Appendix B
Section F

1,2-DICHLOROETHANE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Office of Science and Research

New Jersey Department of Environmental Protection

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EXECUTIVE SUMMARY

1,2-Dichloroethane (ethylene dichloride) is the highest volume synthetic hydrocarbon. Its major use is in the production of vinyl chloride; additionally, it is used as a solvent, in consumer products, as a lead scavenger in gasoline, and as a fumigant. Humans are exposed via the air and water, primarily near industrial sites. The odor threshold in water is 20 mg/L. 1,2-Dichloroethane is a mutagen and has been shown to cause cancer in rats and mice. The multistage model was used to estimate a level of risk to humans from exposure to 1,2-dichloroethane. A health-based maximum contaminant level of 0.3 ug/L was predicted to result in an excess risk of no more than 1 cancer in 10^6 individuals exposed to this level in their drinking water throughout their lifetimes.

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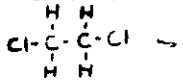
BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties

Chemical name	1,2-Dichloroethane
Synonyms	Ethylene dichloride, ethylene chloride, S-dichloroethane
CAS number	107-06-2
Chemical formula	$C_2H_4Cl_2$
Chemical structure	
Molecular weight	98.96
Physical state	clear, colorless, volatile liquid at room temperature
Melting point	-35.3 °C
Boiling point	83.7 °C
Vapor pressure	64 mm Hg at 20 °C
Specific gravity/density	1.25 at 20 °C
Water solubility	8,820 mg/L
Log octanol/water partition coefficient	1.48
Odor threshold (air)	100 ppm (Verschueren, 1983).
Odor threshold (water)	20 mg/L (Verschueren, 1983).
Conversion factor	1 ppm = 4 mg/m^3

Production and Use

1,2-Dichloroethane is produced in greater amounts than any other hydrocarbon or chlorinated hydrocarbon (Webber, 1985). It is produced by two processes in approximately equal amounts; these are catalytic chlorination of ethylene and catalytic oxychlorination of ethylene with HCl and O_2. Most manufacturing facilities use both of these processes. In 1984, an estimated 13.7 billion pounds were produced in the U.S. (Webber, 1985).

Most of the 1,2-dichloroethane produced in the U.S. (84%) is converted to vinyl chloride, usually at a facility close to the site of 1,2-dichloroethane production. In the process of making vinyl chloride, HCl is recovered and used in 1,2-dichloroethane production. 1,2-dichloroethane is also used (4%) as an intermediate in the production of 1,1,1-trichloroethane, trichloroethylene, perchloroethylene, ethyleneamines, and vinylidene chloride. Other applications include use as a solvent in industry and in consumer products, as a lead scavenger in leaded gasoline, and as a grain fumigant (U.S.EPA, 1985a).

Guidelines, Regulations, and Standards

The current OSHA standards for 1,2-dichlorethane are 50 ppm for time-weighted average, 100 ppm for ceiling concentration, and 200 ppm for peak concentration. These levels are based on non-carcinogenic effects. National Institute for Occupational Safety and Health (NIOSH) has recommended that the time weighted average not exceed 1 ppm and ceiling concentrations not exceed 2 ppm (NIOSH, 1978).

The U.S.EPA's Draft Health Advisory for 1,2-dichloroethane recommends a longer term level of 740 ug/L for a 10 kg child and 2600 ug/L for 70 kg adult, based on non-carcinogenic effects.

The recommended maximum contaminant level (RMCL) finalized by the EPA for 1,2-dichloroethane in drinking water is 0 (U.S.EPA, 1985b). The MCL proposed by U.S.EPA is 5 ug/L (U.S.EPA, 1985c).

ENVIRONMENTAL EXPOSURE

Fate and Transport

1,2-Dichloroethane can be released to air, water, or land during its production and use in the synthesis of other chemicals, and when incorporated into end-stage products, including unleaded gasoline. Seufert et al. (1980) estimated that releases to air, water, and land in 1979 were 11,885, 252, and 101 metric tons, respectively.

The principal mechanism for removal of 1,2-dichloroethane from soil and water is volatilization; biodegradation does not occur to a significant extent. The half-life for removal from a shallow, moving body of water, such as a river, is in the range of hours; longer persistence is expected in a deeper body of water, such as a lake. Experimental data from bluegill sunfish indicates that bioconcentration in aquatic organisms is not likely (Barrows et al., 1980).

The principal means of removal of atmospheric 1,2-dichloroethane is reaction with hydroxyl radicals. The half-life for this reaction has been estimated to be 1 to 4 months.

Ambient Levels

The highest atmospheric levels of 1,2-dichloroethane occur near plants manufacturing or using the compound. In a study of levels near three different facilities, the highest concentration measured was 184 ppb and the mean level at the site where the highest concentration occurred was 27.5 ppb (Elfers, 1979).

Levels were determined at Newark, Camden, and Elizabeth, N.J. daily for a six week period during the summer of 1981 and the following winter (Harkov et al., 1984). During the summer no levels above the detection limit of 0.005 ppb were found, while in the winter it was found in 26-27% of samples at all three sites with a mean level of 0.01 ppb. The peak level observed was 5.3 ppb.

1,2-dichloroethane has been detected in industrial effluents, in river water, and in finished drinking water (U.S.EPA, 1985a). In the Groundwater Supply Survey of 1980 (U.S.EPA, 1982), 1,2-dichloroethane was detected in 7 of 466 randomly chosen water supplies with a mean level of 0.5 ug/L and in 9 of 479 water supplies near potential sources of contamination with a mean level of 2.7 ug/L. In the initial round of A-280 testing, the compound was found in 3 of 635 samples (0.5%), with a mean level of 2.3 ug/L and a range of 0.6 to 5.6 ug/L.

METABOLISM AND PHARMACOKINETICS

Absorption

1,2-Dicholoroethane can be absorbed after oral, inhalation, or dermal exposure (Jakobson et al., 1982; Reitz et al., 1982). Its oral absorption is affected by the vehicle in which it is dissolved; absorption is less complete and a lower peak blood level is reached when the vehicle is oil rather than water (Withey et al., 1982).

Distribution

1,2-Dichloroethane is distributed throughout the body tissues; distribution is similar when exposure is oral or by inhalation (Reitz et al., 1982). Concentrations higher than those in blood are found in adipose tissue, but not in any other organ examined including the liver, kidney, brain, spleen, and lung (Spreafico et al., 1980). Low levels have been detected in the milk of cows administered 1,2-dichloroethane (Sykes and Klein, 1957), as well as in and the milk of women occupationally exposed (Ursova, 1953).

The level of 1,2-dichloroethane achieved in blood and other tissues is not linearly related to the dose given; increasing the dose results in a greater than linearly proportional increase in blood and tissue levels (Spreafico et al., 1980). This occurs because saturation of metabolism is achieved at high doses (see below).

No difference was found in the levels of 1,2-dichloroethane in the blood, liver, lungs, and adipose tissues of male rats 2 hours after either a single oral dose or the last of 11 daily oral doses of 50 mg/kg. This finding indicates that the compound does not tend to bioaccumulate with chronic administration (Spreafico et al., 1980).

Metabolism

The metabolism of 1,2-dichloroethane has been extensively studied both in vivo and in vitro. The major urinary metabolites are chloroacetic acid, thiodiacetic acid, and S-carboxymethylcysteine (Yllner, 1971; Reitz et al., 1982). The latter two compounds arise from degradation of the glutathione conjugates of primary metabolites (Johnson, 1966), and administration of 1,2-dichloroethane causes a rapid decrease in hepatic glutathione content in rats (Johnson, 1965).

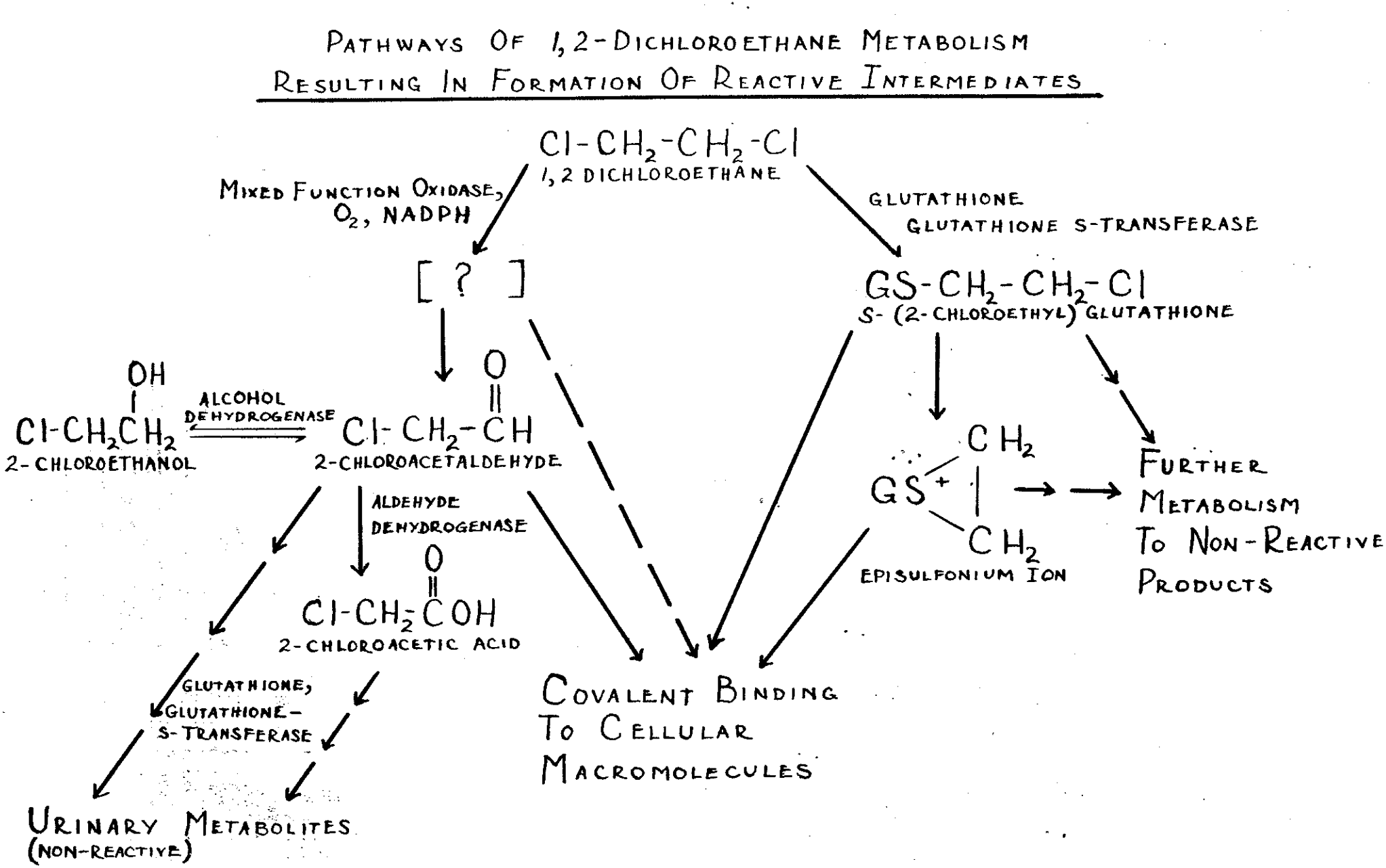
1,2-Dichloroethane is metabolized both in the microsomes and in the cytosol (Anders and Livesey, 1980; Guengerich et al., 1980). Metabolism results in formation of both inactive species and reactive intermediates capable of covalently binding to cellular macromolecules (see Figure 1).

The major pathway of microsomal metabolism involves the mixed function oxidase catalyzed formation of 2-chloroacetaldehyde; this reaction proceeds through one or more unstable intermediates. The aldehyde is converted to 2-chloroacetic acid by aldehyde dehydrogenase. The $^{14}CO_2$ detected in the breath of animals administered (^{14}C)1,2-dichloroethane is believed to derive from the microsomally produced chloroacetic acid (Yllner, 1971).

The aldehyde and the acid react with glutathione, and the resulting conjugates are modifed to S-carboxymethyl cysteine and thiodiacetic acid, which are major urinary metabolites. It is also postulated that glutathione is involved in the production of reactive, covalently binding intermediates by formation of S-(2-chloroethyl)glutathione. This compound can non-enzymatically convert to the highly reactive episulfonium ion (Guengerich et al., 1980).

Additionally, 1,2-dichloroethane is metabolized in the cytosol (Figure 1). The reactions are dependent on glutathione and glutathione S-transferases and result in formation of ethylene and the episulfonium ion (Anders and Livesey, 1980; Guengerich et al., 1980). Degradation products of the episulfonium ion (S,S-ethylene-bis-cysteine and N-acetyl-S-2-hydroxyethylcysteine) have been isolated from the urine of animals treated with 1,2-dichloroethane (Yllner et al., 1971).

FIGURE 1


PATHWAYS OF 1,2-DICHLOROETHANE METABOLISM
RESULTING IN FORMATION OF REACTIVE INTERMEDIATES
Cl-CH2-CH2-Cl
1,2 DICHLOROETHANE
MIXED FUNCTION OXIDASE, O2, NADPH
GLUTATHIONE
GLUTATHIONE S-TRANSFERASE
[?]
GS-CH2-CH2-Cl
S-(2-CHLOROETHYL) GLUTATHIONE
OH
Cl-CH2CH2
2-CHLOROETHANOL
ALCOHOL DEHYDROGENASE
O
Cl-CH2-CH
2-CHLOROACETALDEHYDE
ALDEHYDE DEHYDROGENASE
O
Cl-CH2-COH
2-CHLOROACETIC ACID
CH2
GS+
CH2
EPISULFONIUM ION
FURTHER METABOLISM TO NON-REACTIVE PRODUCTS
GLUTATHIONE, GLUTATHIONE-S-TRANSFERASE
COVALENT BINDING TO CELLULAR MACROMOLECULES
URINARY METABOLITES (NON-REACTIVE)

Macromolecular binding and DNA alkylation were observed after in vivo exposure of rats to 1,2-dichloroethane by both oral and inhalation routes (Reitz, et al., 1982). Binding was not higher in tissues in which 1,2-dichloroethane induced tumors have been observed than in non-target tissues (see below). Comparison of the extent of covalent binding after administration of 1,2-dichloroethane and 1,2-dibromoethane demonstrates that binding from 1,2-dichloroethane is less extensive than from 1,2-dibromoethane (Arfellino et al., 1984).

In vitro studies have shown that covalent binding can be mediated by both microsomal mixed function oxidases and by cytosolic glutathione S-transferases (Banerjee and Van Duuen, 1979; Guengerich et al., 1980; Arfellino et al., 1984). In recent studies aimed toward isolating adducts formed by incubating 1,2-dichloroethane with polynucleotides, adducts were identifiable after microsomal, but not cytosolic, activation (Lin et al., 1985).

Excretion

1,2-Dichloroethane is rapidly eliminated from the body. In rats, the half-life for elimination of a single interaperitoneal dose of up to 25 mg/kg (Spreafico et al., 1980) or a single oral dose of 150 mg/kg or 6 hour inhalation of 150 ppm has been reported to be less that 1 hour. Balance studies have been conducted in rats by Reitz et al. (1982) and in mice by Yllner et al. (1971) to characterize the elimination of (^{14}C)1,2-dichloroethane. In both studies the majority of the compound was eliminated as metabolites in the urine. Exhaled CO_2 derived from metabolic degradation comprised about 10% of the total metabolites. Exhalation of the unchanged compound was the third major route of elimination. Fecal elimination was minor (2% or less of the total).

Elimination is virtually complete 48 hours after dosing, and 1% or less of the administered dose is retained at 72 hours (Yllner, 1971; Reitz et al., 1982).

The proportion eliminated unchanged increases, and the proportion metabolized proportion decreases with increasing dose, because of saturation of metabolic pathways. For example, as the dose given to mice was increased from 50 to 170 mg/kg, the percentage exhaled unchanged increased from 11% to 45% (Yllner, 1971).

Human Exposure and Body Burden

Human exposure to 1,2-dichloroethane can occur via ambient air, drinking water, and food, as well as occupationally and through use of consumer products. As discussed in Ambient Levels (above), the highest atmospheric levels occur near industrial facilities where the compound is

produced or used. An atmospheric level of 6 ppb, slightly above the highest level detected in New Jersey by Harkov et al. (1984), was estimated to result in an intake of 8.2 ug/kg per day in adults and 5.7 ug/kg per day in infants (Lefkiewicz et al., 1982). A drinking water concentration of 5 ug/L, which is similar to the highest level detected in the initial round of A-280 testing, was estimated to result in an intake of 0.14 ug/kg per day in adults and 1.2 ug/kg per day in children. In studies of food containing flour made from grain fumigated with 1,2-dichloroethane, the compound was not detectable after processing the grain to flour and baking it (U.S. EPA, 1981).

1,2-Dichloroethane has been found in the breath of residents of Elizabeth and Bayonne, NJ (Pellizzari et al., 1985). The study was conducted during the fall of 1981, summer of 1982, and winter of 1983. The highest levels were found in the fall of 1981; the median level during this season was 0.38 ppb and the range was 0.10 to 0.51 ppb.

HEALTH EFFECTS

Overview

Acute exposure to 1,2-dichloroethane causes central nervous system (CNS) depression and damage to liver, kidney, lungs, heart, and other organs. Chronic exposure results in similar effects, with the severity depending on the dose and length of exposure. 1,2-Dichloroethane is a mutagen in both mammalian and bacterial *in vitro* systems; DNA alkylation, and DNA damage is seen after *in vivo* exposure. Chronic administration of 1,2-dichloroethane by gavage is associated with an increased incidence of a number of cancers in rats and mice.

Human

Acute. Acute exposure to 1,2-dichloroethane causes the same general effects in man whether exposure occures by the oral, inhalation, or dermal route (reviewed by U.S. E.P.A., 1985a). There is often a latent period before symptoms of toxicity are observed.

The CNS and the gastrointestinal tract are the primary sites affected by acute exposure. Cardiovascular, renal, and hepatic effects can also occur.

The lethal dose in adult males has been estimated to range from 8 to 200 mL (approximately 150 - 3,600 mg/kg), and death usually is attributed to circulatory and respiratory failure. An autopsy of poisoned individuals reveals generalized congestion, necrosis, and hemorrhagic lesions of many organs including the liver, kidney, spleen, brain, heart, and the respiratory and gastrointestinal tracts.

Chronic. Most of the information describing chronic occupational effects of 1,2-dichloroethane is found in reports from foreign countries (Soviet Union, Poland) and was extensively reviewed by U.S.EPA (1985a). Evaluation of many of these studies is difficult because the workers were simultaneously exposed to other solvents, and the data are incomplete or poorly reported. Symptoms associated with chronic exposure are similar to those of acute exposure to sub-lethal doses: anorexia, gastric pain, fatigue, irritability, nervousness, and other neurological effects.

In one study in which information on exposure levels is quite complete, Kozik (1957) associated occupational exposure to 1,2-dichloroethane with effects on the gastrointestinal tract, liver, gallbladder, and CNS. The atmospheric measurements reported in this study were evaluated by NIOSH (1976), and the time-weighted average exposure was estimated to be 10 to 15 ppm, which is considerably lower than the current OSHA standard of 50 ppm.

Animal

Acute. The oral LD_{50} value for 1,2-dichloroethane in rats and male mice has been reported to be 680 mg/kg (McCollister et al., 1956) and 489 mg/kg (Munson et al., 1982), respectively. Exposure to large doses, as for other halogenated solvents, causes CNS depression which can lead to coma and death. Pathologic examination reveals damage to the lungs, liver, kidneys, and adrenal gland (Heppel et al, 1945; Spencer et al., 1951). Clouding of the cornea was observed in dogs and foxes, but not in a number of other species exposed by inhalation to 1,2-dichloroethane (Heppel et al., 1945). Since this effect could be induced in other species by instillation of 1,2-dichloroethane directly into the eye, dogs may be more susceptible than other species because a greater amount of the compound reaches their eyes

Chronic. In most of the studies involving long-term exposure to 1,2-dichloroethane, the compound was administered by inhalation rather than orally.

Two studies employing oral exposure have been conducted. In the NCI carcinogenesis bioassay (1978a), B6C3F1 mice and Osborne-Mendel rats (50 per sex per dosage group, 20 per sex per vehicle control group) were administered technical grade 1,2,-dichloroethane by gavage in corn oil, 5 days per week for 78 weeks, followed by an observation period of 12-13 weeks for mice and 32 weeks for rats. For mice, the time-weighted average doses were 97 and 195 mg/kg in males and 149 and 299 mg/kg in females. For rats, the time-weighted average doses were 47 and 95 mg/kg in both sexes. Treatment related increases in tumor incidence were seen in male and female mice and rats. These will be described fully under Carcinogenicity (below). Dose dependent increased mortality occurred in female, but not male, mice and in male and female rats. The increased mortality in the

mice appeared to be tumor related, while in the rats it was probably caused by non-carcinogenic toxicity. Significantly decreased body weight occurred only in the high dose female mice. Treated rats exhibited such symptoms as hunched backs and labored breathing with greater frequency than the controls.

A subchronic study designed to assess the effects of 1,2-dichloroethane on the immune system was conducted by Munson et al. (1982). 1,2-Dichloroethane was administered to male CD-1 mice for 90 days in drinking water at time-weighted average doses of 3, 24, and 189 mg/kg. The control group consisted of 48 mice and each treatment group consisted of 32. A dose-dependent decrease in growth rate was observed; no effects were seen on the weights of the liver, spleen, lung, thymus, or kidney, or on the hemoglobin, hematocrit, blood chemistry or coagulation, numbers of erythrocytes, leukocytes, or platelets. Furthermore, no alterations were observed in several measures of cellular and humoral immune function.

In a concurrently reported 14-day range-finding study, however, administration of 4.9 and 49 mg/kg by gavage significantly decreased the number of spleen cells forming antibodies to sheep erythrocytes. The discrepancy between the effects observed in the 14-day and 90-day studies may be due to differences in blood levels achieved after bolus and drinking water administration.

A number of subchronic and chronic inhalation studies of 1,2 dichloroethane have been conducted. No adverse effects were observed in guinea pigs, rabbits, monkeys, mice or rats exposed to 100 ppm, 6 or 7 hours per day, 5 days per week, for 4 to 9 months (Heppel et al., 1946; Spencer et al., 1951; Hoffman et al., 1971). No dose-related gross or histopathological changes were seen in Swiss mice or SD rats exposed to up to 150 ppm, 7 hours per day, 5 days per week, for 78 weeks (Maltoni et al., 1980). This study is described in more detail under Carcinogenicity (below).

In a related study, additional rats were exposed simultaneously with the rats used in the Maltoni et al. (1980) study. These animals were examined for effects on hematological and clinical chemistry parameters (Spreafico et al., 1980). No treatment related effects were observed in rats which were exposed to up to 150 ppm for up to 18 months, beginning at 3 months of age. Clinical chemistry changes suggesting effects on liver and kidney function occurred in rats exposed to 50 and 150 ppm for 12 months starting at 14 months of age; these were elevated serum glutamic-pyruvic transaminase and gamma-glutamyl transpeptidase, and decreased serum glutamic-oxalacetic transaminase and cholesterol. Increased serum glutamic-oxalacetic transaminase was seen in these older animals exposed to 5 and 10 ppm.

Repeated exposure to 200 ppm 1,2-dichloroethane (7 hours per day, 5 days per week) has been reported to cause increased mortality, weight loss,

and fatty degeneration of the kidney in rats (Heppel et al., 1946) and no adverse effects in rats (Spencer et al., 1951), increased mortality in mice (Heppel et al., 1946), increased mortality, pulmonary congestion, and necrosis of the liver and adrenal cortex in guinea pigs (Heppel et al., 1946), and no effect in rabbits and monkeys (Heppel et al., 1946). Young rats much more susceptible than adult rats (Heppel et al., 1946).

Increased mortality was seen after repeated exposure to 400-500 ppm 1,2-dichloroethane in rats, guinea pigs, and rabbits (Heppel et al., 1946; Spencer et al., 1951, Hoffman et al., 1971) and monkeys (Spencer et al., 1951), while dogs (Heppel et al., 1946) and cats (Hoffman et al., 1971) were not severely affected. Histological changes were seen in the liver, kidney, heart (Heppel et al., 1946), and adrenal gland (Hoffman et al., 1971) of rats; in the liver, kidney (Heppel et al., 1946; Spencer et al., 1951), heart, and adrenal gland (Hoffman et al., 1971) of guinea pigs; in the liver and kidney of monkeys (Spencer et al., 1951); and in the heart of rabbits (Hoffman et al., 1971) exposed to these concentrations.

As the sub-chronic or chronic exposure level is increased to 1000 ppm, death occurs more quickly and similar histological changes to those seen at lower concentrations are observed. Dogs and cats were less sensitive to 1,000 ppm (7 hours per day, 5 days per week) than were rats, rabbits, or guinea pigs similarly exposed (Heppel et al., 1946).

Behavioral and Central Nervous System

The central nervous system (CNS) is one of the primary targets of 1,2-dichloroethane in both humans and experimental animals. As with other chlorinated organic solvents, acute exposure causes such symptoms as headache, dizziness, lethargy, intoxication, and unconsciousness. Occupational exposure to the compound has been associated with CNS effects such as lethargy, irritability, nervousness, and drowsiness. As discussed above, most of these reports are from the foreign literature and give insufficient information as to the level and duration of exposure and number of subjects (see U.S. EPA, 1985a). Exposure of animals to sufficient concentrations of 1,2-dichloroethane causes effects similar to those seen with other solvents. These include CNS depression resulting in inactivity, narcosis, and finally unconsciousness as levels increase (Heppel et al., 1945).

Reproductive, Embryonic, and Teratogenic

Several studies examining the potential of 1,2-dichloroethane to cause reproductive and developmental toxicity have given negative results.

In a teratology study (Rao et al., 1980), groups of 16 to 30 Sprague-Dawley rats or 19 to 21 New Zealand white rabbits were exposed to 0, 100, or 300 ppm 1,2-dichloroethane for 7 hours per day on days 6-16 and 6-18 of gestation, respectively. Increased mortality and increased

maternal toxicity were observed in the rats exposed to 300 ppm, and all litters were resorbed in this group of animals. Increased mortality occurred in both exposed groups of rabbits. No effect on the incidence of malformations, litter size, number of resorptions, or fetal body measurements was seen in the rats and rabbits at 100 ppm, or in the rabbits at 300 ppm.

In an evaluation of reproductive function (Rao et al., 1980), Sprague-Dawley rats (20 to 30 per sex per group) were exposed to 0, 25, 75, or 150 ppm 6 hours per day, 5 days per week, for 60 days prior to breeding, and 7 days per week after breeding. The animals were allowed to produce two litters. No treatment related effects were seen on fertility, number of F_1 offspring, pup body weight, survival growth, or organ weight.

Lane et al. (1982) conducted a multigeneration reproduction study in which 1,2-dichloroethane was administered in drinking water to Swiss ICR mice. The animals (10 males and 35 females per group) were exposed to nominal concentrations of 0, 5, 15, or 50 mg/kg for 35 days prior to mating. These doses did not cause adverse maternal effects. The F_0 animals produced two F_1 litters, and the second of these was bred to give two F_2 litters. No dose-related effects on fertility, litter size, pup weight, pup survival, and no dominant lethal or teratogenic effects were observed.

A number of studies carried out in the Soviet Union by Vosovaya reported reproductive toxicity from 1,2-dichloroethane (discussed in U.S. EPA, 1985a). These investigations were judged to be inadequately reported and to contain deficiencies which preclude their serious consideration (U.S.EPA, 1985a). Furthermore, exposure of rats to a concentration of 1,2-dichloroethane 10 times higher than the one reported to decrease fertility by Vosovaya (1974) did not cause reproductive effects (Rao et al., 1980).

Genetic

1,2-dichloroethane produces genetic damage in both bacterial and eukaryotic test systems.

Weak direct mutagenic effects were observed in the Ames test with TA 100 (McCann et al., 1975) and TA1535 (Rannug et al., 1976; Rannug and Ramel, 1977; Rannug et al., 1978). The postulated microsomal metabolites, chloroethanol and chloroacetaldehyde, were also tested by McCann et al. (1975). Chloroethanol was weakly mutagenic, while chloroacetaldehyde was highly mutagenic in TA 100 without metabolic activation.

Experimental results reveal that 1,2-dichloroethane is activated to species mutagenic to bacteria via cytosolic glutathione conjugation, rather than by microsomal mixed function oxidase. The mutation frequency is not increased by microsomal activation (Reitz et al., 1982) or by addition of NADPH to 9000 x g supernatant (Rannug et al., 1978). The mutation frequency

was increased by activation with cytosol (Rannug et al., 1978; Reitz et al., 1978), or glutathione-S-transferase (Rannug and Beije, 1979). Bile or perfusate from rat livers perfused with 1,2-dichloroethane, and bile from mice administered 1,2-dichloroethane was also mutagenic (Rannug and Beije, 1979); this observation is relevant because products of glutathione conjugation are usually excreted in the bile. In addition, chemically synthesized N-acetyl-S-(2-chloroethyl)-L-cysteine, the mercapturic acid end-product of glutathione conjugation of 1,2-dichloroethane, is mutagenic (Rannug and Beije, 1979). Reitz et al. (1982) demonstrated a direct correlation between bacterial mutation frequency and extent of alkylation of DNA by [^{14}C]1,2-dichloroethane.

Several other investigations of the mutagenicity of 1,2-dichloroethane toward bacteria have yielded negative results (see U.S. EPA, 1985a). In most of these studies, however, no precautions were taken to prevent the evaporation of the compound.

In regard to eukaryotic mutagenic effects, positive responses were reported in four mutagenicity tests in Drosophila (see U.S. EPA, 1985a). Two reports demonstrate mutagenicity in mammalian cells; effects at the hypoxanthine guanine phosphoribosyl transferase locus were measured. 1,2-Dichloroethane directly caused dose-related increases in mutations in Chinese hamster ovary cells (Tan and Hsie,1981). In contrast to the results seen in bacteria, mutation frequency was increased by NADPH-dependent S-9 activation. Mutations were also induced in two human lymphoblastoid cell lines, AHH-1 and TK-6 (Crespi et al., 1985); the increased sensitivity of AHH-1 compared to TK6 may be due to higher levels of glutathione S-transferase in AHH-1.

Additionally, low levels of DNA alkylation have been detected after in vivo administration (Reitz et al., 1982; Arfellino et al., 1985) and in vitro incubation (Banerjee and Van Duuren, 1978; Guengerich et al., 1980; Arfellino et al., 1984) (see Metabolism above).

Damage to hepatic DNA from B6C3F1 mice, as determined by the presence of single strand breaks and alkali labile sites, was significantly increased by oral exposure to 100 mg/kg, intraperitoneal administration of 150 mg/kg, and inhalation of 1000 ppm for 4 hours; inhalation of 500 ppm was without effect (Storer et al., 1984).

Carcinogenicity

Studies evaluating the tumorigenic potential of 1,2-dichloroethane have been conducted in rats and mice.

Van Duuren et al. (1979) applied 1,2-dichloroethane (42 or 126

mg/dose) in 0.2 mL acetone to the skin of female ICR Swiss mice (30 per group) three times weekly for several weeks. No statistically significant increases in the incidence of carcinomas of the skin was reported. At the higher dose, however, a statistically significant increase in benign lung papillomas was seen.

A/st male mice (20 per treated group, 50 per control group) were injected intraperitoneally with 0, 20, 40, or 100 mg/kg in tricaprylin 3 times weekly for 8 weeks. Their lungs were then examined for surface adenomas. No significant increase in tumor incidence in the treated animals was observed (Theiss et al., 1977).

In an early inhalation study in which Spencer et al. (1951) exposed Wistar rats (15 per sex) to 200 ppm 1,2-dichloroethane (7 hours per day, 151 times during a 212 day period) no evidence of carcinogenicity was seen.

In a carcinogenesis bioassay conducted by Maltoni et al. (1980), Sprague-Dawley rats (age 12 weeks, 90 per group per sex) and Swiss mice (age 11 weeks, 90 per group per sex, with 249 instead of 180 in the control group) were exposed to 1,2-dichloroethane (99.8% pure) 7 hours per day, 5 days per week, for 78 weeks. The doses used were 0, 5, 10, 50, and 250-150 ppm (250 ppm was used for a few days at the beginning of the experiment and then decreased to 150 ppm because of toxicity). The study included two rat and one mouse control groups; one of the rat control groups was kept in an inhalation chamber and the other two control groups were not. The animals were allowed to live until spontaneous death; the last rat died at 160 weeks.

No dose-related increase in mortality was seen in rats or male mice; mortality was slightly increased in the female rats exposed to the highest dose. Complete gross and histological examination of each animal revealed no significant increase in incidence of any type of tumor.

A recently reported inhalation study evaluated the synergistic effects of disulfiram and ethanol on 1,2-dichloroethane carcinogenicity (Cheever et al., 1985). Disulfiram potentiates the carcinogenicity of the related compound, 1,2-dibromoethane (Plotnick et al., 1980). The incidence of hemangiosarcomas, hepatocellular carcinomas, and renal tumors was greatly increased by co-administration of disulfiram. This effect may be related to disulfiram inhibition of aldehyde dehydrogenase; inhibition of this enzyme could increase levels of the reactive haloacetaldehyde intermediate. Sprague-Dawley rats (50 per sex per group) were exposed to 1,2-dichloroethane (50 ppm, 7 hours per day, 5 days per week), disulfiram (0.05% in drinking water), ethanol (5% in drinking water), 1,2-dichloroethane plus disulfiram or ethanol, or air and water alone for 24 months. Simultaneous exposure to disulfiram and 1,2-dichloroethane caused an increased incidence of intrahepatic bile duct cholangiomas, female

mammary neoplasms, and male interstitial testicular tumors compared to rats exposed to 1,2-dichloroethane alone. The incidence of these tumors did not appear to be increased by ethanol or by 1,2-dichloroethane alone.

A bioassay conducted by the NCI (1978a) showed 1,2-dichloroethane to be carcinogenic in B6C3F1 mice and Osborne-Mendel rats. The animals (50 per sex per dose) were administered 1,2-dichloroethane (99% pure, Hooper et al., 1980) in corn oil by gavage for 78 weeks, followed by an observation period of 32 weeks for rats and 12-13 weeks for mice. The initial doses were calculated from the results of preliminary subchronic range-finding studies. In mice, the time-weighted average doses were 195 and 299 mg/kg per day for high-dose males and females, respectively; and 97 and 149 mg/kg per day for low-dose males and females, respectively. For rats of both sexes, the time-weighted average doses were 95 and 47 mg/kg per day.

Two types of control groups, each containing 20 animals per sex per species, were used. One control group was untreated and the other was given the corn oil vehicle by gavage.

A dose-dependent increase in mortality was observed in the female mice and in the rats of both sexes. The increased mortality in mice appeared tumor-related, while in rats it was apparently caused by non-tumor toxicity.

A statistically significant increase in subcutaneous fibromas, squamous cell carcinomas of the forestomach, and hemangiosarcomas was seen in male rats, and in female rats, the incidence of mammary adenocarcinomas was significantly increased. Hepatocellular carcinomas and alveolar/bronchial adenomas in male mice and mammary adenocarcinomas, endometrial stromal tumors, and alveolar/bronchial adenomas in female mice were significantly increased by 1,2-dichloroethane. Incidence of these tumor types is shown in Table I.

Possible reasons for the discrepancy in results of the inhalation bioassay (Maltoni et al., 1980) and the NCI gavage study (1978) have been proposed. The tissue distribution and metabolism of 1,2-dichloroethane are similar after oral or inhalation exposure. However, higher peak blood levels, which may result in saturation of normal metabolic pathways, and greater total dose (area under the time-concentration curve) occurred after the bolus doses given by gavage, while the inhalation doses used resulted in a lower, more constant blood level (Spreafico et al., 1980; Reitz et al., 1982). Also relevant are the observations of Storer et al. (1984) as to the DNA damage caused by 1,2-dichloroethane given by different routes. Inhalation of 500 ppm for 4 hours had no effect, while an oral dose of 100 mg/kg caused DNA damage.

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

The bioassay conducted by the National Cancer Institute (NCI) (1978a) in which 1,2-dichloroethane was administered to rats and mice by gavage for 78 weeks was judged most appropriate for risk assessment. Statistically significant increases were seen in squamous cell forestomach carcinomas and hemangiosarcomas in male rats, mammary adenocarcinomas in female rats, hepatocellular carcinomas in male mice, mammary adenocarcinomas in female mice, and alveolar/bronchial carcinomas in mice of both sexes. The incidence of these tumors is shown in Table I. Data for the incidence of these tumors were fitted to the multistage model using an updated version of GLOBAL82 by K.S. Crump & Co. (1985). The daily dose to the animal representing an excess cancer risk of 10^{-6} was calculated for these tumors, and the equivalent human doses based on a surface area conversion were determined.

The dose required to cause an excess risk of 10^{-6} was lower for hemangiosacrcomas in male rats than for the other tumor types. This tumor type was also significantly increased in rats exposed to the closely related carcinogen, 1,2-dibromoethane, by gavage or inhalation (NCI, 1978b; NTP, 1982). For these reasons, the data set for hemangiosarcomas in male rats was used to calculate the MCL.

Calculation of the Health-Based Maximum Contaminant Level

The incidence of hemangiosarcomas in male rats obtained from NCI (1978a) was fitted to the multistage model using an updated version of GLOBAL82 by K.S. Crump & Co. (1985). All calculations were provided by K.S. Crump and Co.

$$P(d) = 1 - \exp(-qo - q_1 d - \ldots - q_k d^k)$$

where:

$qi \geq 0$, $i = 0,1,\ldots,k$, and where d is dose, P(d) is the lifetime probability of cancer at dose d and k, qo, ..., qk are parameters. In practice, k is set equal to the number of dose groups less one.

Extra risk above background is defined as

$$[P(d) - P(0)]/[1 - P(0)],$$

for the multistage model. Extra risk may be interpreted as the probability of the occurrence of a cancer at a dose d, given that no cancer would have occurred without any dose.

The male rats used in the NCI bioassay received time-weighted average doses of 0, 47, or 95 mg/kg per day by gavage in corn oil.

Parameters of the multistage model are estimated by the method of maximum likelihood. The likelihood method is used to calculate confidence limits.

The upper 95% confidence limit on the slope, or potency (q_1^*) derived from the model, is 2.05×10^{-2}. The dose to the test animal that represents 10^{-6} risk is 4.87×10^{-5} mg/kg per day.

Animal-to-human extrapolation is based upon the assumption that both animals and humans are equally susceptible (in terms of extra risk) to the carcinogen when dose is measured in the same unit for both species.

In this report, the mg/m^2 body surface area per day will be used for animal-to-human extrapolation. When the surface area conversion basis is used, then the human dose (Dh) measured in mg/kg per day is given by

$$Dh = Da\ (Wa/Wh)^{1/3},$$

where Da is the animal dose (10^{-6} risk), Wa and Wh are the weights of animals and humans, respectively, measured in the same units.[1]

Thus,

$$Dh(mg/kg/day) = 4.87 \times 10^{-5}\ mg/kg/day\ (.35/70)^{1/3} = 8.33 \times 10^{-6}\ mg/kg/day$$

The maximum contaminant level (MCL) that would deliver the human dose is calculated by:

$$MCL(ug/L) = \frac{Dh(mg/kg/d) \times Wh(kg) \times 1000\ (ug/mg)}{V(L/d)}$$

where V = water volume consumed daily by human

$$MCL(ug/L) = \frac{8.33 \times 10^{-6} \times 70\ kg \times 1000\ ug/mg}{2\ L}$$

$$= 0.29\ ug/L$$

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1 Let Wa and Wh be in kg, and let Sa and Sh be the surface areas of animals and humans, respectively, in m^2. Surface area is approximately proportional to body weight to the 2/3 power; this means that $Sa = KWa^{2/3}$ and $Sh = KWh^{2/3}$ for some constant K. The animal dose mg/m^2 per day that is equivalent to Da is therefore $DaWa/Sa = DaWa^{1/3}/K$. Under the surface area method for converting risk, this also represents the equivalent human dose in mg/m^2 per day. Converting the units of this dose to mg/kg per day yields $Dh = (DaWa^{1/3}/K)\ (Sh/Wh) = (DaWa^{1/3}/K)\ (KWh^{2/3}/Wh) = Da(Wa/Wh)^{1/3}$.

Therefore, using the multistage model, the drinking water MCL derived from the 95% upper bound on the 10^{-6} risk was determined to be 0.3 ug/L.

Assumptions and Uncertainty

It was assumed that the average human body weight is 70 kg and that water consumption by humans is 2 L per day.

Conclusions

A health-based lifetime maximum contaminant level of 0.3 ug/L was derived. Exposure to this level should result in an incidence of excess cancer of no more than 1 in 10^6.

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