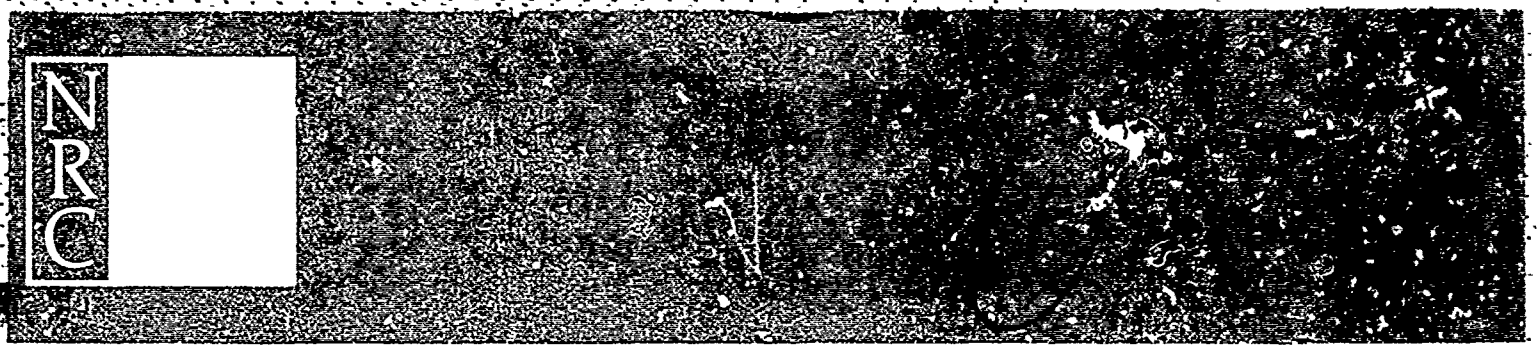

Emergency and Continuous Exposure Limits for Selected Airborne Contaminants

Volume 1

Committee on Toxicology
Board on Toxicology and Environmental Health Hazards
Commission on Life Sciences
National Research Council

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This document is one in a series prepared by the Committee that form the basis of the recommendations for EELs and CELs for selected chemicals. Since the Committee began recommending EELs and CELs for its military sponsors (U.S. Army, Navy, and Air Force), the scope of its recommendations has been expanded in response to a request by the National Aeronautics and Space Administration. The CELs, in particular, grew out of a Navy request for exposure limits for atmospheric contaminants in submarines. The EELs and

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20. Cont.

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EMERGENCY AND CONTINUOUS EXPOSURE LIMITS FOR SELECTED AIRBORNE CONTAMINANTS

Volume 1

prepared by the

COMMITTEE ON TOXICOLOGY

Board on Toxicology and Environmental Health Hazards
Commission on Life Sciences
National Research Council

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council. whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competencies and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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NOTE ON TIMING OF RELEASE OF REPORT: This report was completed in May 1983. It was originally intended that it be released with Volume 2. However, Volume 2 has been delayed, and Volume 1 is, therefore, being issued separately.

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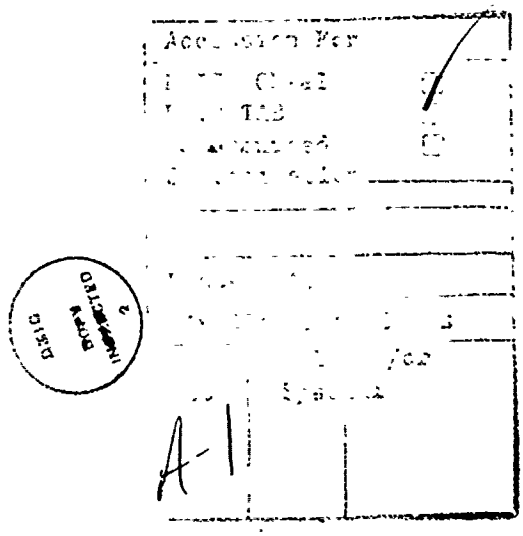
ACKNOWLEDGMENTS

This document reflects an ongoing effort by the Committee on Toxicology in the past several years to review and update earlier recommendations that were made with regard to exposure to a variety of airborne contaminants primarily of concern to the Department of Defense and to the National Aeronautics and Space Administration. The preparation of this document has been possible only because of the dedicated efforts of all current members of the Committee on Toxicology and many other members who previously served on the Committee.

The document has been evaluated in total by the current members of the Committee; however, much of the work was initially done by former members. The contributions of the following individuals is particularly noted: Dr. Joseph Rodricks, Environ Corporation, Washington, D.C.; Dr. Philip Watanabe, Dow Chemical USA, Midland, MI; 10. Ian Higgins, University of Michigan, Ann Arbor, MI; Dr. Wendell Kilgore, University of California, Davis, CA; Dr. H. George Mandel, The George Washington University, Washington, D.C.; Dr. Charles Reinhardt, E.I. duPont de Nemours and Company, Newark, DE; and Dr. Lawrence Fishbein, National Center for Toxicological Research.



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CONTENTS

INTRODUCTION

The National Research Council's Committee on Toxicology recommends emergency exposure limits (EELs), short-term public limits (STPLs), and short-term public emergency limits (SPELs - formerly called public emergency limits, or PELs) for a variety of chemicals of concern to its sponsoring agencies. The definitions and applicability of these limits and the criteria used to establish them were originally outlined in two documents prepared by the Committee (NRC, 1964, 1971). In a revision of these documents (NRC, 1979), the Committee summarized the principles used to establish exposure limits for short durations. The Committee has also recommended continuous exposure limits (CELs) in response to specific sponsor requests.

This document is one in a series prepared by the Committee that form the basis of the recommendations for EELs and CELs for selected chemicals. Since the Committee began recommending EELs and CELs for its military sponsors (U.S. Army, Navy, and Air Force), the scope of its recommendations has been expanded in response to a request by the National Aeronautics and Space Administration. The CELs, in particular, grew out of a Navy request for exposure limits for atmospheric contaminants in submarines. The EELs and CELs have been used as design criteria by the sponsors in considering the suitability of materials for particular missions (as in a submarine or a spacecraft) and in assessing the habitability of particular enclosed environments. They are recommended for narrowly defined occupational groups and are not intended for application in general industrial settings or as exposure limits for the general public.

The EEL is defined as a ceiling limit for an unpredictable single exposure, usually lasting 60 min or less, and never more than 24 h -- an occurrence expected to be rare in the lifetime of any person. It reflects an acceptance of the statistical likelihood of the occurrence of a nonincapacitating, reversible effect in an exposed population. It is designed to avoid substantial decrements in performance during emergencies and might contain no uncertainty factor. The use of uncertainty factors will depend on the specific compound in question and on the type of effect produced by the compound.

The CEL is recommended in specific situations where there may be exposure to a chemical continuously for up to 90 d. It is defined as a ceiling limit designed to avoid adverse health effects, either immediate or delayed, and to avoid degradation in crew performance that might endanger the objectives of a particular mission. Because data on continuous exposures are rarely available, uncertainty factors might be used, depending on the judgment of the Committee.

Table 1 summarizes the EELs and CELs for selected chemicals previously recommended by the Committee and revised recommendations made on the basis of information presented in this report.

TABLE 1.

Emergency and Continuous Exposure Limits

Compound	Duration of Exposure	Recommended Exposure Limit[a] Previous	Current
Acetone	60 min	15,000	8,500
	24 hr	2,000	1,000
	90 d	300	200
Acrolein	10 min	--	0.1
	60 min	0.2	0.05[b]
	24 h	0.1	0.01[b]
	90 d	0.1	0.01
Arsine	60 min	1.0	1.0
	24 h	0.1	0.1
	90 d	0.01	--
Carbon disulfide	10 min	200	200
	30 min	100	100
	60 min	50	50
Chloroform	60 min	200	100
	24 h	30	30
	90 d	3	1
Fluorine	10 min	15	15
	30 min	10	10
	60 min	5	7.5
Mercury vapor mg/m^3	24 h	2 mg/m^3	0.2
	90 d	0.01 mg/m^3	0.01
mg/m^3			
Methane	24 h	5,000	5,000
	90 d	5,000	5,000
Ozone	60 min	1	1
	24 h	0.1	0.1
	90 d	0.02	0.02
Sulfuric acid mg/m^3	10 min	5 mg/m^3	5
	30 min	2 mg/m^3	2
mg/m^3			
	60 min	1 mg/m^3	1
mg/m^3			

[a]ppm, unless otherwise stated.
[b]Tentative recommendation.

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ACETONE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Structural formula:	CH_3COCH_3
Molecular weight:	58.08
Chemical name:	2-Propanone
Synonyms:	Acetone; dimethyl ketone; dimethyl ketal; -ketopropane
CAS number:	67641
Melting point:	-95.35°C
Boiling point:	56.2°C
Density:	0.7899 (20°/4°)
Index of refraction:	1.3588 (20°/0°)
Vapor pressure:	226.3 mm Hg (25°C)
Flash point:	Tag closed cup; -4°F (-20°C); tag open cup, -2°F (-19°C)
Fire point:	-2°F (-19°C)
Flammable limits in air:	2.6-12.8% by volume; autoignition temperature, 1,000°F (538°C)
Solubility:	Miscible with water in all proportions; miscible with alcohol, dimethylformamide, chloroform, ether, and most oils
Stability:	Chemically stable liquid
General characteristics:	A colorless liquid with a pungent odor and taste; volatile and extremely flammable; forms explosive mixtures with air or oxygen.
Other chemical properties:	Forms crystalline compounds with alkali bisulfites; reducing agents convert it to isopropyl alcohol (Hays, 1958).
Conversion factors:	ppm = 0.42 (mg/m^3) mg/m^3 = 2.38 (ppm)

OCCURRENCE AND USE

Acetone occurs naturally, being found in plants and animals, such as fowl and fish (Walter et al., 1975). It is the only methyl ketone detected in animal tissues. In some pathologic conditions associated with excessive fat catabolism, mammals accumulate acetone; acetoacetate and ß-hydroxybutyrate are then found as "ketone bodies" or "acetone bodies" in the blood.

Acetone is used as a solvent for resins, lacquers, oils, fats, waxes, rubber cements, plastics, cotton, cellulose acetate, and acetylene. It is used in the production of ketene, acetic anhydride, methyl methacrylate, diacetone alcohol, methyl isobutyl ketone, isophorone, chloroform, iodoform, and vitamin C. It is used in the paint, lacquer, and varnish industry; in the rubber, plastics, dyeing,

celluloid, photographic, and explosives industries; and in the manufacture of artificial silk and leather.

Acetone may be found in such products as solvents, cooking fuels, corn remover, drawing inks, fuel-system deicer, glue, nail-polish remover, paint-brush cleaners, paint and varnish removers, and china, film, fishing-rod, metal, plastic, and shoe cements. U.S. production of acetone in 1973 was a billion pounds.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Several pertinent examples of effects on humans of uncontrolled and controlled exposure to acetone are listed in Tables 2 and 3.

EFFECTS ON ANIMALS

Acute, Subchronic, and Chronic Exposure

Results of acute, subchronic, and chronic exposure of animals to acetone are summarized in Table 4. Excretion of this relatively nontoxic substance prevents its accumulation, unless doses are overwhelming. The rate of elimination is about 2.3%/h (Haggard et al., 1944).

Carcinogenicity, Mutagenicity, and Teratogenicity

McLaughlin et al. (1963) injected 0.05 ml of undiluted acetone into the yolk sac of fertile chick eggs before incubation. The hatch yield was 70%, with no evidence of teratogenicity. The same investigators (1964) similarly injected 39 and 78 mg of acetone into the yolk sac of fertile chick eggs before incubation. The hatch yields were 80% and 50%, respectively, again with no evidence of teratogenicity.

Caujolle et al. (1966) exposed 72- and 96-h-old chick embryos to various doses of acetone. The LD_{50} and ED_{50} values for malformations were 48.6 mg and 18.0 mg, respectively, for the 72-h-old embryos and 28.7 mg and 25.0 mg for the 96-h-old embryos.

Park and Koprowska (1) painted the cervical tissue of virgin C3H/HcJ mice with acetone r up to 5 mo; no tumors resulted. A 1% solution of benzo[a]pyrene in acetone induced invasive carcinoma in all the test animals.

Mazzucco (1975) reported that acetone, often used as a vehicle for skin carcinogens, did not lower the skin collagen content of mice (unlike benzene and toluene). Stenback et al. (1977) reported that p-amino-o-nitrophenol, p-phenylenediamine, and sodium thioglycollate were nontoxic when applied to mouse and rabbit skin in acetone solution.

In a study of the carcinogenic potential of prostaglandins, control male albino Swiss mice treated topically with only acetone

exhibited no tumors, whereas experimental mice treated with combinations of 3-methylcholanthrene and prostaglandins in acetone solution developed tumors (Lupulescu, 1978).

McCann et al. (1975) tested acetone for mutagenicity in the Salmonella/microsome test and found it to be without effect.

PHARMACOKINETICS

Absorption and Distribution

An acetone inhalation study was performed in man (100-500 ppm) and beagles (100, 500, and 1,000 ppm) for 2-4 h (DiVincenzo et al., 1973). In both species, the acetone concentrations in the breath and blood were directly proportional to the magnitude of exposure, and the acetone half-life in blood (3 h) was the same for both man and dog. Exercise significantly increased the extent of acetone absorption in man. Blood acetone in man increased sharply during exposure and reached maximums in 2 h of 2 mg/L and 10 mg/L in subjects exposed at 100 and 500 ppm, respectively. The acetone excreted 24 h after exposure was only a fraction of the quantity absorbed. Results of routine biochemical tests were unaffected in the human subjects by any of the exposures used. The beagles absorbed approximately 5 times more acetone than man under comparable conditions (expressed as amount absorbed per kilogram of body weight).

Rats were given various doses of acetone intraperitoneally to determine tissue absorption and distribution patterns 1-2 h after treatment (Haggard et al., 1944). At 100 mg/kg, blood acetone was 113 mg/L, tissue acetone was 90 mg/kg, and acetone was metabolized and eliminated in urine and expired air at 10 mg/kg. At 500 mg/kg, the corresponding figures were 570 mg/L, 464 mg/kg, and 30 mg/kg; and at 1,000 mg/kg, they were 1,150 mg/L, 941 mg/kg, and 59 mg/kg. At 2,000 mg/kg, blood and tissue concentrations were almost double those at 1,000 mg/kg, but the amount eliminated was 4 times as large. Three rats at rest were given acetone orally at 40, 50, and 60 mg/kg. At the lowest dose, blood acetone reached 41 mg/L; tissue acetone, about 34 mg/kg; and acetone was metabolized or eliminated at about 3 mg/kg. At 60 mg/kg, the corresponding figures were 63 mg/L, 53 mg/kg, and 7 mg/kg. Acetone clearance from the blood of a 68-kg man given acetone orally at 80 mg/kg was determined from alveolar air concentrations and compared with the rat clearance rate. Blood acetone started at 72 mg/L, and disappeared in 27 h; in rats, disappearance took only 10.5 h.

Mongrel dogs exposed to acetone vapor at 140-310 ppm (0.36-0.80 µg/ml) retained 52% at respiratory rates of 5-18/min (Egle, 1973). Retention was lower (42%) in an animal whose respiratory rate was higher (21-40/min). Total retention of acetone at respiratory rates of 10-15/min increased significantly ($p < 0.01$) from 52% at vapor concentrations of 180-280 ppm (0.46-0.72 mg/ml) to 59% at concentrations of 530-680 ppm (1.35-1.75 mg/ml).

Metabolism and Excretion

Four rats were given acetone intraperitoneally at 3,000 mg/kg within a few minutes (Haggard et al., 1944). After a 4-h period for distribution of the acetone, blood was withdrawn successively from different rats at intervals of up to 47 h. In the first 15 h, acetone was lost at about 100 mg/L per liter of blood, with smaller and decreasing losses up to virtually complete disappearance by 47 h.

These same authors reported that in simulated industrial exposures at 5.35 mg/L (in air) for 8 h/d for 9 d, it was observed that acetone accumulated if the amount of acetone absorbed in the first 8 h exceeded the amount that could be eliminated during the following 16 h in ambient air. At the next 8-h challenge, blood acetone increased over that of the earlier exposure. In humans exposed to acetone at 1, 3, and 5 mg/L (420, 1,270, and 2,100 ppm) in ambient air, the relation of exposure to blood acetone after 8 h was as follows:

Exposure, ppm	Blood Acetone Concentration, mg/L
420	30
1,270	99
2,100	162

Blood acetone in the subject who had 162 mg/L 8 h after the first exposure decreased to 79 mg/L on 16-h recovery. After a second 8-h exposure, it increased to 180 mg/L and decreased to 89 mg/L on 16-h recovery. After a third 8-h exposure, blood acetone increased to 182 mg/L and decreased to 91 mg/L after 16 h.

INHALATION EXPOSURE LIMITS

Table 5 lists the recommended occupational exposure limits for acetone in various countries. The American Conference of Governmental Industrial Hygienists (1980) recommends a threshold limit value-time weighted average (TLV-TWA) concentration for acetone of 750 ppm on the basis of data suggesting that only mild irritation has been observed at exposures below 1,000 ppm.

On the basis of odor perception threshold, Tkach (1968) suggested that the minimal perceptible acetone concentration should be 1.096 mg/m^3 for the most sensitive persons.

COMMITTEE RECOMMENDATIONS

EXPOSURE LIMITS

In 1958, the Committee recommended the following maximal concentrations of acetone for various durations of exposure (Hays, 1958):

Concentration, ppm	Duration of Exposure
15,000	1 h
10,000	4 h
5,000	8 h
300	1 wk
100	30 d
40	60 d
25	90 d

These concentrations were derived from the estimated maximal amount of acetone that could be absorbed during the exposure, assuming 100% absorption from the respiratory tract. These recommendations were applicable for single exposures during the stated duration of exposure.

In 1966, the Committee suggested the following EELs and CEL for acetone:

60-min EEL: 15,000 ppm
24-h EEL: 2,000 ppm
90-d CEL: 300 ppm

Nelson et al. (1943) concluded that 500 ppm was the highest tolerable concentration of acetone for an 8-h exposure, on the grounds that 500 ppm produced eye, nose, and throat irritation in experimental subjects. These sensory responses were unpleasant, but not necessarily "toxic." The data suggested that a 90-d continuous exposure not exceed 200 ppm.

Haggard et al. (1944) reported no indications of toxicity in exposures of men to acetone at 2,100 ppm (5 mg/L) in air for 8 h/d. They considered this an upper limit of exposure. They also considered a blood content of 340 mg/L as an upper limit. These authors also reported that 1.0 mg/L in air resulted in 8 mg/L in blood when exposure was for 1 h and the subjects were at rest. If this relation is linear, 42 mg/L in air would result in 340 mg/L in blood; this concentration would equal 17,500 ppm for men at rest or 8,750 ppm for men at exercise.

Raleigh and McGee (1972) studied the effects of exposures of filter press operators to acetone. Their data supported a TLV of 1,000 ppm. Both subjective and objective test data were obtained. Vigliani and Zurlo (1955) reported that Italian workers exposed to 700-1,000 ppm for 3 h/d over 7-15 yr showed inflammation of the respiratory tract, stomach, and duodenum and occasional attacks of giddiness and asthenia. At 1,000 ppm, they excreted acetone at 160 mg/L in urine. By the morning after exposure, they excreted acetone at 10 mg/L. These investigators, reporting from the Workers Clinic in Milan, recommended 500 ppm as a maximal exposure concentration for workers (8 h/d). Under these circumstances, 1,000 ppm would be tenable as an EEL for 24 h.

If 1.34 mg/L in urine equals 1.00 mg/L in blood (from Haggard et al., 1944), then 160 mg/L in urine equals 119 mg/L in blood at 1,000 ppm in air (3-h exposure), and 2,807 ppm in air equals 334 mg/L in blood (upper limit of Haggard et al., 3 h.), and 8,421 ppm equals 334

mg/L in blood (1 h). Thus, the data of both Haggard et al. (1944) and Vigliani and Zurlo (1955) suggest a concentration of about 8,500 ppm as a 1-h EEL for moderately active men.

The data of Vigliani and Zurlo (1955) also support a figure of 200 ppm for a 90-d CEL as do those of Nelson et al. (1943). Additional support for this concentration is provided by the data of Raleigh and McGee (1972) on repeated exposures to acetone in the work place.

To summarize, the Committee currently recommends the following:

60-min	EEL:	8,500 ppm
24-h	EEL:	1,000 ppm
90-d	CEL:	200 ppm

RESEARCH RECOMMENDATIONS

Because of the wide use of acetone (1.9 billion pounds in 1973), it is suggested that information on the following subjects be obtained:

Cataract formation: The marked ability of acetone to produce cataracts in the guinea pig suggests that chronically exposed workers be examined to determine whether man is similarly affected.

Chronic health effects in workers: Available data are insufficient for determining chronic health effects in workers.

Reproduction: Information on reproductive effects of acetone in animals and man is incomplete.

Skin effects: Acetone is a cutaneous irritant. Data are required to determine methods for avoiding exposures that lead to dermatitis.

TABLE 2

Effects on Humans of Uncontrolled Exposure to Acetone

No.[a]	Age, yr[a]	Sex[a]	Agents[a]	Concentration[a]	Duration[a]	Clinical Effects	Pathology[a]	Ref.
1	12	ND	Damp acetone dressing	ND	ND	Death	ND	Cossmann (1903), as quoted by Lehmann and Flury (1943)
2	18, 19	F	Acetone vapor and MEK[b] vapor	330-500 ppm (acetone), 400-500 ppm (MEK)	1 d	Gastric distress and fainting in 1 worker, fainting and seizure in 1 worker	ND	Smith and Mayers (1944), as quoted by Walter et al. (1975)
ND	ND	ND	Acetone[c]	1,000 ppm	3 h/d for 7-15 yr	Chronic inflammation of respiratory tract, stomach, and duodenum; occasional attacks	At end of shift, acetone exhaled at 0.2 mg/L of air and present in urine at 160 mg/L; next morning, acetone exhaled at 0.3 ng/L and in urine at 10 mg/L.	Vigliani and Zurlo (1955)

TABLE 2 (cont'd)

No.[a]	Age, yr[a]	Sex[a]	Agents[a]	Concentration[a]	Duration[a]	Clinical Effects	Pathology[a]	Ref.
4	30-57	M	Acetone vapor	12,000 ppm	4-5 h	Weakness of extremities, headache, eye irritation, light-headedness, feelings of drunkenness and vertigo	Acetone in 2 workers' urine at 2.4 mg/100 ml 45 min after immobilization; in other 2 workers' urine at 0.5-1.3 mg/100 ml up to 7 d after exposure	Ross (1973) as quoted by Walter et al. (1975)
1	48	M	Commercial organic solvent containing benzene, methanol, and acetone	ND	2.3 h	Death	Epiglottic hyperemia, abundant pulmonary edema, negative results in tissues analyzed for common toxicants	Winek et al. (1973)
9 4	ND	M	Acetone vapor exposure of filter press operators	1,006 ppm (average)	6 h/d for 2-3 yr	Slight eye, nose and throat irritation at 1,000-1,500 ppm	No remarkable findings	Raleigh and McGee (1972)

TABLE 2 (cont'd)

No.[a]	Age, yr[a]	Sex[a]	Agents[a]	Concentration[a]	Duration[a]	Clinical Effects	Pathology[a]	Ref.
8	30-57	M	Acetone vapor	12,000 ppm (TLV, 1,000)	0.5 d	Irritation of mucous membranes of eyes, nose, and throat; nausea and vomiting	Acetone in urine at 4-7 mg/100 ml at initial consultation, at 0.39-1.29 mg/100 ml 7 d after exposure	Ross (1975)
1	41	M	Acetone vapor	ND	3 mo; 40% of time was spent fitting polyvinyl chloride piping (cleaned with acetone and other solvents)	Hyposmia and parosmia associated with solvent exposure; otherwise, normal results of physical examination	Inability to identify standard solutions by smell; improved after exposure ended	Emmett (1976)
4	ND	F(2), M(2)	Acetone vapor and liquid	ND	Acute	Death	Lesions of the parenchymal organs, e.g., liver and kidneys	Mirchev (1978)

[a]ND = no data available.
[b]MEK = methyl ethyl ketone.
[c]Might not have been "pure" exposure.

TABLE 3

Effects on Humans of Controlled Exposure to Acetone

No.[a]	Age, yr[a]	Sex[a]	Agents	Concentration	Duration	Clinical Effects[a]	Pathology	Ref.
6	ND	M	Acetone	1 ml applied to the forearm surface	90 min	ND	Mild cutaneous edema and hyperemia with moderate layer disorganization; electron microscope showed disrupted desmosomes and keratin, vacuolization, and organelle changes; cell damage primarily in the stratum corneum and stratum spinosum	Lupulescu et al., 1973, as quoted by Walter et al. (1975)
24	18-28	M	Acetone gas	250-270 ppm, 500-750 ppm	6 h, with 1 h free from exposure after the first 3 h (2 d)[b]	Period of heartbeat in 500 ppm group shortened, that in control group (no exposure) lengthened	Galvanic skin reflex decreased in exposed groups; cerebral activities higher in exposed groups than control group	Suzuki (1973)

TABLE 3 (cont'd)

No.[a]	Age, yr[a]	Sex[a]	Agents	Concentration	Duration	Clinical Effects[a]	Pathology	Ref.
10	18-25	M, F	Acetone vapor	127-131 ppm	4 h	ND	Acetone concentration in expired air decreased slowly after cessation of exposure; much retained acetone eliminated through lungs as unchanged solvent; mean retention of acetone after 2-h exposure 17.6 ± 5.1% in men, 11.3 ± 5.4% in women; acetone uptake higher in men than in women; respiratory excretion, 16.3 ± 2.8%	Nomiyama and Nomiyama (1974 a, b)
ND	ND	ND	Acetone (percutaneous absorption)	Topical application to 12.5 cm^2 of skin	2 h/d for 4 consecutive days, 4 h/d for 4 consecutive days	Fairly rapid skin penetration of acetone; concentration of acetone in blood, alveolar air, and urine decreased rapidly to normal value by next morning	2 h/d: acetone in blood, alveolar air, and urine at 5-12 µg/ml, 5-12 ppm, and 8-14 µg/ml, respectively; 4 h/d: acetone in blood, alveolar air, and urine at 26-44 µg/ml, 25-34 ppm, and 29-41 µg/ml[b]	Fukabori et al. (1979)

[a]ND = no data available.
[b]2-h application to 12.5 cm^2 of skin corresponds to about 2-h exposure at 50-150 ppm in air.

TABLE 4

Effects on Animals of Exposure to Acetone

Compound Purity[a]	Species, Strain, Sex, Number[a]	Route of Administration	Dose[a]	Duration[a,b]	Effects	Reference
"pure, undiluted"	Rat, rabbit, dog; ND ND; 35 rats, 14 rabbits, 8 dogs	Intravenous (also by stomach tube in rabbits)	Rats 4,000-8,700 mg/kg; rabbits 790-7900 mg/kg; dogs, ND	Effects usually noted immediately	Maximal tolerated dose for rats was 4,000 mg/kg; and minimal lethal dose, 5,000 mg/kg or more; 2 rabbits given 3,950 mg/kg intravenously died at end of 50-85 sec injection period; injection into anesthetized dogs decreased blood pressure	Walton et al., (1928) as quoted by Walter et al. (1975)
ND	Rabbit, ND, ND, ND	Inhalation	ND	ND	Loss in weight, in some cases to 1/3 original; symptoms of intoxication included irritation, CNS disturbances, decreases in RBC and Hb, and increases in urobilin	Bassi and Ghezzi (1936) as quoted in Chemical Abstracts (1937).
ND	Guinea pig, ND, F, 10	Inhalation	20,000 ppm	24.4 h	8 of 10 animals died during or soon after exposure ended; by 865 min after exposure, 10 animals were comatose; gradual but regular slowing in heart rate	Specht et al. (1939) Specht et al. (1940) as quoted by Walter et al. (1975)

TABLE 4 (cont'd)

Compound Purity[a]	Species, Strain, Sex, Number[a]	Route of Administration	Dose[a]	Duration[a,b]	Effects	Reference
ND	Rat, ND, ND, ND	Inhalation	2,110-126,000 ppm	ND	At 42,000 ppm, death in 4.5-5.5 h; at 84,000 ppm, in 2.5-3 h; at 126,000 ppm, in 1.75-2.25 h	Haggard et al. (1944) as quoted by Walter et al. (1975)
ND	Rabbit, albino, ND, ND	Topical application to eyes	0.005 ml	1 min	Corneal injury covering 3/4 of eye surface or more severe damage covering smaller area	Carpenter and Smyth (1946) as quoted by Walter et al. (1975)
ND	Rabbit, ND M + F, 4 each	Intracranial injection	700 mg/kg	4-6 times on alternate days	Convulsions followed each injection within 5-15 sec; examination of ether-extracted brains suggested that acetone directly or indirectly caused brain fat dissolution, leading to demyelination and other insulation defects	Anderson (1949) as quoted by Walter et al. (1975)
ND	Rat, ND, M + F, 10	Oral	490 mg/kg	ND	Isonicotinic acid hydrazide-induced convulsions and maximal electroshock seizures completely inhibited; against electroshock seizures, acetone ED_{50} was 220 mg/kg, TD_{50} was 2,450 mg/kg, and the LD_{50} was 3,460 mg/kg	Kohli et al. (1967) as quoted by Walter et al. (1975)

TABLE 4 (cont'd)

Compound Purity[a]	Species, Strain, Sex, Number[a]	Route of Administration	Dose[a]	Duration[a,b]	Effects	Reference
ND	Rat, Sprague-Dawley, M, 6-12	Oral	ND	ND	Ataxia, dyspnea, and cyanosis at 3,950 mg/kg in young adults; maximal permissible limit for single oral exposure is approx. 4.0 mg/kg for rats	Kimura et al. (1971) as quoted by Walter et al. (1975)
ND	Guinea pig, random-bred, albino, M + F, 28	Topical application onto clipped skin of dorsal thorax or subcutaneously (0.05 ml 1:1 acetone/saline or 0.05 ml 5% acetone in saline)	1 ml 2 times/d	5 d/wk for 4 or 8 wk; controls received saline in an identical manner or nothing (exposure acute and subchronic)	Cataracts in 9 of 28 guinea pigs over a period of 3-8 wk; lens changes began as early as 8 wk and as late as 6 mo and consisted of subcapsular foci or extensive vacuolated areas extending from periphery toward lens center; histologic appearance of lenses similar to that of senile cataracts and some forms of diabetic cataracts	Rengstorff et al. (1971)
Acetone vapor, obtained by passing air through pure acetone at 0°C	Dog, mongrel M + F, ND, (12-26 kg)	Inhalation	0.36-0.80 µg/ml	ND (type of exposure unknown)	Uptake of acetone by total respiratory tract 65-70%	Egle (1973)
Acetone as 25% solution in water	Rat, Sprague-Dawley, M, ND, (180-235 g)	Oral	2.5 mg/kg	0-40 h elapsed between exposure and sacrifice (type of exposure unknown)	Pretreatment with acetone increased hepatic microsomal activity, as shown by increased capacity to bind $^{14}CCl_4$ and $^{14}CHCl_3$ covalently and to N-demethylate DMN.	Sipes et al. (1973)

TABLE 4 (cont'd)

Compound Purity[a]	Species, Strain, Sex, Number[a]	Route of Administration	Dose[a]	Duration[a,b]	Effects	Reference
ND (probably absolute acetone)	Rabbit, New Zealand White, M + F, 20 (10 test, 10 control)	Application directly onto skin of dorsal thorax	1 ml	3 times/wk for 3 wk (controls received saline in an identical manner)	None developed lens abnormalities during 6 mo observation period	Rengstorff et al. (1974)
Insecticides in acetone solution	Mice, ND, F, ND	Dermal and oral	0.1 ml dermally in acetone at 1 mg/kg	Sacrificed 5, 15, 30, and 60 min; 8 and 48 h after application	Penetration of acetone twice as rapid through the GI tract as dermally	Ahdaya et al. (1978)
Diterpene esters in acetone solution	Mice, albino LACA, F, 6	Topical administration to inner surface of one ear (other ear used as control)	5 l of various dilutions	Observation periods of 30 min-24 h	Persistent inflammatory changes	Evans and Schmidt (1979)

TABLE 4 (cont'd)

Compound Purity[a]	Species, Strain, Sex, Number[a]	Route of Administration	Dose[a]	Duration[a,b]	Effects	Reference
ND	Rat, Sprague-Dawley, M, ND	Inhalation	12,600 - 50,600 ppm	3 h/d 5 d/wk for 8 wk (exposure subchronic)	No residual toxic effects, according to biochemical assays and histopathologic examination of of sacrified specimens	Bruckner and Peterson (1978)
ND	Rat, ND ND, ND	Inhalation	1.657 kg/m^3	90 d (exposure chronic)	Disordered antagonist muscle activity and decreased serum cholinesterase activity and urinary coproporphyrin levels	Osintseva et al. (1967)

[a]ND = no data available.
[b]Type of exposure acute, unless otherwise noted.

TABLE 5

Occupational Exposure Limits for Acetone

Country	Concentration,[a] mg/m^3	Year	Ref.
United States	2,400 (TWA)	1974	Winell, 1975
East Germany	2,400 (TWA)	1974	Winell, 1975
West Germany	1,000 (TWA)	1973	Winell, 1975
Sweden	1,200 (TWA)	1975	Winell, 1975
Czechoslovakia	800 (TWA)	1969	Winell, 1975
USSR	200 (C)	1972	Winell, 1975
Italy	1,000 (TWA)	1975	Soc. Ital. Di Med. Del Lav., 1975
Japan	1,200 mg/m^3 (TWA)	1964	Japan Assoc. Ind. Hlth., 1971

[a]TWA = time-weighted average concentration; C = ceiling concentration.

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ACROLEIN

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Structural formula:	CH_2CHCHO
Molecular weight:	56
Chemical name:	2-Propenal
Synonyms:	Acrylic aldehyde
CAS number:	107-02-08
Boiling point:	52.7°C
Melting point:	-87°C
General characteristics:	It is a pungent, volatile, flammable liquid
Conversion factors:	ppm = 0.43 (mg/m^3) mg/m^3 = 2.35 (ppm)

OCCURRENCE AND USE

Acrolein is used as a warning agent in methyl chloride refrigerant and (as Papite) was used as a lacrimatory agent in World War I (Grant, 1974). It is also used as an intermediate in the preparation of resins and pharmaceuticals and in organic syntheses. It has had some use as an aquatic herbicide. It is prepared industrially by passing glycerol vapors over magnesium sulfate heated to 330-340°C (Windholz et al., 1976). Acrolein is considered a potential submarine contaminant and atmospheric pollutant. Urban air is said to contain acrolein at an average concentration of 0.006 ppm (Community Air Quality Committee, 1968).

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Early studies on acrolein examined effects of short-term exposures, from 5 sec to 5 min. In one study, Yant et al. (1930) subjected seven human volunteers to acrolein at 1 ppm. Slight nasal irritation was experienced within 1 min, and moderate nasal irritation and intolerable eye irritation with lacrimation within 5 min. According to a table published by the Shell Chemical Corporation, (1958), acrolein at 0.25 ppm produced moderate irritation of sensory organs in humans (number of subjects unstated). Darley et al. (1960) exposed human volunteers to acrolein for 5 min; 0.6 ppm caused slight eye irritation, 1.3-1.6 ppm caused mild irritation, and 2-2.3 ppm produced severe irritation. Sim and Pattle (1957) reported that a 10-min exposure at 8 ppm and a 5-min exposure at 1.2 ppm elicited extreme irritation in humans and described the response as "only just tolerable." A series of studies conducted by Stephens et al. (1961) revealed that acrolein exposure at 0.5 ppm produced eye irritation within 5 min in 10-35% of subjects and within 12 min in 91% of subjects.

Weber-Tschopp et al. (1977) reported the acute effects of acrolein on human volunteers. Groups of healthy subjects were exposed to acrolein at 0-0.6 ppm under the following three sets of experimental conditions:

Group I. 53 subjects (31 males and 22 females), 40 min at continuously increasing concentration.

Group II. 42 subjects (17 males and 25 females), four 1.5 min exposures at various concentrations.

Group III. 46 subjects (21 males and 25 females), 60 min at constant at 0.3 ppm.

Irritation, discomfort, and eye blinking rate were measured during exposures; all increased with increasing acrolein concentration and duration of exposure. Respiratory frequency was also measured. For deriving 1-h EELs, the data derived from Group III are most appropriate. Those subjects experienced discomfort during the first 20-30 min, but the intensity of discomfort did not increase thereafter. Irritation of the throat was significant at 10 min. Acute (subjective) irritation was reported as "considerable" after 10-20 min at 0.3 ppm. In this same group, respiratory frequency decreased during the course of the experiment, and a 10% decrease in frequency was observed in 60% of exposed subjects within 20 min. A summary of the effects of continuous exposure at 0.3 ppm (Group III) is presented in Table 6.

EFFECTS ON ANIMALS

The most extensive animal study of acrolein toxicity available is that reported by Lyon et al. (1970). The study featured both repeated and continuous exposures to acrolein under conditions relevant to the establishment of 90-d CELs for humans. There are other recently reported animal data which are reviewed here. These studies do not provide data useful for establishing CELs, but they do afford some insight into the mode of action of acrolein and suggest a possible treatment for intoxication.

Murphy et al. (1963) observed a significant decrease in respiratory frequency and a significant increase in total respiratory flow resistance and tidal volume in guinea pigs after exposure to acrolein at 0.4-1.0 ppm for 2 h. The authors postulated that acrolein primarily increases the respiratory resistance and that, as a compensatory mechanism, the tidal volume increases and the respiratory frequency decreases. The change in respiratory resistance was said to be caused by bronchoconstriction, inasmuch as this change was eliminated by treatment with bronchodilating substances, such as atropine and epinephrine.

Davis et al. (1967) observed an increase in respiratory resistance and tidal volume in guinea pigs after exposure at 17 ppm for 60 min. Decreases in respiratory frequency and minute volume and prolongation of the expiration cycle were also noted. The authors presumed that the receptors were stimulated by an irritant to trigger a reflex-like

safety mechanism in the upper respiratory tracts, which decreased further inhalation of the irritant by prolonging expiration, lowering respiratory frequency, and decreasing minute volume. The decrease in respiratory frequency and the increased expiration cycle, which Weber-Tschopp et al. (1977) noted in humans exposed to acrolein, indicated a close similarity between humans and guinea pigs with regard to the effects of this substance on respiratory function. Because of this, Weber-Tschopp et al. (1977) proposed that acrolein may cause bronchoconstriction in humans at the concentration at which the respiratory effects were recorded (0.3 ppm).

In 1970, Philippin et al. reported the results of a study of the effects of acute (6 h) and extended (6 h/d for 2 wk) exposures of mice to acrolein. These investigators examined effects on swimming performance and body weight and analyzed the lungs histologically. The acute LC_{50} was 66 ppm. In extended exposure, 6 ppm produced significant reductions in body weight; histologic examination of the lungs revealed atelectasis, inflammatory responses with edema and, in 2 of 15 cases, dilatation of alveoli and bronchioles.

Sinkuvene (1970) studied the effects of continuous acrolein exposure on albino rats. The experiments were performed on 80 male rats divided into four groups. Each group consisted of 10 healthy animals and 10 with chronic pulmonary insufficiency (experimental silicosis). One group served as a control and the others were exposed to acrolein at about 0.3, 0.056, and 0.011 ppm for 16 d. At the highest concentration, weight gain was significantly reduced by the sixth week in the healthy animals and by the fifth week in the animals with silicosis; there was a change in the chronaxy of antagonistic muscles in both healthy and silicotic animals and a sharp change (not specified) in blood cholinesterase activity. The author reported that "changes" were observed in the healthy animals at 0.056 ppm, but did not specify them; the "silicotic" animals displayed statistically significant changes in the chronaxy of antagonistic muscles and in vitamin C content. After 61 d at 0.011 ppm, no effects were observed in either healthy or silicotic animals; this result is in accord with that projected from the data of Lyon et al. (1970), as described below.

The most telling animal data are those from the work of Lyon et al. (1970), which included both repeated and continuous exposures. Rats, guinea pigs, monkeys, and dogs were exposed to acrolein repeatedly at 0.7 or 3.7 ppm 8 h/d, 5 d/wk, for 6 wk or continuously at 0.21, 0.43, 1.0, or 1.8 ppm 24 h/d for 90 d. The results were as follows:

0.7 ppm (repeated exposure): There were no deaths, and all animals appeared normal throughout. All animals gained weight normally throughout. Lung sections from all animals showed chronic inflammatory changes and occasional emphysema (more prominent in dogs and monkeys).

3.7 ppm (repeated exposure): During the first week, dogs and monkeys salivated excessively, blinked frequently, and kept their eyes closed. Dogs had ocular discharge and breathed with difficulty. During the next 4 wk, dogs continued to experience eye irritation. Two of 9 monkeys died (on days 6 and 9) and had

pulmonary and hepatic lesions. Test animals (especially rats) gained weight more slowly. There were nonspecific inflammatory changes in lung, liver, and kidney. Squamous metaplasia of the trachea occurred in dogs and monkeys. There was necrotizing bronchitis with squamous metaplasia of the lungs in 7 of 9 monkeys.

0.21 and 0.23 ppm (continuous exposure): All animals appeared normal throughout, except one monkey that developed infection over one eye in the fifth week and died in the sixth week. Sections from 2 of 4 dogs showed moderate emphysema, acute congestion, and hemorrhage; the other 2 showed thyroid hyperplasia. Weight gain was normal in all animals. Monkeys, dogs, and guinea pigs had nonspecific inflammatory changes in liver, lungs, kidneys, and heart.

1.0 ppm (continuous exposure): Dogs and monkeys were visibly affected from the start and had ocular and nasal discharge throughout. Monkeys kept their eyes closed for extended periods. One died on day 28, probably from infection caused by a bite on the shoulder. Weight gains were normal, except in rats. Guinea pigs and rats showed pulmonary inflammation and occasional liver necrosis.

1.8 ppm (continuous exposure): There were no deaths, although monkeys and dogs were severely irritated. There were nonspecific inflammatory changes in brain, heart, lungs, and kidneys of all animals. All the monkeys had squamous metaplasia and 6 of 9 had basal cell hyperplasia of the trachea. The dogs had confluent bronchial pneumonia.

INHALATION EXPOSURE LIMITS

In 1976, the Committee on Threshold Limit Values of the ACGIH established a TLV of 0.1 ppm; this limit was considered sufficiently low to minimize, but not entirely prevent, irritation in all exposed persons. This information and a 0.1-ppm TLV for acrolein were in the 1980 documentation (ACGIH, 1980).

COMMITTEE RECOMMENDATIONS

EXPOSURE LIMITS

In 1969, the Committee on Toxicology made the following tentative recommendations for EELs and CEL for acrolein:

1-h EEL:	0.2 ppm
24-h EEL:	0.1 ppm
90-d CEL:	0.1 ppm

The Committee considered the limiting factor for acrolein to be irritation of the eyes and respiratory tract. The data on which these recommendations were based were somewhat limited, and the Committee considered it desirable that additional long-term exposure data be obtained on guinea pigs, primates, and human volunteers.

The animal data available when the Committee on Toxicology made its tentative recommendations were derived from short-term, high-concentration exposures, and it appears that they were not considered useful for purposes of recommending EELs or CELs.

On the basis of the human data given earlier, which represent the most extensive human experience available, the Committee's previous tentative recommendation of a 0.2 ppm limit for a 1-h exposure is insufficiently protective. Discomfort, irritation, and respiratory effects were observed at 0.09-0.3 ppm in exposures well short of 1 h. It is not possible to assign, on the basis of these data, a definitive EEL for acrolein, and another tentative recommendation seems appropriate, considering the lack of data for 1-h exposures to lower concentrations of acrolein. Such data are necessary for more definitive exposure limits to be derived. The Committee suggests that an EEL of 0.05 ppm for a 1-h exposure may be sufficient to protect most people from anything except discomfort, although irritation and decreased respiratory frequency will probably still occur in some.

No human data are available that can be used directly to assign an EEL for a 24-h exposure. The Committee proposes that a 5-fold margin of safety be applied to compensate for the absence of information regarding the effects of 24-h exposures and tentatively recommends a value of 0.01 ppm for 24-h exposures to acrolein.

Human data are now available to permit a recommendation regarding a 10-min EEL. None of the effects reported by Weber-Tschopp et al. (1977) at 0.3 ppm for 10-min appears to be incapacitating; however, some effects such as decrease in respiratory frequency occurred in more than 47% of exposed people (see Table 5). In contrast, exposure to 0.09 ppm resulted in only discomfort and eye irritation; for this reason, it appears that 0.1 ppm for a 10-min period should adequately satisfy the requirements of an EEL. This recommendation is consistent with the other short-term human exposure data cited above.

The studies of repeated and continuous exposures of experimental animals to acrolein conducted by Lyon et al. (1970) appear to be the most extensive of their type available. For most of the effects measured, dogs and monkeys are more sensitive to exposure than rodents. Assuming that humans are as sensitive as dogs and monkeys, it appears that the earlier tentative recommendation of 0.1 ppm for continuous 90-d exposure to acrolein provides little, if any, margin of safety. Downward adjustment by a factor of 10 is recommended. This leads to 0.01 ppm, which is in agreement with the community air-quality guide recommended by the Community Air Quality Committee (1968) for 90-d continuous exposures.

To summarize, the following EELs and CEL are suggested:

10-min EEL:	0.1 ppm
60-min EEL:	0.05 ppm (tentative)
24-h EEL:	0.01 ppm (tentative)
90-d CEL:	0.01 ppm

TABLE 6

Percentage of Human Subjects Affected by Exposure to Acrolein at 0.3 ppm (Weber-Tschopp et al., 1977).[a]

Effect	Percentage of Subjects Affected At 10 min	At 20 min
Desire to leave room	50	72
Medium eye irritation	18	35
Strong to very strong eye irritation	3	18
Medium nose irritation	7	19
Strong to very strong nose irritation	1	4
Medium throat irritation	1	2
Strong to very strong throat irritation	0	1
Doubling of eye blinking rate	66	70
Decrease in respiratory frequency by 10%	47	60

[a]In other subjects in same study, average threshold concentration of acrolein for irritation was 0.09-0.30 ppm.

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ARSINE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES:

Structural formula:	AsH_3
Molecular weight:	77.9
Synonyms:	Hydrogen arsenide, arsenuretted hydrogen
CAS number:	7784-42-1
Physical state:	Colorless gas
Melting point:	-116.3°C
Boiling point:	-55°C
Density:	2.69 (air = 1)
Odor threshold:	1-10 ppm (garlic-like odor)
Conversion factors:	ppm = 0.31 (mg/m^3) mg/m^3 = 3.23 (ppm)

OCCURRENCE AND USE

Arsine is not used industrially, but is formed whenever nascent (freshly formed) hydrogen comes into contact with a solution that contains inorganic arsenic (Sittig, 1979). Exposure to arsine gas may result from the action of acids on metals that contain arsenic or from the use of impure sulfuric or hydrochloric acid that contains arsenic (Patty, 1963).

SUMMARY OF TOXICITY INFORMATION

Arsine is the most acutely toxic form of arsenic. Its lethal capacity by inhalation suggested its use as a chemical-warfare agent (Gates et al., 1946). Its toxic manifestations are methemoglobinemia and hemolysis. Secondary effects resulting from hemolysis include renal and hepatic damage, hemoglobinuria, anuria, anoxia, jaundice, and hemolytic anemia. Results of acute toxicity studies are summarized in Tables 7 and 8. Little information on subchronic toxicity is available. Guinea pigs exposed to arsine at 0.5-2.0 ppm 1-3 h/d for up to 144 h showed evidence of decreases in red and white blood cell counts and hemoglobin concentration (Nau et al., 1944); there was also some evidence of peripheral nerve damage.

There have been numerous cases of accidental arsine poisoning (mostly acute) in man; little information is available on the arsine concentrations involved. Arsine concentrations thought to produce physiologic effects in man are shown in Table 9. ACGIH has established a TLV of 0.05 ppm for occupational exposure. Similar values have been established in other countries (Table 10). Gates et al. (1946) estimated minimal disabling exposure to arsine for humans of 5.0 mg/L for 2 min and 0.2 mg/L for 30 min.

COMMITTEE RECOMMENDATIONS

EXPOSURE LIMITS

Previous EEL and CEL recommendations made by the Committee (1961 and 1966) for arsine exposure are as follows:

	Concentrations, ppm	
Duration	1961	1966
1 h	1.0	1.0
8 h	0.05	--
24 h	0.01	0.1
90 d	--	0.01

There is little additional information available for revising the 1966 recommendations and additional animal toxicity studies are necessary for the determination of an appropriate CEL. The Committee, thus, recommends that the 1-h and 24-h EELs be 1.0 and 0.1 ppm, respectively; these concentrations agree with the estimates provided by Gates et al. (1946) and Henderson and Haggard (1943). The Committee does not recommend a 90-d CEL because data are insufficient.

TABLE 7

LD_{50} of Arsine after
Intraperitoneal Injection (Levvy, 1946)

Species	LD_{50} mg/kg
Mouse	3.0
Rabbit	2.5
Cat	2.0-2.5
Sheep	3.0

TABLE 8

Acute Toxicity of Arsine in Mice After Inhalation
(Levvy, 1947)[a]

Concentration mg/L	Concentration ppm	Duration of Exposure	Mortality,[a] %	Estimated Duration for 50% Mortality
2.5	783	0.50 min	93	0.40 min
		0.33 min	20	
1.0	313	1.25 min	57	1.18 min
		0.83	13	
0.50	157	10 min	100	2.4 min
		5 min	93	
		2.5 min	57	
		1.7 min	0	
0.25	78.3	15 min	70	12 min
		9 min	33	
0.10	31.3	70 min	100	50 min
		50 min	50	
0.025	7.8	30 h	100	24 h
		27 h	50	
		24 h	50	
		21 h	50	
		18 h	0	
		15 h	0	

[a]Thirty mice in each experiment with arsine at 0.1 to 2.5 mg/L; six mice used in each experiment with arsine at 0.025 mg/L.

TABLE 9

Effects of Various Concentrations of Arsine on Humans
(Henderson and Haggard, 1943)

	Concentration, ppm
Maximum concentration allowable for prolonged exposure	1
Slight symptoms after exposure of several hours	3-10
Maximum concentration that can be inhaled for 1 hour without serious consequences	6-30
Dangerous after exposure of 30-60 minutes	16-60
Fatal after exposure of 30 minutes	250

TABLE 10

Occupational Exposure Limits for Arsine

Country	Year	MAC	Reference
United States	197	0.05 ppm (0.2 mg/m3)	Winnell, 1975
W. Germany	19	0.2 mg/m^3	"
E. Germany	197	0.2 mg/m^3	"
Sweden	1975	0.05 mg/m^3	"
Czechoslovakia	1969	0.2 mg/m^3	"
USSR	1972	0.3 mg/m^3 (ceiling value)	"
Italy	1975	0.1 mg/m^3	Soc. Ital. Med. Lav., 1975
Japan	1965	0.05 ppm (0.2 mg/m^3) (Avg. conc. for a working day)	Japan Assoc. Ind. Health, 1971

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CARBON DISULFIDE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES (Hildenskoild, 1959; Windholz et al., 1976; NIOSH, 1977; Seppalainen and Haltia, 1980)

Structural formula:	CS_2
Molecular weight:	76.14
Chemical names:	Carbon disulfide, CS_2; carbon bisulfide; dithiocarbonic anhydride
CAS number:	CAS No. 75-15-0
Freezing point:	-116°C
Boiling point:	46.5°C (at 1 atm)
Odor:	Odorless or sweet, ethereal (when pure), pungent (when impure)
Odor detection threshold:	0.02-0.08 ppm
Flash point, closed cup:	-30°C
Ignition temperature:	100°C
Explosive range:	1-50% in air
Vapor density:	2.67
Vapor pressure:	100 mm Hg at -0.5°C; 300 mm Hg at 17.8°C
Solubility in water:	0.294% at 20°C
Miscibility:	Miscible in methanol, ethanol, ether, benzene, chloroform, and oils
Reactions:	Reacts with mercapto, amino, and hydroxy groups.
Solubility coefficient:	Air to blood, 2.5; blood to tissues, 5.6.
Conversion factors:	ppm = 0.32 (mg/m^3) mg/m^3 = 3.13 (ppm)

OCCURRENCE AND USE

CS_2 is not a natural constituent of the environment and was discovered in the laboratory in 1796. Its narcotic effects were tested in 1848 and industrial use began in 1851. First used as a solvent for phosphorus in the manufacture of matches, CS_2 was later used as a solvent for fats, lacquers, and camphor; for refining paraffins and petroleum; for the extraction of natural oils, and, most extensively, for the vulcanization of rubber. Today, its most important use, occupational exposure, and injury potential occur in the production of viscose rayon fibers for textile applications and cellophane films for packaging. It is also used in pesticide production, in extraction of oils, and as a laboratory reagent (Seppalainen and Haltia, 1980). Approximately 782 million pounds were produced in the United States in 1974 (U.S. Dept. of Commerce, 1976). NIOSH (1977) estimated that 30,000 full-time U.S. employees were potentially exposed to CS_2. In 1965, the U.S. Coast Guard expressed interest to the Committee on Toxicology in short-term exposure limits in connection with transportation of molten sulfur and bulk transfer of CS_2.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Data on the effects of exposure to CS_2 are summarized in Table 11.

Uncontrolled Exposure

According to Bittersohl et al. (1972), exposure to CS_2 at 300 ppm produces slight symptoms of poisoning after several hours; at 400 ppm, it gives rise to prenarcotic symptoms; at 1,150 ppm for 30 min, it leads to severe forms of poisoning; and at 3,200-3,800 ppm, it is life-threatening. According to Paluch (1954), exposure at 2,000-3,300 ppm leads to narcosis in 30 min, and death occurs after 30-60 min of exposure at 5,000 ppm.

Acute psychosis was a common manifestation of CS_2 poisoning in rubber vulcanization plants until this process was discontinued at the end of the nineteenth century. During World War II, many cases of chronic poisoning, in which peripheral neuropathy was the leading complaint, occurred in the viscose rayon industry (Vigliani, 1954). There are several epidemiological reports of occupational disease after low-concentration, long-term exposure to CS_2 or a combination of CS_2 and hydrogen-sulfide (H_2S) (NIOSH, 1977).

Peripheral neuropathy, as revealed by lowering of maximal motor nerve conduction velocities (MCVs), was found in 118 workers (110 controls) exposed at 20-60 ppm for 1-27 yr; exposure was at less than 30 ppm during the last 12 yr (Seppalainen et al., 1972). Similarly, MCVs of peroneal nerves were lowered and abnormal electromyograms were prevalent in a study of 254 subjects (54 controls) exposed at 20-80 ppm for 2-31 yr, with exposure at less than 20 ppm during the last 3 yr (Gilioli et al., 1978). Another study (Knave et al., 1974) reported lowered MCVs in a group of 51 subjects (52 controls) exposed at less than 20 ppm for 1-30 yr.

CNS effects reported by Styblova (1977) consisted of abnormal electroencephalograms (EEGs) in 33.2% of 250 workers (compared with 6.6% of 61 controls) employed in the production of rayon staple. EEGs were abnormal in 39% of 54 subjects (compared with 12% in controls) exposed at 10-15 ppm for 10-15 yr (Seppalainen and Linoila, 1976).

Psychic effects of CS_2 have also been measured epidemiologically. Mancuso and Locke (1972) found an increased risk of suicide among 4,899 viscose rayon workers, and another study (Hanninen et al., 1978) of 206 workers (and 152 controls) found psychomotor disturbances and personality changes indicative of depression. Psychologic testing of 102 workers showed an impairment of intelligence functions and performance tests compared with those in controls (Cassitto et al., 1978).

The exact CS_2 concentration necessary to produce neurologic disease in humans is unknown, but Seppalainen and Haltia (1980) stated recently that no new cases had occurred among workers who started their work in the Finnish viscose rayon industry in the late 1960s or thereafter, when airborne CS_2 concentrations were mostly below 10 ppm and at times 10-20 ppm. However, mild cases of polyneuropathy appeared in a viscose film factory in Finland, where the mean exposure had remained about the same for 17 yr, and where the Finnish TLV of 10 ppm had frequently been

exceeded, although concentrations usually stayed below 20 ppm (Seppalainen and Haltia, 1980).

Tiller et al. (1968) found a 2.5-fold excess mortality from coronary heart disease among viscose rayon workers exposed to CS_2 for 10 yr or more. A prospective Finnish study (Hernberg et al., 1973) of 343 male viscose rayon workers exposed at 10-30 ppm found the 5-yr mortality from coronary heart disease was almost 5 times that in a comparison cohort (other causes of death were evenly distributed). Another study (Gavrilescu and Lilis, 1967) reported atherosclerosis and hypertension in workers exposed to CS_2 at concentrations as low as 7 ppm.

Teleky (1955) claimed on the basis of first-hand experience that reduction of corneal reflex was the first sign of toxic action in workers chronically exposed to CS_2 vapor.

Controlled Exposure

Mack et al. (1974) exposed men 21-40 yr old to CS_2 at 10, 20, 40, or 80 ppm for 6 h and at 20 ppm 6 h/d for 5 d, in a study of inhibition of drug metabolism. They noted that exposure at 10-20 ppm for 6 h could retard the normal metabolism of such common drugs as analgesics, hypnotics, antidiabetics, and anticonvulsants.

Clinical and Pathologic Effects

Cardiovascular effects similar to those seen in atherosclerosis have been ascribed to CS_2 exposure. Long-term exposure can produce vascular changes in the heart, eyes, brain and kidneys (NIOSH 1977). Hypertension, angina, abnormal plasma glucose and creatinine concentrations, and electrocardiographic changes have all been found.

Neurologic effects vary with the degree of exposure. Heavy (but not specified) occupational exposure, now a thing of the past, used to cause dramatic behavioral changes after weeks or months of exposure. Patients often were manic or depressed and could become so frenzied that the attacked their workmates and relatives, or committed suicide (Seppalainen and Haltia, 1980). Long-term, lower-level (20-170 ppm) exposure has been causally associated with toxic encephalopathy (pseudobulbar paralysis, mental deterioration, extrapyramidal signs), although signs and symptoms of peripheral neuropathy usually predominate. This begins within 4-6 mo of occupational exposure at 170 ppm or after several years at 65-100 ppm. Neuropathy predominantly affects the legs, causing difficulty in walking and absence of reflexes in severe cases, but not complete paralysis. Neuropathy also develops at lower concentrations (20-40 ppm) with symptoms of paresthesia, muscle pain, diminished muscle strength, and distal sensory loss. Both encephalopathy and neuropathy may worsen for 1-2 yr after occupational exposure stops, but partial recovery may then take place, or almost complete recovery if the damage has not been too severe (Seppalainen and Haltia, 1980).

Renal effects, such as nephrosclerosis, were seen in some autopsies of patients with CS_2 poisoning. Chronic renal dysfunction was also found among workers with 10 yr or more of exposure to CS_2 (Toyama and Sakurai, 1967). CS_2 exposure affects the eye by inducing vascular rigidity, slowed circulation, increased ophthalmic pressure, and retinal

microaneurysms (Goto and Hotta, 1967; Goto et al., 1971, 1972; Hotta et al., 1972; Maugeri et al., 1966; Raitta and Tolonen, 1975; Raitta et al., 1974; Savic, 1967; Szymankowa, 1968). Retinal degeneration and conjunctival inflammation were reported at concentrations below 3 ppm (Szymankowa, 1968), although methods used to determine the concentrations were not reported (NIOSH, 1977).

Reproductive effects, resulting in impaired sexual function (impotence and loss of libido), are frequent complaints in chronic poisoning. Androsterone and testosterone excretion are reduced (Delic et al., 1966; Delpech, 1856). Female viscose rayon workers reportedly may develop menstrual and ovarian dysfunction at concentrations of less than 3 ppm (Vasilyeva, 1973). Infertility, threatened pregnancy terminations, and spontaneous abortions have been reported, the latter at concentrations down to 9 ppm and below (Petrov, 1969). Other results of CS_2 exposure include respiratory effects (Ranelletti, 1933) and hepatic effects including liver enlargement in the presence of normal liver function. Gastrointestinal effects among heavily exposed workers, possibly due to changes in autonomic nervous system function, include epigastric pain, nausea, and dyspepsia (Seppalainen and Tolenen, 1974).

Skin and mucous membranes are severely irritated by CS_2.

EFFECTS ON ANIMALS

The neurotoxic effects of prolonged exposure to CS_2 recently have been summarized by Seppalaienen and Haltia (1980). Dogs exposed at 400 ppm 8h/d, 5 d/wk develop hindlimb weakness (from peripheral neuropathy) after 5-8 wk and forelimb weakness after 9 wk. Other signs of intoxication include ataxia, jerking, choreiform movements, loss of position sense, and behavioral changes (apprehension, excitation, and aggressiveness). Rabbits exposed at 750 ppm 6 h/d, 5 d/wk slowly lost weight after 4 wk and developed hindlimb difficulties after 7 wk. Rats exposed at 750 ppm 6 h/d, 5 d/wk exhibited motor impairment after 18 wk, and animals exposed at 770 ppm displayed similar signs after only 8 wk. During exposure, MCVs decrease in rats and rabbits before paresis is evident. When weakness is apparent in rabbits, paretic muscles display fibrillation potentials indicative of denervation. Pathologic studies using contemporary techniques show that a central-peripheral distal axonopathy underlies the polyneuropathy. The dominant feature in exposed animals is the appearance of giant axonal swellings filled with 10-nm neurofilaments multifocally in the distal parts of long spinal cord tracts and distally in long peripheral nerves. Distal nerve fiber breakdown follows the development of these swellings and results in motor and sensory denervation.

Other effects reported include vascular damage, reproductive changes, and fetal effects. Several experimental studies (Guarino and Arciello, 1954; Lewey, 1941; Petrov, 1969) have shown that CS_2 causes vascular changes in various organs. Testicular damage (few spermatogonia and degenerated Leydig cells) was found by Gondzik (1971) in rats given CS_2 at 12.5-25 mg/kg intraperitoneally in peanut oil. Embryotoxicity in rats exposed to CS_2 and H_2S at 3.2 ppm was reported by Bariliak and co-workers (1975). Bronchitis was found in rats exposed to as low as 0.3 ppm plus H_2S at 0.7 ppm (Misiakiewicz et al., 1972).

Effects on animals of exposure to CS_2 are summarized in Table 12.

PHARMACOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Respiratory absorption seems to be proportional to the concentration of CS_2 in the air (Demus, 1967). Previously nonexposed subjects breathing CS_2 at 17-30 ppm absorbed 80% in the first 15 min. After equilibrium is reached in about 1-2 h, 40-50% of the vapor is retained (Vigliani, 1961). CS_2 is also absorbed via the skin. Once absorbed, CS_2 is taken up twice as much in red blood cells as in plasma. About 70% is metabolized (Demus, 1967). CO_2 and CO have been identified as metabolites (Dalvi and Neal, 1978; DeMatteis and Seawright, 1973). In man, CS_2 disappears rapidly from the bloodstream and accumulates in lipid-rich tissues and organs.

Experimental studies have revealed initial distribution to the liver, with a more uniform distribution occurring later. Human studies have shown that 10-30% of CS_2 is exhaled and 1% eliminated in urine, leaving about 70-90% available for biotransformation. Three metabolites have been isolated from human urine, including the principal urinary CS_2 metabolite thiocarbamide (thiourea) and mercaptothioaxolinone (Pergal et al., 1972a, b).

Sites and Mechanisms of Toxicity

Several hypotheses have been developed to explain the toxic action of CS_2 (World Health Organization, 1979):

- Chelation by metabolites of various trace metals essential for enzyme function;
- Enzyme inhibition;
- Disturbance of vitamin metabolism, especially of B_6 and nicotinic acid;
- Disturbance of catecholamine metabolism; and
- Disturbance of lipid metabolism.

INHALATION EXPOSURE LIMITS

Exposure limits established for CS_2 in various countries (Japan Assoc. Ind. Health, 1971; Soc. Ital. Med. Lav., 1975; Winnell, 1975) are given below:

United States	1974	20 ppm (60 mg/m^3) (TWA)
W. Germany	1974	60 mg/m^3 (TWA)
E. Germany	1973	50 mg/m^3 (TWA)
Sweden	1975	30 mg/m^3 (TWA)
Czechoslovakia	1969	30 mg/m^3 (TWA)
USSR	1972	10 mg/m^3 (ceiling)
Italy	1975	30 mg/m^3 (TWA)
Japan	1961	60 mg/m^3 (TWA)

COMMITTEE RECOMMENDATIONS

EXPOSURE LIMITS

In 1965, the Committee recommended the follwing EELs for CS_2:

10-min EEL:	200 ppm
30-min EEL:	100 ppm
60-min EEL:	50 ppm

The most thoroughly documented effects--neurologic and cardiovascular disease--develop after prolonged exposure to CS_2 at a minimum concentration of 10 ppm (and an unknown concentration of H_2S, which commmonly coexists with CS_2). Exposure at similar concentrations over a period of years has given rise to reproductive disorders, embryotoxicity, and spontaneous abortions. Retinal changes and menstrual and ovarian dysfunction reportedly occur at concentrations of less than 3 ppm (Szymankowa, 1968; Vasilyeva, 1973), although sampling and analytical methods were poorly documented and control groups were sometimes lacking in these studies.

The Committee is unaware of any report on carcinogenesis or mutagenesis resulting from exposure to CS_2. One study (Bariliak et al, 1975), which NIOSH (1977) considered "tentative," reported a "weak teratogenic effect" in rats after low-concentration exposure (3.2 ppm) to a combination of CS_2 and H_2S.

An English translation of work by Bittersohl et al. (1972) stated that CS_2 induces minor symptoms after several hours of exposure at 300 ppm, with distinct signs of poisoning at 400 ppm and severe poisoning after 0.5 h at 1,150 ppm. There is therefore no basis for changing the emergency exposure limits (EELs) previously established by the Committee in 1965. Therefore, the following EELs are recommended:

10-min EEL:	200 ppm
30-min EEL:	100 ppm
60-min EEL:	50 ppm

RESEARCH RECOMMENDATIONS

Short-term toxicity studies on animals may be useful in ascertaining how concentration and time are related over short periods (up to 24 h). It is suggested that dose-response studies in animals be conducted.

If there is a concern over long-term exposure, experimental animal studies are needed to determine whether such exposure to airborne CS_2 at low concentrations causes damage to the nervous system (including the retina) and the reproductive, cardiovascular, and renal systems.

TABLE 11

Effects of Occupational Exposure to Carbon Disulfide plus Hydrogen Sulfide[a]

Workers		Concentration, mg/m³[b]		Duration: Mean or Range,		
No.	Age Mean or Range, yr	CS_2	H_2S	yr	Effects	Reference
100	-	450-1,000	--	--	Polyneuritis in 88%; gastric disturbances in 28%	Vigliani, 1954
43	53	30-1,500	--	21	Encephalopathy	"
107	32	200-400	--	1-9	Ophthalmic pressure 138/110, vs. 115/87 in controls	Maugeri et al., 1966
185	25-35	62-174	--	5	Eye burning in 96% of rayon-production workers, 44% of cell-fiber workers; pupillary light reaction abnormal in cell-fiber workers	Savic, 1967
100	39	31-137	--	10	Psychomotor and psychologic disturbances	Hanninen, 1971
125	47	124	--	13	Coronary heart disease in 5.6%, vs. 1.2% in controls	Cirla et al., 1972
33	22	40-81	--	2	Asthenospermia, hypospermia, teratospermia	Lancranjan et al., 1969
116	50	62	--	5	Coronary heart disease in 16.5%, vs. 2.7% in controls	Locati et al., 1970
28	44	62	--	13	Coronary heart disease in 3.6%, vs. 1.2% in controls	Cirla et al., 1972
38	51	29-118[c]	--	20	Ocular vascular rigidity	Raitta and Tolonen, 1975
100	48	29-118[c]	--	15	Ophthalmic circulation slowed	Raitta et al., 1974

TABLE 11 (cont'd)

Effects of Occupational Exposure to Carbon DIsulfide plus Hydrogen Sulfide[a]

Workers: No.	Workers: Age Mean or Range, yr	Concentration, mg/m³[b]: CS_2	Concentration, mg/m³[b]: H_2S	Duration: Mean or Range, yr	Effects	Reference
36	42	29-118[c]	--	6	Peripheral nerve and CNS damage; conduction velocites lowered; EMG abnormal	Seppalainen et al., 1972
397	35-64	29-118[c]	--	--	Coronary heart disease cause of 42% of deaths in highly exposed workers, 24% in moderately exposed, 14% nationally	Tiller et al., 1968
630	20-40	13-50	--	--	Immunologic reactions decreased; job absenteeism increased	Kashin, 1965
138	50	22-44	--	10	Arteriosclerotic changes in 30.4%; hypertension in 23.2%	Gavrilescu and Lilis, 1967
94	18	12-31	10	1	Hypotension, nervous system excitability	Kramarenko et al., 1970
189	30	28	-	3	Spontaneous abortions in 14.3%, vs. 6.8% in controls; premature births in 8.6%, vs. 2.8% in controls	Petrov, 1969

TABLE 11 (cont'd)

Effects of Occupational Exposure to Carbon Disulfide plus Hydrogen Sulfide[a]

Workers		Concentration, mg/m³[b]		Duration: Mean or Range,		
No.	Age Mean or Range, yr	CS_2	H_2S	yr	Effects	Reference
209	20-40	22	10	--	Menstruation irregular, painful, abundant, prolonged	Vasilyeva, 1973
60	25	16	--	--	Muscular power diminished; reflexes slowed	Vasilyeva, 1973
500	18-60	9	--	1-30	Retinal degeneration, conjunctival inflammation, temporary corneal opacities, color-vision disturbances	Szymankova, 1968
500	20-40	-	10	--	Menstruation abundant, painful, prolonged	Vasilyeva, 1973
94	18	3-9	10	1	Hypotension; nervous system excitability	Kramarenko et al., 1970

[a]Adapted from NIOSH (1977).

[b]1 mg/m³ = 0.321 ppm.

[c]These studies based on same cohort of workers, exposed to carbon disulfide plus hydrogen sulfide at concentrations averaging 29-88 mg/m³ in 1960, 59-118 mg/m³ in 1950, and higher before 1950. Hydrogen sulfide concentration included in that given for carbon disulfide and estimated to be about 10% of total.

TABLE 12

Effects on Animals of Exposure to Carbon Disulfide or to Carbon Disulfide Plus Hydrogen Sulfide

Species	Concentration[b] CS_2	Concentration[b] H_2S	Duration	Effects	Reference
Rat	2,330	0	6 h/d, 5 d/wk, 10 wk; then 3 d/wk, 2 wk	Lethargy; loss of motor control, lowered MCV with no recovery in 12 wk	Seppalainen and Linnoila, 1976
Rat	2,330	0	6 h/d, 5 d/wk, 2-5 wk	Lethargy; lowered but reversible MCV	Seppalainen and Linnoila, 1976
Rat	2,000	0	2 h/d throughout pregnancy	Increased fetal mortality, decreased fertility	Yaroslavskii, 1969
Rat	1,500	0	5 hr/d, 6 d/wk, 1-15 mo	Weakness; paralysis, myelin and neuron degeneration; weight loss	Szendzikowski et al., 1973
Rat	12	[c]	60-110 d before mating and during pregnancy	Increased fetal mortality, teratogenesis	Bariliak et al., 1975
Rat	1.0 1.0 0.1 0.1	0.1 0 0.1 0	160 d	Inflammation of bronchi; weight changes; increased serum aspartate, aminotransferase, and blood cholinesterase activities; most severe with combined exposures	Misiakiewicz et al, 1972

TABLE 12 (cont'd)

Effects on Animals of Exposure to Carbon Disulfide or to Carbon Disulfide Plus Hydrogen Sulfide

Species	Concentration[b] CS_2	Concentration[b] H_2S	Duration	Effects	Reference
Mouse	2,000	0	2 h/d throughout	Increased fetal mortality; decreased fertility	Yaroslavskii, 1969
Rabbit	780-2,300	0	6 h/d 5 d/wk, 38 wk	Paralysis; CNS damage; slight liver damage; weight loss	Cohen et al., 1958
Rabbit	930	140	30 min/d, 120 d	Abnormalities of bone marrow, kidneys, and spleen; decreased spermatogenesis; loss of appetite; blood changes; most severe with combined exposure	Wakatsuki and Higashikawa, 1959; Wakatsuki, 1959
	930	0			
	0	140			
Rat	78	0	4 mo (every other day)[d]	Testicular lesions; no spermatogenesis	Gondzik, 1971
Rat	78	0	2 mo (every other day)[d]	Decreased number of spermatozoa; blood vessels engorged and vessel walls thickened	Gondzik, 1971
Rat	39	0	2 mo (every other day[d])	No effects	Gondzik, 1971

[a]Adopted from NIOSH (1977).
[b]mg/m^3 for inhalation mg/kg for injection; 1 mg/m^3 = 0.321 ppm. Exposure by inhalation, except where noted.
[c]Hydrogen sulfide concentration included in that given for carbon disulfide.
[d]Exposure intraperitoneal.

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CHLOROFORM

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Structural Formula:	$CHCl_3$
Molecular weight:	119.39
Chemical Names:	Chloroform, Trichloromethane
CAS number:	67-66-3
Physical state:	Colorless liquid
Specific gravity:	1.49845 (15°/4°C)
Melting point:	-63.5°C
Boiling point:	61.2°C
Vapor pressure:	200 Torr (25°C)
Solubility:	1.0/100 ml of water at 15°C; soluble in ethanol, ethyl ether, benzene, acetone, and CS_2
Flammability:	Not flammable by standard tests in air.
Conversion factors:	ppm = 0.2 (mg/m^3) mg/m^3 = 5.0 (ppm)

OCCURRENCE AND USE

Chloroform was widely used for many years as an anesthetic. Because it led to liver injury (often delayed) and cardiac sensitization, this use has been generally eliminated. Chloroform has some use as a solvent, but most of it is used as a chemical intermediate. Although its use as a solvent in industry is not extensive, it may be found as a constituent in solvent mixtures, and it is still commonly used as a laboratory solvent. Until recently, it was used as a flavoring agent in toothpaste. Chloroform is a contaminant of submarine atmospheres. It arises mainly from "off-gassing" of adhesives and plastics and possibly from medical uses (National Research Council, 1970).

Although the resulting concentrations are low, the process of chlorinating water yields chloroform at a few parts per billion. Higher quantities are produced during chlorination of sewage. Some chloroform appears to be produced by microorganisms in soil and water.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Much of the toxicologic information on chloroform has been developed because of its use as an anesthetic. The literature is replete with papers on anesthetic potency and liver injury.

High concentrations of chloroform result in narcosis and anesthesia. The most outstanding effect of acute exposure is depression of the central nervous system (see Table 13). Responses associated with exposure at less than anesthetic or preanesthetic concentrations are typically inebriation and excitation passing into narcosis. Vomiting and gastrointestinal upset may be observed.

Exposure at high concentrations may result in cardiac sensitization to epinephrine and similar compounds, as well as liver and kidney injury (see Table 14). In cases of chronic or repeated exposure to chloroform, liver injury is most typical (cf. the effects of carbon tetrachloride). Although injury to the kidney is not as common as that to the liver, it may be observed from either acute or chronic exposure.

Numerous reviews on the toxicity of chloroform are available (Challen et al., 1958; Davidson et al., 1982; NIOSH, 1974; Scholler, 1968; Van Dyke et al., 1964; Von Oettingen, 1955; Winslow and Gerstner, 1978; Zimmerman, 1968).

Considering the long history of chloroform, there is surprisingly little epidemiologic literature on chronic exposure to it. There have been almost no quantitative toxicologic studies of human responses to chronic exposure to chloroform. Challen et al. (1958) studied an industrial operation in which chloroform was being used. Groups exposed at 77-237 ppm exhibited definite symptoms. Apparently, there were also some high peak concentrations for very short periods. Symptoms were gastrointestinal distress and depression. Another group with shorter service was exposed at 21-71 ppm and had comparable symptoms. Both groups were tested for liver injury, but none was found. The authors believed, however, that there may have been mild liver injury, and they recommended that atmospheric exposure be kept below 50 ppm.

Bomski et al. (1967) reported on an investigation of a pharmaceutical plant that used chloroform as a solvent. Smaller amounts of methanol and methylene chloride were also used. Estimates of the airborne chloroform varied from 2 to 205 ppm (0.01-1.0 mg/L). Actual time-weighted average exposures of the workers were not reported; it is not clear if the room concentrations adequately described the workers' actual exposure. Complaints of headache, nausea, eructation, and loss of appetite were reported, as well as enlargement of the liver (25% of workers) and spleen. Results of liver function tests were not reliable.

EFFECTS ON ANIMALS

Acute Exposure

When chloroform was given by gavage to male rats, an LD_{50} of 2,000 mg/kg (confidence range, 1,050-3,800 mg/kg) was determined (Torkelson et al., 1976). Deaths generally occurred in 2.4 h, but some were delayed as long as 2 wk after treatment. Gross pathologic examination showed liver and kidney changes at doses as low as 250 mg/kg. Thompson et al. (1974) fed chloroform to pregnant rats at 20 mg/kg per day for 10 d without effect on the dams; 50 mg/kg appeared to cause fatty changes. These data are discussed in more detail in the section on teratology below.

Oettel (1936) indicated that chloroform was more irritating to the skin and eyes than many other chlorinated solvents. Oettel's conclusions have been confirmed by Torkelson et al. (1976). One or two 24-h applications on the skin of rabbits resulted in hyperemia and moderate necrosis. Healing of abraded skin appeared to be delayed by

application of a cotton pad soaked in chloroform. Absorption through the intact skin of rabbits was indicated by weight loss and degenerative changes in the kidney tubules, but the animals survived doses as high as 3,980 mg/kg. When the liquid was instilled into the eyes of rabbits, some corneal injury was evident, in addition to conjunctivitis. The authors concluded that chloroform was more irritating to rabbit skin and eyes than most common fat solvents tested by the same technique in their laboratory.

Chronic Exposure

Several studies describing long-term oral administration of chloroform are available, but they were designed to evaluate carcinogenic response and have limited value in evaluating noncarcinogenic effects. They are discussed in the following section.

Despite its long use, few reports on inhalation of chloroform are available. Repeated 7-h exposures to chloroform at 85, 50, or 25 ppm 5 d/wk for 6 mo resulted in adverse effects in all or some of the species studied: rats, rabbits, guinea pigs, and dogs. The effects at 25 ppm were slight and reversible. Rats exposed 1, 2, or 4 h/d were not adversely affected. Cloudy swelling of the kidneys and centrilobular granular degeneration and necrosis of the liver were the principal adverse effects (Torkelson et al., 1976).

The effects of chloroform exposure in animals are summarized in Table 15.

Teratogenesis

Chloroform appears to be unique among the smaller chlorinated aliphatics, in that it is the only one that appears to be somewhat teratogenic and highly embryotoxic in animals. Schwetz et al. (1974) exposed pregnant Sprague-Dawley rats to chloroform vapor at 0, 30, 100, or 300 ppm 7 h/d. Exposures were given on days 6-15 of gestation, and cesarean sections were done to evaluate embryonal and fetal development. According to the authors:

> Exposure to chloroform caused an apparent decrease in the conception rate and a high incidence of fetal resorption (300 ppm), retarded fetal development (30, 100, 300 ppm), decreased fetal body measurements (30, 300 ppm) and a low incidence of acaudate fetuses with imperforate anus (100 ppm). Chloroform was not highly teratogenic but was highly embryotoxic. The results of this study disclosed no relationship between maternal toxicity and embryo or fetotoxicity as the result of exposure to chloroform by inhalation.

In another inhalation study, Murray et al. (1[illegible] evaluated the effect of inhaled chloroform on embryonal and [illegible] development in CF-1 mice. Pregnant mice were exposed to chloroform at 0 or 100 ppm 7 h/d on days 1-7, 6-15, or 8-15 of gestation. Exposure on days 6-15 or 1-7 produced a significant decrease in the incidence of pregnancy, but did not cause significant teratogenicity. A significant increase in the incidence of cleft palate was observed among the offspring of mice

exposed on days 8-15 of gestation; no effect on the incidence of pregnancy was discerned. A significant increase in serum glutamic pyruvic transaminase (SGPT) activity was observed in mice exposed on days 6-15. Bred mice that were not pregnant had significantly higher SGPT activity than pregnant mice. Similar results were reported by Dilley et al. (1977), who exposed pregnant rats to chloroform vapor at 4,441 ppm (duration of daily exposure not stated) and produced increased fetal mortality and decreased fetal weight gain, but no teratologic effects.

Thompson et al. (1974) failed to produce teratogenic effects in Sprague-Dawley rats given chloroform by intubation at 0, 20, 50, or 126 mg/kg/per day on days 6-15 of gestation or in Dutch belted rabbits given chloroform at 0, 20, 35, or 50 mg/kg/per day on days 6-18. These authors stated:

> The occurrence of anorexia and weight gain suppression in dams of both species, as well as subclinical nephrosis in the rat and hepatotoxicity in the rabbit, indicated that maximum tolerated doses of chloroform were used. Fetotoxicity in the form of reduced birth weights was observed at the highest dose level in both species. There was no evidence of teratogenicity in either species at any dose tested.

It appears that chloroform has more fetotoxic effect when inhaled than when given by gavage. Thompson et al. (1974) speculated that doses given by gavage may result in different blood chloroform contents; that accounts for the apparent discrepancy with the effects seen after inhalation.

Mutagenesis

Chloroform failed to produced mutagenic changes in cultures of Chinese hamster lung fibroblast cells (Sturrock, 1977) or in the Salmonella/microsome test with typhimurium strains TA1535, 1537, 1538, 98, and 100 (Simmon et al., 1977).

Carcinogenesis

The available data from carcinogenicity studies in mice were summarized by IARC (1972). Chloroform has since been studied in Osborne-Mendel rats and B6C3F1 mice in the NCI bioassay program (Weisburger, 1977). Male (but not female) rats developed kidney epithelial tumors at 180 and 90 mg/kg per day. Mice of both sexes developed hepatocellular carcinomas at 138 and 277 mg/kg per day (males) and 238 and 477 mg/kg per day (females). The relationship of this study (in which the maximal tolerated dose was given by repeated gavage) to industrial exposure (in which vapors were inhaled) has been questioned (Reitz et al., 1978; Roe et al., 1979; Stokinger, 1977).

Data are available from long-term studies in rats, mice, and dogs fed a toothpaste base containing chloroform (Heywood et al., 1979; Palmer et al., 1979; Roe et al., 1979). Rats, mice, and dogs were fed lower doses than those used in the NCI bioassay study. Table 16 summarizes the studies. The males of only one of four strains of mice

developed an excess of tumors. No excess was found in the females of any strain, nor in the dogs and rats.

Adenomas in the renal cortex and hypernephromas regarded as possibly malignant occurred in male mice fed 60 mg/kg per day, but not 17 mg/kg per day (Roe et al., 1979). The importance of these tumors in indicating a carcinogenic effect is not clear, inasmuch as they had not spread to other organs and have since been observed in control mice of the same strain (ICI-Swiss).

The metabolic relationship of the data from high-dose studies in animals to man as discussed by Reitz et al. (1978), is presented in the following section.

PHARMACOKINETICS AND MOLECULAR INTERACTION

There are so many references to the absorption, excretion, and metabolism of chloroform that the data are at times understandably contradictory. There is no question but that chloroform is rapidly absorbed through the lungs, GI tract, and to some extent the skin; that some is metabolized; and that some is excreted in expired air. Chloroform has been shown to be metabolized by microsomal mixed-function oxidases (MFOs) to CO_2 (Paul and Rubinstein, 1963; Van Dyke et al., 1964) and by a sulfhydryl-dependent pathway to CO (Stevens and Anders, 1979).

Differences in doses may account for the apparent discrepancies in routes of elimination proposed by various investigators and there are wide differences between species in ability to excrete unchanged chloroform (see Table 17, from Reitz et al., 1978).

These data suggest that chloroform metabolism is less efficient in man than in the rodent species. Because metabolism of chloroform to a reactive intermediate is likely to mediate toxicity (discussed below), the metabolism data suggest that man would be less sensitive than rodents; this is generally consistent with the available data (Reitz et al., 1978).

The mechanism of action of toxicity of chloroform has been studied by several investigators. All data tend to support the hypothesis that microsomal-enzyme-mediated metabolism of chloroform to a reactive intermediate is responsible for its hepatoxic and nephrotoxic effects (Ilett et al., 1973; Lavigne and Marchand, 1974; Pohl, 1979). Ilett et al. (1973) have shown that the microsomal MFO inducer, phenobarbital, increases toxicity, whereas piperonyl butoxide--an inhibitor of MFOs--inhibits toxicity in mice treated with chloroform. Furthermore, induction and inhibition of MFOs is correlated with intracellular macromolecular binding reactions in the liver and kidneys; that suggests formation of a reactive intermediate. It has been postulated that phosgene is the reactive intermediate formed from chloroform (Bhooshan et al., 1977; Pohl, 1979) and that intracellular glutathione is the primary nucleophile responsible for detoxification (Brown et al., 1974a; Docks and Krishna, 1976).

Reitz et al. (1980) and Moore et al. (1980) have postulated that the carcinogenic effect observed in animals after oral administration of chloroform has an epigenetic mechanism. This conclusion was based on the lack of genotoxic activity of chloroform and the pronounced cytotoxicity in the target organs susceptible to tumor formation.

Chloroform has not been shown to be active in in vitro mutagenicity tests, and this is consistent with its low interaction with DNA in vivo (fewer than 3 alkylations/10^6 DNA nucleotides), compared with dimethylnitrosamine (900 alkylations/10^6 DNA nucleotides), which mediates its carcinogenic effect through direct interaction with DNA (Reitz et al., 1980). DNA damage measured by DNA repair was not observable when carcinogenic doses of chloroform were administered to mice. In contrast with the lack of genotoxic activity of chloroform at carcinogenic doses, cytotoxicity observed histopathologically and indicated by increased DNA synthesis (regeneration after cellular death) was marked in the liver and kidneys of mice that received carcinogenic doses (Reitz et al., 1980; Moore et al., 1980). These data suggest that the tumors induced by chloroform may have been secondary to tissue toxicity and thus that the risk of carcinogenesis may be diminished below cytotoxic doses.

INHALATION EXPOSURE LIMITS

Work place inhalation exposure limits recommended for chloroform are summarized in Table 18.

COMMITTEE RECOMMENDATIONS

EXPOSURE LIMITS

In 1970, the Committee on Toxicology recommended EELs and CEL for chloroform as follows:

1-h EEL:	200 ppm
24-h EEL:	30 ppm
90-d CEL:	3 ppm

Chloroform is easily absorbed, and substantial amounts are retained during inhalation. It concentrates heavily in adipose and adrenal tissues, but much is also retained by brain, kidney, and blood.

There are qualitative and quantitative differences in metabolism between man and animals, and humans metabolize it more slowly. CO_2 is a major metabolite in all species, with the liver and to some extent the kidneys being involved. Metabolism also results in formation of small amounts of phosgene, carbenes, and free radicals. Covalent binding to DNA or nucleic acids is not an important aspect of metabolism.

Exposure to chloroform at high concentrations produces anesthesia. After acute high doses or repeated at lower doses, hepatotoxicity is the major effect in humans and is, sometimes, accompanied by renal toxicity.

Chloroform is fetotoxic in animals, in four of six studies, with effects at 100 ppm but not 30 ppm in rats (Schwetz et al., 1974). It is not teratogenic.

Long-term studies in animals demonstrated that chloroform has a carcinogenic potential (Davidson et al., 1982). Epidemiologic studies

revealed that anesthesiologists from the chloroform era had a higher cancer mortality rate than those of the postchloroform period (Linde and Mesnick, 1980). However, confounding factors limit interpretation of these findings.

Acute human studies showed that 390 ppm is tolerated for 30 min without complaint, whereas 1,030 ppm results in dizziness, intracranial pressure, and nausea in 7 min, with headache for several hours (Lehmann and Flury, 1943). Symptoms were experienced by workers in a plant manufacturing chloroform-containing lozenges when the chloroform concentration was 21-71 ppm and exposure was for 4 h/d over a period of 10-24 mo (Challen et al., 1958). Severe symptoms occurred in other workers in this plant exposed at 77-232 ppm for 3-10 yr. The aforementioned acute and chronic information, taken with data on the fetotoxic potential of chloroform, appears to support a 1-h EEL of 100 ppm and a 24-h EEL of 30 ppm. The reduction of the 1-h EEL from 200 to 100 ppm is based on the fetotoxic potential of chloroform, as related to possible exposure of women of childbearing-age.

The long-term studies are more difficult to evaluate. Because a carcinogenic potential cannot be excluded, caution is required in the interpretation of the findings. Furthermore, all sources of chloroform contamination of the atmosphere should be minimized in confined areas where workers are exposed for long periods.

The data of Roe et al. (1979) show that mice given chloroform by gavage (in toothpaste) at 17 mg/kg per day were not affected, whereas those exposed at 60 mg/kg per day developed tumors. The data of Torkelson et al. (1976) showed that rats inhaling chloroform at 50 and 85 ppm 7 h/d, 5 d/wk for 6 mo developed liver and renal histopathologic conditions, whereas adverse effects produced at 25 ppm were reversed when exposure was stopped. These rats were exposed 21% of the time (35 of a possible 168 h/wk) Exposure in this manner at 50 ppm (the lower of the first two concentrations) would be equivalent to continuous exposure at 10 ppm. Use of a 10-fold uncertainty factor yields a concentration of 1 ppm.

With exposure at 1 ppm, a human breathing at 10 L/min (an average resting rate) would inhale 70.4 mg of chloroform over a 24-h period (1 ppm = 4.89 mg/m^3), or about 1 mg/kg per day. Gavaged mice exposed at 60 mg/kg per day developed tumors; those exposed at 17 mg/kg per day did not. Therefore, exposure at 1 ppm would be considerably less than the long-term exposure of mice that did not develop tumors. The Committee suggests that the 90-d CEL for chloroform be reduced from 3 ppm to 1 ppm, on the basis of the long-term animal studies.

In summary, the Committee recommends the following EELs and CEL:

1-h EEL:	100 ppm
24-h EEL:	30 ppm
90-d CEL:	1 ppm

TABLE 13

Chloroform Inhalation Exposures and Effects in Humans

Concentration, ppm	Exposure Duration, min	Effects	Ref.
20,000	30-24	Anesthesia; nausea; vomiting; jaundice; delayed chloroform poisoning	Whitaker and Jones (1965)
922	3	Dizziness, vertigo	Lehmann and Schmidt-Kehl (1936)
1,107	2	Dizziness, vertigo	
7,236	15	Dizziness, light intoxication	Lehmann and Hasegawa (1910)
205	approx. 1	Perception of light transient odor	Lehman and Schmidt-Kehl (1936)
14,420-16,480	NG[a]	Limited narcotic concentration	Lehman and Flury (1943)
4,120		Fainting sensation; vomiting	
1,483		Dizziness and salivation after a few minutes	
1,030		Dizziness, intracranial pressure, and nausea in 7 min; after-effect of fatigue and headache for several hours	
391		Tolerated for 30 min without complaint	
206-309		Lowest concentration detected by smell	

[a] Not given, except as listed under "effects."

TABLE 14

Six Cases of Delayed Chloroform Poisoning

Age, yr	Dosage	Effects	Laboratory Test and Autopsy Findings	Ref.
37	3 administrations: 3 capsules, each 20 minims; "very little" from drop bottle; 3 capsules, each 20 minims and anesthesia on open mask	Restless, coma and convulsions, on 2nd postpartum day, vomiting, jaundice; increased pulse and temperature; died on 8th postpartum day	Blood urea: 198/100 cc on 3rd day, 303 mg/100 cc on 5th day; blood NPN: 187 mg; amino acid nitrogen: 8.2 mg %; urine: acid, albumin, red blood cells, pus, high urobilinogen; liver: soft, yellow, advanced necrosis, and fatty degeneration; kidneys: swollen, fatty deposits, necrosis; heart: fatty degeneration	Gibberd (1935)
30	2 inhalations of unspecified amount separated by 2 h, and anesthesia on open mask	Drowsy, swelling of hands, jaundice; coma; increased temperature and pulse; extreme hyperpnea; no vomiting; died 5th postpartum day	blood urea: 105 mg/100 cc on 2nd day; 360 mg/100 cc on 5th day; plasma bicarbonate: 0.003 m; urine: uric acid, albumin, pus, 2.35% urea on 3rd day; liver: yellow, mottled, soft, diffuse centrilobular necrosis, fat mostly in periphery	Gibberd (1935)
25	Full anesthesia on open mask "long time"	Drowsy, jaundice; coma on 4th day, muscular twitching; increased temperature, vomiting; died on 6th postpartum day	Blood: 0.093% sugar, urea at 60 mg/100 cc; urine: deep orange, pH 6.0, 0.4% albumin, diacetic acid; liver: soft, flabby, recent shrinkage, yellow, widespread necrosis; kidneys: congestion of cortical vessels; heart: fatty changes	Gibberd (1935)

TABLE 14 (cont'd)

Age, yr	Dosage	Laboratory Test Effects	And Autopsy Findings	Ref.
24	Unspecified	Restless; delirium; coma; jaundice; drowsy, increased temperature; muscle twitching; no vomiting; recovered	Urine: albumin, bilirubin, urobilin	Lunt (1953)
35	. doses, unspecified	Drowsiness, mental confusion, coma, jaundice, tenderness over liver, hiccups; restless, no vomiting; recovered	Urine: albumin bilirubin, urobilin	Lunt (1953)
23	2 doses, unspecified	Jaundice; nausea; general weakening; slight icterus; recovered	No observations	Lunt (1953)

TABLE 15

Chloroform Inhalation Exposure and Effects in Animals

Species	Dosages	Exposure Duration	Effects	Ref.
Dog	1-2 oz. (total)	1-2 h	Anesthesia; central hyaline necrosis; acute yellow atrophy and fatty degeneration of the kidneys	Whipple and and Sperry (1909)
Dog	13,450-15,546 ppm	60-285 min	Narcosis; respiratory rate fluctuation; decrease in blood pressure and body temperature; death	von Oettingen et al. (1949)
Mouse	6,765 ppm	0.5 h	Narcosis; death	Fuhner (1923)
Cat	7,175 ppm	7.8	Light narcosis	Lehmann and Schmidt-Kehl (1936)
Mouse	400 and 800 ppm	4 h	Fatty infiltration of liver, liver necrosis, increased SOCT activity	Kylin et al. (1963)
Mouse	100 ppm	4 h	Moderate fatty infiltration of liver	Kylin et al. (1963)
	200 ppm	4 h	Some liver necrosis, increased SOCT activity	
Rat	85 ppm 6 mo	7 h/d 5 5 d/wk, 6 mo	Male: increased mortality (pneumonia), centrilobular degeneration in liver, and renal histopathology; female: liver and kidney effects similar to those in males	Torkelson et al. (1976)
Guinea pig	85 ppm	7 h/d, 5 d/wk, 6 mo	Male: no effects; Female: slight pneumonitis	Torkelson et al. (1976)
Rabbit	85 ppm	7 h/d, 5 d/wk, 6 mo	Male: marked pneumonitis and liver necrosis; female: liver and kidney pathologic conditions	Torkelson et al. (1976)

TABLE 15 (cont'd)

Species	Dosages	Exposure Duration	Effects	Ref.
Rat	50 ppm	7 h/d, 5 d/wk 60 mo	Male: similar to effects at 85 ppm but less in degree, decreased body weight, and liver and kidney pathologic conditions; female: less affected than male liver/kidney pathology	Torkelson et al. (1976)
Guinea pig	50 ppm	7 h/d, 5 d/wk 60 mo	No effects	Torkelson et al. (1976)
Rabbit	50 ppm	7 h/d, 5 d/wk 60 mo	No effects	Torkelson et al. (1976)
Rat	25 ppm	7 h/d, 5 d/wk 6 mo	Slight histopathologic effects in liver and kidney effects, but not considered significant, because no dose-response relation	
Guinea pig	25 ppm	7 h/d, 5 d/wk 6 mo	Some liver and kidney effects, but not considered signficant, because no dose-response relation	Torkelson et al. (1976)
Rabbit	25 ppm	7 h/d, 5 d/wk 6 mo	Male: Some tubular nephritis; female: some tubular nephritis and liver and other kidney effects (no dose-response relation)	Torkelson et al. (1976)
Dog	25 ppm	7 h/d, 5 d/wk 6 mo	Male: no change; female: swelling of renal tubular epithelium	Torkelson et al. (1976)
Rat	25 ppm	4, 2, or 1 h/d 5 d/wk, 6 mo	No adverse effects	Torkelson et al. (1976)

TABLE 16

Summary of Carcinogenicity Studies of Chloroform Carried Out at Huntingdon Research Center

Species	Dosage, mg/kg per day[a]	No. Animals Male	No. Animals Female	Duration of Exposure	Excess of Neoplasms	Reference
Rat:						
Sprague/Dawley	60	50	50	95 wk	None	Palmer et al. (1979)
Mouse:						
ICI-Swiss	17	52	52	80 wk	None	Roe et al. (1979)
		60	52	80 wk	Renal tumors	
	60	52	80 wk	None		
C57BL	60	52	--	80 wk	None	
CBA	60	52	--	80 wk	None	
CF/1	60	52	--	80 wk	None	
Dog:						
Beagle	15	8	8	7-1/2 yr	None	Heywood et al. (1979)
	30	8	8	7-1/2 yr	None	

[a]6 d/wk.

TABLE 17

Interspecies Comparisons of Chloroform Excretion[a]

Species	Oral Dose, mg/kg	$CHCl_3$ Excreted Unchanged, % of dose	Ref.
Mouse	60	6	Brown et al. (1974b)
Rat	60	20	Brown et al. (1974b)
Monkey	60	78	Brown et al. (1974b)
Man	7	7-66	Fry et al. (1972)

[a]Adapted from Reitz et al. (1978)

TABLE 18

Chloroform Inhalation Exposure Limits

Institution	Kind of Limit	Concentration	Reference
ACGIH	TLV-TWA	10 ppm	ACGIH (1980)
OSHA	Ceiling	50 ppm	OSHA (1981)
NRC Panel on Air Standards for Manned Space Flight	90 d 1,000 d	5 ppm 1 ppm	NRC (1968)
Italy	MAC	20 ppm	Soc. Ital. Med. Lav. (1975)
Japan	MAC	50 ppm	Jap. Assoc. Ind. Health (1971)

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FLUORINE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Structural formula:	F_2
Molecular weight:	37.996
CAS number:	7782-41-4
Melting point:	-220°C
Boiling point:	-188°C
Density:	1.5127
Physical state:	A pale yellow, diatomic gas, it is the most reactive nonmetal.

General characteristics: It has a higher oxidation potential than ozone and reacts vigorously with almost all oxidizable substances at room temperature, frequently with ignition. It reacts violently with most organic compounds, usually causing extensive fragmentation of the molecule (O'Donnell, 1973; Windholz et al., 1976).

Other properties: Fluorine decomposes in water, yielding hydrogen fluoride (HF), oxygen difluoride (OF_2), hydrogen peroxide (H_2O_2), oxygen, and ozone. However, F_2 persists in saturated water vapor for up to 1 h (Slabbey and Fletcher, 1958).

Conversion factors: ppm = 0.64 (mg/m^3)
mg/m^3 = 1.56 (ppm)

OCCURRENCE AND USE

Elemental fluorine does not occur in nature. Because it is the most electronegative element, it is extremely difficult to prepare; electrolysis of a KF=HF mixture, a procedure introduced in 1886, is still in use.

Although numerous fluorocarbon compounds are used as lubricants, coolants, refrigerants, etc., many of these are prepared from HF, rather than F_2, because the reactions of the latter are difficult to control. Fluorine gas is used to manufacture uranium hexafluoride (UF_6) for the separation of uranium isotopes. The elemental gas is also used to manufacture sulfur hexafluoride (SF_6), a stable gas with high dielectric and insulating capacities for high-voltage systems. Fluorine is also used as an oxidant in rocket-fuel mixtures (ACGIH, 1980).

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Uncontrolled Exposure

Women and children living in a village in the vicinity of an aluminum factory in northern Italy suffered blemishes that were thought to have resulted from stack effluents, among which might have been fluorine or fluorides (Cavagna et al., 1969). Examination of those affected

revealed no signs of fluorosis, and their urinary fluoride concentrations were normal. Animal experiments with extracts of stack effluents revealed no adverse effects at the concentrations used. The authors concluded that there was no evidence of an association of fluorine or fluorides with the observed skin conditions (Cavagna et al., 1969).

Lyon (1962) reported that 61 workers exposed to fluorine who excreted fluoride at an average of 1.1 mg/L for 7 yr (2,535 determinations) had better health records than the 2,000 employees used as controls and had fewer respiratory complaints. The average F_2 exposure was not known, but the author speculated that it was "greatly in excess of 0.1 ppm." The same author observed that intermittent industrial exposures to F_2 at up to 30 ppm for 5-30 min had no ill effects. No other reports of uncontrolled F_2 exposures, accidental or occupational, are known to the Committee.

Controlled Exposure

Outdoor "spill" tests conducted by the U.S. Air Force revealed that single "short-term" F_2 exposures at 25 ppm (duration not reported) were "intolerably irritating," and exposure at 50 ppm made breathing impossible (Rickey, 1959). The number of subjects involved in this study was not reported.

Belles (1965) observed nine male volunteers exposed to F_2 under controlled conditions. Most of the subjects found that 15-25 ppm caused some nasal and eye irritation after two or three breaths. All subjects tolerated repeated short-term (duration unspecified) exposures at up to 10 ppm without discomfort. Additional details of this study were not available to the Committee.

Keplinger and Suissa (1968) exposed 5 volunteers (aged 19-50) to F_2 under a variety of conditions that permitted accurate measurement of F_2 concentrations. Exposure took place under a mask that covered the eyes and nose, but not the mouth. Thus, the effects of F_2 on respiration were not routinely measured (some subjects did inhale and some data on respiratory effects were obtained). The results of this study are summarized in Table 19. The authors also noted that, when exposure was repeated weekly, the subjects did not perceive as much irritation as they had on first exposure. The apparent development of tolerance is consistent with that seen in experimental animals. Finally, the authors studied the effects of exposure at 10 ppm for 3-5 min every 15 min for 2 or 3 h. All subjects tolerated such repeated exposures with only slight irritation of the eyes and skin.

EFFECTS ON ANIMALS

Acute exposure

Almost all animal studies of F_2 toxicity known to the Committee were acute (single exposures). The most comprehensive of such studies, and the only ones involving actual measurement of the concentrations of F_2 at which the animals were exposed, were reported by Keplinger and Suissa (1968). The only known earlier studies were conducted during World War II; they involved only lethal concentrations (the

concentrations were not monitored) and provide no information useful for present purposes (Ricca, 1970).

Data obtained by Keplinger and Suissa from exposures at sublethal concentrations are summarized in Tables 20-23. These data were collected after determination of LC_{50}s in the five species studied; the concentrations used were then fixed at 50%, 25%, 12.5%, and 6% of the LC_{50} values. The most pronounced effects of the F_2 exposures observed were irritation of the eyes and respiratory tract. Dyspnea was also observed frequently. Although kidney and liver effects were observed, they occurred only at exposures greater than those producing diffuse congestion of the lung. Thus, only lung pathology data are reported in Tables 20-23.

In rats, mice, guinea pigs, and rabbits, effects observed after exposures at approximately 50% and 25% of the LC_{50} values were not observed at approximately 12.5% of the LC_{50} values (see Tables 20-23). The lack of data on the LC_{50} value for dogs prevents determination of whether the same pattern holds for this species. The ranges of maximal no-observed-effect concentration for the five species were as follows:

Duration, min	No-observed-effect concentration, ppm	ppm-min
5	51-88	260-440
15	49-70	740-1,100
30	32-35	960-1,100
60	28-38[a]	1,500-2,300

[a] Includes dog data.

For both dogs and rats, complete blood counts (hemoglobin, hematocrit, erythrocyte count, and total and differential leukocyte counts) were measured before exposure and on the second, seventh, fourteenth, and twenty-first days after exposure. No measurable changes were noted in these counts after any of the exposures.

Short-Term Exposure

Keplinger (1969) studied the effects of intermittent exposure to F_2 by exposing mice, rats, and rabbits four times at weekly intervals. Two magnitudes of exposure were used: one that caused slight effects after a single exposure and one that produced marked effects after such an exposure. The animals were sacrificed 7, 14, 21, or 45 d after the last exposure. The results of these studies are summarized in Table 24. The author concluded that four weekly exposures to F_2 caused no more and in some cases less, damage than a single exposure at the same concentration. The data suggest the development of a tolerance to F_2. It was also shown that the LC_{50} value for mice was increased by pre-exposing the test animals to F_2. This provides additional evidence of the development of tolerance.

PHARMACOKINETICS

The extent to which fluoride (F^-) toxicity data may provide insight

into F_2 toxicity cannot be ascertained. Presumably, if F_2 were metabolized only to F^-, then data on the latter would be of some value. There is, however, no evidence on the chemical fate of F_2 in animal systems. Indeed, it is expected that F_2 will cause extensive chemical changes in biomolecules. Ricca (1970) reported that F_2 can oxidize proteins and fats, and it is likely that numerous degradation products of biomolecules are produced after F_2 exposures. Therefore, it does not seem reasonable to assume that fluoride toxicity is importantly related to that expected for F_2.

COMMITTEE RECOMMENDATIONS

EXPOSURE LIMITS

In 1968 (NRC, 1968), the Committee recommended the following EELs for F_2:

10-min EEL:	15 ppm
30-min EEL:	10 ppm
60-min EEL:	5 ppm

The 15-ppm EEL proposed for exposures up to 10 min was based on the human data described above. It assumes that minor, nonincapacitating eye irritation (a most useful early warning of F_2 exposure) may occur and will not result in degradation in performance during an emergency exposure. The previously cited data support such a conclusion, and no recent data are available to suggest changes in the 10-min EEL. EELs for 30 and 60 min cannot be derived by consideration of the human exposure data, because exposures did not exceed 15 min. Animal toxicity data are available for 30- and 60-min exposures and can be used to establish such EELs.

The 10-min EEL of 15 ppm (Ct = 150 ppm-min) is approximately 30% of the Ct of the most sensitive test animal and reflects a no-observed-effect exposure (500 ppm-min, calculated by interpolation of the 5-min and 15-min data). The Ct values for 30- and 60-min exposures of the most sensitive test animal are 960 and 1,500 ppm-min, respectively. If the same safety factor as that based on the 10-min exposure data (0.3) is applied, then acceptable Ct values for humans for 30- and 60-min exposures are 290 and 450 ppm-min, respectively. Thus, for a 30-min exposure, an EEL of (290 ppm-min)/(30 min) = 9.7 ppm, or 10 ppm, is appropriate. Similarly, for a 60-min exposure, an EEL of (450 ppm-min)/(60 min) = 7.5 ppm is acceptable.
Thus, recommended EELs for F_2 are as follows:

10-min EEL:	15 ppm
30-min EEL:	10 ppm
60-min EEL:	7.5 ppm

TABLE 19

Irritation Caused by Fluorine in Volunteer Human Subjects[a]

Concentration, ppm	Time, min	Effects
10	3	No irritation of eyes and nose
10	5	No irritation of eyes and nose; not uncomfortable
10	15	No irritation of eyes and nose, inhaled without irritation of respiratory tract
23	5	Slight irritation to eyes; could inhale without respiratory difficulty (inhaled intermittently over the 5-min period)
50	3	Irritation of the eyes; slight irritation of the nose
67	-	Irritation of eyes and nose; although exposure was quite irritating, concentration not unbearable
78	1	Irritation of the eyes and nose; (less irritating to eyes than cigarette smoke); face slightly irritated after exposure; inhalation caused coughing
100	1	Very irritating to eyes and nose; eyes burned after exposure; felt like "film" over the eyes after exposure; skin felt sticky and slightly irritated after exposure; subjects did not inhale
100	0.5	Very irritating to eyes and nose; no after-effect

[a]Keplinger and Suissa, 1968.

TABLE 20

Sublethal Effects of Fluorine in Animals Exposed for 5 Minutes[a]

Species (Strain)[b]	Concentration, ppm[c]	Toxic Signs	Gross Lung Pathology
Rat (Osborne Mendel)	500	Marked irritation of eyes and respiratory tract; dyspnea	Severe diffuse congestion
	350	Irritation; dyspnea	Moderate diffuse congestion
	175	Eye irritation; slight dyspnea	Mild diffuse congestion
	88	None	No change
	44	None	No change
Mouse (Swiss Webster)	467	Marked irritation of eyes and respiratory tract; dyspnea	Severe diffuse congestion
	300	Irritation; dyspnea	Moderate diffuse congestion
	174	Slight dyspnea; irritation	Very mild diffuse congestion
	79	None	No change
	38	None	No change
Rabbit (New Zealand)	410	Irritation; dyspnea	Moderate diffuse congestion
	134	Slight dyspnea	No change
	51	None	No change
	26	None	No change

[a]Keplinger and Suissa, 1968.

[b]The text of the report is unclear in the matter of the sex and number of animals used. LC_{50} determinations were made with 10 animals per group. It appears that 5 animals per group were used for the sublethal studies, but this is not certain.

[c]Purity of F_2 not specified, but contamination highly unlikely. Each concentration determined by measurement of samples from exposure chamber. Lowest four concentrations used for each species are approximately 50%, 25%, 12.5% and 6% of LC_{50} values, except for unexplained deviation in studies in rabbits.

TABLE 21

Sublethal Effects of Fluorine in Animals Exposed for 15 Minutes[a]

Species (Strain)[b]	Concentration, ppm[c]	Toxic Signs	Gross Lung Pathology
Rats (Osborne Mendel)	195	Irritation; dyspnea	Moderate diffuse congestion
	98	None	Very mild diffuse congestion
	49	None	No change
Mouse (Swiss Webster)	188	Irritation; dyspnea	Moderate diffuse congestion
	87	None	Very mild diffuse congestion
	65	None	No change
Guinea pig (New England)	198	Irritation; dyspnea	Mild diffuse congestion
	100	None	Very mild diffuse congestion
	70	None	No change
Dog (unspecified)	93	Eye irritation	Slight congestion
	39	None	No change

[a]Keplinger and Suissa, 1968.

[b]The text of the report is unclear in the matter of the sex and number of animals used. LC_{50} determinations were made with 10 animals per group. It appears that 5 animals per group were used for the sublethal studies, but this is not certain.

[c]Purity of F_2 not specified, but contamination highly unlikely. Each concentration determined by measurement of samples from exposure chamber. Concentrations used for the rat were approximately 50%, 25%, and 12.5%, of LC_{50} values; concentrations corresponding to 12.5% of the LC_{50} were used in mice and guinea pigs. It is unclear how concentrations were selected for the dog.

TABLE 22

Sublethal Effects of Fluorine in Animals Exposed for 30 Minutes[a]

Species (Strain)[b]	Concentration, ppm[c]	Toxic Signs	Gross Lung Pathology
Rat (Osborne Mendel)	140	Irritation of eyes and nose;slight dyspnea	Moderate diffuse congestion
	70	None	Very mild diffuse congestion
	35	None	No change
	18	None	No change
Mouse (Swiss-Webster)	113	Irritation and dyspnea	Mild diffuse congestion
	67	None	Very mild diffuse congestion
	32	None	No change
	16	None	No change
Rabbit (New Zealand)	135	Irritation	Mild diffuse congestion
	71	None	Very mild diffuse congestion
	32	None	No change
	19	None	No change

[a]Keplinger and Suissa, 1968.

[b]The text of the report is unclear in the matter of the sex and number of animals used. LC_{50} determinations were made with 10 animals per group. It appears that 5 animals per group were used for the sublethal studies, but this is not certain.

[c]Purity of F_2 not specified, but contamination highly unlikely. Each concentration determined by measurement of samples from exposure chamber. Concentrations used for each species were approximately 50%, 25%, 12.5%, 6% of LC_{50} values.

TABLE 23

Sublethal Effects of Fluorine in Animals Exposed for 60 Minutes[a]

Species (Strain)[b]	Concentration, ppm[c]	Toxic Signs	Gross Lung Pathology
Rats (Osborne Mendel)	93	Irritation and dyspnea	Mild diffuse congestion
	47	None	Very mild diffuse congestion
	28	None	No change
	14	None	No change
Mouse (Swiss Webster)	150	Irritation, dyspnea	Severe diffuse congestion
	75	Dyspnea	Mild diffuse congestion
	50	None	Very mild diffuse congestion
	30	None	No change
Guinea pig (New England)	135	Irritation; dyspnea	Mild diffuse congestion
	75	None	No change
Dog (Unspecified)	93	Irritation; cough; slight dyspnea; vomiting	Small areas of hemorrhage
	68	Eye irritation	No change
	38	None	No change
	15	None	No change

[a]Keplinger and Suissa, 1968.

[b]The text of the report is unclear in the matter of the sex and number of animals used. LC_{50} determinations were made with 10 animals per group. It appears that 5 animals per group were used for the sublethal studies, but this is not certain.

[c]Purity of F_2 not specified, but contamination highly unlikely. Each concentration determined by measurement of samples from exposure chamber. Concentrations used for the rat were approximately 50%, 25%, 12.5%, and 6% of the LC_{50} values; 100%, 50%, 30%, and 20% of the LC_{50} value was used in mice; and 50% and 25% of the LC_{50} value was used in guinea pigs. It is unclear how concentrations were selected for the dog. Concentrations equal to 6% of LC_{50} were not used in of mice and guinea pigs.

TABLE 24

Pathology in Mice and Rats after Single and Repeated Exposures to Fluorine[a]

Species (Strain)[c]	Time, min	Conc., ppm[d]	Repeated exposures[b]			Single exposure[b]		
			Lung	Kidney	Liver	Lung	Kidney	Liver
Mouse/Swiss-Webster	5	130	1	N	N	1	P	N
	5	321	1	P	N	3	P	P
	30	64	1	N	N	1	P	N
	30	55	1	N	N	1	P	N
Rat (Osborne Mendel)	5	150	1	N	N	1	P	N
	5	325	1-2	N	N	3	P	P
	30	68	1	N	N	1	P	N
	60	75	1-2	N	N	1	P	N
	60	140	2-3	N	N	4	P	P
Rabbits (New Zealand)	15	56-73	N	N	N	N	N	N
	30	49-55	N	N	N	N	N	N

[a]Keplinger, 1969.

[b]Four exposures at weekly intervals. N = normal or no change; P = some pathology; 1,2,3,4 = degree of gross lung pathologic change (1 mildest and 4 most severe).

[c]Sex unspecified; 10 mice or rats per group; number of rabbits per group unspecified.

[d]Concentration determined by measurement.

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MERCURY VAPOR

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROERTIES

Structural formula:	Hg
Molecular weight:	200.59
Synonyms:	Quicksilver
CAS number:	7439-97 6
Physical state:	A silver-white, heavy, liquid metal, which is slightly volatile at ordinary temperatures
Vapor pressure:	2×10^{-3} mm
Specific gravity:	13.59

OCCURRENCE AND USE

Mercury has many uses besides its well-known use in thermometers, barometers, and manometers. It is used in arc lamps, switches, and fungicides. Gold extraction and other industrial applications use mercury (Windholz et al., 1976; ACGIH, 1980). It is a component of submarine atmospheres and some solid-fuel rocket propellants.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Acute toxicity of mercury is characterized by nausea, vomiting, abdominal pain, bronchitis, bloody diarrhea, and anuria with uremia. (Windholz et al., 1976; ACGIH, 1980) Chronic toxicity is characterized by tremors, weakness, sensory abnormalities, memory loss, erethism, muscle pains, gingivitis, emotion or intellect changes, and kidney damage (Browning, 1969).

Milne et al. (1970) reported that four workmen became ill for a few days to a month after exposure to a mercury-contaminated atmosphere for 2.5, 4, and 5 h. Mercury concentrations ranged from 1.1 to 2.9 mg/m^3. Popseu et al. (1979) claimed that workers exposed for over a year to an atmosphere containing mercury at 0.15-0.44 mg/m^3 in a chemical plant suffered no apparent mercury poisoning. Their urinary mercury excretion was 890 g/L. Smith et al. (1971) evaluated blood mercury and urinary excretion of mercury in 1000 workers chronically exposed to elementary mercury in the workplace 40 h/wk. He reported that symptoms of mercury poisoning were seen when the concentration in the atmosphere exceeded 0.1 mg/m^3. This confirmed earlier work reported by Neal et al. (1941). Friberg (1951) and Seifert and Neudert (1954) reported that mercury poisoning occurred when concentrations remained around 0.1 mg/m^3.

Smith's data on blood and urinary mercury concentrations follow:

Mercury concentration in air, mg/m3	Mercury in Blood µg/100 ml	Mercury in Urine, µg/L
0.1	6	260
0.025	2.5	100

These can be compared to normal values of 0.8 µg/100 ml in blood (Study Group on Mercury Hazards, 1971) and 8 µg/L in urine (Solloman, 1957).

Lauwerys and Buchet (1973) reported on 40 chemical and biologic workers chronically exposed to mercury vapors and 23 biologic technicians who had not been exposed (controls). The data are summarized below.

No.	Mercury Conc., mg/m^3	Mercury in Blood, µg/100 ml	Mercury in Urine, µg/g of creatinine	RBC-ChE, % of control
23	0	0.65	2.3	100
32	0.04	0.96	7.5	94
8	0.04	1.2	23.5	80

Increased plasma galactosidase and plasma catalase activities were also detected.

Factory workers exposed to elemental mercury (in a mercury cell chlorine plant) were found to have ulnar nerve conduction deficits when their urinary excretion of mercury exceeded 250 µg/L, despite the fact that they were asymptomatic and appeared normal when examined by an industrial physician (Levine et al. 1982).

Other mercury studies are reported in Threshold Limit Values (ACGIH, 1980). There is no evidence that exposure to mercury leads to excess cancer mortality in humans (Woo and Arcos, 1981).

EFFECTS ON ANIMALS

Acute Toxicity

Rabbits exposed for 4 h to saturated vapors of mercury (27 mg/m^3) suffered severe poisoning of brain, colon, heart, liver, lungs, and kidneys (Ashe et al. 1953).

The rat oral LD_{50} of $HgCl_2$ is 210 mg/kg.

Subacute Toxicity

Guinea pigs exposed 10 h/d for 4 d to mercury vapor at 6 mg/m^3 developed neurotic effects and hemorrhagic colitis. Mercury was stored in the kidneys (Holzmann, 1931).

Chronic Toxicity

Dogs, rabbits, and rats showed no effects when exposed to mercury vapor at 0.1 mg/m^3 for 83 wk (Fraser et al., 1934)

Carcinogenicity

There does not appear to be any useful animal information on carcinogenic hazards of exposure to mercury.

INHALATION EXPOSURE LIMITS

An international committee chaired by Lars Friberg met in 1968 (Report of an International Committee, 1969) to consider threshold limit values for occupational exposure to mercury. Goldwater pointed out that in the study conducted by Neal et al. (1941), on which the current standard for inorganic mercury depended, cases of mercurialism occurred at 0.1 mg/m^3 and at all higher concentrations and that the use of 0.1 mg/m^3 as a standard was therefore not proper, because it allowed no safety factor. Some studies conducted since then have suggested that 0.1 mg/m^3 is adequate; others have found occasional cases of toxicity at lower concentrations. For example, Smith et al. (1971) found no significant incidence of effects at 0.1 mg/m^3; these authors, however, also agreed that the use of that concentration as a TLV allowed no safety factor. Friberg quoted examples of mercury poisoning at concentrations around 0.1 mg/m^3 (Friberg, 1951; Seifert and Neudert, 1954). As a result, the ACGIH TLV-TWA for inorganic mercury, originally set at 0.1 mg/m^3, was reduced to 0.05 mg/m^3 in 1971. Biologic changes may occur in persons exposed to mercury vapor at concentrations below the current TLV (Lauwerys and Buchet, 1973). There appears to be an increase in the concentration of mercury in the blood and urine, with a concomitant slight decrease in RBC cholinesterase activity and increase in plasma galactosidase and plasma catalase activities. There is no evidence that these abnormalities have any health implications, but they may be useful in surveillance of exposed persons.

On the basis of Swedish experience, a TLV of 0.01 mg/m^3 for alkyl mercury compounds was suggested by ACGIH in 1948. Despite the lack of evidence of mercury poisoning between 0.01 and 0.1 mg/m^3, this TLV recommendation has been retained. Because of the great toxicity of organic mercurials, occupational TLVs of 0.05 mg/m^3 for inorganic and 0.01 mg/m^3 for organic mercury seem reasonable (ACGIH, 1980). NIOSH recommended that the permissible exposure limit for inorganic mercury in the workplace be set at 0.05 mg/m^3 in 1973. A 24-h EEL of 0.001 mg/m^3 was recommended to NASA in 1979 (Katz, 1979).

COMMITTEE RECOMMENDATIONS

EXPOSURE LIMITS

In 1966, the Committee recommended a 24-h EEL of 2.0 mg/m^3 and a 90-d CEL of 0.01 mg/m^3 for mercury.

The data of Milne et al. (1970) suggest that a 24-h EEL should be below 1.1 mg/m^3. The data of Popescu et al. (1979) show that, although long-term exposure at 0.44 mg/m^3 produced no apparent mercury poisoning, urinary and blood contents were increased and

showed accumulation of mercury. This and other long-term exposure studies among workers (8-h workday) suggest that a 24 h continuous exposure at 0.2 mg/m^3 could be tolerated without ill effects. The EEl recommended by Katz (1979) of 0.001 mg/m^3 appears to be exceedingly cautious, and the 1966 recommendation of this Committee (2.0 mg/m^3) appears somewhat high. The Committee believes that a 24-h EEL of 0.2 mg/m^3 is supported by the data on humans cited here and recommends this exposure limit.

The long-term exposure results of Smith (1972), Popescu et al. (1979), and Lauwerys and Buchet (1973) support retention of the 1966 recommendation for a 90-d CEL of 0.01 mg/m^3.

To summarize, the Committee recommends the following exposure limits for mercury vapor:

24-h EEL: 0.2 mg/m^3
90-d CEL: 0.01 mg/m^3

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METHANE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Structural formula:	CH_4
Molecular weight:	16.04
CAS number:	74-82-8
Boiling point:	-161.49°C
Freezing point:	-182.48°C
Vapor pressure:	40 mm Hg (-86.3°C)
Flash point:	-187.78°C
Flammability limits:	5.3-14%
Physical state:	A colorless, odorless, flammable gas and the major component of natural gas. It forms explosive mixtures with air and is moderately soluble in water.

SUMMARY OF TOXICITY INFORMATION

Little information is available on the toxicity of methane. It appears that toxic effects of methane, considered biologically inert, are related to the oxygen deprivation that occurs when the simple alkane is present in air at a high concentration. Hunter (1978) stated that miners evacuate coal pits when the methane concentration in air reaches 2.5% by volume; it is not clear whether evacuation is prompted by the threat of a health hazard or by the danger of explosion.

Kamens and Stern (1973) referred to a literature survey that indicated that methane is biologically inert and that exposure to methane at 10,000 ppm had no toxic effect; conditions of exposure and identification of the test animal were not given, but a U.S. Department of Health, Education and Welfare report was cited (1970).

A report by Pennington and Fuerst (1971) supported the biologic inertness of methane. Suspensions of rabbit erythrocytes were exposed for 18 h to methane by bubbling through the suspensions at 150 ml/min. Such exposure had little or no effect on the color or morphology of the red cells, on the pH of the medium, on the ATP content of the cells, or on the electrophoretic pattern and UV/VIS absorption spectra of the hemoglobin obtained from exposed cells.

Forney and Harger (1972), however, offered evidence that methane has mild anesthetic properties that cannot be explained by oxygen deficiency alone, although such deficiency does seem to be the most important factor. Two of six mice exposed to 70% methane in air died in 18 min, whereas mice exposed to 70% nitrogen in air developed only ataxia. Animals exposed to 50-90% methane in oxygen showed mild depression and a marked decrease in locomotion, but no ataxia. Thus, the toxic effect of methane is much greater than that of nitrogen when available oxygen is low, but methane has little effect when oxygen is readily available. It seems that the toxicity of methane should be

discussed not alone, but rather with respect to the partial pressure of oxygen in the atmosphere in question.

Carpenter (1954) demonstrated an anesthetic effect of methane under hyperbaric conditions in mice; 50% of a group of mice exposed to 2.9 atm of methane did not develop convulsions in response to electroshock treatment.

EXPLOSION HAZARD OF METHANE

Methane forms explosive mixtures with air and the loudest explosions occur when one volume of methane is mixed with 10 volumes of air (or 2 volumes of oxygen) (Windholz et al., 1976). Air containing less than 5.5% methane no longer explodes. The CRC Handbook of Chemistry and Physics (Weast, 1978-1979) gave the limits of flammability of methane as 5% and 15% by volume in air at room temperature.

INHALATION EXPOSURE LIMITS

ACGIH (1982) lists methane in its category of simple asphyxiants. This is described as being gases and vapors, which when present in high concentrations in air, act as simple asphyxiants without other significant physiologic effects. TLVs are not recommended because the limiting factor is the available oxygen.

COMMITTEE RECOMMENDATIONS

EXPOSURE LIMITS

In 1966, the Committee on Toxicology set an EEL and a CEL for methane:

24-h EEL:	5,000 ppm
90-d CEL:	5,000 ppm

No rationale accompanied these limits.

It is obvious that an exposure limit that presents an explosion hazard cannot be recommended, even if it is well below a concentration that would produce toxicity; thus, exposure limits should not exceed 5% by volume in air.

Animals exposed to methane at 10,000 ppm showed no toxic efects; an uncertainty factor of 2 is suggested to derive an EEL-- 5,000 ppm. There is no evidence that duration of exposure is important in methane toxicity. Therefore, no change in the previously recommended exposure limits seems necessary.

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OZONE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Structural formula:	O_3
Molecular weight:	48.0
CAS number:	10028-15-6
Boiling point:	-111.9°C
Density a a gas:	2.144 g/L at 0°C
Density as a liquid:	1.514 g/ml at -195.4°C

General characteristics: A polymeric, highly reactive form of oxygen. It is a bluish explosive gas or blue liquid. It is a powerful oxidizing agent with deodorant and antiseptic properties. It is a respiratory, ocular, and nasal irritant with a characteristic odor.

Conversion factors: ppm = 0.5 (mg/m^3)
mg/m^3 = 2.0 (ppm)

OCCURRENCE AND USE

Ozone is used in organic synthesis and for bleaching waxes, textiles, and oils. It is produced by the action of ultraviolet radiation in sunlight on oxygen. It can be prepared in the laboratory by passing dry air between two plate electrodes connected to an alternating current of several thousand volts.

Airplanes flying at high altitudes may contain ozone at up to 0.5 ppm in the cabin (ACGIH, 1979; Windholz et al., 1976). Ozone in submarine atmospheres is in the parts-per-billion range (NRC, 1974).

Possible ozone contaminants include oxides of nitrogen, hydrogen peroxide, and free radicals (HO_2, OH, HO_3, O_4) (Svirbely and Saltzman, 1957).

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Healthy men have been exposed deliberately to ozone at up to 0.75 ppm for 2 h (Bates et al., 1972; Folinsbee et al., 1975; Hazucha, 1974; Hazucha et al., 1973). Light exercise was also taken at this concentration. A reduction in ventilatory capacity (25% reduction in forced expiratory volume) was reported. Chamber exposures have since shown that a critical ozone concentration for a ventilatory response is probably around 0.3-0.5 ppm (Kleinman et al., 1981).

Exposure of male volunteers at 0.4 ppm for 4 h combined with exercise (700 kg-m per minute) caused significant changes in forced vital capacity (FVC), maximal midexpiratory flow (MMF), and airway resistance (Hackney et al., 1975a). Some subjects with hyperreactive airways have responded to ozone at concentrations as low as 0.37 ppm. Most studies have failed to show any effect at 0.25 ppm. There is also a suggestion in the literature that effects may be greater on the

second day of exposure (Hackney et al., 1975b). A group of young male volunteers were exposed at 0.5 ppm for 2 h. There were only minimal effects on the first day. However, when the exposure was repeated on the next day, 5 of 7 subjects showed significant effects. Twenty subjects were exposed to ozone at 0.5 ppm for 6 h (Kerr et al., 1975). Medium exercise on a bicycle ergometer (100 W at 60 rpm) was used. The subjects experienced dry cough and chest discomfort after exposure. Chest discomfort ranged from tightness on full inspiration to generalized chest pain that was accentuated by exercise, cough, and irritation of the nose and throat. Significant changes from control values were reported for several lung-function tests (specific airway conductance, pulmonary resistance, FVC, and forced expiratory volume in 3 s).

There has been some suggestion that ozone at low concentrations may be carcinogenic or mutagenic in man. Chromosomal abnormalities have been produced in plants and animals, sometimes after low ozone exposures (0.2 ppm for 5 h) (Zelac et al., 1971). Minor chromosomal abnormalities have also been observed in the circulating lymphocytes of humans who have been exposed experimentally at 0.5 ppm for 6-10 h (Merz et al., 1975). So far, however, there is no convincing evidence that ozone at low concentrations causes cancer or congenital malformations in man.

EFFECTS ON ANIMALS

Mittler et al. (1956) reported LC_{50}s for 3-h exposures to ozone as follows:

Mice:	21 ppm
Rats:	21.8 ppm
Cats:	34.5 ppm
Rabbits:	36 ppm
Guinea pigs:	51.7 ppm

Svirbely and Saltzman (1957) reported LC_{50}s for 4-h exposures as follows:

Mice:	2.1- 9.9 ppm
Rats:	7.2-12.3 ppm
Hamsters :	15.8 ppm

Diggle and Gage (1955) investigated toxicity in rats and mice after 4-h exposures to ozone and concluded that the LC_{50} was around 10-12 ppm. Generally, lethal exposures to ozone are accompanied by dyspnea and lethargy, and autopsy reveals lung edema.

Eye effects of ozone exposure were studied in rabbits by Mettier et al. (1960) and Hine et al. (1960). Exposure of rabbits for 1.9-2.8 ppm for 4 h produced no ocular effects, and exposure at 2 ppm 4 h/d was also without eye effects.

Morphologic changes have been reported in the respiratory tracts of animals as a result of exposure to ozone at 0.2-0.25 ppm. Cats were exposed at 0.25, 0.5, and 1.0 ppm for 4.7-6.6 h (Boatman et al., 1974). At all three concentrations, there was considerable

desquamation of the ciliated airway lining cells, the degree of damage being roughly proportional to the ozone concentration. Cytoplasmic vacuolization of ciliated cells and condensation of mitochondria were the most consistent morphologic changes. The mitrochondrial alterations were seen after exposure at all concentrations and were most frequent in the medium-sized airways, 0.8-1.7 mm in diameter. In rats exposed at 0.2 ppm for 3 h (Stephens et al., 1974), degenerative changes were observed in Type I cells, which were replaced by Type II cells. Morphologic changes have also been reported by Mellick et al. (1977) in rhesus monkeys after exposure at 0.5 ppm for 8 h; similar but milder changes were observed in Bonnet monkeys after exposure at 0.2 ppm.

Enzyme alterations have been reported in the respiratory tracts of various animals at about these concentrations. Increased activity of lung glutathione peroxidase and glutathione reductase and increased succinate-dependent lung mitochondrial oxygen consumption have been reported in rats exposed continuously for a week at 0.2 (Chow et al., 1974; Mustafa et al., 1975). Decreases in lysozyme, acid phosphatase, and ß-glucuronidase activity in alveolar macrophages (which appear to be related to dose up to 1 ppm) have been observed in rabbits exposed at 0.25-0.5 ppm ozone for 4 h (Hurst et al., 1970). Decreased red cell acetylcholinesterase and increased osmotic fragility have also been reported in man after exposure at 0.37-0.5 ppm for 2 h (Hackney et al., 1975b) Whether the increased fragility is due to the enzyme alterations or to the spherocytosis that may also occur at this concentration seems debatable.

An increased susceptibility to pulmonary streptococcal infection has been shown to result from exposure to ozone at as low as 0.08 ppm for 3 h (Coffin and Blommer, 1970). This could be due in part to impairment of the bactericidal capabilities of the macrophage, which appears to occur as a result of exposures at about 0.3 ppm.

EPIDEMIOLOGIC STUDIES

Attempts have been made to relate mortality (California Dept. of Public Health, 1955, 1956, 1957) and morbidity (Brant and Hill, 1964; Wayne and Wehrle, 1969) to daily concentrations of oxidant in California. Mortality was at first thought to be related to oxidant concentration; but more refined analyses have shown that the increased temperatures with which the oxidant is positively correlated probably accounts for any association. Morbidity, as indicated by hospital admissions, has not been convincingly shown to be correlated with oxidant concentration. Attempts to correlate oxidant exposure with influenza or other respiratory infections have not been successful. There is some evidence that some asthmatics may have attacks when peak concentrations of oxidant reach 0.25 ppm (Renzetti, 1955), with maximal hourly concentrations of 0.05 or 0.06 ppm.

A study that carried considerable weight in reaching the initial ozone ambient air quality standard of 0.08 ppm was based on the performance of cross-country runners in California (Wayne et al., 1967). A significant relationship was observed between the oxidant concentrations during and 1-3 h before the race and the percentage of runners whose performance decreased compared with that in the previous

home meet. Deterioration began at concentrations around 0.03 ppm--appreciably lower than the national standard. A threshold concentration of 0.012 ppm was later suggested. This study is very hard to interpret. The validity of the suggested threshold is highly questionable, and the conclusion that the deterioration in performance was due to the oxidant concentrations is debatable. All in all, the study seems most unsuitable for standard-setting.

INHALATION EXPOSURE LIMITS

According to ACGIH (1979), the TLV-TWA for ozone is 0.1 ppm and the TLV-STEL is 0.3 ppm. The TLV-TWA for ozone was revised downward from an original recommendation of 1 ppm. ACGIH stated that a TLV-TWA of 0.1 ppm "represents a limit which, although it results in no ostensible injury, may result in premature aging in a manner similar to that from continued exposure to ionizing radiation, if exposure is sufficiently prolonged." OSHA (1982) has established the Federal Standard for ozone in the work environment at 0.1 ppm.

On the basis of a review of air quality criteria for photochemical oxidants, (U.S. Dept. of HEW, 1970) a 1-h National Primary Ambient Air Quality Standard for ozone was set at 0.08 ppm in 1971. This was revised in 1979 to 0.12 ppm (EPA, 1979).

A panel of the NRC Committee on Medical and Biologic Effects of Environmental Pollutants revised the 0.08-ppm standard for the U.S. Senate Committee on Public Works (NRC, 1977). The panel summarized its assessment of the health risk from 0.08 ppm as follows: (1) There are risks that may not be negligible, and (2) they are not dangerously high.

COMMITTEE RECOMMENDATIONS

EXPOSURE LIMITS

The ACGIH TLV-TWA differs from the EELs and CEL for ozone previously suggested by the Committee in 1966, which were 1.0 ppm for 1 h, 0.1 ppm for 24 h, and 0.02 ppm for 90 d. Specifically, 1.0 ppm for 1 h is much less restrictive than the ACGIH TLV-STEL of 0.1 ppm for 15 min. However, 0.1 ppm for 24 h is more stringent than the ACGIH TLV-TWA of 0.1 ppm for a 40-h workweek, except that the working shifts are interspersed with periods of lower (i.e., nonworking background) exposure.

It seems unlikely that rare exposure at the present EEL of 1.0 ppm for 1 h will result in serious effects. This is not much higher than the 0.75 ppm at which human volunteers have been exposed in a number of chamber experiments.

As far as the Committee has been able to learn, no one has been deliberately exposed to ozone at 0.1 ppm for 24 h. The nearest approach was a study in which two groups of 6 males were exposed at 0.2 and 0.5 ppm 3 h/d, 6 d/wk, for 12 wk (Bennett, 1962). No change in vital capacity or forced expiratory volume and no increase in upper respiratory infections per person, compared with controls, were

observed at 0.2 ppm. At 0.5 ppm, there were reversible signs of irritation of terminal bronchi and bronchioles (Bennett, 1962).

Comparison of Seventh Day Adventists living in San Diego (daily maximal hourly average oxidant concentration, 0.07 ppm) with those living in the San Gabriel Valley (comparable concentration, 0.14 ppm) showed no differences in the prevalence of respiratory disease symptoms and chronic bronchitis or in lung function. These data suggest that the current 24-h EEL of 0.1 ppm is adequate.

The 90-d CEL for ozone of 0.02 ppm does not appear to pose a hazard. Airborne concentrations in a number of cities are above this, and the background concentration of ozone in surface air at sea level is reported to be about 0.01-0.03 ppm (NRC, 1977). Given the fact that the CEL for ozone is in the range of ambient background concentrations, there was consideration to raising the 90-d exposure limit. However, because of the limited data on continuous exposure to ozone, the Committee believes that it would not now be prudent to suggest changes. When additional data on the effects of long-term continuous exposure to ozone at low airborne concentrations become available, the CEL should again be reviewed.

In summary, the Committee does not recommend a change in the previously established EELs and CEL for ozone:

1-h	EEL:	1 ppm
24-h	EEL:	0.1 ppm
90-d	CEL:	0.02 ppm

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SULFURIC ACID

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL DATA

Structural formula:	H_2SO_4
Molecular weight:	98.08
Synonyms:	Oil of vitriol
CAS number:	7664-93-9
Boiling point:	290°C
Density:	1.84

General characteristics: It is a clear, colorless, oily liquid. It is corrosive and in concentrated form is a strong oxidizing agent. At 340°C, it decomposes into sulfur trioxide (SO_3) and water. The odor threshold for most people is 1 mg/m^3 (Amdur et al., 1952). It is miscible with water and alcohol, with the generation of much heat and with contraction in volume.

OCCURRENCE AND USE

Sulfuric acid is prepared by the contact process or the chamber process (Duecker and West, 1959). It is widely used industrially, principally in the manufacture of fertilizers, explosives, dyestuffs, other acids, parchment paper, and glue and in the purification of petroleum and the pickling of metal (ACGIH, 1980). Dilute sulfuric acid has been used in the treatment of gastric hypoacidity (Windholz et al., 1976).

SUMMARY OF TOXICITY INFORMATION

A vast literature related to inhalation exposure of animals and humans to sulfuric acid (0.1-1 mg/m^3) has been collected by Carson et al. (1981) in connection with the health effects of automobile exhaust under various conditions.

EFFECTS ON HUMANS

Accidental exposure to sulfuric acid can result during its manufacture and during the handling of concentrated and dilute solutions.

H_2SO_4 is corrosive to all body tissues (Proctor and Hughes, 1978). The concentrated acid acts through its severe dehydrating action, whereas the dilute form is irritating due to its acid properties. Inhalation of concentrated vapor can be extremely irritating to the upper respiratory tract and may cause serious lung damage. Skin contact with concentrated acid may produce severe necrosis and frequent skin contact with dilute solutions may cause dermatitis. Eye contact with concentrated sulfuric acid can cause severe damage including glaucoma and cataracts (Grant, 1974). Fine sprays of sulfuric acid can cause stinging and burning, but the effects are generally transient.

Controlled Human Exposure

Amdur and associates (1952) reported results of exposure of normal unacclimated human subjects to the inhalation of sulfuric acid mist at 0.35-5 mg/m^3 for 5-15 min. Concentrations below 1 mg/m^3 could not be detected by odor, taste, or irritation. For two persons, the threshold was 1 mg/m^3; a concentration of 3 mg/m^3 was noticed by all; and 5 mg/m^3 was very objectionable to some, but less so to others. A deep breath at the last concentration usually produced coughing. Pneumotachographic tracings showed respiratory changes in 15 subjects exposed to measured sulfuric acid mist concentrations. Although sulfuric acid mist, unlike pure SO_2, is capable of penetrating to the deeper, more sensitive portions of the lung, 1 mg/m^3 is unlikely to result in injury to the lung. Particle size of H_2SO_4 mist in the atmosphere plays an important role in producing toxic effects. The smaller particles (0.8 μm) are the most effective.

Uncontrolled Human Exposure

Premysl (1951) found the lungs of sulfuric acid plant workers less affected than those of workers exposed to dust. There was some evidence of corrosion of dental enamel. Raule (1954) stated that the maximum tolerated dose for those unaccustomed to H_2SO_4 was 1 mg/m^3, but those used to it could tolerate three to four times as much. Chronically exposed workers may have various lesions of the skin, tracheobronchitis, stomatitis, conjunctivitis, or gastritis. Malcolm and Paul (1961) found severe erosion of the teeth in battery plant workers. Forming-room workers (sulfuric acid mist at 3-16 mg/m^3) were most severely affected; charging-room workers (0.8-2.5 mg/m^3) were less affected.

Newhouse and associates (1978) assessed pulmonary mucociliary function after exposure at industrial TLVs to sulfur dioxide (5 ppm) and sulfuric acid mist (1 mg/m^3). Bronchial clearance was measured in two sets of 10 healthy, exercising, nonsmoking adults under control and exposure conditions. A [^{99m}Tc]albumin saline aerosol (MMD, 3 μm) was inhaled as a bolus in late inspiration under controlled conditions to produce reproducible deposition in large airways. Lung retention of radioactivity was measured using a gamma camera and computer analysis. Clearance after exposure to both SO_2 and H_2SO_4 was a significant factor ($P < 0.05$) compared with control values. Maximal midexpiratory flow rates (MMFCs) were significantly reduced ($P < 0.01$) after exposure to SO_2 (mean decrease, 8.5%), but only slightly reduced after exposure to H_2SO_4 (1.4%). The speeding in clearance was probably an irritant response in both cases. For SO_2, the response appeared predominantly reflex, whereas H_2SO_4 showed evidence of direct effect.

EFFECTS ON ANIMALS

Schlesinger et al. (1978) studied the effect of chronic inhalation exposure to sulfuric acid mist on mucociliary clearance from the lungs in donkeys. Four animals were exposed 1 h/d, 5 d/wk for 6 mo. The mean mass concentration of acid mist was 102-106 μg/m^3. The MMD was

0.5 m. Clearance was monitored by serial, external, in vivo measurements of retention of an insoluble, radioactively tagged ferric oxide aerosol, which was inhaled after exposure to the acid mist. Bronchial clearance became erratic within the first week of exposure; rates were significantly lower than control values on many test days, although the degree of response varied among the four animals. Two animals exhibited sustained impairment of clearance toward the end of the 6-mo period and continued to have erratic clearance during a 3-mo followup period. No changes in the regional deposition of the ferric oxide occurred during the course of the study in any of the animals. It was proposed that alterations in bronchial mucociliary clearance may be an early, if not the first, physiologic effect of inhalation of sulfuric acid mist, and this may be a factor in the pathogenesis of chronic bronchitis in populations exposed to the sulfur oxide-particle complex in the ambient air, which often includes sulfuric acid.

Cavender et al. (1977) examined the acute pulmonary lesions caused by ozone and sulfuric acid mist in rats and guinea pigs. Rats were not affected by sulfuric acid mist at concentrations up to 100 mg/m^3, except for reduced body weight at the higher concentrations. A true alveolitis developed in guinea pigs exposed to sulfuric acid mist at more than 20 mg/m^3. The ozone lesion was primarily confined to the terminal bronchioles and proximal alveoli. In combination studies with ozone at up to 2 ppm and sulfuric acid mist at up to 10 mg/m^3, the pulmonary lesion and lung and body-weight data were essentially the same as after exposure to ozone alone, and the number of statistically significant synergistic effects in rats and guinea pigs was about what one would expect to occur by chance alone.

In another study Cavender et al. (1979) examined rats and guinea pigs exposed to ozone at 0.5 ppm, sulfuric acid mist at 10 mg/m^3, or their combination 6 h/d, 5 d/wk for 6 mo. Exposure-related microscopic alterations were seen in the lungs of guinea pigs exposed to ozone alone or in combination with sulfuric acid mist. No other microscopic lesions were seen in rats or guinea pigs. No biologically relevant synergistic effects were noted in animals exposed to the combination of ozone and sulfuric acid mist.

According to Yoshida et al. (1970), guinea pigs that inhaled (46 exposures twice a week for a period of 23 weeks) sulfuric acid mist alone developed breathing difficulties. The formation of lung abscesses was also observed. Inhalation of the mist remarkably reinforced experimental asthma caused by albumin sensitization.

Schlesinger et al. (1978) concluded from their studies with donkeys that changes in bronchial clearance rate were observed at H_2SO_4 concentrations that produced no measurable effect on regional deposition, pulmonary resistance, or dynamic compliance; thus, alteration rate may be a sensitive indicator of acute response to submicrometer respiratory irritants.

Fenters et al. (1979) investigated the effects of exposure of mice to sulfuric acid mist at 1.4 mg/m^3, to carbon particles at 1.5 mg/m^3, and to mixtures of the two at 1.5 mg/m^3 3 h/d, 5 d/wk for up to 20 wk. The immunologic state of the animals was examined directly by the primary response of splenocytes after specific antigen stimulation and indirectly by infectivity studies. A measure of the effects on the immune system without the antigenic stimulation was

obtained by determination of serum immunoglobulin concentrations. Significant alterations in immunoglobulin titer, decrease in primary antibody response in splenocyte antigenic stimulation, and decrease in resistance to respiratory infection (as measured by mortality, survival time, and pulmonary consolidation) after 20 wk of exposure were noted. In addition, bactericidal capacity of lungs was reduced in mice exposed to either sulfuric acid, carbon alone, or mixtures of the two. Subtle morphologic changes in the respiratory tract were detected by scanning electron microscopy. Thus, the alterations in the defense system suggest that prolonged exposure to low concentrations of sulfuric acid or to mixtures with carbon particles reduces the ability of mice to resist the secondary stress of respiratory infection.

Alarie et al. (1973) exposed groups of cynomolgus monkeys to sulfuric acid mist at 0.38-4.79 mg/m^3 continuously for 78 wk. Particle size varied from submicrometer to 4 m in MMD. Groups of guinea pigs were exposed at 0.10 or 0.08 mg/m^3 with MMD of 2.8 and 0.8 μm, respectively, continuously for 52 wk. No deleterious effects were seen in guinea pigs. In the monkeys, concentrations of 2.43 and 4.79 mg/m^3 with MMD of 3.60 and 0.73 μm, respectively, produced definite deleterious effects on pulmonary structures and deterioration in pulmonary function. At lower concentrations, these effects were less pronounced or absent. Microscopic changes consisted of focal epithelial hyperplasia and focal thickening of the bronchiolar walls.

In a later study, Alarie et al. (1975) exposed groups of cynomolgus monkeys and guinea pigs to mixtures of sulfur dioxide at 0.1-5.0 ppm, fly ash at 0.5 mg/m^3, and sulfuric acid mist at 0.1-1 mg/m^3 for 52 wk (guinea pigs) or 78 wk (monkeys). Pulmonary function tests and serum biochemical and hematological analyses were conducted before and periodically during exposure. At the termination of exposure, the lungs were examined microscopically. Analysis of the data revealed that sulfuric acid mist was responsible for the effects observed. No synergistic action of the pollutants was detected.

COMMITTEE RECOMMENDATIONS

EXPOSURE LIMITS

The work of Amdur et al. (1952) showed that H_2SO_4 at up to 5 mg/m^3 was tolerated by humans for 15 min in an experimental setting. The work of Kerr et al. (1981) demonstrated that pulmonary function was not affected by exposure of humans to H_2SO_4 at 0.1 mg/m^3 for 4 h in a chamber. Cynomolgus monkeys exposed chronically to H_2SO_4 up to 4.8 mg/m^3 suffered changes in respiratory function and structures. The results of these investigations suggest that humans can be exposed to H_2SO_4 atmospheric mists at 5 mg/m^3 for short periods without injury.

The EELs set in 1969 are therefore still applicable:

10-min EEL:	5 mg/m^3
30-min EEL:	2 mg/m^3
60-min EEL:	1 mg/m^3

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