral spirits, or kerosene is a widely used method of cleaning oils and grease from metal. Solvents with a flash point below 100° F. should not be used for this purpose. The operation should always be provided with suitable mechanical exhaust ventilation, preferably a hood as small as practical with exhaust sufficient to control any mist or vapor, and an exhaust volume of at least 100 c.f.m. per square foot of hood face. The hood may be of conventional spray-booth type or a much smaller one and may or may not be fitted with a fire door and automatic extinguishers. The fire hazard attendant to spraying a high-flash petroleum solvent is no more than that attendant to spraying many lacquers and paints.

### *D. Degreasing Machines*

From the viewpoint of hygiene and safety there are three major questions involving degreasing machines: (1) Is the machine being operated safely? (2) Are excessive amounts of vapor escaping into the room atmosphere? (3) How should such escape be prevented or controlled?

There are many angles to be considered before answering these questions. A degreasing machine is essentially a heated chamber in which to boil a grease solvent, space above the

boiling solvent for hot solvent vapors, a condenser above this for cooling and condensing the vapor to liquid, and an extension of the sides above the condenser to minimize air currents inside the machine. The air space above the vapor inside a degreaser contains a vapor-air mixture somewhat richer in solvent vapor nearer the vapor line.

### 1. *Classes of Degreasing Machines*

*Vapor degreasers.* In vapor degreasers the work is lowered into the vapor above the boiling solvent, and the solvent condensing upon the cool metal surface dissolves and washes away oil and grease films. This action should be continued until the metal reaches the temperature of the solvent vapor; whereupon it becomes dry. The length of time required will depend upon the size, shape, surface area, temperature, and specific heat of the parts to be cleaned. If the material is not allowed to remain long enough to reach the temperature of the vapor, considerable solvent will be dragged out with the dripping parts.

*Immersion degreasers.* Where articles to be degreased have intricate shapes or are heavily contaminated with dirt and grease, immersion in boiling solvent gives not only prolonged solvent action but the mechanical scrubbing of the boiling liquid.

The usual practice is to combine immersion and vapor cleaning in a two- or three-chamber machine.

*Spray degreasers.* Where insoluble matter is of such a nature or extent as not to be removed by immersion in boiling solvent, spray degreasing may be necessary. In this case the work is first lowered into the vapor to remove oil and grease, then pressure-sprayed with warm solvent, and finally given a vapor rinse to remove all traces of oil and grease. In order to conserve solvent and preserve health it is essential that any spraying be done below the vapor level of the degreaser in such a manner as not to disturb the vapor level, and that baffles or screens be placed so as to prevent the rebound or ricochet of droplets of solvent into the area above the vapor level.

All these methods are applicable to either hand-operated or conveyORIZED machines. Where the work is of sufficient quantity to justify the cost, conveyORIZED equipment is more satisfactory, in that solvent loss, with its attendant exposure possibly harmful to health, is easier to control.

### 2. *Operation of Degreasing Machines*

Condensers on the safer operating equipment consist of water jackets or a set of pipe coils or a combination of the two extending around the tank at some distance from the top. Some vapor-type degreasers using tetrachloroethylene, without condenser units, depend upon a bimetallic thermostat control to keep the vapor within the tank. The use of a mechanical device as the sole means of keeping the vapor from overflowing the tank is open to criticism; and when the thermostat is placed within a few inches of the top of the tank the device is not sufficiently quick and certain of action to be dependable and safe. The purpose of the condenser is to prevent the escape of the concentrated vapors into the room. The vertical distance between the lowest point at which vapors can escape from the degreaser machine and the highest normal vapor level is called the "free board." The free board should be at least 15 inches and not less than half the width of the machine. That portion of the condenser above the vapor line should be maintained above room temperature and below 110° F. The effluent water should be regulated to this same range, and a temperature indicator or control is desirable.

*Solvents.* The preferred solvent for water-cooled degreasers is trichloroethylene, but tetrachloroethylene can be used in these machines after they have been adjusted to suit the characteristics of the higher boiling solvent. The machines not equipped with water-cooled condensers are designed to operate with tetrachloroethylene only and should not, under any circumstances, be operated with other more volatile solvents such as trichloroethylene. Carbon tetrachloride and ethylene dichloride also have been used in water-cooled machines. Carbon

tetrachloride because of its volatility, greater toxicity, and susceptibility to hydrolysis into acid is not usually considered a suitable solvent for degreasing machines. Ethylene dichloride not only involves the toxicity problem common to some extent to all chlorinated hydrocarbons, but also is inflammable. It flashes at 56° F. by the closed-cup method, and vapor-air mixtures ranging from 6.2 to 15.9 per cent by volume ethylene dichloride will explode with violence when ignited.

Trichloroethylene at room temperature will not burn but trichloroethylene vapors when heated above 110° F. have a narrow inflammable range around 20 per cent by volume. This range increases with temperature and above 135° the inflammable range is from about 15 to 40 per cent by volume. The ignition temperature is 770°. These conditions do not ordinarily occur in plant atmospheres but may occur within a degreaser. Trichloroethylene vapors will not explode violently under any circumstances but may burn slowly to form dense smoke and gases such as chlorine, hydrogen chloride, and phosgene. Although tetrachloroethylene vapor will not ignite or burn, oils or greases accumulated during cleaning will, and for that reason sources of ignition, especially overheating with gas or electric heaters, should be avoided during distillation for sludge removal. Also, welding on or in a degreaser when it contains any solvent should be avoided.

Fatalities have resulted from the use of solvent degreasers. Intoxication results chiefly from inhalation of vapors. It is doubtful if systemic industrial poisoning results from absorption of these materials through the skin of the hands, but skin irritation as a result of defatting may result from these as from other fat solvents.

*Stabilizers.* Commercial degreasing solvents sold under trade names usually contain a small amount of a material known as a stabilizer. The purpose of the stabilizer, frequently organic amines, is to neutralize any free hydrochloric acid that might result from: (1) oxidation of the degreasing liquid in the presence of air, (2) hydrolysis in the presence of water, or (3) pyrolysis under the influence of high temperatures. Some of these stabilizers are highly toxic materials that may cause serious injury to health by inhalation or absorption through the skin and although the amount supplied in commercial degreasing solvents has not, so far as we are aware, caused injury, the addition of the concentrated stabilizer in the plant by unqualified men is a dangerous practice, which should not be encouraged.

*Heat source and controls.* Degreasers may be heated by electricity, gas, or steam—steam being usually preferred. In the case of electricity and gas, thermostatic controls should be provided in the boiling chamber to prevent overheating. Gas-fired units should be provided with a flue from the combustion chamber to remove products of combustion. In the case of steam, the pressure should never exceed 25 lb. for trichloroethylene, and preferably it should not exceed 15 lb.; tetrachloroethylene requires pressure up to 50 lb. All machines should have thermostatic controls located a few inches above the normal vapor level to shut off the source of heat if the vapor rises above the condensing surface.

By-pass steam lines for emergency operation if the safety steam shutoff valve becomes plugged should not be so easy for anyone to operate as to nullify the safety features of the steam shutoff.

*Sludge removal.* Sludge and metal chips should be removed as often as necessary to prevent their accumulation. The solvent should be distilled off until the heating surface or element is nearly, but not quite, exposed or until the solvent vapors fail to rise to the collecting trough. After cooling, the oil and solvent should be drained off and the sludge removed. A fire hazard may exist during the cleaning of machines heated by gas or electricity because the flash point of the residual oil may be reached and because trichloroethylene itself is inflammable at elevated temperatures. After sludge and solvent removal a degreaser must be thoroughly ventilated mechanically before undertaking any maintenance work involving flames or welding. A person should not be permitted to enter or place his head within a degreaser until after all compartments have been blown free of vapors. When



entering a degreaser he should then wear a supplied-air respirator as well as a life line held by an attendant, because in such circumstances not only very high and anesthetic concentrations of vapor may be encountered but also the oxygen content of the atmosphere may be insufficient. Such an atmosphere may cause unconsciousness with little or no warning.

*Location of equipment.* Degreasers should be installed in large open departments with good general ventilation but away from drafts such as from open windows, spray booths, space heaters, ventilating duct openings, or fans. When degreasers are installed in pits, mechanical-exhaust ventilation should be provided at the lowest part of the pit. It is not good practice to locate a degreaser beside a vat that evolves steam which may enter and condense in the degreaser. Open flames, electric heating elements, and some welding operations within 50 ft. of a degreaser should be vented to the exterior, because if a high concentration of chlorinated solvent vapor comes in contact with a flame, arc, or hot surface corrosive and irritant gases are formed.

*Ventilation.* A properly constructed and operated degreasing unit located in a room of over 30,000 cu.ft. need not require a direct exhaust system; such a system may cause serious solvent loss and may or may not offer satisfactory control for an improperly constructed or operated machine. Several fatalities have resulted from carelessness during the cleaning of degreasers or the entering of conveyORIZED machines to make emergency adjustments, but there have been few injuries or fatalities attributed to exposures arising from the normal operation. Two fatalities recently attributed<sup>22</sup> to prolonged exposure to trichloroethylene vapors arising from degreasing machines occurred where the degreasers were equipped with direct-exhaust systems. This supports the general opinion that individual exhaust systems do not necessarily offer satisfactory control for faulty operating practices. General ventilation is a desirable safeguard even where direct-exhaust systems have been installed. Degreasers should be kept covered when not in use but frequent, abrupt covering and uncovering during operation is worse than leaving the cover off as it tends to fan the vapors out of the machine. For the conveyORIZED, enclosed machine a relatively small volume of air exhausted just inside the opening at which the operator stands for loading or unloading causes a slight indraft and controls the exposure without increasing solvent loss. A considerably greater volume of exhaust correctly applied outside the machine is likewise effective in control without causing excessive solvent loss. A slot at the top of an open degreaser offers satisfactory control but may increase solvent loss, especially if the volume exceeds 30 c.f.m. per square foot of tank surface.

*Common causes of solvent loss and its attendant atmospheric pollution.* Five general and very common causes of solvent loss and atmospheric contamination may be pointed out:

(1) Air motion of more than about 50 f.p.m. across an open-top degreaser especially when directed lengthwise. Drafts should be eliminated and degreasers covered when not in use.

(2) Mechanical displacement of solvent vapor. Overloading may drive vapor out of the machine by physical displacement, especially where there is insufficient clearance between the sides of the rack or the work and the machine. Also when the load is great in relation to the heat input it will cool and condense so much vapor as to cause the vapor level to fall and draw air into the degreaser. The area above the vapor level in a degreaser is filled with a more or less rich solvent-air mixture. When the vapor level is lowered, the volume of this vapor-air mixture is increased by drawing in room air and when the level is brought back to normal some of the mixture is forced out into the room. The heat input should be sufficient to prevent the vapor line from falling below the bottom of the condenser under maximum load. Machines not equipped with water condensers but equipped only with bimetallic thermostats placed well up on the side of the machine may displace an appreciable volume of vapor-air mixture each time the vapor rises to the thermostat. Where the change of vapor level exceeds 6 or 8 in. in the normal operation of the machine excessive solvent loss and

<sup>22</sup> *Ind. Bull. N. Y. State Dept. Labor*, No. 22, 122 (1943).

air contamination will result. The greater the change in level and the more frequent its occurrence the greater the air contamination.

(3) Improper operation of condenser. All too frequently, exposures can be traced to failure to open the valve to start the condenser operating before heat is applied to the boiling compartment. It is desirable practice to provide a safety control to make it impossible to heat the boiling chamber before water is turned on in the condenser. It is also a mistake to turn too much water through the condenser. The effluent water should never be below room temperature and may safely range up to 110° F. with trichloroethylene and 130° with tetrachloroethylene. If the temperature of the condenser water falls below that of the room, water may be condensed from the room air and enter the solvent causing a mixed vapor of water and solvent to form and float above the true-vapor level. This condition, which results in excess solvent loss, is made apparent by a fog or white mist floating in the bath. Water from any other source such as material degreased, or a leaky condenser, will do the same thing. Water is further undesirable because of its tendency to produce corrosive acid by hydrolysis of the solvent. The control of the temperature of the condenser should not be left to guesswork, but the water flow should be adjusted by a key valve, or other means, to give the correct temperature reading on an indicator and the water turned on full at the shutoff valve. This adjustment should be made either for the minimum temperature while operating under full load or for maximum while idling.

(4) Speed of work. One of the hardest things to control on hand-operated open-top machines is the speed of the work, which ordinarily should not exceed 10 to 20 f.p.m. while work is being lowered into or raised out of the machine, as well as when work is moved within it. Speeds above this may displace vapor or mix it with air by agitation.

(5) Carry out. The work should always remain in the vapor until it appears dry, otherwise liquid solvent will be carried out to evaporate in the room air. Absorbents such as rope, cloth, or wood should not be a part of the work degreased or a part of the rack or hoist. Solvent may also be carried out in tubes, cups, intricate shapes, and recesses. This kind of work should be racked at an angle or should be tilted or rotated in the vapor zone until all liquid has been drained out.

### Metalizing (Metal Spraying)

Metals, in the form of wire, are fed through a spray gun, in which a hydrogen, or acetylene, torch melts the wire. Compressed air, or other gas, is used to atomize and spray the metal onto the surface to be coated. The exposures involve not only air-borne particles of the sprayed metal and its oxides, but also ozone, nitrogen oxides, and ultraviolet light. Obviously the spraying of the more toxic metals offers the more serious potential inhalation exposures.

Many installations are automatic, but, where the gun requires close attention, goggles for protection from ultraviolet rays are necessary.

Process ventilation, with a properly designed hood, is the control method of choice. Many operations are successfully controlled in small enclosures with a relatively small volume but good velocity of air flow.

Ventilation requirements depend on the metal atomized, the velocity and volume of gases from the spray gun, the size and contour of the surface sprayed, the shape and fit of the enclosure, and the size of the enclosure opening.

### **Milling and Baking**

Milling and baking operations involve few exposures harmful to health. Flour dust is the most common exposure and there have been complaints of nasal irritation and asthmatic attacks resulting from the inhalation of flour dusts. When such attacks occur, they would appear to be due to an allergic reaction. "Improvers" that are added to flour are not significant sources of harmful dust. The explosibility of flour dust is of more concern than the possibly harmful effects of inhalation. Well-engineered dust control should be practiced and it should include the prevention of any accumulation of dust where it can be a potential source of an explosive dust cloud.

Bleaching processes employing chlorine, chlorine oxide, or nitrogen trichloride are possible sources of toxic-gas exposures requiring careful handling and the provision of gas masks for emergency use. In the preparation and use of powdered sugar icing, which is frequently mixed and applied by hand, sugar dermatitis involving the nails occasionally results. Lard oil, when applied to pans by means of swabs, sometimes gives rise to skin irritation. Where ovens are allowed to cool between bakes, carbon monoxide in dangerous amounts may be generated during the warm-up period.

### **Mining**

The subject of mining is too broad to be given more than a superficial touch here and the discussion will be confined to generalizations. In nearly all operations underground, dampness and wet surroundings are encountered. Dry drilling, blasting, dry mucking, loading and unloading cars, timbering, and ore crushing are dusty operations necessitating control measures.

In metal mines the metals may constitute an exposure problem as, for instance, in mining lead, zinc, arsenic, or mercury. The sulfide ores of lead and mercury are not readily absorbed, however, and therefore have a relatively low toxicity. The inhalation of iron oxide ore in relatively pure state causes a non-disabling mottling of the lungs, a condition termed "siderosis."

In mining lead, zinc, and mercury ores the silica mixed with the ore may exceed 90 per cent of the mined material. Rigid dust control is indicated: wet drilling, wetting of muck piles and the work face, sprinkling of haulage ways, the use of water jets, and well-engineered ventilation.

In coal mining, jack-hammer, dry-cutting, and shot-firing operations produce much dust, as do shoveling and loading operations. These operations are productive of amounts of dust that not only are harmful to health but also have been the source of many coal-dust explosions in mines. Wet drilling and cutting have largely replaced the dry methods; and ventilation, dust traps, spray jets, and other measures have also been applied to the control of what was once one of the

dustiest operations in the United States. Work in rock frequently involves exposure to dust high in quartz content, especially in the anthracite mines.

The condition of coal-dust deposits in the lungs has been termed anthracosis and, where a combination of coal and silica dust has produced lung pathology, anthraco-silicosis. A high mortality rate from respiratory diseases has been found in persons exposed to excessive anthracite dust.<sup>27</sup>

In addition to the dust exposures in mining, there are exposures to those injurious gaseous combustion products accompanying the use of explosives, the major ones of which are nitrogen dioxide, carbon monoxide, sulfur dioxide, and hydrogen sulfide. Approved explosives are designed with the proper oxygen balance so that the production of toxic gases is held at a minimum. Nevertheless, it is necessary to provide control measures for these gases where explosives are used underground. The control may consist of ventilation, or sufficient time for natural diffusion and absorption. The use of personal respiratory protection is at times necessary for either gases or dusts.

Naturally occurring gases such as methane, hydrogen, carbon dioxide, and hydrogen sulfide, as well as oxygen deficiency, must be controlled by ventilation. The use of Diesel engines in mines necessitates sufficient ventilation to control the minor amount of aldehydes, carbon monoxide, and nitrogen dioxide present in the exhaust gas.

In pegmatite and pyrophyllite mines, when considerable quartz is encountered, free silica becomes the criterion for dust control. In sandstone and quartzite quarrying and mining, the dust control obviously must be of a high order. Among mica workers, where little or no silica is involved, there is some question concerning the control standards that should be enforced. There seems no logic, however, in permitting dustiness above fifty million particles per cubic foot of air; and there are considerable data<sup>28</sup> indicating the need for more rigid control.

Tremolite talc miners, exposed to rather high concentrations of the asbestine variety of talc dust, have been reported<sup>29</sup> to have a high incidence of advanced fibrosis, although the free silica content of the atmospheric dust was believed less than 1 per cent.

In salt mining, there are exposures to blasting gases and to salt dust, which is irritant to mucous surfaces and even causes some dermatitis.

In all mining work, periodic physical examinations of workers are even more important than they are in work above ground. Sanitation<sup>30</sup> is an important control measure.

<sup>27</sup> R. R. Sayers, J. J. Bloomfield, J. M. DallaValle, R. R. Jones, W. C. Dreessen, D. K. Brundage, and R. H. Britten, *U.S. Pub. Health Bull.* No. 221 (1936).

<sup>28</sup> W. C. Dreessen, J. M. DallaValle, T. I. Edwards, R. R. Sayers, H. F. Easom, and M. F. Trice, *U.S. Pub. Health Bull.* No. 250 (1940).

<sup>29</sup> W. Siegal, A. R. Smith, and L. Greenburg, *Am. J. Roentgenol. Radium Therapy*, 49, 11 (1943).

<sup>30</sup> R. R. Sayers, *U.S. Bur. Mines, Miners' Circ.* No. 28 (1924).

### Motor Testing

In motor testing, carbon monoxide, noise, and heat furnish the problems for consideration. Carbon monoxide is readily controlled by the correct application of exhaust ventilation; the control of noise is a more difficult engineering problem; while temperature control is frequently more or less incidental to the control of exhaust gases and noise. Where there are individual test chambers provided with exterior controls and instrumentation, the problems are readily solved. Where many engines are operated simultaneously in one room, the exhaust gases are readily removed through flexible connections to exhaust ducts, but noise control is not easy. Walls and ceilings can be deadened with fireproof, sound-absorbing materials, or curtains and irregular space arrangements may be used to absorb sound and avoid reverberation, but the only way of lowering general noise production is by segregating the operations. In some rooms with many closely stationed, simultaneous test operations it has not been practical to bring the general noise level below 100 decibels which, though well tolerated by many individuals, is at least very annoying to some. The question of possible ill effects is an open one but it is generally believed that the low-frequency engine-test noises of this level do not have a permanent adverse effect upon the hearing of workmen.

### Nickel

The element nickel and its compounds, with one exception, are of little significance as industrial poisons. The exception is a toxic gas, nickel carbonyl. See pages 626-628 and 725.

Nickel is found in nature as the sulfide, which, after concentration and grinding, is roasted. The sulfur is removed as sulfur dioxide, leaving nickel oxide. Sulfur dioxide is not present in the atmosphere of smelters in significant quantities, as the smelting furnaces remove the gas efficiently.

Nickel oxide is reduced to the metal in either open-hearth or electric furnaces. The electric furnaces generally require exhaust ventilation because of excessive fumes. Fluorspar is used as a flux and fluoride concentrations should be recognized and controlled in order to avoid nasal irritation and fluoride storage.

Strong mineral acids are used during the fabrication of nickel, especially nitric acid in pickling processes. Lead is employed as a coating on rods and tubes which are cold-drawn, and there is a potential exposure involved in the application of the lead. Furnaces that have inert atmospheres should be checked for carbon monoxide leakage.

### Painting

Paints consist of pigments, binders, thinners, wetting agents, and driers. The pigments may be any of the following: the oxides or other compounds of lead,

zinc, titanium, chromium, iron, antimony, or cadmium; metallic zinc, bronze, brass, or aluminum; carbon, talc, china clay, quartz silica, diatomaceous earth, or mica; barium sulfate, calcium carbonate, or calcium sulfate; or organic dyes. The binders include oils, gums, natural and synthetic resins, casein, cellulose esters, gilsonite pitch or tar, dibutyl, diethyl, and diamyl phthalates, and tricresyl phosphate. The thinners include turpentine, aliphatic and aromatic hydrocarbons, esters, alcohols, and ketones. Wetting agents have been relatively innocuous. Driers include lead, cobalt, and manganese compounds.

Paint is applied by brushing, dipping, tumbling, and spraying. The necessity for ventilation control of the solvents during application and drying is common to all methods. Potential exposures include: (1) ingestion of lead and other toxic pigments, and (2) difficulties arising from sensitivity to the irritant effects of zinc chromate, of certain incompletely reacted resins such as cashew shell liquid-formaldehyde resin, and of the thinners, especially wood turpentine, which may cause dermatitis upon contact with the skin. A more serious exposure involves inhalation of excessive amounts of solvent vapor arising from painted surfaces in poorly ventilated areas. In addition to exposures possibly harmful to health, vapor explosions must be considered, especially in the initial period in drying ovens.

In spray-painting there are potential exposures to pigments, mists, and solvent vapors during spraying and to solvent vapors during drying. It is desirable to provide all spraying operations with booths engineered to prevent contact of significant vapor or mist with the faces of workmen. Although recommended air-flow velocities for spray booths are on the order of 100 to 200 l.f.m., much depends upon the spray gun, the size and shape and location of the booth, size and shape of the object, the pigments and solvents involved, and other factors. This is discussed more fully in Chapter Ten. Set rules for air volumes and velocities are not in order, but either the ventilation control should prevent significant vapor, mist, and pigment exposure or the operator should wear a respirator, preferably one of the supplied-air types. The painting of the interiors of cabs, busses, and railroad cars is an exposure difficult to control without resorting to personal respiratory protection. Any type of filter respirator must necessarily be a compromise because none so far advanced adequately protect against both pigments and solvent vapor. As in the case of air cleaners for ventilation systems, the important consideration is not the amount of contaminant removed by the filter but the amount that passes through.

### Paint Manufacture

The mixing of dry pigments with oils and varnishes constitutes the principal health hazard of this industry. Lead oxides, lead carbonate, and other leaded pigments, as well as cadmium compounds and numerous toxic dry colors, are usually purchased by the paint manufacturer in paper sacks. A dangerous dust

exposure occurs when the pigments are added to the mixers unless exhaust ventilation is used. In lieu of such ventilation it is common practice for the workmen to wear approved respirators, as the time of exposure is only a minor portion of each work period.

Paint manufacture is generally conducted in a building of three or four stories so that materials may flow by gravity from operation to operation. Some of the finer products go to stone mills for production of the proper dispersion; other products require roll mills and Banbury mixers. Stones used for grinding pigments and oil generally contain free silica: stone dressing must have exhaust ventilation if silicosis is to be prevented.

After being thinned and tinted, the products are placed in cans by automatic machinery or hand operation, depending on the volumes handled. The chief harmful effect from the paints after the pigments and oils have been blended is dermatitis, but this is rather rare in modern plants where cleanliness is rigidly enforced and coveralls and laundry service are provided.

Turpentine and hydrogenated naphthas are the most common thinners. Hydrogenated naphthas generally consist of saturated cyclic hydrocarbons, but the absence of benzene should not be taken for granted. The saturated cyclic compounds have low toxicity (see Chapter Twenty-Five, Turpentine).

## Paper Manufacture

### *Pulping*

Wood pulp produced by treatment of wood with steam in digesters is the chief source of paper. In the *sulfate process* (sulfide) the shredded wood is digested with steam in tanks under pressure of about 125 p.s.i. using up to 8.5 lb. of sodium sulfide and 23 lb. of sodium hydroxide per 100 pounds of wood. During cooking, relief gases are released into the atmosphere from the top of the digester or along with the condensate, which contains commercial quantities of "sulfate wood turpentine." These gases contain methyl alcohol, acetone, aldehydes, traces of acetic and formic acids, ammonia, hydrogen sulfide, ammonium sulfide, methyl mercaptan, and dimethyl sulfide. The gases also arise from the pulp and digestion liquor and they persist with the pulp during washing, screening, and some subsequent processes. The liquor is partially evaporated in evaporators, salt cake (sodium sulfate) is added, and the mixture sprayed into recovery furnaces, where the water is removed and the other volatile matter burned, leaving the alkali and sodium sulfide to be reused. The resultant heat is utilized and combustion gases are released from high stacks. These stack gases contain both sulfurous gases and particulate matter that consists of sodium sulfate, sodium carbonate, and sodium sulfide. The odor in and around the plant is exceedingly disagreeable. Although in most instances gases and vapors are in very low concentrations, there are opportunities for harmful exposures and for explosions of inflammable gases or vapors.

Various methods have been tried for controlling the escape of odorous gases. These include passing the gases into high stacks, scrubbing them through caustic, passing them through the furnace with or without previous washing with water sprays, and treating them with waste bleach water. Electric precipitation has also been suggested for the stacks.<sup>81</sup>

The *sulfite process* is similar except that the digester liquor is an aqueous solution of sulfurous acid with lime or other base to form bisulfites. The sulfur dioxide is obtained either as a compressed gas or from the burning of sulfur or the roasting of pyrite ores. The relief gas in this process contains high amounts of sulfur dioxide, which must be recovered for economical operation. This is accomplished by separators and coolers.

### *Bleaching*

Bleaching is usually accomplished by the use of chlorine, which may be supplied from cylinders of the compressed gas or from bleaching powder. Chlorine hydrate may form where gaseous chlorine enters the vat and be carried to the surface, where it emits chlorine into the atmosphere. However, the exposure to chlorine is ordinarily not difficult to control by process or general ventilation.

### *Coating*

Paper is coated by various types of coating machines and the materials used include borax, clay, mica, talc, casein, soda ash, dyes, plastics, gums, varnishes, linseed oil, and organic solvents. The principal exposures arising from these operations involve: (1) acrolein and other aldehydes resulting from the atmospheric oxidation of linseed oil, and (2) solvent vapors from the coating and subsequent drying of the paper, when coating mixtures dissolved in organic solvents are used. When the coating and drying are done in air-conditioned rooms, the environmental-control problems sometimes become difficult.

## **Photographic Industry**

Dermatitis and skin sensitization are the hazards of the photographic industry. Nasal and bronchial irritation and asthma are also reported from contact with developers and other photographic chemicals. The aminophenols are among the most common sources of skin disease from developers. Other irritating chemicals include caustics, iron salts, mercuric chloride, strong acids, bromides, iodides, pyrogalllic acid, and silver nitrate. The last substance is reported to have caused argyria, a condition in which silver is deposited beneath the skin. It is difficult, if not impossible, to remove the deposits completely.

The prevention of dermatitis lies in reducing to a minimum the contact of

<sup>81</sup>J. M. DallaValle and H. C. Dudley, *U.S. Pub. Health Repts.*, 54, 35 (1939).



the chemicals with the skin. Cleanliness, protective clothing, and protective creams are the triumvirate for controlling the hazard.

### Plastics and Synthetic Resins

Synthetic resins that have undergone complete condensation cause little difficulty in the cold, but where heat is applied, or an imperfectly combined component is present, skin irritation and sensitization may result. The phenol-formaldehyde and urea-formaldehyde resins owe their irritant and sensitizing properties chiefly to formaldehyde,<sup>32</sup> but phenol and furfural (phenol-furfural resins) may also have some irritant effect. It is advisable to provide process ventilation for any dust-producing or vapor-producing process involving the manufacture, fabrication, or use of plastics whereby formaldehyde is released into the workroom atmosphere. Hexamethylenetetramine, which has a bad reputation as a sensitizer, is harmful because it releases formaldehyde.<sup>33</sup> Cashew nutshell liquid-formaldehyde resin is particularly offensive if any uncombined cashew nutshell liquid remains in the resin. "Oil stop," a waterproof resin made by mixing cashew nutshell liquid to a paste with powdered paraform (a polymer of formaldehyde) and allowing it to "set" or condense, is popular with electricians. Both of the constituents are irritants and sensitizers and there is a high incidence of dermatitis among users who carelessly contaminate their hands and clothing with the mixture.

Plastic glues for the manufacture of plywood, laminated asbestos, fiberboard, glass fabric, and similar products may be made of incompletely condensed resins containing formaldehyde along with acids, alkalies, peroxides, and other irritants and sensitizers. The screening, sealing, and mixing of such powdered glues are productive of dust and conducive to dermatitis.

Many plastics such as vinyl chloride, vinyl acetate, polyethylene, polystyrene, and methyl methacrylate have proved to be more or less inert physiologically. Antioxidants and stabilizers added to some plastics, however, may occasionally cause adverse physiological effects. The majority of the dermatitis cases arising from prolonged contact with plastics of this nature are caused by plasticizers added to eliminate brittleness and to produce flexibility. Some of these plasticizers are susceptible to the effects of heat and moisture and may separate from plastics that are in prolonged contact with the skin and cause either primary irritation or, more likely, sensitization. This presents a use problem rather than a production problem. These plasticizers<sup>34</sup> include derivatives of glycol, glycolic acid, phthalic acid, phosphoric acid, ricinoleic acid, and sebacic acid.

In evaluating and controlling exposures arising from the manufacture, fabrication, or use of plastics, dermatitis is the primary consideration, but eye irritation and even the possibility of lung irritation should be considered. Dusts,

<sup>32</sup> A. G. Cranch, *Ind. Med.*, 15, 168 (1946).

<sup>33</sup> L. Schwartz, *J. Investigative Dermatol.*, 6, 239 (1945).

especially those involving incompletely reacted materials, and irritant gases or vapors should be controlled by engineering methods; excessively warm and humid atmospheres also should be controlled; and direct skin contact with suspected irritants or sensitizers should be avoided. A supervised program of personal cleanliness and frequent changes of clothing are the best personal control measures wherever dermatitis is involved.

Occasionally persons do not respond to "hardening" and the standard preventive and protective measures. In such cases of unusual susceptibility it is necessary to transfer the workers to other work.

### Pottery Industry

Silicosis and lead poisoning are the traditional occupational diseases of potters. Free silica is present as flint in the pottery slip in amounts that make dust control of a high order imperative. Respirable sizes of dust commonly show 40–50 per cent free silica in slip houses. The use of lead compounds in decorating ware also necessitates a high degree of dust elimination.

Most of the dangerous silica operations are concentrated in a few departments. The slip house normally has more than half of the total significantly exposed workers. Lead exposure is confined to sprays and dust from ware prior to its being fired.

Jiggering and batting out normally do not involve harmful exposures. Stampers should be provided with exhaust ventilation, however, as should finishers. Dish makers do not have significant dust exposures. This statement also applies to casting shops. Bisque and glaze kiln placing and drawing are dust-free operations. Flatware brushing is one of the dustiest occupations outside of the slip house and it requires control. The transfer of raw materials from boxcars to storage bins may involve excessive dust exposures.

It is poor hygienic practice to draw hot air directly from the fire chambers of the kilns into the workrooms to heat them: a system of heat exchangers should be used.

### Quartz Crystal Cutting

The manufacture of quartz crystals for radio oscillators results in several processes that may cause harm to the health of workers. Quartz dust, solvents, and x-radiation may be present in damaging quantities.

Both Goss<sup>34</sup> and Schulte<sup>35</sup> have shown that dust counts from cutting operations are closely related to the degree of contamination of the oil. Oil that contains much quartz dust will spread the quartz into the air along with oil spray. Schulte also found, however, that clean oil was not always an insurance of a safe process. Exhaust ventilation is required for adequate control.

<sup>34</sup> A. E. Goss, *J. Ind. Hyg. Toxicol.*, 16, 208 (1944).

<sup>35</sup> H. F. Schulte, *Ind. Med.*, 14, 68 (1945).

Xylene, carbon tetrachloride, and methyl alcohol are commonly used to remove cement from the crystal-mounting bases. These materials may be present in hazardous concentrations. Other alcohols and lacquer thinners are used in lesser amounts.

Etching compounds composed of fluoride salts with weak acids or hydrofluoric acid itself are used to reduce the amount of grinding required. Protective clothing and ventilation are required to protect workmen.

X-rays of low power (35,000 volts) are employed to test the quartz crystals. The exposures should be appraised by measuring any stray radiation, and periodic blood counts should be made on operators who are routinely exposed.

Dermatitis, resulting from excessive contact with the solvents and oils, has been of frequent occurrence.

### **Radio Manufacture**

The majority of the potential exposures in radio manufacture have been discussed under Chlorinated Oils and Waxes, Electroplating, Heat-Treating, Metal Cleaning, Plastics and Resins, Quartz Crystal Cutting, Sand Blasting, Soldering, Spray-Painting, and Welding.

Where Halowax is used on coils or wires, rigid control is required to avoid dispersing the vapors as well as to avoid skin contact. Paraform introduces both a dust and a formaldehyde gas exposure, either of which may cause skin irritation or sensitization.

Copper cyanide plating operations may be sources of excessive amounts of cyanogen or hydrogen cyanide gases, and zinc cyanide baths may be sources of excess alkaline cyanide mists unless ventilated.

Carbon tetrachloride is frequently found in open containers around radio and wire soldering operations. It may present a harmful exposure and its use may be unnecessary.

### **Radium Dial Painting**

Radium dial painting is treated at some length in Chapter Nine. Radioactive dusts of respirable size probably offer more of an inhalation hazard than does radon, because any particles of radioactive material lodged in the respiratory tract would continue to emit rays for an indefinite period unless removed by ciliary action or other means. Where dial painters are permitted to mix their own paints, radioactive particles can be demonstrated by ultraviolet light on the skin, the clothing, personal belongings, in desk drawers, or any place where the work tools are kept. A factor that may minimize this potential exposure is that the particles of radioactive material are for the most part well above the respirable range in size. The fact that they must be filtered out of air samples collected for radon analysis, however, is a definite indication that air-borne dust particles exist. If the dust exposure is controlled, the radon gas exposure may

not be a serious factor even when it is well above the accepted permissible limit. Centralized, carefully controlled mixing and scrupulous housekeeping evaluated by ultraviolet light are very important control factors. Methods of dust removal must be such as not to present an exposure through redispersion. Drying ovens should be provided with sufficient mechanical ventilation to afford an inward flow through all openings under operating conditions. Radioactive dust should not be permitted to collect in cabinets or ovens whence it may be dispersed by opening or closing the doors.

Before a technique was developed to give anything approaching dependable and reproducible results much time and money were spent and much mental anguish resulted from the collection and analysis of expired air for radon to evaluate radium stored in the body. Some of the difficulties that had to be recognized and overcome were: (1) failure of sampling flasks to retain a vacuum, (2) collecting breath samples in an atmosphere containing more radon than the expired breath, (3) lack of uniformity or agreement on the method of collecting expired breath, which gave samples ranging from alveolar air to those somewhat diluted with room air, and (4) failure to wait long enough after exposure to desaturate the body from its unfixed radium. Two factors that introduced errors in sampling room air were failure of the sampling flasks to retain a vacuum, and the aspiration of radioactive dust particles into sampling flasks, resulting in phenomenally high quantities of radon per sample.

A gamma-ray exposure meter employing a Geiger-Mueller tube, an ultraviolet light, and a velometer are the three most important tools for evaluating the environment. The important thing is to locate bad housekeeping and possible exposure sources, and then to make certain that suitable ventilation or other control is applied. Determinations of radon in properly collected room-air samples are useful to indicate the presence or absence of unsuspected radioactive materials in the room.

### **Sand Refining**

Sand refining for the production of a pure graded product may involve serious exposures to quartz dust. Where the raw product contains fine quartz grains, or the cryptocrystalline variety of quartz, or grains that have been fractured by explosives and drills, there is a serious potential exposure that requires careful control.

Where the refining of such a product involves rotary-kiln drying, screening, elevating, storing, and car loading without the benefit of modern engineering control measures, exposures have been found to range upward of one hundred million particles of quartz per cubic foot of air in and around the mills, with a visible cloud of dust that pollutes the atmosphere for a considerable distance leeward of the plant.

This type of plant has been brought under satisfactory control by enclosing and exhausting elevators, screens, chutes, bins, conveyors, and other dust-pro-

ducing operations; combining the dust-laden exhausted air with the hot rotary drier effluent; and scrubbing both through a homemade collector consisting of water sprays, baffles, and a bed of coke which is also sprayed with water. The heated particles of quartz, though too small to be collected by impingement, are readily collected after each has formed the nucleus of a water droplet in a cooled, supersaturated atmosphere. The collector was the source of huge quantities of "silica flour" that presented a disposal problem until uses for this by-product were developed.

### **Shipbuilding and Repair**

Before a vessel enters a drydock for the purpose of undergoing construction work, repairs, or alterations of any kind, all tanks, compartments, or lines that have contained inflammable liquids should be cleaned and freed of inflammable vapor to comply with the code of the National Fire Protection Association concerning marine fire hazards. The atmosphere in all unventilated areas or compartments should be checked for harmful or inflammable gases and for oxygen deficiency by a qualified chemist or industrial hygienist, who should examine each compartment before workmen are permitted to enter. Tests through long sampling lines from the deck are not reliable.

Tankers that have carried gasoline or volatile crude oils require frequent, periodic checks even after a "gas-free" status has been established. Any rust on the walls or sludge on the floors of compartments may continue to dissipate inflammable vapor. The pumping of ballast also may introduce inflammables from some inaccessible part of the pipe lines or storage tanks.

When work is conducted in tanks used for transporting leaded gasoline, the lead exposure involved in welding or cutting operations on rust coated surfaces is not significant; general ventilation, sufficient to control welding fumes, furnishes satisfactory control for lead exposures. The amount of adsorbed or occluded lead in the rust is so small that, except in very dense suspensions of rust in the atmosphere, the exposure is negligible even for prolonged periods. Where extensive and prolonged scratch brushing or other dust-producing work is performed, a respirator to filter out the iron oxide is advisable.

Repairs on pipe lines should be undertaken only after all "hot work" on the hull and in tanks and compartments has been completed. Heat must never be applied to any closed line or section of line; all lines must be opened by cold operation for examination; and, if any welding or torch cutting is to be done on a line that may contain inflammables, a blast of air should be blown through it before, and during, the operation. Work of any nature on refrigeration lines must be under the direction of a man who is qualified to recognize and control the hazards involved.

The most generally widespread exposures in shipbuilding and repair are those connected with welding and flame cutting; and since these are discussed under welding, they will not be enlarged upon here more than to point out that

free silica content is low and the stone is moist; but if the operation is objectionably dusty, a mist spray can be applied effectively without causing gumming of the fines sufficient to interfere with the operation of conveyor belts, chutes, or buckets. This spray has been used to best advantage at the shovel. Ordinarily, secondary crushers are excessively dusty unless the hopper and belt loading zone is enclosed and exhausted or the crusher is equipped with sprays. Conveyors, likewise, create dust at their terminals unless enclosed and exhausted, or subjected to water sprays.

Vibrating and rotary screens are the most prolific sources of dust when not enclosed, and frequently produce dust clouds of one hundred million to one billion particles per cubic foot of air. Even one of the least harmful or offensive dusts, such as relatively pure calcium carbonate, when present in such excessive amounts is not only objectionable from the standpoint of inhalation, but is an accident hazard because it interferes with vision. The situation is especially bad if, as sometimes happens, these screens are located at or near the top of a several story structure with wood floors that have wide cracks that continually sift dust down throughout the structure.

Bagging operations are very dusty unless well engineered. Water-mist spray at dust dispersion points, or suitable enclosures and dust-control systems, are necessary. Chirico<sup>27</sup> has developed successful control measures for many of these dusty operations.

Granite cutting has been found to require dust-control measures; maximum permissible concentrations of ten to twenty million particles per cubic foot have been proposed and twenty is perhaps more generally accepted.

Cement dust, also discussed under Cement, is somewhat alkaline and causes irritation of the intact skin. Opinions differ as to the maximum permissible dustiness, but fifty million particles per cubic foot of air appears to be lenient.

### **Welding**

General safety precautions are covered by A.S.A. War Standard Z49.1 (1944). This authoritative information covering gas welding and cutting and electrical welding is being revised and expanded.

Eye protection is needed for both intense visible light and ultraviolet radiation from electric welding. The skin also must be shielded to avoid burns. Gas welding does not release significant ultraviolet light. Goggles are necessary, however, to reduce glare and to prevent eye damage from sparks. Flame-resistant clothing is advisable for all types of welding.

When plain steel electrodes are used, long-continued exposures with inadequate ventilation may cause a chronic bronchial cough. The condition clears in a few weeks after exposure ceases. The lungs of welders may have sufficient deposition of iron oxide fume to cause characteristic x-ray findings (siderosis). This condition is benign and is not associated with disability or discomfort.

Siderosis complicates the diagnosis of silicosis where there is an associated or subsequent exposure to free silica.

In unventilated spaces nitrogen dioxide can be generated in harmful quantities: this is especially true of gas welding and shrinking<sup>28</sup> operations.

Coated welding rods release both iron oxide and fume containing the constituents of the coating. Repeated laboratory studies show that harmful amounts of fume are not produced. The only exception occurs in confined quarters with no ventilation.

Where the room volume is relatively large, over 50,000 cubic feet with the space per welder over 10,000 cubic feet, and construction is of conventional building materials, dilution and natural ventilation are believed to be sufficient to prevent the accumulation of significant fume levels in the general atmosphere when welding clean carbon steel with steel rods and electrodes.

Welding on surfaces coated with cadmium is dangerous and deaths have occurred where there was no exhaust ventilation. Cadmium oxide may cause a chemical pneumonitis fatal within 24 hours.

Zinc-coated surfaces, during welding, release large amounts of zinc oxide which can cause metal-fume fever. The condition is unpleasant but has no permanent effects after 24 hours. Welding on painted metal is hazardous to a degree dependent upon the composition of the paint. Paints containing lead may cause plumbism.

Welding on aluminum or stainless steel introduces a fluoride exposure from the flux used. In the absence of control measures nasal irritation is common and long-continued exposures might result in fluorosis.

Tuberculosis is no more frequent among welders than among the average population. Animal studies indicate that welding fumes neither predispose to tuberculosis nor reactivate healed lesions. The incidence of pneumonia among welders also approximates that of the general public.

Local exhaust ventilation is advisable for welding processes for the following reasons: (1) to prevent throat and bronchial irritation; (2) to avoid siderosis which may be mistaken for silicosis; (3) to eliminate toxic quantities of lead, manganese, cadmium, fluorides, and so forth, when present; (4) to prevent deaths, which occasionally occur from welding in confined spaces. Recirculating the air through a mechanical filter cannot be considered satisfactory ventilation control where nitrogen dioxide is involved.

Spot welding (electric-resistance welding) does not produce harmful quantities of gases or rays. When the parts are oil covered, offensive oil smoke may be given off. Burns from flying sparks are possible and in spot welding stainless steel penetration of metallic particles into the finger tips has been demonstrated by x-ray photographs.

<sup>28</sup> F. E. Adley, *J. Ind. Hyg. Toxicol.*, 28, 17 (1946).

It is believed worth while to describe an unpublicized case of severe welding-fume poisoning which may be of significance. A compressed-air tank 4 ft. in diameter and 20 ft. long was repaired by welding the pitted or corroded areas at the bottom of the tank. The only opening to the atmosphere was an  $11 \times 15$  in. manhole in the top at one end. This and a supply of compressed air in a similar tank which was connected to the center top of this tank by a  $1/4$ -in. line were the only provisions for ventilation. The welding work required about  $1\frac{3}{4}$  hours, during which time about sixty  $3/16$ -in. coated rods were used. The composition of the steel rod was not significant except perhaps for the presence of 7.5 per cent manganese in the coating material.

The workman noticed no irritation or serious discomfort during work but complained of being warm and unable to see because of the dense smoke. In the late afternoon within half an hour after finishing the job he noticed moderate chest pains of growing intensity, followed by a feeling of stiffness of his toes. The stiffness developed to a feeling of cramps, with the toes drawn downward, and, within about 1 hour after exposure, he experienced great difficulty in walking a few feet from his garage to his house because of inability to control the use of his legs, apparently due to partial paralysis. This workman was unable to sleep at all during the night because of excessive pains in his legs and feet. The pains continued the next day, but the chest pain was less noticeable. The man remained in bed but did not call a physician. During the next night his left arm suffered considerable loss of function and these conditions prevailed throughout the next day and night before a physician was called. When the physician arrived approximately 66 hours after the exposure, the man was immediately hospitalized and he remained in the hospital for a period of 2 months. He suffered a severe pulmonary congestion and paralysis of both arms and both legs. Three weeks after leaving the hospital he was able to get around some and was improving, but still suffered partial paralysis of both arms and legs. Further data on the case are not available.

Analysis of the tank atmosphere was not made. Neither cadmium nor lead was present but doubtless there was, besides iron fume, a considerable amount of nitrogen dioxide gas and manganese fume. This case is described as of possible interest in the portrayal of the effects of nitrogen-dioxide and manganese fumes from welding with manganese bearing rods in unventilated spaces. The symptoms were not typical of nitrogen dioxide exposures. Fumes collected later in an operation in which the same type rods were used in a ventilated room yielded 26 mg. of iron oxide to 1 mg. of manganese.



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