TR 77-565

INFORMATION PROFILES ON POTENTIAL OCCUPATIONAL HAZARDS

Jane E. Hoecker
Patrick R. Durkin
Arnold Hanchett
Leslie N. Davis
William M. Meylan
Stephen J. Bosch

Center for Chemical Hazard Assessment
Syracuse Research Corporation
Merrill Lane
Syracuse, New York 13210

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Project Officer - Jimmy Perkins

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National Institute for Occupational Safety and Health
5600 Fishers Lane, Room 1-58
Rockville, Maryland 20857

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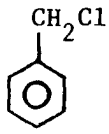
INDIVIDUAL CHEMICAL COMPOUNDS

BENZYL CHLORIDE (α-chlorotoluene)

1. Chemical Structure



2. Chemical Abstracts Service Number

100-44-7

3. Registry of Toxic Effects of Chemical Substances Number

XS89250

4. Production Figures and Economic Trends in Production

Production of benzyl chloride was reported at 80 million lbs. in 1972 (USITC, 1972). Currently, about 89 million lbs. (SRC estimate) are produced based upon an 84% utilization of capacity (Carlson and Erskine, 1973).

The growth rate for benzyl chloride is expected to be 4% per year through 1979 (Chem. Prof., 1975).

5. Uses

Uses for benzyl chloride are as follows (Chem. Prof., 1975):

n-Butyl benzyl phthalate	67%
Benzyl alcohol	13%
Quaternary amines	12%
All other	8%
	100%

6. Number of Companies Producing and Using

The four manufacturers producing benzyl chloride are Monsanto Co., Stauffer Chem. Co., Tenneco, Inc., and UOP, Inc. at four different locations (SRI, 1977).

More than 90% of production is captively used by three of the producing companies (SRC estimate).

7. Biological Effects of Exposure

a) Target Organs

Benzyl chloride is highly irritating to the eyes, ears, nose, and throat and can cause lung edema (Smyth, 1956). On dermal applications, this

Table 1. Acute Toxicity of Benzyl Chloride

Organism	Route	LD_{50} or LC_{50}	Reference
Rat	oral	1231 mg/kg	NIOSH, 1976
	subcutaneous	1000 mg/kg	Druckrey et al., 1970
	inhalation	150 ppm x 2 hr.	Mikhailova, 1964
Mouse	oral	1624 mg/kg	NIOSH, 1976
	inhalation	80 ppm x 2 hr.	Mikhailova, 1964

chemical is a strong sensitizing agent in guinea pigs (Von Oettingen, 1955). Mikhailova (1964) reports that exposure to benzyl chloride can cause leucopenia.

b) Acute Effects

Information on the acute toxicity of benzyl chloride is summarized in Table 1. In addition, Flury and Zernik (1931) found that inhalation of 16 ppm benzyl chloride for eight hours is dangerous to cats. In a paper not reviewed for this report, Kurlzandskii and coworkers (1975) have discussed acute toxicity data on benzyl chloride.

In acute *in vitro* exposures, benzyl chloride has been found to be moderately toxic to Ehrlich-Landschutz diploid ascites tumor cells (Holmberg and Malmfors, 1974).

c) Subchronic Effects

No information has been encountered on the subchronic toxicity of benzyl chloride.

d) Chronic Effects

i) Carcinogenicity - Subcutaneous injections of rats with benzyl chloride over a period of 51 weeks has resulted in the development of local sarcomas with lung metastases. At weekly doses of 40 mg/kg, tumors developed in 3 of 14 treated animals within 500 days. At weekly doses of 80 mg/kg, sarcomas developed in 6 of 8 treated animals within 500 days (Druckrey *et al.*, 1970; Preussmann, 1968). However, in mice given 8 to 12 intraperitoneal injections, three times per week, for total doses of 600 mg/kg, 1500 mg/kg, and 2,000 mg/kg, the tumor incidence was not significantly different from control animals after 24 weeks (Poirier *et al.*, 1975).

ii) Mutagenicity - At treatment levels of 2 mg/plate, benzyl chloride is mutagenic to strains TA98 and TA100 of *Salmonella typhimurium* (McCann *et al.*, 1975).

iii) Teratogenicity - No studies have been encountered on the teratogenicity of benzyl chloride.

iv) Other Chronic Studies - The hazards of chronic inhalation poisoning by benzyl chloride have been discussed by Kurlyandskii and Ordynskii (1973). This paper has not been reviewed for this profile.

e. Human Effects

Exposures to benzyl chloride at 16 ppm for one minute are reportedly intolerable to man (Flury and Zernik, 1931). At 32 ppm, benzyl chloride causes severe irritation to the eyes and respiratory tract (Von Oettingen, 1955).

8. Threshold Limit Value

The TLV for benzyl chloride is 1 ppm (ACGIH, 1971). This value is apparently based on the reports of Flury and Zernik (1931) and Smyth (1956).

9. Other Standards

In the U.S.S.R., the maximum allowable concentration of benzyl chloride in the workplace is 0.1 ppm (Winnell, 1975).

Benzyl chloride must have a corrosive material label during transport (D.O.T., 1976).

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Smyth, H.F., Jr. (1956), Am. Ind. Hyg. Assoc. Quart., 17: 129.

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Von Oettingen, W.F. (1955), U.S. Dept. of Health, Education, and Welfare, Public Health Service Publication No. 414, Washington, D.C., pp.300-302, summarized in IARC, 1976.

Winell, M.A. (1975), Ambio., 4: 34-36.

CARBON BLACK

1. Chemical Structure

C

2. Chemical Abstracts Service Number

7440-44-0

3. Registry of Toxic Effects of Chemical Substances Number

FF52500

4. Production Figures and Economic Trends in Production

About 3 billion pounds (demand) of carbon black were produced in 1976 (Chem. Prof., 1976). Production is expected to increase at the rate of 2% per year through 1980 (Chem. Prof., 1976b).

5. Uses

By far the major use of carbon black is in the production of rubber for tires. Breakdown of usage is as follows:

Rubber	91%
Exports	3%
All other	6%
	100%

6. Number of Companies Producing and Using

The following companies produce carbon black at 32 locations (SRI, 1977).

Ashland Oil Inc.
Cabot Corp.
Cities Service Co.
Continental Carbon Co.
Harmon Colors Corp.
J.M. Huber Corp.
International Minerals & Chemical Corp.
Phillips Petroleum Co.
Sid Richardson Carbon Co.

7. Biological Effects of Exposure

a) Target Organs

Little detailed information is available on organ damage caused by carbon black exposure. In chronic inhalation exposures, bronchopneumonia and

emphysema were noted in mice and monkeys, respectively. However, the emphysema was not definitely attributed to carbon black. In addition, accumulation of carbon black by phagocytic cells and increased amyloidois were noted in the liver, spleen, and kidneys of exposed animals (Nau et al., 1962). Vacher and coworkers (1973) have demonstrated that carbon black, administered intravenously to mice, causes blockade of the reticuloendothelial system as evidenced by a decrease in the phagocytic index.

b) Acute Effects

The acute LD_{50} of carbon black, administered intravenously to mice, is 440 mg/kg, with a 95% confidence interval of 374 mg/kg to 517 mg/kg (Vacher et al., 1973).

c) Subchronic Effects

No studies have been encountered on the subchronic toxicity of carbon black.

d) Chronic Effects

i) Carcinogenicity

On dermal application to mice, four of fourteen carbon black fractions were found to result in increased malignant tumor development when croton oil was used as a promoting agent (Von Haam and Malette, 1952). In addition, a benzene extract of one of three carbon blacks tested was shown to result in an increased tumor incidence in mice (Nau et al., 1958a). However, unfractionated carbon black administered orally, dermally, or subcutaneously to rats or mice resulted in no increased tumor development (Von Haam et al., 1958). Similarly, no increased tumor incidence attributed to carbon black was found in chronic oral, dermal, or inhalation exposures of hamsters, mice, guinea pigs, rabbits, and monkeys (Nau et al., 1958a and b, and 1962). Single or double subcutaneous or intravenous injections of whole carbon black also resulted in no increased tumor incidence in mice, guinea pigs, or rabbits over a 20 month post-treatment observation period (Nau et al., 1960). Carbon black inhibits the activity of some carcinogens, presumably due to adsorption of the carcinogen on to some component of carbon black (Nau et al., 1958a; Von Haam et al., 1958).

ii) Mutagenicity

No studies have been encountered on the mutagenicity of carbon black.

iii) Teratogenicity

No studies have been encountered on the teratogenicity of carbon black.

iv) Other Chronic Effects

Nau and coworkers (1962) subjected hamsters, mice, guinea pigs, rabbits, and monkeys to prolonged inhalation exposures to two types of carbon black: channel black which was tested at 2.4 mg/cubic meter and furnace black which was tested at 1.6 mg/cubic meter. Animals were exposed for seven hours per day, five days per week. Mice, which were exposed for their entire lifespan, showed increased lung weight, accumulation of carbon black in the pulmonary system, as well as changes in the liver, spleen, and kidney (described in Section 7a). Monkeys, which were exposed for up to 13,000 hours, evidenced electrocardiographic changes which were indicative of right atrial and right ventrical strain. Mice, fed diets containing 10% whole carbon black or carbon black fractions for 12-18 months, experienced no apparent adverse effects (Nau et al., 1958b). Similarly, no adverse effects were attributed to multiple dermal applications of carbon black over 9 to 25 month periods in mice, rabbits, and monkeys (Nau et al., 1958a).

e) Human Effects

An epidemiological study of workers in the carbon black industry found no evidence for increased cancer mortality or morbidity associated with occupational exposure to carbon black (Ingalls and Risquez-Iribarren, 1961).

Inhalation of carbon dust particles at a concentration of 50 mg/ml results in slight irritation of the throat and increased mucociliary transport (Camner et al., 1973).

8. TLV

Based on a monitoring study in rubber plants by Sands and Benitez (1960), the TLV for carbon black has been set at 3.5 mg per cubic meter (ACGIH, 1971). This is identical to the standard set by OSHA (1974).

9. Other Standards

No other standards for carbon black have been encountered.

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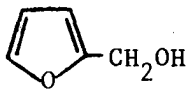
Furfuryl Alcohol (2-hydroxymethylfuran)

1. Molecular Structure



2. Chemical Abstracts Service Number

98-00-0

3. Registry of Toxic Effects of Chemical Substances Number

LU91000

4. Production Figures and Economic Trends in Production

Production of furfuryl alcohol in 1974 was 50 million lbs. (Bradley, 1975). The average growth rate for this compound is expected to be 3% annually through 1979 (Bradley, 1975).

5. Uses

Furfuryl alcohol is mainly used as a starting monomer in the production of "furan resins" or "furan polymers," and is also used to produce THFA (tetrahydrofurfuryl alcohol) (Bradley, 1975).

6. Number of Companies Producing and Using

Furfuryl alcohol is manufactured by the Quaker Oats Company at three different locations (SRI, 1977).

Since 20 companies produce "furan resins" or "furan polymers," it may be assumed that at least that many companies use furfuryl alcohol (SRI, 1977; Bradley, 1975).

7. Biological Effects of Exposure

a) Target Organs

Furfuryl alcohol mainly effects the central nervous system, causing death by respiratory depression (Fine, 1950).

It displays an antispasmodic effect on smooth muscles while causing paralysis of sensory nerves and, in rabbits, paralysis of skeletal muscles (Fine, 1950). Jacobson and coworkers (1958) report pulmonary damage as well.

b) Acute Effects

The acute effects of furfuryl alcohol on laboratory animals are summarized in Table 1.

Chernousov (1974) reports that when applied in 1-50% solutions to guinea pig skin, furfuryl alcohol proved mildly irritating and somewhat allergenic.

c) Subchronic Effects

Rats and mice exposed to 19 ppm daily for 6 weeks showed no toxic effects except for moderate pulmonary congestion; no significant cell changes were observed, however (ACGIH, 1971).

d) Chronic Effects

No information on the chronic effects of exposure to furfuryl alcohol was available.

e) Human Effects

While small doses of furfuryl alcohol stimulate respiration, larger doses appear to depress respiration in addition to reducing body temperature, producing nausea, salivation, diarrhea, dizziness, and diuresis (ACGIH, 1971). Jacobson et al. (1958) state that furfuryl alcohol distributes itself uniformly through the body and has little effect on particular enzymes in special cell structure.

Jacobson et al. (1958) mention a study in which human subjects were able to detect furfuryl alcohol in concentrations around 8 ppm. It is described by the same volunteers as sweet, alcoholic, and ether-like.

Virtamo (1976) cites a study of ten iron and steel foundries where 22% of the measurements for furfuryl alcohol concentrations in the air of core-making areas exceeded the acceptable TLV.

8. TLV

The TLV standard recommended by ACGIH (1971) is 5.0 ppm.

9. Other Standards

OSHA recommends a limit in air of 50 ppm (Federal Register, 1974).

10. Other Data

A method for determination of furfuryl alcohol in the environment is presented by Kemka (1971), while Sakuma (1975) states that difficulties were encountered in introducing cigarette smoke, a source of furfuryl alcohol, into gas chromatographs.

In studies performed on sarcoma inhibition, furfuryl alcohol was found to inhibit grafted sarcoma M.C.D.B.I. in groups of mice by 3%, but this is considered to be insignificant (P=0.5) (Boyland, 1940).

Table 1. Acute Effects of Furfuryl Alcohol

Organism	Route	Dose	Response	Reference
Mouse	n.s.	700 ppm x 10 min.	No toxic effects	ACGIH, 1971
Mouse	oral	40 mg/kg	LD_{50}	Boyland, 1940
Rat	n.s.	700 ppm x 4 hr.	16% died	ACGIH, 1971
Rat	n.s.	700 ppm x 8 hr.	25% died	ACGIH, 1971
Rat	oral	275 mg/kg 2% aqueous sol'n	LD_{50}	Fine, 1950
Rat	ihl	233 ppm x 4 hr.	LC_{50}	Jacobson et al., 1958
Rabbit	sub. cut.	600 mg/kg 2% aqueous sol'n	Lethal	Fine, 1950
Rabbit	i.v.	650 mg/kg 10% aqueous sol'n	LD_{50}	Fine, 1950

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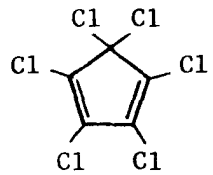
HEXACHLOROCYCLOPENTADIENE

1. Chemical Structure



2. Chemical Abstracts Service Number

77-47-4

3. Registry of Toxic Effects of Chemical Substances Number

GY12250

4. Production Figures and Economic Trends in Production

At present 9-12 million lbs. of hexachlorocyclopentadiene are produced annually (SRC estimate based upon use data).

The growth rate is expected to increase by approximately 10% annually until 1980 (Blackford, 1976), based upon the major uses.

5. Uses

Hexachlorocyclopentadiene is used to produce the flame retardant chlorendic anhydride, which has applications in polyesters, and to produce chlorendic acid which is used as a flame retardant in resins (Blackford, 1976; Pattison and Hindersinn, 1971). These fire retardant uses consume about 8 million lbs. annually.

Hexachlorocyclopentadiene is also used as an intermediate in the production of pesticides, such as aldrin, dieldrin, endosulfan, Pentac, etc. (Whetstone, 1964; Ayers and Johnson, 1976). Aldrin and dieldrin use in the U.S. has been outlawed, so production of these is for export only.

6. Number of Companies Producing and Using

Northwest Industries, Inc. and Occidental Petroleum Corp. manufacture hexachlorocyclopentadiene in three different locations.

The bulk of production is captively consumed. The remainder is probably sold to several pesticide producers.

7. Biological Effects of Exposure

a) Target Organs

Hexachlorocyclopentadiene is apparently a potent irritant. Inhalation of this compound causes lacrimation, salivation, and gasping respiration in mice, rabbits, rats, and guinea pigs. Long term inhalation results in degenerative changes of the brain, heart, liver, adrenals, and kidneys as well as severe lung damage (Treon et al., 1955).

b) Acute Effects

Deichman (1969) states that the oral LD_{50} of the compound for albino rats is 280 mg/kg and that the dermal LD_{50} for rabbits ranges from 430 mg/kg to 610 mg/kg. Without specifying the route of administration, Melnikov (1971) states that the LD_{50} for rats is 3,100 mg/kg.

c) Subchronic Effects

No information has been encountered.

d) Chronic Effects

One hundred and fifty exposures, each lasting seven hours, to 0.15 ppm over a 216 day period killed four of five mice but were not lethal to rabbits, rats, and guinea pigs. However, as summarized above, these exposures resulted in labored respiration, irritation, and a variety of pathological changes (Treon et al., 1955).

e) Human Effects

Inhalation of this compound is irritating to the respiratory tract and causes lacrimation in humans (ACGIH, 1971).

8. TLV

The TLV for this compound has been set at 0.01 ppm (ACGIH, 1971).

9. Other Standards

No other standards have been encountered.

10. Other Data

Hexachlorocyclopentadiene is a minor thermal decomposition product of mirex (Holloman et al., 1975).

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Pattison, V.A. and Hindersinn, R.R. (1971), "Halogenated Flame Retardants," Kirk-Othmer supplement p. 477-480.

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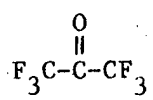
Whetstone, R.R. (1964), "Chlorocarbons and Chlorohydrocarbons," Kirk-Othmer, 5: 240-252.

HEXAFLUOROACETONE

1. Chemical Structure



The IUPAC official name for this compound is hexafluoropropanone.

2. Chemical Abstract Service (CAS) Number

684-76-2

3. Registry of Toxic Effects of Chemical Substances (RTECS) Number

UC24500

4. Production Figures and Economic Trends in Production

Production and growth figures are not available for this compound.

5. Uses

Hexafluoroacetone is used as a chemical intermediate. A gas at room temperature, it forms various hydrates with water which are used as solvents for resins and polymers. Other derivatives are used to make water repellent coatings for textiles and also to produce polymers (Woolf, 1966).

6. Number of Companies Producing and Using

Hexafluoroacetone is manufactured by Allied Chemical Corporation and DuPont at six different locations (SRI, 1977).

A substantial percentage of production is probably captively used to make various derivatives which are commercially important, such as hexafluoroacetone sesquihydrate. However, information as to the exact number of users of hexafluoroacetone is not available.

7. Biological Effects of Exposure

a. Target Organs

Data on organ damage from acute hexafluoroacetone exposure is somewhat inconsistent. On acute oral and inhalation exposures of rats and dogs, Borzelleca and Lester (1964) noted little evidence of lung damage and no signs of heart, liver, or kidney damage. However, citing an unpublished report from Haskell Laboratory, ACGIH (1971) stated that the liver, kidney, testes, and thymus of rats showed injury after a single inhalation exposure to 200 ppm for four hours. Subchronic inhalation exposures of rats and dogs to hexafluoroacetone resulted in pathological changes in the testes, spleen, thymus, lymph nodes, and bone marrow (ACGIH, 1971). Acute dermal exposure results in eschar formation.

b. Acute Toxicity

The acute toxicity of hexafluoroacetone is summarized in Table 1. Central nervous system depression seems to be the major sign of acute intoxication (Crank et al., 1970; Borzelleca and Lester, 1964 and 1965). Borzelleca and Lester (1965) were unable to relate CNS depression to inhibition of brain cholinesterase.

c. Subacute Toxicity

Rats and dogs have been subjected to 90 day inhalation exposure to 0.1, 1.0, and 12 ppm hexafluoroacetone. At the highest concentration, both organisms developed severe testicular damage along with slight hypoplasia of the spleen, thymus, and lymph nodes. Rats also showed some signs of lymphocytosis and renal dysfunction. Anemia, neutrophilia, hyperglycemia, and hypoalbuminuria developed in dogs. At 1 ppm, the most notable effects were increased lung weight in dogs and renal dysfunction in rats. Exposure to 0.1 ppm caused no marked adverse effect in either organism (ACGIH, 1973). Hexafluoroacetone given subcutaneously to rats at doses of 50 mg/day for twelve days caused significant decreases in total body weight and in the weight of the testes, thymus, and seminal vesicles (Crank et al., 1970).

d. Chronic Toxicity

Brittelli and coworkers (1977) have found that hexafluoroacetone, given to pregnant rats on days 6 to 16 of gestation, causes gross external, soft tissue, and skeletal abnormalities at doses ranging from 1 mg/kg/day to 25 mg/kg/day.

e. Toxicity to Humans

No information has been encountered on the effects of hexafluoroacetone on humans.

8. TLV

Based on an unpublished study from Haskell Laboratory, the TLV for hexafluoroacetone has been set at 0.1 ppm (ACGIH, 1971).

9. Other Standards

No other standards for hexafluoroacetone have been encountered.

Table 1. Acute Toxicity of Hexafluoroacetone

Extent of Compound Hydration	Organism	Route	Dose	Response	Reference
	Rat	Oral	191 mg/kg	LD_{50}	Borzelleca and Lester, 1964
		Inhalation	275 ppm x 3 hr	LC_{50}	Borzelleca and Lester, 1964
			900 ppm x 0.5 hr	LC_{50}	Borzelleca and Lester, 1965
		Inhalation	300 ppm x 4 hr	Lethal	ACGIH, 1971
Hydrate	Rat	Oral	190 mg/kg	LD_{50}	Borzelleca and Lester, 1965
	Rabbit	Dermal	113 mg/kg	LD_{50}	Borzelleca and Lester, 1965
	Dog	Inhalation	5000 ppm x 0.5 hr	Not lethal	Borzelleca and Lester, 1965
			10,000 ppm x 0.5 hr	Lethal	Borzelleca and Lester, 1965
Sesquihydrate	Mouse	Oral	300 mg/kg	LD_{50}	Crank et al., 1970
		Intraperitoneal	250 mg/kg	LD_{50}	Crank et al., 1970
Trihydrate	Not specified	Not specified	190 mg/kg	LD_{50}	Melnikov, 1971

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HYDROGEN CHLORIDE (gas)

1. Chemical Structure

H - Cl

2. Chemical Abstract Service (CAS) Number

7647-01-0

3. Registry of Toxic Effects of Chemical Substances (RTECS) Number

MW96250

4. Production Figures and Economic Trends in Production

Hydrogen chloride is a gas at normal room temperature and atmospheric pressure and dissolves in water to become hydrochloric acid. By far the largest use of hydrogen chloride gas at present is for the chlorination of organic compounds (Haas, 1971). The annual production of HCl(g) probably falls in the range of 4-5 billion lbs. (SRC estimate based upon the assumption that most of the HCl(g) produced is used to make hydrochloric acid.)

Growth of the industry is probably dependent upon the manufacture of organic chlorinated compounds. On that basis, production of HCl(g) will increase at several percent per year.

5. Uses

Hydrogen chloride gas is primarily used to make hydrochloric acid.

6. Number of Companies Producing and Using

Of the 39 companies (83 locations) which produce hydrochloric acid, at least 10 are known to produce anhydrous hydrogen chloride. Additionally, it should be assumed that a number of other companies will generate HCl(g) during various organic syntheses.

It is assumed that the number of companies using HCl(g) will be about the same or perhaps smaller than the number generating it (SRC estimate).

7. Biological Effects of Exposure

a) Target Organs

Because of its highly corrosive nature, hydrogen chloride gas is irritating in all concentrations to eyes and mucous membranes (Machle et al., 1942) with pathological changes occurring in bronchial and tracheal epithelium (Patty, 1949). Machle et al. (1942) add that alveolar epithelial changes and

vascular injury also occur. In addition to lung damage, liver injury occurs in many instances (Machle et al., 1942; Patty, 1949).

b) Acute Effects

Following exposure to the volatile products (including hydrogen chloride) of burning vinyl chloride - vinyl acetate copolymer fibers or veniplast, mice died within 2-10 days (Eitingon et al., 1975). White rats and mice exposed to heated Freon-12 suffered toxic reactions due to pyrolysis products, hydrogen flouride, and hydrogen chloride gas (Cheren`kii and Shugaev, 1974).

Table 1 summarizes the acute effects of hydrogen chloride gas exposure to experimental animals.

c) Subchronic Effects

Table 2 summarizes the effects of subchronic exposures to hydrogen chloride.

d) Chronic Effects

i) Carcinogenicity - No information available.

ii) Mutagenicity - No information available.

iii) Teratogenicity - Pavlova (1976) describes possible teratogenic effects to offspring of rats exposed to hydrogen chloride.

iv) Other - Sanotskii and coworkers (1976) report that pregnancy in rats may modify their sensitivity to poisoning by hydrogen chloride.

e) Human Effects

Due to its highly irritating nature, hydrogen chloride gas is rarely a cause of acute intoxication by inhalation (Patty, 1949). Firefighters who were exposed to one to four polyvinyl chloride (PVC) fires, however, suffered acute intoxication by hydrogen chloride which is formed by burning PVC. Symptoms displayed by the 170 firefighters were chest, neck, and throat pain, dizziness, severe headache, and irregular pulse. One fatality occurred (Dyer and Esch, 1976). Exposure to skin also results in severe burns (Patty, 1949).

Chronic exposure, which occurs in some industrial situations, commonly causes tooth decay (Elkins, 1959), bleeding of gums and nose, ulcers of oral and nasal mucosa, and sensitive skin (Patty, 1949). Although any concentration over 10 ppm is greatly irritating, it has been claimed that workers constantly exposed develop immunity to hydrogen chloride gas (Elkins, 1959).

Patty (1949) comments that concentrations of 50-100 ppm are impossible to work in, difficult but not impossible at 10-50 ppm, and possible at 10 ppm.

Table 1. Acute Effects

Organism	Route	Dose	Response	Reference
Mouse	Inhalation	13,745 ppm x 5 min.	LC_{50}	Darmer et al., 1974
Mouse	Inhalation	2,644 ppm x 3 min.	LC_{50}	Darmer et al., 1974
Rat	Inhalation	40,989 ppm x 5 min.	LC_{50}	Darmer et al., 1974
Rat	Inhalation	4,701 ppm x 30 min.	LC_{50}	Darmer et al., 1974
Rabbit	Inhalation	4,416 ppm x 30 min.	LC_{LO}	NIOSH, 1976
Guinea Pig	Inhalation	4,416 ppm x 30 min.	LC_{LO}	NIOSH, 1976
Rabbit, Guinea Pig	Inhalation	4,570 ppm x 30 min.	Lethal	Machle et al., 1942
Rabbit, Guinea Pig	Inhalation	714 ppm x 6 hr.	Lethal	Machle et al., 1942
Cat, Rabbit, Guinea Pig	Inhalation	(3,400 ppm) x 1.5 hr.	Death in 2-6 days	Patty, 1949
Cat, Rabbit, Guinea Pig	Inhalation	(1,350 ppm) x less than 1.5 hr.	Severe irritation, dippnea, corneal clouding	Patty, 1949
Cat, Rabbit, Guinea Pig	Inhalation	675 ppm x 2-6 hr.	Some fatalities	Patty, 1949
Cat, Rabbit, Guinea Pig	Inhalation	300 ppm x 6 hr.	Slight corneal corrosion; upper respiratory irritation	Patty, 1949
Cat, Rabbit, Guinea Pig	Inhalation	100-140 ppm x 6 hr.	Effects same but less than for 300 ppm x 6 hr.	Patty, 1949

Table 2. Subchronic Effects

Organism	Route	Dose	Response	Reference
Guinea Pig, Rabbit, Pigeon	Inhalation	100 ppm x 6 hr/day x 50 days	Slight unrest, nose and eye irritation; decreased hemoglobin	Patty, 1949
Monkey and Unspecified Smaller Animals	Inhalation	33 ppm x 6 hr/day x 20 days	No harm observed; larger doses incurred weight loss proportionate to severity of exposure	Patty, 1949
3 Rabbits, 3 Guinea Pigs, 1 Monkey	Inhalation	34 ppm x 6 hr/day x 5 days/wk x 4 wks	No toxic effects observed immediately; no changes in pathology	Machle et al., 1942

Henderson and Haggard (1943) add that concentrations of 1,000-2,000 ppm are dangerous even for short exposures.

8. TLV

The TLV for hydrogen chloride gas is recommended to be 5 ppm (about 7 mg/m^3), which is not great enough to be toxic, but is marginal for extreme irritation (ACGIH, 1971).

9. Other Standards

Most recommendations for exposure to hydrogen chloride gas are 5 ppm (Smyth, 1956; Czechoslovakia, 1969 - cited by ACGIH, 1971; OSHA-Federal Register, 1974). Elkins (1959) and Cook (1945) recommend 10 ppm (ACGIH, 1971), while the 1966 Soviet level is set at 4 ppm (ACGIH, 1971).

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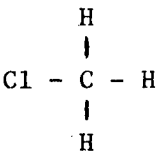
METHYL CHLORIDE

1. Chemical Structure



The IUPAC official name for methyl chloride is chloromethane.

2. Chemical Abstracts Service Number

74-87-3

3. Registry of Toxic Effects of Chemical Substances Number

PA63000

4. Production Figures and Economic Trends in Production

In 1976 the production of methyl chloride totaled 387 million pounds (USITC, 1976p). The growth rate is projected to rise 6% annually through 1980 (Chem. Prof., 1976a).

5. Uses

Methyl chloride is used primarily in the production of silicones and tetramethyl lead, and has additional minor uses as listed below:

Silicones	40%
Tetramethyl lead	35%
Butyl rubber	4%
Methyl cellulose	4%
Herbicides	4%
Quaternary amines	4%
Misc.	9%
	100%

6. Number of Companies Producing and Using

Methyl chloride is produced by the following companies at a total of 12 locations (SRI, 1977).

Allied Chem. Corp.
Continental Oil Co.
Diamond Shamrock Corp.
Dow Chem. U.S.A.

Ethyl Corp.
Gen. Elec. Co.
Stauffer Chem. Co.
Union Carbide Corp.

There are numerous companies which use methyl chloride.

7. Biological Effects of Exposure

a) Target Organs

The toxic action of methyl chloride is believed to result from the methylation of essential enzymes, cofactors, and proteins, thereby rendering them inactive (Davis et al., 1977).

The literature consistently cites evidence of damage to liver, kidneys and central nervous system (Davis et al., 1977; ACGIH, 1971; Fairhall, 1957) with some reports of lung congestion in addition to hemorrhage of epicardium and endocardium (McNally, 1946; Mackie, 1961). Mackie (1961) also mentions finding many lipoid filled histiocytes in the leptomeninges of the brain hemispheres.

b) Acute Effects

Table 1 summarizes the effects of acute exposure to methyl chloride.

c) Subchronic Effects

Weissbecker and coworkers (1971) report increased mucus flow in cats inhaling cigarette smoke. They attributed this result to methyl chloride which was found to be a constituent of cigarette smoke.

Chickens exposed 3 weeks to methyl chloride concentrations of 2,000 ppm beginning when 11 weeks old developed weak and abducted legs. Death occurred after 5-6 weeks exposure following gradual debility and paralysis (EPA, 1977).

Dogs inhaling more than 1,000 ppm methyl chloride 6 hours daily died after 2-6 exposures (Davis et al., 1977).

d) Chronic Effects

i) Carcinogenicity

No literature is available.

ii) Mutagenicity

Methyl chloride was found to be mutagenic to Salmonella typhimurium tester strain TA1535 according to Andrews and coworkers (1976).

Table 1. Acute Effects - Methyl Chloride

Organism	Route	Dose	Response	Reference
Mouse	ihl	3,146 ppm x 7 hrs.	LC_{Lo}	NIOSH, 1976
Mouse	ihl	500 ppm x 6 hr/day x 1 wk.	Convulsions; death by terminal hemoglobinuria	Von Oettingen, 1964
Mouse	ihl	500 ppm x 6 hr/day x 15 wks.	If survived, permanent tonic contraction of adductor muscles of hind and fore limbs	Von Oettingen, 1964
Rat	ihl	200-2,000 ppm x 1 hr.	LD_{50} in 14 days	
Rat	ihl	3,000 and 4,000 ppm x 6 hr/day	Died 1 or 2 days after 3rd-5th exposure; severe spasmodic dyspnea	Von Oettingen, 1964
Guinea pig	ihl	20,000 ppm x 2 hrs.	LC_{Lo}	NIOSH, 1976
Guinea pig	ihl	2,000 ppm x 6 hr/day	Succumbed after 2nd-3rd exposure	Von Oettingen, 1964
Rabbit	ihl	2,000-4,000 ppm x 6 hr/day	Died 1-2 days after 3rd-5th exposure; severe spasmodic dyspnea	Von Oettingen, 1964
Rabbit	ihl	4,883 or 2,570 ppm x 25 min.	Depressed respiration	Von Oettingen, 1964
Rabbit	ihl	8,147 ppm x 25 min.	Increased irritation & restlessness; convulsions	Von Oettingen, 1964
Rabbit	ihl	257 ppm x 20 hrs.	Some survivors became paralyzed	Von Oettingen, 1964

Table 1. Acute Effects - Methyl Chloride (Cont'd.)

Organism	Route	Dose	Response	Reference
Cat	ihl	30,840 or 87,380 ppm x 10 min.	Restlessness	Von Oettingen, 1964
Cat	ihl	2,000 ppm x 6 hr/day	Very weak after 1 wk. of exposure, loss of coordination; further exposure resulted in dyspneic respiration and loss of appetite	Von Oettingen, 1964
Dog	ihl	$\geq$ 1,000 ppm x 6 hr/day	Died after 2-6 doses	Von Oettingen, 1964
Dog	ihl	15,000-40,000 ppm x 5 min.	Increased resp. & cardiac rates and arterial and venous pressure	Davis et al., 1977
Monkey	ihl	2,000 ppm x 6 hr/day	Convulsions after 4-7 exposures	Von Oettingen, 1964

Table 2. Chronic Effects - Methyl Chloride

Organism	Route	Dose	Response	Reference
Frogs		2,000 ppm x 131 days 300 ppm x 448 days	No deaths	Davis et al., 1977
Mice	Inhalation	500 ppm x 6 hrs. daily x 15 weeks	If survived developed permanent tonic contraction of adductor muscles in hind and fore limbs.	Davis et al., 1977

iii) Teratogenicity

No reports of teratogenicity were encountered.

iv) Other

In laboratory experiments, chronic methyl chloride exposures of greater than 300 ppm are not tolerated well in mice, guinea pigs, goats, dogs, rabbits, rats, and monkeys. Most of these animals survived 64 weeks exposure of 300 ppm with no evidence of chronic accumulation (Davis et al., 1977). However, doses over 500 ppm are considered dangerous (ACGIH, 1971). Chronic exposure to cats and rabbits results in general weakening with loss of appetite, and causes hyperactive tendon reflexes. Dogs, guinea pigs and monkeys suffered muscular spasticity while rats did not (Davis et al., 1977).

Table 2 cites further examples of chronic effects of methyl chloride exposure.

e) Human Effects

Methyl chloride poisoning can closely imitate alcohol intoxication with symptoms mimicing endemic encephalitis, infective hepatitis, and incipient peritonitis. In mild cases of poisoning, clinical symptoms often include nausea, vomiting, colicky pains and diarrhea (Davis et al., 1977). Mackie (1961), reports vertigo, general weakness, blurred vision, drowsiness, and muscle incoordination as additional symptoms. Further exposure affects the central nervous system resulting in severe headaches, slurred speech, confusion, loss of equilibrium (Davis et al., 1977), insomnia, nightmares, paraesthesia, hiccups, muscle tremors, ptosis and dysphagia (Mackie, 1961). Acute and fatal intoxication are evidenced by opisthomatic spasms or generalized epileptiform seizures alternated with deep unconsciousness (Mackie, 1961). Rapid pulse and respiration accompany a sweet but offensive breath odor, as well as lowered blood pressure and rise in body temperature (Davis et al., 1977; McNally, 1946).

As seen by the symptoms given above, the central nervous system is damaged by methyl chloride poisoning (Davis et al., 1977). If victims recover from acute exposures, personality changes may occur (EPA, 1977), and sequelae including foot-drop, muscle incoordination, blurred and double vision, and amnesia may be observed for up to a year following the exposure (Mackie, 1961).

Poisoning also results in hepatic and renal damage (Fairhall, 1957), and according to McNally (1946) congestion of the lungs occurs as well as petechial hemorrhages of pleura, epicardium, and endocardium. He reports additionally that primary anemia and mild leukocytosis may develop. Urine of acute poisoning victims contained acetone and, in 2 out of 8 cases, formates (McNally, 1946). Fairhall (1957) cites depression of bone marrow activity.

Liver damage may be expressed as jaundice and porphyrinuria, and renal disturbances are characterized by albuminuria and oliguria which may be followed by anuria (Davis et al., 1977).

8. TLV

The accepted standard for methyl chloride has been set by the ACGIH (1971) at 100 ppm (approximately 210 mg/m^3), which is also the level recommended by OSHA (Fed. Reg., 1974).

9. Other Standards

Based on chronic poisoning of rats, a maximum acceptable concentration of 5 mg/m^3 is established in industrial plants in Russia (Davis et al., 1977). Other standards listed by ACGIH (1971) are as follows: Cook (1945) 200 ppm; Smith (1956) 100 ppm; Elkins (1959) 50 ppm; ANSI (1969) 100 ppm; USSR (1967) 2.5 ppm; Czechoslovakia (1969) 50 ppm.

The Federal Insecticide, Fungicide and Rodenticide Act requires methyl chloride to be labelled as follows: "Warning: Flammable! May Be Fatal if Inhaled. Contact With Liquid May Produce Burns. Do Not Breathe Vapors. Do Not Get In Eyes Or On Skin. Do Not Use Near Heat Or Open Flame" (Fed. Reg., 1962c; Davis et al., 1977).

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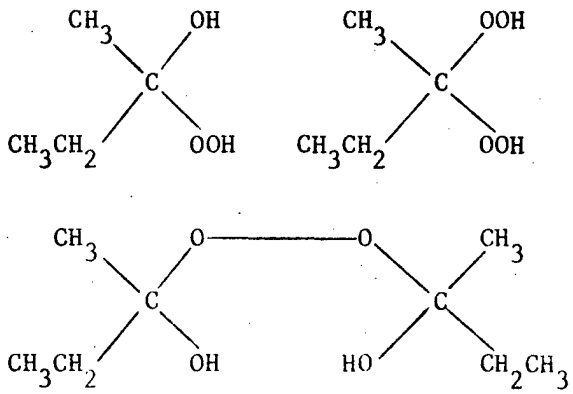
METHYL ETHYL KETONE PEROXIDE (2-butanone peroxide)

1. Molecular Structure (Kirk-Othmer, 1963)



2. Chemical Abstract Service Number

1338-23-4

3. Registry of Toxic Effects of Chemical Substances Number

EL94500

4. Production Figures and Economic Trends in Production

In 1975 6.36 million lbs of methyl ethyl ketone peroxide were produced (USITC, 1975).

Production has been relatively the same, annually, since 1973. Significant growth should not be expected to result from the current uses.

5. Uses

Methyl ethyl ketone peroxide has its major application as a curing agent for thermoset polyester (Mageli and Sheppard, 1967). Also, there are numerous patents describing the use of methyl ethyl ketone peroxide as a crosslinking agent and catalyst in the production of polyester An example of its use is in curing systems for reinforced plastics for food handling applications (Varco, 1975).

6. Number of Companies Producing and Using

The following companies produce this chemical in seven locations (SRI, 1977):

Akzona Inc., Burt, N.Y.
Dart Industries Inc., Elyria, Ohio
The Norac Company, Inc., Azusa, Cal.
Pennwalt Corporation, Philadelphia, Pa.
Reichhold Chemicals, Inc., Austin, Tx.
Tenneco Inc., Elizabeth, N.J.
Witco Chemical Corporation, Marshall, Tx.

About 50 companies produce polyester fibers and resins (SRI, 1977), and it is likely that most of these use the chemical.

7. Biological Effects of Exposure

a. Target Organs

Given orally, by inhalation, or by intraperitoneal injection, methyl ethyl ketone peroxide causes hyperemia of the lungs with petechial or gross hemorrhage in mice and rats. Subacute exposures have been associated with mild liver damage in rats. In addition, this compound can be severely irritating to the eyes and skin. In rabbits, maximum non-irritating strengths were found to be 1.5% and 0.6% for the skin and eyes, respectively (Floyd and Stokinger, 1958).

b. Acute Effects

Table 1 summarizes information on the acute toxicity of methyl ethyl ketone peroxide. Lethal doses of this compound cause central nervous system depression (NCPCC, 1969). In rats, the primary signs of intoxication are weakness, loss of equilibrium, and prostration. In surviving animals, weight gain is normal (Floyd and Stokinger, 1958).

c. Subchronic Effects

Intraperitoneal injections of mice with methyl ethyl ketone peroxide at 65 mg/kg for seven consecutive days reportedly caused no mortality (Anon., 1957). Floyd and Stokinger (1958) found that intraperitoneal injection of 13 mg/kg, three times per week for seven weeks, killed two of five treated rats. Oral doses of 96.8 mg/kg killed all of five treated rats. Although methyl ethyl ketone peroxide was shown to form methemoglobin in rat blood *in vitro*, this effect could not be demonstrated in *in vivo* subchronic exposures. In rats, three injections given over a one week period resulted in depletion of liver glycogen and dissociation of hepatic cords. In rabbits, subacute dermal applications resulted in increased serum albumin/globulin ratios (Floyd and Stokinger, 1958).

d. Chronic Effects

Kotin and Falk (1963) report that mice given a total dose of 40 μM ($\sim$ 7 mg) methyl ethyl ketone peroxide developed malignant tumors, the first of which appeared after fifteen months. One subcutaneous sarcoma, three malignant lymphomas, and a pulmonary adenoma were noted in 34 of the 50 mice surviving exposure.

Tuinov and Ivanova (1976) indicate that inhalation exposure of rats to methyl ethyl ketone peroxide interferes with deoxyribonuclease.

No other studies on chronic toxicity have been encountered.

Table 1. Acute Toxicity of Methyl Ethyl Ketone Peroxide

Organism	Route	LD_{50} or LC_{50}	Reference
Rat	Oral	484 mg/kg	Floyd and Stokinger, 1958
	Intraperitoneal	470 mg/kg	Floyd and Stokinger, 1958
	Inhalation	200 ppm x 4 hr	Floyd and Stokinger, 1958
Mouse	Oral	470 mg/kg	Anonymous, 1957
	Inhalation	170 ppm x 4 hr	Floyd and Stokinger, 1958

e. Human Effects

Chemical burns of the gastrointestinal tract, as well as residual scarring and stricture of the esophagus, were noted in an individual surviving ingestion of two ounces of a 60% methyl ethyl ketone peroxide solution (NCPCC, 1969).

8. TLV

Based on the work of Floyd and Stokinger (1958) and by comparison to benzol peroxide and hydrogen peroxide, the TLV for methyl ethyl ketone peroxide has been set at 0.2 ppm (ACGIH, 1971).

9. Other Standards

No other standards have been encountered.

References

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OXALIC ACID

1. Molecular Structure

2. Chemical Abstracts Service Number

144-62-7

3. Registry of Toxic Effects of Chemical Substances Number

RO24500

4. Production Figures and Economic Trends in Production

In 1974 18 million lbs. of oxalic acid were manufactured (Allison, 1975).

Since 1959 production has remained stable in the range of 18 to 23 million lbs. produced annually (Allison, 1975).

5. Uses

Of the total oxalic acid manufactured, 75% is consumed in three end uses: (1) textile finishing, stripping, and cleaning; (2) metal and equipment cleaning; and (3) use as chemical intermediate. Some of the more important derivatives are ammonium oxalate and ferric ammonium oxalate, both used in blueprint photography, and diethyl oxalate, used as an intermediate in dye manufacture. The remainder of production goes to various miscellaneous uses including leather tanning (Allison, 1975).

6. Number of Companies Producing and Using

The following companies in 7 locations manufacture oxalic acid (SRI, 1977):

Allied Chemical Corp.
Frank Enterprises
Heico, Inc.
Mallinckrodt, Inc.
Pfizer, Inc.

Numerous companies use oxalic acid.

7. Biological Effects of Exposure

a) Target Organs

Very little literature was found concerning organ damage resulting from exposure to oxalic acid. The literature obtained indicates that oxalic

Table 1. Dose Response Data for Oxalic Acid Administered to Various Mammals

Organism	Route	Dose	Response	Reference
Rat	via stomach tube	60-80 mg/100 g body wt.	renal proximal tubular insufficiency	Pavel, 1971
Rabbit (ear)	immersion of ear	saturated solution of anhydrous oxalic acid (9.1%, 72°F) 1 min.	no cutaneous reaction	Klauder et al., 1955
Rabbit (ear)	immersion of ear	saturated solution of anhydrous oxalic acid (9.1%, 72°F) 5 min.	redness and scaliness, no ulcerations	Klauder et al., 1955
Rabbit (shaved back)	saturated lintine disc	saturated solution of anhydrous oxalic acid (9.1%, 72°F), 24 hours	no reaction	Klauder et al., 1955
Dog	i.v.	5 mg/kg body wt.	moderate, temporary hypotension	Singh et al., 1973
Dog	oral	1000 mg/kg body wt.	LD_{Lo}	NIOSH, 1976

acid acts as a strong acid to produce local irritation and burns to eyes, skin, and mucous membranes (ACGIH, 1971; Klauder et al., 1955). Pavel (1971) reports renal damage to rats when this compound is administered by stomach tube.

b) Acute Effects

Table 1 summarizes the acute toxicity of oxalic acid to experimental animals.

When ingested oxalic acid acts as a strong poison and has proved fatal at a small dose (ACGIH, 1971).

Isolated frog hearts perfused with a solution of > 15 μg/ml oxalic acid respond with a negative inotropic effect (Singh et al., 1973).

c) Subchronic Effects

No literature is available relating subchronic effects of oxalic acid exposure.

d) Chronic Effects

No literature is available concerning chronic effects.

e) Human Effects

Oxalic acid acts like a strong acid causing severe local burns of eyes, skin, and mucous membranes (ACGIH, 1971). Symptoms range from brief irritation to skin discoloration, gangrenous ulcerations, and pain. In cases of hand exposure, fingernails may discolor and fall off. External symptoms of oxalic acid ingestion are remarkably similar to those resulting from skin exposure, with pain and discoloration in extremities predominating. In addition, tetanus of the extremities and facial muscles occurs (Klauder, 1955). NIOSH (1976) reports an LD_{Lo} of 100 mg/kg, while a fatal dose of 5g is cited by ACGIH (1971).

Oxalic acid found naturally in foods may cause adverse reactions when ingested (Sapeika, 1974).

8. TLV

Since oxalic acid behaves similarly to strong acids when inhaled, a TLV of 1 mg/m^3 is recommended (ACGIH, 1971), which is in agreement with the OSHA TWA standard (NIOSH, 1976).

9. Other Standards

No other standards were encountered in the literature.

10. Other Data

Mammalian synthesis and metabolism of oxalic acid is a topic of active research (Smith et al., 1971; 1972; Son et al., 1972; Berg et al., 1975; Singh and Mongia, 1973).

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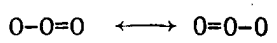
OZONE

1. Chemical Structure



2. Chemical Abstract Service (CAS) Number

10028-15-6

3. Registry of Toxic Effects of Chemical Substances (RTECS) Number

RS82250

4. Production Figures and Economic Trends in Production

As of 1967, over 12 million lbs. of ozone were consumed annually in industrial and municipal installations in the U.S. (Manley and Niegowski, 1967). Current consumption of ozone is probably two or three times higher at present (SRC estimate).

5. Uses

Ozone is used commercially in the purification of drinking water, preparation of chemicals, treatment of industrial wastes, deodorization of air and sewage gases, and the preservation of goods in cold storage (Manley and Niegowski, 1967).

6. Number of Companies Producing and Using

The nature of ozone requires that it be generated at the site of use (Manley and Niegowski, 1967). Therefore, there are many ozone generators or ozonators located in the U.S.

7. Biological Effects of Exposure

a. Target Organs

The lungs are the primary site of ozone induced tissue damage. Acute exposures lead to pulmonary congestion, edema, and hemorrhage (Bils, 1970; Stokinger, 1957). Subchronic exposures result in significant changes in lung function (Jaffe, 1967). Ozone may also cause a defect in oxygen dissociation from oxyhemoglobin (Brinkman and Lamberts, 1958).

In addition to its effects on the lungs, ozone is radiomimetic and may cause decreased life-span in chronically exposed animals (Stokinger, 1965).

b. Acute Effects

Over four hour exposure periods, the acute LC_{50}'s of ozone for mice, rats, and hamsters are 3.8, 4.8, and 10.5 ppm, respectively. The toxicity of ozone to mice can be reduced by administering reducing agents prior to exposure, by interrupting exposure periods with periods of normal air, or by subjecting the animal to sublethal concentrations of ozone. Ozone toxicity is enhanced by exercise (Stokinger, 1957). Exposure to 1 ppm for one or two days causes dose-related damage to alveolar tissue (Bils, 1970). Young mice are more susceptible to ozone than older animals (Stokinger, 1957; Bils, 1970). Ozone has also been shown to exacerbate pulmonary infections in mice and guinea pigs (Dreisbach, 1974; Stokinger, 1965).

c. Subchronic Effects

Exposures to ozone at 1 ppm for six hours per day, five days per week, for four weeks caused no lethality in twenty-five exposed mice (Stokinger, 1957). However, exposures to 0.1 or 0.2 ppm for seven hours per day, for three weeks caused a slight increase in neonatal mortality in mice (Jaffe, 1967).

d. Chronic Effects

i) Carcinogenicity - In a strain of tumor-susceptible mice, ozone increased the incidence of pulmonary adenoma. In a strain of tumor-resistant mice, exposure to 4.5 ppm for two hours per day, every three days for 75 days, increased the incidence of hyperplasia, squamous metaplasia, and pulmonary ademona. These mice also developed pneumonia and septal fibrosis (Werthamer et al., 1970).

ii) Other Chronic Effects - No information has been encountered on the teratogenicity or mutagenicity of ozone. Bronchiolitis and bronchitis have been noted in mice exposed to about 1 ppm for six hours per day for one year (Stokinger et al., 1957).

e. Human Effects

Occupational exposures to ozone at concentrations as low as 2 ppm cause pulmonary congestion (Challen et al., 1958; Kleinfeld and Giel, 1956). This effect is not seen at 0.2 ppm (Challen et al., 1958). Exposure to ozone at estimated concentrations of 0.2 to 11.2 ppm for two hours resulted in unconsciousness but no apparent lung damage (Kelly and Gill, 1965).

Volunteers exposed to ozone at 1 to 3 ppm experienced dryness of the throat, cough, chest pain, and headache (Hallett, 1965). On more prolonged exposures to concentrations greater than 0.1 ppm, headache, dryness of the throat, and irritation of the eyes and respiratory tract develop (Stokinger, 1957; Wilska, 1951; and Truche, 1951). Impaired lung function occurs after acute exposures to 1.5 ppm for 2 hours (Griswold et al., 1957) or subacute

exposures to 0.5 ppm, three hours per day, six days per week, for twelve weeks (Jaffe, 1967). The outcome of intelligence tests is not affected by ozone exposures of 0.3 ppm for seventy minutes (Hore and Gibson, 1968). Visual acuity, however, is reduced by ozone at concentrations of 0.2 ppm (Dreisbach, 1974).

At 0.5 ppm, the odor of ozone can be detected by most people. Some individuals can detect ozone at concentrations as low as 0.01 ppm. At 0.1 ppm, five per cent of the exposed individuals will experience eye irritation (Dreisbach, 1974).

8. TLV

The current TLV for ozone is 0.1 ppm which may cause premature aging in some individuals (ACGIH, 1971). The OSHA (1974) standard for ozone is also 0.1 ppm.

9. Other Standards

None encountered.

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TALC

1. Molecular Structure

The molecular formula for talc is $Mg_3SiO_{10}(OH_2)$, which theoretically contains: 31.7% MgO, 63.5% SiO_2, and 4.8% H_2O (Mulryan, 1969).

2. Chemical Abstract Service Number

14807-96-6

3. Registry of Toxic Effects of Chemical Substances Number

VV87900

4. Production and Trends

U.S. mines annually produce talc in the range of 1,000 short tons per year (Cooper and Hartwell, 1970; Cosslett, 1975).

Annual growth rate for consumption demand is forecasted at 3.0-4.3% (Cooper and Hartwell, 1970).

5. Uses (Cosslett, 1975)

Ceramics	35%
Paint	18
Roofing	4
Insecticides	4
Paper	8
Toilet Preparations	4
Elastomers	3
Other	24
	100%

The "other" category contains literally hundreds of uses.

6. Producer and User Data

During 1968 talc was produced from 52 mines in ten different states (Cooper and Hartwell, 1970).

There are numerous users of talc.

7. Biological Effects of Exposure

A considerable amount of information is available on the biological effects of crude industrial talc. This information has been reviewed by Siegal and coworkers (1943), Schepers and Durkan (1955a and b), and Kleinfeld and co-workers (1963).

a) Target Organs

Fibrous industrial talc causes pneumoconiosis often accompanied by chronic hypertrophic pulmonary osteoarthropathy in humans exposed for long periods of time. Details of this effect are summarized in Section 7e. In experimental mammals, pure talc induces a cytogenic rather than fibrogenic effect on the lungs. Although some fibrogenic agents such as quartz and tremolite may have an additive effect on lung damage, some evidence has been found to suggest that pure talc inhibits the pathogenicity of quartz (Schepers and Durkan, 1955a).

b) Acute Effects

No studies encountered.

c) Subchronic Effects

Rats evidenced no adverse response when given 100 mg of pure talc intraveneously in a series of eighteen injections over a period of ten weeks. Rabbits, however, given 1000 mg in a series of twenty injections, developed bronchitis, bronchiolectasia, endarteritis proliferans, macrophage catarrh, and pleural thickening. Guinea pigs given 150 mg of pure talc in three equal intratracheal injections developed bronchiolectasia and bronchitis, perivascular and peribronchial cellular proliferation and fibrosis, and fibrocellular pleural sclerosis. For all injections, the particle size of the talc was less than three microns (Schepers and Durkan, 1955).

d) Chronic Effects

No studies encountered.

e) Human Effects

Many case histories are available on talc workers who developed pneumoconiosis after employment periods ranging from 1 to 37 years (Kleinfeld et al., 1963; McLaughlin et al., 1949; Porro et al., 1942; Schepers and Durkan, 1955b; Siegal et al., 1943). The clinical signs and symptoms include dyspnea, cough, chest pain, and weakness. Most of the reports have noted the similarity of talc-induced pneumoconiosis to asbestosis. Early studies suggested that tremolite, rather than pure talc, was the primary pathogenic agent (Porro et al., 1942; Siegal et al., 1943) and histological evidence supporting this supposition has been advanced by Schepers and Durkan (1955b).

8. TLV

The TLV for fibrous talc is five fibers, exceeding five microns in length, per milliliter of air (ACGIH, 1971).

9. Other Standards

The OSHA (1974) standard for fibrous talc is the same as that for asbestos. The standard for nonfibrous talc is twenty million particles per cubic foot of air.

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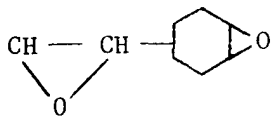
VINYL CYCLOHEXENE DIOXIDE (7-oxabicyclo(4.1.0)heptane, 3-oxiranyl)

1. Molecular Structure



2. Chemical Abstracts Service Number

4223-10-3

3. Registry of Toxic Effects of Chemical Substances Number

RN86400

4. Production Figures and Economic Trends in Production

Production figures are not available from the literature. USITC reports do not list it, which may indicate that production and sales have been less than 1,000 lbs. or $1,000 annually.

If commercial importance is just beginning, then rapid growth can be expected depending upon use.

5. Use

Recent patent literature indicates that vinyl cyclohexene dioxide is used as a monomer in the production of epoxy resins used for coatings and adhesives.

6. Number of Companies Producing and Using

Union Carbide Corp. (Taft, La.) is the sole manufacturer of this compound (SRI, 1977).

Literature citing those companies which use vinyl cyclohexene dioxide is not available.

7. Biological Effects of Exposure

a) Target Organs

Vinyl cyclohexene dioxide is irritating to the eyes and skin of rabbits (Weil et al., 1963). It can cause acute respiratory tract irritation and congestion of the lungs (IARC, 1976). In addition to its irritant properties, vinyl cyclohexene dioxide has been associated with testicular atrophy (Kodama et al., 1961; Hine and Row, 1963), leucopenia, and necrosis of the thymus (Kodama et al., 1961).

b) Acute Effects

Information on the acute toxicity of vinyl cyclohexene dioxide is summarized in Table 1. In addition, Weil and coworkers (1963) report that inhalation of concentrated vapor for eight hours causes no death in rats and that this compound does not cause sensitization in guinea pigs.

c) Subchronic Effects

No studies encountered.

d) Chronic Effects

Several studies have demonstrated the carcinogenicity of vinyl cyclohexene dioxide in rodents. After twice weekly intraperitoneal injections of 250 mg/kg for ten weeks, one of fourteen treated rats developed a sarcoma of the peritoneal cavity after seven months. In mice, dermal applications of 16 mg, five times per week, for twelve months, resulted in skin tumors in eleven of the twenty treated animals. Nine of these animals had squamous cell carcinomas or sarcomas (Hendry et al., 1951). Similarly, Kotin and Falk (1963) note one skin tumor and four malignant lymphomas in sixteen of twenty mice surviving a total dose of about 70 mg vinyl cyclohexene dioxide. The first tumor developed after fourteen months. At about the same total dose, 78 mg given dermally in acetone, eighteen mice developed four tumors, one of which was cancerous. The median latent period to tumor development was 19.5 months (Weil et al., 1963). Of thirty mice receiving thrice weekly dermal application of 0.1 ml of a 10% solution of vinyl cyclohexene dioxide in benzene, fourteen mice developed tumors. In nine of these mice, squamous cell carcinomas were noted (Van Duuren et al., 1963).

In addition to its carcinogenic effects, vinyl cyclohexene dioxide inhibits the growth of Walker cell carcinoma in rats (Hendry et al., 1951).

e) Human Effects

No studies have been encountered in the effects of this compound on humans.

8. TLV

None

9. Other Standards

None encountered.

Table 1. Acute Toxicity of Vinyl Cyclohexene Dioxide

Organism	route	LD_{50} or LC_{50}	Reference
rat	oral	2830 mg/kg	Weil et al., 1963
	inhalation	800 ppm x 4 hr.	Hine and Rome, 1963
rabbit	dermal	681(275-1720) mg/kg	Weil et al., 1963

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WOOD DUST

1. Molecular Structure

Wood dust consists basically of small particles of cellulose polymers of complex structure. However, depending on the origin of the dust, many other chemicals associated with the plant may be present in the dust, which accounts for the variability in the toxicity of wood dusts of various sources (see 7b below).

2. Chemical Abstract Service Number

There is no Chemical Abstract Service number for wood dust.

3. Registry of Toxic Effects of Chemical Substances Number

There is no Registry of Toxic Effects number for wood dust.

Wood Dust (Wood Flour)

4. Production and Trends

In 1975, 8.8 billion lbs. of groundwood was used in the production of paper (Davenport, 1976). Groundwood is available in at least seven grades, varying in fineness and uniformity (Whitney, 1967). The percentage which is wood dust depends upon the definition of dust.

Based upon the use of wood flour (which is probably dust) as a filler for various types of resins and plastics, production of wood flour for these uses must amount to at least 1.0 billion lbs. per year (SRC estimate).

5. Uses

The two major uses of wood dust are the production of paper and the application as a filler material for phenolic, amino, and other types of resins (Whitney, 1967; Seymour, 1968; Seymour, 1976).

6. Producers: many

Users: many

7. Biological Effects of Exposure

All information in this profile on the biological effects of exposure to wood dust are summarized from the documentation of the wood dust TLV (ACGIH, 1971). No more recent studies were encountered in a routine search of various computerized data bases. Almost all of this information concerns human effects attributable to occupational exposure.

a) Target Organs

Wood dust can adversely affect the respiratory tract or skin. Respiratory tract diseases include bronchitis, emphysema, chronic interstitial pneumonitis, bronchial asthma, allergic alveolitis, bronchial pneumonia, fibroid lungs, and bronchiectasis. Dermal effects have been characterized as primary irritant dermatitis. Details on these effects are given in Section 7e.

b) Acute Effects

Haslean and Kadec (1964) have divided woods into three classes based on toxicity. The first class, consisting of oak, beech, maple, and ash, are relatively nontoxic. The second class, which is comprised of pine, larch, and mahogany, are highly toxic. The last class consists of strongly allergenic woods including yew and mansonia.

c) Subchronic Effects

No studies have been encountered on the subchronic effects of wood dust in experimental mammals.

d) Chronic Effects

i) Carcinogenicity - Over the period of 1956 to 1965, certain workers in the wood industry in Great Britain had a 1000 times greater incidence of adenocarcinoma than the general male population. The carcinomas were primarily of the nasal cavity and accessory sinuses. Oak, beech, and mahogany were the chief types of wood implicated in this effect. An undefined constituent of hardwood was presumed to be the active agent (Acheson et al., 1968). Inhalation of wood dust has also been associated with cancers of the larynx, tonsils, tongue, and lung (Hueper, 1942).

ii) Mutagenicity, Teratogenicity, and Other Chronic Effects

No studies have been encountered on the mutagenicity or teratogenicity of wood dust. The chronic respiratory effects of wood dust in humans are described in the following section.

e) Human Effects

In addition to its carcinogenic properties, wood dust causes chronic respiratory diseases in humans. Average exposure levels of 40 mg/cubic meter have been associated with pathological changes in the lungs of wood workers (Michaels, 1967). Exposure to cork dust at levels ranging from 165 to 1260 particles/cubic centimeter for twenty years resulted in a high incidence of bronchitis and emphysema in workers (Cancella, 1960 and 1963). Redwood dust has been implicated in the development of a chronic interstitial pneumonitis which is thought to be caused by a component of the tree bark (Cohen, 1967). High concentrations of Coniosporum corticale spores from diseased maple trees

causes lung hypersensitivity and granulomatous disease in exposed workers (Wenzel and Emanuel, 1967). This effect probably involves both a direct toxic response and a delayed allergic reaction (Emanuel et al., 1962). Gandevia and Milne (1970) and Pepys (1969) have described cases of bronchial asthma, allergic alveolitis, bronchial pneumonia, fibroid lung, and bronchiectasis caused by exposure to various wood dusts or diseased barks.

Skin contact with many different types of wood can lead to dermatitis. Moderate exposure can cause eczematous dermatitis and heavy exposure can result in sensitization with irritation to the eyes and respiratory tract. However, hemlock, spruce, pine, and cedar do not commonly cause allergic reactions (Suskind, 1967). Along with dermatitis, drowsiness has been reported in workers inhaling South African Box Wood dust, which contains a bradycardiogenic alkaloid (Hunter, 1962).

8. TLV

Based on the studies cited in this profile, the recommended TLV for non-allergenic wood dust is 5.0 mg/cubic meter (ACGIH, 1971).

9. Other Standards

Haslean and Kadac (1964) recommended limits of 10, 5, and 1 mg/cubic meter for nontoxic, toxic, and allergenic wood dusts, respectively.

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CLASSES OF CHEMICAL COMPOUNDS

BORON AND ITS COMPOUNDS

1. Molecular Structure

2. Chemical Abstract Service Number

3. Registry of Toxic Effects of Chemical Substances Number

The above information for the boron compounds in this profile is provided in Table 1.

In choosing the compounds listed, consideration was given to the extent of production and use in industrial processes, as well as to the likely toxicological hazard.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Boron

World production of elemental boron was probably less than 20,000 lbs. in 1969 (Blue and Treskon, 1970). No recent data is available.

Boron is used in the manufacture of pyrotechnics, chemical synthesis, vacuum tubes, abrasives, nuclear shielding, solar battery coatings, semiconductors, filament and structural fibers for aircraft and spacecraft, and as a grain refiner in aluminum manufacturing as well as a steel hardener (Lawler, 1977).

The following companies produce boron at the listed locations (SRI, 1977):

Belmont Smelting	Brooklyn, N.Y.
Kawecki Berylco	Boyertown, Pa.
Kerr-McGee	Henderson, Nevada
Callery Chem.	Callery, Pa.

Diborane

No production figures are available for diborane. Diborane is a precursor to higher boranes, amine boranes, carboranes, and borohydrides. It is also a catalyst, and is used in energy cells and in the co-polymerization of butadiene-styrene (Lawler, 1977; Blue and Treskon, 1970).

Diborane is produced by Airco (Santa Clara, Calif.), Callery Chemicals (Callery, Pa.), and G.D. Searle at seven different locations (SRI, 1977).

Table 1. Compounds in the Boron Class

Compound	CAS Number	RTECS Number	Molecular Formula
Boron	7440-42-8	ED73500	B
Diborane	1304-00-3	HQ92750	$H_3B\text{-}BH_3$
Sodium Borohydride	16940-66-2	ED33250	$NaBH_4$
Boron Trichloride	10294-34-5	ED19250	BCl_3
Boron Tribromide	10294-33-4	ED74000	BBr_3
Boron Trifluoride	7637-07-2	ED22750	BF_3
Nickel Fluoborate	--	QR66500	$Ni(BF_4)_2$
Potassium Fluoborate	14075-53-7	ED28000	KBF_4
Boric Acid (Orthoboric acid)	10043-35-3	ED45500	H_3BO_3
Boric Oxide	1303-86-2	--	B_2O_3
Borax (Sodium Metaborate)	1344-90-7	VZ22750	$Na_2B_2O_4 \cdot 4H_2O$
			$Na_2B_2O_4 \cdot 8H_2O$

Sodium Borohydride

Production figures for sodium borohydride are not available.

It is used in the synthesis of other borohydrides, reduction of aldehydes and ketones, vat dyes, pharmaceuticals, blowing agents, hair wave formulations, and also as a catalyst (Lawler, 1977).

Sodium borohydride is produced by Callery Chemicals (Callery, Pa.) and Thiokol (Danvers, Mass.; Elma, Wash.) (SRI, 1977).

Boron Trichloride

Production figures for boron trichloride are not available.

It is an intermediate used in the preparation of other boron compounds; an acidic catalyst for organic reactions; a source of boron for the gaseous boriding of metals; used in the purification of metal alloys to remove nitrides, carbides, and oxides; a polymerization agent for driers; and is a stabilizer for liquid SO_3 (Lawler, 1977; Iverson and Draganov, 1964).

The Kerr-McGee Corp. (Henderson, Nevada) manufactures boron trichloride.

Boron Tribromide

Production figures for boron tribromide are not available.

It finds use in the electronics industry, especially as a semiconductor dopant, and is a brominating agent (Lawler, 1977; Blue and Treskon, 1970).

Eagle-Picher Industries (Miami, Okla.; Quapaw, Okla.) and Kerr-McGee (Henderson, Nevada) produce boron tribromide (SRI, 1977).

Boron Trifluoride

In 1970, the total supply of boron trifluoride catalyst complexes was estimated to be 40,000 lbs. (Blue and Treskon, 1970).

It is used as a catalyst for epoxy complexes and in neutron analysis (Lawler, 1977; Blue and Treskon, 1970).

Allied Chemicals (Marcus Hook, Pa.) manufactures boron trifluoride (SRI, 1977).

Nickel Fluoborate

No production figures are available for nickel fluoborate.

It is used in electroplating baths (Lawler, 1977) and is produced by the following companies at the locations listed (SRI, 1977):

Allied Chem. Corp.	Marcus Hook, Pa.
C.P. Chems., Inc.	Sewaren, N.J.
Harstan Chem. Corp.	Brooklyn, N.Y.
Kewanee Ind., Inc.	Cleveland, Ohio
Pennwalt Corp.	Tulsa, Oklahoma
Thiokol Corp.	Danvers, Mass.

Potassium Fluoborate

Production figures for potassium fluoborate are not available.

It is used as a binder and cooling agent in grinding wheels, in electrolyte brightening of aluminum and in silver solder flux (Lawler, 1977).

Potassium fluoborate is produced by the companies listed below (SRI, 1977):

Allied Chem. Corp.	Marcus Hook, Pa.
Borden, Inc.	Plant City, Fla.
Kawecki Berylco Ind., Inc.	Boyertown, Pa.
Kewanee Ind., Inc.	Cleveland, Ohio
Pennwalt Corp.	Tulsa, Okla.
Thiokol Corp.	Danvers, Mass.

Boric Acid

In 1969, 70,000 tons of boric acid (B_2O_3 content basis) were estimated to have been produced (Blue and Treskon, 1970). No growth figures or more recent data are available.

Boric acid has a wide variety of uses, including manufacture of ceramic glazings, synthesis of boron compounds, glass fibers, citrus fruit wash, cosmetics, dyes, fluxes, electrolytic condensers, flameproofing, pharmaceuticals and eye washes (Lawler, 1977).

Between 25-30% of the total production is exported (Blue and Treskon, 1970).

Boric acid is manufactured by Kerr-McGee (Trona, Calif.), Stauffer Chemical (San Francisco, Calif.) and U.S. Borax (Wilmington, Calif.) (SRI, 1977).

Boric Oxide

In 1969, an estimated 19,000 tons of boric oxide were manufactured (Blue and Treskon, 1970). More recent production figures are not available.

Boric oxide is used in glass and boron compound synthesis, in fluxes, enamels, and drying agents, and is a catalyst (Nies, 1964; Lawler, 1977).

Eagle-Picher Industries (Miami, Oklahoma; Quapaw, Oklahoma) and Stauffer Chemical (San Francisco, Calif.) manufacture boric oxide (SRI, 1977).

Borax (Sodium Metaborate)

Production figures for borax are not available.

It is used in adhesives, detergents, herbicides, textile finishing, and in photography (Lawler, 1977).

Borax is manufactured by U.S. Borax (Wilmington, Calif.) (SRI, 1977).

7. Biological Effects of Exposure

a) Target Organs

Boric acid and sodium borate appear to have similar pathological effects on the liver, kidneys, gastrointestinal tract, and nervous system. Both compounds have been associated with congestion and edema of the brain and meninges, scattered perivascular hemorrhages, cloudy swelling, and granular degeneration of the kidney tubules, as well as congestion and fatty changes of the liver in cases of acute fatal human poisoning. Acute intoxication of mice, rats, and dogs with boric acid by oral or parenteral routes lead to glomerular and tubular damage as well as pronounced hyperchromatism and shrinkage of certain nerve cells in the central nervous system (Levinskas, 1964). On chronic administration [route, dosage, and species not given], both boric acid and sodium borate cause reddening and inflammation of the gastrointestinal mucosa, cerebral edema, and degenerative changes of the liver and kidney (Moeschlin, 1965). Rats given daily intramuscular injections of boric acid at 180-600 mg/kg for 30 days developed cloudy swelling and fatty infiltration of the liver. Similarly, dogs given daily intravenous injections of boric acid at doses up to 50 mg/kg evidenced renal damage and cloudy swelling of the liver. Neither boric acid nor sodium borate are very irritating to the skin of humans. However, alkaline solutions of borate ion up to pH 8.16, produced slight to marked irritation of the skin when topically applied to rabbits. Aqueous solutions of 5% boric acid were non-irritating (Levinskas, 1964).

Diborane, boron trifluoride, and boron trichloride seem to exert their primary toxic effect on the lungs. Inhalation of diborane at concentrations of less than 100 ppm for 4 hours caused pulmonary edema in rats and mice (Jacobson and Lawson, 1952). After four hour inhalation exposures to diborane at concentrations of 45 ppm and 100 ppm, rats developed pulmonary edema and hemorrhage. In dogs, inhalation exposure to 50 to 60 ppm for 15 minutes caused some kidney damage along with lung edema and hemorrhage. On subchronic inhalation exposures to about 2 ppm diborane for 4 months, pulmonary effects, in rats varied from congestion to pneumonia (Krackow, 1953). Lung and kidney

damage has been noted in hamsters exposed to diborane at atmospheric concentrations of 50 to 1000 ppm for up to 12 hours. Lung damage was characterized by capillary dilation, vascular congestion, edema, focal areas of atelectasis, and peripheral emphysema. Kidney damage consisted of some vascular congestion (Stumpe, 1960). Boron trifluoride, on repeated inhalation exposure to several species of laboratory mammals at a concentration of 100 ppm, caused severe pulmonary irritation leading to pneumonia and mild renal tubular degeneration (ACGIH, 1971c; Levinskas, 1964). Boron trichloride caused pulmonary damage and irritation to exposed skin on acute inhalation exposure [dose and organism not specified] (Levinskas, 1964).

Less information is available on the pathological effects of the other boron compounds. Boron oxide, on dermal application to rabbits at 1 gram per day, every other day, for 6 days, caused erythema. Exposure to boron oxide dust produced an immediate inflammatory response in the eyes of rabbits (ACGIH, 1971a; Levinskas, 1964). Sodium borohydride, when applied directly to the eyes of rabbits, produced irreversible damage. This compound was most irritating when applied to the dry skin of rabbits at 400 mg/kg. However, when the skin was moistened, the same dose of sodium borohydride caused edema, necrosis, and blanching. Potassium fluoroborate caused no signs of irritation when applied to the skin and eyes of rabbits (Levinskas, 1964).

b) Acute Effects

Information on the acute toxicity of boron and eight boron compounds is summarized in Table 2. The mechanism by which these chemicals exert their toxic effects is poorly understood (Moeschlin, 1965; Levinskas, 1964). For certain boron compounds, the major toxic effects may not be related to boron itself. For instance, the toxicity of boron tribromide has been attributed to the formation of hydrogen bromide, the decomposition product of boron tribromide in water (ACGIH, 1971b). Similarly, death from intravenous injections of sodium borohydride at 16 to 18 mg/kg [organism not specified] may be due to the formation of gas embolisms caused by the evolution of hydrogen when this compound reacts with water (Levinskas, 1964).

The signs of acute intoxication have been described for boric acid, sodium borate, and diborane. Both boric acid and sodium borate given to dogs at single oral doses of 416 to 1000 mg/kg caused diarrhea, increased excretion of mucous in the gastrointestinal tract, and increased urinary excretion of nitrogen. Single oral or parenteral doses of boric acid caused depression, ataxia, occasional convulsions, and decreased body temperature in mice, rats, and guinea pigs. Along with these signs, dogs had persistent vomiting (Levinskas, 1964).

Diborane affects both respiration and cardiovascular function. Inhalation exposure to about 340 ppm diborane for 15 minutes caused an increase in the respiratory rate, decreased blood pressure, bradycardia, and an exaggerated T-wave in dogs. These effects were not seen at diborane concentrations of up to 13 ppm and exposure periods of 1 to 4 hours (Krackow, 1953).

Table 2. The Acute Toxicity of Boron and Some Boron Compounds

Toxicant	Organism	Route	Dose	Effect	Reference
Boron	mouse	oral	2000 mg/kg	LD_{50}	NIOSH, 1976
Boric acid	rat	oral	2660 mg/kg	LD_{50}	NIOSH, 1976
		intravenous	1330 mg/kg	LD_{50}	NIOSH, 1976
	mouse	oral	3450 mg/kg	LD_{50}	NIOSH, 1976
		subcutaneous	1740 mg/kg	LD_{50}	NIOSH, 1976
		intravenous	1780 mg/kg	LD_{50}	NIOSH, 1976
	guinea pig	subcutaneous	1200 mg/kg	LD_{50}	NIOSH, 1976
Boron trichloride	rat	inhalation	20 ppm x 7 hrs	lethal to all ten exposed animals	Levinskas, 1964
	mouse	inhalation	20 ppm x 7 hrs	lethal to all ten exposed animals	Levinskas, 1964
	guinea pig	inhalation	85 ppm x 7 hrs	not lethal	Levinskas, 1964
Boron trifluoride	rat	inhalation	750 ppm x 5.5 hrs	lethal to 1 of 10 animals	Levinskas, 1964
	mouse	inhalation	750 ppm x 5.5 hrs	lethal to 1 of 10 animals	Levinskas, 1964
	guinea pig	inhalation	750 ppm x 5.5 hrs	lethal to all 10 exposed animals	Levinskas, 1964
Diborane	rat	inhalation	50 ppm x 4 hrs	LC_{50}	NIOSH, 1976
	mouse	inhalation	30 ppm x 4 hrs	LC_{50}	NIOSH, 1976
	guinea pig	inhalation	53 ppm x 10.5 hrs	LC_{Lo}	NIOSH, 1976
Nickel fluoroborate	rat	oral	500 mg/kg	LD_{Lo}	NIOSH, 1976
	mouse	inhalation	530 mg/m^3 x 10 min.	LC_{Lo}	NIOSH, 1976
Potassium fluoroborate	rat	intraperitoneal	240 mg/kg	LD_{50}	Levinskas, 1964
	mouse	intraperitoneal	590 mg/kg	LD_{50}	Levinskas, 1964
	rabbit	intraperitoneal	380 mg/kg	LD_{50}	Levinskas, 1964
Sodium borohydride	rat	oral	160 mg/kg	lethal to 2 of 5 animals	Levinskas, 1964
		intraperitoneal	18 mg/kg	approx. lethal dose	Levinskas, 1964
Sodium borate	rat	oral	2660 mg/kg	LD_{50}	NIOSH, 1976

In hamsters, inhalation exposures to diborane at concentrations of 50 to 1000 ppm for less than twelve hours caused an increase in the rate and depth of respiration (Stumpe, 1960). Labored respiration and frothing from the nose have been noted in mice and rats exposed for 4 hours to diborane at concentrations of less than 100 ppm (Jacobson and Lawson, 1962).

c) Subchronic Effects

The most commonly noted effect of subchronic exposure to boric acid is growth inhibition. This effect has been produced in rats given boric acid in the diet [104 and 198 ppm for 8 weeks], in drinking water [0.25% for 30 days and 4% for 2 weeks], and in subcutaneous injections [5-50 mg/kg/day for 90 days]. In addition, rats given intramuscular injections of boric acid at doses of 180 to 600 mg/kg for 30 days developed moderate cloudy swelling and fatty infiltration of the liver. When given in the diet at 5000 ppm [duration not specified], boric acid inhibits estrus in mice (Levinskas, 1965).

Inhalation of boron oxide particles, 1 to 10 microns in diameter, at a concentration of 40 mg/m^3 for six hours per day, five days per week, for six weeks, produced no toxic effects in rats or guinea pigs. However, similar exposures to 100 mg/m^3 for 10 weeks and 500 mg/m^3 for 6 weeks resulted in increased urinary excretion of creatine (Levinskas, 1964). Inhalation of boron oxide particles having a mass median diameter of 1.9 to 2.5 microns caused nasal irritation in rats at 470 mg/m^3, six hours per day, five days per week, for 10 weeks. On the same exposure schedule, 175 mg/m^3 for 12 weeks and 77 mg/m^3 for 24 weeks resulted in no signs of adverse effects in rats. However, dogs exposed to boron oxide at 57 mg/m^3 for 23 weeks developed increases in urine volume, urine acidity, and urinary creatine levels. Intragastric intubation of rats with a boric acid slurry in water at 500 mg/kg for 3 weeks resulted in no adverse effects (ACGIH, 1971a).

Inhalation of diborane at concentrations of 1 to 2 ppm was lethal to 5 of 10 exposed rats after 21 exposures [duration not specified] but was not lethal to guinea pigs after 95 exposures. Of two dogs exposed to this concentration, one died after 14 exposures but the other survived 130 exposures. No pathological changes were noted in any of these animals. At diborane concentrations of 6 ppm, rats developed mild rhinitis and most animals died after 7 to 113 exposures. This concentration was fatal to dogs after 10 to 25 exposures (Levinskas, 1964). Rats exposed to 5 ppm for 2 weeks or 2 ppm for 4 months [all exposures at 6 hours per day, five days per week] developed pulmonary effects ranging from simple congestion to organized pneumonia (Krackow, 1953). Repeated exposure to diborane vapors has also been shown to cause lesions in the spinal cord of dogs (ACGIH, 1971d).

Inhalation of boron trifluoride at 100 ppm for 30 exposures [exposure schedule not specified] caused weight loss, dental fluorosis, a decrease in serum inorganic phosphate, and high mortality in mice, guinea pigs, rats, rabbits, cats, and dogs. Concentrations of 15 ppm were fatal to some mice, guinea pigs, and rats but not to rabbits, cats, and dogs (Levinskas, 1964).

Pneumonitis and dental fluorosis was seen in rats, rabbits, and guinea pigs after 128 exposures to boron trifluoride at 12.8, 3-4, and 1.5 ppm (ACGIH, 1971c).

d) Chronic Effects

i) Carcinogenicity

Of twenty mice given twice weekly intravaginal injections of 0.1 ml of a 2% boric acid solution for a total of 100 injections, one mouse developed a squamous tumor of low grade malignancy in the vagina. One urogenital tumor also developed in this control group. This tumor was characterized as a polyploid hyperplasia of the corpus uteri. Lung adenomas were noted in both treated and control mice (Boyland et al., 1966).

ii) Mutagenicity

No information has been encountered on the mutagenicity of boron or the boron compounds under review.

iii) Teratogenicity

Boric acid caused rumplessness, curled toe, and facial palate defects in chicks when injected into eggs at a dose of 2.5 mg per egg (Landauer, 1952).

iv) Other Chronic Effects

Low levels of boron in the diet of rats had no effect on reproduction, size, and survival rate of litters. Boric acid given intramuscularly to rats at "constant" doses of 0.7 to 3.3 mg/kg for two generations had no effect on growth, reproduction, or survival of young (Levinskas, 1964).

e) Human Effects

At least 144 cases of acute human poisoning by boric acid have been reported. Of these, about one half were fatal (Levinskas, 1964). Single fatal oral doses have been estimated to be 2-3 grams for infants, 5-6 grams for children, and 15-20 grams for adults (Moeschlin, 1965). Sodium borate is somewhat less toxic with the fatal oral dose estimated at 15-30 grams. The signs and symptoms of boric acid and sodium borate intoxication in humans are similar. Regardless of the route of administration nausea is commonly noted in addition to mild shock, vomiting, and diarrhea. In adults, headache, marked weakness, and changes in mood are often seen. In children, the predominant features of intoxication are signs of meningeal irritation, convulsions, coma, and delirium. An intense scarlatiniform rash followed by desquamation of the skin may also develop. Death is sometimes preceded by a rise in body temperature, a weak rapid pulse, and central nervous system depression (Levinskas, 1964). Chronic intoxication by boric acid or sodium borate can lead to diarrhea,

reduced body weight, anemia, weakness, drowsiness, and states of delusion (Moeschlin, 1965). Daily doses of 5 to 10 grams sodium borate [duration not specified] have been associated with an increase in protein metabolism and urinary nitrogen excretion (Levinskas, 1964).

Repeated inhalation exposure to diborane [extent of exposure not specified] leads to headache, dizziness, chills, muscular weakness, tremors, and abnormal hepatic and renal function (Hamilton and Hardy, 1974). In cases of acute intoxication, symptoms include tightness of the chest, cough, headache, nausea, chills, dizziness, and drowsiness. These effects usually disappear rapidly once exposure is terminated (Levinskas, 1964).

No information is available on the adverse effects of boron trifluoride to humans. In a group of workers exposed to small amounts of this compound for up to seven years, no signs of chronic effects were noted (Levinskas, 1964).

8. TLV's

The TLV's for boron oxide, boron tribromide, and diborane, are 10 mg/m^3, 1 ppm, and 0.1 ppm, respectively (ACGIH, 1971a, b, and d). These limits are given as time weighted averages. The ceiling limit for boron trifluoride is 1 ppm (ACGIH, 1971c).

9. Other Standards

Torkelson and coworkers (1961) have recommended a limit of 0.3 ppm for boron trifluoride to prevent lung damage. The OSHA standards for boron oxide and diborane are 15 mg/m^3 and 0.1 ppm, respectively (OSHA, 1974).

10. Other Data

The odor threshold for diborane is between 1.7 and 3.4 ppm (Krackow, 1953). The corresponding value for boron trifluoride is 1.5 ppm (Levinskas, 1964). Given the available toxicity data, odor cannot be regarded as a satisfactory warning for exposure to either chemical.

Table 3 presents the number of reported human exposures to boron compounds (NIOSH, 1977).

Table 3. Occupational Exposure to Boron Compounds (NIOSH, 1977)

Compound	Number of Exposures
Boron oxide	21,240
Sodium perborate	401,040
Sodium pentaborate	390
Sodium metaborate	127,800
Sodium octaborate	1,020
Sodium tetrahydrate	1,500
Ammonium pentaborate	1,770
Barium metaborate	3,720
Potassium tetraborate	17,490
Zinc borates	6,240
Boron	22,890
Boron carbide	67,950
Boron nitride	300
Boron tribromide	900
Boron trifluoride	3,810
Boron trichloride	1,080
Boron trifluoride monoethylamine	1,410
Fluoboric acid	40,440
Cupric fluoborate	21,690
Nickel fluoborate	8,370
Stannous fluoborate	15,000
Potassium fluoborate	9,240
Stannous perborate	840
Calcium borate	240
Sodium borohydride	540,000
Diborane	1,140
Borax	2,490,000

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BROMINATED AROMATIC COMPOUNDS

1. Molecular Structure

2. Chemical Abstract Service Number

3. Registry of Toxic Effects of Chemical Substances Number

The above information for the commercially significant brominated aromatic selected for this profile is listed in Table 1.

In choosing these compounds consideration was given to the extent of production and use in industrial processes, in addition to the likely toxicological hazard regardless of the relative commercial significance of the compound.

4. Production Figures and Economic Trends

5. Uses

6. Produces and User Data

Bromobenzene

Production and growth figures were not encountered. Bromobenzene is used as a solvent, fuel additive, and in organic syntheses (Stenger and Atchison, 1964; Lawler, 1977).

Dow Chemical (Midland, Mich.) produces bromobenzene (SRI, 1977), which is consumed by an unknown number of users.

Bromo- and Polybrominated Biphenyls

About 806,000 lbs. were produced in 1976 for export only (Fishbein, 1977).

These compounds are primarily used as flame-retardants and are produced by Michigan Chemical (St. Louis, Mich.) and White Chemical (Bayonne, N.J.) (Mumma and Wallace, 1975).

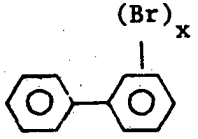
An unknown number of foreign users consume these compounds.

7. Biological Effects of Exposure

a) Target Organs

According to Gillette and coworkers (1974), acute doses of bromobenzene [route and dosage unspecified] result in lung and liver necroses in rats. Lung necrosis was also observed in mice, with the bronchiolar and

Table 1. Brominated Aromatic Compounds

Compound	CAS Number	RTECS Number	Molecular Structure
Bromobenzene	108-86-1	CY90000	
Polybrominated Biphenyls	---	---	

bronchial cells being the site of lesion. In humans, bromobenzene is irritating to skin (Windholz, 1976).

Most of the information encountered on polybrominated biphenyls (PBB's) concerned the use of Firemaster BP-6, a mixture of PBB's which was accidentally confused with a cattle feed supplement in Michigan in 1973. BP-6 was composed of 60-70% of 2,4,5,2',4',5'-hexabromobiphenyl, with the remainder consisting of lesser amounts of tetra-, penta-, and hepta-homologs in addition to various brominated naphthalenes (Kay, 1977; Corbett et al., 1975). It has not yet been determined which of the constituents was responsible for the toxic action that was observed (Kay, 1977).

The toxic activity of (PBB's) is exerted primarily on the liver and kidneys, marked by hyperplasia and necrosis (Kay, 1977). Affected to a lesser extent are the thyroid, uterus, skin, gall bladder, gastrointestinal tract, myocardium and endocardium, and body tissues, especially fatty tissues (Kay, 1977; Moorhead et al., 1977).

Cattle that were examined following contamination by Firemaster BP-6 suffered liver changes such as fatty deposits and vacuolation replacing liver cells, amyloidosis, and necrosis (Corbett et al., 1975). Liver enlargement is commonly reported in laboratory exposures of cows (Moorhead et al., 1977) and rodents (Corbett et al., 1975) to PBB's. Cagen and associates (1977a) report that the liver weight increase from PBB exposure is significantly dose-related.

Kidney damage is seen as enlargement, distention from fluid buildup, pale coloration; lymph nodes surrounding the kidneys also appeared "enlarged and edematous." In addition, degeneration of tubule epithelium, duct and tubule dilation, cloudy swelling, congestion and detachment from supporting membranes were also observed in experiments performed on pregnant heifers (Moorhead et al., 1977).

Further pathological findings from PBB exposure are discussed in reviews by Sleight and Sanger (1976), Kay (1977), Moorhead and coworkers (1977), and Corbett and coworkers (1975).

Bioaccumulation of PBB's occurs in exposed animals, especially in hepatic and adipose tissue, as well as in eggs and milk (Sleight and Sanger, 1976).

Octabromobiphenyl has been shown to induce ultrastructural changes in rat liver, and is seen as hepatomegaly and cellular enlargement, with cytoplasm foamy and vacuolated and occasional inclusion bodies (Sleight and Sanger, 1976; Dent et al., 1976; Kay, 1977). Eighteen weeks after 2 to 4 weeks of dietary administration of octabromobiphenyl to rats, high concentrations of bromine were found in body tissues (Dent et al., 1976).

b) Acute Effects

The acute toxicity of polybrominated biphenyls is presented in Table 2.

Table 2. Acute Effects of Polybrominated Biphenyls

Organism	Route	Dose	Response	Reference
BB-8 (an octabromobiphenyl)				
Rats	oral	2 g/kg	No pathological changes up to 2 weeks	Kay, 1977
Rats	oral	1000 mg/kg	Liver hyperplasia, cytoplasmic inclusions	Kay, 1977
Rats	oral	3000 mg/kg daily x 2 days	Liver hyperplasia, cytoplasmic inclusions	Kay, 1977
Firemaster PB-6				
Rats	oral	21.5 g/kg	50% survival	Kay, 1977
Rabbits, albino	dermal	2.15-10.0 g/kg	Skin irritation	Kay, 1977
Rabbits	dermal	5 g/kg	Liver enlargement	Kay, 1977
PBB's (unspecified constituents)				
Rats	(unspecified)	21.5 g/kg	LD_{50}	Sleight & Sanger, 1976
Rats	I.P.	(dose unspecified)	Liver enzyme induction	Kay, 1977
Japanese quail	oral injection	1000 mg/kg (PBB 75% bromine)	Delayed reduction in phenabarbital sleeping time (24-48 hours)	Kay, 1977

A study by Dent and associates (1976) reviews the metabolic alterations associated with acute administration to rats of Firemaster BP-6, a mixture of polybrominated biphenyls.

When applied to rabbit ears, octabromobiphenyl caused reddening and some scaling of the skin, while the polar fraction of PBB applied to rabbit ears resulted in acnegenesis (Kay, 1977).

c) Subchronic Effects

Corbett and coworkers (1975) fed pregnant rats and mice Firemaster BP-6 (a mixture of polybrominated biphenyls) at doses of 50, 100, and 1,000 ppm during days 7-18 of pregnancy in mice and days 7-20 in rats. Fetuses were excised for examination the day before expected birth. Several rats and mice died before the scheduled time of sacrifice from extensive gastrointestinal hemorrhage.

In both species, the mean fetal weight decreased in a dose-related manner, and in rats, late fetal mortality was experienced at 1,000 ppm, including exencephaly (also occurred at 100 ppm), cleft palate, and hydronephrosis.

An additional experiment with non-pregnant mice fed BP-6 at 1,000 ppm resulted in liver changes, such as swollen hepatocytes and coagulative necrosis, as well as significantly high levels of PBB in the liver and fatty tissues (Corbett et al., 1975).

Cagen and Gibson (1977b) exposed newborn mice to PBB's through their mother's milk for 15 days, resulting in a liver weight increase of 42% in the mothers and more than twice that of controls in the newborn mice. This test implies either that newborns are more susceptible to the toxic action of PBB's or that the chemical is concentrated in the mother's milk.

Rats fed a commercial PBB mixture at 0, 1, 10, 100 and 500 ppm for 30 and 60 days showed marked liver weight increase, with massive swelling and vacuolation of hepatocytes, and significant increases of smooth endoplasmic reticulum at 100 and 500 ppm. Myclin bodies were also observed at these doses. At 1 ppm enlargement of liver mitochondria was noted. Rats fed the same doses for 60 days exhibited the same lesions as those fed for 30 days. Guinea pigs suffered greater effects than rats on the same dosage schedule in that at 10 ppm, 2 out of 6 survived 30 days, and at 500 ppm, all 6 died within 15 days (Sleight and Sanger, 1976).

Moorhead and associates (1977) report on an experimental study of pregnant heifers given 25 g of PBB daily until each was close to death (33 to 66 days). The symptoms of toxicosis observed included loss of apetite, extreme lacrimation, salivation, emaciation, diarrhea, dehydration, depression and abortion. Heart and respiratory rates declined progressively and urine specific gravity was reduced. Gross pathology revealed subcutaneous hemorrhage and enphysema, thymus atrophy, fetal mortality, enlarged pale kidneys, secondary

Table 3. Subchronic Effects of PBB's

Organism	Route	Dose	Response	Reference
Chickens	oral	5, 10, 20 ppm in diet x 8 weeks	No effect on egg production, hatchability, offspring growth rate	Kay, 1977
Rats, timed-pregnant	oral	50, 100, 1000 ppm in diet during days 7-20 of pregnancy	Fatal gastrointestinal hemorrhage, reduced fetal weight	Corbett et al., 1975
Mice	oral	50, 100, 1000 ppm in diet during day 7-18 of pregnancy	Decreasing fetal weight related to dosage, fat storage, teratogenic	Corbett et al., 1975
Mice, pregnant	oral	0, 100, 200 ppm in diet during days 4-16 of pregnancy	Dead or resorbed fetuses	Corbett et al., 1975
Mice, pregnant	oral	0, 100, 200 ppm in diet during days 8-16 of pregnancy	Reduced fetal weight	Corbett et al., 1975
Mice, pregnant	oral	0, 5, 100 ppm in diet during days 8-16 of pregnancy	No effects on fetuses	Kay, 1977
Mice	oral	0, 5, 100 ppm in diet postnatal, days 1-29	Increased deaths of newborns	Kay, 1977
Cow	oral	1.13 g/day x 15 days	Intrahepatic bile duct hyperplasia, liver & gallbladder; no deaths	Kay, 1977
Sheep	oral	50 mg/day x 30 days		

pneumonia, thickened gall bladder walls. In addition, edema and hemorrhage of rectal mucosa, and edema of abomasal folds were noted.

Microscopic examination found significant lesions of the eyelids (characterized by hyperkeratosis), gallbladder, and kidneys (Moorhead et al., 1977). Three of six fetuses were found to be edamatous and hemorrhagic (Moorhead et al., 1977). Further pathological findings are discussed in the review by Moorhead and coworkers (1977).

Table 3 lists subchronic effects for various PBB's.

d) Chronic Effects

i) Carcinogenicity

No evidence of carcinogenicity due to PBB exposure has been encountered according to a review by Kay (1977).

No information regarding bromobenzene carcinogenicity was encountered.

ii) Mutagenicity

No data were encountered.

iii) Teratogenicity

Cleft palate, hydronephrosis, and exencephaly observed in mice born to mothers fed 100 and 1,000 ppm PBB for 12 days of pregnancy (Corbett et al., 1975).

iv) Other

Cows from the herds in Michigan which were fed PBB-contaminated feed exhibited essentially the same symptoms as cattle tested in the laboratory (see Section 7c - Chronic Effects). These symptoms included anorexia and weight loss, abnormal hoof growth, reduced milk production, and hepatomas; pregnant cows often delivered late by 2 to 4 weeks, with many calves stillborn or dead shortly after birth (Corbett et al., 1975).

Kay (1977) adds that udder shrinkage often occurred in cows recently "freshened" as did fetal resorption with return to estrus. Cows in a herd exposed to the contaminated feed for only 16 days developed hyperkeratosis, weight loss, and reduced milk production which persisted even after the PBB's were withdrawn from their diet. Among cows that died 6 months after feeding on PBB's, autopsies revealed liver and kidney changes. Body fat levels of PBB in aborted and poisoned live calves measured between 120 and 400 ppm. Further pathological changes are reviewed by Kay (1977) and Corbett and coworkers (1975).

e) Human Effects

Following the cattle contamination incident in Michigan, exposed persons were tested for PBB levels in blood and other tissues. Blood PBB levels ranged from 0.002 to 2.26 ppm (Kay, 1977), human milk was found to have PBB levels up to 92.66 ppm, adipose tissue had up to 174 ppm (Dunckel, 1975). None of these values was associated with health problems, although "anecdotal symptoms" such as appetite loss, rashes, and gastrointestinal disturbances were told, none having been confirmed clinically (Kay, 1977).

Kay (1977) postulates that PBB, being fat soluble, is probably biomagnified from species to species, and has strong possibility of being biomagnified in man.

Information regarding the human effects of bromobenzene was scarce, except that it is a known skin irritant (Windholz, 1976).

8. TLV

TLV's for bromobenzene and PBB's have not been established.

9. Other Standards

In November 1974, tolerance levels for PBB's were set by the U.S. Food and Drug Administration at 0.3 ppm for milk and meat, and 0.05 ppm for eggs and finished feeds (Dunckel, 1975).

10. Other Data

No teratogenic effects have been observed as a result of sperm damage seen in PBB-exposed calves (Kay, 1977).

Table 4 lists the number of reported human exposures to various brominated aromatics (NIOSH, 1977).

Table 4. Reported Occupational Exposures To Brominated Aromatics

Compound	Number of Exposures
Dibromoethylbenzene	420
Bromobenzene	18,540
β-Bromostyrene	660
?-bromobenzene	720

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COBALT AND ITS COMPOUNDS

1. Molecular Structure

2. Chemical Abstracts Service (CAS) Number

3. Registry of Toxic Effects of Chemical Substances (RTECS) Number

The above information for the commercially significant cobalt compounds selected for this profile is listed in Table 1.

In choosing the compounds listed, consideration was given to the extent of production and use in industrial processes, as well as the likely toxicological hazard regardless of the relative commercial significance of the compound.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Cobalt

In 1974, 6,479 tons of cobalt metal were domestically consumed for metal products, and about 2,500 tons were consumed for cobalt salts, driers, and catalysts (Kawaguchi, 1976).

Breakdown of cobalt usage is as follows (Kawaguchi, 1976):

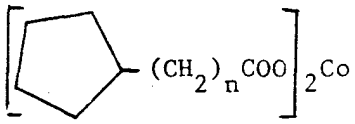
Steel	5.5%
Super alloys	23%
Other alloys	43.5%
Salts and driers	20%
Catalyst	8%

Fifteen different companies produce cobalt (Chem. Week, 1976).

Cobalt Naphthenate

Naphthenates are derivatives of naphthenic acids, alicyclic monocarboxylic acids with a five (or occasionally six) member ring. Naphthenic acids are isolated from crude petroleum, in which they occur naturally. Commercial naphthenic acid is a complex mixture of these acids, which vary in the length of the alkyl chain as well as the ring size. "Cobalt naphthenate" is a commercial term for material which consists of cobalt derivatives of commercial grade naphthenic acid. Therefore, cobalt naphthenate is not a pure compound, but a mixture of a very large number of compounds which vary mainly in the length of the alkyl chain and occasionally also in the size of the alkyl ring (see structural formula, Table 1).

Table 1. Cobalt and Its Compounds

Compound	CAS No.	RTECS No.	Molecular Formula
Cobalt (metal)	7440-48-4	GF87500	Co
Cobalt naphthenate*	---	QK89250	
Cobaltous acetate	71-48-7	AG31500	$Co(C_2H_3O_2)_2 \cdot 4H_2O$
Cobaltous sulfate	10124-43-3	GG31000	$CoSO_4$
Cobalt oxide	1307-96-6	GG28000	Co_2O_3
Cobaltous nitrate	10141-05-6	GG11090	$Co(NO_3)_2$
Cobaltous chloride	7646-79-9	GF98000	$CoCl_2$

*Actually a mixture of many cobalt naphthenates which have widely varying alkyl chain lengths (see formula) (Revzin and Savos'kin, 1971).

In 1975, 2.79 million lbs. of cobalt naphthenate were used (USITC, 1975). Growth is not expected to increase, but may decrease 1% annually (Chem. Prof., 1976d).

Cobalt naphthenate, used in paint driers (Bradley, 1975a), is produced by the following companies (SRI, 1977):

Ferro Corp.	Bedford, Ohio
Interstab Chems. Inc.	New Brunswick, N.J.
Mooney Chems., Inc.	Franklin, Pa.
The Shepherd Chem. Co.	Cincinnati, Ohio
Tenneco Inc.	Elizabeth, N.J.
	Long Beach, Calif.
Troy Chem. Corp.	Newark, N.J.
Witco Chem. Corp.	Clearing, Ill.
	Lynwood, Calif.

Cobaltous Acetate

Based on production figures for synthesis compounds and production figures for acetic acid salts, cobaltous acetate is produced in the range of one million lbs. per year (USITC, 1975).

Cobaltous acetate is used in the synthesis of other cobalt salts and compounds, driers, sympathetic inks, feed supplement, sealings in aluminum anodizing, and as a catalyst (Lawler, 1977).

The following companies produce cobaltous acetate (SRI, 1977):

C.P. Chems., Inc.	Sewaren, N.J.
Kewanee Indust., Inc.	Cleveland, Ohio
Mooney Chems., Inc.	Franklin, Pa.
Richardson-Merrell, Inc.	Phillipsburg, N.J.
The Shepherd Chem. Co.	Cincinnati, Ohio

Cobaltous Sulfate

Recent production figures for cobaltous sulfate are not available; in 1962, however, 502,000 lbs. were produced (Morral, 1964).

Cobaltous sulfate is used in the synthesis of other cobalt compounds, pigments, glazes, feed supplements, and catalysts (Lawler, 1977).

The companies listed below produce cobaltous sulfate (SRI, 1977):

City Chem. Corp.	Jersey City, N.J.
C.P. Chems., Inc.	Sewaren, N.J.
Engelhard Minerals and Chems. Corp.	Bowmanstown, Pa.
	Quincy, Ill.
Ferro Corp.	Bedford, Ohio

Kewanee Indust., Inc.	Cleveland, Ohio
Mallinckrodt, Inc.	St. Louis, Mo.
McGean Chem. Co., Inc.	Cleveland, Ohio
Mooney Chems., Inc.	Franklin, Pa.
Richardson-Merrell, Inc.	Phillipsburg, N.J.
The Shepherd Chem. Co.	Cincinnati, Ohio

Cobalt Oxide

Production in 1962 of cobalt oxide was 457,000 lbs. (Morral, 1964); no recent figures are available.

Cobalt oxide is used in ceramic colors, glazes, cobalt compound synthesis, and as a catalyst (Lawler, 1977).

The following companies produce cobalt oxide (SRI, 1977):

Catalysts and Chems., Inc.	Louisville, Ky.
Kewanee Indust., Inc.	Cleveland, Ohio
McGean Chem. Co., Inc.	Cleveland, Ohio
Richardson-Merrell, Inc.	Phillipsburg, N.J.

Cobaltous Chloride

Figures for production of cobaltous chloride are not available.

Cobaltous chloride is used as an ammonia absorbent, in gas masks, electroplating, inks, humidity indicators, flux, lubricants, fertilizer nutrients, feed supplements, and as a catalyst (Lawler, 1977).

Producers of cobaltous chloride are as follows (SRI, 1977):

Kewanee Indust., Inc.	Cleveland, Ohio
McGean Chem. Co., Inc.	Cleveland, Ohio
Mooney Chems., Inc.	Franklin, Pa.
Richardson-Merrell, Inc.	Phillipsburg, N.J.
The Shepherd Chem. Co.	Cincinnati, Ohio
Thiokol Corp.	Danvers, Mass.

7. Biological Effects of Exposure

a. Target Organs

Cobalt and cobalt compounds appear to exert their major biolgocial effects on the lungs, blood, and pancreas. Of these, the effects on the lungs may be the most significant in assessing the potential hazards to humans. Inhalation of metallic cobalt or intratracheal injections of cobalt salts (doses not specified) are reported to cause pulmonary irritation, with edema or hemorrhage, which may lead to fatal pneumonia (Browning, 1961). Intratracheal

injections of metallic cobalt have caused obliterative bronchiolitis in experimental mammals (doses and organisms not specified). Repeated inhalation exposures to 75% tungsten carbide and 25% cobalt have caused gross pulmonary lesions which were attributed to cobalt. For the most part, lung damage from cobalt exposure is associated with cobaltous, rather than cobaltic, compounds (Browning, 1961). As detailed in Section 7e, cobalt is the suspected etiologic agent in certain occupational lung diseases.

Cobalt also causes erythrocytosis in experimental mammals. The effective single dose in rats has been shown to be 40 mg/kg by oral administration and 2.5 mg/kg by injection (Patty, 1963). In dogs, this effect is elicited at doses as low as 0.8 mg/kg (route and duration not specified). This effect is accompanied by hyperplasia of the bone marrow and metaplasia in the liver, spleen, and kidneys (Browning, 1961).

The effect of cobalt on the pancreas is quite specific. Rabbits given injections of cobaltous chloride evidenced reversible damage to the alpha cells which was accompanied by hyperglycemia (Browning, 1961). Unspecified degenerative changes in the pancreas have been associated with acute cobalt poisoning (Patty, 1963).

In addition to these effects, acute cobalt poisoning also has been shown to cause tubular degeneration in the kidneys, hemorrhage in the liver and adrenals, as well as paleness and shrinkage of the myocardium (Patty, 1963). In humans, cobalt also affects thyroid function (see Section 7e).

b. Acute Effects

Information on the acute toxicity of cobalt and some commercially significant cobalt compounds is summarized in Table 2. The signs of acute intoxication in laboratory mammals are reported to include cutaneous vasodilatation, diarrhea, loss of appetite, paralysis of the hind limbs, and decreases in body temperature and blood pressure. High doses have caused anemia, while low doses have been associated with albuminuria (Patty, 1963).

c. Subchronic Effects

Metallic cobalt had a cumulative toxic effect when given intratracheally to rats at daily doses of 5 mg per animal (Patty, 1963). Doses of 30 mg/day for 30 days were lethal to rats. Diet has been shown to have a substantial effect on the subchronic toxicity of cobalt when administered to rats in drinking water. In animals given only milk, daily doses of 0.5 mg and 1.0 mg were lethal over a 14 week period. Rats fed standard laboratory chow tolerated doses of 1 mg/day for the same period. Animals may also develop tolerance to cobalt. Rats given subcutaneous doses of 10 mg/day for 13 days were able to tolerate single doses of cobalt which were lethal to rats without prior cobalt exposure (Patty, 1963).

Table 2. The Acute Toxicity of Cobalt and Some Cobalt Compounds (NIOSH, 1976)

Compound	Organism	Route	Dose	Effect
Cobalt	Rat	Oral	1500 mg/kg	LD_{LO}
		Intratracheal	25 mg/kg	LD_{LO}
	Mouse	Intraperitoneal	22 mg/kg	LD_{50}
	Rabbit	Oral	20 mg/kg	LD_{LO}
Cobalt naphthenate	Rat	Oral	3900 mg/kg	LD_{50}
Cobaltous acetate	Mouse	Intravenous	31 mg/kg	LD_{50}
	Rabbit	Intravenous	25 mg/kg	LD_{50}
Cobaltous chloride	Rat	Oral	80 mg/kg	LD_{50}
		Intravenous	20 mg/kg	LD_{50}
	Mouse	Oral	80 mg/kg	LD_{50}
		Intraperitoneal	49 mg/kg	LD_{50}
		Subcutaneous	100 mg/kg	LD_{LO}
	Rabbit	Oral	1272 mg/kg	LD_{LO}
	Guinea Pig	Oral	55 mg/kg	LD_{50}
		Dermal	165 mg/kg	LD_{LO}
		Intraperitoneal	165 mg/kg	LD_{LO}
Cobaltous oxide	Rat	Oral	1700 mg/kg	LD_{50}
	Mouse	Intramuscular	800 mg/kg	LD_{LO}
Cobaltous nitrate	Rabbit	Oral	400 mg/kg	LD_{LO}
Cobaltous sulfate	Mouse	Intraperitoneal	54 mg/kg	LD_{50}

d. Chronic Effects

i) Carcinogenicity - Both metallic cobalt and cobaltous oxide have been shown to be carcinogenic in rodents. Heath (1956, 1960) noted malignant tumors at the injection site of 17 of 30 rats given intramuscular injections of metallic cobalt powder in the thigh muscle at doses of 28 mg/rat. In most cases, the tumors were derived from muscle tissue. The process seemed to involve breakdown of the differentiated muscle fibers into myoblasts which then developed into malignant varients. In a similar study, cobaltous oxide was injected into the thigh muscles of rats at 30 mg/rat and mice at 20 mg/mouse. No tumor attributed to this treatment developed in mice. In rats, 5 of 10 animals developed sarcomas at the injection site with an average latent period of 260 days. As in the studies by Heath, the tumors appeared to be of striated muscle cell origin. Metastases, involving the lymph nodes and lungs, were found in 4 of the 5 animals with tumors (Gilman and Ruckerbauer, 1962). Nearly identical results were found when rats were given 20 mg intramuscular injections in both thigh muscles. Twelve of 24 treated animals developed sarcomas of striated muscle cell origin with frequent metastases to the lungs and lymph nodes. Cobalt sulfide, which is not included on the list of commercially significant cobalt compounds, had an even greater carcinogenic effect (Gilman, 1962).

Patty (1963) summarized a study in rabbits which suggested that cobalt caused adenocarcinomas of the lungs and spindle-cell sarcomas of bone. NIOSH (1976) summarizes a study in rabbits indicating that subcutaneous injection of cobaltous nitrate at doses of 7.76 mg/kg/day for five days caused neoplastic effects.

ii) Teratogenicity and Mutagenicity - No information has been encountered on these effects.

iii) Other Chronic Effects - Patty (1963) has summarized two studies on the chronic inhalation toxicity of cobalt. One study involved three years' exposure of unspecified mammals to a cobalt metal blend containing 6% cobalt and several carbides. At doses of 20 mg cobalt/m^3, pathological effects included focal fibrotic lesions, hyperplasia of the bronchial epithelium, and developing granulomas in areas of dust deposition. In the other study, animals were exposed daily to cobalt metal fumes at 1 mg cobalt/m^3 for two years. No pulmonary damage was noted.

e. Human Effects

Cobaltous chloride has been involved in cases of acute and subchronic human poisoning. A single oral dose of 500 mg caused vomiting, diarrhea, and a "feeling of heat" (Browning, 1961). Accidental ingestion of 30 g by a 19 month old boy caused vomiting, restlessness, drowsiness, cyanosis, and eventual death (Deichmann, 1969). In some instances, cobalt chloride has had a goiterogenic effect, causing enlargement of the thyroid with symptoms of myxedema. However, in several instances, cobaltous chloride exposure has led to no clinical signs of adverse thyroid function (Browning, 1961; Moeschlin, 1965; Diechman, 1969).

Cobaltous acetate, used as an additive in beer, has been implicated in 20 deaths from myocardial insufficiency (Deichmann, 1969).

Much of the industrial experience with cobalt compounds has concerned the possible adverse effects in the lungs. Cobalt is a possible etiologic agent in "hard metal disease." This condition is characterized by abnormal chest x-rays, cough, dyspnea, and expectoration, and can be either reversible or progressive. This disease is found in workers engaged in the manufacture or processing of hard metals in which cobalt is used as a binder. While no definite proof exists that cobalt is the causative agent (Hunter, 1975), some reviewers have suggested that cobalt is the probable cause (Hamilton and Hardy, 1974; ACGIH, 1971). While pure metallic cobalt has not been implicated in causing lung damage, workers involved in the calcination of cobalt nitrate suffered from conjunctivitis and upper respiratory tract irritation. Of the four plants surveyed, exposure levels measured as cobalt were 79 mg/m^3 in one plant and 3-4 micrograms/m^3 in the other three. Granulated conglomerate markings in the lungs were found in 24% of the white male workers given x-ray examinations (Browning, 1961). Recent industrial surveys have suggested that no respiratory problems develop at cobalt concentrations of 0.1 mg/m^3 or below. However, some individuals appear to be hypersensitive to cobalt exposure, and deaths have resulted from exposures to 1-2 mg cobalt/m^3 (ACGIH, 1971).

In addition to adverse effects on the lungs, cobalt has been shown to cause acute allergic dermatitis. This condition is characterized by erythematous papular type eruptions localized primarily at the ankles, elbow flexures, and neck. Patch tests have proved positive for metallic cobalt powder (Browning, 1968).

Cobalt acetate, when inhaled as a dry powder, has caused vomiting, severe pain and tenderness in the epigastrium, weakness and pain in the limbs, and hematemesis with occult blood stools (Browning, 1961; Moeschlin, 1965).

There is no epidemiologic evidence linking cobalt exposure to cancer in humans (Hamilton and Hardy, 1974; Patty, 1963).

8. TLV

The time-weighted average TLV for cobalt metal dust and cobalt fume is 0.1 mg/m^3 as cobalt (ACGIH, 1971).

9. Other Standards

The OSHA standard for cobalt is also 0.1 mg/m^3 (OSHA, 1974).

10. Other Data

Cobalt is an essential element in animals. It is a component of vitamin B_{12}, certain enzymes, and is involved in the production of erythropoietin (Browning, 1961; Patty, 1963). Estimates of normal dietary intake have not been

encountered. Patty (1963) indicates that spinach contains 0.7 ppm cobalt on a dry weight basis. Cobalt deficiency leads to normocytic anemia (Browning, 1961).

The treatment of cobalt poisoning has been discussed by Moeschlin (1965) and Deichmann (1969).

Table 3 lists the number of reported human occupational exposures to cobalt and various cobalt compounds (NIOSH, 1977).

Table 3. Reported Occupational Exposures to Cobalt Compounds

Compound	No. of Exposures
Cobalt neodecanoate	1,080
Cobalt	393,300
Cobalt naphthenate	54,000
Cobalt tallate	15,630
Cobalt-2-ethylhexanoate	3,120
Cobalt linoleate	360
Cobalt decanoate	1,080
Cobalt octanoate	1,320
Cobaltous acetate	13,050
Cobalt hydroxide	810
Cobaltous carbonate	4,320
Cobaltous sulfate	7,950
Cobalt oxides	45,000
Cobaltous nitrate	6,000
Cobaltous chloride	7,380
Cobalt titanate	330
Cobalt oxalate	1,350
Cobalt past drier	5,670
Cobaltic and cobaltous cyanide	7,560
Cobalt drier	279,120
Cobalt monoxide	8,610

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FUMIGANTS

1. Molecular Structure

2. Chemical Abstracts Service (CAS) Numbers

3. Registry of Toxic Effects of Chemical Substances (RTECS) Numbers

The above information for the fumigants selected for this profile is listed in Table 1, along with common synonyms for the compounds (in parentheses).

In choosing the compounds listed, consideration was given to the extent of production as well as the likely toxicological hazard regardless of the relative commercial significance of the compound.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Trichloronitromethane (Chloropicrin)

In 1975 chloropicrin was produced in the amount of 5.7 million lbs., a figure nearly 20% higher than the 1974 volume (USITC, 1975, 1974).

Chloropicrin is used as a fumigant in the agricultural treatment of tobacco, tomatoes, fruits, vegetables, and other field crops. Non-agricultural uses as a fumigant include commodities and space, lawns, soils, industrial, and institutional uses (Landel, 1976).

Chloropicrin is not commercially used for any function other than fumigation.

Producers of this compound are the following (Landel, 1976):

Dow Chem.	Pittsburg, Cal.
IMC Chem.	Astabula, Ohio
Niklor Chem.	Long Beach, Cal.

In addition to the three producers, Great Lakes Chemical also uses chloropicrin in the production of fumigants (SRI, 1977).

Bromomethane

In 1976, 35.9 million lbs. of bromomethane were produced (USITC, 1976), with an expected annual growth rate of 7% through 1979 (Chem. Prof., 1975c).

Table 1. Fumigants

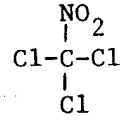
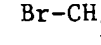
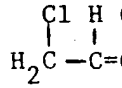
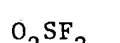
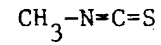
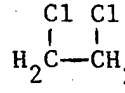
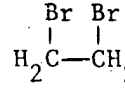
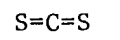
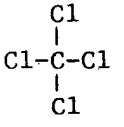
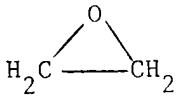
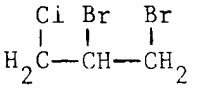
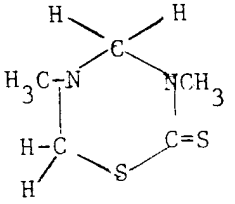
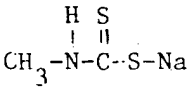
Compound	CAS Number	RTECS Number	Molecular Structure
Trichloronitromethane (Chloropicrin)	76-06-2	PB63000	
Bromomethane (Methyl bromide)	74-83-9	PA49000	
1,3-Dichloropropene (Telone II®)	542-75-6	UC83100	
Sulfuryl fluoride (Vikane®)	2699-79-8	WT50750	
Methyl isothiocyanate	556-61-6	---	
1,2-Dichloroethane (Ethylene dichloride)	107-06-2	KI05250	
1,2-Dibromoethane (Ethylene dibromide)	106-93-4	KH92750	
Carbon disulfide	75-15-0	FF66500	
Carbon tetrachloride	56-23-5	FG49000	

Table 1. Fumigants (Cont'd)

Compound	CAS Number	RTECS Number	Molecular Structure
Ethylene oxide	75-21-8	KX24500	
1,2-Dibromo-3-chloropropane (Nemagon) (DBCP)	96-12-8	TX87500	
3,5-Dimethyl-1,3,5(2H)-tetrahydrothiodiazine-2-thione (Mylone®)	533-74-4	---	
Sodium N-methyldithiocarbamate (Metham)	137-42-8	---	

Uses of bromomethane are as follows (Chem. Prof., 1975c):

Soil fumigant	55%
Space fumigant	15%
Export	25%
Misc.	5%

The companies listed below produce bromomethane (SRI, 1977):

Dow Chem.	Midland, Mich.
Great Lakes Chem.	El Dorado, Ark.
Velsicol Chem.	El Dorado, Ark.

The producers are the primary using companies.

1,3-Dichloropropene (Telone II®)

About 21.4 million lbs. of 1,3-dichloropropene were consumed for fumigant uses in 1975 (Landel, 1976). Dow Chemical is planning a major expansion of its capacity by 1978 (Landel, 1976).

Used primarily as a general soil fumigant for agricultural crops (Landel, 1976), 1,3-dichloropropene is also used in mixtures with 1,2-dichloropropane and related three-carbon chlorinated hydrocarbons, as a soil fumigant marketed under the tradename D-D® by Shell.

The producer of 1,3-dichloropropene is Dow Chemical (Freeport, Texas) (SRI, 1977).

Sulfuryl Fluoride (Vikane®)

In 1975, 0.9 million lbs. of sulfuryl fluoride were used for fumigant purposes, although Dow's manufacturing capacity is estimated at 3 million lbs. per year (Landel, 1976).

Growth figures are not available.

Used almost entirely in the control of structural pests (Landel, 1976), sulfuryl fluoride is produced by Dow Chemical (Pittsburg, Cal.) (SRI, 1977).

Methyl Isothiocyanate

While methyl isothiocyanate, a soil fumigant, may be applied directly to soil in a 20-40% solution with hydrocarbon solvents, it probably appears in soil mostly as the active breakdown product of Mylone® and metham, also soil fumigants (Metcalf, 1968).

Mylone®, which has a total annual domestic consumption of approximately 0.1 million lbs., is produced by Stauffer Chemical Company. Metham is also

produced by Stauffer Chemical Company, which has a total capacity of 3 million lbs. per year, and Chemical Formulators, Inc. (Landel, 1976).

Methyl isothiocyanate is used in the control of nematodes, fungi, and weeds (Metcalf, 1968).

Carbon Disulfide

In 1975, 469 million lbs. of carbon disulfide were produced (Klapproth, 1976); however, only 4.5 million lbs. were used for the purpose of fumigation (Landel, 1976).

Overall growth is projected at 3.1% annually through 1979 (Chem. Prof., 1975e).

Carbon disulfide is used in the production of the following (Chem. Prof., 1975e):

Rayon	33%
Cellophane	15%
Carbon tetrachloride	32%
Other	20%

As a fumigant, this compound is mainly used in the fumigation of space and commodities (Landel, 1976).

The companies listed below produce carbon disulfide (Klapproth, 1976):

FMC Corp.	South Charleston, W.Va.
Pennwalt	Greens Bayou, Tex.
PPG Ind.	Natrium, W.Va.
Stauffer	Delaware City, Del.
	LeMoyne, Ala.

Carbon Tetrachloride

In 1976, 850 million lbs. of carbon tetrachloride were made (USITC, 1976), of which only 20 million lbs. were used for fumigants (Landel, 1976).

Growth is projected to rise 3% or decline 10% yearly through 1979 (Chem. Prof., 1975f).

By far, the main use of carbon tetrachloride is in the production of fluorocarbons 11 and 12 (Chem. Prof., 1975f). As a fumigant, carbon tetrachloride is used in the fumigation of space and commodities (Landel, 1976).

The following companies produce carbon tetrachloride (SRI, 1977):

Allied Chem.	Moundsville, W.Va.
Dow Chem.	Freeport, Tex.
	Pittsburg, Cal.
DuPont	Corpus Christi, Tex.
FMC	S. Charleston, W.Va.
Stauffer	Louisville, Ky.
	LeMoyne, Ala.
Vulcan	Geismar, La.
	Wichita, Kansas

1,2-Dibromo-3-chloropropane (Nemagon, DBCP)

In 1975 about 25 million lbs. of 1,2-dibromo-3-chloropropane (DBCP) were made (Landel, 1976).

Growth figures were not encountered.

DBCP is used as a soil fumigant for a wide variety of agricultural crops (Landel, 1976).

The following companies produce DBCP (SRI, 1977):

Amvac Chem.	Los Angeles, Cal.
Dow Chem.	Magnolia, Ark.
	Midland, Mich.
Velsicol Chem.	El Dorado, Ark.
Hooker Chem.	Lathrop, Cal.
Shell Chem.	Denver, Col.
	Mobile, Ala.

1,2-Dibromoethane (Ethylene dibromide)

Of the 275 million lbs. of 1,2-dibromoethane produced in 1975 (USITC, 1975), only 5 million lbs. were consumed in the production of fumigants (Landel, 1976).

Overall production is declining because of its primary use in leaded fuels (Allison, 1975).

Ethylene dibromide is mainly used as a scavenger in anti-knock preparations for tetra-alkyl lead gasolines. Some is also used to produce vinyl bromide, which is used in flame retardants. Small amounts are used as solvents for resins, gums, and waxes, and as an intermediate in the synthesis of dyes and medicines (Allison, 1975; Carlson and Erskine, 1975).

In addition to its use as a general fumigant for agricultural crops, ethylene dibromide is used to fumigate commodities and space, lawns, and has industrial applications as well (Landel, 1976).

The companies listed below produce ethylene dibromide (SRI, 1977):

Dow Chem.	Magnolia, Ark.
Ethyl Corp.	Magnolia, Ark.
Great Lakes Chem.	El Dorado, Ark.
PPG Corp.	Beaumont, Tex.

1,2-Dichloroethane (Ethylene dichloride)

In 1976, 7.9 billion lbs. of 1,2-dichloroethane were produced (USITC, 1976). Only 4.0 million lbs., however, were consumed for fumigant purposes in 1975 (Landel, 1976).

Overall growth is projected to be 4-5% per year through 1981 (Chem. Prof., 1977b).

1,2-Dichloroethane is used for the following purposes (Chem. Prof., 1977b):

Vinyl chloride monomer	80%
Chlorinated solvent intermediate	10%
Lead scavenger	3%
Misc. and export	7%

For fumigant uses, all of the 1,2-dichloroethane is used for space and commodity applications (Landel, 1976).

The following companies produce 1,2-dichloroethane (SRI, 1977):

Allied Chem. Corp.	Baton Rouge, La.
Continental Oil Co.	Westlake, La.
Diamond Shamrock Corp.	Deer Park, Tex.
Dow Chem. U.S.A.	Freeport, Tex.
	Oyster Creek, Tex.
	Plaquemine, La.
Ethyl Corp.	Baton Rouge, La.
	Pasadena, Tex.
B.F. Goodrich Co.	Calvert City, Ky.
PPG Indust., Inc.	Lake Charles, La.
	Guayanilla, P.R.
Shell Chem. Co.	Deer Park, Tex.
	Norco, La.
Stauffer Chem. Co.	Carson, Calif.
Union Carbide Corp.	Taft, La.
	Texas City, Tex.
Vulcan Materials Co.	Geismar, La.

Ethylene Oxide

Of the 4.47 billion lbs. of ethylene oxide produced in 1975 (USITC, 1975), only 0.1 million lbs. were used as fumigants (Landel, 1976).

Overall growth of ethylene oxide is expected to be 6% annually through 1979 (Chem. Prof., 1975d).

Listed below are the main uses of ethylene oxide (Chem. Prof., 1975d):

Ethylene glycol	60%
Surfactants	11%
Ethanolamines	6.5%
Glycol ethers	7%
Other	16.5%

When used as a fumigant, this compound is primarily applied to space and commodities (Landel, 1976).

The following companies produce ethylene oxide (SRI, 1977):

BASF Wyandotte Corp.	Geismar, La.
Calcasieu Chem. Corp.	Lake Charles, La.
Celanese Corp.	Clear Lake, Tex.
Dow Chem. U.S.A.	Freeport, Tex.
	Plaquemine, La.
Eastman Kodak Co.	Longview, Tex.
Northern Natural Gas Co.	Morris, Ill.
Olin Corp.	Brandenburg, Ky.
PPG Indust., Inc.	Beaumont, Tex.
	Guayanilla, P.R.
Shell Chem. Co.	Geismar, La.
SunOlin Chem. Co.	Claymont, Del.
Texaco Inc.	Port Neches, Tex.
Union Carbide Corp.	Seadrift, Tex.
	Taft, La.
	Penuelas, P.R.

7. Biological Effects of Exposure

a. Target Organs

Bromomethane has been shown to affect the lungs, heart, liver, kidneys, pancreas, thyroid, and parathyroid glands. In inhalation exposures to bromomethane at concentrations of 5000 ppm and above for 3 to 10 minutes, guinea pigs developed lung congestion and edema. In addition, degenerative changes were noted in the heart muscle, liver, kidneys, and pancreas. Rats fed for four months on diets which had been fumigated with bromomethane (bromide residue of 20 to 46 mg/kg) developed pathological changes of the thyroid and parathyroid

glands. Rabbits, given single subcutaneous injections of bromomethane at doses of 50 mg/kg and above, evidenced reductions in platelet count, blood serotonin, and blood water. Bromomethane has also been shown to affect several oxidative-reductive reactions in the neuro-endocrine regulation of metabolism in rabbits exposed to vapor concentrations of 25 ppm for 14 weeks (Davis et al., 1977).

1,3-Dichloropropene is a severe irritant to the eyes, skin, and mucosa of the respiratory tract (Hamilton and Hardy, 1974). Application of this compound to the skin of rabbits, for periods as brief as 30 seconds, resulted in severe irritation, erythema, and vesiculation. Acute oral intoxication of rats with a mixture of 1,3-dichloropropene and 1,2-dichloropropane caused stomach distention, erosion, and occasional hemorrhage of the gastrointestinal mucosa, hemorrhage in the lungs, and fatty degeneration of the liver. Acute inhalation exposure of rats to this mixture caused severe lung edema, interstitial and alveolar hemorrhage, distention of the stomach and upper intestine, and fatty degeneration of the liver. Repeated inhalation exposures of rats, guinea pigs, and rabbits to 1,3-dichloropropene at 2200 ppm for 7 hours per day, for 8 days, caused fatty degeneration of the liver and kidneys as well as visceral congestion (Hine et al., 1953).

Little information is available on the pathological effects of the other fumigants under review. Chloropicrin is extremely irritating to the mucous membranes, causes pulmonary edema, and influences the formation of hemoglobin (Hamilton and Hardy, 1974; Moeschlin, 1965). Both sulfuryl fluoride and methyl isothiocyanate are also highly irritating to the skin and respiratory tract (Merck Index, 1976). Single inhalation exposures to sulfuryl fluoride cause pulmonary edema, and multiple exposures cause kidney and lung injury. Dental fluorosis has been noted in mice after inhalation exposures to sulfuryl flouride at 20 ppm, 7 hours per day, for 12 months (ACGIH, 1971c).

b. Acute Effects

Information on the acute toxicity of bromomethane, chloropicrin, 1,3-dichloropropene, methyl isothiocyanate, 1,2-dibromo-3-chloropropane, and sulfuryl fluoride is summarized in Table 2.

The major symptoms of acute bromomethane intoxication in laboratory mammals include unsteady gait, twitching, convulsions, and coma. Rabbits given subcutaneous injections of bromomethane at 20-120 mg/kg experienced paralysis of the hind limbs, cessation of drinking, and reduced urine output. In mice, rats, and rabbits, the acute toxic action of bromomethane is antagonized by cysteine (Davis et al., 1977).

In rats and mice, acute oral intoxications with a mixture of 1,3-dichloropropene and 1,2-dichloropropane caused hyperexcitability, tremors, ataxia, depression, and dyspnea. Rats subjected to acute inhalation exposures to this mixture developed essentially the same signs plus respiratory distress, lachrymation, and mucous nasal discharge. When applied topically to rabbits, the major signs of intoxication were lethargy and respiratory depression (Hine et al., 1953).

Table 2. Acute Toxicity of Selected Fumigants (NIOSH, 1976a)

Compound	Organism	Route	Dose	Response
Bromomethane	Rat	Inhalation	3120 ppm x 15 min	LC_{Lo}
	Rabbit	Inhalation	6425 ppm x 1 hr	LC_{Lo}
	Guinea pig	Inhalation	300 ppm x 9 hr	LC_{Lo}
Chloropicrin	Rat	Oral	250 mg/kg	LD_{50}
	Cat	Inhalation	800 mg/m^3 x 20 min	LC_{Lo}
	Rabbit	Inhalation	800 mg/m^3 x 20 min	LC_{Lo}
	Guinea pig	Inhalation	800 mg/m^3 x 20 min	LC_{Lo}
1,3-Dichloropropene	Rat	Oral	250 mg/kg	LD_{50}
	Rat	Inhalation	1000 ppm x 4 hr	LC_{50}
	Mouse	Oral	300 mg/kg	LD_{Lo}
	Rabbit	Dermal	2100 mg/kg	LC_{50}
Methyl isothiocyanate	Rat	Oral	305 mg/kg	LD_{50}
	Mouse	Oral	97 mg/kg	LD_{50}
Sulfuryl fluoride	Rat	Oral	100 mg/kg	LD_{50}
	Guinea pig	Oral	100 mg/kg	LD_{50}
1,2-Dibromo-3-chloropropane	Rat	Oral	173 mg/kg	LD_{50}
	Mouse	Oral	257 mg/kg	LD_{50}
	Guinea pig	Oral	150 mg/kg	LD_{50}
	Rat	Inhalation	103 ppm x 8 hr	LC_{50}
	Rabbit	Dermal	1400 mg/kg	LD_{50}

Chloropicrin is a mild narcotic agent (Moeschlin, 1965). Acutely toxic oral exposures cause severe nausea, vomiting, colic, and diarrhea in humans (Merck Index, 1976; see also Section 7e).

Sulfuryl fluoride reportedly causes tremors and convulsions during acute inhalation exposures of laboratory mammals and is about one-third to one-half as toxic as methyl bromide (ACGIH, 1971c).

No information has been encountered on the acute toxic effects of methyl isothiocyanate.

c. Subchronic Effects

Subchronic inhalation exposures to bromomethane led to signs of neural impairment. Nine of the 30 rats exposed to 180 ppm, 7-8 hours per day, for 9 days, became moribund and two rats developed convulsions. After 16 to 58 days, five rats had developed convulsions. Rabbits exposed to 33 or 65 ppm, 8 hours per day, 5 days per week, evidenced paralysis after 22 days. No effects were seen in rats, guinea pigs, and monkeys under the same exposure conditions. At bromomethane levels of 16 ppm, all organisms tolerated this exposure schedule for 6 months. Mice, exposed twice for 18 hours at three month intervals, showed alterations in conditioned reflex activity at bromomethane levels of 500 mg/m^3. No effects were seen at 100 mg/m^3 (Davis et al., 1977).

Subchronic oral toxicity studies of bromomethane have involved feeding animals on diets which had been fumigated with bromomethane. In these studies, exposure levels are measured as residual bromide in the food. Rats fed on diets with residual bromide levels of 20 to 46 mg/kg for 4 months had normal weight gain and no abnormal changes in hemoglobin content and red or white blood cell counts. Cats fed on diets with bromide levels of 0.5 and 1.25 mg/kg evidenced no change in motor response. Unspecified adverse effects were noted in dogs fed on diets containing 150 mg/kg residual bromide. In that no effects were noted in comparable exposures to sodium bromide, the toxic effects of bromomethane were attributed to methylation of cellular macromolecules rather than generation of the bromide ion (Davis et al., 1977).

Little information has been encounterd on the subchronic toxic effects of the other fumigants. Rats, guinea pigs, and rabbits exposed to 1,3-dichloropropene vapors at 2200 ppm for 7 hours per day, for 8 days, experienced marked mortality (Hine et al., 1953). Rats, guinea pigs, and mice subjected to inhalation exposures of sulfuryl fluoride at 20 ppm, 7 hours per day, developed unspecified "significant" effects after 6 months and "slight" reversible injury after 12 months. In mice, dental fluorosis was also noted (ACGIH, 1971c).

d. Chronic Effects

No information has been encountered on the carcinogenicity, mutagenicity, or teratogenicity of these compounds, other than for 1,2-dibromo-3-chloropropane (see Section 10).

e. Human Effects

The acute effects of bromomethane on humans has been described in some detail. This information is derived not only from occupational exposures but also from the former use of bromomethane in fire extinguishers. At least 63 cases of fatal bromomethane inhalation exposures have been reported since 1899. These cases usually involved exposures to levels of 300 to 60,000 ppm. In fatal exposures, a latent period of 30 minutes to 48 hours is often noted prior to the onset of symptoms. Initial signs and symptoms include malaise, headache, visual disturbances, nausea, and vomiting. These are followed by tremors, twitching, convulsions, and periods of unconsciousness. Pulmonary edema may develop. Death often occurs during convulsive seizure. In cases of severe non-fatal exposure, severe headache, marked cerebellar and labyrinthal disturbances, myoclonus, and tremors are often noted. These may be accompanied by epileptiform convulsions, asthenia, ataxia, blurred vision, diplopia, and temporary blindness. Although recovery is usually complete, some cases of permanent brain damage have been noted. Mild intoxication is characterized by vertigo, lassitude, headache, and motor ataxia. Occasionally, extrapyramidal symptoms and temporary myoclonus may develop. Gastrointestinal disturbances can include nausea, vomiting, and diarrhea (Davis et al., 1977).

Chronic bromomethane intoxication in humans is characterized by severe nervous encephalitic type lesions. The most frequently noted signs are visual and speech disorders and mental confusion. In more severe cases, cerebellar ataxia, vertigo with vomiting, intention tremor, and adiadochokinesis may develop. Lesions of the pyramidal tract are evidenced by paresis, hemiplegia, myoclonic twitching, choreatic-athetotic movements, and convulsions. Sensory disturbances include paresthesia, hyperesthesia, amblyopia, and transient amaurosis (Moeschlin, 1965).

Skin contact with bromomethane caused itching, erythema, vesiculation, and blister formation or dermatitis (Davis et al., 1977).

Acute chloropicrin intoxication in humans is characterized by lachrymation, vomiting, nausea, coughing, and pulmonary edema. Vapor concentrations of 0.3 to 0.37 ppm caused painful eye irritation in humans exposed for 3 to 30 seconds. Concentrations of 15 ppm could not be tolerated for more than one minute. This compound also causes skin irritation (ACGIH, 1971b; Hamilton and Hardy, 1974).

One incident of human poisoning by sulfuryl fluoride has been described. Symptoms included nausea, vomiting, abdominal pain, and pruritis. One day after exposure, fluoride was detected in the serum. Dental fluorosis has been cited as a possible long-term hazard from sulfuryl fluoride exposure (ACGIH, 1971c).

8. TLV's

The time-weighted average TLV's for bromomethane and sulfuryl fluoride are 20 ppm and 5 ppm, respectively (ACGIH, 1971a, 1971c). The ceiling limit for chloropicrin is 0.1 ppm (ACGIH, 1971b).

9. Other Standards

The OSHA (1974) standard for bromomethane, sulfuryl fluoride, and chloropicrin are the same as the corresponding TLV's. A manufacturer of sulfuryl fluoride recommended 10 ppm as the maximum safe exposure level for workers (ACGIH, 1971c).

10. Other Data

By agreement with the NIOSH project officer, toxicity information on the following fumigants were not included in this profile: carbon disulfide, carbon tetrachloride, 1,2-dibromo-3-chloropropane, ethylene dibromide, ethylene dichloride, and ethylene oxide. These compounds were omitted because detailed reports have been completed or are in progress by NIOSH or other NIOSH contractors. Capsule summaries of each chemical are given below.

Carbon Disulfide - This compound is a nervous system poison which causes polyneuritis involving both motor and sensory nerves (Hunter, 1975). The major signs of chronic intoxication are nervousness, irritability, fatigue, headache, loss of appetite, and insomnia. This compound has proven to be a serious occupational poison. Based largely on human exposure data, the time-weighted average TLV is 20 ppm (ACGIH, 1971d).

Carbon Tetrachloride - A NIOSH criteria document is available on carbon tetrachloride. This compound has been shown to be carcinogenic in mice and hamsters, tumorogenic in rats, and teratogenic in rats (NIOSH, 1976a). In workers, exposure to levels as low as 20 ppm induced nausea, vomiting, headache, and dizziness. The time-weighted average TLV is 10 ppm (ACGIH, 1971a). A more reasonable standard of 2 ppm is recommended in the NIOSH criteria document.

1,2-Dibromo-3-chloropropane - This compound has been shown to be carcinogenic in rats and mice (NIOSH, 1976a). Recently, it has been associated with sterility in male workers.

1,2-Dibromoethane - This compound has been shown to be carcinogenic in rats and mice (NIOSH, 1976a). In experimental mammals, subchronic exposures led to liver damage and lung irritation. Acute intoxication is characterized by central nervous system depression, liver and kidney damage, and lung irritation. The ceiling limit for worker exposure is 25 ppm (ACGIH, 1971f).

1,2-Dichloroethane - A NIOSH criteria document is available on this compound. Acute human intoxication is characterized by nausea, vomiting, dizziness, headache, and weakness. Kidney, liver, and lung damage have been noted. Chronic human exposure is associated with anorexia, nausea, vomiting, epigastric pain, and liver and kidney injury. The recommended standard for exposure is 5 ppm (time-weighted average) with a ceiling limit of 15 ppm (NIOSH, 1976b).

Ethylene oxide - This compound has been shown to be mutagenic (NIOSH, 1976a). Ethylene oxide is highly irritating to the skin and respiratory tract. Subchronic exosure in laboratory mammals caused lung, liver, adrenal, and testicular damage as well as hind limb paralysis. The current time-weighted average TLV is 50 ppm (ACGIH, 1971h).

Table 3 lists the number of reported human occupational exposures to various fumigants (NIOSH, 1977).

Table 3. Reported Human Occupational Exposures to Fumigants (NIOSH, 1977)

Compound	Number of Exposures
Chloropicrin	82,470
Ethylene dibromide	86,160
Methyl bromide	82,410
Ethylene oxide	164,640
Carbon disulfide	1,129,740
Carbon tetrachloride	1,667,250
Ethylene dichloride (1,2)	1,697,700
DBCP (1,2-Dibromo-3-chloropropane)	5,220
Telone II (1,3-Dichloropropene	4,560
Vikane (Sulfuryl fluoride)	9,120
Methyl isothiocyanate	1,710

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GLYCIDYL ETHERS

1. Chemical Structures

2. Chemical Abstract Service (CAS) Numbers

3. Registry of Toxic Effects of Chemical Substances (RTECS) Numbers

The above information for the commercially significant glycidyl ethers selected for this profile is listed in Table 1 along with the chemical names.

In choosing the compounds listed, consideration was given to the extent of production and use in industrial processes. Seven individual compounds and a mixture (n-alkyl glycidyl ethers) met this criterion.

4. Production Figures and Economic Trends

It is estimated that one to two million pounds of alcohol were consumed in the production of mixed n-alkyl gylcidyl ethers in 1970 (Deacetis, 1975). Accordingly, the production of mixed n-alkyl glycidyl ethers in 1970 is estimated to have been 1.1-2.1 million pounds.

In 1973 about 6 million pounds of epichlorohydrin were consumed in the production of all glycidyl ethers (Oosterhof, 1975a). If an annual growth rate of about 5% is assumed for mixed n-glycidyl ethers, then approximately 0.5-1.0 million pounds of epichlorohydrin were used for mixed n-alkyl glycidyl ethers. The remaining 5.0-5.5 million pounds of epichlorohydrin were used in the manufacture of allyl, phenyl, and butyl glycidyl ethers. Therefore, approximately 6-7 million pounds of allyl, phenyl, and butyl glycidyl ethers were produced in 1973.

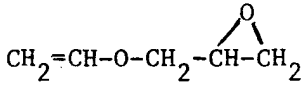
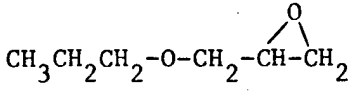
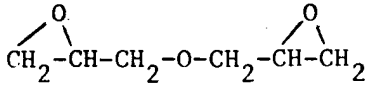
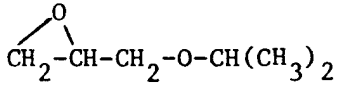
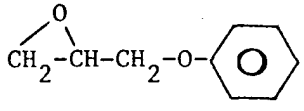
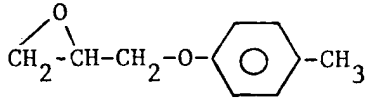
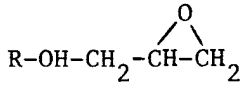
Accurate growth rate estimates for the individual glycidyl ethers are not available. However, the epoxy resin products in which they are used have a projected growth rate of approximately 2-10% per year (Deacetis, 1975; Oosterhof, 1975a, b), suggesting a similar growth rate for glycidyl ethers.

5. Uses

Glycidyl ethers such as allyl, butyl, and phenyl are used as reactive diluents for epoxy resins and as stabilizers for PVC resins, chlorinated paraffins, and other halogenated products (Deacetis, 1975; Oosterhof, 1975a). For example, 10-12% butyl glycidyl ether is added as a reactive diluent in Dow Chemical's liquid resin D.E.R. 334^{R}, a diglycidyl ether of bisphenol A used in structural applications for castings, caulkings, and sealants (Oosterhof, 1975b). Allyl glycidyl ether is also used as a monomer in the production of specialty resins and polymers (Panzer, 1977).

Mixed n-alkyl glycidyl ethers are formed by condensation of higher alcohols with epichlorohydrin. They typically contain ethers produced from a mixture of

Table 1. Compounds in the Glycidyl Ether Class

Compound	Chemical Name	Chemical Abstract Service Number	Registry of Toxic Effects Chemical Substances Number	Molecular Structure
Allyl glycidyl ether	1-(allyloxy)-2,3-epoxypropane	106-92-3	RR08750	
Butyl glycidyl ether	1-(butoxy)-2,3-epoxypropane	2426-08-6	TX42000	
Glycidyl ether	bis(2,3-epoxypropyl) ether	2238-07-5	none	
Isopropyl glycidyl ether	1,2-epoxy-3-isopropoxypropane	4016-14-2	TZ35000	
Phenyl glycidyl ether	1,2-epoxy-3-phenoxypropane	122-60-1	TZ36750	
Cresyl glycidyl ether	1,2-epoxy-3-(tolyloxy)propane	26447-14-3	none	
n-Alkyl glycidyl ethers	(mixture)	none	none	

straight chain alcohols containing from twelve to fourteen carbon atoms, and from a mixture of straight chain alcohols containing from sixteen to eighteen carbon atoms. These mixtures were developed by Procter & Gamble for use in the synthesis of specialty anionic surfactants (Oosterhof, 1975a).

6. Producer and User Data

The following companies produce the listed glycidyl ethers (SRI, 1977; Panzer, 1977):

Shell Chemical Company (Deer Park, Texas)	allyl glycidyl ether butyl glycidyl ether phenyl glycidyl ether
Dow Chemical Company (Freeport, Texas)	butyl glycidyl ether cresyl glycidyl ether
Alcolac, Inc. (Baltimore, Maryland)	allyl glycidyl ether
Procter & Gamble Company (Ivorydale, Ohio; Kansas City, Kansas)	mixed n-alkyl glycidyl ethers

No data are available on the number of users of glycidyl ethers. The largest users are probably the producers who use their production captively, such as Procter & Gamble and Dow.

7. Biological Effects of Exposure

Almost all of the available information on the toxicology of industrially significant glycidyl ethers comes from a single study which included allyl glycidyl ether, n-butyl glycidyl ether, and phenyl glycidyl ether (Hine et al., 1956).

a. Target Organs

Hine and coworkers (1956) found that the respiratory tract, skin, and eyes are the organs most consistently affected by glycidyl ethers. Acute oral, dermal, and inhalation exposures to allyl glycidyl ether, n-butyl glycidyl ether, or phenyl glycidyl ether resulted in lung irritation with pneumonitis in rats, mice, and rabbits. Hyperemia of the adrenal gland and adhesions of the stomach to adjacent tissue after oral administration were also noted. Both allyl glycidyl ether and n-butyl glycidyl ether occasionally produced signs of liver damage.

Subchronic inhalation exposure of rats to allyl glycidyl ether at 260 ppm caused slight irritation of the eyes and respiratory distress without frank lung damage. At 400 ppm, however, lungs of exposed animals became emphysematous with diffuse areas of hemorrhage. Additional pathological changes included mottled liver, congested adrenals, distension of the stomach, and corneal opacity in one rat. At higher concentrations - 600 ppm and 900 ppm - eye and respiratory tract irritation were pronounced, and corneal opacity developed in most animals. In addition to adrenal and liver alterations, two of

ten rats at 900 ppm developed necrotic spleens. Similar subacute inhalation exposure to phenyl glycidyl ether resulted only in slight eye and respiratory tract irritation with infrequent pathological changes in the lungs and liver.

On single eye and skin applications to rabbits, allyl glycidyl ether proved to be a severe skin and eye irritant. Both n-butyl glycidyl ether and phenyl glycidyl ether were mild irritants. On repeated dermal applications, however, phenyl glycidyl ether produced significantly greater irritation than either allyl glycidyl ether or n-butyl glycidyl ether. Both phenyl glycidyl ether and allyl glycidyl ether produced maximum irritation by the fourth day of treatment (Hine et al., 1956).

Little additional information is available on organ damage caused by glycidyl ethers. Czajkowska and Stetkiewicz (1972) found that phenyl glycidyl ether causes skin necrosis, injury to subcutaneous tissue, and changes in other internal organs after oral and dermal administration to rats and rabbits. Abasov (1971) has examined the effects of phenyl glycidyl ether on the eyes and skin. Details of this study were not available for this review. Thorgeirsson and coworkers (1975) indicated that butyl glycidyl ether is allergenic in guinea pigs.

b. Acute Toxicity

Acute toxicity data on allyl glycidyl, n-butyl glycidyl, and phenyl glycidyl ethers are summarized in Table 2. On oral and inhalation exposures, allyl glycidyl ether appears to be somewhat more toxic than n-butyl glycidyl ether or phenyl glycidyl ether. Central nervous system depression is a common feature of glycidyl ether intoxication by these routes of administration. On dermal application, no remarkable differences are apparent on the toxicity of the three glycidyl ethers, and central nervous system depression is apparent only with phenyl glycidyl ether (Hine et al., 1956).

c. Subchronic Toxicity

Hine and coworkers (1956) exposed rats to various vapor concentrations of allyl glycidyl ether and phenyl glycidyl ether for seven hours per day, five days per week, for five to ten weeks. Organ damage associated with these exposures has been described in Section 7a. In addition, rats exposed to allyl glycidyl ether at concentrations of 260 ppm and above had abnormally low weight gain. At 400 ppm, an increase in kidney weight per unit body weight was noted. Exposures to 600 ppm and 900 ppm caused marked lethality by the fifth week. Phenyl glycidyl ether, which was tested only at 100 ppm, resulted in significantly increased hemoglobin levels as well as the pathological changes previously cited.

d. Chronic Toxicity

No information has been encountered on the carcinogenicity, mutagenicity, or teratogenicity of any of the commercially significant glycidyl ethers. Diglycidyl ether, a bifunctional epoxide, has been shown to be mutagenic in

Table 2. Acute Toxicity of Some Glycidyl Ethers

Compound	Organism	Route	LD_{50} or LC_{50}*	Reference
Allyl glycidyl ether	Rat	Oral	922 mg/kg	Marhold, 1972
			1600 (1390-1840) mg/kg	Hine et al., 1956
		Inhalation	>860 ppm x 4 hr	Marhold, 1972
			670 (510-880) ppm x 8 hr	Hine et al., 1956
	Mouse	Oral	390 (320-480) mg/kg	Hine et al., 1956
		Inhalation	270 (206-774) x 4 hr	Hine et al., 1956
	Rabbit	Dermal	2550 (1410-5710) mg/kg	Hine et al., 1956
n-Butyl glycidyl ether	Rat	Oral	2260 mg/kg	Hine et al., 1956
			2050 (1560-2690) mg/kg	Smyth et al., 1962
		Intraperitoneal	1190 mg/kg	Hine et al., 1956
		Inhalation	1030 (890-1240) ppm x 8 hr	Hine et al., 1956
	Mouse	Oral	1530 (1170-2000) mg/kg	Hine et al., 1956
		Intraperitoneal	700 mg/kg	Hine et al., 1956
		Inhalation	>3500 ppm x 4 hr	Hine et al., 1956
	Rabbit	Dermal	4930 (3730-6500) mg/kg	Hine et al., 1956
			2520 (1280-4970) mg/kg	Smyth et al., 1962
Phenyl glycidyl ether	Rat	Oral	3800 mg/kg	Czajkowska and Stetkiewicz, 1972
			3850 (3110-4780) mg/kg	Hine et al., 1956
			4260 (3900-4660) mg/kg	Smyth et al., 1954
		Inhalation	>100 ppm x 8 hr	Hine et al., 1956
	Mouse	Oral	1400 (1180-1670) mg/kg	Hine et al., 1956
		Inhalation	>100 ppm x 4 hr	Hine et al., 1956
	Rabbit	Dermal	2990 (1470-6100) mg/kg	Hine et al., 1956
			1500 (1070-2100) mg/kg	Smyth et al., 1954
			2600 mg/kg	Czajkowska and Stetkiewicz, 1972

*95% Confidence interval in parentheses.

bacteria (Wade et al., 1976), and the potential carcinogenicity of this ether has been evaluated (IARC, 1976).

e. Effects on Humans

Hine and coworkers (1956) have reported on ten cases of dermatitis from allyl glycidyl ether, thirteen cases from phenyl glycidyl ether, and one case of eye irritation from allyl glycidyl ether. Some cases appear to have involved sensitization to both glycidyl ethers.

8. TLV's

Based on the work of Hine and coworkers (1956), the TLV for glycidyl ether has been set at 5 ppm (ACGIH, 1971). Apparently, based on the same study, the TLV's for n-butyl glycidyl ether and phenyl glycidyl ether are 50 ppm and 10 ppm, respectively.

9. Other Standards

The OSHA standards for allyl glycidyl ether, n-butyl glycidyl ether, and phenyl glycidyl ether are 10 ppm, 50 ppm, and 10 ppm. OSHA also has set a 50 ppm standard for isopropyl glycidyl ether (OSHA, 1974). These limits are given as time weighted averages.

10. Other Data

Table 3 lists the number of reported human occupational exposures to glycidyl ethers (NIOSH, 1977).

Table 3. Reported Human Occupational Exposures to the Glycidyl Ethers (NIOSH, 1977)

Compound	Number of Reported Exposures
Allyl glycidyl ether	6,450
Butyl glycidyl ether	17,580
Phenyl glycidyl ether	5,850
Glycidyl ethers	118,350
Diglycidyl ether of bisphenol A	37,020

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INORGANIC AZIDES

1. Molecular Structure

2. Chemical Abstracts Service Number

3. Registry of Toxic Effects of Chemical Substances Number

The above information for the compounds selected for this profile is listed in Table 1. The compounds listed were selected on the basis of commercial significance as well as the likely toxicological hazard, regardless of commercial importance.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Sodium Azide

In 1963, about 100,000 lbs. of sodium azide were consumed in the U.S. (Reichle, 1966). More recent production figures were not encountered; however, this compound is the largest volume azide in commercial production. In addition, the use of air bags in automobiles could greatly increase current production volumes.

In the past, the most important commercial use of sodium azide may have been in the preparation of lead azide for explosives (Rinkenbach, 1965). However, the use of a sodium azide mixture to produce nitrogen gas for air bag inflation in automobiles may soon become more important.

In addition to numerous listings for air bag inflators, a survey of recent patent literature revealed the following uses for sodium azide: intermediate for herbicide production, production of photosensitive polymers, antibacterials, antidepressants, propellants, denitrification preventor for fertilizers, and various organic syntheses.

Sodium azide is currently being used in a farm product, at a 15% concentration, for control of soil borne diseases in vegetable crops in Florida and in peanuts in Virginia, North Carolina, and Georgia (Farm Chem., 1976). The product, called Smite 15G, is marketed by PPG Industries.

Sodium azide is also used (in concentrations of 0.1%) as a preservative in diluents used in automatic blood cell counters (Chem. Eng. News, 1976).

The following companies produce sodium azide at the listed locations (Chemical Week, 1976):

Table 1. Inorganic Azides

Compound	CAS Number	RTECS Number	Molecular Formula
Sodium Azide	26628-22-8	VY80500	NaN_3
Lead Azide	13424-46-9	OF86500	PbN_6
Hydrazoic acid	7782-79-8	MW28000	HN_3

Atomergic Chemetals Co.	Plainview, N.Y.
Dynamit Nobel AG	Northvale, N.J.
Guardian Chemical	Happauge, N.Y.
Fairmount Chem.	Newark, N.J.
Lonza, Inc.	Mapleton, Ill.
PPG, Inc. (Ayers & Johnson, 1976)	---

Lead Azide

Production figures are not available. Lead azide is used as a detonating initiator for commercial blasting caps and military ammunition (Rinkenbach, 1965).

A listing of producers is not available; however, it is possible that lead azide is produced at government facilities operated by contractors, such as DuPont (SRC estimate).

Hydrazoic Acid

Production figures are not available.

Hydrazoic acid is used in the preparation of inorganic, organic, and organometallic azides and derivatives (Reichle, 1966).

There is no commercial data on production or sale of hydrazoic acid in the available literature.

7. Biological Effects of Exposure

The inorganic azides have a reputation as dangerous materials. Hydrazoic acid and its heavy metal salt, lead azide, are highly explosive which may account for the paucity of references to its pharmacological and physiological properties (Sutton, 1963). Since the percussion sensitivity of lead azide led to its important use for primers in munitions, it is not surprising that essentially no toxicological data on PbN_6 was encountered. The azide anion can be considered responsible for the similar biological effects of hydrazoic acid and sodium azide. However, since HN_3 is a volatile liquid, the inhalation toxicity of the vapor is of additional concern.

a) Target Organs

Hydrazoic acid and sodium azide are powerful hypotensive agents (μg/kg range) which dilate blood vessels by direct action on the smooth muscles. Azide also stimulates cardiac muscle and dilates the coronary vessels directly, thereby increasing the force of contraction and blood flow (Graham, 1949; Graham et al., 1948).

The greatest effect of azide is in the stimulation of the central nervous system (CNS), which leads to increased respiration and cardiac rate

and force. With larger doses, (mg rather than μg/kg range) (Table 2), stimulation may be severe enough to cause convulsive seizures, which are characteristically followed by a period of depression leading to collapse and asphyxia from respiratory failure (Graham, 1949; Graham et al., 1948). Some survivors show injury and demyelination of nerve fibers, including the optic nerves and tracts, in the CNS (Hicks, 1950). Blindness and ataxia are manifestations of the CNS damage produced by repeated doses in monkeys (Hurst, 1942; Mettler and Sax, 1972).

b) Acute Effects

The symptoms observed in animals after relatively large doses of sodium azide (Table 2) are respiratory stimulation and violent tonic convulsions leading to respiratory depression and death by asphyxiation (Graham, 1949). Mice, rats, guinea pigs, and rabbits dosed by oral, subcutaneous, intramuscular, intraperitoneal, or intravenous routes all showed similar symptoms which varied only in degree and rapidity of onset with varying dosage levels.

Hydrazoic acid has essentially the same toxicity (21.5 mg/kg) and symptomology for mice when injected intraperitoneally (Graham et al., 1948). When administered by injections and inhalation to mice, rats, guinea pigs, and rabbits, early irritation of mucous membranes with excessive salivation was noted. Inhalation of lethal doses of the vapor or spray produced, in addition, asthma and an acute bronchial inflammation in guinea pigs. Certain of the animals died of pulmonary edema, right side heart failure, and constriction of the gut which led to hepatic engorgement. When death was delayed from 3 hours to 3 days, pathological changes were observed only in the lungs. Intraperitoneal, intramuscular, intravenous, and subcutaneous injections of hydrazoic acid all gave rise to pulmonary damage.

Fairhall and coworkers, (1943) considered the acute toxicity of hydrazoic acid vapor comparable to that of hydrogen sulfide or hydrogen cyanide. Their results appear in Table 2.

Sublethal doses of sodium azide and hydrazoic acid give rise to a marked depression of blood pressure, coronary dilation, and mild respiratory stimulation with variable occurrences of convulsions (Graham et al., 1948; Graham, 1949). A long period of weakness, respiratory depression, and muscle flaccidity is followed by recovery.

Repeated intraperitoneal injections of sodium azide in rats (5 to 10 mg/kg every 15 to 30 minutes for 3 to 6 hours) resulted in severe intoxication (Hicks, 1950). At first the animals typically became stuporous, occasionally followed by brief generalized convulsions, and then comatose. This coma usually lasted 1 to 2 hours, after which the rats slowly recovered to a large extent during the next 12 hours. Hicks (1950) described nervous system lesions caused by the poisoning. Of 37 rats poisoned to the point of convulsions and coma, 15 died in the acute stages, 11 survived without brain lesions developing, and 11 survived to undergo varying degrees of destructive lesions (Table

Table 2. Acute Toxicity of Inorganic Azides

Organism	Route	Dose	Response	Reference
Hydrazoic Acid				
Mouse	I.P.	21.5 mg/kg	LD_{50}	Graham, 1948
Rat	Inhalation	849-967 ppm	0/14 died in 60 minutes	Fairhall et al., 1943
Rat	Inhalation	1024 ppm	3/8 died in 60 minutes	Fairhall et al., 1943
Rat	Inhalation	1081 ppm	3/4 died in 60 minutes	Fairhall et al., 1943
Rat	Inhalation	1138 ppm	17/18 died in 60 minutes	Fairhall et al., 1943
Rat	Inhalation	1162-1365 ppm	16/16 died in 60 minutes	Fairhall et al., 1943
Rat	Inhalation	1566 ppm	2/2 died in 30 minutes	Fairhall et al., 1943
Rat	Inhalation	1872 ppm	2/2 died in 19 minutes	Fairhall et al., 1943
Rat	Inhalation	2080 ppm	2/2 died in 16 minutes	Fairhall et al., 1943
Rat	Inhalation	2900 ppm	2/2 died in 10 minutes	Fairhall et al., 1943
Sodium Azide				
Rat	Oral	40 mg/kg	0/3 died in 3 hours	Fairhall et al., 1943
Rat	Oral	45 mg/kg	5/8 died in 3 hours	Fairhall et al., 1943
Rat	Oral	46 mg/kg	3/3 died in 3 hours	Fairhall et al., 1943
Rat	I.P.	25 mg/kg	0/4 died in 3 hours	Fairhall et al., 1943
Rat	I.P.	33 mg/kg	8/12 died in 3 hours	Fairhall et al., 1943
Rat	I.P.	37 mg/kg	5/5 died in 3 hours	Fairhall et al., 1943
Rat	I.P.	75 mg/kg	LD_{75} died in 3 hours	Fairhall et al., 1943
Rat	S.C.	33 mg/kg	0/5 died in 3 hours	Fairhall et al., 1943
Rat	S.C.	35 mg/kg	4/9 died in 3 hours	Fairhall et al., 1943
Rat	S.C.	38 mg/kg	8/8 died in 3 hours	Fairhall et al., 1943
Mouse	Oral	27 mg/kg	LD_{50}	Graham, 1949
Mouse	Oral	37.4 mg/kg	LD_{50}	Roth et al., 1956
Mouse	I.V.	19 mg/kg	LD_{50}	Graham, 1949
Mouse	I.P.	28-34 mg/kg	LD_{50}	Graham, 1949
Mouse	I.P.	18 mg/kg	LD_{50}	Graham et al., 1948
Mouse	I.P.	15-20 mg/kg	LD_{50}	Hicks, 1950
Mouse	I.P.	23.7 mg/kg	LD_{5}	Graham, 1949
Mouse	Unspecified	27 mg/kg	LD_{50}	Boyland & Gallico, 1952
Monkey	I.V.	12 mg/kg	LD_{Lo}	Mettler & Sax, 1972
Monkey	Intramuscular	20 mg/kg	Sick but survived	Hurst, 1942
Monkey	Intramuscular	10-12 mg/kg repeated	death after 3 to 4 doses	Hurst, 1942
Monkey	Intramuscular	5 mg/kg daily	5/6 died in 60 to 130 days	Hurst, 1942

Table 3. Summary of the Principal Lesions of the Nervous System Caused by Azide Poisoning in Eleven Rats (Hicks, 1950)

	Animals in Which Region Indicated Showed Lesions
Corpus callosum	6
Corpus striatum (gray matter)	10
Corpus striatum (white matter)	10
Optic tracts	8
Olfactory bulb	2
Thalamus	1

3). They were almost exclusively limited to the corpus callosum, the corpus striatum, especially the bundles of myelinated fibers, and the optic nerve and tracts. Generally mild lesions with no particular distribution pattern were found in the hearts of most of the animals with brain lesions and in one or two instances where pathologic brain changes were absent. In one animal that showed severe lesions there was well developed necrosis of the tubular epithelium of the testis, and one other animal showed a few necrotic cells.

c) Subchronic Effects

Hurst (1942) noted as persistent symptoms in monkeys following a single large or repeated smaller doses of sodium azide temporary or permanent blindness with pupil dilatation, incoordination, cerebellar ataxia, paresis or rigidity, fibrillary muscular tremors and apathy. The animals died or were killed after 2 to 204 days, having received a total of 35 to 206 mg/kg in 2 to 165 doses. Repeated administration often produced necrosis or demyelination in the optic nerves and tracts and necrosis in the caudate nucleus and putamen of the lenticular nucleus. Lesions in the other parts of the grey and white matter are much less frequent and severe.

d) Chronic Effects

i) Carcinogenicity

No reference to any cancerous or pre-cancerous histology was encountered.

ii) Mutagenicity

No evidence was encountered to suggest that HN_3, NaN_3, or PbN_6 may be mutagenic.

iii) Teratology

No studies were encountered.

iv) Other

Mettler and Sax (1972) described a syndrome of ataxia in monkeys, developing from 1 to 55 weeks after receiving convulsant doses (8-16 mg/kg, I.V.) of sodium azide. Dosing immediately produced progressive cerebellar damage leading to states ranging from restricted Purkinje cell loss in the semilunar lobules to total decortication.

e) Human Effects

Stern (1927) described acute hydrazoic acid poisoning in a chemist who accidently inhaled fumes. The principle signs recorded were inflammation of the mucous membranes, conjunctivitis and bronchitis, swelling of both knee joints, large blue lesions on the legs, and fever lasting several days.

Kocher (1930) intentionally inhaled a 1 per cent solution of HN_3 and noted a fall of blood pressure to 70/50 before he collapsed. Recovery occurred in about 15 minutes and, apart from residual headaches for half an hour, was complete.

Graham et al., (1948) examined workers exposed to hydrazoic acid for 1-15 years in the manufacture of lead azide from lead nitrate and sodium azide (Table 4). Detailed physical examinations revealed no evidence of any pathological condition which could be attributed to occupational exposure. Workers experienced throbbing headaches, palpitation, episodes of weakness and unsteadiness and mild eye and nose irritation. They stated that symptoms were noted only when the fume concentration was "high." The range of hydrazoic acid in the atmosphere lay between 0.3 and 3.9 ppm. Exposure to these concentrations caused definite hypotension in the workers.

Sodium azide has been used experimentally for the therapy of hypertension. Black and coworkers (1954) found that sodium azide produces a larger fall in blood pressure in hypertensive patients than in normotensive individuals. Oral doses of 0.65 to 1.3 mg (approx. 0.01 to 0.02 mg/kg) produced a prompt fall of blood pressure which lasted 10 to 15 minutes. The administration of up to 1.3 mg three times daily for 10 days to nine normal individuals did not have a sustained effect on the pressure. The only other effect observed was an occasional transient pounding sensation in the head shortly after taking the drug. The fall in pressure was not accompanied by any significant change in pulse or respiration rate. Of 30 hypertensive individuals treated with 0.65 to 3.9 mg orally for 1 week to 2 1/2 years, 15 were found to maintain their pressure near normotensive levels. In 3 patients who took sodium azide for more than one year, there was no evidence of any organic damage on the basis of routine clinical studies. In 20 of the patients, continued treatment was followed by an increased sensitivity to the drug, necessitating a reduction in daily dosage.

8. TLV

A recommended ceiling TLV of 100 ppb for sodium azide in air has been proposed by the ACGIH (NIOSH, 1976). It is clear from animal studies data on medicinal use that dust concentrations should be kept at low levels if hypotension is to be avoided (Sutton, 1963).

No threshold limit values for hydrazoic acid have been proposed. The odor and irritant properties of hydrazoic acid do not present sufficient warning to prevent the occurrence of alarming symptoms. Imperial Chemicals Industries has suggested that concentrations greater than 1 ppm indicate an unsatisfactory situation for prolonged exposure (Sutton, 1963). The use of sodium azide in organic synthesis may result in significant hydrazoic acid exposure.

9. Other Standards

No other standards were encountered.

Table 4. Occupational History of Workers Exposed to HN_3 in the Manufacture of Lead Azide from Lead Nitrate and Sodium Azide (Graham et al., 1948).

Case Number	Years of Continuous Exposure	Age
1	15	43
2	circa 1	31
3	circa 1	31
4	16	54
5	2	36
6	circa 1	44
7	circa 1	35
8	10	44
9	1.6/12	41
10	8	52

10. Other Data

Table 5 lists the number of reported human exposures to inorganic azides (NIOSH, 1977).

Table 5. (NIOSH, 1977)

Compound	Number of Exposures
Sodium azide	3900
Lead azide	6780

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INORGANIC CHROMIUM COMPOUNDS

1. Molecular Formula

2. Chemical Abstracts Service Number

3. Registry of Toxic Effects of Chemical Substances Number

The above information for the inorganic chromium compounds selected for the profile is listed in Table 1.

In choosing the compounds listed, consideration was given to the extent of production and use in industrial processes as well as the likely toxicological hazard regardless of the relative commercial significance of the compound.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Chromium (III) carbonyl

No production data were encountered.

Chromium (III) carbonyl has been used in the vapor deposition of pure chromium metal and in the preparation of chromous oxide (Hartford and Copson, 1964).

The producers of chromium carbonyl are Pressure Chemical Co. (Pittsburgh, Pa.) and Strem Chemicals Inc. (Danvers, Mass.) (SRI, 1977).

Chromium (III) chloride

Production figures are not available.

Chromium (III) chloride is used in chromizing, in the preparation of high-quality chromium metal, as a starting point in the synthesis of organic chromium compounds, and as a catalyst for polyolefin formation and hydrogen chloride oxidation, in addition to leather tanning and mordant dyeing of cotton and silk (Lawler, 1977; Hartford and Copson, 1964).

The producers of chromium (III) chloride are Glover M. Birk (New Albany, Ill.) and McGean Chemical Co., Inc. (Cleveland, Ohio) (SRI, 1977).

Chromium (III) fluoride

Production figures were not encountered.

Table 1. Inorganic Chromium Compounds

Compound	CAS Number	RTECS Number	Molecular Formula
Chromium carbonyl	13007-92-6	GB50750	$Cr(CO)_6$
Chromium (III) chloride	10025-73-7	GB54250	$CrCl_3$
Chromium (III) chromate	---	GB55500	$Cr_2(CrO_4)_3$
Chromium (III) fluoride	7788-97-8	GB61500	CrF_3
Chromium (III) oxide	1308-38-9	GB64750	Cr_2O_3
Chromium (III) sulfate	10101-53-8	GB72000	$Cr_2(SO_4)_3 \cdot 6H_2O$

Chromium (III) fluoride is used as a catalyst for fluorocarbons in dyeing woolens and in the mothproofing of wool fabrics (Lawler, 1977).

Kewanee Industries, Inc. (Cleveland, Ohio) is the sole producer of chromium (III) fluoride (SRI, 1977).

Chromium oxide

In 1973, Chromium (III) oxide production, which is recovered from chromite ore imported into the U.S., totalled 627 thousand tons, of which 93 thousand tons were used for chemical purposes (Treskon, 1975).

In addition to its use in the synthesis of rubber and chromium compounds, such as chromic chloride and chromic hydroxide, chromium (III) oxide is used in pigments for glass and ceramics (Lawler, 1977).

The following companies produce this compound at the locations listed (SRI, 1977):

Hercules, Inc.	Glens Falls, N.Y.
Mineral Pigments Corp.	Beltsville, Md.
Minnesota Mining & Mfg. Co.	Copley, Ohio
Pfizer Inc.	Lehigh Gap, Pa.
Rockwood Industries, Inc.	South Plainfield, N.J.
Smith Chem. & Color Co., Inc.	Jamaica, N.Y.
Southern California Chem. Co., Inc.	Garland, Tx.
	Santa Fe Springs, Calif.

Chromium (III) sulfate

Production data were not available.

Chromium (III) sulfate is used as a textile mordant, in green paints and inks, ceramic glazes and varnishes (Lawler, 1977).

The companies listed below produce this compound (SRI, 1977):

Allied Chem. Corp.	Chicago, Ill.
Glover M. Birk	New Albany, Ind.
Diamond Shamrock Corp.	Kearney, N.J.
Hydrite Chem. Co.	Milwaukee, Wisc.

7. Biological Effects of Exposure

The biological effects of chromium and chromium compounds has been reviewed in some detail (Browning, 1969; Hamilton and Hardy, 1974; Hunter, 1975; Moeschlin, 1965; NIOSH, 1975). However, the great majority of the available information is on hexavalent chromium. A criteria document on this topic is available (NIOSH, 1975). The little information on non-hexavalent chromium which would be readily obtained from standard reference sources is summarized below.

a) Target Organs

No information has been encountered in the pathologic effects of mono- and trivalent chromium compounds. As indicated in Section 7e, some trivalent compounds may be skin sensitizers in humans.

b) Acute Effects

Trivalent chromium compounds are generally considered to be less toxic than hexavalent chromium (ACGIH, 1976). Information on the acute toxicity of some non-hexavalent chromium compounds is summarized in Table 2.

c) Subchronic Effects

No information has been encountered.

d) Chronic Effects

The potential carcinogenicity of some trivalent chromium compounds has been evaluated. NIOSH (1976) indicates that a Russian study found that intraperitoneal injections of chromium (III) oxide, at total doses of 100 mg/kg, caused cancer in rats and mice. Intraplueral and intramuscular injections of chromium (III) chromate led to a high incidence, 86% to 97%, of implantation-site cancers. Intrabronchial implants of chromium (III) chromate resulted in six squamous cell carcinomas of the lung and two adenocarcinomas at the implantation site in 100 treated rats. Similar treatment with chromium (III) oxide resulted in no tumors (NIOSH, 1975).

e) Human Effects

In tannery workers suffering from chronic dermatitis, both chromium (III) sulfate and chromium (III) chloride gave positive results on patch tests (Hamilton and Hardy, 1975). Chromium (III) fluoride also yielded positive results in patch tests of workers suffering from cement eczema. However, among different workers with occupationally related eczema, chromium (III) sulfate and chromium (III) chloride gave negative patch test results (NIOSH, 1975).

Six cases of pneumoconiosis have been found in a group of 106 workers exposed to chromium (III) oxide [0-13.2 mg/m^3] and chromium (III) sulfate [0-2.7 mg/m^3]. Sixty-four of these workers had been exposed for over 10 years. Another plant, which produced chromium (III) oxide, sodium bicarbonate, and lead chromate and employed 30-50 people, reported no deaths from any cause between 1938 and 1947 (NIOSH, 1975).

Chromium (III) compounds appear to have an interesting effect on glucose metabolism. In patients with maturity onset diabetes, chromium (III) chloride, at doses of 0.06 mg to 1 mg, three times daily, for 15 to 120 days, improved glucose tolerance (NIOSH, 1975).

Table 2. The Acute Toxicity of Some Non-hexavalent Chromium Compounds (NIOSH, 1976)

Compound	Organism	Route	Dose	Effect
Chromium carbonyl	mouse	intravenous	30 mg/kg	LD_{50}
Chromium chloride	rat	oral	1870 mg/kg	LD_{50}
	mouse	intraperitoneal	140 mg/kg	LD_{50}
		subcutaneous	800 mg/kg	LD_{Lo}
		intravenous	400 mg/kg	LD_{Lo}
	guinea pig	dermal	202 mg/kg	LD_{Lo}
		intraperitoneal	200 mg/kg	LD_{Lo}
Chromium fluoride	guinea pig	oral	150 mg/kg	LD_{Lo}
		subcutaneous	120 mg/kg	LD_{Lo}
Chromium sulfate	mouse	intravenous	85 mg/kg	LD_{Lo}

Chromium (III), but not chromium (VI), has been shown to bind strongly with human plasma proteins at physiologic pH (NIOSH, 1975).

8. TLV

The time-weighted average TLV for soluble chromic and chromous salts is 0.5 mg/m^3 (ACGIH, 1971).

9. Other Standards

No other standards have been encountered.

10. Other Data

Table 3 lists the number of reported occupational exposures to various chromium compounds (NIOSH, 1977).

Table 3. Reported Human Occupational Exposures to Inorganic Chromium Compounds (NIOSH, 1977)

Compound	Number of Exposures
Chromic oxide	212,730
Chromic chloride	7,710
Chromic fluoride	15,330
Chromium potassium sulfate	91,380
Chromium sulfate	7,920
Chromic phosphate	20,070
Chromic nitrate	9,960
Chromic sulfate, basic	7,920
Chromous chloride	7,530

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IRON AND ITS COMPOUNDS

1. Molecular Structure

2. Chemical Abstract Service Number

3. Registry of Toxic Effects of Chemical Substances Numbers

The above information for the commercially significant iron compounds selected for this profile is listed in Table 1 along with the chemical names.

In choosing the compounds listed, consideration was given to the extent of production and use in industrial processes, as well as the likely toxicological hazard regardless of the relative commercial significance of the compound (as long as there was some evidence of commercial production and use). The selection of seven individual compounds and a mixture (ferric oxides) was based on these criteria.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Ferric Ammonium Citrate

No information was available on production volume or trends for ferric ammonium citrate. It is used in blueprint photography, as a feed additive, and has applications in the pharmaceutical industry (Lawler, 1977).

Ferric ammonium citrate is produced by Mallinckrodt, Inc. (Brooklyn, New York; Groton, Connecticut) (SRI, 1977).

Ferric Nitrate

No information was encountered on production figures or trends for ferric nitrate. It is used as a dying mordant, in tanning, weighting silk, processing uranium ore, an in medicines (Lawler, 1977).

Ferric nitrate is produced by Allied Chemical Corp. (Buffalo, N.Y.); Richardson-Merrell, Inc. (Phillipsburg, N.J.); and The Shepherd Chemical Co. (Cincinnati, Ohio) (SRI, 1977).

Iron Carbonyl

Although no production data was encountered for iron carbonyl, it is produced in very small quantities (SRC estimate). It has application as an intermediate in organic syntheses and is a source of iron metal powder (Lawler, 1977).

Table 1. Iron Compounds

Compound	Chemical Name	Chemical Abstract Service Number	Registry of Toxic Effects of Chemical Substances Number	Molecular Formula
Ferric ammonium citrate	-	1185-57-5	N.A.	*
Ferric nitrate	-	7782-61-8	NO71750	$Fe(NO_3)_3 \cdot 9H_2O$
Iron carbonyl	-	13463-40-6	NO49000	$Fe(CO)_5$
Ferric Chloride	-	7705-08-0	LJ91000	$FeCl_3$
Ferrous sulfate	-	7720-78-7	NO85000	$FeSO_4 \cdot 7H_2O$
Ferric oxides	-	1309-37-1	NO74000	Fe_2O_3, FeO, and mixed oxides
Ferrous chloride	-	7758-94-3	NO54000	$FeCl_2$
Ferrocene	Di-2,4-cyclopentadien-1-yliron	102-54-5	LK07000	$Fe(C_5H_5)_2$

*Ferric ammonium citrate is a nonstochiometric material produced by reacting ferric hydroxide and citric acid in an aqueous ammonia solution, then evaporating the water. It consists therefore of roughly 8% NH_3, 15% Fe, and 75% citric acid hydrate. The color (brown to green) depends on the degree of hydration. The citric acid hydrate may comprise from 65 - 80% of the weight of the material. The more common green ferric ammonium citrate contains the higher concentrations of citric acid and water of hydration.

Iron carbonyl is produced by Pressure Chemical Co. (Pittsburgh, Pennsylvania) (SRI, 1977).

Ferric Chloride

In 1975, the demand for ferric chloride was estimated to be 115,000 tons; U.S. production capacity, however, is 236,000 tons. Growth is expected to average 10% annually through 1979 (Chem. Prof., 1975i).

The major use of ferric chloride is in the treatment of sewage. Breakdown of usage is as follows (Chem. Prof., 1975i):

Sewage Treatment	85%
Etchant for photo engraving, rotogravure, and electronic circuits	10%
Drinking water treatment and other	5%

Ferric chloride is produced by the following companies (SRI, 1977):

Associated Metals & Minerals Corp.	Texas City, Texas
Catco, Inc.	Fontana, Calif.
Conservation Chemical Co.	Gary, Indiana
	St. Louis, Missouri
Dow Chemical U.S.A.	Midland, Michigan
E.I. du Pont de Nemours & Co., Inc.	Edge Moor, Delaware
Philip A. Hunt Chemical Corp.	Chicago, Illinois
	Cleveland, Ohio
	Los Angeles, Calif.
	Palisades Park, N.J.
Imperial West Chemical Co.	Antioch, Calif.
K.A. Steel Chemicals, Inc.	Des Plaines, Illinois
	Gary, Indiana
	Lemont, Illinois
Pennwalt Corp.	Wyandotte, Michigan
Southern California Chem. Co., Inc.	Bayonne, N.J.
	Garland, Texas
	Santa Fe Springs, Calif.
	Union, Illinois

Ferrous Sulfate

Demand for ferrous sulfate was estimated to be 285,000 tons in 1976, while U.S. capacity is 370,000 tons. Growth is projected at 5% annually through 1980 (Chem. Prof., 1976e).

Ferrous sulfate is used primarily in iron oxide pigments and salts. Breakdown of usage is as follows (Chem. Prof., 1976e):

Iron oxide pigments and salts	80%
Trace compound in fertilizer & stock feed	8%
Water treatment	5%
Catalyst component	3%
Other	4%

Producers of ferrous sulfate are the following (SRI, 1977):

American Cyanamid Co.	Savannah, Georgia
Brewer Chemical Corp.	Honolulu, Hawaii
Catco, Inc.	Fontana, Calif.
Conservation Chemical Co.	Kansas City, Missouri
The Cosmin Corp.	Baltimore, Maryland
K.A. Steel Chemicals, Inc.	Des Plaines, Illinois
Liquid Chem. Corp.	Hanford, Calif.
Mallinckrodt, Inc.	St. Louis, Missouri
N L Industries, Inc.	St. Louis, Missouri Sayreville, N.J.
Pfizer, Inc.	Easton, Pennsylvania East St. Louis, Illinois
Quality Chemicals Ltd.	Baltimore, Maryland

Ferric Oxides

Production of pigment-grade iron (III) oxide was 119,539 tons in 1964 (Casey and Doyle, 1967).

Ferric oxide is used extensively as a red pigment for rubber, paints, paper, linoleum, and ceramics. It is also used as a polishing agent for glass, metals, and diamonds (Casey and Doyle, 1967).

Producers of ferric oxide are the following (SRI, 1977):

American Colloid Co.	Aberdeen, Miss.
BASF Wyandotte Corp.	Wyandotte, Mich.
Cities Service Co.	Monmouth Junction, N.J. St. Louis, Missouri Trenton, N.J.
Combustion Engineering, Inc.	Camden, N.J.
Engelhard Minerals & Chem. Corp.	Bowmanstown, Pennsylvania Quincy, Illinois
Hoover Color Corp.	Hiwassi, Virginia Irvington, N.J.
Leber Mining Co., Inc.	Stamps, Arkansas
Mineral Pigments Corp.	Beltsville, Maryland
Pfizer, Inc.	Easton, Pa. East St. Louis, Illinois Emeryville, Calif.

Republic Steel Corp.	Gadsden, Alabama
Rockwood Indust. Inc.	South Planfield, N.J.
Smith Chem. & Color Co., Inc.	Jamaica, N.Y.
Tamms Industry Co.	Itasca, Illinois
	Bellflower, Calif.

Ferrous Chloride

No information is available for production and growth of ferrous chloride. It is used in pharmaceuticals, as a reducing agent and mordant in dye manufacturing, and is used in the production of ferric chloride (Casey and Doyle, 1967).

The following manufacturers produce ferrous chloride (SRI, 1977):

Catco, Inc.	Fontana, Calif.
Conservation Chem. Co.	Gary, Indiana
	St. Louis, Missouri
Dow Chem. U.S.A.	Midland, Michigan
Imperial West Chem. Co.	Antioch, Calif.
K.A. Steel Chems., Inc.	Lemont, Illinois
Kramer Chems., Inc.	Paterson, N.J.
Southern California Chem. Co., Inc.	Bayonne, N.J.
	Garland, Texas
	Santa Fe Springs, Calif.
	Union, Illinois
Thiokol Corp.	Danvers, Massachusetts

Ferrocene

No information on the production or growth of ferrocene was available. It is used as a smoke inhibitor and as a photomask for integrated circuit manufacturing (Lawler, 1977).

Ferrocene is produced by Pressure Chem. Co. (Pittsburgh, Pa.) and Syntex Corp. (Boulder, Colo.).

No information on the number of users is available.

7. Biological Effects of Exposure

a) Target Organs

Based on an analysis of the clinical signs of intoxication by ferrous compounds, Moeschlin (1965) states that these compounds exert their primary effects in the gastrointestinal tract and central nervous system. Effects on the gastrointestinal tract include hemorrhage, lesions of the gastric mucosa and hemorrhagic gastroenteritis. Neurological effects include altered respiratory rates and convulsions. In addition, acute exposure to ferrous compounds has been associated with damage to the liver, kidneys, and lungs and decreased blood clotting ability (Hoppe, 1955a & 1955b; Moeschlin, 1965).

The pathological effects of ferric compounds have not been characterized in detail. Acute inhalation exposures to ferric oxide cause lung edema in rats (Gage, 1970). As detailed in Section 7e, chronic exposure to ferric oxide dust in humans causes pulmonary siderosis. This effect, however, is regarded as relatively benign (ACGIH, 1971; Moeschlin, 1965).

Chronic exposure to iron compounds can result in high levels of iron with consequent damage to the liver, pancreas, myocardium, and other organs (Moeschlin, 1965).

b) Acute Effects

Information on the acute toxicity of iron compounds is summarized in Table 2. For the most part, ferrous compounds are more toxic than ferric compounds. Of the compounds under review, iron pentacarbonyl is by far the most toxic which is most likely due to the potential for the release of the carbonyl ligand as carbon monoxide.

The signs of intoxication by ferrous sulfate have been examined in some detail. In guinea pigs, initial signs of intoxication include weakness, paralysis of the limbs, diarrhea, and tonic-myclonic convulsions which may be fatal. Animals surviving the initial phase of intoxication usually show signs of improvement for 12 to 24 hours after dosing. At this time, death may occur due to severe shock (Moeschlin, 1965). Similar signs of intoxication have been noted in mice given acute lethal doses of ferrous sulfate (Hoppe et al., 1955b; Hosking, 1970). For most of the ferrous salts, including ferrous sulfate and ferrous chloride, respiratory failure precedes cardiac arrest (Hoppe et al., 1955a). Exposures of 33 ppm of iron pentacarbonyl for 5.5 hours to rats led to lethargy, respiratory difficulty, and an increase in carboxyhemoglobin (Gage, 1970).

Beliles (1972) has found that pregnant mice are not significantly more susceptible to ferrous sulfate than non-pregnant mice. The fetal LD_{50}, based on maternal intravenous dose, was found to be 75 mg/kg.

c) Subchronic Effects

Oral administration of ferrous sulfate to cats at doses of 25, 50, 100, 200, and 400 mg/kg/day, five days per week, for two weeks caused death only at the highest dose. Occasional vomiting and diarrhea were seen in cats at the lower doses (Hoppe et al., 1955b). In a review of the early literature on iron poisoning, Hoppe and coworkers (1955a) indicate that "small amounts" of ferrous chloride given intravenously or subcutaneously to rabbits and dogs over a four month period cause "chronic and sometimes fatal poisoning."

No apparent adverse effects were seen in rats exposed to 7 ppm iron pentacarbonyl for 5.5 hours per exposure, for 18 exposures (Gage, 1970).

Table 2. Acute Toxicity of Various Iron Compounds

Compound	Organism	Route	LD_{50} or LC_{50}	Reference
Ferric ammonium citrate	mouse	oral	5000 mg/kg	Hoppe et al., 1955a
	guinea pig	oral	1750 mg/kg	Hoppe et al., 1955a
	rabbit	oral	2800 mg/kg	Hoppe et al., 1955a
Ferric chloride	rat	oral	900 mg/kg	NIOSH, 1976
	mouse	oral	1500 mg/kg	Hoppe et al., 1955a
			1272 mg/kg	Hosking, 1970
		iv	136 mg/kg	Hosking, 1970
		intraperitoneal	68 mg/kg	NIOSH, 1976
	rabbit	oral	1200 mg/kg	Hoppe et al., 1955a
		iv	7.2 mg/kg	Patty, 1958
	guinea pig	oral	600 mg/kg	Hoppe et al., 1955a
Ferric nitrate	rat	oral	3250 mg/kg	Smyth et al., 1969
Ferrocene	rat	oral	1320 mg/kg	NIOSH, 1976
		intraperitoneal	500 mg/kg	NIOSH, 1976
	mouse	oral	1550 mg/kg	NIOSH, 1976
		intraperitoneal	355 mg/kg	NIOSH, 1976
Ferrous chloride	rat	oral	600 mg/kg	Hoppe et al., 1955a
	mouse	intraperitoneal	59 mg/kg	NIOSH, 1976
	rabbit	oral	1000 mg/kg	Hoppe et al., 1955a
Ferrous sulfate	rat	oral	1480 mg/kg	Hoppe et al., 1955b
	mouse	oral	407 mg/kg	Hosking, 1970
			1412 mg/kg	Beliles, 1972
			4500 mg/kg	Hoppe et al., 1955a
		intraperitoneal	128 mg/kg	Hosking, 1970
			100 mg/kg	NIOSH, 1976
		iv	115 mg/kg	Beliles, 1972
			35 mg/kg	Hosking, 1970
	rabbit	oral	3000 mg/kg	Hoppe et al., 1955a
		iv	99 mg/kg	Patty, 1958
	guinea pig	oral	1500 mg/kg	Hoppe et al., 1955a
	cat	oral	> 500 mg/kg	Hoppe et al., 1955a
	dog	oral	800 mg/kg	Hoppe et al., 1955a

Table 2. (Cont'd.)

Compound	Organism	Route	LD_{50} or LC_{50}	Reference
Iron pentacarbonyl	rat	inhalation	0.114 ppm x 30 min.	Sunderman et al., 1959
	mouse	inhalation	0.274 ppm x 30 min.	Sunderman et al., 1959
	rabbit	oral	18 mg/kg	Deichmann & Le Blanc, 1943
		dermal	38 mg/kg	Deichmann & Le Blanc, 1943
		iv	17 mg/kg	Deichmann & Le Blanc, 1943
		inhalation	250 ppm x 45 min.	NIOSH, 1976
	guinea pig	oral	36 mg/kg	Deichmann & Le Blanc, 1943

d) Chronic Effects

i) Carcinogenicity

Haddon and Horning (1960) have examined the tumorogenicity of several iron compounds in mice. Sixteen weekly subcutaneous injections of ferrous sulfate at 2.5 mg per mouse, per injection resulted in a fibroma in one of the thirteen surviving animals. Ferrocene, ferric oxide, and metallic sponge iron caused no tumors in the treated mice. In hamsters, intratrachial injections of benzo(α)pyrene with iron oxide dust resulted in some proliferative changes in the bronchial mucosa (Saffiotti et al., 1963). As summarized in the next section, an increased incidence of lung cancer has been reported in workers exposed to iron oxide (Faulds, 1957).

ii) Other Chronic Effects

No information has been encountered on the mutagenicity, teratogenicity, and other chronic effects of iron compounds.

e) Human Effects

Relatively detailed information is available on the chronic effects of ferric oxide dust and the acute effects of ferrous sulfate on humans. Little information has been encountered on the human effects of other iron compounds.

Chronic inhalation exposure to ferric oxide results in a condition known as iron pneumoconiosis or pulmonary siderosis. This condition is characterized by the development of discrete densities on chest X-ray films and has been found in workers in a variety of occupations including: silver polishers, workers manufacturing electrolytic iron oxide (McLaughlin et al., 1945), arc welders (Doig and McLaughlin, 1936), hematite miners (Stewart and Faulds, 1934), boiler scalers (Dunner and Herman, 1944), carbon arc and acetylene welders (Doig and McLaughlin, 1948) and iron and steel grinders in foundries (Prendergass and Leopold, 1945). It is generally believed that this condition develops after six to ten years exposure to 10-15 mg/m^3 (Kleinfeld et al., 1969; Sentz and Rakow, 1969; Weber, 1955). Workers with pulmonary siderosis usually show no apparent adverse effects (Fawcitt, 1943; Fleisher et al., 1945; Hamlin and Weber, 1950). The concensus appears to be that this condition does not have obvious pathological consequences (McLaughlin, 1951; Moeschlin, 1965). However, Faulds (1957) has described massive pulmonary fibrosis and a marked increase in the incidence of lung cancer among hematite miners. In that these workers were also apparently exposed to silica dust, the role of iron oxide in the development of pulmonary fibrosis and lung cancer is unclear.

Ferrous sulfate once enjoyed wide use as a pharmaceutical (Moeschlin, 1965) and several studies are available on acute intoxication in humans. Hoppe and coworkers (1955a) summarized thirty-six cases of ferrous sulfate poisoning and estimated that the average lethal dose for humans is 900 mg/kg. As outlined

below, Jacobs and coworkers (1965) have identified four phases of ferrous sulfate intoxication:

Phase I: 1-6 hours - vomiting, diarrhea, malaise, shock, dyspnea, and coma
Phase II: 6-12 hours - period of apparent improvement
Phase III: 12-48 hours - metabolic acidosis, CNS abnormalities, hepatic dysfunction, and bleeding diathesis
Phase IV: > 48 hours - intestinal obstruction caused by fibrosis and scarring

These phases are consistant with other reported cases of ferrous sulfate poisoning (Covey, 1964; Vuthibhagdee and Harris, 1972; Wallack and Winkelstein, 1974).

Cases of human intoxication by ferrous chloride, ferric ammonium citrate, and ferric chloride have also been summarized by Hoppe and coworkers (1955a). The general signs of intoxication appear to be similar to ferrous sulfate poisoning. Ferric salts cause skin irritation and contraction of the blood vessels (ACGIH, 1971c).

Iron pentacarbonyl intoxication is characterized by giddiness, headache, and occasionally dyspnea and vomiting. Twelve to 36 hours after exposure is terminated, dyspnea, fever, cyanosis, and cough develop. In fatal exposures, death occurs in 4 to 11 days (ACGIH, 1971b).

8. TLV's

The TLV's for iron oxide, iron pentacarbonyl, and iron salts are 10 mg/m^3, 0.08 mg/m^3, and 1 mg/m^3, respectively (ACGIH, 1971a,b, and c).

9. Other Standards

Drinker and coworkers (1935) initially recommended a standard of 10 mg/m^3 for iron oxide but later raised the recommended standard to 30 mg/m^3 (Drinker and Nelson, 1944). The latter standard was also recommended by the U.S. Department of Labor (1941). Smyth (1956) felt that an exposure limit of 15 mg/m^3 was necessary to prevent injury and Weber (1955) felt that a limit of 5 mg/m^3 was needed to prevent pulmonary siderosis. Similar recommendations for other iron compounds have not been encountered.

10. Other Data

Levels of plasma-bound iron have been recommended as an index of exposure to iron dust (Patty, 1958). Moeschlin (1965) has discussed the diagnosis and treatment of poisoning by iron compounds.

Table 3 lists the number of reported occupational exposures to iron and its compounds (NIOSH, 1977).

Table 3. Reported Occupational Exposures To Iron And Its Compounds

Compound	Number of Exposures
Iron	592,920
Iron ammonium sulfate	79,260
Ferric ammonium citrate	80,010
Ferric nitrate	14,610
Ferrous sulfide	1,275,000
Iron disulfide (pyrite)	1,620
Iron carbonate	2,790
Iron carbonyl	2,100
Ferric acetylacetonate	690
Ferric ammonium oxalate	750
Ferric chloride	130,320
Ferrous sulfate	25,830
Ferric sulfate	8,070
Ferrous chloride	4,380
Iron naphthenate	180
Iron blue	152,340
Ferric pyrophosphate	11,910
Iron oxides	1,890,000
Iron phosphate	33,960
Iron silicate	34,560
Iron ore	4,350
Ferric chloride	1,620
Iron dithiocarbamate	450

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MANGANESE AND ITS COMPOUNDS

1. Molecular Structure

2. Chemical Abstract Service (CAS) Number

3. Registry of Toxic Effects of Chemical Substances (RTECS) Number

The above information for the commercially significant manganese compounds chosen for this profile is listed in Table 1.

In selecting the compounds listed, consideration was given to the amount of production and use in industrial processes, in addition to the likely toxicological hazard regardless of the relative commercial significance of the compound.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Manganese Metal

In 1975 about 22 thousand short tons of high purity manganese metal were produced (Trekson, 1976b).

Manganese is used primarily as an alloying agent in non-ferrous alloys (Bacon, 1967).

The following companies produce manganese metal. At least 19 locations are involved (Chemical Week, 1976).

Alfa Div. Ventron Corp.
Atlantic Equip. Engrs.
Atomergic Chemetals Co.
Belmont Metals Inc. Div.,
  Belmont Smelting & Refining Wks. Inc.
Bram Metallurgical-Chem. Co.
C.E. Minerals, Div. Combustion Engrg.
Cerac, Inc.
Cotronics Corp.
Diamond Shamrock Corp.
Electronic Space Products, Inc.
Engelhard Minerals & Chems. Corp.,
  Philipp Bros. Div.
Fairmount Chem. Co., Inc.
Foote Mineral Co.

Table 1. Compounds in the Manganese Class

Compound	CAS No.	RTECS No.	Molecular Structure
Manganese (metal)	7439-96-5	0092750	Mn
Manganese sulfate	7785-87-7	OP10500	$MnSO_4 \cdot H_2O$
Manganese dioxide	1313-13-9	OP03500	MnO_2
Manganous chloride	7773-01-5	0096250	$MnCl_2 \cdot 4H_2O$
Potassium permanganate	7722-64-7	SD64750	$KMnO_4$
Manganous ethylenebisdithiocarbamate (Maneb)	301-03-1	OP07000	$\overline{Mn\text{-}SSCNH(CH_2)_2NHCSS}$
Methylcyclopentadienyl manganese tricarbonyl (MMT)	---	OP14500	$(CH_3)C_5H_4Mn(CO)_3$

Glidden Metals, Glidden Durkee Div., SCM Corp.
Kerr-McGee Chem. Corp.
Pesses Co.
Revere Copper and Brass, Inc.
Union Carbide Corp.
United Minerals & Chem. Corp.

Managanese Sulfate

Demand for manganese sulfate in 1975 was estimated at 32,000 tons. Growth is expected to average 3% per year (Chem. Prof., 1975h).

The bulk of production is used in fertilizers and as a stockfeed nutrient. Overall usage breakdown is as follows (Chem. Prof., 1975h):

Fertilizer and stockfeed nutrient	80%
Fungicide	5%
Synthetic manganese dioxide	5%
Other	10%

Manganese sulfate is produced by the following companies at the locations listed (SRI, 1977):

Carus Corp.	La Salle, Ill.
City Chem. Corp.	Jersey City, N.J.
Eagle-Picher Indust., Inc.	Cedartown, Ga.
	Galena, Kan.
Eastman-Kodak Co.	Kingsport, Tenn.
Engelhard Minerals & Chem. Corp.	Bowmantown, Pa.
	Quincy, Ill.
Richardson-Merrell, Inc.	Phillipsburg, N.J.

Manganese dioxide

Manganese dioxide is produced in the range of 16,000 tons per year (Treskon, 1976b).

It is used as a depolarizer in dry cell batteries, in the synthesis of ferrites, glass, pyrotechnics, and other manganese compounds (Lawler, 1977).

The following companies produce manganese dioxide at the locations listed (SRI, 1977):

Combustion Engineering, Inc.	Brownsville, Tx.
	Camden, N.J.
	Wilmington, Dela.
Diamond Shamrock Corp.	Curtis Bay, Md.
Engelhard Minerals & Chems. Corp.	Quincy, Ill.
Gen. Metallic Oxides Co.	Jersey City, N.J.

Hummel Chem. Co., Inc.	S. Plainfield, N.J.
Kerr-McGee Corp.	Henderson, Nev.
Richardson-Merrell, Inc.	Cincinnati, Oh.
Sterling Drug, Inc.	Rensselaer, N.Y.

Manganous Chloride

Figures on the production of manganous chloride are not available, but probably more than 2-3 million lbs. are produced annually based on uses (SRC estimate).

Manganous chloride is used in the synthesis of manganese compounds and Maneb (a fungicide), as a catalyst, and in cotton dyeing, flux, and flashing for bricks (Lawler, 1977).

Manganous chloride is produced by Diamond Shamrock Corporation (Curtis Bay, Md.), Mineral Research & Development Corporation (Concord, N.C.), and Richardson-Merrell, Inc. (Phillipsburg, N.J.) (SRI, 1977).

Potassium Permangenate

Production of potassium permangenate is in the neighborhood of 4,000 tons per year (Hay, 1967). It is used as an oxidizing agent, bleach, catalyst, disinfectant, plant growth regulator, in descaling steel, flux, water treatment and purification, welding rod coatings, and in gas purification (Lawler, 1977).

Carus Chemicals (La Salle, Ill.) is the sole manufacturer according to SRI (1977).

Manganous Ethylenebisdithiocarbamate (Maneb)

Approximately 7 million lbs. of Maneb were consumed in 1975 (Ayers and Johnson, 1976). Maneb is a fungicide for agricultural crops and home and garden use (Ayers and Johnson, 1976). Manufacturers are Blue Spruce (Bound Brook, N.J.), DuPont (LaPorte, Tx.), and Rohm and Haas (Philadelphia, Pa.) (SRI, 1977).

Methylcyclopentadienyl Manganese Tricarbonyl

Figures on production are not available, but are probably sizeable considering its use (SRC estimate). It is used as an antiknock gasoline additive, combustion improver, and fuel oil additive (Hay, 1967).

The Ethyl Corporation (Orangeburg, S.C.) and Pressure Chemicals (Pittsburgh, Pa.) are its manufacturers.

7. Biological Effects of Exposure

a. Target Organs

Manganese, manganese dioxide, manganous chloride, and manganous sulfate exert their major chronic pathological effects on the brain and lung. Degeneration of the cells of the basal ganglia appears to be the primary central nervous system lesion (Moeschlin, 1965). An autopsy of an individual with chronic manganese poisoning revealed atrophy of the frontal lobes and gliosis and degeneration of the basal ganglia (Hunter, 1975). In the lungs, these manganese compounds attack the respiratory epithelium (Hamilton and Hardy, 1974). Mice exposed to manganese oxide dust evidenced mononuclear cell interstitial infiltration of the lungs which led to necrosis and hemorrhage (Hunter, 1975). While other organs do not appear to be primary targets, occasional hepatic and hematologic changes have been reported (Hamilton and Hardy, 1974). No information has been encountered on the acute pathological effects of these compounds.

Potassium permanganate has not been implicated in cases of chronic manganese poisoning. On acute oral administration, this compound may cause severe irritation and hemorrhage of the gastrointestinal tract (Moeschlin, 1965).

Both methyl cyclopentadienyl manganese tricarbonyl (MMT) and manganese cyclopentadienyl tricarbonyl (MCT) also exert neurological effects. Acute MCT intoxication causes atrophic changes in the nerve cells, along with erythrocytosis, lowered osmotic pressure of the erythrocytes, edema, hemmorhage, decreased blood pressure, and increased permeability of the blood vessels. Chronic poisoning by MCT has been associated with neuromuscular excitability, renal damage, and decreased immunobiological stability. While MMT also causes clinical signs characteristic of central nervous system involvement (see Sections 7b and 7c), the liver and kidneys are the primary target organs in acute exposures. Pathological changes included degeneration of the liver cells and renal tubules. Chronic inhalation exposure to MMT causes bronchitis, peribronchitis, interstitial pneumonia, and lung abscesses in experimental mammals (ACGIH, 1971b). Hysell and coworkers (1974) report that acute exposure of rats to MMT causes pathological changes of the lungs, liver, and kidneys, and that these effects could not be attributed solely to the toxicity of manganese.

b. Acute Effects

Information on the acute toxicity of manganese and its compounds is summarized in Table 2.

Little attention has been paid to the acute toxic effects of manganese and inorganic manganese compounds. Potassium permanganate, which has been used as a pharmaceutical, causes gastric discomfort and vomiting when taken orally as a 1% solution (Moeschlin, 1965).

Table 2. Acute Toxicity of Manganese Compounds (NIOSH, 1976)

Compound	Organism	Route	Dose	Effect
Manganese	Mouse	Intraperitoneal	53 mg/kg	LD_{50}
Manganous chloride	Mouse	Intraperitoneal	121 mg/kg	LD_{50}
		Subcutaneous	210 mg/kg	LD_{Lo}
	Rabbit	Parenteral	18 mg/kg	LD_{Lo}
	Dog	Parenteral	56 mg/kg	LD_{Lo}
Manganese dioxide	Rabbit	Intravenous	45 mg/kg	LD_{Lo}
Manganous sulfate	Mouse	Intraperitoneal	120 mg/kg	LD_{50}
Potassium permangenate	Rat	Oral	1,090 mg/kg	LD_{50}
	Mouse	Subcutaneous	500 mg/kg	LD_{50}
Manganous ethylenebisdithiocarbamate (Maneb)	Rat	Oral	6,750 mg/kg	LD_{50}
Methylcyclopentadienyl manganese tricarbonyl (MMT)	Rat	Oral	58 mg/kg	LD_{50}
		Dermal	665 mg/kg	LD_{50}
		Inhalation	220 mg/m^3	LD_{50}
	Mouse	Oral	352 mg/kg	LD_{50}
		Inhalation	17 mg/m^3 x 7 hr.	LC_{Lo}
	Rabbit	Oral	95 mg/kg	LD_{50}
		Dermal	1,350 mg/kg	LD_{50}
		Intravenous	6.6 mg/kg	LD_{50}
		Inhalation	411 mg/m^3 x 7 hr.	LC_{Lo}

Table 2. Acute Toxicity of Manganese Compounds (Cont'd)

Compound	Organism	Route	Dose	Effect
Methylcyclopentadienyl manganese tricarbonyl (MMT) (Cont'd)	Guinea pig	Oral	905 mg/kg	LD_{50}
		Inhalation	411 mg/m^3 x 7 hr.	LC_{Lo}
	Cat	Inhalation	223 mg/m^3 x 7 hr.	LC_{Lo}
	Dog	Inhalation	489 mg/m^3 x 2 hr.	LC_{Lo}
Manganese cyclopentadienyl tricarbonyl (MCT)	Rats	Inhalation	120 mg/m^3 x 2 hr.	Lethal to 80%*

* ACGIH, 1971b

Regardless of the route of exposure, acute intoxication with MMT is characterized by "mild excitement, hyperactivity, tremors, severe clonic spasms, weakness, slow and labored respiration, occassional mild, clonic convulsions, and terminal coma" (ACGIH, 1971b). In addition, Hysell and coworkers (1974) noted a serosanguinous nasal discharge in rats on acute intoxication by MMT.

c. Subchronic Effects

No information has been encountered on the subchronic effects of these compounds on experimental mammals.

d. Chronic Effects

i) Carcinogenicity - A study summarized by NIOSH (1976) found that oral administration of manganese ethylenebisdithiocarbamate (Maneb) at a total dose of 64 g/kg given over a 95 week period caused cancer in rats.

ii) Mutagenicity - No information has been encountered on the mutagenicity of these compounds.

iii) Teratogenicity - Maneb, given to pregnant rats on day 11 or 13 of organogenesis as single oral doses of 1,000-4,000 mg/kg, caused a variety of facial and skeletal abnormalities in the offspring. Doses of 500 mg/kg had no teratogenic effect (Petrova-Vergieva and Ivanova-Tchemishanska, 1973).

iv) Other Chronic Effects - Manganese chloride, given daily to monkeys by intraperitoneal injections for eighteen months, caused signs of damage to the extrapyramidal nervous system. These signs included choreic movements which progressed to a state of rigidity and subsequent tremor resembling paralysis agitans (Hunter, 1975).

Chronic exposure to MCT causes renal and neural damage and decreased resistance to infection. These effects were seen in rats, guinea pigs, and rabbits exposed for four hours a day over a period of eleven months to vapors of MCT at concentrations averaging 1 mg/m^3. Chronic inhalation exposure to MMT causes lung damage as described in Section 7a. Two dogs evidenced no signs of adverse effects after 100 day exposures to MMT at concentrations of about 12 mg/m^3.

e. Human Effects

Chronic manganese poisoning in man produces a characteristic pattern of gradually developing Parkinsonism. Symptoms include apathy, sleepiness, muscular pains and cramps, ankle and patellar clonus, retropulsion, propulsion, mask-like facies, and uncontrollable laughter (Hamilton and Hardy, 1974). This pattern of chronic neurological disturbances has been documented most clearly in cases of exposure to manganese ore and manganese dioxide. Since 1837, nearly 500 cases have been reported (Hunter, 1975). Manganese dust concentrations as low as 2.7 mg/m^3 have been associated with the development of this

syndrome. However, most investigators feel that concentrations of 5 mg/m^3 are safe (ACGIH, 1971a). Individuals with advanced cases of this form of chronic manganese poisoning seldom recover completely. Although behavioral effects are often ameliorated once exposure is terminated, motor impairment is usually permanent (Hunter, 1975).

Chronic exposure to inorganic manganese compounds also causes an increased incidence of pneumonia. In one study cited by Hunter (1975), a tenfold increase in fatal cases of pneumonia was seen in a town grossly contaminated with oxides of manganese. Several cases of an increased incidence of pneumonia in workers chronically exposed to manganese compounds has been summarized by Hunter (1975) and Moeschlin (1965). Manganese concentrations averaging 210 mg/m^3 have been associated with this effect (ACGIH, 1975).

The inhalation of finely divided manganese can lead to metal fume fever (Hamilton and Hardy, 1974).

Cases of human intoxication from organic manganese compounds have not been encountered. MMT may be expected to have the same neurotoxic effects as tetraethyl lead (ACGIH, 1971b).

8. TLV's

Measured as manganese, the TLV for manganese and inorganic manganese compounds is 5 mg/m^3. This TLV is felt to provide a small margin of safety, and workers should not be exposed to concentrations in excess of this limit (ACGIH, 1971a). The TLV's for MCT and MMT are 0.1 mg/m^3 and 0.2 mg/m^3, respectively (ACGIH, 1971b).

9. Other Standards

Other standards for manganese and inorganic manganese compounds include 0.3 mg/m^3 in the U.S.S.R. and 2 mg/m^3 in Czechoslovakia. Various researchers have recommended standards ranging from 5 mg/m^3 to 100 mg/m^3 (ACGIH, 1971a).

The maximum permissible concentration of MCT vapor in the U.S.S.R. is 0.1 mg/m^3 (ACGIH, 1971b).

10. Other Data

Normal dietary intake of manganese is about 10 mg/day (Moeschlin, 1965). Hamilton and Hardy (1974) have suggested that measurements of manganese levels in the feces or manganese levels in the hair may serve as useful indices of manganese exposure.

Table 3 lists the number of reported human occupational exposures to manganese compounds (NIOSH, 1977).

Table 3. Reported Human Occupational Exposures to Manganese Compounds (NIOSH, 1977)

Compound	Number of Exposures
Manganese	249,090
Manganese naphthenate	16,950
Manganese sulfate	15,330
Manganese hydroxide	1,380
Manganese gluconate	7,020
Manganese abietite	1,470
Manganese citrate	1,230
Manganese carbonate	6,690
Manganese oxide	90,000
Manganous chloride	3,780
Manganous oxide	40,350
Potassium permangenate	123,150
Manganese phosphate	13,230
Manganese acetate	720
Manganese glycerophosphate	2,400
Manganous ethylenebisdithiocarbamate (Maneb)	9,090
Manganese drier	234,510
Manganese 2-amino-5-chloro-p-toluenesulfonate	180
Methylcyclopentadienyl manganese tricarbonyl	68,160
Manganese 2-naphthol-4,8-disulfonate	210
Manganese hypophosphite	2,010
Manganese titanate	1,920

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MERCAPTANS

1. Molecular Structure

2. Chemical Abstracts Service (CAS) Number

3. Registry of Toxic Effects of Chemical Substances (RTECS) Number

The above information for the commercially significant mercaptans (alkyl thiols) is presented in Table 1. Their standard (IUPAC) chemical names are also shown.

In choosing the compounds listed, consideration was given to the amount of production and use in industrial processes.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Methyl Mercaptan

Based on a production of 17 million lbs. of methionine in 1975 (Althouse, 1976), the 1975 production of methyl mercaptan was about 6 million lbs. Proposed increases in the methionine capacities could more than double the requirement in production of methyl mercaptan (Althouse, 1976).

This compound is used as an intermediate in the production of methionine and as a food supplement in animal feeds (Althouse, 1976; Turk, 1969). Minor uses include applications as a catalyst, jet fuel additive, and in pharmaceuticals (Lawler, 1977).

Producers are as follows (SRI, 1977):

Dow Chem.	Pittsburg, Calif.
Pennwalt Corp.	Beaumont, Tex.
	Greens Bayou, Tex.
Amoco Corp.	Texas City, Tex.

At least two methionine producers and several unknown others use methyl mercaptan.

Ethyl Mercaptan

Based on 1971 production estimates for pesticides synthesized from ethyl mercaptan (Johnson, 1972), approximately 2 million lbs. were produced in 1971.

No growth figures are available.

Table 1. Compounds in the Mercaptan Class

Compound	CAS No.	RTECS No.	Molecular Structure	Standard Chemical Name
Methyl mercaptan	74-93-1	PB43750	CH_3-SH	Methanethiol
Ethyl mercaptan	75-08-1	KI96250	CH_3-CH_2-SH	Ethanethiol
n-Propyl mercaptan	107-03-9	TZ73000	$CH_3-CH_2-CH_2-SH$	Propanethiol
n-Butyl mercaptan	109-79-5	---	$CH_3-(CH_2)_2-CH_2-SH$	Butanethiol
t-Butyl mercaptan	75-66-1	---	$CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-SH$	1,1-Dimethylethanethiol

Ethyl mercaptan is used in the synthesis of various pesticides, the largest volume pesticide produced being Eptam® (Ayers et al., 1976; Turk, 1969). Other uses include gas odorants and adhesive stabilizers (Lawler, 1977).

The following companies produce ethyl mercaptan (SRI, 1977):

Helmerich & Payne	Baytown, Tex.
Pennwalt Corp.	Beaumont, Tex.
	Greens Bayou, Tex.
Phillips Petroleum	Phillips, Tex.

Only one producer of pesticides and an unknown number of other companies use ethyl mercaptan.

n-Propyl Mercaptan

Based upon 1971 production estimates for pesticides synthesized from propyl mercaptan (Johnson, 1972), about one million lbs. were produced in 1971.

No growth figures are available.

The primary use of n-propyl mercaptan is as an intermediate in the synthesis of pesticides, particularly Vernam® (Ayers et al., 1976). It is also used as a gas odorant (Lawler, 1977) and polymerization regulator (USITC, 1975).

The Pennwalt Corp. (Greens Bayou, Tex.) and Phillips Petroleum (Phillips, Tex.) produce n-propyl mercaptan (SRI, 1977).

It is used by one major pesticide producer and probably an unknown number of other companies.

n-Butyl Mercaptan

Production figures for n-butyl mercaptan were not encountered.

The major use of n-butyl mercaptan is in the production of organophosphorus compounds and thiolcarbamates; more specifically, insecticides, herbicides, acaricides, and defoliants (Turk, 1969).

The Pennwalt Corp. (Greens Bayou, Tex.) and Phillips Petroleum (Phillips, Tex.) produce n-butyl mercaptan (SRI, 1977).

t-Butyl Mercaptan

Figures for the production of t-butyl mercaptan are not available.

The primary use of t-butyl mercaptan is that of an odorant in the gas industries, serving as a "warning agent" (Turk, 1969).

The following companies produce t-butyl mercaptan (SRI, 1977):

Helmerich and Payne, Inc.	Baytown, Tex.
Pennwalt Corp.	Greens Bayou, Tex.
Phillips Petroleum	Phillips, Tex.

7. Biological Effects of Exposure

Very little information has been encountered on the biological effects of mercaptans. Fairchild and Stokinger (1958) have studied the acute toxicity of ethyl mercaptan, n-propyl mercaptan, n-butyl mercaptan, t-butyl mercaptan, and various other mercaptans of little commercial significance. Little additional information has been obtained from the other sources cited below.

a. Target Organs

All of the commercially significant mercaptans studied by Fairchild and Stokinger (1958) caused similar patterns of organ damage. Single oral or intraperitoneal near-lethal doses of these compounds caused both kidney and liver damage in rats. Kidney damage was usually restricted to cloudy swelling of the tubules and hyaline casts in the lumina. Less commonly, degeneration and necrosis of the tubular epithelium, thickening of Bowman's capsule, and hyaline deposition in glomerular tufts were also noted. Liver damage consisted of lymphocytic infiltration, occasional necrotic foci with small hemmorhages, and varying degrees of fatty swelling or degeneration. In addition to signs of liver and kidney damage, acute inhalation exposures of rats and mice to these mercaptans caused lung damage and irritation of the respiratory tract. Signs of respiratory tract irritation occurred within 15 minutes during inhalation exposures and were evidenced by animals rubbing and closing their eyes, watering of the eyes, and occasional sneezing. Repiratory tract pathology varied from mild to severe hyperemia of the trachea and lungs, capillary engorgement, patchy edema, and occasional hemorrhage (Fairchild and Stokinger, 1958). Acute non-lethal inhalation exposures to methyl mercaptan also is reported to cause lung edema (ACGIH, 1971a). Acute inhalation exposures to n-propyl mercaptan and n-butyl mercaptan also caused corneal opacities in mice. Direct application of 0.1 ml n-propyl mercaptan to the eyes of rabbits caused severe irritation which persisted for up to eight days. This irritation was characterized by a heavy discharge from the eyes, severe redness of the palpebral conjunctivae, and chemosis. The other mercaptans (ethyl, n-butyl, and t-butyl) caused only slight to moderate eye irritation which did not persist past 48 hours (Fairchild and Stokinger, 1958).

b. Acute Effects

Information on the acute toxicity of commercially significant mercaptans is summarized in Table 2. These compounds produced signs of intoxication similar to those caused by hydrogen sulfide (ACGIH, 1971a and b; Fairchild and Stokinger, 1958). Acutely toxic doses of these compounds, given orally or intraperitoneally to rats, or by inhalation to rats and mice, initially caused restlessness, increased respiration, incoordination, and muscular weakness. This was followed by skeletal muscle paralysis, cyanosis, lethargy and/or sedation, respiratory depression, coma, and death. In addition, large oral doses of these mercaptans caused diarrhea in rats (Fairchild and Stokinger,

Table 2. The Acute Toxicity of Some Commercially Significant Mercaptans

Compound	Organism	Route	LD_{50} or LC_{50}	Reference
Methyl mercaptan	Mouse	Subcutaneous	2.4 mg/kg	NIOSH, 1976
Ethyl mercaptan	Rat	Oral	682 mg/kg	Fairchild and Stokinger, 1958
		Intraperitoneal	450 mg/kg	Fairchild and Stokinger, 1958
		Inhalation	4420 ppm x 4 hours	Fairchild and Stokinger, 1958
	Mouse	Inhalation	2770 ppm x 4 hours	Fairchild and Stokinger, 1958
n-Propyl mercaptan	Rat	Oral	1790 mg/kg	Fairchild and Stokinger, 1958
		Intraperitoneal	515 mg/kg	Fairchild and Stokinger, 1958
		Inhalation	7300 ppm x 4 hours	Fairchild and Stokinger, 1958
	Mouse	Inhalation	4010 ppm x 4 hours	Fairchild and Stokinger, 1958
n-Butyl mercaptan	Rat	Oral	1500 mg/kg	Fairchild and Stokinger, 1958
		Intraperitoneal	399 mg/kg	Fairchild and Stokinger, 1958
		Inhalation	4020 ppm x 4 hours	Fairchild and Stokinger, 1958
	Mouse	Inhalation	2500 ppm x 4 hours	Fairchild and Stokinger, 1958
	Dog	Inhalation	700 ppm x 0.5 hours (LC_{LO})	NIOSH, 1976
t-Butyl mercaptan	Rat	Oral	4729 mg/kg	Fairchild and Stokinger, 1958
		Intraperitoneal	590 mg/kg	Fairchild and Stokinger, 1958
		Inhalation	22,200 ppm x 4 hours	Fairchild and Stokinger, 1958
	Mice	Inhalation	16,500 ppm x 4 hours	Fairchild and Stokinger, 1958

1958). Death, in cases of fatal exposure to methyl mercaptan, has been attributed to respiratory paralysis (ACGIH, 1971a). Fairchild and Stokinger (1958) have noted that even-numbered carbon straight chain mercaptans are significantly more toxic by all routes of administration than are n-propyl or t-butyl mercaptan and that mice are more susceptible than rats to inhalation exposures.

c. Subchronic Effects

No information has been encountered.

d. Chronic Effects

A summary of a Russian study (Blinova, 1965) indicates that the chronic inhalation "threshold effect" for ethyl mercaptan exposure to small animals is 40 ppm. Neither species nor duration of exposure are specified (ACGIH, 1971c).

e. Human Effects

Ethyl mercaptan, at concentrations of about 4 ppm, caused headache nausea, and irritation in exposed humans. Concentrations of about 0.4 ppm caused no detectable effects (ACGIH, 1971b). At unspecified high concentrations, this mercaptan is reported to cause collapse, cyanosis, increased pulse rate, and convulsions (Moeschlin, 1965).

A case of accidental inhalation exposure to methyl mercaptan reportedly led to coma, the development of acute hemolytic anemia, methemoglobinemia, and death (ACGIH, 1971a).

8. TLV

The time-weighted average limits for methyl mercaptan, ethyl mercaptan, and n-butyl mercaptan are all set at 0.5 ppm (ACGIH, 1971a, 1971b, and 1971c).

9. Other Standards

OSHA (1974) has set ceiling limits for exposure to methyl mercaptan, ethyl mercaptan, and n-butyl mercaptan at 10 ppm.

10. Other Data

The odor threshold for n-butyl mercaptan is 0.01 to 0.0001 ppm (ACGIH, 1971c). Similarly, the unpleasant odor of both methyl mercaptan and ethyl mercaptan make it unlikely that the TLV's for these compounds could be inadvertently exceeded in the workplace (ACGIH, 1971a and 1971b).

While the toxicologic properties of the commercially significant mercaptans discussed in previous sections are relatively similar to each other, certain other mercaptans may act quite differently. Fairchild and Stokinger (1958) found that t-octyl mercaptan, unlike these other mercaptans, caused central

nervous system stimulation. This observation may be significant in considering the potential hazards of commercially significant higher molecular weight mercaptans (e.g., n-octyl mercaptan) on which no toxicity information was encountered.

Table 3 lists the number of reported human exposures to various mercaptans (NIOSH, 1977).

Table 3. Reported Human Occupational Exposures To Mercaptans (NIOSH, 1977)

Compound	Number of Exposures
Methyl mercaptan	19,140
Ethyl mercaptan	23,130
n-,sec-,t-Butyl mercaptans	19,410
n-Octyl mercaptans	18,660
t-,n-Dodecyl mercaptans	21,150

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NITRILES

1. Chemical Structures

2. Chemical Abstract Service (CAS) Numbers

3. Registry of Toxic Effects of Chemical Substances (RTECS) Numbers

The above information on the commercially significant nitriles selected for this profile is listed in Table 1, along with common synonyms for the compounds (in parentheses) and standard chemical nomenclature.

In choosing the compounds listed, consideration was given to the extent of production and use in industrial processes, as well as the likely toxicological hazard regardless of the relative commercial significance of the compound (as long as there was some evidence of commercial production and use). Several compounds are included which have a functional group other than nitrile. These were included on the basis of high production figures and/or especially interesting biological effects.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Acetonitrile

The only available information concerning production volume for acetonitrile is that 2.1 million pounds were produced in 1962 (USITC, 1962). However, sales totaled 7.8 million pounds in 1975 (USITC, 1975), suggesting that production volume has roughly quadrupled over the last 15 years. No growth projections are available.

Acetonitrile is used as a distillation solvent, especially in the extraction of butadiene (Kirshenbaum and Cahn, 1964; Carlson and Erskine, 1974). It also has uses as a general solvent and extractant.

Acetonitrile is produced by DuPont (Beaumont, Texas) and Vistron (Lima, Ohio) (SRI, 1977).

There are 15 commercial producers of butadiene (SRI, 1977). All of them are potential users of acetonitrile for extraction purposes. A number of other companies also probably use it as a solvent and it may have some minor applications as a reagent.

Table 1. Compounds in the Nitrile Class

Compound	Chemical Abstract Service Number	Registry of Toxic Effects of Chemical Substances Number	Chemical Structure	Standard Chemical Name
Acetonitrile (Methyl cyanide)	75-05-8	AL77000	CH_3CN	Cyanomethane
Acetone cyanohydrin (2-Methyl lactonitrile)	75-86-5	OD92750	$(CH_3)_2COHCN$	2-Cyanopropanol
Acrylonitrile	107-13-1	AT52500	$CH_2=CHCN$	Cyanoethene
Adiponitrile	111-69-3		$NC(CH_2)_4CN$	1,4-Dicyanobutane
Benzonitrile	100-47-0	D124500	C_6H_5CN	Cyanobenzene
n-Butyronitrile	109-74-0	ET87500	$CH_3(CH_2)_2CN$	1-Cyanopropane
iso-Butyronitrile	78-82-0	TZ49000	$(CH_3)_2CCN$	2-Cyanopropane
Glycolonitrile (Formaldehyde cyanohydrin)	107-16-4	MC75250	$HOCH_2CN$	Cyanomethanol
Malononitrile	109-77-3	0031500	$CH_2(CN)_2$	Dicyanomethane

Acetone Cyanohydrin

The major use of this chemical is in the preparation of α-methacrylic acid and its esters, particularly methyl methacrylate (Blackford, 1976; Lurie, 1965). These products are polymerized to form useful resins such as plexiglas.

In 1975, approximately 473 million pounds of acetone cyanohydrin were produced to make methyl methacrylate. In previous years another 100 million pounds of acetone cyanohydrin were made for methacrylic acid production (Blackford, 1976). Therefore, about 573 million pounds of acetone cyanohydrin were produced in 1975.

The growth rate for acetone cyanohydrin production is expected to average 9% annually through 1980 (Blackford, 1976).

Acetone cyanohydrin is produced by DuPont (Memphis, Tennessee) and Rohm and Haas (Deer Park, Texas) (SRI, 1977).

Nearly all the production is captively used by the producers (Blackford, 1976).

Acrylonitrile

Production of acrylonitrile in 1976 was 1.5 billion pounds (USTIC, 1976 preliminary). Production is expected to increase by 8 - 10% per year through 1981 (Chem. Prof., 1977).

Uses for acrylonitrile are as follows (Chem. Prof., 1977):

acrylic and modacrylic fibres	50%
ABS and SAN resins	20
adiponitrile	10
nitrile rubber	5
exports	10
miscellaneous	5

Acrylonitrile is produced by the following manufacturers (SRI, 1977):

American Cyanamid (New Orleans, Louisiana)
DuPont (Memphis, Tennessee; Beaumont, Texas)
Monsanto (Alvin, Texas)
Vistron (Standard Oil of Ohio) (Lima, Ohio)

User breakdown for acrylonitrile is as follows (SRI, 1977):

	Number of Users	Number of Locations
ABS and SAN resins	7	11
nitrile rubber	5	6
adiponitrile	2	4
fibers	5	6

There are at least 13 different companies using acrylonitrile at about 27 different locations.

Adiponitrile

In 1976 1.5 billion pounds of acrylonitrile were produced, 10% of which was used to make adiponitrile (USITC, 1976; Chem. Prof., 1977). Therefore, production of adiponitrile was about 150 million pounds. No growth rates are available; however, the fact that adiponitrile is used to produce a nylon intermediate suggests a growth rate of at least several per cent per annum.

The major use for adiponitrile is in the production of hexamethylenediamine which in turn is used to make nylon (Carlson and Erskine, 1974).

Adiponitrile is manufactured by Celanese Corporation (Bay City, Texas) and DuPont (Laplace, Louisiana; Orange, Texas; Victoria, Texas) (SRI, 1977). All of the production is captively used (SRI, 1977).

Benzonitrile

No production figure is available from the literature. Benzonitrile is made from benzoic acid. Since this is a minor use for benzoic acid (Allison, 1975), it is estimated that the annual production of benzonitrile is less than one million pounds.

Benzonitrile is used as an organic solvent, especially for liquid phase reactions and polymerizations. It is also used as an intermediate in the production of benzoguanimine (Ingwalson, 1971).

Benzonitrile is manufactured by Velsicol Chemicals (Chattanooga, Tennessee).

Data for the number of users or sites of use are not available.

n-Butyronitrile

No production figures or trends are available. This compound is used as an intermediate in the synthesis of industrial, specialty, and pharmaceutical chemical products (Ingwalson, 1971).

n-Butyronitrile is manufactured by Eastman Kodak Company at Longview, Texas (SRI, 1977).

Data for the number of users is not available.

iso-Butyronitrile

Production figures and growth rates for this chemical are not available.

iso-Butyronitrile has been tested as a gasoline additive and as a catalyst for ethylene polymerization. It has also been used in various chemical syntheses (Ingwalson, 1971). A survey of the recent patent literature indicates that iso-butyronitrile can be used for the synthesis of pharmaceuticals, stabilizers for alkenylphenols, plant growth regulators, and stabilizers for various polymerized compositions.

This chemical is produced by Air Products and Chemicals, Inc. (Pensacola, Florida) and Eastman Kodak Company (Longview, Texas) (SRI, 1977).

Data on the number of users is not available.

Glyconitrile

No production data or trends are available for this chemical. The only domestic manufacturer of glyconitrile indicated that it is used for a variety of chemical syntheses, but would not elaborate.

A survey of the recent patent literature indicates that glyconitrile can be used in the synthesis of hydantoin, chloroacetonitrile, glycine, α-aminonitriles, aminoethylpiperazines, etc. It can also be used as an additive to nitrile barrier resins and as an intermediate in the synthesis of various bactericides and fungicides.

Glyconitrile is produced by Kay-Fries Chemicals, Inc., Montvale, New Jersey (SRI, 1977). According to the producer, there are more than several users of the chemical.

Malononitrile

No production or trends data are available.

One of the most important commercial uses of malononitrile is its condensation reaction with o-chlorobenzaldehyde to form o-chlorobenzalmalononitrile, a military and riot control chemical agent (CS) which is a good tear gas with no lasting effects if an individual is quickly removed from the contaminated area. Malononitrile may also be used in the synthesis of Vitamin B-1, has application as an oil-soluble polar additive to lubricating oils to suppress viscosity-index decrease, and is a valuable intermediate to products in the plastics and agricultural-chemical industries (Ingwalson, 1971).

Malononitrile is produced by Kay-Fries Chemicals (Stony Point, New York) and Lonza, Inc. (Mapleton, Illinois) (SRI, 1977).

The number of users of malononitrile is not available.

7. Biological Effects of Exposure

a. Target Organs

Exposure to the various nitriles under consideration has been associated with damage to the liver, kidneys, lungs, adrenal glands, gastrointestinal tract, and skin. However, the limited available information suggests that marked differences in target organs may exist among the various nitriles. As might be expected, the type of tissue pathology also seems somewhat dependent on the route of administration and the species tested.

Liver injury has been induced in some experimental mammals by acrylonitrile, malononitrile, and acetone cyanohydrin. Subchronic inhalation exposure to acrylonitrile caused liver damage in cats but not in rats, rabbits, guinea pigs, or monkeys (Dudley et al., 1942). Acute inhalation exposure of rats to acrylonitrile also does not appear to cause liver injury (Jaeger et al., 1974). Malononitrile, on subchronic exposure to rabbits, causes enlargement of the liver and damage to liver parenchymal cells (Krysiak et al., 1976). Moderate dystrophic lesions of the liver have been seen in rats after chronic oral administration of acetone cyanohydrin (Constantinescu, 1972; Motoe et al., 1971). Dorigan and coworkers (1976) indicated that liver enlargement is associated with chronic exposure to acetonitrile. Liver pathology, however, was not described. Similarly, Haguender and coworkers (1974) found that high concentrations of n-butyronitrile accumulated in the liver of rats after intraperitoneal injection but specific pathological changes were not mentioned.

Kidney damage has been associated with exposure to acrylonitrile and malononitrile. In rats, rabbits, cats, guinea pigs, and monkeys, subchronic inhalation exposure to acrylonitrile resulted in moderate interstitial nephritis (Dudley et al., 1942). Kidney enlargement with damage to kidney epithelial cells has been found after subchronic inhalation exposure of rabbits to malononitrile (Krysiak et al., 1976).

Different patterns of adrenal gland and gastrointestinal tract damage have been found after exposure of rats to acrylonitrile, n-butyronitrile, and propionitrile. Pronounced bilateral adrenal apoplexy has been associated with single oral doses of acrylonitrile (Szabo and Reynolds, 1975) while multiple sublethal doses result in atrophy of the zona fasciculata and hypertrophy of the zona glomerulosa of the adrenal gland (Szabo et al., 1976a). Propionitrile on acute exposure produces duodenal ulcers but no adrenal gland damage in rats, while n-butyronitrile causes both duodenal ulcers and adrenal necrosis (Szabo and Reynolds, 1975). On subchronic exposure, n-butyronitrile causes severe chronic duodenal ulcers (Szabo et al., 1976b). Krysiak and coworkers (1976) found that subchronic exposure of rabbits to malononitrile causes enlargement of the supraadrenal gland.

Few details are available on other potential target organs. Acrylonitrile has been shown to cause bronchopneumonia in a variety of mammals in subchronic inhalation exposures (Dudley et al., 1942), congestive plethora

and hemorrhaging of the skin on dermal exposure in rats (Zotova, 1976), and signs of lesions of the central nervous system as well as mucosal irritation on prolonged inhalation exposure in rats and rabbits (Knoblock et al., 1972). Sterner (1949) stated that both acetonitrile and acrylonitrile caused greater pulmonary irritation than hydrogen cyanide. Malononitrile, in subchronic exposures, caused an increase in the weight of spleens in rabbits (Krysiak et al., 1976). Lethal intraperitoneal doses of n-butyronitrile resulted in accumulation of both n-butyronitrile and cyanides in the liver, stomach, intestines, kidneys, and testes of rats (Haguender et al., 1974).

b. Acute Effects

The mechanism(s) by which the nitriles exert their acute toxic effects is not entirely clear. The lethal action of acetonitrile has been attributed to the in vivo formation of the cyanide ion (Hunter, 1975; Haguender et al., 1975). Similarly, a number of investigators have proposed that the toxic effects of acrylonitrile are closely related to the formation of cyanide in the body (Brieger et al., 1952; Dudley and Neal, 1942; Hashimoto and Kanai, 1965; Magos, 1962; Minami et al., 1973). However, based on comparative metabolism studies, Gut and coworkers (1975) have suggested that cyanide plays a minor role in acrylonitrile toxicity to rats but may play a major role in mice. While the differences among acrylonitrile, n-butyronitrile, and propionitrile in their effects on the adrenal gland and gastrointestinal tract are suggestive of different modes of action (see Section 7a), the roles of metabolic differences have not been examined. The mode of action of cyanide in fatal exposures appears to be respiratory paralysis due to inhibition of oxidative processes at the cellular level, with pathological changes including hemorrhage of the lungs and congestion of the brain, liver, kidneys, and spleen (Sterner, 1949).

Acute toxicity data on acetonitrile, acrylonitrile, and the other nitriles under review are summarized in Tables 2, 3, and 4, respectively. In that cyanide formation may play a role in the toxicity of at least some of the nitriles, these tables also include estimates of toxicity relative to hydrocyanic acid. These estimates are calculated as the toxicity of the nitrile divided by the corresponding value (same species and route) for hydrocyanic acid given in the Registry of Toxic Effects of Chemical Substances. Because such toxicity estimates can vary markedly due to a number of different factors, this approach is admittedly limited. For instance, Jaeger and coworkers (1974) have shown that inhalation toxicity of acrylonitrile is greater by a factor of nearly three in fasted rats (LC_{50} of 150 ppm) than in fed rats (LC_{50} of 425 ppm). Similarily, Kimura and coworkers (1971) have shown that 14 day old rats are almost twenty times more susceptible to acetonitrile intoxication than young adult rats. Thus, only large differences in toxicity should be regarded as significant.

Acetonitrile administered orally or parenterally, is clearly less toxic than hydrocyanic acid to a variety of experimental mammals with estimates of relative toxicity ranging from 134 to 1027 (see Table 2). Quantitative estimates of relative inhalation toxicity could not be made because the inhalation

Table 2. Acute Toxicity of Acetonitrile to Experimental Mammals (see text for details)

Organism	Route	Dose	Effect	Toxicity Relative to Hydrocyanic Acid	Reference
Rat	Oral	3800 mg/kg	LD_{50}	1027*	NIOSH, 1976
		2460 mg/kg	LD_{50}	664*	Ingwalson, 1971
		3600-3800 mg/kg	LD_{50}	1000-1027*	Brown et al., 1975
	I.P.	920 mg/kg	LD_{50}	308*	Brown et al., 1975
		1500 mg/kg	Lethal	502*	Haguender et al., 1975
	S.C.	3600 mg/kg	LD_{50}	<1200*	Brown et al., 1975
		3900 mg/kg	LD_{50}	<1300*	Cuny and Quivy, 1939
	Inhalation	8000 ppm x 4 hr	LCLo		NIOSH, 1976
		4000 ppm**	Lethal to 3 of 30 animals		Ingwalson, 1971
		8000 ppm**	Lethal to 10 of 30 animals		Ingwalson, 1971
		32,000 ppm**	Lethal to 17 of 30 animals		Ingwalson, 1971
Mouse	I.P.	400 mg/kg	LD_{50}	134	Brown et al., 1975
		1920 mg/kg	LD_{50}	642	NIOSH, 1976
	S.C.	700 mg/kg	LDLo	233	NIOSH, 1976
Rabbit	Dermal	975 mg/kg	LD_{50}	---	Ingwalson, 1971

* Based on corresponding values of hydrocyanic acid toxicity to mice.
** Exposure period not specified.

Table 3. Acute Toxicity of Acrylonitrile (NIOSH, 1976)

Organism	Route	Dose	Response	Toxicity Relative to Hydrocyanic Acid
Rat	oral	93 mg/kg	LD50	25*
	inhalation	500 ppm x 4hrs	LCLo	--
	subcutaneous	96 mg/kg	LD50	32*
Mouse	inhalation	784 ppm x 4hrs	LC100	--
	intraperitoneal	15 mg/kg	LDLo	5
Rabbits	oral	93 mg/kg	LD50	25
	dermal	280 mg/kg	LC50	--
Guinea pig	dermal	250 mg/kg	LD50	--

*Based on corresponding values of hydrocyanic acid toxicity to mice.

Table 4. Acute Toxicity of Various Nitriles (NIOSH, 1976)

Compound	Organism	Route	Dose	Response	Relative Toxicity to Hydrocyanic Acid
Adiponitrile	Rat	Oral	300 mg/kg	LD_{50}	81*
	Mouse	Intraperitoneal	40 mg/kg	LD_{50}	13
	Guinea pig	Subcutaneous	50 mg/kg	LD_{50}	500
Benzonitrile	Rat	Oral	720 mg/kg	LDLo	>195*
	Rat	Inhalation	950 ppm x 8 hr	LDLo	---
	Rat	Dermal	1200 mg/kg	LD_{50}	---
	Mouse	Subcutaneous	180 mg/kg	LDLo	60
n-Butyronitrile	Rat	Oral	500 mg/kg	LD_{50}	135*
	Rat	Inhalation	400 ppm x n.s.	LCLo	---
	Mouse	Oral	100 mg/kg	LDLo	27
	Rabbit	Dermal	500 mg/kg	LD_{50}	---
	Guinea pig	Dermal	100 mg/kg	LDLo	---
iso-Butyronitrile 2-cyanopropane	Rat	Oral	102 mg/kg	LD_{50}	135*
	Rat	Inhalation	1000 ppm x 4 hr	LCLo	---
	Rabbit	Dermal	310 mg/kg	LD_{50}	---
Glyconitrile	Rat	Oral	16 mg/kg	LD_{50}	4.3*
	Rat	Inhalation	250 ppm x n.s.	LCLo	---
	Mouse	Subcutaneous	15 mg/kg	LDLo	5.0
	Rabbit	Dermal	5 mg/kg	LD_{50}	---

* Compared to corresponding route in mouse.

Table 4. Acute Toxicity of Various Nitriles (Cont'd)

Compound	Organism	Route	Dose	Response	Relative Toxicity to Hydrocyanic Acid
Malononitrile	Rat	Oral	61 mg/kg	LD_{50}	16*
	Rat	n.s.	7 mg/kg	LDLo	---
	Mouse	Oral	19 mg/kg	LD_{50}	5.1
	Mouse	Intraperitoneal	13 mg/kg	LD_{50}	4.3
	Mouse	n.s.	8 mg/kg	LDLo	---
	Rabbit	n.s.	6.5 mg/kg	LDLo	---
	Dog	n.s.	6.5 mg/kg	LDLo	---
Acetone Cyanohydrin [2-hydroxy-2-methyl-propionitrile]	Rat	Oral	17 mg/kg	LD_{50}	4.6*
	Rat	Inhalation	63 ppm x 4 hr	LCLo	---
	Rat	Subcutaneous	8.5 mg/kg	LDLo	2.8*
	Mouse	Oral	3 mg/kg	LD_{50}	0.8
	Mouse	Inhalation	575 ppm x 2 hr	LC_{50}	---
	Mouse	Intraperitoneal	1 mg/kg	LDLo	0.33
	Rabbit	Oral	14 mg/kg	LD_{50}	3.8
	Rabbit	Dermal	17 mg/kg	LD_{50}	---
	Guinea pig	Oral	9 mg/kg	LD_{50}	2.4

* Compared to corresponding route in mouse.

periods used for hydrocyanic acid were too short, e.g., LC_{50} in rats of 544 ppm x 5 minutes (NIOSH, 1976). Nonetheless, acetonitrile - with an inhalation LC_{50} in rats of greater than 8000 ppm x 4 hours - is also less toxic than hydrocyanic acid by this route. Acrylonitrile is markedly more toxic than acetonitrile but somewhat less toxic than hydrocyanic acid (see Table 3). Additional information on the inhalation toxicity of acrylonitrile is summarized in Table 4. The remaining nitriles may be divided into two groups. The first group consists of adiponitrile, benzonitrile, n-butyronitrile, and iso-butyronitrile. These chemicals are much less toxic than hydrocyanic acid, somewhat less toxic than acrylonitrile, but more toxic than acetonitrile. The second group consists of glyconitrile, malononitrile, and acetone cyanohydrin. These chemicals are at least as toxic as acrylonitrile and are not substantially less toxic than hydrocyanic acid. The profound differences in the toxicities of iso-butyronitrile and acetone cyanohydrin are especially interesting in that these two nitriles differ in structure only by the presence of a hydroxyl group on acetone cyanohydrin. Based on the data given in Tables 2, 3, and 4 the relative acute toxicities of the nitriles appear to be: acetonitrile (least toxic) << benzonitrile ≈ n-butyronitrile ≈ iso-butyronitrile ≈ adiponitrile < acrylonitrile < malononitrile < glyconitrile < acetone cyanohydrin (most toxic).

More recent acute toxicity estimates of malononitrile (Krysiak et al., 1976) and benzonitrile (Agaev, 1975) do not differ markedly from those given in Table 4.

c. Subchronic Effects

Information of subchronic toxicity has been found only for acrylonitrile. After inhalation exposures to 56 ppm acrylonitrile for 4 hours/day, 5 days/week, for 8 weeks, monkeys evidenced no signs of toxic effects but the single dog tested developed transitory hindlimb weakness. After exposure to 100 ppm for 4 hours/day, 5 days/week, for 8 weeks, rats showed no effects, guinea pigs evidenced signs of slight lethargy, and rabbits had reduced weight gain. Four cats, on identical inhalation exposures, developed occasional vomiting, listlessness, and weight loss. In addition, one cat showed signs of hindlimb weakness. Over the same exposure schedule to 153 ppm, 50 per cent of the rats died after 2-3 weeks. Guinea pigs and rabbits evidenced signs of eye and nose irritation as well as reduced weight gain (guinea pigs only). All four cats in this exposure series developed transitory hindlimb weakness in addition to marked nasal and conjunctional irritation. Monkeys developed weakness, loss of appetite, salivation, and vomiting (Dudley et al., 1942).

d. Chronic Effects

i) Carcinogenicity

DuPont Co. has recently determined that workers exposed to acrylonitrile experience higher cancer incidence rates (Anon., 1977).

Dorigan and coworkers (1976) indicate that acetonitrile yielded equivocal results in a two year rat study. Details of this report have not been encountered in the literature search. Neither hydrocyanic acid nor any of the nitriles under study are cited as having carcinogenic effects in the 1976 Registry of Toxic Effects of Chemical Substances (NIOSH, 1976).

ii) Mutagenicity

No information has been encountered on the mutagenicity of the nitriles under study.

iii) Teratogenicity

Dorigan and coworkers (1976) indicate that acetonitrile administered intraperitoneally to rats at doses of about 156 mg/kg and 780 mg/kg resulted in fetal malformations. In pigs, acetonitrile administered in days 10-40 of gestation [route and dose not specified] resulted in no teratogenic effects. Acetonitrile is not listed in Shepard's (1973) catalogue of teratogens and is not cited by NIOSH (1976) as having been tested for teratogenicity.

iv) Other Chronic Effects

Relatively little information is available on other aspects of chronic exposure to nitriles. As described in Section 7a, histological changes in the adrenal gland of rats occurred after 60 day exposures to contaminated water containing 0.2% acrylamide (Szabo et al., 1976a). Similar exposures to n-butyronitrile resulted in severe chronic duodenal ulcers (Szabo et al., 1976b). After inhalation exposures to acrylonitrile at a concentration of about 220 ppm (50 mg/cubic meter) for six months, rats and rabbits developed respiratory, cardiovascular, and kidney disorders as well as signs of neural lesions in the central nervous system (Knoblock et al., 1972). In rats, prolonged exposure to acetone cyanohydrin has been associated with liver and kidney damage as well as alterations in liver and serum enzyme levels (Constantinescu, 1972; Motoe et al., 1971). Dorigan and coworkers (1976) state that chronic exposure to acetonitrile is associated with growth retardation, metabolic disturbances, and liver enlargement. Agaev and coworkers (1977) have recently examined the chronic toxicity of benzonitrile. Details of this study were not available for this profile.

e. Human Effects

Human fatalities have been associated with acetonitrile exposure. In one incident, accidental exposure to high but unspecified levels of acetonitrile was associated with one death and several cases of severe illness which were attributed to thiocyanate rather than cyanide poisoning (Amdur, 1959; Grabois, 1955). More recently, a 19 year old male became ill after cleaning a floor with acetonitrile. Symptoms included vomiting, nausea, and

mental confusion which progressed to periods of coma interrupted by convulsions. High levels of hydrogen cyanide and acetonitrile were found in the liver, kidney, spleen, heart, and lungs (Daquidt et al., 1974). These signs of intoxication are consistent with those of other cyanides (Sterner, 1949).

Experimental exposure of humans to 160 ppm acetonitrile for 4 hours resulted in slight facial flushing in one individual 2 hours after inhalation and slight bronchial tightness five hours later. Similar exposures to 80 ppm caused no apparent effects. At 40 ppm, all individuals could detect odor during the first 2 or 3 hours after exposure but evidenced signs of olfactory fatigue after this period. Increased blood cyanide levels were not found although a rise in urinary thiocyanates was noted (Pozzani et al., 1959).

Although presumably more toxic than acetonitrile, acrylonitrile has not been associated with worker fatalities from acute exposure (Hunter, 1975). However, workmen exposed to acrylonitrile suffer nausea, vomiting, weakness, fatigue, and diarrhea (Wilson, 1944). Workers exposed to acrylonitrile have recently been shown to experience a higher incidence of cancer (Anon., 1977).

Contamination of beech-nut meal with glycolonitrile resulted in the death of three individuals. The cause of death was assumed to be hydrocyanic acid poisoning (Patscheider and Dirnhofer, 1973).

8. TLV's

Based largely on the study by Pozzani and coworkers (1959), the TLV for acetonitrile has been set at 40 ppm (ACGIH, 1971). Based on various animal studies (Dudley et al., 1942; Dudley and Neal, 1942; Magos, 1962; Hashimoto and Kanai, 1965) and by analogy to the 10 ppm TLV set for hydrocyanic acid, the TLV for acrylonitrile is 20 ppm (ACGIH, 1971). OSHA is currently considering emergency controls for acrylonitrile because of its possible carcinogenic effects in humans.

9. Other Standards

Dudley and Neal (1942), based partly on the data summarized in Table 5, recommended a maximum practical exposure level to acetonitrile of 20 ppm. Given the effects of 4 hour exposures of dogs to 29 ppm and 55 ppm (see Table 5), this standard seems more reasonable than the current TLV.

Knoblock and coworkers (1972) have suggested 5 mg/cubic meter ($\sim$ 2.2 ppm) as a maximum permissible concentration of acrylonitrile in air based on their chronic toxicity studies in rats and rabbits (see Section 7.d.-iv).

Agaev (1975) has recommended 1 mg/cubic meter as a maximum permissible concentration of benzonitrile in air.

Table 5. Physiological Response to 4-Hour Inhalation Exposures to Acrylonitrile (Dudley and Neal, 1942; modified from Sterner, 1949)

Animal	Concentration (ppm)	Response
Rat	575	Fatal in 2-6 hours
	129	Slight transitory effects
	97	Slight transitory effects
Cat	600	Fatal within 1 1/2 hours after test
	267	Marked salivation and signs of pain; no deaths
	152	Markedly toxic, sometimes fatal
Rabbit	258	Fatal after 4-5 hours
	133	Marked transitory effects
	97	Slight transitory effects
Guinea pig	575	Delayed death from lung edema, 3-6 days after exposure
	267	Reduced food consumption for 4 days
Monkey	133	Marked transitory effects
Dog	110	Fatal to three fourths of the animals
	98	Convulsions and coma; no death
	55	Transitory paralysis; one death
	29	Very slight effects

10. Other Data

Henkel and Mletzko (1974) have examined the effects of combined exposure to acrylonitrile and noise. The study has not been obtained for this review.

Table 6 lists the number of reported human occupational exposures to nitrile compounds (NIOSH, 1977).

Table 6. Reported Human Occupational Exposures to Nitriles (NIOSH, 1977)

Compound	Number of Reported Exposures
Acetonitrile	22,560
Acrylonitrile	158,280
Benzonitrile	2,100

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NITROBENZENES

1. Molecular Structures

2. Chemical Abstract Service (CAS) Numbers

3. Registry of Toxic Effects of Chemical Substances (RTECS) Numbers

The above information for nitrobenzene and m-dinitrobenzene is listed in Table 1.

In choosing these compounds, consideration was given to their commercial significance and relative toxicological hazard.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Nitrobenzene

Production of nitrobenzene in 1975 was 414 million lbs. (USITC, 1975). The growth rate is expected to average 8.5% annually through 1980. Of the total produced, 97.5% is used as an intermediate in the manufacture of aniline (Chem. Prof., 1976a). The remainder is used in the production of dyes and explosives and as a solvent (Howard et al., 1976).

Nitrobenzene is produced by the following companies at the locations listed (Chem. Prof., 1976a):

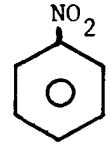
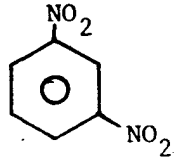
American Cyanamid	Bound Brook, New Jersey
	Willow Island, West Virginia
DuPont	Beaumont, Texas
	Gibbstown, New Jersey
First Chemical	Pascagoula, Mississippi
Mobay Chemical	New Martinsville, West Virginia
Rubicon	Geismar, Louisiana

Nearly all of the production is used captively to make aniline. The remainder of production is sold to a number of different companies for the uses mentioned previously.

m-Dinitrobenzene

No production figures are available for m-dinitrobenzene; however, based on estimates of its intermediate use, production may be in the range of 100,000 lbs. per year (SRC estimate).

Table 1. Compounds in the Nitrobenzene Class

Compound	IUPAC Chemical Name	CAS Number	RTECS Number	Molecular Structure
Nitrobenzene	Nitrobenzene	98-95-3	DA64750	
m-Dinitrobenzene	1,3-Dinitrobenzene	99-65-0	CZ73500	

m-Dinitrobenzene is used in organic synthesis and production of dye intermediates such as m-nitroaniline and m-phenylenediamine (Thirtle, 1968; Kouris and Northcott, 1963).

Producers of m-dinitrobenzene are DuPont (probably at Deepwater Point, New Jersey), Sigma Corporation (St. Louis, Missouri), and American Hoechst (Coventry, Rhode Island).

At least three dye manufacturers produce dyes derived from m-dinitrobenzene intermediates.

7. Biological Effects of Exposure

a) Target Organs

Damage to the liver and central nervous system are the most common effects of poisoning by nitrobenzene and m-dinitrobenzene. Liver function may be impaired or atrophy may develop (Rejsek, 1947), or, as in a case reported by Beritic (1956), the liver may enlarge. Symptoms of central nervous system injury include: respiratory stress, dizziness, tremors, impairment of righting reflex, and coma (Smith et al., 1967). In addition, Von Oettingen (1941) noted staggering gait and clonic-tonic convulsions in dogs resulting from acute exposure to nitrobenzene.

Occurrence of kidney damage attributed to nitrobenzene exposure has also been reported (Kazakova, 1956; Howard et al., 1976) as has damage to spleen, adrenal cortex (Yamada, 1958), bone marrow (Myślak et al., 1971), heart muscle (Kazakova, 1956; Myślak et al., 1971), and gastro-intestinal tract (Howard et al., 1976).

b) Acute Effects

Hematologic changes, including methemoglobin and Heinz body formation, from poisoning by either chemical are commonly reported (Magos and Sziza, 1958; Beritic, 1956; Smith et al., 1967). It has been noted that m-dinitrobenzene is more toxic than nitrobenzene (Howard et al., 1976), especially in the amount of methemoglobin and Heinz bodies formed in cats injected intraperitoneally with either chemical (Bredow and Jung, 1943). Kiese (1949) found verdoglobinemia in dogs exposed to m-dinitrobenzene, while Vasilenko and Zvezdai (1972) found nitroxyhemoglobin and sulfhemoglobin in rabbits poisoned with nitrobenzene. Anemia is also a feature of poisoning by nitrobenzene and m-dinitrobenzene (Kiese, 1949; Beritic, 1956; Yamada, 1958).

c) Subchronic Effects

Rats inhaling nitrobenzene at concentrations between 0.08-0.8 mg/m^3 continuously for 73 days developed muscle chronaxy disturbances, increase in blood cholinesterase activity, and methemoglobin formation followed by a persistent increase in sulfhemoglobin. However, at a concentration of 0.008 mg/m^3 there was no effect (Rusakov et al., 1973).

Table 2. Acute Toxicity of Various Nitrobenzenes

Organism	Route	Dose (mg/kg)	Response	Reference
m-Dinitrobenzene				
Rats	Oral	50	No deaths	Hanavan, 1975
Dogs	Oral	600 mg*	Minimum lethal dose	Von Oettingen, 1941
Dogs	I.V.	10	Serum iron rose sharply after 1 day and returned to normal in 6 days	Cammerer et al., 1949
Dogs	I.V.	10-20	Methemoglobinemia, verdoglobinemia, Heinz bodies, liver damage, cerebral paralysis, convulsions, anemia, increase in white blood cells; LD_{50} about 10 mg/kg	Kiese, 1949a
Rabbits	Oral	400-500 mg*	Minimum lethal dose	Von Oettingen, 1941
Rabbits	Dermal	200	No deaths	Hanavan, 1975
Blackbird	Oral	42	LD_{50}	Schafer, 1972
Starling	Oral	>100	LD_{50}	Schafer, 1972

*Total dose

Table 2. Acute Toxicity of Various Nitrobenzenes (Cont'd)

Organism	Route	Dose (mg/kg)	Response	Reference
Nitrobenzene				
Rats	Oral	640	LD_{50}	Christensen and Luginbyhl, 1974
Rats	Oral	664	LD_{50}	Smyth et al., 1970
Rats	I.P.	836	100% mortality within 24-48 hours, 44.5% methemoglobin level	Magos and Sziza, 1958
Rats	S.C.	100-200	Sulfhemoglobin, nitroxy-hemoglobin, methemoglobin, Heinz bodies	Vasilenko and Zvezdai, 1972
Rats	S.C.	800	Lethal dose	Christensen and Luginbyhl, 1974
Mice	I.P.	996	100% mortality within 24 hours; CNS disturbances, i.e., righting reflex impaired, coma, shallow respiration, tremor, respiratory arrest	Smith et al., 1967
Mice	S.C.	480	Lethal dose	Christensen and Luginbyhl, 1974
Mice	Inhalation	50-80 mg/l	Toxic level	Pislaru et al., 1962
Dogs	Oral	750-1000	Minimum lethal dose	Von Oettingen, 1941
Dogs	Oral	500-700	Salivation, unrest, tremors, delirium, increased pulse, staggering gait, clonic-tonic convulsions	Von Oettingen, 1941
Dogs	Oral	750	Lethal dose	Christensen and Luginbyhl, 1974

Table 2. Acute Toxicity of Various Nitrobenzenes (Cont'd)

Organism	Route	Dose (mg/kg)	Response	Reference
Nitrobenzene (cont'd)				
Dogs	I.V.	150-25	Minimum lethal dose	Von Oettingen, 1941
Rabbits	Oral	600	Lethal dose	Christensen and Luginbyhl, 1974
Rabbits	Dermal	600	Lethal dose	Christensen and Luginbyhl, 1974

Table 3. Acute Effects of Nitrobenzene Administered by I.P. Injection into Rats (Magos and Sziza, 1958)

Dose (mMol/kg)	% Methemoglobin	Time to Death (hr)
1.76	44.5	---
2.73	33.0	---
4.69	34.0	---
6.79	44.5	24-28
9.29	58.0	8-24
13.69	58.0	8-24

No subchronic toxicity data for m-dinitrobenzene has been encountered.

d) Chronic and Special Effects

i) Carcinogenicity - No carcinogenicity data were encountered.

ii) Mutagenicity - Concentrations of nitrobenzene between 0.001-0.004 M decreased the viability of Actinomyces sphaeroides spores by 6-80% (Romanova and Rapoport, 1971).

iii) Teratogenicity - No teratogenicity data were encountered.

iv) Other - Yamada (1958) relates a study on the chronic administration of nitrobenzene to rabbits via subcutaneous injections. The first signs of chronic poisoning were anemia and increased reticulocyte levels. Eventually, metabolic detoxification mechanisms broke down, resulting in a reduced capacity for amination, acylation, and hydroxylation reactions accompanied by greatly increased output of urinary metabolites. The animals suffered loss of appetite and severe weight loss. The histopathology associated with this study is discussed in detail by Yamada (1958).

Further data on chronic effects are listed in Table 4. No information was available on chronic effects of m-dinitrobenzene.

e) Human Effects

Human poisoning by dinitrobenzene results in headache, chest pressure, malaise, nausea, and vomiting with eventual cyanosis. In cases of severe poisoning, liver function was impaired or the liver developed atrophy (Rejsek, 1947). Rejsek (1947) points out that complete relapses of acute effects may occur upon ingestion of alcohol or exposure to sunlight. Individual variations in genetic makeup, nutritional state, body fat stores, and health in general affect susceptibility to poisoning by dinitrobenzene (Howard et al., 1976). Two women exposed similarly, for example, were affected differently in that one developed methemoglobinemia, moderate anemia, and liver enlargement, while the other developed anemia with Heinz body formation but sustained no liver damage (Beritic, 1956).

Nitrobenzene exerts its toxic effects on the hematologic system by formation of methemoglobin and development of anoxemia due to low levels of hemoglobin (Howard et al., 1976). Children accidentally poisoned by an oil containing 2-10% nitrobenzene rubbed on their skin developed cyanosis which, in cases where death occurred, was preceded by shock, vomiting, respiratory difficulties, and bronchopneumonia (Zeitoun, 1959).

Parkes and Neill (1953) report also that dizziness and aminoaciduria resulted after ingestion of nitrobenzene. Complete recovery from suicidal ingestions of nitrobenzene have been noted with no signs of permanent tissue damage, although temporary injury to bone marrow, heart muscle, and liver followed ingestion of 50 ml nitrobenzene (Myślak et al., 1971).

Table 4. Chronic Effects of Nitrobenzene

Organism	Route	Dose (mg/kg)	Response	Reference
Rabbits	S.C.	840 daily x 24 weeks	7 of 8 rabbits died within 14 weeks; anemia, emaciation, and degradation of liver, spleen, and adrenal cortex	Yamada, 1958
Guinea Pigs	S.C.	200 every other day x 6 months	Fluctuations of urinary 17-oxo-corticosteroids; body weight loss; decreased motor functions	Makotchenko and Akhmetov, 1972

As with m-dinitrobenzene, individual susceptibility to nitrobenzene varies; as little as one gram may be lethal, but 3-100 g may be followed by recovery (Wirtschafter and Wolpaw, 1944).

8. TLV

The TLV for nitrobenzene is established at 1 ppm (about 5 mg/m^3) by ACGIH (1971b), a level sufficiently low so as to prevent significant changes in the blood and symptoms of mild intoxication as well. The TLV for all isomers of dinitrobenzene is 1 mg/m^3, which is estimated from the toxicity of polynitro compounds relative to that of mononitro derivatives (ACGIH, 1971a). The same value has been adopted by the USSR and Czechoslovakia.

9. Other Standards

Other TLV levels have been established for nitrobenzene as follows (ACGIH, 1971b):

Cook (1945) -	5 ppm
Smyth (1956) -	1 ppm
Elkins (1959) -	1 ppm
USSR (1967) -	0.6 ppm
Czechoslovakia (1969) -	1 ppm

10. Other Data

The minimum level of nitrobenzene detectable by human olfaction was found to be 0.0182 mg/m^3 (Andreyescheva and Nuttonson, 1971). In addition, visual sensitivity to light decreased and the amplitude of intrinsic brain rhythm potential was disrupted by smelling subthreshold levels of nitrobenzene (Andreyeshcheva and Nuttonson, 1971).

Table 5 lists the number of reported human occupational exposures to nitrobenzene and m-dinitrobenzene (NIOSH, 1977).

Table 5. Reported Human Occupational Exposures to Nitrobenzenes (NIOSH, 1977)

Compound	Number of Exposures
Nitrobenzene	19,080
m-Dinitrobenzene	1,710
o,p-Dinitrobenzene	360

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NITROPHENOLS

1. Molecular Structure

2. Chemical Abstract Service Number

3. Registry of Toxic Effects of Chemical Substances Number

The above information for the commercially significant nitrophenols selected for this profile is listed in Table 1.

In selecting the compounds listed, consideration was given to the size of production, in addition to the possible toxicological hazard regardless of the relative commercial significance of the compound.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

m-Nitrophenol

No production figures are available, but uses would suggest that production is less than 1 million lbs. annually (SRC estimate).

m-Nitrophenol is used in the manufacture of dye intermediates such as anisidine and m-aminophenol (Kouris and Northcott, 1963; Matsuguma, 1967).

m-Nitrophenol is produced by R.S.A. Corp. (Ardsley, N.Y.) and probably used by several dye manufacturers.

o-Nitrophenol

o-Nitrophenol is produced in the amount of 10-15 million lbs. annually (Howard et al., 1976). Its chief use is in the synthesis of o-aminophenol, o-nitroanisole, and other dyestuffs (Matsuguma, 1967; Howard et al., 1976).

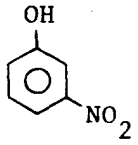
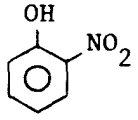
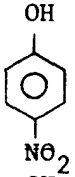
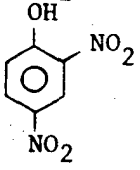
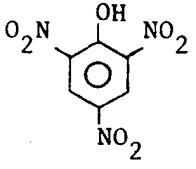
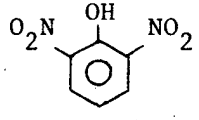
Martin Marietta Chemicals (Sodyeco, N.C.) and Monsanto (Sauget, Ill.) manufacture o-nitrophenol (SRI, 1977).

In addition to the two producers, at least three other companies use o-nitrophenol to make intermediates.

p-Nitrophenol

While demand for p-nitrophenol was 36 million lbs. in 1975, growth is expected to advance 3-4% per year through 1980 (Chem. Prof., 1976b). It is

Table 1. Compounds in the Nitrophenol Class

Compound	CAS Number	RTECS Number	Molecular Structure	Standard Chemical Name
m-Nitrophenol	554-84-7	SM19250		3-nitrophenol
o-Nitrophenol	88-75-5	SM21000		2-nitrophenol
p-Nitrophenol	100-02-7	SM22750		4-nitrophenol
2,4,-Dinitrophenol (DNP)	51-28-5	SL28000		2,4-dinitrophenol
2,6-Dinitrophenol	573-56-8	SL29750		2,6-dinitrophenol
2,4,6-Trinitrophenol (Picric acid)	88-89-1	TJ78750		2,4,6-trinitrophenol

mainly used in the manufacture of ethyl and methyl parathions (87%); the remainder is used in the synthesis of dyestuffs, acetyl-p-aminophenol, and in leather treatment (Chem. Prof., 1976b).

DuPont (Deepwater Point, N.J.) and Monsanto (Anniston, Ala.), the producers, are also captive users. Five other companies use p-nitrophenol to make pesticides, and about six other companies use it in dye preparations.

2,4-Dinitrophenol (DNP)

The most recent production figure for 2,4-dinitrophenol is 863,000 lbs. in 1968 (USITC, 1968). Approximate consumption per year is estimated at one million lbs. (Howard et al., 1976).

It is used as a chemical intermediate for sulfur dyes, azo dyes (2,4-diaminophenol, 4-nitro-2-aminophenol), photochemicals, pest control agents, wood preservatives, and explosives (Matsuguma, 1967).

Martin Marietta Chemicals (Sodyeco, N.C.) produces 2,4-dinitrophenol while at least six dye and pesticide manufacturers use it.

2,4,6-Trinitrophenol (Picric acid)

No production and growth figures are available.

Picric acid is used as an intermediate in the production of picramic acid and other dye intermediates, explosives, germicides, fungicides, analytical reagents, photochemicals, and pharmaceuticals (Matsuguma, 1967; Blackford, 1975).

Production of picric acid is by Martin Marietta Chemicals (Sodyeco, N.C.) (SRI, 1977).

It has numerous small users and probably only a couple of larger users in dye production.

7. Biological Effects of Exposure

a) Target Organs

Exposure to the nitrophenol compounds selected for this profile cause damage to the kidneys, eyes, liver, spleen, gastrointestinal tract, central nervous system, cardiovascular system, testicles, and skin.

Specifically, picric acid (2,4,6-trinitrophenol) has caused dermatitis and skin sensitivity (Schwartz, 1944; Von Oettingen, 1941) evidenced by edema, papulae and vesicles, and subsequent desquamation. In addition, irritation to conjunctiva has been observed (ACGIH, 1971). A single acute oral dose to rabbits resulted in severe kidney damage (Von Oettingen, 1941).

Makhinya (1969) reports that warm-blooded animals chronically exposed to the nitrophenol isomers developed gastrointestinal irregularities (gastritis, enteritis, and colitis) as well as hepatitis, neuritis, and hyperplasia of the spleen. Ogino and Yasukura (1957) observed cataract formation in guinea pigs given p-nitrophenol. They found that o- and m- nitrophenol are non-cataractogenic in guinea pigs.

The damaging effects of 2,4-dinitrophenol are wide-ranging in that almost all the organs are affected in some way. Acute oral exposures cause erosion of tongue, mouth, esophagus, and mucous membrane of the stomach. Congestion of conjunctiva has also been noted (Howard et al., 1976).

Subchronic exposures to 2,4-dinitrophenol have led to cataracts and gastrointestinal disturbances (Horner, 1942). Subchronic dietary intake in rats resulted in enlarged spleen, slight renal degeneration, liver congestion and swelling, and testicular atrophy. Pathological changes of the kidney included dilation of proximal tubules with some dehydrated and necrotic cells (Spencer et al., 1948).

Cataract development from 2,4-dinitrophenol exposure has been shown to be reversible in animals, but not in humans (Howard et al., 1976). A definite dose-related response was shown in ducks and rabbits (Gehring and Buerge, 1969), while in guinea pigs, a vitamin C-supplemented diet prevented cataracts (Ogino and Yasukura, 1957).

Buschke (1947) demonstrated the cataractogenic activity of 2,6-dinitrophenol in eyes of chickens.

b) Acute Effects

As previously discussed, 2,4-dinitrophenol causes cataracts which have been shown to be reversible and dose-related (Howard et al., 1976; Gehring and Buerge, 1969). Interestingly, in the case of reversibility, the cataracts disappeared while the chemical was still being administered in the diet (Howard et al., 1976). Time of cataract development in ducks is related to the route of administration as follows: oral (1-3 hours); intraperitoneal (30 min.); intraocular (less than 10 min.). In rabbits cataract susceptibility decreases with the animal's age (Howard et al., 1976).

Other effects of acute poisoning by 2,4-dinitrophenol include increased respiratory rate, and blood pressure, high body temperature, both reduced and increased heart rates, tremors, and early onset of rigor mortis followed soon by death. Similar responses to 2,4-dinitrophenol poisoning have been observed in mice, rats, rabbits, and dogs. It is not clear yet if circulatory and respiratory changes result directly from action on the central nervous system or as secondary responses to anoxemia (Howard et al., 1976).

Shen (1962) has shown that acute 2,4-dinitrophenol exposures stimulate both aortic and carotid chemoreceptors of dogs. This stimulation induces

a striking elevation of respiration associated with a parallel hyperthermic reaction.

Table 2 lists acute effects of the nitrophenol compounds.

c) Subchronic Effects

Ogino and Yasukura (1957) reported on an extensive study of cataract development induced by 2,4-dinitrophenol in guinea pigs. Cataracts developed in those animals fed a vitamin C-deficient diet with daily oral doses of DNP. Control animals receiving vitamin C-supplemented diets incurred no eye lesions. The exact role of vitamin C is not clear. Subchronic administration of p-nitrophenol produced cataracts while o- and m-nitrophenol did not; apparently the para-positioning of the hydroxyl and nitro- groups is necessary in cataract induction.

Table 3 lists other subchronic effects resulting from exposure to nitrophenolic compounds.

d) Chronic Effects

i) Carcinogenicity

Spencer and associates (1948) report that no tumors were produced in rats fed 0.01-0.1% 2,4-dinitrophenol daily for 179 days.

o-Nitrophenol was applied in 20% solution with dioxane to mouse skin twice weekly. After 12 weeks, 30 mice survived, none of which had developed tumors. An identical experiment performed with p-nitrophenol gave the same results (Boutwell and Bosch, 1959).

ii) Mutagenicity

When mice were injected intraperitoneally with 2,4-dinitrophenol, bone marrow cells collected 24 hours later showed chromatid-type breaks. No linear relationship was observed, however, between frequency of breaks and 2,4-dinitrophenol dosage (Micra and Manna, 1971).

Buselmaier and coworkers (1973) demonstrated the ineffectiveness of p-nitrophenol as a mutagenic agent in mice.

iii) Teratogenicity

Hagstrom and Lonning (1966) showed that sea urchin larvae treated with DNP developed several marked irregularities. Details of this study are reported in a review by Howard and associates (1976).

2,4-Dinitrophenol was shown to produce a synergistic teratogenic effect when administered with insulin into yolk sacs of chicken eggs. Insulin

Table 2. Acute Effects - Nitrophenols

Compound	Organism	Dose (mg/kg)	Route	Response	Reference
m-Nitrophenol	rats	933	oral	LD_{50}	MacEwen and Vernot, 1972
	rats	447	oral	LD_{50}	Marhold, 1972
	mice	1414	oral	LD_{50}	MacEwen and Vernot, 1972
	dogs	83	I.V.	Lethal dose	Christensen & Luginbyhl, 1974
o-Nitrophenol	rats	2828	oral	LD_{50}	MacEwen and Vernot, 1972
	mice	1297	oral	LD_{50}	MacEwen and Vernot, 1972
	mice	600	I.M.	Lethal dose	Dittmer, 1959
	rabbits	1700	S.C.	Lethal dose	Dittmer, 1959
	rabbits	?	dermal	Not corrosive to skin	Hanavan, 1975
	cats	600	S.C.	Lethal dose	Dittmer, 1959
	dogs	100	I.V.	Lethal dose	Dittmer, 1959
p-Nitrophenol	rats	350	oral	LD_{50}	Christensen & Luginbyhl, 1974
	rats	616	oral	LD_{50}	MacEwen and Vernot, 1972
	rats	97	I.P.	LD_{50}	Dittmer, 1959
	mice	467	oral	LD_{50}	MacEwen and Vernot, 1972
	mice	107.6	I.P.	LD_{50}	Lawford et al., 1954
	mice	75	I.P.	Lethal dose	Christensen & Luginbyhl, 1974
	rabbits	?	dermal	Not corrosive to skin	Hanavan, 1975
	dogs	10	I.V.	Lethal dose	Dittmer, 1959
	dogs	500	I.P.	LD_{Lo}	NIOSH, 1976
	dogs	10	I.V.	LD_{Lo}	NIOSH, 1976
	cat	150	?	LD_{50}	Melnikov, 1971
	pigeon	65	I.M.	LD_{Lo}	NIOSH, 1976
2,4-Dinitrophenol	rats	30	oral	LD_{50}	Schafer, 1972
	rats	71	oral	LD_{50}; tremors, prostration, increased respiratory rate, tonic convulsions, rigor mortis prior to or immediately after death	Kaiser, 1964
	rats	32.7	I.P.	LD_{50}	Lawford et al., 1954

Table 2. Acute Effects - Nitrophenols (Cont'd.)

Compound	Organism	Dose (mg/kg)	Route	Response	Reference
2,4-Dinitrophenol (Cont'd.)	rats	35	I.P.	LD_{50} at 18-21° environmental temperature	Harvey, 1959
	rats	10-20	I.P.	Oxygen consumption increased 17-21%	Harvey, 1959
	rats	50	I.P.	100% mortality	Obbink & Dalderup, 1964
	rats	25	I.P.	25% mortality; average time to death was 94 minutes	Gatz & Jones, 1970
	rats	0.027-0.10	--	LD_{50}	Berg, 1976
	rats	31	I.P.	100% mortality; average time to death was 77 min.	Gatz & Jones, 1970
	rats	39	I.P.	100% mortality; average time to death was 12 min.	Gatz & Jones, 1970
	rats	60	I.P.	LD_{50}; tremors, prostration, increased respiration, tonic convulsions, rigor mortis prior to or immediately after death	Kaiser, 1964
	rats	25	S.C.	LD_{50}; 10 mg/kg caused no deaths while 50 mg/kg produced 100% mortality	Tainter & Cutting, 1933
	mice	72	oral	LD_{50}; tremors, prostration, increased respiratory rate, tonic convulsions, rigor mortis prior to or immediately after death	Kaiser, 1964
	mice	52	I.P.	LD_{50}; tremors, prostration, increased respiration, tonic convulsions, rigor mortis prior to or immediately after death	Kaiser, 1964
	mice	25.9	I.P.	LD_{50}	Ilivicky & Casida, 1969
	mice	26	I.P.	LD_{50}	Lawford et al., 1954

Table 2. Acute Effects - Nitrophenols (Cont'd.)

Compound	Organism	Dose (mg/kg)	Route	Response	Reference
2,4,-Dinitrophenol (Cont'd.)	mice	36	I.P.	LD_{50} at 18-21°C environmental temperature	Harvey, 1959
	mice	>5	I.P.	100% mortality at 39-41°C environmental temperature	Harvey, 1959
	mice	56	I.V.	LD_{50}; tremors, prostration, increased respiration, tonic convulsions, rigor mortis prior to or immediately after death	Kaiser, 1964
	mice	58	S.C.	LD_{50}; tremors, prostration, increased respiration, tonic convulsions, rigor mortis prior to or immediately after death	Kaiser, 1964
	rabbits	30	oral	LD_{50}	NIOSH, 1976
	rabbits	30	S.C.	LD_{50}	Tainter & Cutting, 1933
	dogs	30	oral	LD_{Lo}	NIOSH, 1976
	dogs	30	I.P.	Minimum lethal dose	Harvey, 1959
	dogs	22	S.C.	LD_{50}; no deaths were caused by doses up to 20 mg/kg but 25 mg/kg produced 100% mortality	Tainter & Cutting, 1933
	dogs	20-30	I.V.	LD_{50}	Tainter & Cutting, 1933
	dogs	15	I.V.	LD_{Lo}	NIOSH, 1976
	dogs	20	I.M.	LD_{50}	Tainter & Cutting, 1933
	dogs	15	I.M.	LD_{Lo}	NIOSH, 1976
	starling	46	oral	LD_{50}	Schafer, 1972
	blackbird	13	oral	LD_{50}	Schafer, 1972
	pigeon	7	I.M.	LD_{Lo}	NIOSH, 1976
	guinea pig	81	oral	LD_{50}	NIOSH, 1976
	guinea pig	700	skin	LD_{Lo}	NIOSH, 1976

Table 2. Acute Effects - Nitrophenols (Cont'd.)

Compound	Organism	Dose (mg/kg)	Route	Response	Reference
2,4,6-Trinitrophenol					
	cats	500 mg*	oral	Nausea, vomiting, fatigue pain, increased reflex excitability within 45 min. tonic & clonic convulsions, ascending paralysis causing death by respiratory failure	Von Oettingen, 1941
	dogs	60	?	Slowing of respiration and heart beat; death by respiratory paralysis; LD_{Lo}	Von Oettingen, 1941
	rabbits	400 mg*	?	Convulsions & death in 3 hours	Von Oettingen, 1941
	rabbits	140-250 mg*		Lowered body temperature, slowing of heart rate, rise & subsequent fall in blood pressure	Von Oettingen, 1941
	rabbits	350-1000 mg*	oral	Severe damage to the kidneys	Von Oettingen, 1941
	rabbits	120 mg/kg	oral	LD_{Lo}	NIOSH, 1976

* Total dose.

Table 3. Subchronic Effects - Nitrophenols

Organism	Route	Dose (mg/kg)	Response	Reference
2,4-Dinitrophenol				
Rats	Dietary	0.2% x 24 days	40% mortality; emaciation, enlarged spleen, slight renal degeneration; liver congestion, testicular atrophy, cloudy swelling of liver	Spencer et al., 1948
Rats	I.V., I.P.	20, twice daily x 3-4 days	urine volume increased up to 3.5 times w/in 12 hrs. for 5-7 days; renal damage including dilation of proximal tubules w/some dehydrated & necrotic cells; tubular reabsorption depressed	Eisenbach et al., 1967
Ducklings	Dietary	0.25% x 35 days	100% incidence of bilateral cataracts w/in 24 hrs.; 40% mortality after 35 days	Spencer et al., 1948
Guinea pigs	I.P.	10; daily	Cataracts in animals in 14-18 days fed w/Vit. C-deficient diet, Vit. C supplemented diet prevented cataracts	Ogino & Yasukura, 1957
p-Nitrophenol				
Guinea pigs	I.P.	25; daily	Cataracts developed in Vit. C-deficient animals in 7-11 days	Ogino & Yasukura, 1957

alone is a known teratogen; with 2,4-dinitrophenol the effects were even greater, resulting in increased embryo mortality and shortened upper beaks (Landauer and Clark, 1964).

iv) Other

Chronic administration of the mononitrophenol isomers to warm-blooded animals altered neurohumoral regulation. Pathological effects included gastritis, enteritis, colitis, hepatitis, neuritis, and hyperplasia of the spleen (Makhinya, 1969).

Rats fed 0.10% 2,4-dinitrophenol for 6 months suffered a reduction in body weight gain of 10-15% (Spencer et al., 1948).

e) Humans

Exposure in industry to picric acid is through skin or by inhalation. According to Schwartz (1944) chronic skin contact in munitions workers commonly results in sensitization dermatitis. Yellow coloration of skin and conjunctiva may also result, in addition to edema, papulae and vesicles with eventual desquamation, especially around the mouth and sides of the nose (ACGIH, 1971; Howard et al., 1976).

In systemic poisoning, darkened urine and albuminuria can occur; toxic doses may cause erythrocyte destruction (ACGIH, 1971).

Of the nitrophenols selected for study in this profile, 2,4-dinitrophenol (DNP) produces the most profound toxic effects. Its extensive use as an antiobesity drug three decades ago provided many examples for study. Of the estimated 100,000 persons treated for obesity with DNP, 8-23% developed cutaneous lesions and many also incurred cataracts. Other reactions observed include gastrointestinal disturbances, agranulocytosis of bone marrow, neuritis, cardiovascular complications, and hepatic and renal damage. Many fatalities were reported (Horner, 1942; Howard et al., 1976). Symptoms of subacute poisoning cover anorexia, nausea, vomiting, colic diarrhea, weight loss, night sweating, weakness, headaches, and dizziness. Acute exposures cause sudden pallor, severe thirst, profuse sweating, restlessness, dyspnea and moderate to severe hyperthermia (Horner, 1942; Parascandola, 1974). Suicidal doses reported by Swamy (1940) resulted in additional symptoms such as cyanosis, shock, incoherence, feeble pulse, rapid respiration, congested conjunctiva, with death following in 5-6 hours. Post mortem examinations revealed erosion of esophageal tissues and mucous membrane of the stomach.

Saita (1949) reports that toxic exposure to DNP caused hemolytic anemia, neutropenia and eosinophilia.

Horner (1942) further reports of fatalities occurring among DNP exposed alcoholics and persons with renal or hepatic diseases whose sensitivity to DNP was apparently greater due to these conditions.

8. TLV

The TLV established for picric acid is 0.1 mg/m^3 (ACGIH, 1971). This value is the same recommended by OSHA (Fed. Reg., 1974).

TLV's for the other nitrophenol compounds are not available.

9. Other Standards

No other standards were encountered.

10. Other Data

Table 4 lists the number of reported human exposures to various nitrophenols (NIOSH, 1977).

Table 4. Reported Occupational Exposures To Nitrophenols

Compound	Number of Exposures
m-, o-, p-Nitrophenols	13,800
2,4-Dinitrophenol	4,560

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NITROTOLUENES

1. Molecular Structures

2. Chemical Abstract Service Numbers

3. Registry of Toxic Effects of Chemical Substances Numbers

The above information for commercially significant nitrotoluene compounds selected for this profile is provided in Table 1, along with standard chemical nomenclature.

In choosing the compounds listed, consideration was given to the extent of production and use in industrial processes, as well as the likely toxicological hazard.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

o-Nitrotoluene

Approximate consumption of o-nitrotoluene is estimated to be 10-12 million lbs. annually (Howard et al., 1976).

It is used for the production of o-toluidine and other dye intermediates by at least several dye manufacturers (Howard et al., 1976; Gunn and Cooke, 1976).

o-Nitrotoluene is produced by DuPont (Deepwater, N.J.) and First Mississippi Corp. (Pascagoula, Miss.) (SRI, 1977).

m-Nitrotoluene

Approximately 1 million lbs. of m-nitrotoluene are produced per year based on production volumes of para- and ortho-isomers (SRC estimate).

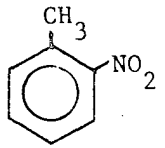
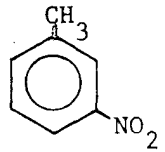
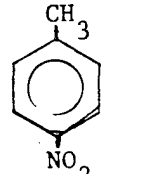
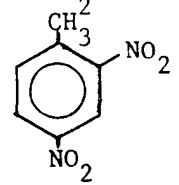
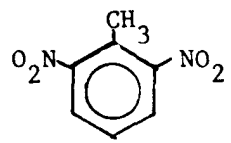
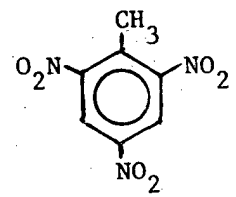
It is used by several dye manufacturers in the preparation of m-nitrobenzaldehyde, m-toluidine, and dye intermediates (Gunn and Cooke, 1976; Matsuguma, 1967a).

m-Nitrotoluene is manufactured by DuPont (Deepwater, N.J.) and First Mississippi Corp. (Pascagoula, Miss.) (SRI, 1977; USITC, 1975)

p-Nitrotoluene

Current production of p-nitrotoluene is estimated to be about 20-25 million lbs. annually. No growth projections are available.

Table 1. Compounds in the Nitrotoluene Class

Compound	CAS No.	RTES No.	Molecular Structure	Standard Chemical Name
o-Nitrotoluene	88-72-7	XT31500		2-Nitrotoluene
m-Nitrotoluene	99-08-1	XT29750		3-Nitrotoluene
p-Nitrotoluene	99-99-0	XT33250		4-Nitrotoluene
2,4-Dinitrotoluene	121-14-2	XT15750		2,4-Dinitrotoluene
2,6-Dinitrotoluene	606-20-2	XT19250		2,6-Dinitrotoluene
2,4- and 2,6-Dinitrotoluene (Mixture)	--	XT15750500		
2,4,6-Trinitrotoluene (TNT)	118-96-7	XU01750		2,4,6-Trinitrotoluene

Approximately 20-25% of production is used to produce 5-nitro-o-toluenesulfonic acid. The other 70-75% of production is used to make p-toluidine and other dye intermediates (Howard et al., 1976).

p-Nitrotoluene is produced by DuPont (Deepwater, N.J.) and First Mississippi Corp. (Pascagoula, Miss.) (SRI, 1977) and is probably used by at least five dye manufacturers.

2,4-Dinitrotoluene and 2,4 (and 2,6-)-Dinitrotoluene

In 1975, 308 million lbs. of 2,4-dinitrotoluene were produced while 273 million lbs. of 2,4 (and 2,6-)-dinitrotoluene were made (USITC, 1975). Based upon major use growth projections, the dinitrotoluene market should increase 6.5-7.5% per year (Gunn and Cooke, 1976).

The bulk of production is used to manufacture toluene diisocyanate (TDI). Other uses include gelatinizing and water-proofing in explosives and dye intermediates (Gunn and Cook, 1976).

2,4-Dinitrotoluene and 2,4 (and 2,6-)-dinitrotoluene are produced by the following companies at the listed locations:

Air Products & Chemicals	Pensacola, Fla.
DuPont	Deepwater, N.J.
Mobay	Cedar Bayou, Tex.
	New Martinsville, W.Va.
Rubicon Chem.	Geismar, La.

Eight companies produce TDI; in addition, several other companies probably use the chemical.

2,4,6-Trinitrotoluene

The production of 2,4,6-trinitrotoluene (TNT) in 1976 was estimated to be 48 million lbs. As TNT is used almost exclusively in the manufacture of military explosives, production is not expected to increase unless war breaks out (Gunn and Cooke, 1976). The producers are government-owned and contractor operated with facilities at the following locations (Howard et al., 1976):

Radford, Va.
Newport, Ind.
Chattanooga, Tenn.
Joliet, Ill.

7. Biological Effects of Exposure

a. Target Organs

Most of the literature reviewed for this profile centered on the toxicity of trinitrotoluene. No discussions regarding organs affected by either

Table 2. Acute Effects - Nitrotoluenes

Organism	Route	Dose	Response	Reference
2,4-Dinitrotoluene				
Rats	oral	50 mg/kg	no deaths	Hanavan, 1975
Rats	oral	268 mg/kg	LD_{50}	MacEwen & Vernot, 1972
Rats	inhal.	200 ppm	no deaths when inhaled for 1 hr.	Hanavan, 1975
Mice	oral	1625 mg/kg	LD_{50}	MacEwen & Vernot, 1972
Rabbits	topical	200 mg/kg	no deaths; not corrosive to skin	Hanavan, 1975
Cats	oral	27 mg/kg	minimum lethal dose	Spector, 1956
2,6-Dinitrotoluene				
Rats	oral	177 mg/kg	LD_{50}	NIOSH, 1976
Mice	oral	1000 mg/kg	LD_{50}	NIOSH, 1976
2,4- & 2,6-Dinitrotoluene (Mixed)				
Rabbits	topical	1000 mg/kg	approx. lethal dose; not corrosive to skin	Hanavan, 1975
m-Nitrotoluene				
Rats	oral	2282 mg/kg	LD_{50}	Hanavan, 1975
Rats	oral	1072 mg/kg	LD_{50}	Christensen & Luginbyhl, 1974
Rats	inhal.	200 ppm	no deaths when inhaled for 1 hr.	Hanavan, 1975
Mice	oral	330 mg/kg	LD_{50}	Kosachevskaya, 1967
Rabbits	oral	2400 mg/kg	LD_{50}	Kosachevskaya, 1967
Rabbits	topical	20 mg/kg	no deaths; not corrosive to skin	Hanavan, 1975
Guinea pigs	oral	3600 mg/kg	LD_{50}	Kosachevskaya, 1967
o-Nitrotoluene				
Rats	oral	2144 mg/kg	LD_{50}	Hanavan, 1975
Rats	oral	891 mg/kg	LD_{50}	Christensen & Luginbyhl, 1974
Rats	inhal.	200 ppm	no deaths when inhaled for 1 hr.	Hanavan, 1975
Mice	oral	2462 mg/kg	LD_{50}	Christensen & Luginbyhl, 1974
Rabbits	topical	200 mg/kg	no deaths; not corrosive to skin	Hanavan, 1975

Table 2. Acute Effects - Nitrotoluenes (Cont'd.)

Organism	Route	Dose	Response	Reference
p-Nitrotoluene				
Rats	oral	2144 mg/kg	LD_{50}	Christensen & Luginbyhl, 1974
Rats	oral	2144 mg/kg	LD_{50}	Hanavan, 1975
Rats	I.P.	939.4 mg/kg	100% mortality within 24-48 hrs.; 23.6 methemoglobin formation	Magos & Sziza, 1958
Rats	inhal.	200 ppm	no deaths when inhaled for 1 hr.	Hanavan, 1975
Mice	oral	1231 mg/kg	LD_{50}	Christensen & Luginbyhl, 1974
Rabbits	topical	200 mg/kg	no deaths; no corrosion to skin	Hanavan, 1975
2,4,6-Trinitrotoluene				
Rats	S.C.	> 700 mg/kg	lethal dose	Spector, 1956
Rabbits	S.C.	500-700 mg/kg	lethal dose	Spector, 1956
Rabbits	oral	500 mg/kg	LD_{Lo}	NIOSH, 1976
Cats	oral	480 mg/kg	lethal dose	Spector, 1956
Cats	S.C.	200 mg/kg	lethal dose	Spector, 1956
Cats	oral	1850 mg/kg	LD_{Lo}	NIOSH, 1976

nitrotoluene or dinitrotoluene were encountered, although Makotchenko (1974) notes that nitro-containing toluene compounds generally cause gastric secretion and central nervous system disorders in addition to adrenal cortical dysfunction.

McConnel and Flinn (1946) report that all organs suffered from trinitrotoluene poisoning, displaying extensive hemorrhage. The organ most commonly affected, however, is the liver. Pathological changes include enlargement and fatty dystrophy (Mul'menko and Levina, 1974; Djerassi and Vitany, 1975; Fairhall, 1957).

Also reported to suffer damage are gall bladder, stomach, adrenal cortex, and pancreas, all showing disturbances in their normal secretions (Kleiner, 1969, 1971, 1972; Kleiner et al., 1974; Soboleva, 1969; Makotchenko, 1974).

The central nervous system displays injury through peripheral neuropathy (Soboleva, 1969; Sollmann, 1957; Makotchenko, 1974; Jacob and Maroun, 1969).

Makienko and Karamanov (1973) report both carious and non-carious tooth damage and diseases of the oral cavity and periodontal mucous membranes. Exposure to trinitrotoluene among workers in TNT factories also causes severe dermatitis and skin irritation (Von Oettingen, 1941; Schwartz, 1944). Hassman and Juran (1968) found cataracts in over one-third of 61 workers in a TNT factory.

Other organs showing damage from trinitrotoluene exposure are the spleen, which may become enlarged (Djerassi and Vitany, 1975) and cardiac muscles (Sollman, 1957).

b. Acute Effects

Considerable variation apparently exists in the sensitivity among common mammalian species to poisoning by trinitrotoluene (Howard et al., 1976).

Table 2 summarizes the acute effects of poisoning by nitrotoluene compounds.

c. Subchronic Effects

Kovalenko (1973) found that rats fed nitrotoluene compounds for 1 to 3 months developed hematologic alterations. He noted that these compounds decreased in degree of toxicity as follows: trinitrotoluene > dinitrotoluene > m-nitrotoluene > p-nitrotoluene > o-nitrotoluene.

Dogs poisoned with trinitrotoluene suffered anemia with destruction of red blood cells, decreased hemoglobin levels, and a compensatory increase in reticulocyte count. Repeated injections to dogs also resulted in disturbances

Table 3. Subchronic Effects - Nitrotoluenes

Organism	Route	Dose	Response	Reference
2,4- & 2,6-Dinitrotoluene (Mixed)				
Rabbits	dermal	1000-10 doses/ 2 wks.	no cumulative toxicity	Hanavan, 1975
Trinitrotoluene				
Dogs	S.C.	20-50 mg/kg; every other day for 3 mos.	decreased bile secretion; increased cholic acid and bilirubin concentrations in bile; during third month cholic acids decreased and cholesterol increased	Kleiner, 1971
Dogs	oral	5-100 mg/kg x 2-3 doses	ataxia, diarrhea, incoordination, darkened urine	Kleiner, 1969, 1971, 1972; Kleiner et al., 1974
Dogs	oral	50 mg/kg/day x 12 wks.	CNS injury	Kleiner, 1969, 1971, 1972; Kleiner et al., 1974
Dogs	oral	2 mg/kg/day x 10 days	Signs of intoxication	Von Oettingen et al., 1944
Dogs	oral	100 mg/kg/day x 4 wks.	not fatal	Von Oettingen et al., 1944
Rats	oral	100 mg/kg; 3-30 days	decreased levels of total protein & albumin; increases in β- and γ-globulin in blood serum; protein-fatty dystrophy of liver; serotonin level decreased & activity of monoamine oxidase in liver & brain increased	Mulmenko & Levina, 1974
Rats	oral	100 mg/kg; daily for 45 days	decreased leukocyte phagocytic activity which was antagonized by 50 μg/kg Vit. B_{12} treatment or 5 mg/kg Vit. PP for the first 40 days of TNT administration	Kuzovleva et al., 1973
Rats	oral	30 mg/kg x 6 days	reduction in phagocytic activity	Jaffe et al., 1973
Rabbits	S.C.	200 mg/kg every other day x 17-57 days	All survived	Jaffe et al., 1973
Cats	S.C.	50 mg/kg/day x 4-9 days	fatal	Jaffe et al., 1973

Table 4. Chronic Effects - Nitrotoluenes

Organism	Route	Dose	Response	Reference
Trinitrotoluene				
Dogs	S.C.	0.1-1.0 or 5-20 mg/kg for 1.5 yrs.	Disruption of pancreatic exacrinous function; changes in pancreatic secretion volume & activities of trypsin, amylase, and lipase	Kleiner, 1971
Dogs	S.C.	0.1 or 5-20 mg/kg, every other day for up to 2.5 yrs.	elevated ammonia, phosphates, & lactic acid levels in the gastric juice	Kleiner, 1969
Dogs, Rats, & Rabbits	S.C.	5-20 mg/kg, every other day for 2 yrs.	changes in external secretory activity & incretory function of pancreas; dystrophy in acinic & incretory apparatus of the pancreas	Kleiner et al., 1974
Dogs	dermal and inhal.	up to 2 yrs.	disruption of secretory and evacuating functions of stomach; changes in volume of gastric secretion; acid & enzyme-forming functions displayed wave-like nature	Kleiner, 1972
Rats	oral	10 mg/kg; daily for 100 days	decreased leukocyte phagocytic activity which was antagonized by 50 µg/kg Vit. B_{12} treatment or 5 mg/kg Vit. PP for first 40 days of TNT administration	Kuzovleva et al., 1973

of bile, pancreatic, and gastric secretions (Kleiner, 1969, 1971, 1972; Kleiner et al., 1974).

Shils and Goldwater (1953) report that diet affects the susceptibility of rats to poisoning by 2,4-dinitrotoluene. Specifically, they claim that high fat diets increased resistance to injected 2,4-dinitrotoluene, but not when that compound was administered in the diet. On the other hand, high protein diets reduced mortality incidence from 2,4-dinitrotoluene poisoning, no matter how the compound was administered. Poisoning by trinitrotoluene, however, is not affected by diets high in either fat or protein.

Table 3 lists the effects of subchronic poisoning by the nitrotoluenes.

d. Chronic Effects

i) Carcinogenicity

No information on carcinogenicity was encountered.

ii) Mutagenicity

Spores of Actinomyces sphaeroides exposed to 0.001-0.004 M of p-nitrotoluene for 2 hours suffered decreased viability of 6-80% (Romanova and Rapoport, 1971).

iii) Teratogenicity

No information on teratogenicity was encountered.

iv) Other

The chronic effects of poisoning by trinitrotoluene are listed in Table 4.

e. Human Effects

In general, chronic poisoning by nitro-containing toluene compounds causes loss of adrenal cortex hormone activity, disturbances in gastric secretion, polyneuritis, and loss of muscular strength and energy (Makotchenko, 1974).

The early symptoms of poisoning by dinitrotoluene include headache, fatigue, chest pain, weight loss, nausea, and vomiting. Symptoms of more advanced poisoning are jaundice and secondary anemia (ACGIH, 1971a).

A review by Howard and coworkers (1976) reports that the acute effects of trinitrotoluene poisoning are liver damage, manifested by jaundice, with acute yellow atrophy, and aplastic anemia. Other common clinical symptoms are dermatitis, cyanosis, formation of sulfhemoglobin and methemoglobin, and gastrointestinal disturbances. They further indicate that severe aplastic anemia

observed among TNT workers may result from hemolysis of red blood cells, interference of hematopoiesis and depressed bone marrow function, which occur during TNT exposure.

Other changes in the blood resulting from acute and chronic TNT exposure include reduced hemoglobin levels and red blood cell counts accompanied by polychromasia, poikilocytosis, anisocytosis, reticulocytosis, and eosinophilia, along with increased leukocyte and lymphocyte counts (Jaffe et al., 1973).

Fatalities resulting from aplastic anemia due to TNT exposure were reported by several researchers (Hart et al., 1944; Eddy, 1944; Sievers et al., 1946).

McConnell and Flinn (1946) observed that nutritional state, concurrent illnesses, and age could alter susceptibility to TNT exposure. They found that hepatitis occurred most often in younger victims (average age 30) and aplastic anemia in older victims (average age 45). Fatalities resulted from both conditions. Liver damage included degeneration, atrophy, marked decrease in size and weight, and destruction of all parenchymal cells.

Also a major feature of TNT poisoning is its local irritating effect on skin and mucous membranes (El Ghawabi et al., 1974; Von Oettingen, 1941; Schwartz, 1944). The severe dermatitis and irritation linked to such exposure may possibly be due to an allergic sensitivity to TNT (Howard et al., 1976).

Tooth damage, both carious and non-carious, was reported by Makienko and Karamanov (1973). Nearly half of a group of 360 persons chronically exposed to small doses of TNT for at least 5 years showed only a single cataract as the sole symptom of poisoning (Zakharova and Manoilova, 1971).

Howard and coworkers (1976) cite a study by Sollmann (1957) which mentions cardiac muscle and menstrual irregularities resulting from TNT exposure as well.

Alcohol ingestion has been found to precipitate recurrences of symptoms of acute TNT intoxication (Jacob and Maroun, 1969; Hassman, 1971).

8. TLV

By analogy with the limits established for nitro- and dinitrobenzenes, a limit of 1.5 mg/m^3 has been set for dinitrotoluene (ACGIH, 1971a). This value is the same recommended by OSHA (Fed. Reg., 1974).

In order to prevent methemoglobin formation and other effects, the TLV for nitrotoluene has been established at 5 ppm (about 30 mg/m^3) (ACGIH, 1971b).

The TLV for trinitrotoluene is set at 1.5 mg/m^3 (ACGIH, 1971c). OSHA recommends the same value (Fed. Reg., 1974).

OSHA also recommends a standard TLV value of 5 ppm for the isomers of nitrotoluene (Fed. Reg., 1974).

9. Other Standards

Other TLV's for trinitrotoluene are as follows: 1.5 mg/m^3, Cook (1945); 1.5 mg/m^3 is too high, Smyth (1956); 1.5 mg/m^3, Elkins (1959); 1.0 mg/m^3, U.S.S.R. (1967) and Czechoslovakia (1969) (ACGIH, 1971c).

10. Other Data

Table 5 lists the number of reported human occupational exposures to various nitrotoluenes.

Table 5. Number of Reported Human Occupational Exposures To Nitrotoluenes (NIOSH, 1977)

Compound	No. of Exposures
o-, m-, p-Nitrotoluenes	8,190
2,4-Dinitrotoluene	6,780
Trinitrotoluene	6,780

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ORGANIC ANHYDRIDES

1. Molecular Structure

2. Chemical Abstracts Service (CAS) Number

3. Registry of Toxic Effects of Chemical Substances (RTECS) Number

The above information for the commercially significant organic anhydrides selected for this profile is listed in Table 1.

In choosing these compounds, consideration was given to the extent of production and use in industrial processes, in addition to the likely toxicological hazard regardless of the relative commercial significance of the compound.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Acetic Anhydride

In 1975, 1,458 million lbs. of acetic anhydride were produced (USITC, 1975), with an expected growth rate of 1% annually through 1979 (Chem. Prof., 1975b).

It is used primarily in the manufacture of cellulose acetate, with other minor uses as follows (Chem. Prof., 1975b):

Cellulose acetate	90%
Aspirin	1.4%
Other, including cellulose esters	8.6%

Producers of acetic anhydrides are the following (SRI, 1977):

Celanese Corp.	Pampa, Tex.
	Narrows, Va.
	Rock Hill, S.C.
Eastman Kodak	Kingsport, Tenn.
FMC	Meadville, Pa.
Union Carbide	Brownsville, Tex.

A large portion is captively used by producers to make cellulose acetate. Four companies produce aspirin.

Table 1. Organic Anhydrides

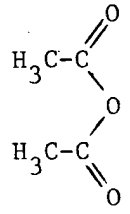
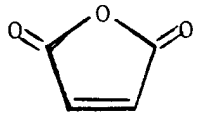
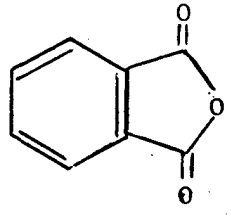
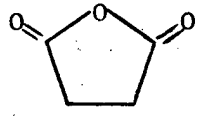
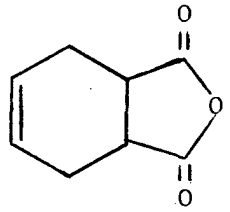
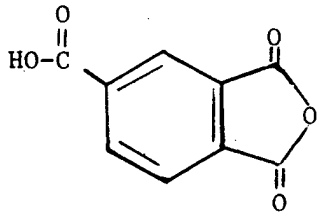
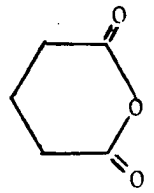
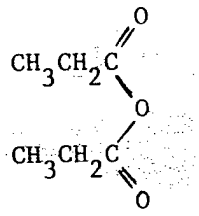
Compound	CAS No.	RTECS No.	Molecular Structure
Acetic anhydride	108-24-7	AK19250	
Maleic anhydride	108-31-6	ON36750	
Phthalic anhydride	85-44-9	TI31500	
Succinic anhydride	108-30-5	WN08750	

Table 1. Organic Anhydrides (Cont'd)

Compound	CAS No.	RTECS No.	Molecular Structure
Tetrahydrophthalic anhydride	85-43-8	GW57750	
Trimellitic anhydride	552-30-7	DC20500	
Glutaric anhydride	108-55-4	MA38500	
Propionic anhydride	123-62-6	UF91000	

Maleic Anhydride

In 1976, 264 million lbs. of maleic anhydride were produced (USITC, 1976). Growth rate is expected to be approximately 6% per year through 1979 (Chem. Prof., 1975a).

Usage breakdown is as follows (Chem. Prof., 1975a):

Polyester resins	61%
Fumaric acid	16%
Agricultural pesticides	9%
Alkyd resins	4%
Other	10%

The following companies produce maleic anhydride at the locations listed (SRI, 1977):

Allied Chem.	Moundsville, W.Va.
Koppers	Bridgeville, Pa.
	Cicero, Ill.
Monsanto	St. Louis, Mo.
Petro-Tex	Houston, Tex.
Reichhold Chem.	Morris, Ill.
	Elizabeth, N.J.
Tenneco	Fords, N.J.
USS Chem.	Neville Island, Pa.

There are many users of maleic anhydride.

Phthalic Anhydride

In 1976, 902 million lbs. of phthalic anhydride were produced (USITC, 1976). Growth is expected to rise at a rate of 6.5% annually through 1981 (Chem. Prof., 1977a).

It is used mainly in the production of plasticizers. Breakdown of usage is as follows (Chem. Prof., 1977a):

Plasticizers	53%
Alkyd resins	21%
Polyester resins	20%
Misc.	6%

The producers of phthalic anhydride are the following companies (Chem. Prof., 1977a):

Allied Chem.	El Segundo, Cal.
BASF Wyandotte	Kearing, N.J.
Chevron Chem.	Richmond, Cal.
Exxon	Baton Rouge, La.

Hooker	Arecibo, P.R.
Koppers	Bridgeville, Pa.
	Cicero, Ill.
Monsanto	Bridgeport, N.J.
	Texas City, Tex.
Stepan	Millsdale, Ill.
U.S. Steel	Neville Is., Pa.

There are many users of phthalic anhydride.

Succinic Anhydride

In 1971 and 1974, 0.5 to 1.0 million lbs. of maleic anyhydride were consumed to make succinic acid anhydride (Blackford, 1976). Therefore, production of succinic acid anhydride was about 0.5 to 1.0 million lbs. per year.

Succinic anhydride is used in the production of synthetic adhesive resins, alkyd resins, elastomers, lubricants, pharmaceuticals, photographic chemicals, plastics and resins, synthetic fibers, and textiles (Turi, 1969).

Allied Chemicals (Buffalo, N.Y.) produces succinic anhydride (SRI, 1977).

Tetrahydrophthalic Anhydride

In 1974, less than 2 million lbs. of maleic anhydride were used to make tetrahydrophthalic anhydride (Blackford, 1976). This would mean that less than 3 million lbs. of this compound were produced in 1974.

It is used to produce unsaturated polyester resins and alkyd resins with increased resistance to water and solvents (Blackford, 1976).

Petro-Tex Chemicals (Houston, Tex.) produces tetrahydrophthalic anhydride. Perhaps 30 to 50 producers of polyester and alkyd resins are users or potential users of this compound.

Trimellitic Anhydride

In 1975, 16.2 million lbs. of trimellitic acid esters were produced (USITC, 1975). These esters are made from trimellitic anhydride (Towle et al., 1968). The production of trimellitic anhydride, therefore, may have been in the range of 8 to 10 million lbs. Although production of the esters fell sharply from 1974 to 1975 (almost 40%), it can be expected that growth will rebound at a rate of almost 10% per year (SRC estimate). Industry capacity for trimellitic anhydride is 50 million lbs. annually (Connolly, 1976).

This compound is used in water-based alkyds as a surface coating and in the production of esters that are used as plasticizers (Towle et al., 1968; Connolly, 1976).

Amoco Chemicals (Joliet, Ill.) produces trimillitic anhydride (Connolly, 1976).

About 12 different ester producers are listed by USITC (1975). In addition, manufacturers of surface-coatings will also use this compound.

Glutaric Anhydride

Information for production and uses are not available for this compound.

Glutaric anhydride is produced by Aldrich Chem. (Milwaukee, Wis.) and Union Carbide (Institute and S. Charleston, W. Va.) (SRI, 1977).

Propionic Anhydride

Production figures are not available.

Propionic anhydride is used as an esterifying agent for certain perfume oils, fats, oils, and especially cellulose. It is used in the production of alkyd resins, dyestuffs, and drugs, and has been used as a dehydrating agent in some sulfonations and nitrations (Windholz et al., 1976). It also has major use in the production of cellulose tripropionate and cellulose acetate propionate for plastics and fibers (Wocasek, 1968).

Eastman Kodak (Kingsport, Tenn.) and Union Carbide (Institute and S. Charleston, W. Va.) produce propionic anhydride (SRI, 1977).

7. Biological Effects of Exposure

a. Target Organs

Acetic, maleic, and phthalic anhydrides exert their highly irritating effects on the eyes, skin, and upper respiratory tract with possible injury to the lungs (Hunter, 1976; Hamilton and Hardy, 1974a, 1974b; Moeschlin, 1965; ACGIH, 1971a, 1971b, 1971c). Symptomology of these effects is covered in Section 7e (Human Effects).

b. Acute Effects

The acute effects of exposure to the various organic anhydrides are presented in Table 2.

c. Subchronic Effects

No information was encountered on subchronic effects.

d. Chronic Effects

i) Carcinogenicity - Succinic anhydride is reported to be carcinogenic (NIOSH, 1976); no information is available on the nature of the testing.

Table 2. Acute Effects of Organic Anhydrides

Organism	Route	Dose (mg/kg)	Response	Reference
Acetic anhydride				
Rats	Oral	1780	LD_{50}	NIOSH, 1976
Rats	Inhalation	1000 ppm x 4 H	LC_{Lo}	Carpenter et al., 1949
Rabbits	Skin	4000	LD_{50}	NIOSH, 1976
Maleic anhydride				
Rats	Oral	850	LD_{Lo}	NIOSH, 1976
Mice	Oral	60	LD_{50}	Boyland, 1940
Phthalic anhydride				
Rats	Oral	800-1600	LD_{50}	Patty, 1963
Rats	Oral	4020	LD_{50}	NIOSH, 1976
Guinea Pig	Oral	100	LD_{Lo}	NIOSH, 1976
Guinea Pig	I.P.	<100	LD_{50}	Patty, 1963
Tetrahydrophthalic anhydride				
Rats	Oral	4590	LD_{Lo}	Marhold, 1972
Mice	I.P.	500	LD_{Lo}	NIOSH, 1976
Trimellitic anhydride				
Mice	Oral	2500	LD_{50}	NIOSH, 1976
Glutaric anhydride				
Rats	Oral	4460	LD_{Lo}	NIOSH, 1976
Rabbits	Skin	1780	LD_{Lo}	NIOSH, 1976
Propionic anhydride				
Rats	Oral	2360	LD_{50}	NIOSH, 1976

Table 3. Chronic Effects of Organic Anhydrides

Organism	Route	Dose	Response	Reference
Succinic anhydride				
Rats	SCU	2600 mg/kg x 65 wks	TD_{Lo}	NIOSH, 1976
Maleic anhydride				
Rats	SCU	1 mg twice weekly x 61 weeks	TD_{Lo}; local fibrosarcoma formation	Dickens and Jones, 1963

ii) Mutagenicity - No information is available.

iii) Teratogenicity - No information is available.

iv) Other - Table 3 lists the effects of chronic administration of succinic and maleic anhydrides.

e. Human Effects

Acetic, maleic, and phthalic anhydrides are all strong irritants to eyes, skin, and upper respiratory tract, and are sometimes damaging to the lungs (ACGIH, 1971a, 1971b, 1971c).

Skin exposure to acetic anhydride causes a delayed bulbous dermatitis with a great deal of desquamation (Hunter, 1976), while exposure to the liquid will result in skin burns and serious corneal injury (ACGIH, 1971a). It is also a strong lachrymator (Hamilton and Hardy, 1974a; ACGIH, 1971a).

Exposure to phthalic and maleic anhydrides cause similar irritations to the skin and, in addition, are greatly irritating to the mucous membranes of the upper respiratory tract. Symptoms include rhinitis, nose bleeding, and bronchitis (Moeschlin, 1965; ACGIH, 1971b, 1971c). Windholz et al. (1976) claim that pulmonary edema may also occur.

All three anhydrides have been noted to be skin sensitizers. Maleic and phthalic anhydrides may also cause pulmonary sensitization (Hamilton and Hardy, 1974a; ACGIH, 1971b, 1971c).

No systemic effects are known for these three compounds (ACGIH, 1971a; Hamilton and Hardy, 1974b).

Extended industrial exposure to maleic and phthalic anhydrides have been shown to induce fatigue and general weakness (Moeschlin, 1965).

8. TLV

The TLV's recommended by ACGIH (1971a, 1971b, 1971c) for organic anhydride are as follows:

Acetic anhydride	5 ppm (20 mg/m^3)
Maleic anhydride	0.25 ppm (1 mg/m^3)
Phthalic anhydride	2 ppm (12 mg/m^3)

The TLV for acetic anhydride was chosen by analogy with acetic acid, while the value for maleic anhydride was chosen on the basis of its analogous but more toxic action compared with phthalic anhydride (ACGIH, 1971a, 1971b, 1971c).

9. Other Standards

The standards recommended by OSHA (Fed. Reg., 1974a, 1974b, 1974c) are the same as those given by ACGIH (1971a, 1971b, 1971c).

The U.S.S.R. and Czechoslovakia (1969) recommended TLV's for phthalic anhydride are 0.2 ppm and 1 ppm, respectively (ACGIH, 1971c).

10. Other

Table 4 lists the number of reported human occupational exposures to organic anhydrides (NIOSH, 1977).

Table 4. Reported Human Occupational Exposures To Organic Anhydrides (NIOSH, 1977)

Compound	Number of Exposures
Phthalic anhydride	66,810
Maleic anhydride	30,900
Acetic anhydride	13,290
Trimellitic anhydride	18,090
Tetrachlorophthalic anhydride	60
Propionic anhydride	60

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1. Molecular Formula

2. Chemical Abstracts Service (CAS) Number

3. Registry of Toxic Effects of Chemical Substances (RTECS) Number

The above information for the compounds chosen for this profile is listed in Table 1. The compounds listed were selected on the basis of commercial significance, with consideration being given to the likely toxicological hazard, regardless of commercial significance.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Arsanilic Acid (and sodium salt)

No individual production figures are available; however, of the 5.9 million lbs. of all arsenic and bismuth medicinals produced in 1974 (USITC, 1974), arsanilic acid is believed to share a respectable percentage of the total (SRC estimate).

In addition to its common use as a feed additive for poultry (Carapella, 1963; Ertel, 1976), arsanilic acid is also an intermediate in the synthesis of N-carbamoylarsanilic acid, an anti-protozoan agent (Lawler, 1977).

The following companies produce arsanilic acid (SRI, 1977):

Abbott Labs	N. Chicago, Ill.
Fleming Labs	Charlotte, N.C.
Rohn & Haas	Myerstown, Pa.

Carbarsone (N-Carbamoylarsanilic Acid)

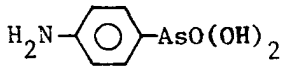
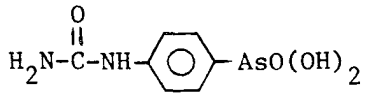
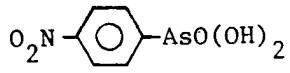
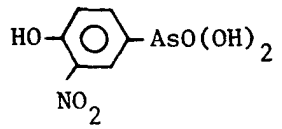
Production figures are not available.

Carbarsone is used as an anti-protozoan agent (Lawler, 1977).

The following companies produce N-carbamoylarsanilic acid (SRI, 1977):

Eli Lilly	Lafayette, Ind.
Polychemical Labs	Bronx, N.Y.
Rohn & Haas	Myerstown, Pa.
R.S.A. Corp.	Ardsley, N.Y.

Table 1. Organoarsenicals

Compound	CAS No.	RTECS No.	Molecular Formula
Arsanilic acid (p-Aminobenzenearsonic acid)	98-50-0	CF78750	
Carbarsone (N-Carbamoylarsanilic acid) (p-Ureidobenzenearsonic acid)	121-59-5	CF92750	
Nitarsone (p-Nitrobenzenearsonic acid)	98-72-6	CY61250	
Roxarsone (4-Hydroxy-3-nitrobenzenearsonic acid)	121-19-7	CY52500	

Nitarsone (p-Nitrobenzenearsonic Acid)

No production figures are available.

Nitarsone, an anti-protozoan agent, is produced by Salsbury Labs (Charles City, Iowa) (USITC, 1975).

Roxarsone

No production figures are available.

An anti-protozoan agent, roxarsone is produced by Salsbury Labs (Charles City, Iowa) (USITC, 1975).

Table 2 lists organoarsenical pesticides (SRI, 1977; Lawler, 1977; USITC, 1975; Spencer, 1968; Farm. Chem., 1972).

7. Biological Effects of Exposure

The experimental and industrial toxicology of arsenic and arsenic compounds has been reviewed in some detail by Browning (1969), Hunter (1975), and Moeschlin (1965). However, for the industrially significant organoarsenicals identified in this profile, these reviews are of limited use because they do not include important experimental studies and often do not identify the individual arsenicals under discussion. Consequently, much of the information in this profile is drawn from primary references cited by NIOSH (1976) and various other sources.

a. Target Organs

The pathological effects of acute oral intoxication with N-carbamoylarsanilic acid were examined by David and coworkers (1931) in guinea pigs, rabbits, and cats. Organ damage was found to be essentially similar to that elicited in rabbits and cats by 3-acetyl-amino-4-hydroxyphenylarsonic acid (Anderson and Leake, 1930). On gross examination, lethal doses caused: distention of the stomach, large intestine, and bladder; congestion of the lungs, liver, and kidneys; and occasional hemorrhage in the kidneys. Microscopically, major findings included: congestion of the lungs, liver, spleen, and kidney; tubular degeneration of the kidneys with occasional hemorrhages; moderate granulation of cardiac fibers; and disorganization of muscle fibers in the stomach.

Hemorrhagic effects, along with signs of gastrointestinal irritation, have been noted in acute oral intoxication of chickens, turkeys, rats, and dogs with 4-hydroxy-3-nitrobenzenearsonic acid (Kerr et al., 1963). On necropsy all organisms exhibited dose-related inflammation of the intestines and liver. Chickens and turkeys also had hemorrhages in the gall bladder, spleen, and kidneys. In rats, additional findings included hemorrhagic nephritis and adrenal hemorrhage. Dogs developed generalized jaundice, congestion of the kidneys, hematuria, sometimes severe hemorrhages along the gastrointestinal tract, and localized hemorrhages in the lungs. In rats, additional organ

Table 2. Organoarsenical Pesticides

Bis(dimethylthiocarbamylthio)methyl arsine
Dimethylarsinic acid (cacodylic acid)
Disodium methanearsonate (DSMA)
Methylarsinic sulfide
Copper aceto-arsenite (Paris Green)
Ammonium methanearsonate (AMA)
Monosodium methanearsonate (MSMA)
Monoammonium methanearsonate (MAMA)
Calcium acid methanearsonate (CAMA)
Amine methanearsonate
Methylarsine oxide
Methylarsine sulfide

damage from acute oral exposure included nephritis and gastritis. In a 90 day rat feeding study of 4-hydroxy-3-nitrobenzenearsenic acid at dietary levels of 25 to 200 ppm, irritation of the intestinal tract, as well as paleness of the spleen and kidneys, were the major signs of organ damage (Kerr et al., 1963).

Browning (1969) reported that organic arsenicals, especially trivalent compounds, have caused serious eye injury.

b. Acute Effects

Information on the acute toxicity of selected organoarsenicals is summarized in Table 3. Except for N-carbamoylarsanilic acid and 4-hydroxy-3-nitrobenzenearsonic acid, few details have been obtained on the acute toxic effects of these chemicals.

The major signs of acute N-carbamoylarsanilic acid intoxication in guinea pigs, rabbits, and cats were lethargy, anorexia, and soft stools. In fatal exposures, death occurred 3 to 14 days after dosing. Constriction of the pupils, bloating of the abdomen, muscle relaxation, increased respiration, and convulsions occurred just prior to death. Monkeys tolerated five daily oral doses of 100 mg/kg (David et al., 1931). Sandground (1944) noted that the acute toxic effects of intraperitoneal injections of both N-carbamoylarsanilic acid and arsanilic acid to rats could be antagonized by pretreatment with para-aminobenzoic acid and a variety of other aromatic compounds. The antagonistic effect appeared to be related to free carboxyl groups and was assumed to be caused by chemical combination of the antagonist with the arsenical. Based on acute oral toxicity studies in rabbits and cats, Leake and coworkers (1930) noted that the toxicity of N-carbamoylarsanilic acid is reduced by replacing the oxygen in the carbamide group with sulfur.

The limited data on the acute toxic effects of 4-hydroxy-3-nitrobenzenearsonic acid suggests a pattern somewhat different than that noted above. In acute oral intoxications of chickens, dogs, and rats, the onset of acute toxic effects was rapid and no signs of delayed toxicity were noted. In fatal exposures, death occurred within 48 hours. In rats, the major signs of toxicity were progressive weakness and incoordination of the hindquarters. In chickens, marked depression of rapid onset was the primary sign prior to death (Kerr et al., 1963).

Age may affect the response of some organisms to acute poisoning. Goldenthal (1971) noted that 1 to 3 day old Sprague-Dawley rats were more susceptible to arsanilic acid (LD_{50} 216 mg/kg) than adult Charles River rats (LD_{50} > 1000 mg/kg). Although this specific effect may have been due to strain differences, young rats are often more susceptible to toxicants than adult rats. No effect of age on susceptibility to acute oral intoxication by 4-hydroxy-3-nitrobenzenearsonic acid was noted by Kerr and coworkers (1963) in studies on 3 and 12 week old chickens.

Table 3. Acute Toxicity of Several Organoarsenicals

Compound	Organism	Route	Dose	Effect	Reference
Arsanilic acid	Rat, young	Oral	216 mg/kg	LD_{50}	Goldenthal, 1971
	Rat, adult	Oral	>1000 mg/kg	LD_{50}	Goldenthal, 1971
	Rat	Intraperitoneal	400 mg/kg	Lethal	Sandground, 1944
N-Carbamoylarsanilic acid	Rat	Oral	510 mg/kg	LD_{50}	NIOSH, 1976
		Intraperitoneal	1000 mg/kg	Lethal	Sandground, 1944
	Rabbit	Oral	200 mg/kg	Lethal	David et al., 1931
	Cat	Oral	250 mg/kg	Lethal	David et al., 1931
	Guinea pig	Oral	200 mg/kg	Lethal	David et al., 1931
Cupric acetoarsenite	Rat	Oral	22 mg/kg	LD_{50}	NIOSH, 1976
	Unspecified mammal	Oral	18 mg/kg	LD_{50}	NIOSH, 1976
Hydroxydimethyl arsine oxide (Cacodylic acid)	Rat	Oral	1350 mg/kg	LD_{50}	NIOSH, 1976
	Mouse	Intraperitoneal	500 mg/kg	LD_{Lo}	NIOSH, 1976
		Unspecified	185 mg/kg	LD_{50}	NIOSH, 1976
	Dog	Subcutaneous	1000 mg/kg	LD_{Lo}	NIOSH, 1976
4-Hydroxy-3-nitrobenzenearsonic acid	Rat	Oral	155 mg/kg	LD_{50}	Kerr et al., 1963
		Intraperitoneal	66 mg/kg	LD_{50}	Kerr et al., 1963
Methanearsonic acid, calcium salt	Mouse	Intraperitoneal	500 mg/kg	LD_{50}	NIOSH, 1976
Methanearsonic acid, disodium salt	Rat	Oral	1800 mg/kg	LD_{50}	NIOSH, 1976
	Unspecified mammal	Oral	1000 mg/kg	LD_{50}	NIOSH, 1976

Table 3. Acute Toxicity of Several Organoarsenicals (Cont'd)

Compound	Organism	Route	Dose	Effect	Reference
Methanearsonic acid, monosodium salt	Rat	Oral	700 mg/kg	LD_{50}	NIOSH, 1976
	Unspecified mammal	Unspecified	50 mg/kg	LD_{50}	NIOSH, 1976
p-Nitrobenzenearsonic acid	Rat	Oral	100 mg/kg	LD_{Lo}	NIOSH, 1976
Sodium cacodylic acid	Rabbit	Subcutaneous	500 mg/kg	LD_{Lo}	NIOSH, 1976

c. Subchronic Effects

Several subchronic studies have been conducted on 4-hydroxy-3-nitrobenzenearsonic acid. In weanling female rats, dietary levels of 12.5 ppm over 78 days resulted in a significant increase in weight gain. This effect was not seen at levels of 25 to 200 ppm or in rats on a vitamin deficient diet (Kessler et al., 1954). Weaned pigs on diets containing 50, 100, and 200 ppm of this compound for 4 weeks also evidenced an increased weight gain. However, at 200 ppm, signs of incoordination and sensitivity to touch developed after 2 to 3 weeks. After 4 weeks, the animals lost control of the rear limbs, were unable to stand, and could not control urination. Similar, but less severe, effects were noted in animals on diets of 100 ppm for 5 weeks. Diets of 50 ppm for 5 weeks produced no signs of adverse effects (Carpenter, 1951). In rats and chickens, dietary levels of 400 ppm were lethal over 90 day periods. Levels of 25 to 200 ppm caused no mortality. Because renal damage - a typical sign of inorganic arsenic poisoning - was not noted in fatally exposed animals, Kerr and coworkers (1963) suggested that the subchronic toxic effects of 4-hydroxy-3-nitrobenzenearsonic acid were not attributable to the in vivo generation of inorganic arsenic from this compound.

d. Chronic Effects

i) Carcinogenicity - In female rats, single oral doses of N-carbamoylarsanilic acid at 500 mg/rat induced a lobular carcinoma of the breast in one of 19 animals surviving the 6 month observation period. No breast carcinomas were noted in 89 control rats (Griswold et al., 1966). NIOSH (1976) summarizes a study indicating that hydroxydimethyl arsine oxide caused neoplasms in mice after subcutaneous administration of a total dose of 464 mg/kg.

ii) Mutagenicity and Teratogenicity - No studies have been encountered on these effects.

iii) Other Chronic Effects - In two year feeding studies of 4-hydroxy-3-nitro-benzenearsonic acid at dietary levels of 50 and 200 ppm, no adverse effects were noted in dogs, rats, or mice. Similarly, dermal application of a 1% solution at 2 drops per application, 3 applications per week, for one year caused no adverse effects in mice. Single subcutaneous injections of 12 mg/female mouse and 5 mg/male mouse were also without apparent effect over a two year observation period (Prier et al., 1963).

e. Human Effects

Cupric acetoarsenite has been implicated in human occupational poisoning. Browning (1969) summarized a case in which a worker chronically exposed to this chemical developed severe gastrointestinal symptoms, exfoliative dermatitis, conjuctivitis, upper respiratory tract irritation, and polyneuritis. Hunter (1975) cited this chemical as a cause of chronic arsenical poisoning in workers. Symptoms reportedly included coryza, vomiting, conjunctivitis, laryngitis, and dermatitis. Hunter (1975) also indicated that this chemical has been implicated in two cases of skin cancer in chronically exposed workers.

Moeschlin (1965) reported that N-carbamoylarsanilic acid, which has been used as an antiamoebic agent, caused several cases of severe and sometimes fatal poisoning.

8. TLV's

The time-weighted average TLV for arsenic and its compounds is 0.5 mg/m^3 (ACGIH, 1971). Specific standards have not been set for the organoarsenicals under review.

9. Other Standards

No other standards have been encountered for the organoarsenicals under review.

10. Other Data

Table 4 lists the number of reported human exposures to various organoarsenicals (SRI, 1977).

Table 4. Reported Human Exposure to Organoarsenical Compounds

Compound	No. of Exposures
Arsanilic acid	4,650
Cacodylic acid (dimethylarsinic acid)	6,000

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ORGANOISOCYANATES

1. Molecular Structure

2. Chemical Abstracts Service (CAS) Number

3. Registry of Toxic Effects of Chemical Substances (RTECS) Number

The above information for the organoisocyanates selected for this profile is listed in Table 1.

In choosing the compounds listed, consideration was given to the extent of production and use in industrial processes, as well as the likely toxicological hazard regardless of the relative commercial significance of the compounds.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Toluene-2,4-diisocyanate and Toluene-2,6-diisocyanate

In 1975, 479 million lbs. of toluene diisocyanate (TDI) were produced in an 80%-20% mixture of the 2,4- and 2,6-isomers, respectively (USITC, 1975). Therefore, about 383 million lbs. of the 2,4-isomer were made, and 96 million lbs. of the 2,6-isomer.

Growth for the TDI market is projected at 8-10% per year through 1981 (Chem. Prof., 1977c).

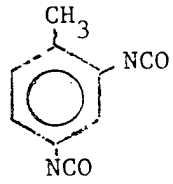
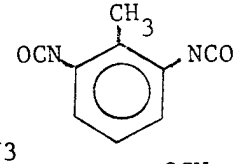
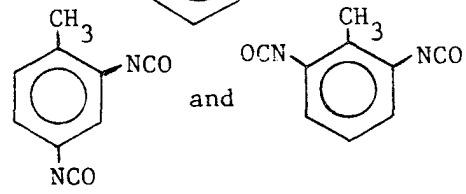
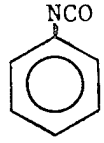
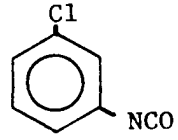
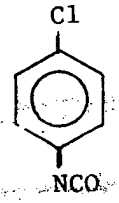
TDI is used for the following purposes (Lawler, 1977):

Flexible urethane foam	69%
Polyurethane coatings	4%
Elastomers & misc.	2%
Exports	25%

The producers of TDI are the companies listed below (SRI, 1977):

Allied Chem.	Moundsville, W.Va.
BASF Wyandotte	Geismar, La.
Dow	Freeport, Tex.
DuPont	Deepwater Point, N.J.
Mobay	New Martinsville, W.Va.
	Cedar Bayou, Tex.
Olin	Astabula, Ohio
	Lake Charles, La.
Rubicon	Geismar, La.
Union Carbide	Institute, W.Va.

Table 1. Organoisocyanates

Compound	CAS Number	RTECS Number	Molecular Structure
Toluene-2,4-diisocyanate (TDI)	584-84-9	CZ63000	
Toluene-2,5-diisocyanate (TDI)	91-08-7	---	
Toluene-2,4- and 2,6-diisocyanate (TDI)	---	CZ63000500	
Methyl isocyanate	624-83-9	NQ94500	CH_3-NCO
Phenyl isocyanate	103-71-9	DA36750	
m-Chlorophenyl isocyanate	2909-38-8	NQ85000	
p-Chlorophenyl isocyanate	104-12-1	NQ85750	

Methyl Isocyanate

U.S. consumption of methyl isocyanate reportedly reached 27-30 million lbs. in 1975 (Soder, 1976). Based on growth rates of its derivatives, methyl isocyanate's production should grow at the rate of 5-10% per year.

Virtually all of the methyl isocyanate produced in the U.S. is consumed by about a dozen companies as an intermediate in the manufacture of pesticides (Soder, 1976). About 60% of the consumption is used for carbaryl (Sevin®) production.

Story Chemicals (Muskegon, Mich.) and Union Carbide (Institute, W.Va.) produce methyl isocyanate (SRI, 1977).

Phenyl Isocyanate

Based on consumption figures for herbicides synthesized from phenyl isocyanate (Ayers et al., 1976), production of phenyl isocyanate was about 0.2 million lbs. in 1975. The market for phenyl isocyanate-derived herbicides is expected to remain constant for the next five years (Soder, 1976).

This compound is used as an intermediate in the production of specialized herbicides, namely propham and Tupersan® (Ayers et al., 1976).

Production is performed by the following companies (SRI, 1977):

Mobay	New Martinsville, W.Va.
Story Chem.	Muskegon, Mich.
Upjohn	La Porte, Tex.

The two herbicide producers (PPG and DuPont) are probably the main users of phenyl isocyanate.

m-Chlorophenyl Isocyanate and p-Chlorophenyl Isocyanate

Based on consumption figures for herbicides synthesized from chlorophenyl isocyanates in 1975 (Ayers et al., 1976), production was about 1 million lbs. and 0.2 million lbs. for m-chlorophenyl isocyanate and p-chlorophenyl isocyanate, respectively.

The market for herbicides made from these chemicals is expected to remain constant for the next five years (Soder, 1976).

Both chemicals are used as intermediates in the production of herbicides, as shown below (Ayers et al., 1976):

Compound	Herbicide	Herbicide Producer
m-chlorophenyl isocyanate	Furloe®	PPG
	Carbyne®	Gulf
p-chlorophenyl isocyanate	Telvar®	DuPont

Mobay (New Martinsville, W.Va.) produces m-chlorophenyl isocyanate, while Mobay and Story Chemicals (Muskegon, Mich.) produce p-chlorophenyl isocyanate (SRI, 1977).

The main users are probably those herbicide producers shown above.

7. Biological Effects of Exposure

The acronym TDI generally designates toluene-2,4-diisocyanate in the literature, although it occasionally refers to mixtures of unspecified proportions of the 2,4- and 2,6-isomers. Additional detailed information on TDI may be found in the NIOSH criteria document, "Occupational Exposure to Toluene Diisocyanate."

a. Target Organs

TDI has been shown to be a potent inhalation irritant with qualitatively similar effects in rats, mice, guinea pigs, and rabbits (Duncan et al., 1962; Zapp, 1957). The upper respiratory tract is affected, primarily in the trachea and larger intrapulmonary air passages. The skin, eyes, and gastrointestinal tract are also susceptible to irritation.

Inhalation of methyl isocyanate also results in lung damage and is corrosive when applied dermally to rabbits (ACGIH, 1971a).

b. Acute Effects

During acute inhalation toxicity testing of TDI in mice, rats, guinea pigs, and rabbits, all species exhibited mouth breathing, lacrimation, and salivation. The characteristic terminal response was one of gasping for air (Duncan et al., 1962). Zapp (1957) showed that a concentration of 600 ppm x 6 hours was lethal to rats, whereas 60 ppm x 6 hours was not. Those dying showed acute pulmonary congestion and edema. Acute oral, inhalation, and skin toxicities are tabulated in Table 2.

To determine the sequence of pathologic changes, Duncan et al. (1962) exposed mice, rats, guinea pigs, and rabbits to 2, 5, or 10 ppm TDI for four hours and serially sacrificed them up to four weeks following the single exposure. The reaction was similar between species and was generally limited to the trachea and lungs. The initial reaction to 2 ppm consisted of focal desquamation of necrotic superficial epithelium with virtually complete healing by the seventh post-exposure day. Both 5 and 10 ppm produced the same basic response. Two hours following exposure the response was characterized by subepithelial edema, necrosis, ulceration of tracheal and bronchial epithelium, and mild infiltration of acute inflammatory cells. A pseudomembrane formed in the larger air passages of some animals. Seven days after exposure bronchopneumonia had developed. Subsequently, ulcerated areas were either re-epithelialized or granulation tissue occluded the lumen of the bronchioles. Fibrous tissue infiltrated the walls of the air passages. The findings at two and four weeks represented a more advanced pattern of bronchiolitis fibrosa obliterans in all species.

Table 2. Acute Toxicity of Organoisocyanates

Compound	Organism	Route	Dose	Effect	Reference
Toluene diisocyanate	Rat	Oral	5800 mg/kg	LD_{50}	Zapp, 1957
	Rat	Oral	6170 mg/kg	LD_{50}	NIOSH, 1976
	Rat	Inhalation	14 ppm x 4 hrs	LC_{50}	Duncan et al., 1962
	Mouse	Inhalation	10 ppm x 4 hrs	LC_{50}	Duncan et al., 1962
	Rabbit	Inhalation	11 ppm x 4 hrs	LC_{50}	Duncan et al., 1962
	Rabbit	Inhalation	8 ppm x 4 hrs	LC_{50}	NIOSH, 1976
	Guinea pig	Inhalation	13 ppm x 4 hrs	LC_{50}	Duncan et al., 1962
Methyl isocyanate	Rat	Oral	71 mg/kg	LD_{50}	Smyth et al., 1969
	Rat	Inhalation	21 ppm x 2 hrs	LC_{50}	ACGIH, 1971a
	Rat	Inhalation	5 ppm x 4 hrs	LC_{50}	ACGIH, 1971a
	Mouse	Inhalation	37 mg/m^3 x 1 hr	LC_{Lo}	NIOSH, 1976
	Guinea pig	Inhalation	37 mg/m^3 x 1 hr	LC_{Lo}	NIOSH, 1976
	Rabbit	Skin	220 mg/kg	LD_{50}	Smyth et al., 1969
m-Chlorophenyl isocyanate	Rat	Inhalation	60 mg/m^3 x 4 hrs	LC_{Lo}	NIOSH, 1976
	Mouse	Inhalation	69 mg/m^3 x 2 hrs	LC_{50}	NIOSH, 1976
	Mammal, unspecified	Inhalation	64 mg/m^3	LC_{50}	NIOSH, 1976
p-Chlorophenyl isocyanate	Rat	Oral	4710 mg/kg	LD_{50}	NIOSH, 1976
	Mouse	Oral	530 mg/kg	LD_{50}	NIOSH, 1976
	Mouse	Inhalation	53 ppm x 1 hr	LC_{Lo}	NIOSH, 1976
Phenyl isocyanate	Rat	Oral	940 mg/kg	LD_{50}	NIOSH, 1976

Pathological examination revealed a corrosive action on the stomach as well as a possible toxic effect on the liver in rats exposed to TDI orally at the LD_{50} (5800 mg/kg) (Zapp, 1957).

Skin absorption of TDI failed to kill or produce injury to the internal organs of rabbits with doses as large as 16,000 mg/kg (Zapp, 1957). Severe local skin irritation did result, and application to the eyes resulted in marked irritation of the eyelids and mild damage to the corneal epithelium.

Smyth and coworkers (1969) report a skin LD_{50} of 220 mg/kg for methyl isocyanate in rabbits.

When a cotton plug saturated with methyl isocyanate was fastened to the ear of a rabbit for 30 minutes, erythema and edema spread to the entire ear, with necrosis and perforation of the ear developing. A few drops sprinkled on the ear corroded the tissue (ACGIH, 1971a).

c. Subchronic Effects

Subchronic inhalation studies of TDI in rats, guinea pigs, rabbits, and dogs are summarized in Table 3 (Zapp, 1957). Subchronic oral testing, in which each of a group of six rats received by stomach tube 1500 mg/kg/day, resulted in the death of 3 rats within a total of 10 treatments. Pathological examination revealed injury to the gastrointestinal tract and liver, as it did following acute oral exposures.

Repeated daily six hour exposures at 0.1 ppm were reported to cause inflammation of the tracheo-bronchial mucosa with fibrosa obliterans as the terminal lesion (ACGIH, 1971b).

d. Chronic Effects

No information was encountered.

e. Human Effects

The isocyanates in vapor form have a strongly irritating effect on all mucous membranes (Zapp, 1957). After eight days to two months of exposure to 2,4- and 2,6-TDI, workers complained of eye, throat, and bronchial irritation, followed by asthmatic attacks. Unpublished reports from the U.S. and published foreign reports have confirmed the occurrence of asthmatic reactions in men exposed to TDI and other diisocyanates. Case reports indicate that bronchospasm is the chief immediate effect of TDI, and suggest that there is a wide range of individual susceptibility (Duncan *et al.*, 1962). With prolonged exposures, significant respiratory distress is evidenced by dry painful coughing, chest pains, and occasional blood-streaking of scant sputum (Hamilton and Hardy, 1974).

Table 3. Subchronic Inhalation Toxicity of Toluene-2,4-diisocyanate (Zapp, 1957)

Organism	Dose	No. of 6 Hour Exposures	Effect
a. Rats	1-2 ppm	10	No injury
b. Rats	1-2 ppm	30	Tracheobronchitis
c. 2 Rats from "b"	5 ppm	8, 11	Death. Both showed emphysema without pulmonary edema, and one showed definite bronchitis.
d. 5 Rats	1.5 ppm	79	4 of 5 showed bronchitis of varying degree.
e. Guinea pigs	1.5 ppm	23, 40, 57, 61, 79	All showed bronchitis with varying degrees of bronchial pneumonia.
f. Rabbits	1.5 ppm	3, 5, 19, 52, 71	1 death at 3 and 5 hours; bronchitis - all exposures; 71 hour exposure exhibited slight pulmonary edema.
4 Dogs	1.5 ppm	0.5 to 2 hour exposures daily, totalling 35 to 37 exposures over 4 months.	Lacrimation, coughing, restlessness, spitting up of white frothy material. Mild congestion and inflammation of trachea and large bronchi. Thick mucous plugs in some bronchial branches.
Rats, guinea pigs, rabbits	9 ppm	6 exposures, no duration specified.	3 of 6 rats died exhibiting bronchitis and definite bronchial pneumonia. All survivors showed bronchitis and minimal pneumonia.

Industrial exposure to aromatic diisocyanates (unspecified proportion of TDI) in the manufacture of the polyurethane Desmodur® resulted in four fatalities out of 100 cases (Moeschlin, 1965). In experiments it caused necrosis of the mucous membranes with formation of a non-biodegradable plastic compound, which is secondarily enclosed by granulation tissue (bronchiolitis obliterans). Inhalation of more than 0.03 ppm causes rhinitis, pharyngitis, and bronchitis, together with fatigue, breathlessness, and night sweats accompanied by rhonchi and râles in the chest (Hunter, 1976). Cyanosis and fever may occur, especially if there is pulmonary edema or bronchopneumonia. More rarely, pain, subicterus, and priapism are observed (Moeschlin, 1965). In severe cases, death may occur from progressive bronchiolitis obliterans or from secondary infection of the lung and secondary cardiac decompensation. In practically all reported cases, chest disorders have cleared rapidly after removal from contact with the toluene diisocyanates (Hunter, 1976; Zapp, 1957).

An allergic mechanism is suggested for the action of TDI by the fact that many of the workers who have recovered have experienced recurrent symptoms (often violently) following further contact with even very low concentrations (Hunter, 1976). Permanent disabilities seem to be rare but have been reported in several cases, some following repeated exposure after recovery from an earlier attack. Hamilton and Hardy (1974) point out that the nature of the sensitivity to TDI has not been clearly established. There is experimental evidence for antigen-antibody mechanisms, while other observations suggest that a direct effect on susceptible tissues is responsible. It is not clear whether chronic injury occurs, either in response to repeated acute episodes or to long-term, low-level exposures to TDI without permanent symptoms.

Zapp (1957) conducted patch tests of polyurethane foam (TDI polymer) on volunteers. Squares (1 x 1 x 1/16") were applied by adhesive tape to the arms and legs of 209 men and women for 6 days. None of the subjects showed skin irritation after the first 24 hours of contact. Three showed some erythema after 6 days, but none showed a reaction when the patches were re-applied 10 days later.

Inhalation of methyl isocyanate vapor is dangerous at even great dilutions, resulting in injury to lungs and pulmonary edema (ACGIH, 1971a). Acute experiments of one to five minute duration were performed on four human subjects. At 0.4 ppm the subjects could not perceive odor and experienced no eye, nose, or throat irritation. At 2 ppm no odor was detected but the subjects experienced irritation and lacrymation. At 4 ppm these symptoms were more marked, and exposure was unbearable at 21 ppm.

Even though concentrations of methyl isocyanate may be below recommended levels (Sections 8 and 9), significant exposures through the skin may be possible (NIOSH, 1976).

Phenyl isocyanate is also irritating to human eyes (Windholz, 1976).

8. TLV

Toluene-2,4-diisocyanate

A threshold limit of 0.02 ppm is recommended. This value is felt to be sufficiently low to prevent substantially all sensitization and minimize recurrent attacks (ACGIH, 1971b).

Methyl Isocyanate

On the basis of irritation to the mucous membranes and prevention of sensitizing doses, a TLV of 0.02 ppm is recommended (ACGIH, 1971a).

9. Other Standards

Toluene-2,4-diisocyanate

The OSHA standard is 0.02 ppm ceiling concentration in air (NIOSH, 1976). A NIOSH criteria document on the "Occupational Exposure to Toluene Diisocyanates" recommends a time weighted average air concentration of 5 ppb (NIOSH, 1976).

Methyl Isocyanate

The OSHA time weighted average air concentration standard is 0.02 ppm (NIOSH, 1976).

Draft technical standards for toluene-2,4-diisocyanate and methyl isocyanate have been developed under the joint NIOSH/OSHA standards completion program (NIOSH, 1976).

10. Other Data

Table 4 lists the number of reported human occupational exposures to organoisocyanates (NIOSH, 1977).

Table 4. Reported Human Occupational Exposure to Organoisocyanates (NIOSH, 1977)

Compound	No. of Exposures
Toluene-2,4-diisocyanate	48,240
Toluene-2,6-diisocyanate	3,480
Diphenylmethane-4,4'-diisocyanate	1,530
Polymethylene polyphenylisocyanate	293,160
Methyl isocyanate	25,470
n-Butyl isocyanate	23,790
Phenyl isocyanate	23,610
Methylene bisphenyl isocyanate	32,730
Methylisothiocyanate	1,710
Polymethylene diphenylisocyanate	313,170

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ORGANOLEAD COMPOUNDS

1. Molecular Structure

2. Chemical Abstracts Service Number

3. Registry of Toxic Effects of Chemical Substances Number

The above information for the organoleads selected for this profile is listed in Table 1, along with common synonyms for the compounds.

In choosing the compounds listed, consideration was given to the extent of production and use in industrial processes, as well as the likely toxicological hazard, regardless of the relative commercial significance of the compound.

4. Production Figures and Economic Trends

5. Uses

6. Producer and User Data

Lead Naphthenate

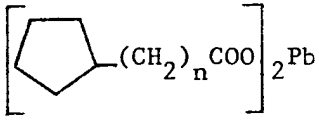
Naphthenates are derivatives of naphthenic acids, alicyclic monocarboxylic acids with a five (or occasionally six) member ring. Naphthenic acids are isolated from crude petroleum, in which they occur naturally. Commercial naphthenic acid is a complex mixture of these acids, which vary in the length of the alkyl chain as well as the ring size. "Lead naphthenate" is a commercial term for material which consists of lead derivatives of commercial grade naphthenic acid. Therefore, lead naphthenate is not a pure compound, but a mixture of a very large number of compounds which vary mainly in the length of the alkyl chain and occasionally also in the size of the alkyl ring (see structural formula, Table 1).

Production of lead naphthenate, which amounted to 4.1 million lbs. in 1975 (USITC, 1975), is declining due to restrictions of lead content in paints which is lead naphthenate's almost exclusive use (Bradley, 1975a).

The following companies produce lead naphthenate (SRI, 1977):

Ferro Corp.	Bedford, Ohio
Interstab Chem.	New Brunswick, N.J.
Mooney Chem.	Franklin, Pa.
Norac Co.	Lodi, N.J.
Shepherd Chem.	Cincinnati, Ohio
Sherwin-Williams	Cleveland, Ohio
	Emeryville, Calif.
	Garland, Tex.
Tenneco	Elizabeth, N.J.
	Long Beach, Calif.
Troy Chem.	Newark, N.J.
Wilco Chem.	Clearing, Ill.
	Lynwood, Cal.

Table 1. Organolead Compounds

Compound	CAS Number	RTECS Number	Molecular Formula
Lead naphthenate*	50825-29-1	OG20250	
Tetramethyl lead (TML)	75-74-1	TP47250	$Pb(CH_3)_4$
Tetraethyl lead (TEL)	78-00-2	TP45500	$Pb(CH_2CH_3)_4$

* Actually a mixture of many lead naphthenates which have widely varying alkyl chain lengths (see formula) (Revzin and Savos'kin, 1971).

Tetramethyl Lead and Tetraethyl Lead

While 315 million lbs. of tetraethyl lead were produced in 1975 (USITC, 1975), about 40 million lbs. of tetramethyl lead were made (SRC estimate based on USITC, 1975, and Bradley, 1975). In addition, other alkyl leads and their mixtures (i.e., tetra(ethyl-methyl) leads, triethylmethyl, diethyldimethyl, and ethyltrimethyl leads) were produced in the amount of 300 million lbs. in 1975 (SRC estimate based on USITC, 1975 and Bradley, 1975).

Growth of the lead alkyl industry is expected to decline by 10-12% per year (Chem. Prof., 1976c), due to governmental regulations restricting the use of lead in gasoline.

The companies listed below produce lead alkyls (Chem. Prof., 1976c):

DuPont	Antioch, Calif.
	Deepwater, N.J.
Ethyl Corp.	Baton Rouge, La.
	Houston, Tex.
Houston Chem.	Beaumont, Tex.
Nalco Chem.	Freeport, Tex.

7. Biological Effects of Exposure

a) Target Organs

Organolead compounds generally exert their toxic effects on the central nervous system and are accompanied by symptoms ranging from behavioral disorders and hyperagitation to convulsions and paralysis (Cremer and Callaway, 1961; Schepers, 1964; Allen et al., 1974).

Performing extensive laboratory tests on rats with tetramethyl lead (TML) and tetraethyl lead (TEL), Schepers (1964) found that both compounds effected changes in the liver, kidneys, pancreas, stomach, thyroid, lungs and heart.

In addition, TEL affected the endocrine system and also produced changes in the thymus, adrenals, and testes. These histological abnormalities were noted by Schepers (1964) regardless of the route of administration [oral, skin, or inhalation] of TEL.

Liver pathology included hypoplasia, hypotrophy of hepatocytes, and gross discoloration, by both TML and TEL acute exposure. With chronic exposure, the liver became swollen and crumbly (Schepers, 1964).

Acute doses of either TML or TEL caused emphysema, pulmonary edema, "concentric hypertrophy of myocardial fibers associated with capillary distention," and hyperemia. On the other hand, pancreatic lesions, stomach degeneration, and interstitial testicular edema appear to be dose-related responses. Other organ

damage includes duodenitis, changes in kidney glomerular ground structure, pituitary hypoplasia, cardiac enlargement, and peripancreatic inflammation with involvement of the omentum (Schepers, 1964).

TML and TEL exerted very different effects on the central nervous systems of rats tested by Schepers (1964). While TML exerts an overall depressant effect with eventual coma in the animals, TEL produces great agitation and aggression. He has suggested that the lack of hyperstimulation and coma resulting from TML poisoning may be due to its destructive action on the neurons.

No information was available regarding organs affected by lead naphthenate intoxication.

b) Acute Effects

Acute oral TML administration causes rats to become weak, drowsy, sluggish, "flaccid," and either quiet or hyperagitated. Body tremors and convulsions increasing in severity occasionally occur; an eventual coma leads to death (Cremer and Callaway, 1961; Schepers, 1964).

Rats inhaling acute doses of TML, in addition to becoming slightly to greatly agitated, also developed bronchopneumonia (Cremer and Callaway, 1961).

Acute oral doses of TEL in rats caused convulsions, unprovoked aggression, agitation, and weight gain that was significantly greater than controls. Inhaled and intravenous doses in rats caused tremors, agitation, and cyanosis. In rabbits, intravenous TEL produced immediate physiological distress accompanied by quick breathing, stretching, and death in approximately 16 hours (Cremer and Callaway, 1961).

Rats given TEL orally experienced significant increases in organ weight in liver, spleen, and kidneys, due neither to edema nor dehydration (Schepers, 1964).

Table 2 summarizes the acute effects on experimental animals produced by organolead poisoning.

c) Subchronic Effects

Subchronic effects for TML and TEL administered orally to rats gave results similar to the acute effects described in section 7b (Schepers, 1964).

d) Chronic Effects

i) Carcinogenicity

Tetramethyl lead and tetraethyl lead have both been determined to be carcinogenic (IARC, 1973), while lead naphthenate is neoplastic (NIOSH, 1976).

Lymphomas which formed in mice given TEL subcutaneously, were mostly well-differentiated lumphatic leukemias occurring late in the life of the mice (Epstein and Mantel, 1968).

Table 2. Acute Effects of Organolead Compounds

Organism	Route	Dose (mg/kg)	Response	Reference
Lead naphthenate				
rats	oral	5100	LD_{50}	NIOSH, 1976
rats	skin	520	LD_{50}	NIOSH, 1976
Tetramethyl lead				
rats	ivn	26 and 34.3	No signs of poisoning	Cremer & Callaway, 1961
rats	oral	62.5	Wt. loss 1st wk., gradual recovery	Cremer & Callaway, 1961
rats	oral	125	Tremors after 3 days; death	Cremer & Callaway, 1961
rats	oral	250	Agitated, aggression, tremors & convulsions	Cremer & Callaway, 1961
rats	oral	500	Tremors after 24 hours	Cremer & Callaway, 1961
rats		109.3	LD_{50}	Cremer & Callaway, 1961
rats	ihl	533	Slight agitation	Cremer & Callaway, 1961
rats	ihl	269,131	No signs of poisoning; higher dose - slight agitation	Cremer & Callaway, 1961
rats	ip	23-101	Eye & nose dischange (watery), weakness, low temp., wt. loss; some temporary CNS disturbances in fatal cases	Buck & Kumro, 1930
rats	oral	108	Trembling, agitation, convulsions, some wt. loss, death; survivors recovered fully in 2 wks.	Schepers, 1964
rats	oral	10.8	No signs of poisoning	Schepers, 1964
rats	ihl	8.87 mg/l	LC_{50}	Cremer & Callaway, 1961
rats	oral	109	LD_{50}	Cremer & Callaway, 1961
rats	ipr	73	LD_{50}	NIOSH, 1976
rats	par	105	LD_{Lo}	NIOSH, 1976
rabbits	ivn	90	LD_{50}	Buck & Kumro, 1930
mice	ihl	40.8 g/m^3 x 30 min	LC_{Lo} (one day obs.)	ACGIH, 1971a
mice	ihl	8.5 g/m^3 x 30 min	LC_{50} (10 day obs.)	ACGIH, 1971a

Table 2. Acute Effects of Organolead Compounds (Cont'd.)

Organism	Route	Dose (mg/kg)	Response	Reference
Tetraethyl lead				
rats	ihl	90,158,232	Death; highest dose - cyanosis	Cremer & Callaway, 1961
rats	ihl	39.6	Agitated & aggressive; tremors, some deaths	Cremer & Callaway, 1961
rats	ihl	4.8,10.2,20.4	Symptoms of mild poisoning with eventual recovery	Cremer & Callaway, 1961
rats	---	15.4	LD_{50}	Cremer & Callaway, 1961
rats	oral	17	Temporary increases in irritation, agitation, trembling, spasms, back arching, prostration, wt. loss, death; survivers recovered fully in 2 weeks	Schepers, 1964
rats	oral	1.7	No signs of poisoning	Schepers, 1964
rats	ip.	11-30	Eye & nose discharge, weakness; death in 2 days	Buck & Kumro, 1930
rats	oral	16-24	LD_{50}	Epstein & Mantel, 1968
rats	oral	17	LD_{50}	Schepers, 1964
rats	ihl	6 ppm	LC_{50}	NIOSH, 1976
rats	ipr	10	LD_{50}	Buck & Kumro, 1930
rats	ivn	31	LD_{Lo}	Cremer & Callaway, 1961
rats	par	15	LD_{Lo}	NIOSH, 1976
rats	ihl	0.85 mg/1 x 1 hr.	LC_{50}	Cremer & Callaway, 1961
rats	iv	14.4	LD_{50}	ACGIH, 1971
rats	ip	15.05	LD_{50}	ACGIH, 1971
rats	oral	35	LD_{50}	ACGIH, 1971
rabbits	skin	700 kg	Lethal	ACGIH, 1971b
rabbits	I.V.	14,24,20,38	Lethal in 24 hours	Buck & Kumro, 1930
day old mice	par	50-100	LD_{50}	Epstein & Mantel, 1968
mice	scu	86	LD_{50}	Epstein & Mantel, 1968
guinea pigs	skin	990	LD_{Lo}	NIOSH, 1976
dogs	skin	500	LD_{Lo}	NIOSH, 1976

ii) Mutagenicity

No mutagenicity studies were encountered.

iii) Teratogenicity

No information regarding teratogenicity was encountered for organoleads.

iv) Other

Schepers (1964) found that the chronic effects of TEL were the same regardless of the route of administration (i.e., oral, topical, inhalation). These and the effects of chromic TML administration are summarized in Table 3.

e) Human Effects

As stated by Buckley and associates (1973), no cases of lead poisoning due to food chain amplification are known; rather, lead poisoning is a result of occupational exposure to lead-containing compounds or accidental ingestion, most often by children ingesting lead based paints or street dust (Anderson and Clarke, 1974).

Tetraethyl lead, a motor fuel additive, accounts for much of the airborne lead that man breathes, although not in organic form (Buckley et al., 1973). However, inhalation of automobile exhaust fumes from leaded gasoline can cause "muscular pain, headache, nasal inflammation, alternating diarrhea and constipation, sleep disturbances, and other signs of 'vegetative dystonia'" (Browning, 1969). Occupational exposures to TEL, in liquid or vapor forms, in its manufacture have been known to be fatal (Browning, 1969), as has exposure during cleaning of storage tanks which contained leaded fuel. (Sludge in these tanks may contain over 1% TEL.) Lethal doses may be inhaled in as little as one-half hour, although a few hours exposure in a single day or continuously over several days may also have serious or fatal consequences (Browning, 1969).

Leaded fuel itself or its vapors are not as dangerous, as the mixure is approximately 1000 parts gasoline to 1 part TEL. TEL is absorbed either from the gastrointestinal tract or by the skin (Browning, 1969; Patty, 1949).

Browning (1969) lists as symptoms of fatal TEL intoxication, mental disorders with delirium, hallucinations, and mania, with convulsions and coma preceding death, which occurs only a few days following poisoning.

Less severe cases display mental disorientation, sleeplessness, occasionally stomach pains with nausea and vomiting. Apathy and depression alternate with delirium and mania. Once past crisis, partial recovery may follow in one to two weeks, and complete recovery in 4 to 10 weeks. Relapses are not uncommon (Browning, 1969).

Table 3. Chronic Effects of Organolead Compounds

Organism	Route	Dose (mg/kg)	Response	Reference
Tetramethyl lead				
rats	oral	1.08 and 0.001 mg/kg/day/5x per week, to 100 doses	Gradual & increasing onset of poisoning symptoms during treatment, incl. peripheral hyperemia, & irrascibility, & hypermotility	Schepers, 1964
Tetraethyl lead				
rats	oral	0.17 and 0.0017 mg/kg/dose 5 days/wk, to 100 doses	Gradual & increasing onset of poisoning symptoms during treatment, incl. peripheral hyperemia, & irrascibility, & hypermotility	Schepers, 1964
rats	ihl	12 mg/m^3 7hrs/day x x 150 exposures	No deaths; incr. urine lead, 5 times incr. in major organs	ACGIH, 1971b
dogs	ihl	42 mg/m^3 (x 7hrs.)	Death at 7 hours	ACGIH, 1971b
		22 mg/m^3 (x 7hrs.)	Death at 30 hrs of exposure	ACGIH, 1971b
		12 mg/m^3 (x 7hrs.)	Death at 24 & 29 hours	ACGIH, 1971b
rats	oral	0.17 and 0.0017 mg/kg $\bar{x}$ 5 times per wk x 21 wks	No deaths. No changes in body wt. Histological alterations in pancreas, liver, kidneys, CNS, endocrine system	Schepers, 1964

Milder cases result in insomnia, nightmares, restlessness, appetite loss, and gastrointestinal disturbances, which disappear after a few weeks. This was seen in four workers salvaging lead scrap for TEL manufacture (Browning, 1969).

ACGIH (1971a & b), states that workers exposed to TML and TEL showed no significant urine lead levels (TML plant had three times greater atmospheric concentration than TEL plant). Neither group of workers were ill.

8. TLV

The recommended TLV's for tetramethyl lead and tetraethyl lead (via skin exposure) are 0.150 mg/m^3 and 0.100 mg/m^3, respectively (ACGIH, 1971a & b).

9. Other Standards

OSHA recommended skin exposure TWA's for TML and TEL are 70 $\mu g/m^3$ and 75 $\mu g/m^3$, respectively (Fed. Reg., 1974). Other standards for TEL range from 75 to 100 $\mu g/m^3$ (ACGIH, 1971b).

10. Other Data

Table 4 lists the number of reported occupational exposures to various organolead compounds (NIOSH, 1977).

Table 4. Reported Occupational Exposures To Organolead Compounds

Compound	Number of Exposures
Tetraethyl lead	450,000
Tetramethyl lead	450,000
Lead naphthenate	1,808,820
Lead fumarate	3,300
Lead stearate	40,830
Lead tallate	18,330
Lead oleate	8,580
Lead neodecanoate	2,190
Lead phthalate	42,090
Lead 3,3,5-trimethyl hexanoate	1,110

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ORGANOMERCURIALS

1. Molecular Structure

2. Chemical Abstracts Service (CAS) Number

3. Registry of Toxic Effects of Chemical Substances (RTECS) Number

The above information for the commercially significant organomercurials is provided in Table 1. The compounds listed were selected on the extent of industrial use, as well as the likely toxicological hazard.

4. Production Figures and Economic Trend

5. Uses

6. Producer and User Data

Phenylmercuric Acetate (PMA)

In 1975, 0.15 million lbs. of PMA were produced (USITC, 1975). No growth figures were encountered, but growth is not expected to increase due to a ban imposed by EPA on mercury-based pesticides in paints (Treskon, 1976a).

This compound, in addition to its use in paints, is also a crop fungicide (Ayers and Johnson, 1976).

The companies listed below produce PMA (SRI, 1977):

W.A. Cleary Corp.	Somerset, N.J.
Cosan Chem.	Clifton, N.J.
Merck	Hawthorne, N.J.
Tenneco	Elizabeth, N.J.
Troy Chem.	Newark, N.J.

Phenylmercury propionate

Production figures are not available. Phenylmercury propionate, used as a fungicide, is produced by Merck (Hawthorne, N.J.) (SRI, 1977).

Ethyl Mercury Chloride

No production data is available on this compound, which is manufactured by Eli Lilly Co., Layfayette, Indiana. Ethyl mercury chloride is used as a wood preservative. Information on the extent of this use was not available; although 990 humans have been reported exposed to this compound on the job (NIOSH, 1977).

Table 2 lists organomercurial medicinals and pharmaceuticals (SRI, 1977; Bratt, 1967; Lawler, 1977; USITC, 1975).

Table 1. Organomercurials

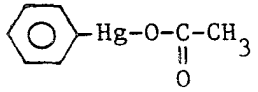
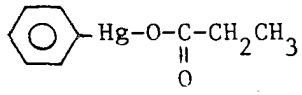
Compound	CAS No.	RTECS No.	Molecular Structure
Phenylmercuric acetate (PMA)	62-38-4	OV64750	
Phenylmercury propionate	103-27-5	OW91000	
Ethyl mercury chloride			$C_2H_5-Hg^+Cl-$

Table 2. Organomercurial Medicinals and Pharmaceuticals

Dibromohydroxymercurifluorescein, disodium salt (Mercurochrome, Merbromin)
Mercuric salicylate
Mercury oleate
Sodium ethylmercurithiosalicylate (Merthiolate)
4-Nitro-3-hydroximercuri-o-cresol anhydride (Nitromersol)
Sodium hydroxymercuri-o-nitro phenalate (Mercurophen)
Mercuric succinimide
Chlormerodrin
Mercuric sodium p-phenolsulfonate
Chloromercuriphenol
Phenylmercuric borate
Thimerosal

7. Biological Effects of Exposure

Several reviews are available on the biological effects of mercury and mercury containing compounds (Browning, 1969; Hamilton and Hardy, 1974; Hunter, 1975; Moeschlin, 1965; and W.H.O., 1976). However, the major compounds discovered in these reviews are inorganic and alkyl mercury compounds, and few specific references are made to the phenylmercurials covered in this profile. Therefore, an attempt has been made to obtain as many primary references as possible on the organomercurials in this profile and to relate the information from these primary sources to the general statements on organomercurial poisoning discussed in the reviews cited above.

a. Target Organs

The kidneys and nerve tissue are the major targets of mercury compounds (Moeschlin, 1965; W.H.O., 1976). Damage to both has been noted in rats exposed to phenylmercuric acetate.

Swensson (1952) administered phenylmercuric acetate to rats by intraperitoneal injection at doses of either 1.25 mg/kg/day or 1.0 mg/kg/day, every other day, for 4 weeks. Cellular injuries were noted in the granular layer of the cerebellum, in Purkinje's cells of the cerebellum, and in the spinal cord. Similar changes were seen in rats treated with methyl mercury chloride, ethyl mercury chloride, methyl mercury dicyandiamine, and ethyl mercury dicyandiamine. None of the rats treated with phenylmercuric acetate developed pareses, but this effect was seen in rats given methyl mercury chloride.

Kidney pathology, without apparent signs of nervous system involvement, was the outstanding effect in rats in two year exposures to both phenylmercuric acetate and mercuric acetate (Fitzhugh et al., 1950). These compounds were administered in the diet at levels up to 160 ppm, measured as mercury content. Early pathological changes in the kidney included hypertrophy and dilatation of the proximal convoluted tubules. This progressed to some tubular atrophy, fibrosis, and moderate cellular inflammatory infiltration. Based on an analysis of mercury residues in the kidneys, phenylmercuric acetate was about twenty times more potent than mercuric acetate in causing these effects. Fitzhugh and coworkers (1950) noted that these kidney changes were similar to those normally seen in older rats and were quite different from the coagulative necrosis of the proximal convoluted tubules characteristic of acute mercury poisoning. Organs which were not apparently damaged by either organomercurial included the liver, testis, thyroid, lung, pancreas, small intestine, colon, adrenal, uterus, and ovary. Bone marrow hyperplasia and focal calcification of heart and leg muscles were noted in some animals but were not unequivocally attributed to the mercury compounds.

Phenylmercuric acetate caused severe skin necrosis in guinea pigs, rats, and mice after acutely toxic subcutaneous injections (Swensson, 1952).

Table 3. The Acute Toxicity of Several Organomercurial Compounds

Compound	Organism	Route	LD_{50}	Reference
Phenylmercuric acetate	Mouse	Oral	26. mg/kg	NIOSH, 1976
		Subcutaneous	37. mg/kg	NIOSH, 1976
		Intraperitoneal	13. mg/kg	Swensson, 1952
Phenylmercuric nitrate	Mouse	Subcutaneous	45. mg/kg	Swensson, 1952
		Intravenous	27. mg/kg	Swensson, 1952
Phenylmercuric nitrate, basic*	Rat	Subcutaneous	63. mg/kg	NIOSH, 1976
	Rabbit	Intravenous	4.96 mg/kg**	Swensson, 1952
Phenylmercury propionate	Rat	Oral	90. mg/kg	NIOSH, 1976

* Mixture of nitratophenylmercury and hydroxyphenyl mercury (1:1).
** Minimum lethal dose

Nervous tissue damage is the major pathologic feature of exposure to short-chain alkyl mercury compounds including ethyl mercury chloride. In experimental mammals, damage is seen both in the central peripheral nervous systems. In man, damage is generally restricted to the central nervous system (Dales, 1972).

b. Acute Effects

Information on the acute toxicity of the selected organomercurials is summarized in Table 3.

c. Subchronic Effects

Phenylmercuric acetate, administered intraperitoneally at doses of 1.25 mg/kg/day or 1.0 mg/kg/day, every other day, caused weight loss accompanied by sluggish and apathetic behavior in rats after 2 weeks. However, over the 4 week total exposure period, paresis did not develop in any of the treated animals.

d. Chronic Effects

i) Carcinogenicity - One of twenty female rats, injected intravaginally twice weekly with 0.1 ml of a 0.5% solution of phenylmercuric acetate for 50 weeks, developed a squamous cell carcinoma of the cervix. Based on the pattern of urogenital tract tumors seen in control animals, this tumor was attributed to phenylmercuric acetate treatment (Boyland et al., 1966).

ii) Mutagenicity - No information has been encountered on the mutagenic effects of the organomercurials under review.

iii) Teratogenicity - No information has been encountered on the teratogenic effects of the organomercurials under review. The adverse effects on infants of prenatal exposure to methylmercury is well documented (W.H.O., 1976).

iv) Other Chronic Effects - Two year dietary exposures to phenylmercuric acetate at 40 and 160 ppm, measured as elemental mercury, resulted in decreased growth rate and kidney enlargement in rats. Reduced survival was noted at 160 ppm. Similar exposures to mercuric acetate at 40 and 160 ppm caused only kidney enlargement. At dietary levels of 10 ppm and below, neither compound caused any apparent adverse effects (Fitzhugh et al., 1950). Browning (1969) reported that tremors and other signs of nervous system intoxication are the major features of chronic organomercurial poisoning.

e. Human Effects

All mercury compounds reportedly cause the same type of damage on acute intoxication: shock, cardiovascular collapse, and acute renal failure (W.H.O., 1976). Organomercurials, as a class, have been associated with skin damage including erythema, intense itching, edema, papules, pustules, and deep

ulcerations (Hamilton and Hardy, 1974). Occupational exposures to phenylmercury compounds have caused dermatitis (W.H.O., 1976; Browning, 1969; Hunter, 1975). Cases of systemic poisoning in man from organomercurial exposure usually involve alkyl- rather than phenylmercurials (Hunter, 1975). No adverse effects were noted in a group of 67 workers exposed to phenylmercury compounds. In this study, mercury levels in the air were about 0.1 mg/m^3 and consisted mainly of elemental mercury (W.H.O., 1976). Swensson (1952) cited phenylmercuric acetate as a human poison but provided no details of exposure or symptomology. Hamilton and Hardy (1974) summarized a study which found a variety of abnormal laboratory findings in a group of workers exposed to mercuric acetate and a number of other organic and inorganic mercurials. No clinical signs of intoxication were noted in these workers.

Severe poisoning by alkyl mercury compounds is characterized by motor incoordination, concentric constriction of visual fields, hearing loss, loss of position sense, artereognois, muscular spasticity or rigidity, emotional disturbances, and mental impairment. In less serious cases, symptoms may be limited to paresthesia, fatigue, and irritability (Dales, 1972).

8. TLV's

The time-weighted average TLV for inorganic mercury vapors and salts and organic mercury compounds other than alkyl mercury is 0.05 mg/m^3 (ACGIH, 1971a). The TLV for alkyl mercury compounds is 0.01 mg/m^3 (ACGIH, 1971b).

9. Other Standards

No other standards for the organomercurials under review have been encountered.

10. Other Data

Table 4 lists the number of reported human exposures to various organomercurial compounds (NIOSH, 1977).

Table 4. Reported Human Occupational Exposures to Organomercurial Compounds (NIOSH, 1977)

Compound	Number of Exposures
Phenyl mercuric acetate (PMA)	34,170
Phenyl mercuric benzoate	1,410
Phenyl mercuric lactate	12,780
Phenyl mercuric oleate	990
Phenyl mercury propionate	162,390
Mercuric thiocyanate	1,140
Ethyl mercury chloride	990

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INDUSTRIAL PROCESSES

IRON AND STEEL FOUNDRIES

1. Standard Industrial Classification and Description

Foundries manufacturing iron and steel castings are classified principally as follows (Anon., 1972):

Gray iron foundries	SIC Code 3321
Malleable iron foundries	SIC Code 3322
Steel Foundries	SIC Code 3323

2. Description of the Process

Foundry work includes four major operations or steps (Anon., 1976; Stimpson, 1947):

First - Pattern making - fabricating precise models of the cast product from metal, wood or plastic materials.

Second - Molding - forming hollow spaces in sand molds with the above patterns or models.

Third - Pouring - casting molten iron or steel in the sand molds that solidify to the rough cast products.

Fourth - Finishing - Shaking the rough castings from the sand mold, and cleaning by sandblasting, tumbling or machining to remove extraneous metal and to finish to the desired dimensions.

The several operations vary widely in size, ranging from small manual bench scale work through manual and mechanized workings in heavy molds (flasks) to very large mechanical operations in sandfilled pits. Most foundries are small and produce a variety of castings. Others, such as in the automotive industry are large and produce only a few kinds of products.

Auxiliary operations include: core molding, in which impregnated sand inserts are formed to shape the hollow sections in the casting; melting the iron and steel pigs, billets, and scrap in furnaces (cupola) if the metal is not supplied molten from large mill furnaces; and transferring the melt in refractory lined ladles to the molds.

The foregoing steps involve many separate operations. Pattern making may use many of the operations of metal and wood working shops. Molding requires preparation of the sand by screening, moistening and mixing with additives such as glue, sugar, resin, etc., ramming the mixture into the flasks and around the pattern, and coating the exposed surfaces with partition compounds, e.g. graphite, after removal of pattern. Pig iron in gray iron foundries is melted in coke fired cupola type shaft furnaces. Steel billets are melted in gas or oiled fired reverberating furnaces.

In addition to the above most common method, the green-sand molding process, other specialized methods are used in the iron and steel foundry industry:

Permanent Molding - Molds are made of metal instead of sand, for permanence.

Investment Casting - Ceramic molds with wax or plastic patterns are used for very precise smooth castings.

Shell Molding - Heated metal patterns are covered with resin coated sand to form a shell or mold that is stripped off after curing.

Die Casting - Mechanically forcing molten metal into dies that shape the product as it solidifies.

Centrifuged Casting - Molten metal is poured into spinning molds to form cylindrical center cavities as in pipes and tubes as the metal distributes against the walls of the mold.

3. Major Chemicals and/or Physical Agents of Potential Concern

Major typical chemical and physical hazards in foundry work are caused by fumes and dusts, vapors, molten metal and noise. The following description of these hazards is summarized from Patty (1949).

During the melting process the cupola may be a source of carbon monoxide. Electric furnaces tend to give rise to dusts of the oxides of iron, silicon, and manganese, depending on the composition of the steel being manufactured. Mold and core making may involve flint or silica dusts and exposure to solvents (such as carbon tetrachloride) used for shellacs and adhesives. The pouring operation may produce smoke and gases from the destructive distillation of sea coal mixed into the molding sand. The shakeout and knockout areas may present severe dust hazards as may casting areas and blast cabinets lacking proper ventilation and exhaust facilities. Patty (1949) suggests that overcrowding in a foundry may also be a factor in impeding the establishment of good environmental control.

The chemical and physical hazards of iron and steel foundry work are fully listed and explained by the following publications of the Public Health Service of the U.S. Department of Health, Education and Welfare, Division of Technical Services, Cincinnati, Ohio, 1976: DHEW (NIOSH) Publications 77-102, 77-103, and 77-104 with respective titles:

"Pattern Shop, Core Room, Molding Shop, and Sandblasting Departments."
"Melting and Pouring Departments."
"Shakeout, Cleaning, Grinding, and Inspection Departments."

4. Number of Workers Exposed or Employed

The total employment in iron and steel foundries in 1974 was about 240,000. Approximately 85% of the total were production workers. These were employed in over 1,300 foundries, 90% of which employed fewer than 250 workers, although some employed more than 5,000 (Anon., 1976 and 1976a, and Anon., 1972a).

5. Trend in Process Use

The growth of the industry as measured by the quantity of pig iron and scrap that was melted was at an annual rate of 3.5% between 1967 and 1972. However, the employment remained approximately the same due to mechanization and other technical improvements. It is expected that these rates of change will continue and that there will be no increase in employment through the mid-1980's (Anon., 1976 and Anon., 1972a).

6. Incidence of Mortality, Injury and Morbidity

The incidences of accidents and illnesses in iron and steel foundries in the U.S. for 1974 are tabulated in Table 1. The averages for all U.S. industry are shown for comparison (Anon., 1976a).

The total lost time figures (Anon., 1976a) were as follows (as days per 100 workers per year):

gray iron foundries	SIC Code 3321	165.8 days
malleable iron foundries	SIC Code 3322	178.7 days
steel foundries	SIC Code 3323	150.9 days
as compared with all industry		54.6

The frequency rates for deaths and permanent disability are as follows for 1975, as cases per million hours of exposure (Anon., 1976b):

gray iron foundries	0.66
malleable iron foundries	0.17
steel foundries	1.03
as compared with all industry	0.38

The fatalities for the entire industry were 0.06 per million hours or about the same as the average for all U.S. industries.

7. Other Pertinent Data

As indicated by the foregoing rates of accidents in foundries, the industry is significantly worse than average.

Table 1. Incidence of Mortality, Injury and Morbidity
(Anon., 1976a)

Classification	SIC Code	Employment 1974 (1000)	Injuries and Illnesses (a)			Injuries (a)			Illnesses (a)		
			Total	Lost Time	Non-fatal ex. Lost Time	Total	Lost Time	Non-Fatal ex. Lost Time	Total	Lost Time	Non-Fatal ex. Lost Time
Gray iron foundries	3321	156.4	32.0	12.3	19.7	31.4	12.1	19.3	0.6	0.2	0.4
Malleable iron foundries	3322	25.0	32.0	12.6	19.4	31.5	12.4	19.1	0.5	0.2	0.3
Steel foundries	3323	66.0	26.2	9.8	16.4	25.3	9.5	15.8	0.9	0.2	0.6
Total Iron & Steel Foundries	332	247.3	30.4	11.6	18.8	29.8	11.4	18.3	0.6	0.2	0.4
All Private Industry		65,400	10.4	3.5	6.9	10.0	3.4	6.6	0.4	0.1	0.2

(a) Cases per 100 workers = 200,000 hours per year.

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MANUFACTURE AND USE OF CEMENT

(1) Standard Industrial Classification and Descriptions

Hydraulic cement manufacture, SIC Code 3241, includes production of natural, portland and volanic cements (Anon., 1972).

Cement uses are classified as follows:

Concrete Block and Brick	SIC Code 3271
Concrete Products n.e.c.	SIC Code 3272
Ready Mix Concrete	SIC Code 3273
Concrete Construction	SIC Code 1771

(2) Description of the Process

Cement Manufacture (Bogue, 1964)

Hydraulic cement is made by heating to incipient fusion pulverized mixtures containing calcareous and argilaceous materials in controlled proportions. The clinker is cooled and pulverized to a fine powder. Gypsum (4-5%) is added to regulate the setting time of the product. Five general types of cement are made, i.e. Type I, II, III, IV, and V. Type I, the major product, is used for general construction. Types II - V have special properties relating to heats of hydration, resistence to sulfates and early strength. Typical analysis of the Type I product is:

	Composition	Compound Classification	
SiO_2	21.3%	Dicalcium Silicate	= 27%
Al_2O_3	6.0	Tricalcium Silicate	= 45
Fe_2O_3	2.7	Tricalcium Aluminate	= 11
CcO	63.2	Tricalcium Aluminoferrite	= 8
MSO	2.9	$CaSO_4$	= 3.1
SO_3	1.8	Free MgO	= 2.9
Loss & Insol	1.5	Free CaO	= 0.5
Total	100.0%		

The raw materials used in the process are natural cement rock, limestone, chalk oyster shells, precipitated carbonate, marl, clag, blast furnace slag, sand, sandstone, silica quartz and gypsum, and are obtained from quarries, pits, or beds as well as by products from other manufacturing operations. Either a wet or dry process for mixing and calcining is used.

Wet Process

In the wet process, the feed mixture is ground, mixed and proportioned as a heavy slurry in a series of closed circuit mills operated to give a uniform fine controlled mixture of the ingredients. The wet slurry is burned in the cement clinker in rotary kilns ranging from 150-500 ft. in

length and 8-16 ft. in diameter. The kilns have steel shells and refractory linings. The clinker is heated to 1400°C - 1600°C with oil or gas or powdered coal blown into kiln counter currently to the feed mix. About 1,000,000 BTU's are required per barrel.

The following reactions occur in the kiln: water is evaporated from slurry, calcareous materials are calcined to CaO; the CaO fuses and reacts with the silica and alumina to form the silicates and the aluminates.

The clinker is cooled on leaving the kiln by air.

The cool clinker is pulverized to below 200 mesh in a ball and pebble mill system and during which gypsum is added to control the setting properties of the product. The pulverized product is transferred to silos for packing into paper bags or for shipment as bulk product by mail or truck.

Dry Process

In the dry process the feed mixture is roughly crushed in course mills and dried in rotary dryers. The dry mix is then finely ground in tube mills in closed circuit with air separators. The fine product is fed into rotary kilns where the same reactions and clinker formation occurs, except that no water evaporation is required.

Cement Products

The principal uses for cement are in building construction. The manufactured products are cement blocks, bricks and ready-mixed concrete, as well as prepared mixes for plastics, paints and grout. The manufacture of the blocks and bricks is comparatively simple. The cement is mixed with sand, fine gravel or other inert aggregate materials and water. The mix is pressed into the desired shapes by hand or mechanically. As ready-mix, the mixture is shipped as the thick mass to the construction sites for direct pouring into formed structures.

Cement is used in addition to the above at large construction sites for foundations, dams, pavement, and many other purposes. In these applications the cement is usually reinforced with metal rods or shapes. Cement is also precast into large formed objects, as containers, rooms, beams, poles and other building forms.

In the above processes for preparing concrete and cement products or end uses, 400-800 pounds of cement are mixed with aggregate material per cubic yard concrete. Four to nine gallons of water are used for each 100 pounds of cement. Many inert materials are used in the aggregate depending on the properties desired in the finished product, such as weight, size, and porosity.

(3) Major Chemical and/or Physical Agents of Potential Concern

None of the materials involved in the process or use of cement are unusually chemically active or injurious. The free lime gives the cement mild alkaline and drying reactions. The skin and other sensitive organs may be irritated if accidentally and continually contacted.

Fine dust as in the feed or product is the principal potential cause for concern involving respiratory and skin problems. The dust condition can be controlled by correct design and maintenance of ventillation systems and by hooding at dust generating spots in the plant, e.g. bagging machines and car loaders. Respirators may be indicated under certain conditions.

Other physical conditions such as moving machinery, motor and rail traffic, tripping hazards and electrical circuits as occur in industrial areas require effective guards, warning signs, good housekeeping, safety training, protective clothing, hard hats, goggles, steel protective shoes, as well as inspection and monitoring (Anon., 1975).

Discussion with safety and health officer of the Portland Cement Association suggests that the only other condition of concern is from noise (Hickey, 1977). Inspection, measuring and hearing tests should be programmed if levels at a near 90 decibils can occur.

(4) Number of Workers

There were 32,900 total workers employed in the cement manufacturing industry in the U.S. in 1974. It is reported that over 85% were production workers (Anon., 1976a, and Anon., 1972a).

There are no data on workers for the use applications, but it is judged to be many times the above and probably in order of 500,000 involving workers throughout the total construction industry, as extrapolated from value added.

(5) Trend of the Process

The maximum annual production, 86,500 tons, was manufactured in 1973, and with an annual increase of 2.5% since 1960. Production fell off to 67,000 tons in 1975, but is expected to increase to 74,000 in 1977. The sales follows economic conditions, especially in residential building, which is the largest use at 27% of total. Highways are 18% (Hickey, 1977). Otherwise the uses of cement divides about as follows (Anon., 1972a):

Ready mix cement	60% (approx.)
Concrete products	15 (approx.)
Highways	12 (approx.)
Others not classified	13 (approx.)

(6) Incidence of Mortality, Injury and Morbidity

The rates of incidence for injuries and illnesses in the several classifications compared with the U.S. average for all manufacturing and contract construction is shown in Table 1 (Anon., 1976a).

Three fatalities occurred in 1976 in cement manufacturing equal to a rate of about 0.05 cases per million hours, which is approximately the same as the average U.S. industrial experience. No data was available specifically for the cement product industry (Hickey, 1977).

The lost time for the disabling accidents were as follows for the several classifications in 1974 and 1973 (weekdays per 100 workers) (Anon., 1976a).

Classification	Code	Lost Time 1974	1973
Cement production	3241	71.9	68.3
Concrete block and brick	3271	131.9	98.3
Other Concrete products	3272	156.0	127.5
Ready mixed concrete	3273	103.4	106.9
Concrete construction	1771	103.5	98.2
Average for U.S. Manufacturing		72.7	68.2
Average for U.S. Contract Construction		99.8	98.1

The foregoing data for the cement manufacturing industry indicate that injuries and illness as well as severity of lost time conditions are better in respect to rates of incidences of cases and about the same in severity as the average figures for U.S. manufacturing. The data for the concrete products industry, however, are significantly poorer than the average for U.S. manufacturing.

Table 1. Classifications for Injuries and Illnesses

Classification	SIC Code	1974 Annual Employment 1000	Injuries & Illnesses (a)			Injuries (a)			Illnesses (a)		
			Total Cases	Lost Time Cases	Non Fatal ex. lost time cases	Total Cases	Lost Time Cases	Non Fatal ex. lost time cases	Total Cases	Lost Time Cases	Non Fatal ex. lost time cases
Hydraulic Cement (b)	3241	32.9	14.5	2.6	11.9	14.1	2.6	11.5	0.4	*	0.4
Cement Products:											
Concrete blocks & brick	3271	n.a.	20.1	8.4	11.6	19.5	8.2	11.2	0.6	0.2	0.4
Concrete Pdts. (n.e.c.)	3272	n.a.	23.9	10.0	13.9	23.0	9.7	13.3	0.9	0.4	0.5
Ready Mix Concrete	3273	n.a.	16.5	6.1	10.4	15.9	5.8	10.0	0.6	0.2	0.4
Concrete Work	1771	n.a.	16.7	7.1	9.6	16.1	6.9	9.1	0.6	0.2	0.4
Average U.S.											
All Manufacturing --		20,043	14.6	4.7	9.9	14.0	4.5	9.5	0.6	0.2	0.4
Contract Construction		3,957	18.3	5.9	12.4	17.9	5.8	12.1	0.4	0.1	0.3

(a) Incidence Rate = Number of cases per 100 workers at 2,000 hours per year.
(b) Total for 3 digit classification - No other 4 digit class issue.
* Less than 0.1 cases.

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PRINTING INDUSTRY

(1) Standard Industrial Classifications and Descriptions.

The printing industry, SIC Code No 27, is classified as follows at 4 digit levels (Anon., 1972).

	SIC Code
Newspaper publishing and printing	2711
Periodical publishing and printing	2721
Book publishing and printing	2731
Book printing	2732
Miscellaneous publishing and printing	2741
Commercial printing, letterpress and screen	2751
Commercial printing, lithographic	2752
Engraving and plate printing	2753
Commercial printing, gravure	2754
Manifold business forms	2761
Greeting card publishing	2771
Blank books, etc.	2782
Service industries for printing trade	2791-5

(2) Description of the Processes

Printing, the art of impressing inked letters, characters, figures and pictures onto paper or other surfaces is performed by one of the four following processes (Brung, 1968):

a) Relief or Letterpress Printing

The inked characters or figures are impressed onto paper or other material from raised surfaces on either hand or machine set cast metal type or more extensively on photo-mechanically prepared metal or plastic printing plates. This method is used principally for newspapers, periodicals and books, and employs about 50% of the industry's workers (Anon., 1976).

b) Lithographic or Planographic Printing

Inked images of the material held to plane cylindrical plates by absorbent oil and additives are transferred to the paper by an intermediate or offset roll procedure. This method is used for small newspapers, books, greeting cards, and checks. Lithography employs about one third the industry's workers and is growing much more rapidly than relief printing (Anon., 1976).

c) Intaglio or Gravure Printing

The inked characters in recessed images formed by etching or engraving into printing plates are transformed to the paper or material by pressure. Specialties, such as paper currency and stock certificates, are printed by the gravure process on high grade smooth paper.

d) Stencil or Screen Printing

Images made with ink of the consistency of thick paint are coated on silk or fine screens and transferred to surfaces by pressure. The nonprinting surfaces are covered by stencils. The method is used for heavy printing such as displays, posters and signs.

The printing process for the above methods starts in the composing rooms. Here the manuscripts are set to type, to photoset, engraved or otherwise prepared for the printing press operation. Over 50% of the workers are employed in this preparatory work for the press room.

For relief printing the type may be set manually, or by linotype machine, either direct cast or from tape. The type may be used directly or for preparing printing plates.

Phototypesetting is an alternate to metal type setting in which a photographic film of the type is prepared (rather than a metal slug). In a typical application, perforated or magnetic type is read by a machine which photographs the characters indicated on the tape. In a variation of phototypesetting, the characters are recalled from a computer, displayed on a cathode ray tube, and photographed in rapid succession.

The output of the various composition technologies are the composition plates which are then formed into press plates of metal, rubber or plastic by electrotyping or stereo typing for flat, cylindrical or blanket fed pressing.

For lithographic plates, greasy crayon is used manually or electrostatically to form the images for offset printing. In the gravure process, the plates are made by etching or engraving the composition into the surface from photographic images. Screen process stencils are made on the screen or silk from transfer images.

In producing photographic films for the above processes, the procedures, conditions, and materials for usual graphic reproductions are employed.

Except for the lithographic process, the above methods are applicable to direct printing onto the paper and material or to indirect printing using intermediate rubber covered cylinders. Lithography uses only the indirect or offset method. Platen, flatbed type presses as well as the direct rotary cylinder presses of the large scale operation can also be used for the other processes.

(3) Major Chemical and Physical Agents of Potential Concern

Chemical Agents

The chemicals and materials used for the foregoing processes are extensive and include especially the following (Carpenter and Hilliard, 1975):

Metals - Lead and lead alloys with tin and antimony for type.
Steel, copper, aluminum, zinc, magnesium, chrome, and brass for plates.
Mercury lamps and miscellaneous devices.

Mineral Acids and Salts - Nitric acid, hydrochloric acid, ferric chloride, etc. for etching.

Carbon Black and Pigments - for inks.

Organic and Petroleum Solvents - such as isopranol, methylene dichloride, napthas for thinning, cleaning and solutions.

Oils and Greases - for ink thickener, lubricants, etc.

Polymers, Gelatin, Cellulosic Esters - for photographic films and materials.

Photographic Emulsions - developers with chromates, diazo and other compounds e.g., silver salts.

Glues, Varnishes, Resins and Paints

The above list contains many substances with toxic, inflammable and other undesirable properties. The extent that they are potentially hazardous varies widely with the process and local conditions. The solvents may be emitted into the environment in the drying and testing operations and by simple surface evaporation at ambient temperatures. Other potentially hazardous materials may contaminate the workers' skin, clothing, and surroundings by washing, handling, spillage and other accidents. Carbon black in the printing ink for example, is readily air borne. Its highly absorbent properties can result in the carrying of potentially hazardous chemicals to the respiratory system and other parts of the workers' bodies.

Physical Conditions

Excessive noise commonly occurs and can cause permanent hearing damage. The standard exposure limit of 90 decibels (A scale) should not be exceeded. Press rooms and other printing plant operations may develop noise at these levels (Anon., 1975; Schillo, 1977).

Other physical conditions that impose potential safety and health hazards result from material and handling operations, moving machinery, cutting and shearing equipment, welding and brazing, hand tools, electrical circuits, loose floor plates, stairs, etc.

Ventilating and air conditioning may be required for suitable control of temperature and humidity. X-ray shielding may be indicated for some of the newer developments.

(4) Number of Workers Exposed or Employed

Approximately 400,000 printing craft workers were employed in printing occupations in 1974 (Anon., 1976). The total includes newspaper and magazine publishers as well as business and government agencies with printing operations. About 50% of the above total employees are classed as production workers (Anon., 1972a).

The entire printing and publishing industry SIC Code 27, employed 1,112,300 in 1974, divided as follows (Anon., 1976a):

Newspaper Industry	35%
Periodical Industry	6
Book Industry	9
Commercial Printing	33
Others	17
	100%

The above were employed in over 13,000 establishments throughout the U.S. ranging up to over 2,500 employees (Anon., 1972a). About 60% were publishing newspapers, 20% periodicals and 15% books.

(5) Trend in Process Use

The growth of the total industry was at an annual rate of 2% for the 5 years (1967-1972) (Anon., 1972a) in terms of paper consumed. The total employment in the industry has increased at about 1.5% per year. The several processes are increasing at the following annual rates in respect to share of the total printing business for 1963-1972 (Carpenter and Hilliard, 1975):

Letterpress process	2.5%
Lithography	10.2
Gravure	10-12
Rotogravure	12-15

The low rate of growth for total employment can be explained by labor saving improvements.

(6) Incidence of Mortality, Injury and Morbidity

The occupational injury and illness incidence rates in the U.S. as reported for 1974 are shown in Table 1 for the several classifications in the printing industry (Anon., 1976a).

As noted, the total printing industry has significantly lower rates than the national industrial average for all the degrees of injuries and illnesses reported.

The incidence of fatalities averaged 0.01 case per million hours as compared with all industry at 0.05 (Anon., 1976b).

Table 1. Occupational Injury and Illnesses Incidence Rates

Classification	SIC Code	1974 Annual Employment 1000	Injuries & Illnesses (a)			Injuries (a)			Illnesses (a)		
			Total Cases	Lost Time Cases	Non Fatal ex. Lost Time Cases	Total Cases	Lost Time Cases	Non Fatal ex. Lost Time Cases	Total Cases	Lost Time Cases	Non Fatal ex. Lost Time Cases
Newspapers (b)	2711	385.4	6.4	2.2	4.2	6.2	2.1	4.1	0.2	*	0.1
Periodicals (b)	2721	88.4	3.2	1.0	2.2	3.2	1.0	2.1	0.1	-	0.1
Books - Publishing	2731	n.a.	4.9	1.6	3.3	4.8	1.5	3.2	0.1	*	0.1
Books - Printing (b)	2732	94.2	6.9	2.2	4.7	6.8	2.1	4.8	0.1	0.1	*
Miscellaneous (b)	2741	n.a.	3.6	1.4	2.2	3.4	1.3	2.1	0.2	-	0.1
Commercial Printing:											
Ex Lithographic	2751	208.1	8.9	3.0	5.9	8.5	2.9	5.6	0.4	0.1	0.2
Lithographic	2752	151.5	9.3	2.8	6.3	9.0	2.7	6.3	0.3	0.1	0.2
Engraving & Plate	2753	n.a.	7.5	2.4	5.1	7.2	2.3	4.9	0.4	-	0.2
Gravure	2754	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Manifold-forms (b)	2761	n.a.	13.4	4.3	9.0	13.2	4.3	8.9	0.2	-	0.1
Greeting Cards (b)	2771	n.a.	6.8	1.8	4.9	6.5	1.8	4.7	0.3	-	0.2
Bankbooks (b)	2782	55.4	11.4	3.5	7.9	11.1	3.4	7.8	0.4	-	0.3
Printing Trade Services (b)	2791-5	n.a.	3.7	1.1	2.8	3.5	1.0	2.4	0.2	0.1	0.2
All Printing	27	1,113	7.5	2.4	5.0	7.2	2.3	4.9	0.2	0.1	0.1
All Manufacturing	-	65,400	10.4	3.5	6.9	10.0	3.4	6.6	0.4	0.1	0.2

(a) Incidence Rate = Number of cases per 100 workers at 2,000 hours per year.
(b) Figures for total 3 digit classification - No other 4 digit class issued.
* Less than 0.05 cases.

The lost time per case averaged 14 days for the printing industry and 16 days for all manufacturing, indicating that in the incidences of lost time cases the conditions were less serious.

It should be noted that over 50% of those employed in the printing industry are exposed to less vulnerable conditions than in the composing rooms, press rooms, and engraving operations. The incidence rates reported for the entire industry thereby mask the hazards presented by these aforementioned operations.

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ROOFING INDUSTRY
(Excluding Manufacture of Roofing Material)

1. Standard Industrial Classification and Description

Roofing, classified with sheet metal work as SIC Code No. 1761 includes installation and repair of roofing, siding, gutters, skylights and similar sections of building structures (Anon., 1972).

2. Description of the Process (Berry, 1968)

Roofing, the top cover of building structures, includes the roof deck, the insulation, if any, and the overall weather protecting surface. The surface cover may be made of one of the following:

Shingles of wood, slate or treated asbestos
Tiles of fired clay
Flexible membranes of tar treated felt or paper
Sheet metals of lead, copper or galvanized steel
Corrugated sheets of asbestos and cement or aluminum or iron

Except for the flexible membrane and flat sheet metal roofing, installation consists of fastening the shingles, tile or sheets to the sheathing or roof structure by nailing or bolting in an overlapping position that covers and protects the nails or bolts. Painting or weather coating may be added. In addition, metal cutting and fitting are required for flashing where there are ducts and other protrusions through the roof. Metal work is also required for gutters, roof drains and down spouts.

Membrane roofs either prepared or built-up at site are made from layers of tar impregnated felt or composition paper and are cemented or nailed to the roof deck. The felt is layered with molten tar or pitch in built-up roofs. Prepared roofing is made of bitumen treated paper or felt. The membrane is finally covered with tar or pitch. Gravel or similar mineral products can be embedded in the top coating as a reinforcement.

The felt may be made of organic fibers, asbestos or glass fibers. The tar or pitch in the coating has a softening point of about 150°F, flash point of about 250°F and by distillation test has less than 10% distillables below 575°F.

Polyvinyl chloride film is used commonly as a nonflammable vapor barrier below the roof covering.

Non-bituminous roofing materials are also used either as sheets or in solutions. The sheets are applied to the felt in built-up roofs. Liquid roofing materials are brushed, sprayed or rolled on to a continuous deck that remain as a film covering after the solvent evaporates. Neoprene, butyl rubber, PVC and a number of other polymers are used.

In addition to asbestos, talc, titanium dioxide and silica are minerals employed as fillers and pigments.

3. Major Chemical and/or Physical Agents of Potential Concern

Chemically, the only substances of potential concern are the bitumens, tars and pitch in the case of built-up roofing. Especially when melted, they contain volatile aromatic compounds that may cause burns and skin irritations. In enclosed spaces they can affect the respiratory surfaces if inhaled. The impregnated asbestos in roofing felts and paper are non-friable and not considered especially injurious (Fricklas, 1977).

Physically, potential concern arises from the elevation at which the work is done and the possible hazard from falling. Burns from accidents during the hoisting, spreading and mopping the hot bituminous materials are also potential hazards (Fricklas, 1977).

Tile, shingles and other roofing materials are relatively innocuous.

4. Number of Workers Exposed or Employed

About 90,000 roofers were employed in 1974. Most roofers worked for roofing contractors on construction and repair work. Others worked for business, government agencies or independently (Anon., 1976).

It is judged that 85% of the above are production workers.

5. Trend in Process Use (Anon., 1976)

Employment of roofers is expected to increase more than 1.5% per year which is approximately the average for all occupations. Repair work is one factor which keeps employment among roofers high. The prepared sheet and built-up roofing has become the largest section of the trade.

6. Incidence of Mortality, Injury and Morbidity

The incidence of accidents and illness in the roofing industry in 1974 is given along with the U.S. average for all construction work in Table 1 (Anon., 1976a).

The above reference (Anon., 1976a), shows that the lost time for roofing was 218 work days per 100 workers in 1974, or over twice the average for all contract construction work, or nearly 100, and one of the highest of all the trades and industries.

No direct data on fatalities for roofing were obtained. However, it is judged from above data to be more than the average for the construction industry (which was 0.16 cases per million hours exposure in 1975), and also more than all industry at 0.06 cases per million hours (Anon., 1976b).

Table 1. Incidence of Mortality, Injury and Morbidity
(Anon., 1976a)

Classification	SIC Code	Employment 1974 (1000)	Injuries and Illnesses (a)			Injuries (a)			Illnesses (a)		
			Total	Lost Time	Non-fatal ex. Lost Time	Total	Lost Time	Non-Fatal ex. Lost Time	Total	Lost Time	Non-Fatal ex. Lost Time
Roofing & Sheet Metal	1761	130.3	26.2	11.5	14.6	25.6	11.3	14.3	0.6	0.3	0.3
Contract Construction		3957.1	18.3	5.9	12.4	17.9	5.8	12.1	0.4	0.1	0.3

(a) Cases per 100 workers or 200,000 hours exposure per year.

7. Other Pertinent Data

As shown by above, roofing has the highest incidence rate for accidents of all classes in the contract construction trades. It is exceeded only in rate of accidents by a few cases in all of industry (Anon., 1976b).

Same causes for the high rate apparently include the elevation of the work, the use of scaffolds, and the handling of hot tar and pitch manually in containers and with spreaders. Life lines and mechanical spreaders have been found to be ineffective in reducing accidents (Fricklas, 1977). Inquiry of the National Roofers Contractors indicated other information had been supplied directly to NIOSH on roofing, health, and safety experience (Mertz, 1977).

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SLAUGHTERING AND RENDERING PLANTS

1. Standard Industrial Classifications and Descriptions

Establishments for slaughtering and rendering animals for meat products under Group Industry No. 201 are classified by SIC code as follows (Anon.,1972):

Meatpacking Plants	Code No. 2011
Sausage and Other Prepared Meat	Code No. 2013
Poultry Dressing Plants	Code No. 2016
Poultry and Eggs Processing	Code No. 7017

2. Description of the Process

Production of meat from the edible animal tissue in slaughter houses and rendering plants involves the following major processing steps (Aunan and Kolari, 1967 and Romans and Ziegler, 1974):

Slaughtering

Stunning or immobilizing the live animal by mechanical, chemical, or electric methods

Bleeding by sticking or cutting manually the carotid arteries and jugular vein of the animal

Skinning to remove hides, mechanically, manually, or scalding in water at 130-160°F

Eviscereting and dressing by manual or mechanical cutting

Chilling for storage near but above 32°F

Packing and shipping as fresh meat

Curing and Processing

Pickle and dry curing by chemical treatments, e.s., salt, nitrate, nitrate and sugar

Smoke treatment with hardwood sawdust smoke at about 150°F

Canning in enameled tin or aluminum cans or in glass bottles

Freezing at 0°F for 2-4 days or quick freezing at -20°F for sale as packaged cuts

Dehydration by heating and air drying in meat products

By-products, e.g., sausage, bologna, etc., are prepared by special mixing, and treatments. Also, edible and unedible fats, tallow, lard, soap, margarine, gland extracts, hides, gelatin, glue, bone meal, bristles, and wool are recovered as by-products.

Rendering Plants

Fat is extracted from the meat and wastes by either steam cooking (250°F at 50 psig), by dry heating under vacuum, or by continuous flash heating and centrifuging. The product may be hydrogenated to tallow, bleeded, deodorized, or otherwise treated to produce greases and lubricants. The residues are recovered as animal feeds and fertilizers.

The above operations involve procedures to improve tenderness, color, flavor, texture, and moisture and to reduce microbial spoilage. Various chemical, physical, bactericidal, enzyme, and antibiotic treatments are used.

3. Major Chemical or Physical Agents of Potential Concern

Knife accidents are the principal type of disabling accidents. Poisoning by carbon dioxide used for anesthetizing the animals before slaughtering can lead to accidents with knives and other machinery. Other hazards are caused by carbon monoxide from trucks and space heaters in poorly ventilated spaces, as well as hydrogen sulfide and methane from decomposing organic matter in closed areas such as trucks. Solvents and cleaning compounds can cause hazardous conditions. There also exist all the potential hazards from moving machines, tripping, etc. that occur in industrial operations plants (Anon., 1977).

In addition to the purely physical hazards described above, employees of slaughtering and rendering plants may be exposed to certain diseases of bacterial origin, such as brucellosis. Brucellosis is an acute or subacute infectious disease with variable manifestations (Borts and Hendricks, 1976). It is characterized by attacks of irregular fever, chills, sweating, and pain in muscles and joints, which may last for months. The disease shows remissions and although relapses are frequent, the brucellosis does produce substantial immunity to reinfection (Hall and Khan, 1972). Because it can be confused with almost any febrile episode, diagnosis is very difficult unless blood cultures are positive.

Brucellae are pleomorphic Gram-negative rods appearing either as a coccus, a bacillus, or a coccobacillus (Christie, 1974). The Brucella species classically infective for man are found in dairy cattle (B. abortus), hogs (B. suis), and sheep and goats (B. melitensis). Each of these species may occasionally infect the other animals. Brucellae are distributed throughout the infected animal and may remain viable for 21 days in a refrigerated carcass. The tissues, blood, placenta and fetus, milk, and urine may be infectious. They may survive the curing of ham, but are killed by smoking, cooking, and pasteurization (Hall and Khan, 1972). Brucellae may invade through the eye, nasopharynx, genital tract, and gut, but unbroken skin is resistant.

Most infections in man are the result of direct contact with sick animals. Certain occupations, especially working in packing plants processing swine, dairy farming, and veterinary surgery can lead to brucellosis. From 1965-1969 swine were listed as the probable source of infection in 37% of the cases in the U.S. (Borts and Hendricks, 1976); 1216 cases were reported between 1966 and

1970, of which 209 (17%) occurred in Iowa. Farm workers and packinghouse employees were responsible for 5/6 of the male cases. Human cases reported in the U.S. declined from 6000+ in 1947 to 197 in 1974. In Iowa, reported human cases decreased from 902 to 29 in the same period. According to Borts and Hendricks (1976), the actual number of brucellosis cases occurring annually is estimated to be 26 times the number reported.

Workers in slaughterhouses and meat-packing facilities are liable to heavy exposure from the nature of their work (Christie, 1974). They cut open carcasses and remove internal organs and are liable to be splashed with blood from infected animals. They often have cuts and scratches, permitting ready entry through the skin. A spectacled slaughterer usually has blood on his glasses; in one slaughterhouse spectacled workers escaped infection more often than those without glasses. The concentration of organisms in the atmosphere when killing is in progress may be high enough to produce aerosol conditions; clerical and other workers in remote parts of the building have been infected. The disposal of animal carcasses is also potentially hazardous (Mayers, 1969). Operatives in U.S. meat packing plants sometimes become infected by eating partially cooked pork during processing (Hunter, 1976). Mayers (1969) discusses 43 cases of brucellosis from June 1966 to May 1967, in a single meat packing plant in Virginia employing approximately 400 workers. One of these cases occurred in a USDA veterinarian, and another in a USDA meat inspector. All of the infected 43 had worked either full or part time in the beef or pork kill areas. The number of days lost from work averaged 19.9 days, varying from 7 to 56 days. The workers infected had been employed from 3 months to 25 years; twelve of them for less than 1 year.

Although one attack does not confer absolute immunity, a recent study suggests that slaughterhouse workers may develop a degree of resistance (Borts and Hendricks, 1976). Of previously infected employees, 3% (1/33) developed clinical brucellosis, compared with 64% (21/33) among a matched group of previously non-infected employees.

Brucellosis may be endemic among cattle and swine, which constitute the principle infection reservoirs for man in the U.S. (Mayers, 1969). The infected animals readily infect one another and their illness tends to be chronic, often shedding the organisms into their environment for many years. Removal of infected animals from herds is the only completely satisfactory solution for eradication. As more infected animals are sent for slaughter, though, the occupational risk for slaughterhouse workers rises (Christie, 1974).

4. Number of Workers Exposed

In 1974 a total of 344,200 workers were employed in the meat industry (Anon., 1976a). Eighty percent were production workers (Anon., 1972a). About 50% of the above were employed in the packing plant, as shown with the several classifications in Section 6.

5. Trends in Process Use

The total red meat eaten in the U.S. annually increased from 160.9 lbs. to 177.9 lbs. per person between 1960 and 1973, or at a rate of about 1% per year. Poultry increased about 3% per year over the same period (Romans and Ziegler, 1974).

6. Incidence of Mortality, Injury, and Morbidity

The rates of incidence for occupational injury and illness are reported in Table 1 for the several classifications in the industry for 1974 (Anon., 1976a).

The incidence of fatalities or permanent disability was 0.03 per million hours in 1975, as compared with the industrial average of 0.05 per million hours (Anon., 1976). However, the incidences of injuries and illnesses are significantly poorer than other food industries or for all manufacturing. Similarly, the lost time per case at 167.3 days per 100 workers in 1974 for the packing plants is 70% above other food industries and more than twice the industrial average (Anon., 1976a). The lost time for the entire meat industry was 142.4 days in 1974.

The high rates of injury and illness compared with industrial average are to be noted and justifies special NIOSH Publication No. 77-127 (Anon., 1977). Meat packing is the third highest in industry in respect to incidence of lost time injuries and illnesses.

Table 1. Occupational Injury and Illness Incidence Rates (Anon., 1976a)

Classification	SIC Code	1974 Annual Employment (1000)	Injuries and Illnesses (a)			Injuries (a)			Illnesses (a)		
			Total Cases	Lost Time Cases	Non-Fatal ex Lost Time	Total Cases	Lost Time Cases	Non-Fatal ex Lost Time	Total Cases	Lost Time Cases	Non-Fatal ex Lost Time
Meat packing plants	2011	171.2	32.5	13.6	188	30.7	12.8	17.8	1.8	0.8	1.0
Sausage and other prepared meats	2013	66.7	22.8	8.9	13.8	22.0	8.3	13.5	0.8	0.4	0.4
Poultry dressing plants	2015	106.5	24.2	8.8	15.4	20.6	7.6	13.0	3.6	1.2	2.4
Total meat products	201	344.2	28.2	11.3	16.9	26.1	10.5	15.6	2.1	0.8	1.3
All foods and kindred products in U.S.	20	171.2	19.6	7.4	12.2	18.8	7.1	11.7	0.8	0.5	0.5
All U.S. industry		65,400	10.4	3.5	6.9	10.0	3.4	6.6	0.4	0.1	0.2

(a) Incidence rate - number of cases per 100 workers at 200 hours per year

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WELDING AND BRAZING

(1) Standard Industrial Classification and Descriptions

Welding and brazing have no industry classification and are considered more generally as occupations that extend throughout many industries. Only the two following miscellaneous classifications related to general applications include welding and brazing specifically (Anon., 1972):

Special Trade Contracters (not elsewhere classified) - Code 1799
Welding Repair, under Miscellaneous Repair Shop - Code 7692

(2) Description of the Process (Fenton, 1970)

Welding and brazing processes for joining metallic parts or objects by fusion are conducted by a number of operating procedures. The following classifications cover the art:

Electric Arc Welding

Fusion is obtained from heat generated by electricity flowing across the airspace from the tip of a covered metal electrode, or welding rod, to the work. The filler metal is obtained from the melting electrode. The high amperage current is supplied by arc welding generating machines or rectifiers.

To prevent oxidation, shielding is provided to protect the fused metal from the air, by covering the rod with a non-metallic coating. An arc stabilizer to blanket the area may also be employed. Other constituents may be included in the electrode covering to form alloys with the deposited metal. Materials used for coating are sodium silicate, ferromanganese, talc, calcium carbamate, titanium dioxide and iron oxide. In addition, shielders may be obtained from an externally supplied gas, CO_2, argon and/or helium.

Submerged arc welding is done with bare metal electrodes using fusible material on the work, and also by using electrodes in which the flux is within the electrode.

Arc welding is the most used method of welding.

Gas Welding

The heat is supplied by combustion of a mixture of fuel gas and oxygen instead of by an electric arc. Acetylene is the principal fuel gas used in welding. Natural gas and other combustible gases can also be used.

Resistance Welding

Resistance welding is the process of fusion and coalescense from heat generated in the work by an electric current, without use of external supply of

metal. It is used principally for spot and seam welding as well as flash, upset and percusion welding.

Other Methods

Miscellaneous methods include indirection welding, laser beam welding, electron beam welding, thermit welding and other specialized procedures for joining the metal parts.

Brazing

Brazing and soldering differ from welding processes in that the base metal work does not melt appreciably. This is done by using filler metal having a melting point considerably lower than that of the work. The filler is destributed between the two surfaces of the work by capillary attraction. Brazing alloys of aluminum, silicon, copper, phosphorus, and silver melt above 800°F. Soldering alloys (mostly tin and lead) melt below 800°F. Cleaning of the surface by chemical and mechanical methods such as acid pickling and sand blasting is required prior to brazing. Soldering requires fluxes, i.e., resins and/or chlorides of zinc and ammonia. Brazing uses borates and florides.

The materials to which welding and brazing processes apply are principally carbon, low alloy and stainless steels, aluminum, nickel and its alloys, and lead.

Flame and arc cutting by welding torch are included as welding operations. Thermal spraying and oxygen cutting are related processes.

(3) Major Chemical and/or Physical Agents of Potential Concern (Battelle, 1973; Saacke, 1975; Jefferson, 1974)

Protective procedures are required to control hazards resulting from fumes, gases, radiation energy, noise, burns and the possibility of electrocution. The fumes result from volatilization of the metals and the non-metals heated. Carbon dioxide produced by the arc shielding procedures is the principal gas to be controlled. Guidelines for ventilation, protective clothing, eye protection, are available and must be applied. Carbon monoxide and nitrogen dioxide may present hazards when welding is done in confined spaces. Fumes from burning chlorine-containing plastics, e.g. PVC, are especially hazardous. When plain steel electrodes are used, long exposure with inadequate ventilation may cause a chronic bronchial cough. The condition clears a few weeks after the exposure ceases. The lungs of welders may have a sufficient deposition of iron oxide fume to cause characteristic x-ray findings (siderosis), which may complicate diagnosis of silicosis when there is associated or subsequent exposure to free silica (Patty, 1949).

In addition to the above, welding and brazing present all the potential physical hazards of industrial and construction operations.

(4) Number of Workers Exposed or Employed

It is reported that 645,000 welders and flame cutters were employed in 1945 (Anon., 1976). Three quarters of the welders were employed in the manufacture of durable goods such as ships, boilers, and heavy machinery and for construction of bridges, buildings and pipelines. Only about one fourth were employed in welding repair shops. Because welders are distributed so thoroughly throughout these operations, it is difficult to judge their numbers compared to employees in related and supportive operations.

(5) Trend of Process

The total number of employed welders is expected to increase between 25-50% before 1985 or at an annual rate of between 2-4%. This is above the national industrial average of about 1.5%.

(6) Incidence of Mortality, Injury and Morbidity

The U.S. Department of Labor report (Bulletin 1932) showing rates of occupational injuries and illnesses (Anon., 1976a) includes no separate figures for welding. The Bureau of Labor Statistics explains that as an occupation, welding has not been separated for the summary. Contact with state, National Safety Council and others developed no data on the occupation. The two classifications noted in section 1 are too broad to give useful data on welding. The only data that may be useful is that the rate for compensation for welders in welding shops is $4.90 per $100 payroll - which extrapolates to approximately the same incidence rate of 3.5 cases per 100 workers as the average for all U.S. industry (Anon., 1976a).

(7) Other Pertinent Data

The increase in current density used as welding procedures are speeded up has added to ventilation problems, radiation and thermal affects, and other hazards. Continued research on these factors in the operation are seriously needed to establish protective equipment and standards (Saacke, 1975). The American Welding Society publication Welding Environment reports the result of such a research study at Battelle Institute.

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