CHRONIC TOXICITY SUMMARY

1,4-DICHLOROBENZENE

(p-dichlorobenzene; di-chloricide; p-dichlorobenzol; Paradow; Paramoth; Parazene; p-chlorophenyl chloride)

CAS Registry Number: 106-46-7

I. Chronic Toxicity Summary

Inhalation reference exposure level	**800 µg/m^3** (100 ppb)
Critical effect(s)	General effects (reduced body weights and food consumption) in rats CNS effects (tremors) in rats Respiratory/dermal effects (nasal and ocular discharge) in rats Liver effects (increased liver weight) in rats, and Kidney effects (increased kidney weight) in rats.
Hazard index target(s)	Nervous system; respiratory system; alimentary system; kidney

II. Chemical Property Summary (HSDB, 1997; CRC, 1994)

Description	White crystals, monoclinic prisms
Molecular formula	$C_6H_4Cl_2$
Molecular weight	147.01 g/mol
Boiling point	174^{o}C
Melting point	52.7^{o}C
Vapor pressure	10 torr @ 54.8^{o}C
Solubility	Soluble in chloroform, carbon disulfide, alcohol, ether, acetone, benzene
Conversion factor	1 ppm = 6.0 mg/m^3 at 25ºC

III. Major Uses and Sources

Commercial grade 1,4-dichlorobenzene (1,4-DCB) is available in the USA as a technical grade liquid, typically containing a small percentage (>0.1% by weight) of meta (1,3-DCB) and ortho (1,2-DCB) isomers; as a solution in solvent or oil suspension; or as crystalline material pressed into various forms (HSDB, 1997). Besides its role as an intermediate in the synthesis of various organics, dyes and pharmaceuticals, 1,4-dichlorobenzene is used as a space or garbage deodorizer for odor control. The insecticidal and germicidal properties of 1,4-dichlorobenzene are used to control fruit borers and ants, moths, blue mold in tobacco seed beds, and mildew and mold on leather or fabrics. In 1996, the latest year tabulated, the statewide mean outdoor monitored concentration of 1,4-DCB was approximately 0.15 ppb

(CARB, 1999). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 30,577 pounds of dichlorobenzene (CARB, 2000).

IV. Effects of Human Exposure

Case reports of human exposure to 1,4-DCB include malaise, nausea, hepatic manifestations (yellow atrophy and cirrhosis), proteinuria, bilirubinuria, hematuria, and anemia. A woman exposed to 1,4-DCB for 6 years developed central nervous system effects, including severe cerebellar ataxia, dysarthria, weakness in all limbs, and hyporeflexia (U.S. EPA, 1985).

No epidemiologic studies of 1,4-DCB exposures were located.

V. Effects of Animal Exposure

Rats, rabbits and guinea pigs were exposed to 0, 96, 158, 341 or 798 ppm (0, 577, 950, 2050 or 4800 mg/m^3) 1,4-DCB by inhalation 7 hours/day, 5 days/week for 6-7 months (Hollingsworth *et al.*, 1956). High dose animals showed marked tremors, weakness, loss of weight, eye irritation and unconsciousness. Liver and kidney changes included cloudy swelling and centrilobular cellular degeneration (liver). In another inhalation study in rats animals were exposed to 0, 75 or 500 ppm (0, 451 or 3006 mg/m^3) for 5 hours/day, 5 days/week for 76 weeks (Riley *et al.*, 1980). The authors found increased kidney and liver weights in the high dose group. Thus 75 ppm was a NOAEL. Studies with oral exposure to 1,4-DCB, including the NTP (1987) chronic bioassay study (maximum dose of 300 mg/kg-day), have also found an increased incidence of renal and hepatic lesions (cellular degeneration and focal necrosis).

Three inhalation reproductive studies, one in rabbits (Hayes *et al.*, 1985), one in mice (Anderson and Hodge, 1976), and one in rats (Chlorobenzene Producers Assn., 1986), found minimal reproductive effects. In rabbits exposed on days 6-18 of gestation to 100, 300, and 800 ppm 1,4-DCB, only the differences in percentage of implantations resorbed and in percentage of litters with resorptions were significantly increased and only in the 300 ppm group (Hayes *et al.*, 1985). No reduction in reproductive performance was observed in mice exposed to 0, 75, 225, or 450 ppm 1,4-DCB for 6 hours/day for 5 days (Anderson and Hodge, 1976).

In a two-generation reproductive study (Chlorobenzene Producers Association, 1986), Sprague-Dawley rats P1 (28/sex/group) were exposed to 0, 50, 150 or 450 ppm (0, 301, 902, or 2705 mg/m^3) of 1,4-DCB vapor, 6 hours/day, 7 days/week for 10 weeks, and then mated for 3 weeks. The second generation F1 weanlings were exposed to 1,4-DCB for 11 weeks and then mated. No developmental abnormalities were observed in pups examined. At 450 ppm significant decreases in live births, pup weights, and pup survival were seen in both the F1 and F2 generations. Non-reproductive effects observed in the parental males in the 150 and 450 ppm groups included significantly increased liver and kidney weights. All dose

levels caused hyaline droplet nephrosis in post-pubescent males; but this change was associated with the formation of alpha-2u-globulin, an abnormality considered specific for male rats with no relative human significance (U.S. EPA, 1991). The Chlorobenzene Producers Association reproductive study was chosen by the U.S. EPA to derive the RfC.

VI. Derivation of Chronic Reference Exposure Level

Study	Chlorobenzene Producers Association, 1986
Study population	Sprague-Dawley rats (28 rats/sex/group)
Exposure method	Discontinuous whole-body inhalation exposures (0, 50, 150 or 450 ppm)
Critical effects	Reduced body weights and food consumption; tremors; nasal and ocular discharge; increased liver and kidney weights
LOAEL	150 ppm
NOAEL	50 ppm
Exposure continuity	6 hr/day for 7 days/week
Average experimental exposure	13 ppm for NOAEL group (50 x 6/24)
Human equivalent concentration	13 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	10 weeks
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.1 ppm (100 ppb, 0.8 mg/m^3, 800 µg/m^3)

The chronic REL for 1,4-dichlorochlorobenzene is also the U.S. EPA RfC. OEHHA agrees with the U.S.EPA analysis. A 3-fold subchronic uncertainty factor (instead of 10) was used by U.S. EPA because of data suggesting limited progression of hepatic lesions (Riley *et al.*, 1980). Ten weeks are also greater than 8% of a rat's two-year lifetime and thus in accord with OEHHA's use of a subchronic UF of 3 (OEHHA, 2000).

For comparison, Riley *et al*. (1980) found a chronic NOAEL of 75 ppm for kidney and liver effects in rats, which is equivalent to 11.2 ppm continuous exposure. Use of an RGDR of 1 and a total UF of 30 (3 for interspecies and 10 for intraspecies) results in a REL estimate of 0.4 ppm.

VII. Data Strengths and Limitations for Development of the REL

The major strengths of the REL for 1,4-dichlorochlorobenzene are the observation of a NOAEL and the demonstration of a dose-response relationship. The major uncertainties are the lack of human data and the lack of chronic, multiple-species health effects data.

VIII. References

Anderson D, and Hodge MCE. 1976. Paradichlorobenzene: Dominant lethal study in the mouse. ICI Report No. CTL/P/296. November.

CARB. 1999. California Air Resources Board. Toxics Air Quality Data. Substance Chooser. Para-Dichlorobenzene. Available online at http://www.arb.ca.gov/aqd/toxics.htm

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Chlorobenzene Producers Association. 1986. Parachlorobenzene: Two-generation reproduction study in Sprague-Dawley rats. Study 86-81-90605. MRID No. 411088-1.

Hayes WC, Hanley TR, Gushow TS, Johnson KA, and John JA. 1985. Teratogenic potential of inhaled dichlorobenzenes in rats and rabbits. Fundam. Appl. Toxicol. 5(1): 190-202.

HSDB. 1997. Hazardous Substances Data Bank. TOMES® Vol. 33. Denver, CO: Micromedex, Inc. (edition expires 7/31/97)

Hollingsworth RL, Rowe VK, Oyen F, Hoyle HR, and Spencer HC. 1956. Toxicity of paradichlorobenzene: Determinations of experimental animals and human subjects. AMA Arch. Ind. Health. 14: 138-147.

NTP. 1987. National Toxicology Program. Toxicology and carcinogenesis studies of 1,4-dichlorobenzene in F344/N rats and B6C3F1 mice (gavage studies). NTP TR 319. NIH Publ. No. 87-2575.

OEHHA. 2000. Office of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program Risk Assessment Guidelines. Part III. Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels. Available on-line at http://www.oehha.ca.gov

Riley RA, Chart IS, Doss A, Gore CW, Patton D, and Weight TM. 1980. Para-dichlorobenzene: Long-term inhalation study in the rat. ICI Report No. CTL/P/447. August, 1980.

U.S. EPA. 1985. U.S. Environmental Protection Agency. Health Assessment Document for Chlorinated Benzenes. EPA/600/8-84/015F. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. Cincinnati, OH: U.S. EPA.

U.S. EPA. 1991. U.S. Environmental Protection Agency. Alpha-2u-Globulin: Association with Chemically Induced Renal Toxicity and Neoplasia in the Male Rat. EPA/625/3-91/019F. Prepared for the Risk Assessment Forum, U.S. EPA, Washington, DC 20460. [as cited in U.S. EPA, 1994.]

U.S.EPA. 1994. U.S. Environmental Protection Agency. 1994. Integrated Risk Information System (IRIS) Database. Reference concentration (RfC) for 1,4-Dichlorobenzene. Available online at http://www.epa.gov/ngispgm3/iris

CHRONIC TOXICITY SUMMARY

1,1-DICHLOROETHYLENE

(DCE; 1,1-dichloroethene; VDC; vinylidene chloride)

CAS Registry Number: 73-35-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**70** m**g/m^3** (20 ppb)
Critical effect(s)	Increased mortality; hepatic effects (mottled livers and increases in liver enzymes) in guinea pigs
Hazard index target(s)	Alimentary system

II. Physical and Chemical Properties (HSDB, 1994; CRC, 1994)

Description	Colorless liquid
Molecular formula	$C_2H_2Cl_2$
Molecular weight	96.95 g/mol
Boiling point	31.7°C
Melting point	–122.5°C
Vapor pressure	500 torr @ 20°C
Solubility	Soluble in water (2.5 g/L); miscible in organic solvents
Conversion factor	3.97 µg/m^3 per ppb at 25 °C

III. Major Uses and Sources

1,1-Dichloroethylene (1,1-DCE) is used in the production of polyvinylidene chloride copolymers (HSDB, 1994). 1,1-DCE containing copolymers include other compounds such as acrylonitrile, vinyl chloride, methacrylonitrile, and methacrylate. These copolymers are used in flexible packaging materials; as flame retardant coatings for fiber, carpet backing, and piping; as coating for steel pipes; and in adhesive applications. Flexible films for food packaging, such as SARAN and VELON wraps, use such polyvinylidene chloride copolymers. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 2458 pounds of vinylidene chloride (CARB, 2000).

IV. Effects of Human Exposure

Limited information exists regarding the human health effects following exposure to 1,1-DCE. A few case reports and mortality studies have reported hepatotoxicity and

nephrotoxicity after repeated, low-level exposures (USEPA, 1976; Ott *et al.*, 1976). However, these investigations were conducted in industrial settings with the possibility of mixed chemical exposures. In preliminary clinical findings reported by the EPA (1976), workers exposed to 1,1-DCE for 6 years or less had a high incidence of hepatotoxicity, with liver scans and measurements of liver enzymes revealing 50% or greater loss in liver function in 27 of 46 exposed workers. Unfortunately, no follow-up study was reported.

V. Effects of Animal Exposure

Several studies have reported on the subchronic or chronic toxicity of 1,1-DCE in laboratory animals exposed either via oral or inhalation routes. The liver is the primary target organ of 1,1-DCE toxicity following acute or chronic inhalation exposure. Such exposure is marked by both biochemical changes (alterations in serum enzyme levels) and histological changes (e.g., midzonal and centrilobular swelling, degeneration, and necrosis) (Gage, 1970; Lee *et al.*, 1977; Plummer *et al.*, 1990; Quast, 1976; Quast *et al.*, 1986). Unfortunately, these longer-term studies used only one or two doses or a limited number of animals.

Male and female rats exposed intermittently (6 hours/day, 5 days/week) to 125 or 200 ppm 1,1-DCE over 30 days exhibited centrilobular fatty degeneration or hepatocellular necrosis (Quast 1976, as cited by USDHHS, 1994). Two other studies identified hepatic changes in rats at lower concentrations of 1,1-DCE (6 hours/day, 5 days/week): cytoplasmic vacuolation after 30- or 90-day exposure to 25 or 75 ppm 1,1-DCE (Balmer *et al.*, 1976, as cited by USDHHS, 1994), and fatty changes after 6 months at 25 ppm 1,1-DCE (Quast *et al.*, 1986).

Laboratory animals appear less tolerant of continuous exposure (23-24 hours per day) than intermittent exposure. Beagle dogs exposed to 100 ppm 1,1-DCE for 8 hours/day, 5 days/week for 42 days had no evidence of hepatotoxicity, but continuous exposure to 48 ppm for 90 days caused liver changes (Prendergast *et al.*, 1967). Similarly, monkeys continuously exposed to 48 ppm for 90 days exhibited focal necrosis and hemosiderin deposition, while no liver toxicity was apparent following 42 days of intermittent exposure to 100 ppm 1,1-DCE (Prendergast *et al.*, 1967). Guinea pigs exposed to 1,1-DCE for 24 hours per day for 90 days (0, 5, 15, 25, or 48 ppm) displayed mottled livers at 15 ppm, and increased liver enzyme levels (serum glutamic-pyruvic transaminase (SGPT) and alkaline phosphatase (AP)) at 48 ppm. A NOAEL of 5 ppm based on liver changes (Prendergast *et al.*, 1967) is indicated by the results.

Data on continuously exposed guinea pigs from Prendergast *et al*. (1967)

ppm 1,1-DCE (mg/m^3)	*Survival*	*Body weight change*	*Liver AP*	*SGPT*
0	312/314	+69.0%	0.08±0.03	10±5
5 (20)	43/45	+58.6%	0.08±0.03	11±3
15 (61)	12/15	+55.3%	Not reported	Not reported
25 (101)	12/15	+74.0%	Not reported	Not reported
48 (191)	8/15	+50.3%	0.19±0.04	>70

Additional adverse effects observed to a lesser extent in laboratory animals include respiratory and renal toxicity. Nephrotoxicity observed following chronic 1,1-DCE exposure included gross organ (increases in kidney weight) (Klimisch *et al.*, 1979; Quast *et al.*, 1986) and histological changes (tubular swelling, degeneration, and necrosis) (Klimisch *et al.*, 1979; Lee *et al.*, 1977; Prendergast *et al.*, 1967). Continuous exposure of rats to 48 ppm 1,1-DCE for 90 days caused nuclear hypertrophy of the renal tubular epithelium (Prendergast *et al.*, 1976). Mice exposed to 25 ppm 1,1-DCE 4 hours/day, 4 or 5 days/week, for 52 weeks displayed severe tubular nephrotoxicity (Maltoni *et al.*, 1985 as cited by USDHHS, 1994). Nasal irritation was observed in rats exposed to 200 ppm for 4 weeks (Gage 1970). But no respiratory effects were attributed to 1,1-DCE exposure in rats, monkeys, dogs, rabbits, or guinea pigs exposed to 100 ppm intermittently for 6 weeks (Prendergast *et al.*, 1967) or in rats exposed to 75 ppm for 18 months (Quast *et al.*, 1986).

Toxicokinetic studies in laboratory animals have demonstrated that 1,1-DCE is readily absorbed and rapidly distributed following inhalation exposure (Dallas *et al.*, 1983; McKenna *et al.*, 1978b). Following inhalation exposure to radioactively labeled 1,1-DCE, rats preferentially accumulate radioactivity in the kidney and liver (McKenna *et al.*, 1978b; Jaeger *et al.*, 1977). Glutathione (GSH) conjugation appears to be the major detoxification route for 1,1-DCE intermediates, and GSH-depleting experimental states, such as drugs and fasting, may tend to increase 1,1-DCE toxicity (Jaeger *et al.*, 1977; McKenna *et al.*, 1978; Reichert *et al.*, 1978). One study greatly increased 1,1-DCE induced lethality and hepatotoxicity in rats by pretreatment with acetaminophen (Wright and Moore, 1991).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Prendergast *et al.* (1967)
Study population	Guinea pigs (15 per group, except 45 animals in 20 mg/m^3 group)
Exposure method	Continuous whole body inhalation (0, 20, 61, 101, or 189 mg/m^3)
Critical effects	Increased mortality at 61, 101, and 189 mg/m^3; hepatic effects (mottled livers and increases in SGPT and AP enzymes) noted at 189 mg/m^3
LOAEL	61 mg/m^3 (15 ppm)
NOAEL	20 mg/m^3 (5 ppm)
Exposure continuity	Continuous
Exposure duration	90 days
Average experimental exposure	20 mg/m^3 for NOAEL group
Human equivalent concentration	20 mg/m^3 for NOAEL group (gas with systemic effects, based on default assumption that RGDR = 1 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	10 (since guinea pig life-span is approx. 6 years)
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.07 mg/m^3 (70 $\mu g/m^3$; 0.02 ppm; 20 ppb)

The principal study (Prendergast *et al.*, 1967) identified adverse hepatic and/or renal effects in rats (15 or 45/group), guinea pigs (15 or 45/group), dogs (2 or 6/group), and monkeys (3, 9, or 21/group) exposed to inhaled 1,1-DCE. Continuous exposure to 1,1-DCE, 24 hours/day over 90 days, demonstrated more severe effects than intermittent exposure, 6 hours/day, 5 days/week for 6 weeks, in the species tested. Unlike the other available subchronic and chronic studies, this principal study included multiple exposure levels of 0, 5, 15, 25 and 48 ppm (0, 20, 61, 101, and 189 mg/m^3). Mortality, hematologic and body weight data were well tabulated and presented in this study. Histopathologic evaluation was conducted on the heart, lung, liver, spleen and kidneys. Following continuous exposure, adverse hepatic effects included focal necrosis in monkeys (LOAEL = 189 mg/m^3, NOAEL = 101 mg/m^3), in dogs (LOAEL = 189 mg/m^3, NOAEL = 101 mg/m^3), and in rats (LOAEL = 189 mg/m^3, NOAEL = 101 mg/m^3); and altered lipid content and increases in SGPT and alkaline phosphatase in guinea pigs (LOAEL = 189 mg/m^3, NOAEL = 20 mg/m^3). Additionally, renal alterations were observed in rats as nuclear hypertrophy in the tubular epithelium (LOAEL = 189 mg/m^3, NOAEL = 61 mg/m^3). Monkeys exposed to 1,1-DCE also displayed a greater than 25% decrease in body weight (LOAEL 189 mg/m^3, NOAEL 20 mg/m^3). The subchronic study by Prendergast *et al.* (1967) was chosen over the chronic studies because of its better design, its use of continuous exposure, and its exhibition of toxic effects below the LOAELs reported in the other studies.

Although limited in number, the other chronic and subchronic studies available consistently demonstrate adverse hepatic effects following 1,1-DCE exposure (Lee *et al.*, 1977; Maltoni *et al.*, 1985; Plummer *et al.*, 1990; Quast *et al.*, 1986). Hepatocellular fatty change was observed in rats exposed to 25 ppm or 75 ppm 1,1-DCE intermittently (6 hrs/d, 5 d/wk) for 18 months. This mid-zonal fatty change was also observed at the 12-month interim sacrifice, but did not appear to progress in severity or incidence over time (Quast *et al.*, 1986). A more severe hepatocellular necrosis and renal tubular necrosis were observed in mice exposed to 55 ppm 1,1-DCE 6 hr/d, 5 d/week for 1 year (Lee *et al.*, 1977).

For comparison, Quast *et al.* (1986) determined a LOAEL of 25 ppm for liver effects of minimal severity in rats after 18 months exposure. Use of continuous time adjustment to 4.5 ppm, multiplication by an RGDR of 1, and division by a total UF of 100 (3 for LOAEL to NOAEL, 3 for interspecies, and 10 for intraspecies) results in an estimate of 45 ppb (200 $\mu g/m^3$).

VII. Data Strengths and Limitations for Development of the REL

Uncertainty factors are appropriate due to the limited number of subchronic and chronic inhalation studies (greater than 1 year duration) in laboratory animals. In addition, few industrial surveys and epidemiological studies are available on the adverse effects of 1,1-DCE in humans; these are limited by small sample size, short follow-up, and/or brief exposure periods. But this limited evidence does suggest an association between repeated exposure to 1,1-DCE and liver damage in humans (EPA, 1976), and the key study is an animal study which found adverse hepatic effects. No toxicokinetic data regarding the absorption, distribution, metabolism or excretion of 1,1-DCE in humans are available.

VIII. References

Balmer MF, Smith FA, Leach LJ, and Yuile CL. 1976. Effects in the liver of methylene chloride inhaled alone and with ethyl alcohol. Am. Ind. Hyg. Assoc. J. 37(6):345-352.

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Dallas CE, Weir FW, Feldman S, Putcha L, and Bruckner JV. 1983. The uptake and disposition of 1,1-dichloroethylene in rats during inhalation exposure. Toxicol. Appl. Pharmacol. 68(1):140-151.

Gage JC. 1970. The subacute inhalation toxicity of 109 industrial chemicals. Br. J. Ind. Med. 27:1-18.

HSDB. 1994. Hazardous Substances Data Bank. TOMES®. Denver, CO: Micromedex.

Jaeger RJ, Shoner LG, and Coffman LJ. 1977. 1,1-Dichloroethylene hepatotoxicity: Proposed mechanism of action and distribution and binding of [^{14}C] radioactivity following inhalation exposure in rats. Environ. Health Perspect. 21:113-119.

Klimisch HJ, Deckardt K, and Mitea D. 1979. [Subchronic toxicity of vinylidene chloride in rats after 6 weeks exposure.] BASF Aktiengesellschaft, Ludwigshafen: 31. (German). HSE Translation No. 9Q. [as cited in USDHHS, 1994.]

Lee CC, Bhandari JC, Winston JM, House WB, Peters PJ, Dixon RL, and Woods JS. 1977. Inhalation toxicity of vinyl chloride and vinylidene chloride. Environ. Health Perspect. 21:25-32.

Maltoni C, Lefemine P, Chieco P, Cotti G, and Patella V. 1985. Experimental research on vinylidene chloride carcinogenesis. In: Archives of Research on Industrial Carcinogenesis. Vol. 3. Maltoni C, Mehlman MA, eds. Princeton, NJ: Princeton Scientific Publishers. [as cited in USDHHS, 1994.]

McKenna MJ, Zempel JA, Madrid EO, and Gehring PJ. 1978. The pharmacokinetics of [14C] vinylidene chloride in rats following inhalation administration. Toxicol. Appl. Pharmacol. 45:599-610.

Ott MG, Fishbeck WA, Townsend JC, and Schneider EJ. 1976. A health study of employees exposed to vinylidene chloride. J. Occup. Med. 18:735-738.

Plummer JL, de la Hall PM, Ilsley AH, Jenner MA, and Cousins MJ. 1990. Influence of enzyme induction and exposure profile on liver injury due to chlorinated hydrocarbon inhalation. Pharmacol. Toxicol. 67:329-335.

Prendergast JA, Jones RA, Jenkins LJ, and Siegel J. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 10:270-289.

Quast JF. 1976. Pathology report on male and female rats exposed to vinylidene chloride vapors for 6 hours per day, 5 days per week during a 30-day period. Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical U.S.A., Midland, MI. [as cited in USDHHS, 1994.]

Quast JF, McKenna MJ, Rampy LW, and Norris JM. 1986. Chronic toxicity and oncogenicity study on inhaled vinylidene chloride in rats. Fundam. Appl. Toxicol. 6:105-144.

Reichert D, Werner HW, and Henschler D. 1978. Role of liver glutathione in 1,1-dichloroethylene metabolism and hepatotoxicity in intact rats and isolated perfused rat liver. Arch. Toxicol. 41:169-179.

USDHHS. 1994. United States Department of Health and Human Services. Toxicological profile for 1,1-dichloroethene (update). U.S. Department of Health & Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. TP-93/07.

U.S. EPA. 1976. United States Environmental Protection Agency. Summary characteristics of selected chemicals of near-term interest. EPA-56014-76-004. Washington, DC: U.S. Environmental Protection Agency. [as cited in USDHHS, 1994.]

Wright PB, and Moore L. 1991. Potentiation of the toxicity of model hepatotoxicants by acetaminophen. Toxicol. Appl. Pharmacol. 109:327-335.

CHRONIC TOXICITY SUMMARY

N,N-DIMETHYLFORMAMIDE

(N-formyldimethylamine)

CAS Registry Number: 68-12-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**80 µg/m^3** (30 ppb)
Critical effect(s)	Liver dysfunction and respiratory irritation in humans
Hazard index target(s)	Alimentary system, respiratory system

II. Chemical Property Summary (HSDB, 1994)

Description	Colorless to very slightly yellow liquid
Molecular formula	C_3H_7NO
Molecular weight	73.09 g/mol
Boiling point	153°C
Melting point	–61°C
Vapor pressure	3.7 torr @ 25°C
Solubility	Soluble in alcohol, ether, acetone, benzene, and chloroform; miscible with water
Conversion factor	2.99 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Dimethylformamide (DMF) is primarily used as a solvent in the production of polyurethane products and acrylic fibers. It is also used in the pharmaceutical industry, in the formulation of pesticides, and in the manufacture of synthetic leathers, fibers, films, and surface coatings (Howard, 1993; Gescher, 1993; Redlich *et al.*, 1988). DMF may be emitted to the environment as a result of its use in a variety of petrochemical industries (Howard, 1993). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 18,249 pounds of DMF (CARB, 2000).

IV. Effects of Human Exposure

Among 100 workers occupationally exposed to DMF for at least one year (mean exposure of 5 years; range = 1-15 years), a statistically significant incidence of hepatic impairment, as indicated by elevated gamma-glutamyl transpeptidase levels and digestive disturbances, was noted (Cirla *et al.*, 1984). Other changes, that were not statistically significant, included

increased SGOT and SGPT and enlarged livers. The mean time-weighted average concentration of DMF was 22 mg/m^3 (range = 8-58 mg/m^3). Symptoms of irritation occurring only during work at statistically significantly higher incidences included watery eyes, dry throat, and coughing. Also, the exposed workers reported a reduced sense of smell and dry coughs at home with a statistically significant difference as compared to controls. Several of the DMF exposed workers also reported alcohol intolerance characterized by a disulfiram-type reaction (facial flushing and palpitations following alcohol ingestion). Alcohol consumption, a potential confounder, was controlled for in the study design.

A similar study was conducted on workers who had been employed in an acrylic acid fiber plant for more than 5 years (Cantenacci *et al.*, 1984). Concentrations to which the workers were exposed were characterized as either an 8-hour TWA of 18 mg/m^3 or an 8-hour TWA of 3 mg/m^3. Measures of liver function including SGOT, SGPT, gamma-glutamyl transferase, and alkaline phosphatase levels were not significantly different between exposed and unexposed workers. However, the U.S. EPA cautions that because only 54 matched pairs of workers were examined, the power of this study was not high enough to reliably detect a difference in enzyme levels.

Redlich *et al*. (1988) characterized a plant-wide outbreak of liver disease among workers in a factory coating fabric with polyurethane. Fifty-eight of 66 (88%) workers participated and each had standard liver screening function tests done at least once. At the work site DMF was being used in poorly ventilated areas without appropriate skin protection. No other major known hepatotoxic exposure was identified. Overall, 36 of 58 (62%) workers tested had elevations of either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels. Enzyme abnormalities occurred almost exclusively in production workers (35 out of 46 abnormal). Only 1 of 12 non-production workers showed elevations in enzyme levels ($p < 0.0001$). Serologic tests excluded known infectious causes of hepatitis in all but 2 workers. Changes, characteristic of liver injury, were confirmed by histologic examination of biopsy specimens from 4 workers. Improvement in liver enzyme abnormalities and symptoms in most patients were seen, after modification of work practices and removal of workers most severely affected from exposure. However, some patients showed persistent elevations of enzyme levels. No measurements or estimates of DMF exposure levels were reported.

Wang *et al*. (1991) investigated the prevalence of liver injury associated with DMF exposure in 183 of 204 (76%) employees of a synthetic leather factory by performing medical examinations, liver function tests, and creatine phosphokinase (CPK) determinations. Air concentrations were measured with personal samplers and gas chromatography. The concentration of DMF in air to which each worker was exposed was categorized as high (DMF exposure index 2: 25-60 ppm; 75-180 mg/m^3), medium (index 1: 10-40 ppm), and low (index 0: <10 ppm). High exposure concentrations were significantly associated with elevated alanine aminotransferase (ALT) levels (i.e., greater than or equal to 35 International Units/liter), a result that did not change after stratification by hepatitis B carrier status. Logistic regression analysis indicated that exposure to high DMF levels was associated with elevated ALT ($p = 0.01$), whereas hepatitis B surface antigen (HBsAg) was slightly but independently associated with elevated ALT ($p = .07$). Workers with normal ALT values had significantly higher mean ALT and aspartate aminotransferase (AST) activities, especially

among those who were not HBsAg carriers. A significant association existed between elevated CPK levels and exposure to DMF. However, an analysis of the CPK isoenzyme among 143 workers did not reveal any specific damage to muscles. Thus the authors ascribed the liver injury to DMF.

U.S. EPA (1994) states that subjective evidence of liver toxicity, such as digestive impairment and alcohol intolerance, is often observed at exposures below those that cause clinical changes in liver enzymes. Thus, the symptoms may be more sensitive indicators of hepatic impairment.

Three unexplained cases of small-for-date third trimester intrauterine deaths were observed in a group of women working as quality control analysts in the pharmaceutical industry (Farquhason *et al.*, 1983). This represented a 30% stillbirth rate as compared with the average for the general population of about 0.26%. While the authors concluded that the occurrence of stillbirth in these women was not likely due to chance, the effects cannot be solely attributed to DMF because the women were exposed to other agents in addition to DMF.

V. Effects of Animal Exposure

Malley *et al*. (1994) exposed male and female Crl:CD rats and mice to 0, 25, 100, or 400 ppm DMF for 6 hr/day, 5 days/week for 18 months (mice) or 2 years (rats). No compound-related effects on clinical observations or survival were observed. Body weights of rats exposed to 100 (males only) and 400 ppm were reduced, while body weights were increased in 400 ppm mice. No hematologic changes were observed in either species. Serum sorbitol dehydrogenase activity was increased in rats exposed to 100 or 400 ppm. DMF-related morphological changes were observed only in liver. Exposure of rats to 100 and 400 ppm produced increased relative liver weights, centrilobular hepatocellular hypertrophy, lipofuscin/hemosiderin accumulation in Kupffer cells, and centrilobular single cell necrosis (400 ppm only). In mice, increased liver weights (100 ppm males, 400 ppm both sexes), centrilobular hepatocellular hypertrophy, accumulation of lipofuscin/hemosiderin in Kupffer cells, and centrilobular single cell necrosis were observed in all exposure groups. These observations occurred in a dose-response fashion and were minimal at 25 ppm. No increase in hepatic cell proliferation was seen in mice or female rats. Slightly higher proliferation was seen in male rats exposed to 400 ppm at 2 weeks and 3 months but not at 12 months. Thus 25 ppm was a chronic NOAEL for both rats and mice.

A developmental toxicity study using three species (mice, rabbits, and rats) and four routes of administration (oral, inhalation, dermal, and intraperitoneal) identified the rabbit as the most sensitive of the three species. Groups of 15 pregnant rabbits were exposed for 6 hours per day on days 8-20 of gestation to 50, 150, or 450 ppm (150, 449, or 1350 mg/m^3) DMF (Hellwig *et al.*, 1991). Slight maternal toxicity, as indicated by non-statistically significant decreases in maternal body weight gain, was observed in the 450 ppm exposure group. An increased number of total malformations per litter was observed in the 450 ppm exposure group. Malformations observed at statistically higher incidences compared to controls included hernia umbilicalis, external variations, pseudoankylosis of the forelimbs, and skeletal

variation and retardation. The authors conclude that there was a clear teratogenic effect in rabbits following maternal exposure to 450 ppm DMF and a marginal effect following exposure to 150 ppm DMF. A NOAEL of 50 ppm for fetal and maternal effects was reported. Inhalation exposure to 150 ppm was calculated by the authors to approximate a daily dose of 45 mg/kg/day, which coincides with previous work on this compound in this species.

VI. Derivation of Chronic Reference Exposure Level

Study	Cirla *et al.*, 1984; Catenacci *et al.*, 1984
Study population	Occupationally exposed workers
Exposure method	Discontinuous inhalation exposures
Critical effects	Digestive disturbances and slight hepatic changes
LOAEL	22 mg/m^3
NOAEL	Not observed
Exposure continuity	8 hr/day (10 m^3/day), 5 days/week (assumed)
Average occupational exposure	7.9 mg/m^3 for LOAEL group (22 x 10/20 x 5/7)
Human equivalent concentration	7.9 mg/m^3
Exposure duration	5 years (mean exposure duration)
LOAEL uncertainty factor	3
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.08 mg/m^3 (80 $\mu g/m^3$, 0.03 ppm, 30 ppb)

The U.S. EPA (1994) based its RfC of 30 $\mu g/m^3$ on the same study but included a Modifying Factor (MF) of 3 due to lack of reproductive toxicity data in the DMF database. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA. Intermediate uncertainty factors were used for LOAEL to NOAEL and subchronic to chronic extrapolation because of the mild nature of the effects observed and the less than chronic exposure duration.

For comparison Hellwig *et al*. (1991) found a developmental NOAEL of 50 ppm in rabbits exposed 6 hours per day on gestation days 8-20, equivalent to continuous exposure of 12.5 ppm. Multiplication by an RGDR of 1 and division by a UF of 30 (3 for interspecies and 10 for intraspecies) results in a REL estimate of 400 ppb. The NOAEL of 25 ppm for rats and mice in the chronic study of Malley *et al*. (1994) leads to a REL estimate of 150 ppb.

VII. Data Strengths and Limitations for Development of the REL

The major strength of the REL for N,N-dimethylformamide is the availability of human health effects data over several years of exposure. The major uncertainties are the difficulty

in estimating exposure patterns and magnitude, the lack of a NOAEL observation, and the lack of complete reproductive and developmental toxicity data.

VIII. References

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

Catenacci G, Grampella D, Terzi R, Sala A, and Pollini G. 1984. Hepatic function in subjects exposed to environmental concentrations of DMF lower than the actually proposed TLV. G. Ital. Med. Lav. 6(3-4):157-158.

Cirla AM, Pisati G, Invernizzi E, and Torricelli P. 1984. Epidemiological study on workers exposed to low dimethylformamide concentrations. G. Ital. Med. Lav. 6(3-4):149-156.

Farquharson RG, Hall MH, and Fullerton WT. 1983. Poor obstetric outcome in three quality control laboratory workers. Lancet 1(8331):983-984. [cited in U.S. EPA, 1994].

Gescher A. 1993. Metabolism of N,N-dimethylformamide: key to the understanding of its toxicity. Chem. Res. Toxicol. 6(3):245-251.

HSDB. 1994. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (TOMES® CD-ROM Version). Denver, CO: Micromedex, Inc. (Edition expires 11/31/94).

Hellwig J, Merkle J, Klimisch HJ, and Jackh R. 1991. Studies on the prenatal toxicity of N,N-dimethylformamide in mice, rats and rabbits. Food Chem. Toxicol. 29(3):192-201.

Howard PH. (ed) 1993. Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Vol. IV: Solvents 2. Chelsea, MI: Lewis Publishers Inc.

Malley LA, Slone TW Jr, Van Pelt C, Elliott GS, Ross PE, Stadler JC, and Kennedy GL Jr. 1994. Chronic toxicity/oncogenicity of dimethylformamide in rats and mice following inhalation exposure. Fundam. Appl. Toxicol. 23(2):268-279.

Redlich C, Beckett WS, Sparer J, Barwick KW, Riely CA, Miller H, Sigal SL, Shalat SL, and Cullen MR. 1988. Liver disease associated with occupational exposure to the solvent dimethylformamide. Ann. Intern. Med. 108:680-686.

U.S. EPA. 1994. U.S. Environmental Protection Agency. IRIS. 1994. Integrated Risk Information System (IRIS). Reference concentration for chronic inhalation exposure (RfC) for N,N,-Dimethylformamide. Available online at http://www.epa.gov/ngispgm3/iris

Wang JD, Lai MY, Chen JS, Lin JM, Chiang JR, Shiau SJ, and Chang WS. 1991. Dimethylformamide-induced liver damage among synthetic leather workers. Arch. Environ. Health 46(3):161-166.

CHRONIC TOXICITY SUMMARY

EPICHLOROHYDRIN

(1-chloro-2,3-epoxy-propane)

CAS Registry Number: 106-89-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**3 µg/m^3** (0.8 ppb)
Critical effects	Histological changes in nasal turbinates in rats
Hazard index target(s)	Respiratory system; eyes

II. Physical and Chemical Properties (HSDB, 1997; CRC, 1994)

Description	Colorless liquid
Molecular formula	C_3H_5ClO
Molecular weight	92.52 g/mol
Density	1.181 g/cm^3 @ 20° C
Boiling point	117° C
Melting point	–26°C
Vapor pressure	13 torr @ 20° C
Solubility	Slightly soluble in water, soluble in most organic solvents
Conversion factor	1 ppm = 3.78 mg/m^3 @ 25° C

III. Major Uses and Sources

Epichlorohydrin is a major raw material used in the manufacture of epoxy and phenoxy resins. It is also used as a solvent and in the synthesis of glycerol. Other uses include that of insect fumigation and as a chemical intermediate for the formation of glycidyl acrylate derivatives such as those used in the formation of eyeglass lenses (HSDB, 1994). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 4841 pounds of epichlorohydrin (CARB, 2000).

IV. Effects of Exposures to Humans

Studies of male reproductive function have shown no evidence of decreased sperm counts in populations occupationally exposed to epichlorohydrin (Milby *et al.*, 1981).

V. Effects of Exposures in Animals

Rats were exposed for 136 weeks (6 hours/day, 5 days/week) to 0, 10, 30, or 100 ppm (0, 38, 113, or 380 mg/m^3) epichlorohydrin (Laskin *et al.*, 1980). Kidney damage in the form of renal tubular degeneration and dilatation was observed in rats exposed to 30 ppm or greater. The observation of severe inflammation in the nasal passages of 90% of the control animals, as well as in the treated animals, prevented comparison of this effect between the two groups.

A subchronic exposure of rats to 9, 17, 27, 56, or 120 ppm (34, 64, 102, 212, or 454 mg/m^3) for 6 hours/day, 5 days/week for 11-19 exposures showed evidence of extrarespiratory effects. These included liver congestion and necrosis and tubular atrophy in the kidneys at the highest concentration (Gage, 1959). Lethargy and weight loss were observed at 56 ppm.

A study on the effects of epichlorohydrin exposure for 10 weeks (6 hours/day, 5 days/week) on male and female fertility in rats and rabbits showed that male rats, exposed to 50 ppm (189 mg/m^3), were significantly less fertile than controls, as measured by successful matings to unexposed females (John *et al.*, 1979; 1983a). No histological changes were observed in the testes of the male rats at the end of exposure. No significant effects on fertility occurred in the exposed female rats. Degenerative changes in the nasal epithelium were observed in the female rats exposed to 25 ppm (94.5 mg/m^3), and in both sexes at 50 ppm.

A teratology study was carried out in rats and rabbits exposed to 0, 2.5, or 25 ppm (0, 9.5, or 95 mg/m^3) epichlorohydrin 7 hours/day during the critical days of gestation. There were no significant differences between controls and treated animals in the incidence of developmental defects, in maternal toxicity, or in histopathology of the lungs, nasal turbinates, or trachea (John *et al.*, 1983b).

Mice and rats (10/sex/concentration/strain) were exposed to 0, 5, 25, or 50 ppm (0, 19, 95, or 190 mg/m^3) epichlorohydrin for 6 hours/day, 5 days/week for 90 days (Quast *et al.*, 1979). Animals were observed for clinical signs of toxicity and were measured biweekly for body weight changes. Body weight measurements, clinical chemistry, hematology, and urinalysis were conducted. Gross and histopathological examinations were performed at the end of the experiment. Exposures of rats to 25 and 50 ppm epichlorohydrin resulted in inflammation, focal erosions, hyperplasia, and metaplasia in the nasal turbinates. No adverse effects were observed in rats exposed to 5 ppm (19 mg/m^3). Mice similarly showed focal erosion, hyperplasia and metaplasia in the epithelium of the nasal turbinates when exposed to 25 ppm epichlorohydrin or greater.

VI. Derivation of Chronic Reference Exposure Level

Study	Quast *et al.* (1979)
Study population	Rats and mice (10 per sex per concentration)
Exposure method	Discontinuous whole-body inhalation
Critical effects	Inflammation, focal erosions, hyperplasia, and metaplasia in the nasal turbinates
LOAEL	25 ppm (94.5 mg/m^3)
NOAEL	5 ppm (19 mg/m^3)
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	90 days
Average experimental exposure	0.89 ppm (5 x 6/24 x 5/7)
Human equivalent concentration	0.083 ppm (gas with extrathoracic respiratory effects, RGDR = 0.093, based on MVa = 0.14 m^3/day , MVh = 20 m^3/day, SAa(ET) = 15 cm^2), SAh(ET) = 200 cm^2
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.0008 ppm (0.8 ppb; 0.003 mg/m^3; 3 $\mu g/m^3$)

The U.S. EPA (1994) based its RfC of 1 $\mu g/m^3$ on the same study but used a subchronic UF of 10 for a 90 day study instead of 3 (OEHHA, 2000).

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for epichlorohydrin include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data, the lack of chronic inhalation exposure studies, the limited reproductive toxicity data, and the small groups tested in the study.

VIII. References

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Gage JC. 1959. The toxicity of epichlorohydrin vapour. Br. J. Ind. Med. 16:11-14.

HSDB. 1997. Hazardous Substances Data Bank. TOMES® Vol. 33. Denver, CO: Micromedex, Inc. (edition expires 7/31/97)

John JA, Quast JF, Murray FJ, *et al.* 1979. The effects of inhaled epichlorohydrin on the semen of rabbits and on the fertility of male and female rats. Toxicology Research Laboratory, Dow Chemical, Midland, MI. July 1979. NIEHS Contract No. NO1-ES-2102 (Unpublished).

John JA, Gushow TS, Ayres JA, Hanley TR, Quast JF, and Rao KS. 1983a. Teratologic evaluation of inhaled epichlorohydrin and allyl chloride in rats and rabbits. Fundam. Appl. Toxicol. 3:437-442.

John JA, Quast JF, Murray FJ, Calhoun LG, and Staples RE. 1983b. Inhalation toxicity of epichlorohydrin: effects on fertility in rats and rabbits. Toxicol. Appl. Pharmacol. 68:415-423.
/
Laskin S, Sellakumar AR, Kuschner M, Nelson N, La Mendola S, Rusch GM, Katz GV, Dulak NC, and Albert RE. 1980. Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. J. Natl. Cancer Inst. 65(4):751-757.

Milby TH, Whorton MD, Stubbs HA, Ross CE, Joyner RE, and Lipshultz LI. 1981. Testicular function among epichlorohydrin workers. Br. J. Ind. Med. 38:372-377.

OEHHA. 2000. Office of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program Risk Assessment Guidelines. Part III. Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels. Available on-line at http://www.oehha.ca.gov

Quast JF, Henck JW, Postma BJ, Schuetz DJ, and McKenna MJ. 1979. Epichlorohydrin - subchronic studies. I. A 90-day inhalation study in laboratory rodents. Toxicology Research Laboratory, Dow Chemical U.S.A., Midland, MI (unpublished).

U.S. EPA. 1994. U.S. Environmental Protection Agency. Reference concentration for epichlorohydrin. Integrated Risk Information System (IRIS), CD-ROM version. Denver, CO: Micromedex, Inc. (Edition expires 10/31/94).

CHRONIC TOXICITY SUMMARY

1,2-EPOXYBUTANE

(1-butene oxide; 1,2-butene oxide; 1,2-butylene oxide; 1,2-epoxybutane; 2-ethyloxirane; ethylethylene oxide; NCI-C55527)

CAS Registry Number: 106-88-7

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20** μ**g/m^3** (6 ppb)
Critical effect(s)	Degenerative lesions of the nasal cavity in mice
Hazard index target(s)	Respiratory system; cardiovascular system

II. Physical and Chemical Properties (HSDB, 1997)

Description	Colorless liquid with disagreeable odor
Molecular formula	C_4H_8O
Molecular weight	72.12 g/mol
Density	0.837 g/cm^3 @ 17°C
Boiling point	63.3°C
Melting point	Not available (CRC, 1994)
Vapor pressure	176 torr @ 25°C
Solubility	Soluble in ethanol, ether, acetone, water
Odor threshold	Unknown
Conversion factor	1 ppm = 2.95 mg/m^3

III. Major Uses or Sources

1,2-Epoxybutane is used as a chemical intermediate, acid scavenger, and stabilizer for chlorinated solvents (Reprotext, 1994). It is highly reactive, flammable, and undergoes exothermic polymerization reactions in the presence of acids, bases, and some salts. It is less volatile than ethylene oxide or propylene oxide (Reprotext, 1994). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 6105 pounds of 1,2-epoxybutane (CARB, 2000).

IV. Effects of Human Exposure

No human toxicological data were found for 1,2-epoxybutane.

V. Effects of Animal Exposure

F344/N rats (50/sex) were exposed to 0, 200, or 400 ppm EBU for 6 hours/day, 5 days/week for 2 years (NTP, 1988). Survival was impaired and concentration-related increases of inflammation, respiratory epithelial hyperplasia, olfactory sensory epithelial atrophy, and hyperostosis of the nasal turbinate bone cavity were observed in male and female rats exposed to either concentration.

B6C3F1 mice (50/sex) were exposed to 0, 50, or 100 ppm EBU for 6 hours/day, 5 days/week for 2 years (NTP, 1988). Survival and body weight gain were reduced significantly at 100 ppm in both sexes. Significant concentration-related increases in incidence of chronic inflammation, epithelial hyperplasia, and erosion of the nasal cavity were noted in both sexes at either concentration. Increases in granulocytic hyperplasia and splenic hematopoiesis were noted at both concentrations in female mice.

Number of mice with lesions in the nasal cavity and olfactory sensory epithelium (NTP, 1988)

Sex		*Males*			*Females*	
EBU concentration	0 ppm	50 ppm	100 ppm	0 ppm	50 ppm	100 ppm
Number of mice studied	49	49	50	50	50	48
Nasal cavity						
Chronic inflammation	0	33	40	0	39	44
Erosion	0	7	17	0	16	24
Regeneration	0	15	17	0	14	15
Epithelial hyperplasia	0	32	45	1	34	35
Squamous metaplasia	1	24	41	0	34	41
Squam. cell papilloma	0	0	1	0	0	0
Olfactory sensory epithelium – atrophy	0	13	32	0	25	35

Male and female mice exposed to 800 ppm (2360 mg/m^3) EBU for 6 hours/day, 5 days/week, for 13 weeks were listless after the first exposure (NTP, 1988). Animals from this group all died by the end of the 13-week exposure. Renal tubular necrosis, and thymic and splenic atrophy were seen in mice exposed to 800 ppm; decreased liver weights were observed following exposure of mice to 400 ppm (1180 mg/m^3) or more. Inflammation of the nasal turbinates was seen in female mice exposed to 100 ppm (295 mg/m^3) or more. No inflammation was observed in controls.

Miller *et al.* (1981) exposed rats and mice of either sex to 0, 75, 150, or 600 ppm (0, 221, 442, or 1770 mg/m^3) EBU 6 hours/day, 5 days/week, for 13 weeks. In this study, no treatment-related effects were noted except for histological lesions in the nasal mucosal epithelium and reduced specific gravity in the urine of rats treated with 600 ppm.

Wolf (1961) observed increased lung weights in rats exposed to 800 ppm of a mixture of epoxybutane isomers. No increase in lung weight was seen at 400 ppm.

Sikov *et al.* (1981) conducted experiments to determine the reproductive toxicity of EBU in rats and rabbits. Rats were exposed to 0, 250, or 1000 ppm (0, 738, or 2950 mg/m^3) 1,2-epoxybutane for 7 hours/day, 5 days/week for 3 weeks prior to gestation, or for 7 hours/day on days 1-19 of gestation. Maternal toxicity in the form of 10% weight loss was observed in rats exposed to 1000 ppm. One death out of 42 occurred in the dams exposed to 1000 ppm. No adverse histological, reproductive, or developmental effects were seen at any concentration. Exposure of rabbits on days 1-24 of gestation to the same concentrations as in the rat experiment showed more severe effects at lower concentrations than those observed in rats. In the rabbits, 6 out of 48 dams died during exposure to 250 ppm, and 14 out of 24 died at 1000 ppm. Extensive maternal mortality in this study prevented evaluation of the reproductive and developmental effects.

VI. Derivation of Chronic Reference Exposure Level

Study	National Toxicology Program (NTP, 1988)
Study population	Rats and mice
Exposure method	Discontinuous inhalation to 0, 50, or 100 ppm EBU
Critical effects	Damage to the upper respiratory epithelium was observed in both species at all concentrations. Mice also showed an increased incidence of granulocytic hyperplasia and splenic hematopoiesis at both concentrations, possibly due to inflammation in the upper respiratory tract.
LOAEL	50 ppm (mice)
NOAEL	Not observed
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	2 years
Average experimental exposure	8.9 ppm for LOAEL group (50 x 6/24 x 5/7)
Human equivalent concentration	1.8 ppm for LOAEL group (gas with extrathoracic respiratory effects, RGDR = 0.20, based on MVa = 0.06 m^3/day, MVh = 20 m^3/day, SAa(ET) = 3.0 cm^2, SAh(ET) = 200 cm^2)
LOAEL uncertainty factor	10 (high incidence of adverse effects)
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.006 ppm (6 ppb; 0.02 mg/m^3; 20 µg/m^3)

The chronic REL is also the U.S. EPA RfC (U.S. EPA, 1994). OEHHA staff reviewed and agreed with U.S. EPA's analysis of the data.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for 1,2-epoxybutane include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathological analysis. Major areas of uncertainty are the lack of adequate human exposure data and the lack of observation of a NOAEL in the key study.

VIII. References

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

HSDB. 1997. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (TOMES® CD-ROM version). Denver, CO: Micromedex, Inc. (edition expires 7/31/97).

Miller RR, Quast JF, Ayres JA, and McKenna MJ. 1981. Inhalation toxicity of butylene oxide. Fundam. Appl. Toxicol. 1(4):319-324. [as cited in: Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington, DC. (CD-ROM version). Denver, CO: Micromedex, Inc. (Edition expires 10/31/94).]

NTP. 1988. National Toxicology Program. Technical Report Series No. 329. Toxicology and Carcinogenesis Studies of 1,2-Epoxybutane (CAS No. 106-88-7) in F344 Rats and B6C3Fl Mice. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. Research Triangle Park, NC: NTP.

REPROTOX. 1994. The REPROTOX(R) System: Reproductive Reviews of Drugs, Chemicals, Physical and Biological Agents. (TOMES® CD-ROM Version). Denver, CO: Micromedex, Inc.

Sikov MR, Cannon WC, Carr DB, Miller RA, Montgomery LF, and Phelps DW. 1981. Teratologic assessment of butylene oxide, styrene oxide, and methyl bromide. Division of Biomedical and Behavioral Science, NIOSH. NIOSH/000993 14. NIOSH Technical Report No. 81-124.

U.S. EPA. 1994. U.S. Environmental Protection Agency. Integrated Risk Information System (IRIS) database. Reference concentration (RfC) for 1,2-epoxybutane. Available online at http://www.epa.gov/ngispgm3/iris

Wolf MA. 1961. Results of repeated exposures of laboratory animals to the vapors of butylene oxide(s) (Mixed isomers). Dow Chemical Biochemical Research Department. EPA/OTS Document No. 878211232. [as cited in: Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington, D.C. (CD ROM version). Denver, CO: Micromedex, Inc. (Edition expires 10/31/94]

CHRONIC TOXICITY SUMMARY

ETHYLENE DICHLORIDE

(1,2-dichloroethane)

CAS Registry Number: 107-06-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**400 µg/m^3** (100 ppb)
Critical effect(s)	Hepatotoxicity; elevated liver enzyme levels in serum of rats.
Hazard index target(s)	Liver

II. Physical and Chemical Properties (HSDB, 2000; CRC, 1994)

Description	Clear, colorless, oily liquid
Molecular formula	$C_2H_4Cl_2$
Molecular weight	98.97 g/mol
Density	1.2351 g/cm^3 @ 20ºC
Boiling point	57.4ºC
Melting point	–96.9ºC
Vapor pressure	64 torr @ 20ºC
Solubility	Slightly soluble in water (0.869 g/100 ml at 20ºC); miscible with alcohol; soluble in ordinary organic solvents
Conversion factor	1 ppm = 4.05 mg/m^3

III. Major Uses or Sources

Ethylene dichloride (EDC) is used primarily in the production of vinyl chloride monomer (HSDB, 2000). It is also an intermediate in the manufacture of trichloroethane and fluorocarbons and is used as a solvent. In California, EDC is also used as a reactant carrier in the production of solid fuel (CARB, 1997). EDC was commonly used as a gasoline additive to scavenge inorganic lead compounds. The transition to the use of lead-free gasoline has essentially eliminated the use of EDC as a fuel additive in this country. EDC was also used as a soil fumigant but is no longer registered for this use on agricultural products in the United States. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 24,935 pounds of ethylene dichloride (CARB, 2000).

IV. Effects of Human Exposure

Toxicological data resulting solely from long-term exposure to EDC in humans are lacking. Nausea, vomiting, dizziness, and unspecified blood changes were reported in a study of workers exposed to levels of 10-37 ppm EDC (Brzozowski *et al.*, 1954). Kozik (1957) reported adverse central nervous system and liver effects in workers occupationally exposed to concentrations of 16 ppm EDC and below. Rosenbaum (1947) also reported nervous system effects in a study of 100 Russian workers exposed for less than 5 years to concentrations of EDC less than 25 ppm.

Immediately following a 30-minute exposure to an unknown concentration of EDC, a 51 year-old male was somnolent and experienced vomiting (Nouchi *et al.*, 1984). Delirious and trembling, the worker was admitted to the hospital 20 hours post-exposure. The liver was palpable, but serum liver enzymes were normal. The patient lapsed into a coma 3.5 hours following admission to the hospital. A marked elevation in serum liver enzymes was noted on the second day of hospitalization, 35 hours post-exposure. Multiple organ failure occurred on the fourth day of hospitalization and the patient died of arrhythmia. At autopsy, the lungs were congested and edematous. Diffuse degenerative changes were observed in the myocardium. Extensive centrilobular necrosis was observed in the liver, and acute centrilobular necrosis was observed in the kidney. Nerve cells in the brain, including Purkinje cells, appeared shrunken with pyknotic nuclei. The latency period for hepatotoxicity of approximately 20 hours suggests that metabolism of the compound yields the reactive agent (see below).

V. Effects of Animal Exposure

As with humans, the absorption and distribution of EDC in rats following ingestion or inhalation is rapid and complete (IARC, 1999). Metabolism in rats and mice is extensive with 85% of the metabolites appearing in urine. Metabolism occurs predominantly via two pathways, one catalyzed by cytochrome P450 and one by glutathione S-transferase. The direct conjugation with glutathione catalyzed by glutathione S-transferase may ultimately result in the putative alkyating agent (episulfonium ion) primarily responsible for toxicity and carcinogenicity. Evidence for DNA-damaging metabolites resulting via the P450 pathway exists (IARC, 1999). However, this pathway appears to be a minor route for toxic metabolite formation.

Acute exposure in mice resulted in toxic effects similar to those seen in the human case study presented above, including liver and kidney damage (Francovitch *et al*., 1986). Acute EDC exposure exhibits a steep dose-response curve with respect to mortality. However, the long-term exposure studies were notable for the limited organ toxicity and mortality observed in comparison to acute studies (IARC, 1999).

Male and female rats (50 per sex) were exposed to 50 ppm EDC 7 hours per day, 5 days per week for 2 years (Cheever *et al.*, 1990). Absolute and relative liver weights were not significantly different from controls. Daily observations, gross pathology, and extensive

histopathology revealed no differences from controls other than a slight increase in unspecified testicular lesions in the EDC group. Additional rats were exposed to 50 ppm EDC with 0.05% disulfiram (a non-carcinogen used extensively in the rubber industry and as a treatment (Antabuse) for alcoholism) in the diet. Disulfiram treatment resulted in increased number of tumors, increased blood levels of EDC, and increased liver (primarily bile duct cysts) and kidney (chronic nephropathy) lesions. It was concluded that some pathways responsible for metabolism of EDC were inhibited by disulfiram, resulting in increased EDC blood levels and bioactivation to toxic metabolites via other metabolic pathways.

Rats (8-10 per sex per group) were exposed to 0, 5, 10, 50, and 150-250 ppm EDC 7 hours per day, 5 days per week for up to 18 months (Spreafico *et al.*, 1980). Serum chemistry measurements were taken after 3, 6, 12, and 18 months of exposure. Rats to be examined after 3, 6 and 18 months of exposure were 3 months of age at the beginning of the experiment, and rats to be examined after 12 months of exposure were 14 months of age at the beginning of the experiment. Complete histological exams were conducted but non-cancer effects were not discussed. No consistent treatment-related changes in serum chemistry parameters were observed at 3, 6, or 18 months of exposure. However, rats exposed to higher levels of EDC for 12 months exhibited changes in serum chemistry indicative of chronic liver damage, primarily increased alanine aminotransferase (ALT) levels at the two highest exposures. Lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) levels were significantly decreased, but did not appear to be dose-related. γ-Glutamyl transpeptidase levels were elevated but at non-significant levels. Indicators of kidney toxicity included increased blood urea nitrogen levels in the 150 ppm group and increased uric acid levels at the two highest exposures. However, the control values for both of these parameters were significantly lower than that seen in rats tested at other times in this study. Thus, the toxicological significance is questionable. Cholesterol was reduced significantly at the higher exposure levels but the toxicological significance of this finding was unknown. The marked difference between serum chemistry parameters following 12 months of exposure, compared to those following 3, 6, and 18 months of exposure, may be due to the considerable difference in the age of the rats at the start of exposure. This study identifies a 12-month LOAEL of 50 ppm and a NOAEL of 10 ppm in rats.

A study examining the interaction between 1,2-dichloroethane and disulfiram (DSF) exposed rats to EDC concentrations of 150, 300, or 450 ppm 5 days per week for 30 days (Igwe *et al.*, 1986a; Igwe *et al.*, 1986b). Increased liver weights and increased 5-nucleotidase (5-NT) activity were observed in rats following exposure to 450 ppm EDC (the LOAEL for this study). This study also determined that the interaction between DSF and EDC greatly increased the toxicity of EDC (i.e., increased serum activities of SDH, APT, and 5-NT, bilateral testicular atrophy, periportal necrosis and cytoplasmic swelling of hepatocytes, and bile duct proliferation). Therefore, any person exposed to DSF either occupationally or therapeutically is likely to be more susceptible to the effects of EDC toxicity.

Rats, rabbits, guinea pigs, dogs, cats, and monkeys were used in exposures ranging from approximately 100 to 1000 ppm EDC (Heppel *et al.*, 1946). At the highest experimental concentration of 963 ppm, high mortality was observed in rats, rabbits, and guinea pigs following exposure 7 hours per day, 5 days per week for two weeks or less. At 963 ppm

guinea pigs exhibited lacrimation and inactivity during exposure; pulmonary congestion was noted at autopsy. Rats exposed to this concentration exhibited degenerative proliferative changes in the renal tubular epithelium and splenitis. Pulmonary congestion and focal hemorrhage were also noted in 2 of 4 rats examined. While 4 of 6 cats exposed to this concentration survived until sacrifice 11 weeks following termination of exposure, congestion and fatty infiltration of the liver were observed at necropsy. Due to high mortality in the rodents at the higher concentration, a subsequent experiment exposed rats and guinea pigs 7 hours per day, 5 days per week to 100 ppm EDC for four months. No increase in mortality or effects on growth was observed in rats exposed to this concentration. The rats were successfully bred and their pups were exposed with the dams. No significant findings were observed upon gross and histological examinations of 10/39 exposed and 10 control rats. This study is severely limited by the methods used to determine the exposure concentration and by the lack of quantitative measurements of toxicity other than death. This study does, however, indicate that fatty infiltration of the liver is one indication of toxicity following multiple exposures to EDC.

In developmental toxicity studies summarized by Zhao *et al.* (1997), rats were exposed to 0, 24.8, and 207.6 mg/m^3 (equivalent to 0, 6, and 51 ppm) EDC for 6 hr/day from two weeks before mating and throughout gestation. Statistically significant increases in pre-implantation loss and decreased male pup weights were observed at the highest dose. Gross skeletal and visceral malformations were not found.

In a developmental study by Payan *et al.* (1995), Sprague-Dawley rats were exposed to 150, 200, 250, or 300 ppm EDC for 6 hrs/day from day 6 to 20 of gestation. Maternal toxicity (reduced body weight gain; death of two females) was observed at the highest exposure. Statistically significant evidence of altered growth and teratogenic effects were not observed at any concentration.

Rao *et al*. (1980) exposed rats and rabbits to 100 or 300 ppm EDC for 7 hr/day on days 6 through 15 (rats) or 6 through 18 (rabbits) of gestation. Maternal toxicity (mortality) was observed in rabbits at 100 ppm, and both species at 300 ppm. One rat exhibited resorption of all implantations at the maternally-toxic dose. Otherwise, no fetotoxic or teratogenic effects were observed in either species. In a reproduction study, rats were exposed to 25, 75, or 150 ppm EDC 6 hr/day, 5 days/week for 60 days before breeding. Exposure following this period was 6 hr/day, 7 days/week. Maternal animals were not exposed to EDC from gestational day 21 through day 4 postpartum. EDC had no effect on reproduction over one generation within two litters.

In a two-generation study conducted by Lane *et al.* (1982), ICR Swiss mice were administered 30, 90, or 290 mg/L EDC in drinking water (equivalent to about 5, 15, or 50 mg/kg bw/day) starting five weeks before mating of the F_0 generation. No treatment-related effects on fertility, gestation, viability, weight gain, or lactation indices were noted. EDC exposure did not result in teratogenic or dominant lethal effects.

No gross or histopathological indications of hepato- or nephrotoxicity were observed in Osborn-Mendel rats (47 or 95 mg/kg bw/day, 5 days/week for both sexes) or B6C3F1 mice

(97 or 195 mg/kg bw/day, 5 days/week for males; 149 or 299 mg/kg bw/day, 5 days/week for females), which were given EDC via gavage for 78 weeks (NCI, 1978). However, rats of each sex and female mice had significantly reduced survival at the highest dose.

In a comparative study of the toxicity of EDC, Morgan *et al.* (1990) administered 0, 500, 1000, 2000, 4000, and 8000 ppm in drinking water to several species of rats for 13 weeks. A statistically significant increase in kidney weight was observed in male and female Fischer 344/N rats administered 1000 ppm or greater in drinking water. However, minimal histological damage was observed only in the kidney of female Fischer 344/N rats. A statistically significant decrease in body weight was observed in rats administered 8000 ppm. Significant decreases in absolute and relative kidney weight were observed in male and female rats administered concentrations of 1000 ppm EDC. A significant increase in relative liver weight was observed in male rats administered 2000 ppm EDC and greater and female rats administered 4000 ppm EDC and greater. Similar but less marked toxicity was observed in the Sprague-Dawley and Osborne-Mendel rats administered 1000 ppm. Additionally, rats were administered EDC in corn oil by gavage at doses of 0, 30, 60, 120, 240, and 480 mg/kg for 13 weeks (Morgan *et al.*, 1990). Rats administered EDC by gavage exhibited high mortality in the higher dose groups. Statistically significant increases in kidney weights were observed in surviving male rats administered EDC and in female rats administered 120 or 240 mg/kg. However, no histological damage to the liver or kidney was observed.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Spreafico *et al.*, 1980.
Study population	Rats (8-10 per sex/group)
Exposure method	Discontinuous whole-body inhalation exposures (0, 5, 10, 50, or 150-250 ppm)
Critical effects	Significant elevation in liver enzymes
Exposure duration	12 months
Exposure continuity	7 hours/day, 5 days/week
LOAEL	50 ppm
NOAEL	10 ppm
Average experimental exposure	2.1 ppm for NOAEL group (10 x 7/24 x 5/7)
Human equivalent concentration	3.2 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.5 for lambda (a) : lambda (h)) (Gargas *et al*., 1989)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.1 ppm (100 ppb; 0.4 mg/m^3; 400 μg/m^3)

Cheever *et al*. (1990) and Spreafico *et al.* (1980) were the only chronic inhalation exposure studies found in the literature that presented non-cancer effects. No reproductive and

developmental effects were observed in studies published in peer-reviewed journals. The study by Spreafico *et al*. (1980) was chosen for REL development based on the utilization of multiple exposure levels and the observation of a NOAEL and a LOAEL for liver effects.

The Agency for Toxic Substances and Disease Registry (ATSDR) calculated a chronic inhalation minimal risk level (MRL) for EDC of 0.2 ppm (ATSDR, 1994). The calculation was based on the study by Cheever *et al*. (1990), which determined a free-standing NOAEL of 50 ppm for lack of liver effects. A LOAEL was not determined. To derive the MRL, the ATSDR applied uncertainty factors (UFs) of 10 each for intraspecies and interspecies variability, and a modifying factor of 3 to account for database deficiencies, to the NOAEL of 50 ppm. The criteria for use of modifying factors are not well specified by ATSDR. Such modifying factors were not used by OEHHA. A continuity correction for discontinuous exposure was not applied. The resulting MRL was 0.2 ppm (0.7 mg/m^3).

For comparison to the proposed REL, a REL developed by OEHHA based on the free-standing NOAEL of 50 ppm determined in rats by Cheever *et al*. (1990) would include a continuity correction (50 ppm x 7/24 x 5/7) resulting in an equivalent continuous level of 10.42 ppm.. Application of an RGDR = 1.5 and UFs of 3 for interspecies and 10 for intraspecies differences result in a REL of 0.5 ppm (2 mg/m^3).

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for ethylene dichloride include the availability of chronic inhalation exposure data, the relatively large number of exposure levels at lower concentrations (allowing for better elucidation of the dose-response relationship for hepatotoxicity), and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data, the small groups tested in the key study, and the lack of health effects data from multiple species.

The small number of animals per group and the relatively modest clinical chemistry findings observed in the Spreafico *et al.* (1980) study may have resulted in false-positives, false-negatives, and lack of clear dose-response relationships. Repeating the study in one or more experimental animal species with full histopathological examination of organs and a greater number of animals/dose would significantly enhance the chronic toxicity database for EDC.

VIII. References

ATSDR. 1994. Agency for Toxic Substances and Disease Registry. Toxicological Profile for 1,2-Dichloroethane (Update). U.S. Department of Health and Human Services, Public Health Service.

Brzozowski J, Czajka J, Dutkiewicz T, Kesy I, and Wojcik J. 1954. Work hygiene and the health condition of workers occupied in combating the *Leptinotarsa decemlineata* with HCH and dichloroethane. Med. Pr. 5: 89-98. [cited in U.S. EPA, 1985].

CARB. 1997. California Air Resources Board. Ethylene Dichloride. In: Toxic Air Contaminant Identification List Summaries. California Environmental Protection Agency, pp. 483-487.

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Cheever KL, Cholakis JM, El-Hawari AM, Kovatch RM, and Weisburger EK. 1990. Ethylene dichloride: The influence of disulfiram or ethanol on oncogenicity, metabolism, and DNA covalent binding in rats. Fundam. Appl. Toxicol. 14:243-261.

Francovitch RJ, Schor NA, and George WJ. 1986. Effects of SKF-525A, phenobarbitol, and 3-methylcholanthrene on ethylene dichloride toxicity following inhalation exposure. J. Am. Coll. Toxicol. 5(2):117-126.

Gargas ML, Burgess RJ, Voisard DE, Cason GH, and Anderson ME. 1989. Partition coefficients of low-molecular weight volatile chemicals in various liquids and tissues. Toxicol. Appl. Pharmacol. 98:87-99.

HSDB. 2000. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD. Available online through Toxicology Data Network at http://toxnet.nlm.nih.gov

Heppel LA, Neal PA, Perrin TL, Endicott KM, and Porterfield VT. 1946. The toxicology of 1,2-dichloroethane (ethylene dichloride). V. The effects of daily inhalations. J. Ind. Hyg. Toxicol. 28(4):113-120.

IARC. 1999. International Agency for Research on Cancer. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. IARC Monogr. Eval. Carcinog. Risks Hum. 71(Pt.2):501-529.

Igwe OJ, Que Hee SS, and Wagner WD. 1986a. Interaction between 1,2-dichloroethane and disulfiram. I. Toxicological effects. Fundam. Appl. Toxicol. 6:733-746.

Igwe OJ, Que Hee SS, and Wagner WD. 1986b. Interaction between 1,2-dichloroethane and tetraethylthiuram disulfide (disulfiram). II. Hepatotoxic manifestations with possible mechanism of action. Toxicol. Appl. Pharmacol. 86:286-297.

Kozik I. 1957. Problems of occupational hygiene in the use of dichloroethane in the aviation industry. Gig. Tr. Prof. Zabol. 1:31-38. [cited in U.S. EPA, 1985].

Lane RW, Riddle BL, and Borzelleca JF. 1982. Effects of 1,2-dichloroethane and 1,1,1-trichloroethane in drinking water on reproduction and development in mice. Toxicol. Appl. Pharmacol. 63:409-421.

Morgan DL, Bucher JR, Elwell MR, Lilja HS, and Krishna Murthy AS. 1990. Comparative toxicity of ethylene dichloride in F344/N, Sprague-Dawley and Osborne-Mendel rats. Food Chem. Toxicol. 28(12):839-845.

NCI. 1978. United States National Cancer Institute. Bioassay of 1,2-dichloroethane for possible carcinogenicity CAS No. 107-06-2 (NCI-CG-TR-55), Washington DC.

Nouchi T, Miura H, Kanayama M, Mizuguchi O, and Takano T. 1984. Fatal intoxication by 1,2-dichloroethane - a case report. Int. Arch. Occup. Environ. Health 54:111-113.

Payan JP, Saillenfait AM, Bonnet P, Fabry JP, Langonne I, and Sabate JP. 1995. Assessment of the developmental toxicity and placental transfer of 1,2-dichloroethane in rats. Fundam. Appl. Toxicol. 28:187-198.

Rao KS, Murray JS, Deacon MM, John JA, Calhoun LL, and Young JT. 1980. Teratogenicity and reproduction studies in animals inhaling ethylene dichloride. In: Banbury Report 5. Ethylene Dichloride: A Potential Health Risk? Ames B, Infante P, and Reitz R. (eds). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory. pp. 149-166.

Rosenbaum ND. 1947. Ethylene dichloride as an industrial poison. Gig. Sanit. 12(2): 17-21. [cited in U.S. EPA, 1985].

Spreafico F, Zuccato E, Marcucci F, Sironi M, Paglialunga S, Madonna M, and Mussini E. 1980. Pharmacokinetics of ethylene dichloride in rats treated by different routes and its long-term inhalatory toxicity. In: Banbury Report 5. Ethylene Dichloride: A Potential Health Risk? Ames B, Infante P, and Reitz R. (eds). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory. pp. 107-129.

U.S. EPA. 1985. U.S. Environmental Protection Agency. Health Assessment Document for 1,2-Dichloroethane (Ethylene Dichloride). U.S. EPA, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. Research Triangle Park, NC: U.S. EPA.

Zhao S-F, Zhang X-C, Zhang L-F, Zhao S-S, Zhang F, Wang Q-F, Wang Y-L, and Bao Y-S. 1997. The evaluation of developmental toxicity of chemicals exposed occupationally using whole embryo culture. Int. J. Dev. Biol. 41:275-282.

CHRONIC TOXICITY SUMMARY

ETHYLENE OXIDE

(oxirane, dimethylene oxide, epoxyethane)

CAS Registry Number: 75-21-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**30** m**g/m^3** (18 ppb)
Critical effect(s)	Neurotoxicity in rats
Hazard index target(s)	Nervous system

II. Physical and Chemical Properties (HSDB, 1995; CRC, 1994)

Description	Colorless gas
Molecular formula	C_2H_4O
Molecular weight	44.06 g/mol
Density	1.80 g/L @ 25ºC
Boiling point	10.6ºC
Melting point	–111.6ºC
Vapor pressure	1095 torr @ 20ºC
Conversion factor	1 ppm = 1.80 mg/m^3

III. Major Uses or Sources

The majority of all ethylene oxide (EtO) produced is used as a chemical intermediate in the production of various compounds including ethylene glycol, glycol ethers, and non-ionic surfactants (ATSDR, 1990). EtO is also used as a fumigant for food and cosmetics, and in hospital sterilization of surgical equipment and heat sensitive materials such as plastics. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 43,972 pounds of ethylene oxide (CARB, 2000).

IV. Effects of Human Exposure

Ten hospital sterilizer workers were matched with controls and examined for physical and neuropsychological health (Estrin *et al.*, 1990). The workers had operated sterilizers using 12% EtO and 88% Freon for an average of 5 years (range 0.5-10 years). Regular monitoring of workroom air had not been done. Measurements at the time of the study indicated concentrations of 15 ppm EtO or less. However, a second measurement showed an air concentration of 250 ppm EtO. A significantly greater percent of exposed workers exhibited

a bilateral reflex reduction in the ankle compared to controls. Nerve conduction tests did not identify significant differences between control and exposed workers, but a highly significant reduction ($p = 0.009$) in finger tapping speed was observed in exposed workers. The exposed group also performed more poorly on tests of spatial and visual abilities, and on tests of visual motor function. The results extended previous work by the same group (Estrin *et al*., 1987).

Cognitive impairment and personality dysfunction were observed more frequently in hospital workers chronically exposed to EtO, compared to a control group (Klees *et al.*, 1990). A group of 22 hospital workers, who had been exposed to an 8-hour TWA of 4.7 ppm EtO for a mean of 6.13 years (range 1-11 years), were matched with 24 control subjects. Neuropsychological function in the workers was classified as either normal or impaired on the basis of the questionnaires and of neuropsychological tests by 2 clinical psychologists (who were unaware of exposure status). (If the classification of the two clinicians did not agree, the subject was classified as "disagreement." Disagreement occurred in 7/23 (30%) of the controls and 10/22 (45%) of the exposed.) Exposed subjects were significantly more frequently classified as impaired (5/12) compared to controls (1/16) ($\chi^2 = 6.0861$; $p<0.05$). The Klees *et al*. (1990) study cites several earlier case reports of EtO neurotoxicity.

Recent studies have identified hemoglobin adducts, sister chromatid exchanges, and other hematological effects as indicators of ethylene oxide exposure (Ribeiro *et al.*, 1994; Sarto *et al.*, 1991). However, a recent study of 68 female workers from 9 hospitals in the U.S. and one in Mexico not only reports biological indicators of ethylene oxide exposure, but also provides a complete blood count with differential (Schulte *et al.*, 1995). The workers were classified as low- or high-exposure based on a mean 8-hour time weighted average of 0.08 or 0.17 ppm EtO. The mean length of employment for workers from U.S. hospitals was 5.5 and 10 years for low- and high-exposure workers, respectively. The mean length of employment in low- and high-exposure workers from the hospital in Mexico was 5.9 and 4.2 years, respectively. In workers from U.S. hospitals only, statistically significant decreases in hematocrit and hemoglobin were observed in high-exposure workers compared to low-exposure workers. Also, a statistically significant increase in lymphocytes and a significant decrease in neutrophils were observed in high-exposure workers compared to controls. In the workers from the hospital in Mexico, a significant relationship of EtO exposure and elevated neutrophil count was observed using regression.

At least 2 epidemiological reports indicate a possible association of EtO exposure and spontaneous abortion. Hemminki *et al.* (1982) analyzed spontaneous abortions in Finnish hospital sterilizing staff using data from a postal questionnaire and from a hospital discharge register. The study included all sterilizing staff employed in Finnish hospitals in 1980; the controls were nursing auxiliaries. When the women were involved in sterilizing procedures during their pregnancies, the frequency of spontaneous abortion was 16.7% versus 5.6% for the non-exposed pregnancies. The independent analysis of spontaneous abortions using the hospital discharge register confirmed the findings. Thus two analyses suggested that EtO exposure may carry a risk of spontaneous abortion among sterilizing staff.

More recently Rowland *et al*. (1996) sent questionnaires to 7,000 dental assistants (ages 18-39 years) registered in California in 1987. Of these, 4,856 responded (69%). They analyzed

1,320 women whose most recent pregnancy was conceived while working full-time. Thirty-two reported exposure to EtO; unexposed dental assistants comprised the comparison group. Among exposed women, the age-adjusted relative risk (RR) of spontaneous abortion was 2.5 [95% (CI) = 1.0-6.3]. The RR for pre-term birth was 2.7 (95% CI = 0.8-8.8) and the RR for post-term birth was 2.1 (95% CI = 0.7-5.9). The RR of any of these adverse outcomes among exposed women was estimated to be 2.5 (95% CI = 1.0-6.1). These results also indicate a possible relationship of EtO and spontaneous abortion.

V. Effects of Animal Exposure

A 2 year inhalation bioassay exposed groups of 80 male rats to 0, 50, or 100 ppm EtO 7 hours per day, 5 days per week for 104 weeks (Lynch *et al.*, 1984). Mean body weights were significantly lower and mortality was significantly higher in both exposure groups. Inflammatory lesions of the lung, nasal cavity, trachea, and inner ear were observed more frequently in EtO exposed rats. Skeletal muscle myopathy, consisting of atrophy and degeneration of skeletal muscle fibers, was observed more frequently in rats exposed to 100 ppm EtO compared to controls. Neoplastic changes were also observed in EtO exposed rats.

Mice (30 per sex) were exposed to 0, 10, 50, 100, or 250 ppm EtO for 6 hours per day, 5 days per week, for 10 weeks (males) or 11 weeks (females) (Snellings *et al.*, 1984). Neuromuscular screening was conducted, and samples of urine and blood were collected. A significantly greater percent of exposed mice exhibited abnormal posture during gait and reduced locomotor activity. A dose-response was observed for these effects, with significant changes at 50 ppm and greater. An abnormal righting reflex was observed in a significantly greater percent of mice exposed to 100 ppm and above. Reduced or absent toe and tail pinch reflexes were observed in a significantly greater percent of mice exposed to 250 ppm EtO. Hematological changes observed in mice exposed to 250 ppm include slight, yet significant, decreases in red blood cell count, packed cell volume, and hemoglobin concentration. Absolute and relative spleen weights were significantly decreased in female mice exposed to 100 and 250 ppm and in male mice exposed to 250 ppm EtO. A significant increase in relative liver weight was observed in female mice exposed to 250 ppm EtO. Male mice exhibited a significant decrease in body weight at 10, 50, and 250 ppm and a significant decrease in absolute testes weights at 50, 100, or 250 ppm EtO. This study indicates a subchronic NOAEL for neurological effects of 10 ppm EtO.

In a study of the testicular effects of EtO, male rats were exposed to 500 ppm EtO 6 hours per day, 3 days per week for 2, 4, 6, or 13 weeks (Kaido *et al.*, 1992). An awkward gait was observed in rats after 6-9 weeks of exposure. Although no significant changes in body weight were observed, a statistically significant dose-related decrease in testes weight was observed at 4, 6, and 13 weeks of exposure. Progressive degeneration and loss of germ cells were also observed during the 13 week exposure. While severe loss of germ cells and marked morphological changes in remaining germ cells were observed at 6 weeks of exposure, some intact spermatids were observed at 13 weeks of exposure. This suggests that recovery of spermatogenesis occurred.

Saillenfait *et al*. (1996) studied the developmental toxicity of EtO in pregnant Sprague-Dawley rats using inhalation exposure during gestation days 6 to 15. Two protocols were used: (1) exposure for 0.5 hr once a day to 0, 400, 800, or 1200 ppm EtO; or (2) exposure for 0.5 hr three times a day to 0, 200, or 400 ppm EtO or to 0, 800, or 1200 ppm EtO. The second protocol caused fetal toxicity as indicated by reduced fetal weight at 800 ppm (the LOAEL for this endpoint) and at 1200 ppm, and overt maternal toxicity manifested as reduced body weight gain at 1200 ppm. No embryolethality or teratogenicity occurred in either exposure protocol.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Snellings *et al*., 1984
Study population	Male and female B6C3F1 mice
Exposure method	Inhalation chamber exposure to 0, 10, 50, 100, or 250 ppm ethylene oxide
Critical effects	Impaired neurological function
LOAEL	50 ppm
NOAEL	10 ppm
Exposure continuity	6-hours/day, 5 days/week
Exposure duration	10 weeks (males), or 11 weeks (females)
Average experimental exposure	1.79 ppm (10 x 8/24 x 5/7)
Human equivalent concentration	1.79 ppm ((gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h)))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	18 ppb (30 $\mu g/m^3$)

Snellings *et al*. (1984) found a subchronic NOAEL of 10 ppm for neurological effects in mice. A neuromuscular screening test indicated that certain reflex responses and locomotor activities were altered in EtO-exposed animals. Human studies have also indicated neurological impairment in ethylene oxide exposed workers.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for ethylene oxide include the use of an animal study with both a LOAEL and a NOAEL and the use of an endpoint seen in both animals and humans.

Major areas of uncertainty are the short time-frame of the key study, the lack of an appropriate human study, and the limited number of developmental toxicity studies.

VIII. References

ATSDR. 1990. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Ethylene Oxide. Prepared under contract No. 205-88-0608 for: US Department of Health and Human Services, Public Health Service, ATSDR.

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Estrin WJ, Bowler RM, Lash A, and Becker CE. 1990. Neurotoxicological evaluation of hospital sterilizer workers exposed to ethylene oxide. Clin. Toxicol. 28(1):1-20.

Estrin WJ, Cavalieri SA, Wald P, Becker CE, Jones JR, and Cone JE. 1987. Evidence of neurologic dysfunction related to long-term ethylene oxide exposure. Arch. Neurol. 44(12):1283-1286.

HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (TOMES® CD-ROM Version). Denver, CO: Micromedex Inc. (Edition expires 7/31/95).

Hemminki K, Mutanen P, Saloniemi I, Niemi ML, and Vainio H. 1982. Spontaneous abortions in hospital staff engaged in sterilising instruments with chemical agents. Br. Med. J. (Clin. Res. Ed.) 285(6353):1461-1463.

Kaido M, Mori K, and Koide O. 1992. Testicular damage caused by inhalation of ethylene oxide in rats: Light and electron microscopic studies. Toxicologic Path. 20(1):32-43.

Klees JE, Lash A, Bowler RM, Shore M, and Becker CE. 1990. Neuropsychological "impairment" in a cohort of hospital workers chronically exposed to ethylene oxide. Clin. Toxicol. 28(1):21-28.

Lynch DW, Lewis TR, Moorman WJ, Burg JR, Groth DH, Khan A, Ackerman LJ, and Cockrell BY. 1984. Carcinogenic and toxicologic effects of inhaled ethylene oxide and propylene oxide in F344 rats. Toxicol. Appl. Pharmacol. 76:69-84.

Ribeiro LR, Salvadori, DMF, Rios ACC, Costa SL, Tates AD, Tornquist M, and Natarajan AT. 1994. Biological monitoring of workers occupationally exposed to ethylene oxide. Mutat. Res. 313:81-87.

Rowland AS, Baird DD, Shore DL, Darden B, and Wilcox AJ. 1996. Ethylene oxide exposure may increase the risk of spontaneous abortion, preterm birth, and postterm birth. Epidemiology 1996;7(4):363-368.

Sarto F, Tornquist MA, Tomanin R, Bartolucci GB, Osterman-Golkar SM, and Ehrenberg L. 1991. Studies of biological and chemical monitoring of low-level exposure to ethylene oxide. Scand. J. Work Env. Health 17:60-64.

Saillenfait AM, Gallissot F, Bonnet P, and Protois JC. 1996. Developmental toxicity of inhaled ethylene oxide in rats following short-duration exposure. Fundam. Appl. Toxicol. 34(2):223-227

Schulte PA, Walker JT, Boeniger MF, Tsuchiya Y, and Halperin WE. 1995. Molecular, cytogenetic, and hematologic effects of ethylene oxide on female hospital workers. J. Occup. Environ. Med. 37(3):313-320.

Snellings WM, Weil CS, and Maronpot RR. 1984. A subchronic inhalation study on the toxicologic potential of ethylene oxide in B6C3F_1 mice. Toxicol. Appl. Pharmacol. 76:510-518.

CHRONIC TOXICITY SUMMARY

GLUTARALDEHYDE

(1,5-pentanedial; 1,5-pentanedione; glutaric dialdehyde; Aldesen; Cidex; Sonacide)

CAS Registry Number: 111-30-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.08 µg/m^3** (0.02 ppb)
Critical effect(s)	Squamous metaplasia of the respiratory epithelium in the nose of male and female mice
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1996; CRC, 1994; Chemfinder, 2000)

Description	Colorless liquid/oil
Molecular formula	$C_5H_8O_2$
Molecular weight	100.12 g/mol
Boiling point	188°C (decomposes) (CRC, 1994)
Melting point	–6°C (Chemfinder, 2000)
Solubility	Soluble in water, alcohol, benzene
Conversion factor	4.1 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Glutaraldehyde is a chemical frequently used as a disinfectant and sterilizing agent against bacteria and viruses (2% solution), an embalming fluid and tissue fixative, a component of leather tanning solutions, and an intermediate in the production of certain sealants, resins, dyes, and electrical products (HSDB, 1996). For commercial purposes, solutions of 99%, 50%, and 20% are available. Glutaraldehyde is also an atmospheric reaction product of cyclohexene. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 29,603 pounds of glutaraldehyde (CARB, 2000).

IV. Effects of Human Exposure

Evidence of the toxicity of glutaraldehyde to humans is limited to reports of occupational exposure from its use as a disinfectant and sterilizing agent. Frequently observed effects from exposure include skin sensitivity resulting in dermatitis, and irritation of the eyes and nose with accompanying rhinitis (Jordan *et al.*, 1972; Corrado *et al.*, 1986; Hansen, 1983; Wiggins *et al.*, 1989). Occupational asthma has also been reported among workers repeatedly exposed

to glutaraldehyde, particularly respiratory technologists who use glutaraldehyde as a sterilizing agent for endoscopes (Chan-Yeung *et al.*, 1993; Stenton *et al.*, 1994; Gannon *et al.*, 1995). Quantitation of the exposure levels that led to glutaraldehyde sensitization was not available from the studies.

V. Effects of Animal Exposure

The histopathology of the respiratory tract in rats and mice exposed to glutaraldehyde by inhalation was examined (Gross *et al.*, 1994). F344 rats and B6C3F1 mice (20 animals of each sex and of each species at each exposure level for a total of 480 rodents) were continuously exposed to glutaraldehyde in recirculating exposure chambers at concentrations of 0, 62.5, 125, 250, 500, or 1000 ppb glutaraldehyde for one day, 4 days, 6 weeks, or 13 weeks. At termination, respiratory tract tissue as well as duodenum and any gross lesions were collected and formalin fixed. Animals were treated with tritiated thymidine two hours before termination to evaluate cell replication in certain respiratory tract tissues. Respiratory tract tissue sections were made as follows: transverse sections of the nose and trachea, frontal section of the carina, and longitudinal section of the lung. Ten male and 10 female mice exposed to 1000 ppb and one female mouse exposed to 500 ppb group died during the course of the study. Two male and 3 female rats exposed to 1000 ppb died during the course of the study. Histopathological examination of animals surviving to the end of the study entailed scoring the severity of the finding from “no response” to “very severe” response on a 0 to 5 scale. Unit length labeling index, the indicator of cell proliferation, was evaluated by autoradiography at two sites: the nasal vestibule and the dorsal atrioturbinate.

Lesions in animals treated with glutaraldehyde appeared primarily in the anterior third of the nose. Lesions were apparently more increased in mice compared to rats due to some level of “background” non-suppurative lesions in the rats. Mice were considered devoid of background lesions. In the 13-week study, female mice were the most sensitive, with lesions averaging a score of 2 (mild and clear, but of limited extent and/or severity). The lesions were characterized as neutrophilic infiltration primarily in the squamous epithelium of the vestibule, with thickening of the epithelium leading to loss of the characteristic surface grooves. Both cell size and number were reported to be increased. Lesions were generally found to increase in nature and severity with increased time and level of exposure. Obstruction of the nasal vestibule was thought to account for the mortality of animals in the higher dose groups. In female mice at 13 weeks, all glutaraldehyde dose groups showed the accumulation of eosinophilic proteinaceous deposits in the respiratory epithelium of the maxilloturbinate margin. Examination of unit length labeling indices as a measure of growth showed significant increases in all treated groups of female mice. No evidence of exposure related lesions was found in the respiratory tract in the trachea, carina, bronchi, or lungs.

Mean Subjective Pathology Scores for Nasal Lesions in Female Mice at 13 Weeks

	Glutaraldehyde	*Intraepithelial neutrophils*	*Subepithelial neutrophils*	*Squamous metaplasia*
	0 ppb	0	0.4	0
	62.5 ppb	2.0	2.0	0
	125 ppb	2.4	2.8	0
	250 ppb	3.2	3.2	0
	500 ppb	2.8	2.8	0.5
	1000 ppb*	--	--	--

*Animals exposed to 1000 ppb died early in the experiment.

Greenspan *et al.* (1985) exposed male and female F-344 rats to 0, 0.3, 1.1 and 3.1 ppm glutaraldehyde and 0, 0.2, 0.63, and 2.1 ppm glutaraldehyde, respectively, in a 9-day study, and both sexes to 0, 21, 49, and 194 ppb glutaraldehyde in a 14 week study. Animal numbers were not specified. Exposures were conducted for 6 hours per day, 5 days per week. In the 9-day study, observations in the high and intermediate dose level groups included reduced body weight gain, inflammation of the nasal and olfactory mucosa, and sensory irritation. In the two highest doses of the 14-week study, statistically significant differences in body weight gain were observed as well as perinasal wetness. No histopathological indication of inflammation in olfactory or nasal mucosa was observed.

Mice were exposed to 0, 0.3, 1.0, and 2.6 ppm glutaraldehyde vapors for 6 hours/day for 4, 9, or 14 days (Zissu *et al.*, 1994). These mice were killed immediately after the exposure period. Other groups exposed to 1.0 ppm for 14 days were killed after recovery periods of 1, 2, and 4 weeks. After 4 days of exposure to the lowest dose, mice showed lesions in the respiratory epithelium of the septum, and the naso- and maxilloturbinates. After exposure to 1.0 ppm glutaraldehyde, lesions were still judged as severe after 2 weeks of recovery.

A study comparing the effects of intra-nasally instilled glutaraldehyde and formaldehyde on rat nasal epithelium found inflammation, epithelial degeneration, respiratory epithelial hypertrophy, and squamous metaplasia in treated animals (St. Clair *et al.*, 1990). Acute inhalation exposure to formaldehyde produced identical lesions. Ten-fold higher concentrations of instilled formaldehyde were required to produce the same effect as instilled glutaraldehyde.

In a chronic study, NTP (1998, 1999) exposed groups of 50 male and 50 female F344/N rats to 0, 250, 500, or 750 ppb glutaraldehyde vapor by inhalation for 6 h/day, 5 days/week, for 104 weeks. Survival of 500 and 750 ppb female rats was less than that of the chamber controls. Mean body weights of all exposed groups of male rats and 500 and 750 ppb female rats were generally less than those of the chamber controls. Increased incidences of nonneoplastic nasal lesions occurred primarily within the anterior section of the nose in 500 and 750 ppb rats and to a lesser extent in 250 ppb rats. The more significant lesions included hyperplasia and inflammation of the squamous and respiratory epithelia and squamous metaplasia of the respiratory epithelium. Thus 250 ppb (1000 $\mu g/m^3$) is a chronic LOAEL for rats.

In the same study NTP (1998, 1999) exposed groups of 50 male and 50 female B6C3F1 mice to 0, 62.5, 125, or 250 ppb glutaraldehyde vapor by inhalation for 6 h/day, 5 days/week, for 104 weeks. Survival of exposed mice was similar to that of the chamber controls. Mean body weights of female mice exposed to 250 ppb were generally less than those of the controls. The incidence of inflammation of the nose was marginally increased in 250 ppb females. Incidences of squamous metaplasia of the respiratory epithelium were increased in 250 ppb males and females and 125 ppb females. Incidences of hyaline degeneration of the respiratory epithelium were increased in all exposed groups of females. Thus 62.5 ppb was a chronic LOAEL for female mice.

Incidence of Nasal Lesions in Female Mice exposed for 104 weeks

	Glutaraldehyde	*Inflammation*	*Respiratory epithelium hyaline degeneration*	*Respiratory epithelium squamous metaplasia*
	0 ppb	6/50	16/50	7/50
	62.5 ppb	7/49	35/49	11/49
	125 ppb	13/50	32/50	16/50
	250 ppb	14/50	30/50	21/50

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	NTP 1998, 1999
Study population	Male and female F344 rats and B6C3F1 mice (50/sex/group)
Exposure method	Continuous inhalation exposure (0, 62.5, 125, and 250 ppb in mice; 0, 250, 500, or 750 ppb in rats)
Critical effects	Respiratory epithelium squamous metaplasia
LOAEL	62.5 ppb (female mice)
NOAEL	Not observed
BMC_{05}	20.5 ppb
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	104 weeks
Equivalent continuous exposure	3.7 ppb (20.5 x 6/24 x 5/7)
Human equivalent concentration	0.62 ppb (gas with extrathoracic respiratory effects, RGDR = 0.17, BW = 28 g, MV = 0.032 L/min, SA = 3 cm^2)
LOAEL uncertainty factor	not needed in BMC approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.02 ppb (0.08 µg/m^3)

Several studies indicate that the upper respiratory tract is a target for the toxicity of glutaraldehyde from inhalation exposure. Reports of toxicity to humans show that exposure can lead to occupational asthma as well as cause irritation of the eyes and nose with accompanying rhinitis. Likewise, animals exposed to glutaraldehyde by the inhalation route show evidence of respiratory irritation with the induction of lesions of the anterior nasal cavities upon long-term exposure (Gross *et al.*, 1994; Greenspan *et al.*, 1985; NTP, 1998, 1999). The NTP (1998, 1999) study yielded a chronic LOAEL for female mice of 62.5 ppb. Gross *et al.* (1994) showed neutrophilic infiltration in the olfactory epithelium in the lowest dose exposure group. (Female mice exposed to 62.5 ppb also showed subepithelial neutrophilic infiltration.) This level was taken to be the subchronic LOAEL. This effect on the nasal epithelium was demonstrated to be both concentration- and exposure duration-dependent.

A benchmark concentration was determined using EPA's version 1.20 BMC software and the dose-response data on respiratory epithelium squamous metaplasia in female mice. The quantal-linear model gave an MLE_{05} of 31.24 ppb, a BMC_{05} of 20.51 ppb, and a p value of 0.9471. With the benchmark approach no LOAEL UF is needed. The study was a lifetime study so the subchronic UF is 1. An interspecies UF of 3 rather than 10 was used since an RGDR adjustment had been made. The default intraspecies UF of 10 was used so that the total UF was 30. The resulting chronic REL for glutaraldehyde is 0.02 ppb (0.08 $\mu g/m^3$).

For comparison with the proposed REL, the study of Gross *et al*. (1994) used 62.5 ppb continuous exposure. Multiplying by the RGDR of 0.17 and dividing by a cumulative uncertainty factor of 300 (3 for a LOAEL, 3 for subchronic, 3 for interspecies, and 10 for intraspecies) results in a REL of 0.035 ppb (0.1 $\mu g/m^3$).

VII. Data Strengths and Limitations for Development of the REL

The major strength of the inhalation REL for glutaraldehyde is the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis. Major areas of uncertainty are the lack of human data, the lack of reproductive and developmental toxicity studies, the lack of dermal sensitization studies, and the lack of observation of a NOAEL.

VIII. References

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

Chan-Yeung M, McMurren T, Catonio-Begley F, and Lam S. 1993. Occupational asthma in a technologist exposed to glutaraldehyde. J. Allergy Clin. Immunol. 91:974-978.

Chemfinder, 2000. Available online at http://www.chemfinder.com

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Corrado OJ, Osman J, and Davies RJ. 1986. Asthma and rhinitis after exposure to glutaraldehyde. Hum. Toxicol. 5:325-328.

Gannon PF, Bright P, Campbell M, O'Hickey SP, and Burge PS. 1995. Occupational asthma to glutaraldehyde and formaldehyde in endoscopy and x-ray departments. Thorax 50:156-159.

Greenspan BJ, Ballantyne B, Fowler EH, and Snellings WM. 1985. Subchronic inhalation toxicity of glutaraldehyde. Toxicologist 5:29 (abstract).

Gross EA, Mellick PW, Kari FW, Miller FJ, and Morgan KT. 1994. Histopathology and cell replication responses in the respiratory tract of rats and mice exposed by inhalation to glutaraldehyde for up to 13 weeks. Fundam. Appl. Toxicol. 23:348-362.

Hansen KS. 1983. Glutaraldehyde occupational dermatitis. Contact Dermatitis 9:81-82.

HSDB. 1996. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (TOMES® CD-ROM Version). Denver, CO: Micromedex, Inc. (Edition expires 7/31/96).

Jordan WP, Dahl MV, and Albert HL. 1972. Contact dermatitis from glutaraldehyde. Arch. Dermatol. 105:94-95.

National Toxicology Program (NTP). 1998. Toxicology and Carcinogenesis Studies of Glutaraldehyde (CAS NO. 111-30-8) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). TR-490. Board Draft.

National Toxicology Program (NTP). 1999. Toxicology and Carcinogenesis Studies of Glutaraldehyde (CAS NO. 111-30-8) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). TR-490. September 1999. NIH Publication No. 99-3980. Available online at http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr490.html

St. Clair MBG, Gross EA, and Morgan KT. 1990. Pathology and cell proliferation induced by intra-nasal instillation of aldehydes in the rat: comparison of glutaraldehyde and formaldehyde. Toxicol. Pathol. 18:353-361.

Stenton SC, Beach JR, Dennis JH, Keaney NP, and Hendrick DJ. 1994. Glutaraldehyde, asthma and work -- a cautionary tale. Occup. Med. 44:95-98.

Wiggins P, McCurdy SA, and Zeidenberg W. 1989. Epistaxis due to glutaraldehyde exposure. J. Occup. Med. 31:854-856.

Zissu D, Gagnaire F, and Bonnet P. 1994. Nasal and pulmonary toxicity of glutaraldehyde in mice. Toxicol. Lett. 71:53-62.

CHRONIC TOXICITY SUMMARY

HYDRAZINE

(diamine; diamide; nitrogen hydride; levoxine)

CAS Registry Number: 302-01-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.2 µg/m^3** (0.1 ppb)
Critical effect(s)	Amyloidosis of the liver and thyroid in hamsters
Hazard index target(s)	Alimentary system; endocrine system

II. Chemical Property Summary (HSDB, 1995; CRC, 1994)

Description	Colorless, oily liquid or white crystals
Molecular formula	N_2H_4
Molecular weight	32.05 g/mol
Boiling point	113.5°C (Merck, 1983; CRC, 1994)
Melting point	2.0°C
Vapor pressure	14.4 torr @ 25°C
Solubility	Miscible with water, methyl-, ethyl-, isobutyl alcohols; slightly miscible with hydrocarbons; insoluble in chloroform, ether
Conversion factor	1.31 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Hydrazine is a highly reactive base and reducing agent. Its primary uses are as a high-energy rocket propellant, as a reactant in military fuel cells, in nickel plating, in the polymerization of urethane, for removal of halogens from wastewater, as an oxygen scavenger in boiler feedwater to inhibit corrosion, and in photographic development (Von Burg and Stout, 1991). Hydrazine was historically used experimentally as a therapeutic agent in the treatment of tuberculosis, sickle cell anemia, and non-specific chronic illnesses (Von Burg and Stout, 1991; Gold, 1987). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1664 pounds of hydrazine (CARB, 2000).

IV. Effects of Human Exposure

One person was occupationally exposed to hydrazine at unknown levels once per week for a period of 6 months (Sotaniemi *et al.*, 1971). The worker showed symptoms of conjunctivitis, tremors, and lethargy for 1-2 days following each exposure. Vomiting, fever, and diarrhea developed on the last day of exposure and progressed to abdominal pain and incoherence. The previously healthy 59-year old individual died three weeks after the last exposure. Evidence of tracheitis, bronchitis, heart muscle degeneration, and liver and kidney damage was found at autopsy. A single case report can not prove a cause and effect relationship between hydrazine exposures and the noted symptoms and death, but the repeated association between exposures and symptoms is highly suspicious. Liver toxicity is also associated with acute exposure to hydrazine.

The only epidemiological studies of human hydrazine exposures found involve workers in a hydrazine manufacturing plant (Wald *et al.*, 1984; Wald, 1985; Morris *et al.*, 1995). Workers were exposed to various durations of at least 6 months between 1945 and 1972 and have been followed through 1992. The studies are based on a review of medical records. Only 78 of 427 workers were believed to have had more than incidental exposure to hydrazine. Only cumulative mortality was reviewed. Health effects reported during or after hydrazine exposure were not examined. No increase in mortality was noted for lung cancer, other cancers, or causes other than cancer. However, these small studies have little power to detect increased mortality, and age of death was not examined. The authors reported that relative risks up to 3.5 could have gone undetected.

Dermal sensitization has also been reported from repeated contact with hydrazine (Van Ketal, 1964; Von Keilig and Speer, 1983; Wrangsjo and Martensson, 1986).

V. Effects of Animal Exposure

An inhalation study of the toxicity and carcinogenicity of hydrazine was conducted in cats, mice, hamsters, and dogs (Vernot *et al.*, 1985). Various animal groups were exposed 6 hours/day, 5 days/weeks for one year to concentrations of 0.05, 0.25, 1.0, and 5.0 ppm anhydrous hydrazine base. Exposed and controls groups were made up of the following animals: 100 Fischer 344 rats/sex at 0.05, 0.25, 1.0, and 5.0 ppm hydrazine plus 150 rats/sex as controls; 400 female C57BL/6 mice at 0.05, 0.25, and 1.0 ppm hydrazine plus 800 female mice as controls; 200 male Golden Syrian hamsters at 0.25, 1.0, and 5.0 ppm hydrazine plus 200 male hamsters as controls; 4 beagle dogs/sex at 0.25 and 1.0 ppm hydrazine plus 4 dogs/sex as controls. Animals were observed post-exposure for the following periods: 18 months for rats, 15 months for mice, 12 months for hamsters, and 38 months for dogs. Animals were observed hourly during the exposure period and daily in the post-exposure period.

No non-cancer toxic effects were observed in mice or dogs, with the exception of a single dog, exposed to 1.0 ppm hydrazine, which showed cyclic elevations in serum glutamic-pyruvic transaminase levels and, upon necropsy at 36 months post-exposure, showed liver

effects described as "clusters of swollen hepatocytes that had highly vacuolated cytoplasm." Of the other species examined, hamsters showed toxicity at the lowest dose levels, particularly amyloidosis in various organs including liver, spleen, kidney, thyroid, and adrenal glands. An increased incidence of amyloidosis was seen at the lowest exposure level (0.25 ppm hydrazine) in the liver and thyroid (67/160 exposed vs. 42/180 control for the liver and 20/117 exposed vs. 9/155 control in the thyroid; $p \leq 0.01$ by Fisher's exact test). This effect was found to be dose related. The incidence of hemosiderosis of the liver was also significantly increased in all exposed groups. Significantly increased incidences of toxic effects observed in the 1.0 and 5.0 ppm hydrazine groups include amyloidosis of the spleen, kidney glomerulus, and adrenals glands, and lymphadenitis of the lymph nodes. Significantly increased toxic effects observed only in the highest dose group include amyloidosis of the kidney interstitium and thyroid, and senile atrophy of the testis. The authors note these effects appear to reflect accelerated changes commonly associated with aging in hamsters.

Incidence of Nonneoplastic Lesions in Male Hamsters (from Table 3 of Vernot *et al*.)

Lesion	*Control*	*0.25 ppm*	*1.0 ppm*	*5.0 ppm*
Liver				
Amyloidosis	42/180 (23)*	67/160 (42)[a]	68/148 (46)[a]	79/159 (50)[a]
Hemosiderosis	42/180 (23)	63/160 (39)[a]	77/148 (52)[a]	94/159 (59)[a]
Bile duct hyperplasia	14/180 (8)	31/160 (19)[a]	28/148 (19)[a]	44/159 (28)[a]
Biliary cyst	45/180 (25)	45/160 (28)	42/148 (28)	55/159 (35)[b]
Thyroid				
Amyloidosis	9/155 (6)	20/117 (17)[a]	11/127 (9)	22/137 (16)[a]
Adrenal				
Amyloidosis	38/177 (22)	49/199 (32)[b]	52/141 (37)[a]	76/153 (50)[a]

* Incidence of lesion (% of animals with lesion)
[a] Incidence significantly greater than control, $p \leq 0.01$
[b] Incidence significantly greater than control, $0.01 < p \leq 0.05$

In the hydrazine exposed rats, effects were observed in the respiratory tract of exposed animals. Specifically, squamous metaplasia of the larynx, trachea, and nasal epithelium (males only) was observed in the highest dose group (5.0 ppm hydrazine). Inflammation was also observed in the larynx and trachea of rats exposed to 5.0 ppm hydrazine. Increased incidence of focal cellular change of the liver was observed in female mice at 1.0 and 5.0 ppm hydrazine. Other effects with increased incidence only in the high dose group include hyperplastic lymph nodes in females, endometriosis, and inflammation of the uterine tube.

The toxic effects from inhalation of hydrazine over a six month period from both intermittent and continuous exposure scenarios were examined (Haun and Kinkead, 1973). Groups of 8 male beagle dogs, 4 female rhesus monkeys, 50 male Sprague-Dawley rats, and 40 female ICR rats per dose group were continuously exposed to 0.2 or 1.0 ppm hydrazine or intermittently (6 hours/day, 5 days/week) to 1.0 or 5.0 ppm hydrazine. A control group consisted of equal numbers of animals. The experimental design was such that each intermittent exposure group had a time-weighted-average matching continuous exposure group. Dose-related body weight reductions were observed in all treated groups as well as

evidence of hepatic degeneration, fatty deposition in the liver, central nervous system depression and lethargy, eye irritation, and anemia.

Toxic effects from the exposure of rats, mice, and dogs to airborne hydrazine at levels of 0, 4.6, or 14 ppm intermittently for 6 months were reported (Comstock *et al.*, 1954). Observed adverse effects included anorexia, irregular breathing, vomiting, fatigue, and emphysema in dogs; pulmonary congestion and emphysema in rats and mice; and lung and liver damage in rats.

Lymphoid bronchial hyperplasia was observed in guinea pigs exposed to 2-6 ppm hydrazine for 5 days/week for 19-47 days (Weatherby and Yard, 1955).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Vernot *et al.*, 1985
Study population	Hamster
Exposure method	Inhalation of 0, 0.25, 1, and 5 ppm
Critical effects	Amyloidosis and hemosiderosis of the liver; thyroid amyloidosis
LOAEL	0.25 ppm
NOAEL	Not observed
Exposure continuity	6 hour/day, 5 days/week
Exposure duration	1 year
Average experimental exposure	0.045 ppm for LOAEL group (0.25 x 6/24 x 5/7)
Human equivalent concentration	0.045 ppm for LOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	10 (low incidence above controls but serious adverse effects)
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.0001 ppm (0.1 ppb, 0.0002 mg/m^3, 0.2 µg/m^3)

Vernot *et al.*(1985) present a thorough examination of chronic health effects from inhalation exposure to hydrazine. This study was chosen for the development of the chronic reference exposure level because (1) it was conducted with an adequate number of animals, (2) the critical/sensitive adverse effect (degenerative change in the liver in hamsters) showed a dose-response relationship, and (3) the findings of this study support data found in studies by other groups.

This study shows a dose-related increase in the incidence of amyloidosis and hemosiderosis in hamsters intermittently exposed by inhalation to levels of hydrazine greater than 0.25 ppm. Other effects noted at 0.25 ppm included weight depression during exposure, mineralization

of the kidney, and amyloidosis of the thyroid. Haun and Kinkead (1973) have also noted lesions of the liver in dogs, monkeys, and mice exposed continuously to 0.2 ppm hydrazine for 6 months by inhalation. Comstock *et al.* (1954) observed liver damage in groups of rats exposed to hydrazine vapors. The single case report of hydrazine inhalation toxicity in humans showed necrosis and degeneration of the liver (Sotaniemi *et al.*, 1971).

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for hydrazine include the availability of chronic inhalation exposure data from a well-conducted study with histopathological analysis. Major areas of uncertainty are the lack of adequate human exposure data, the lack of reproductive and developmental toxicity studies, and the lack of observation of a NOAEL in the key study.

VIII. References

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Comstock CC, Lawson LH, Greene EA, and Oberst FW. 1954. Inhalation toxicity of hydrazine vapor. Arch. Ind. Hyg. Occup. Med. 10:476-490.

Gold J. 1987. Hydrazine sulfate: a current perspective. Nutr. Cancer 9:59-66.

Haun CC, and Kinkead ER. 1973. Chronic inhalation toxicity of hydrazine. Proceedings of the 4th Annual Conference on Environmental Toxicology. Wright-Patterson Air Force Base, OH. AMRL-TR-73-125:351-363.

HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (CD-ROM Version). Denver, CO: Micromedex, Inc. (Edition expires 7/31/96).

Merck. 1983.The Merck Index. 10th ed. Windholz M. (ed.) Rahway, NJ: Merck & Co.

Morris J, Densem JW, Wald NJ, Doll R. 1995. Occupational exposure to hydrazine and subsequent risk of cancer. Occup. Environ. Med. 52(1):43-45.

Sotaniemi E, Hivonen J, Isomaki H, Takkunen J, and Kaila J. 1971. Hydrazine toxicity in the human. Report of a fatal case. Ann. Clin. Res. 3:30-33.

Van Ketal WG. 1964. Contact dermatitis from a hydrazine derivative in a stain remover. Cross-sensitization to apresoline and isoniazid. Acta Derm. Venereol. (Stockh.) 44:49-53.

Vernot EH, MacEwen JD, Bruner RH, Haun CC, Kinkead ER, Prentice DE, Hall A, Schmidt RE, Eason RL, Hubbard GB, and Young JT. 1985. Long-term inhalation toxicity of hydrazine. Fundam. Appl. Toxicol. 5:1050-1064.

Von Burg R, and Stout T. 1991. Toxicology Update: Hydrazine. J. Appl. Toxicol. 11:447-450.

Von Keilig, W. and Speer U 1983. Occupational allergic contact dermatitis from hydrazine. Dermatosen in Beruf und Umwelt 31:25-27.

Wald N, Boreham J, Doll R, and Bonsall J. 1984. Occupational exposure to hydrazine and subsequent risk of cancer. Br. J. Ind. Med. 41(1):31-34.

Wald N. 1985. Hydrazine: epidemiological evidence. IARC Scientific Publication 65:75-80.

Weatherby JH, and Yard AS. 1955. Observations on the subacute toxicity of hydrazine. Arch. Ind. Health 11:413.

Wrangsjo K, and Martensson A. 1986. Hydrazine contact dermatitis from gold plating. Contact Dermatitis, 15:244-245.