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Provisional Peer Reviewed Toxicity Values for

Chloroethane
(CASRN 75-00-3)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration

p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR CHLOROETHANE (CASRN 75-00-3)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and

circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

No reference dose (RfD) assessment is available for chloroethane (ethyl chloride) in the Integrated Risk Information System (IRIS) database (U.S. EPA, 2006a) or in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 1997). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a) includes a Health Effects Assessment for Ethyl Chloride (U.S. EPA, 1987). Although an Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Chloroethane (ATSDR, 1998) is available, no oral minimal risk levels (MRLs) were derived for chloroethane because no relevant oral data were located.

The IRIS database (U.S. EPA, 2006a) includes a reference concentration (RfC) of 10 mg/m^3 (verified 12/20/1990) for chronic exposure to ethyl chloride (chloroethane), based on a NOAEL of 4000 mg/m^3 and a LOAEL of 13,000 mg/m^3 for delayed fetal ossification in a mouse developmental inhalation study (Scortichini et al., 1986). The same critical effect (delayed ossification in mice) from the study of Scortichini et al. (1986) was used by ATSDR (1998) to derive an acute-duration inhalation MRL of 15 ppm (40 mg/m^3) and by CalEPA (2006a) to derive a chronic reference exposure level (REL) of 30,000 $\mu g/m^3$ (30 mg/m^3).

A cancer assessment for chloroethane is not available on IRIS (U.S. EPA, 2006a) or in the HEAST (U.S. EPA, 1997). CalEPA (2006b) includes chloroethane in its List of Chemicals Known to the State to Cause Cancer or Reproductive Toxicity (updated December 2, 2005). The National Toxicology Program (NTP) performed a 2-year inhalation toxicity and carcinogenicity study of ethyl chloride in rats and mice, resulting in the conclusion that there was equivocal

evidence of carcinogenic activity in rats and clear evidence of carcinogenic activity in female mice (NTP, 1989). The International Agency for Research on Cancer (IARC) assigned chloroethane to Group 3 (not classifiable as to its carcinogenicity to humans), based on limited evidence for the carcinogenicity of chloroethane in animals and no available human data (IARC, 1991). NIOSH (2006) includes a warning to handle ethyl chloride with caution in the workplace due to structural similarity to other chloroethanes shown to be carcinogenic in animals. A carcinogenicity assessment for chloroethane is not available from the World Health Organization (WHO, 2006).

An Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Chloroethane is available (ATSDR, 1998). Update literature searches for more recent information were performed for the time period of 1993 to December, 2005 in TOXLINE, MEDLINE (plus PubMed cancer subset), and DART/ETICBACK. Update search of the TOXCENTER database was performed for the time period of August, 2000 to December, 2005. Databases searched without date limitations included TSCATS, RTECS, GENETOX, HSDB and CCRIS. Search of Current Contents encompassed July to December, 2005.

REVIEW OF PERTINENT DATA

Human Studies

Oral Exposure

No data were located regarding the oral toxicity or carcinogenicity of chloroethane in humans.

Inhalation Exposure

Chloroethane has been used as a general anesthetic in humans at inhaled concentrations in the same range (3-4.5%) as its explosive concentration of 4% (40,000 ppm (105,521 mg/m^3))[*] in air. Blood levels required to achieve general anesthesia range from 20 to 30 mg% (mg/100 mL), whereas respiratory failure can be triggered by slightly higher blood levels (40 mg%) (Dobkin and Byles, 1971). Sublethal adverse effects of overexposure to inhaled chloroethane are predominantly neurological (Finch and Lobo, 2005; Hes et al., 1979; Nordin et al., 1988), but may include hepatic effects (Hes et al., 1979). Davidson (1925) reported the results of short-term inhalation exposure of human subjects to chloroethane. Exposure to 13,000 ppm (34,294 mg/m^3) for 12 minutes resulted in feelings of intoxication and reduced reaction time. At an exposure level of 19,000 ppm (50,123 mg/m^3), slight intoxication was reported within 1 minute and progressed to distinct intoxication and mild analgesia within 12 minutes. Higher concentrations (25,000 ppm for 15 minutes, 33,600 ppm for 8 minutes [5,957 and 88,638 mg/m^3 respectively]) resulted in concentration-related incoordination. At the highest exposure level (33,600 ppm), unconsciousness was achieved within 13-17 minutes. Sayers et al. (1929)

[*] Concentrations were determined using the following formulae:
xppm = (y mg/m^3)(24.45)/(molecular weight)
ymg/m^3 = (xppm)(molecular weight)/24.45

reported dizziness and abdominal cramping in two human subjects who inhaled two breaths of a 4% (40,000 ppm) concentration of chloroethane in air or three or four breaths of a 2% concentration.

No studies were located regarding the carcinogenicity of chloroethane in humans exposed by inhalation.

Animal Studies

Oral Exposure

Male and female Fischer 344 rats (10/sex/group) were given drinking water containing 0 or 5700 mg chloroethane/L water for 14 days (Dow Chemical Company, 1995). Estimated chloroethane doses to the male and female rats were 297 and 361 mg/kg-day, respectively. Rats were assessed for clinical signs of toxicity, body weight and food and water consumption. Other parameters evaluated included clinical chemistry [serum aspartate aminotransferase (AST), alanine aminotransferase (AST) and alkaline phosphatase (AP)], hematology, organ weights and gross and histopathological (liver only) examinations. There were no indications of chloroethane-induced toxicity from any of the parameters evaluated. Decreased water consumption (20-25% lower in chloroethane-treated rats, relative to controls) was considered to be the result of reduced palatability. Decreased food consumption and body weight were considered to be secondary to decreased water consumption. Slight changes in selected mean organ weights were within 10% of control values and were consistent with decreased water and food consumption.

In an early study in rabbits (Rowe et al., 1939), administration of 500 or 1000 mg/kg-day of chloroethane by gavage on work days through a total of 60 doses (assumed to be 5 days/week for 12 weeks) did not elicit clinical signs of toxicity or treatment-related effects on body weight gain. Histopathological examinations (tissues not specified) revealed no evidence of treatment-related effects. The available results of this study were limited to a summary statement.

Inhalation Exposure

Groups of male and female Fischer 344 rats (6/sex/exposure concentration) were exposed to chloroethane (99.7% pure) by inhalation at concentrations of 0, 1600, 4000 or 10,000 ppm (0, 4288, 10,720 or 26,800 mg/m^3) for 6 hours/day, 5 days/week for 2 weeks and observed for clinical signs of toxicity (Landry et al., 1982). Body weights were monitored during the study and clinical chemistry, urinalysis, hematology and comprehensive histopathological examinations were performed. Significant increases in relative liver weight (4.9 and 7.5% greater than controls) were noted in male rats of the 4000 and 10,000 ppm groups, respectively, in the absence of liver histopathology or increased levels of serum enzymes. There were no other signs of chloroethane-induced effects. No effects were seen in male beagle dogs (2/group) subjected to the same exposure scenario and analysis.

Landry et al. (1989) exposed groups of B6C3F1 mice (7/sex/group) to chloroethane (99.9% pure) by inhalation at vapor concentrations of 0, 250, 1250 or 5000 ppm (0, 670, 3350 or

13,400 mg/m^3) for 23 hours/day on 11 consecutive days. Body weights were recorded periodically during the study. On the day following the final exposure period, a neurobehavioral battery of tests was performed. Clinical chemistry, hematology and comprehensive histopathological analyses were conducted. The only indication of chloroethane-related effects consisted of significantly increased mean relative liver weight (approximately 9-12% greater than controls) and a minimal increase in degree of hepatocellular vacuolization in 4/7 of the 5,000-ppm male and female mice. These liver effects were not accompanied by increased serum enzyme levels and were considered to be an adaptive response.

In a study designed to assess chloroethane metabolism, Fedtke et al. (1994a) exposed groups of male and female F-344 rats and B6C3F1 mice (2 rats or 10 mice/sex/group) to chloroethane (>99% pure) by inhalation at exposure concentrations of 0 or 15,000 ppm (0 or 40,200 mg/m^3) for 5 days (6 hours/day). At necropsy, livers, lungs, kidneys and uteri were removed and weighed. The only indication of chloroethane-induced toxicity was significantly decreased mean uterine weight (approximately 35% lower than controls, data not shown) in the female mice of the 15,000 ppm exposure level. Body weights and relative uterine weights were not reported, but all groups of mice, including sham-exposed controls, were stated to have lost weight, possibly due to exposure-related stress.

In an unpublished study, Scortichini et al. (1986) assessed the developmental toxicity of chloroethane in CF-1 mice. In a range-finding study, groups of 8-10 bred female CF-1 mice were exposed to 0, 5000, 10,000 or 15,000 ppm of chloroethane (99.9% pure) for 6 hours/day on gestation days 6 through 15. The study authors reported increased locomotor activity and significantly decreased body weight and body weight gain in all chloroethane-exposed dams, but did not include actual data for these findings. In the main study, groups of bred female mice (30/group) were exposed to chloroethane (99.9% pure) by inhalation at target concentrations of 0, 500, 1500 or 5000 ppm (analytical concentrations of 0, 491, 1504 and 4946 ppm; approximately 0, 1300, 4000 and 13,000 mg/m^3) for 6 hours/day on gestation days 6 through 15. Dams were observed daily for clinical signs of chloroethane-induced toxicity. Maternal body weights and food and water consumption were monitored. At sacrifice on gestation day 18, maternal liver weights and gravid uterine weights were recorded. Numbers of pregnant dams, resorptions and live and dead fetuses were noted, as well as fetal weight and sex and gross external fetal alterations. Apparently nonpregnant mice were assessed for evidence of implantation sites. Examinations for signs of visceral alterations were performed on one-half of the fetuses from each litter. All fetuses were examined for evidence of cardiac and skeletal anomalies. Bones of the skull were examined for anomalies in approximately one-half of the fetuses; heads of the other fetuses were assessed for other effects.

There were no indications of chloroethane-induced maternal effects at any exposure level (Scortichini et al., 1986). Evaluation of reproductive parameters in pregnant mice revealed no indication of adverse effects on pregnancy rate, resorption rate, litter size, fetal sex ratios or fetal body weights. No significant exposure-related effects on incidences of fetal visceral anomalies were detected. A small, but significant ($p=0.05$) increase in the incidence of foramina of the skull bones (delayed fetal ossification) was noted in fetuses of the 4946 ppm exposure group (1/126, 1/142, 1/174 and 5/116 fetuses of the 0, 491, 1504 and 4946 ppm exposure groups, respectively). On a per litter basis, respective incidences were 1/22, 1/24, 1/25 and 5/22 litters.

Incidences of litters exhibiting supernumerary ribs were elevated at the higher exposure levels [2/22 (9%), 1/25 (4%), 5/26 (19%) and 4/22 (18%) in 0, 491, 1504 and 4946 ppm exposure groups, respectively]. The statistical significance of this effect was not indicated in the study report and did not appear to increase with increasing exposure concentration on a per fetus basis [2/257 (1%), 1/299 (0.3%), 6/311 (2%), and 2/242 (2%) in 0, 491, 1504, and 4946 ppm groups, respectively]. The authors considered this observed effect to be questionable. There were no other indications of chloroethane-induced fetal effects. Although the authors did not identify it as such, this study identified a NOAEL of 1504 ppm and a LOAEL of 4946 ppm for fetal effects (delayed fetal ossification).

A series of studies were conducted for the National Toxicology Program to assess the toxicity and carcinogenicity of inhaled chloroethane (99.5% pure) in male and female F344/N rats and B6C3F1 mice (NTP, 1989). Preliminary 4-hour and repeated 14-day and 13-week exposure studies (6 hours/day, 5 days/week) were performed prior to a 2-year toxicity and carcinogenicity study. In the 4-hour and repeated 14-day studies, no overt signs of chloroethane-induce toxicity were seen in the rats or mice (5/sex/species) exposed to chloroethane vapors at a concentration of 19,000 ppm (50,920 mg/m^3). No gross or histopathological signs of chloroethane-induced toxicity were seen in rats or mice in the 14-day studies.

In the 13-week repeated exposure study, groups of 10 animals/sex/species were exposed to chloroethane concentrations of 0, 2500, 5000, 10,000 or 19,000 ppm (0, 6700, 13,400, 26,800 or 50,920 mg/m^3) for 6 hours/day, 5 days/week for 13 weeks (NTP, 1989). Animals were observed daily for clinical signs of toxicity. Body weights were recorded weekly. Comprehensive gross and histopathological examinations were performed on each animal.

All rats survived until terminal sacrifice (NTP, 1989). No compound-related clinical signs of toxicity were observed in rats. Mean final body weights of all groups of chloroethane-exposed male and female rats ranged from 4 to 8% lower than respective controls, but were statistically significantly lower ($p<0.01$) only in the 19,000-ppm male rats. Relative mean liver weight was significantly increased only in 19,000-ppm male rats (approximately 14% higher than controls). Gross and histopathologic examinations revealed no signs of chloroethane-related adverse effects in male or female rats.

Chloroethane-exposed mice also survived until terminal sacrifice, with the exception of a single male mouse of the 10,000-ppm exposure group (NTP, 1989). No compound-related clinical signs of toxicity were observed in mice. Final body weights of chloroethane-exposed mice were generally slightly higher than controls. Relative mean liver weight was significantly ($p<0.01$) increased in 19,000-ppm female mice (approximately 18% higher than controls). There were no indications of chloroethane-induced gross or histopathologic effects. Observed nasal cavity hemorrhage of minimal severity in 3/10 male and 6/10 female mice of the 19,000 ppm exposure level was considered by NTP to be an artifact of necropsy in the absence of microscopic lesions in the nasal mucosa of these mice.

In the 2-year toxicity and carcinogenicity bioassay, groups of 50 animals/sex/species were exposed to chloroethane vapor concentrations of 0 (inhalation chamber controls) or 15,000 ppm (40,200 mg/m^3) for 6 hours per day, 5 days per week for 102 weeks (rats) or 100 weeks

(mice). NTP (1989) conducted the 2-year studies using air-exposed controls and a single chloroethane exposure level in order to obtain structure-activity comparative data with results of a concurrent study of bromoethane. The 15,000 ppm level was selected for the 2-year study due to concerns about the potential flammability and explosion hazard of higher concentrations and because no effects were seen in the subchronic study at a slightly higher exposure level. All animals were observed twice per day for clinical signs. Body weights were recorded weekly for the first 12 weeks and monthly thereafter. Comprehensive gross and histopathological examinations were performed for each animal in the study.

No chloroethane-induced clinical signs of toxicity were observed in rats of either sex exposed for 2 years (NTP, 1989). No significant differences in survival were noted between exposed and control groups of rats of either sex, but survival of exposed and control male rats was unusually low at the end of the study. The authors reported that unusually high incidences of mononuclear cell leukemia in both control and exposed groups of male rats may have contributed to the high mortality. The authors also reported that survival for all groups was sufficient through weeks 90 and 95 to evaluate carcinogenicity. At the end of the study (102 weeks), survival for male rats was 16/50 (controls) and 8/50 (exposed) and for female rats was 31/50 (controls) and 22/50 (exposed); however, at 90 weeks, survival was 37/50 (control) and 31/50 (exposed) for respective male groups and 43/50 (control) and 33/50 (exposed) for females. Mean body weights of exposed male rats were 4%-8% lower than those of controls after week 33 and in exposed female rats body weights ranged from 5-13% lower than controls after week 11.

Three exposed female rats displayed uncommon astrocytomas (malignant glial cell tumors of the brain) (NTP, 1989). The authors reported that although the overall incidence of malignant glial cell tumors (3/50) was not statistically significantly different ($p>0.05$) from the concurrent controls (0/50), it was statistically significantly increased ($p<0.05$) relative to incidences for previous chamber control groups at the study laboratory (1/297) or for untreated control female F344/N rats from previous NTP studies (23/1969 = 1%). Primary tumors of glial cell origin were also observed in exposed male rats. One control male had a malignant oligodendroglioma. A benign oligodendroglioma and a malignant astrocytoma were observed in two exposed males.

There were five exposed male rats that had epithelial tumors of several types with similar characteristics (trichoepithelioma, sebaceous gland adenoma and basal cell carcinoma) (NTP, 1989). The combined overall incidence (5/50) was not significantly different from the concurrent control incidence (0/50), but statistical significance ($p<0.05$) could be demonstrated when comparisons were made to historical incidences in chamber controls (2/300) at the study laboratory or in untreated controls (30/1936 = 1.5%) from NTP studies.

NTP (1989) concluded that the study provided equivocal evidence of carcinogenic activity in both male and female F344/N rats, even though comparisons with concurrent controls were negative, because comparisons with historical controls indicated significant differences.

In the 2-year study, chloroethane-exposed female mice, but not male mice or rats of either sex, were hyperactive during daily exposure, but returned to normal shortly after the exposure period ended (NTP, 1989). Survival of 15,000 ppm exposed mice was significantly

lower than that of control mice; statistical significance for reduced survival was demonstrated for exposed male mice after day 330 and for exposed female mice after day 574. All surviving mice were sacrificed at 100 weeks. Mean body weights of exposed male mice were up to 13% higher than control male mice. Mean body weights for exposed and control female mice were generally similar throughout the study.

Decreased survivability in exposed male mice was not related to tumor occurrences (NTP, 1989). The authors noted that greater than normal incidences of nonneoplastic urogenital lesions were observed in both control and exposed male mice and that this occurrence may have contributed to the reduced survival. The overall incidences of alveolar/bronchiolar adenomas (8/48) and of alveolar/bronchiolar adenomas and carcinomas (combined) (10/48) among exposed male mice were statistically significantly greater ($p<0.05$) than respective incidences for control male mice (3/50 and 5/50). The authors, however, considered the study of male B6C3F1 mice inadequate to evaluate carcinogenic activity because of the reduced survival.

Most of the early mortalities in exposed female mice were associated with carcinomas of the uterus (NTP, 1989). The overall incidence of uterine carcinomas (all of endometrial gland origin) in exposed female mice (43/50) was significantly ($p<0.001$) greater than that of the concurrent controls (0/49). Uterine carcinomas were first noted on day 469 of the study. The tumors were highly malignant, invasive and, in 34 animals, metastasized to other organs. Exposed female mice also displayed statistically significantly higher ($p<0.05$, according to a logistic regression test) overall incidences of hepatocellular carcinomas (7/48) and hepatocellular carcinomas and adenomas (combined) (8/48) compared to respective incidences in control female mice (3/49 and 3/49).

Picut et al. (2003) re-evaluated the pathology and incidence data from the NTP (1989) study and confirmed the NTP findings of increased incidences of uterine cancer in female B6C3F1 mice exposed to 15,000 ppm of chloroethane vapors 6 hours/day, 5 days/week for 100 weeks (NTP, 1989).

Based on the results of the NTP (1989) study in which high incidences of uterine carcinomas were observed in mice chronically exposed to chloroethane vapors at a concentration of 15,000 ppm, Bucher et al. (1995) designed a study to assess the potential for chloroethane to induce early changes on sex hormones (estradiol and progesterone). Groups of virgin female B6C3F1 mice (30/group) were exposed to 0 or 15,000 ppm of chloroethane (99.7% pure) by inhalation 6 hours/day for 21 days after having been sham-exposed for an initial 21-day period. There were no clinical signs of chloroethane-induced toxicity and no exposure-related effects on weight gain. No changes were seen in weights of the liver, uterus, or ovary, or in histopathology of the ovaries, pituitary, uterus, or adrenal glands. Blood concentrations of sex hormones were not significantly affected by chloroethane exposure, but variability was high. Compared to the mean duration of estrous cycle during the 21 days of sham exposure (5.15 ± 0.15 days), the mean duration of estrous cycle during the subsequent 21 days of chloroethane exposure (5.52 ± 0.15 days) was slightly but significantly ($p<0.05$) increased. There was also a significant difference ($p<0.05$) in the proportion of time spent in the different estrous stages during exposure compared to the time period of sham exposure in both control and chloroethane-exposed mice. Thus, no

consistent exposure-related patterns of change were found in estrous cyclicity or circulating levels of sex hormones.

In an early study of rabbits (4/group) and rats (12/group) exposed to chloroethane vapors at a concentration of 26,400 mg/m^3 (9847 ppm) for 7.5-8 hours/day, 5 days/week for 6.5 months, no exposure-related clinical signs or effects on weight gain, liver weights or histopathology were observed (Rowe et al., 1939).

Troshina (1964) reported adverse respiratory and liver effects in rats (sex and species unspecified) exposed to chloroethane by inhalation at a concentration of 14,000 mg/m^3 (5222 ppm), 2 hours/day for 60 days. In a subsequent report, Troshina (1966) described several exposure-related effects including disturbed liver function, lowered blood pressure, fatty liver and apparent intraalveolar thickening in the lungs of rats exposed to chloroethane 4 hours/day, 6 days/week for 6 months at chloroethane concentration as low as 8.5 mg/m^3 (3.17 ppm). Both reports are deficient in numerous study details and control groups, which preclude their usefulness for quantitative risk assessment.

Other Studies

Two reports provide evidence for the mutagenicity of chloroethane in the closed-desiccator *Salmonella typhimurium* test for reverse mutations. Riccio et al. (1983) observed mutations in strains TA98, TA100, TA1535 and TA1537 in both the presence and absence of metabolic activation. NTP (1989) observed mutagenic activity in strain TA1535 with or without activation and in strain TA100 only with activation, but no mutagenic activity was observed in strain TA98 with or without activation. Chloroethane was mutagenic to the HPRT (hypoxanthine-guanine phosphoribosyl transferase) locus of Chinese hamster ovary cells both with and without metabolic activation (Ebert et al., 1994). However, exposure of female B6C3F1 mice to chloroethane at a concentration of 25,000 ppm (6 hours/day for 3 days) did not induce unscheduled DNA synthesis; similar exposure of male and female B6C3F1 mice did not result in increased numbers of micronuclei in bone marrow cells (Ebert et al., 1994).

DERIVATION OF A PROVISIONAL SUBCHRONIC RfD FOR CHLOROETHANE

No information was found regarding the oral toxicity of chloroethane in humans. Information regarding repeated-dose oral toxicity of chloroethane in animals was restricted to the results of two limited studies in which no adverse effect levels were identified.

Rowe et al. (1939) reported no clinical or histopathological signs of toxicity, or treatment-related effects on body weight gain among rabbits administered chloroethane doses of 500 or 1,000 mg/kg-day by gavage for 60 doses (assumed to be 5 days/week for 12 weeks). However, available results for this study were limited to a summary statement reporting few details.

Chloroethane did not appear to be toxic to rats given the chemical in drinking water for 14 days at a concentration (5700 mg/L) resulting in doses estimated in the report (Dow, 1995) to be 297 mg/kg-day in male rats and 361 mg/kg-day in female rats. The authors considered decreased water consumption among treated animals (20-25% less than controls) to result from reduced palatability. They concluded that decreased food consumption was secondary to the decreased water consumption and that reduced weight gains and slightly reduced organ weights resulted from reductions in consumption of food and water.

Although Rowe, et al (1939) provide the highest oral NOAEL for the longest dosing period, an unacceptably low level of confidence in the study makes these data unacceptable for use as the point of departure for deriving an oral RfD. The Dow (1995) study reported free-standing drinking water NOAELs of 361 mg/kg-day among female rats and 297 mg/kg-day in male rats dosed for 14 days. The slightly higher dose in female rats was chosen as the point of departure (POD) for deriving a subchronic oral RfD, because both values were freestanding NOAELs. A composite uncertainty factor of 3,000 for a subchronic oral p-RfD was calculated from the following individual uncertainties:

- 10 - inter-human variability
- 10 - mouse to human extrapolation
- 10 - database deficiencies (e.g., no developmental or reproductive oral studies; inhalation developmental data are available)
- 3 - adjustment from 14-day study to subchronic RfD

Subchronic oral p-RfD = (361 mg/kg-day)/3,000 = **0.1 mg/kg-day**

Confidence in the key study, Dow (1995), is medium because the duration of exposure was less than subchronic and because a LOAEL was not identified. Confidence in the database is low because of the lack of studies of appropriate duration and the absence of reproductive and developmental toxicity studies. Consequently, confidence in the subchronic p-RfD is low.

The existing database does not support the derivation of a chronic oral p-RfD because of the lack of 90-day or chronic exposure studies.

DERIVATION OF A PROVISIONAL SUBCHRONIC RfC FOR CHLOROETHANE

As discussed earlier, chloroethane has been used as a general anesthetic in humans. Information regarding chloroethane-induced neurological effects is available for short-term high-level exposure (Davidson, 1925; Dobkin and Byles, 1971; Finch and Lobo, 2005; Hes et al., 1979; Nordin et al., 1988; Sayers et al., 1929). One case report described possible liver effects from repeated abuse of inhaled chloroethane (Hes et al., 1979). These limited human reports are not adequate for purposes of quantitative risk assessment for chloroethane.

Repeated inhalation exposure of adult male and female F344/N rats and B6C3F1 mice resulted in no evidence of exposure-related noncancer effects from exposures as high as 15,000

ppm (6 hours/day, 5 days/week) for up to 2 years, except for hyperactivity in female mice during exposure (NTP, 1989). Other reports (Landry et al., 1982, 1989; Rowe, 1939) found no adverse effects in adult rats, mice or rabbits repeatedly exposed to chloroethane vapors at the highest concentrations tested (10,000, 4843 and 9847 ppm, respectively). However, repeated inhalation exposure of female B6C3F1 mice to a chloroethane vapor concentration of 15,000 ppm (6 hours/day for 5 days) resulted in significantly decreased mean uterine weight (Fedtke et al., 1994a) and slightly increased duration of the estrous cycle (Bucher et al., 1995). Developmental effects (foramina of the skull bones) were noted in fetuses of CF-1 mice exposed to chloroethane at an analytical concentration of 4946 ppm for 6 hours/day on gestation days 6 through 15 (Scortichini et al., 1986). This study served as the basis for a chronic RfC of 10 mg/m^3 for ethyl chloride (chloroethane), which is available on IRIS (U.S. EPA, 2006a).

A point of departure for the provisional subchronic RfC for chloroethane is derived by benchmark dose (BMD) analysis of delayed fetal ossification in the Scortichini et al. (1986) study. All dichotomous models in the EPA Benchmark Dose Modeling Software (BMDS; Version 1.3.2) were fit to the incidence data for foramina of the skull bones on a per litter basis (see Table 1). For each model, a benchmark response (BMR) of 10% extra risk (as recommended by U.S. EPA, 2000) was used to calculate an Effect Concentration (EC_{10}) and its lower 95% confidence limit (LEC_{10}). Table 2 shows the modeling results for each of the dichotomous models.

Table 1. Incidences of foramina of the skull bones in fetuses of CF-1 mouse dams exposed to chloroethane by inhalation for 6 hours/day on gestation days 6 through 15 (Scortichini et al., 1986).

Exposure level (ppm)			
0	491	1504	4946
1/22[a]	1/24	1/25	5/22

[a] Number of affected litters/number of litters examined

All models provided acceptable global goodness of fit (chi square p-value ≥ 0.1). As recommended by U.S. EPA (2000), the model with the lowest Akaike Information Criterion (AIC) value (Gamma model) was selected as the best fitting model, which yielded an EC_{10} of 4442 ppm and an LEC_{10} of 1609 ppm. A plot of the observed and expected fraction of affected litters versus exposure concentration from the results of the Gamma model is shown in Figure 1. The LEC_{10} of 1609 ppm serves as the point of departure for the provisional subchronic RfC for chloroethane.

Table 2. BMD modeling results for foramina of the skull bones (number of litters affected) in fetuses of CF-1 mice (Scortichini et al., 1986).

MODEL	EC_{10} (ppm)	LEC_{10} (ppm)	χ^2 p-value	AIC
Gamma[a]	**4441.64**	**1609.46**	**0.996**	**52.438**
Quantal quadratic	3489.38	2405.34	0.918	52.609
Logistic	3449.15	2462.81	0.856	52.747
Probit	2289.76	3319.11	0.828	52.820
Quantal linear	2868.95	1405.82	0.615	53.497
Multi-stage[c]	2868.95	1405.82	0.615	53.497
Log-logistic[b]	4635.81	1480.59	0.925	54.438
Log-probit[b]	4400.96	2078.46	0.925	54.438
Weibull[a]	4655.54	1609.46	0.925	54.438

[a] Power restricted to >=1

[b] Slope restricted to >=1

[c] Betas restricted to >=0; Degree of polynomial = 1

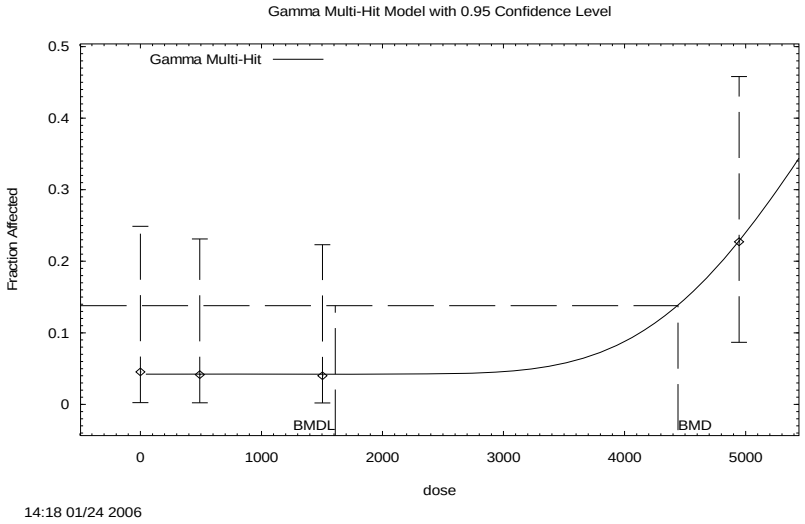

Figure 1. Exposure-response modeling of incidence data for foramina of the skull bones (fraction of litters affected) in fetuses of CF-1 mice exposed to chloroethane for 6 hours/day on gestation days 6 through 15 (Scortichini et al., 1986). BMD = EC_{10}; BMDL = LEC_{10}; Dose = Concentration (ppm)

For extrapolation of developmental effects, the intermittent exposure is duration adjusted as follows:

$$LEC_{10\,[ADJ]} = LEC_{10} \times \frac{6\ \text{hrs/day}}{24\ \text{hrs/day}} = 1609\ \text{ppm} \times \frac{1}{4} = 402\ \text{ppm}\ (1078\ \text{mg/m}^3)$$

Therefore $LEC_{10\ [ADJ]}$ = 402 ppm (1078 mg/m^3). According to U.S. EPA (1994b) methodology for extrarespiratory effects of a category three gas (such as chloroethane), the $LEC_{10[HEC]}$ (human equivalent concentration) is derived by multiplying the $LEC_{10\ [ADJ]}$ by the ratio of the blood:gas partition coefficients ($[H_{b/g}]_A/[H_{b/g}]_H$). A value of 1 is used for the ratio of the blood:gas partition coefficients if the animal blood:gas partition coefficient is greater than the human blood:gas partition coefficient, or if one or more of the blood:gas partition coefficients are not known. The value for humans is 2.69 (Gargas et al., 1989). In the absence of an available blood:gas partition coefficient for chloroethane in the mouse,

$LEC_{10[HEC]} = LEC_{10[ADJ]}$ = 1078 mg/m^3.

The **subchronic p-RfC of 4E+0 mg/m^3** based on delayed fetal ossification (foramina of the skull bones) in the mouse study of Scortichini et al. (1986) is derived by dividing the $LEC_{10[HEC]}$ of 1078 mg/m^3 by a composite uncertainty factor (UF) of 300, as shown below. The subchronic p-RfC of chloroethane is lower than the chronic RfC for this chemical on IRIS (U.S. EPA, 2006a) because of the application of BMDS to derive the LEC_{10}.

Subchronic p-RfC	=	$LEC_{10[HEC]}$ / UF
	=	1078 mg/m^3 / 300
	=	4 mg/m^3 or 4E+0 mg/m^3

The composite UF includes a factor of 3 ($10^{0.5}$) for animal-to-human extrapolation using dosimetric adjustment, 10 for interindividual variability and 10 for database deficiencies.

The interspecies UF of 3 ($10^{0.5}$) reflects a factor of one for pharmacokinetic differences across species (reduced from three due to application of the dosimetric equations) and a factor of 3 ($10^{0.5}$) for pharmacodynamic considerations.

The UF of 10 is used to account for variation in sensitivity within human populations because there is limited information on the degree to which humans of varying gender, age, health status, or genetic makeup might vary in the disposition of, or response to chloroethane.

The default UF of 10 for database deficiencies is selected due to the lack of multigeneration reproductive toxicity study and a developmental toxicity study in a second animal species.

Confidence in the critical study is medium. Although the principal study (Scortichini et al., 1986) was well-conducted, it did not establish a firm exposure-response relationship with an adverse effect and did not include a maternally-toxic exposure level. Confidence in the database is medium. Although well-conducted inhalation studies of repeated exposure of rats and mice are available, most studies did not identify a LOAEL in adult animals. This may be due to the explosion hazard of chloroethane in air at concentrations above 15,000 ppm. Although the selection of developmental toxicity as a critical effect for derivation of a p-RfC is protective of a group considered to be a sensitive subgroup, the database lacks some longer-term exposure studies which might be useful for derivation of both subchronic and chronic provisional values.

Other limitations of the database include the lack of multigeneration reproductive toxicity data and the lack of additional developmental toxicity data to support the results of the principal study. The application of a database deficiencies UF was considered to adequately compensate for the database limitations. Overall, confidence in the subchronic p-RfC is medium.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR CHLOROETHANE

Weight-of-Evidence Descriptor

No data were found on the carcinogenicity of chloroethane in humans. In NTP (1989) animal studies, a high incidence of malignant uterine tumors was observed in chloroethane-exposed female B6C3F1 mice. Inhalation exposure of B6C3F1 mice (but not F344/N rats) resulted in a high incidence of uterine carcinomas (43/50 in chloroethane-exposed mice versus 0/49 in controls), which demonstrates clear evidence of chloroethane carcinogenicity (NTP, 1989). The tumors were invasive and in 34 animals metastasized to a wide variety of organs. Exposed female B6C3F1 mice also displayed significantly increased incidences of hepatocellular carcinomas (7/48) and hepatocellular carcinomas and adenomas (combined) (8/48) compared to respective incidences in controls (3/49 and 3/49), according to a logistic regression test. Other neoplastic lesions that exhibited significantly increased incidences relative to historical (but not concurrent) controls included benign and malignant epithelial neoplasms of the skin in chloroethane-exposed male F344/N rats (trichoepithelioma, 1/50; sebaceous gland adenoma, 1/50; basal cell carcinoma, 3/50; squamous cell carcinoma 2/50) and malignant astrocytomas in the brain of chloroethane-exposed female F344/N rats (3/50). Thus, there is clear evidence for carcinogenicity in female B6C3F1 mice and equivocal evidence for carcinogenicity in male and female F344/N rats. In the absence of data to indicate otherwise, the finding of chloroethane-induced uterine carcinomas in female B6C3F1 mice is considered to be relevant to humans. Chloroethane has not been extensively tested for genotoxicity, but the available studies indicate that chloroethane may be mutagenic (Riccio et al., 1983; NTP, 1989; Ebert et al., 1994). The limited mechanistic data for chloroethane do not provide clear evidence of a specific carcinogenic mode of action.

Based on these observations and in accordance with the U.S. EPA (2005) cancer guidelines, chloroethane is classified as *likely to be carcinogenic to humans* based on two factors: 1) a lack of human data and; 2) animal data that demonstrate a high degree of malignancy in chloroethane-exposed female mice.

Mode of Action Discussion

Several investigators (Fedtke et al., 1994a,b; Gargas et al., 1989; Pottenger et al., 1992) have studied the metabolism of chloroethane in an effort to discern the mechanism for induction of rare uterine tumors in female mice (NTP, 1989). A high-dose dependent disposition and GSH-dependent metabolism in mice has been suggested to account for the development of tumors in mice and not in rats (Pottenger et al., 1992). Fedtke et al. (1994a,b) examined cytochrome P450-dependent and GSH-dependent metabolism in a series of *in vitro* and *in vivo*

experiments in groups of male and female rats and mice exposed to 15,000 ppm chloroethane or air for 6 hours/day for 5 days. The authors concluded that chloroethane may be oxidatively dechlorinated by cytochrome P450 to form acetaldehyde, which enters the 2-carbon pool and is further metabolized to ethanol and acetic acid and that species differences in oxidative metabolism were not significant. In addition, rate constants estimated for rats from these experiments were consistent with those estimated earlier by Gargas et al. (1989) in a PBPK model for chloroalkanes in the rat. In assessing GSH-dependent chloroethane metabolism in rats and mice, Fedtke et al. (1994b) noted the following: 1) chloroethane could be conjugated with glutathione, converted to the mercapturic acid and excreted in the urine as the mercapturic acid (S-ethyl-N-acetyl-L-cysteine) or the non-acetylated intermediate S-ethyl-L-cysteine (mice only); 2) the rate of hepatic glutathione conjugation of chloroethane (measured by GSH-transferase specific activity) was found to be higher in both sexes of mice compared with rats; 3) when GSH concentrations were measured in the lungs, liver, kidneys and uterus, GSH was decreased in the lung and uterus of mice after exposure to 15,000 ppm, 6 hours/day for 5 days, compared with GSH concentrations in these tissues after exposure to air; and 4) decreases in GSH levels in the lungs of rats were smaller than those in mice. These results suggested that tumor formation may be dependent on chloroethane metabolism, which might explain species-specific differences in susceptibility to chloroethane carcinogenicity.

The mode of action by which chloroethane produces uterine tumors in mice is unknown. A hormonally-mediated mode of action has been postulated, but testing for the impact of early exposure (21 days) on sex hormones and estrous cyclicity did not reveal consistent exposure-related effects in B6C3F1 mice (Bucher et al., 1995). In addition, no histopathological effects were seen in ovary, uterus, pituitary or adrenals.

Although chloroethane has not been extensively assessed for genotoxicity, a genotoxic mode of action is plausible because chloroethane has been shown to produce mutagenic effects in several bacterial strains (Riccio et al., 1983; NTP, 1989) and in Chinese hamster ovary cells (Ebert et al., 1994). This genotoxic mode of action for chloroethane carcinogenicity is discussed below within the context of the modified Hill criteria of causality as recommended in the most recent Agency guidelines (U.S. EPA, 2005).

Mutagenic Mode of Action for Uterine Tumors

Key events

This mode of action hypothesizes that, following appearance in the uterine cells, chloroethane or one of its reactive metabolites reacts directly with DNA, or indirectly via induction of oxidative stress, to produce DNA damage leading to mutations in critical genes for tumor initiation.

Strength, consistency, specificity of association

Information to support this hypothetical genotoxic mode of action for chloroethane is limited to chloroethane-induced mutagenicity in several bacterial strains (Riccio et al., 1983; NTP, 1989) and in Chinese hamster ovary cells (Ebert et al., 1994).

Dose-response concordance

The only available chronic cancer bioassay (NTP, 1989) included only one high exposure concentration (15,000 ppm), which resulted in a high incidence (43/50) of uterine carcinomas in female B6C3F1 mice, and there are no dose-response data for precursor events, thus precluding an assessment of dose-response concordance.

Temporal relationships

No data are available to assess the temporal relationship between exposure to chloroethane and development of uterine carcinomas in B6C3F1 mice.

Biological plausibility and coherence

Support to the plausibility and coherence of a hypothetical genotoxic mode of action for chloroethane-induced uterine carcinomas in mice is provided by a limited number of genotoxicity assays in which chloroethane induced a mutagenic response. In the NTP (1989) 2-year cancer bioassay, chronic exposure to a high concentration of chloroethane resulted in a high incidence of uterine carcinomas in mice, but not rats. The basis for this species-specific difference in response is not known, although there is some indication that metabolic differences may play a role. The human relevance of chloroethane-induced uterine carcinomas in mice is assumed in the absence of data to indicate otherwise.

Conclusions

Based on available information regarding the carcinogenicity of chloroethane, increased incidences of uterine carcinomas in chloroethane-exposed mice are considered relevant to human health and marginally suitable for quantitative cancer assessment of chloroethane. Although a mutagenic mode of action is plausible, the available data are inadequate to establish a mode of action. Consistent with U.S. EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), a linear (e.g., non-threshold) extrapolation is indicated when a mode of action is not established.

Quantitative Estimates of Carcinogenic Risk

Oral Exposure

There are no human or animal oral data on which to base an oral cancer assessment for chloroethane.

Inhalation Exposure

The only available inhalation carcinogenicity bioassay (NTP, 1989) used a single choloroethane exposure level (15,000 ppm) at which a high proportion (86%) of female mice developed uterine tumors. Because a mutagenic mode of action cannot be discounted and no other mode of action has been proposed, a linear non-threshold dose-response model would be

appropriate. The U.S. EPA cancer guidelines (U.S. EPA, 2005) specify a linear extrapolation from a BMDL with a BMR in the 1% to 10% range, as determined from the multistage dose-response model. In this case, however, the lowest response (86%) is far from any BMR acceptable as a POD. Therefore, the data are deemed to be inadequate for the calculation of an inhalation unit risk.

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