United States
Environmental Protection
Agency

EPA/690/R-12/007F
Final
11-26-2012

Provisional Peer-Reviewed Toxicity Values for

2-Chloroethanol
(CASRN 107-07-3)

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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
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
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
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 2-CHLOROETHANOL (CASRN 107-07-3)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should 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).

INTRODUCTION

2-Chloroethanol is also known as ethylene chlorohydrin and by 42 other synonyms. It occurs as a colorless, glycerine-like liquid, described as having a sweet, pleasant, faintly ether-like odor (HSDB, 2005). It is an intermediate in the synthesis of ethylene oxide and ethylene glycol and in the production of indigo, dichloroethyl formal (an intermediate for the production of polysulfide elastomers), and thiodiethylene glycol (used in textile printing). It is also an industrial solvent, a preemergent plant growth stimulator, and an extractant for textile printing dyes. The principal use of 2-chloroethanol was formerly in the production of ethylene oxide. Before 1972, as much as one billion pounds of 2-chloroethanol was used for this purpose (NTP, 1985a,b,c). The empirical formula for 2-chloroethanol is C_2H_5ClO, and the molecular structure of 2-choloroethanol is presented in Figure 1. Some physicochemical properties of 2-chloroethanol are provided in Table 1. In this document, "statistically significant" denotes a *p*-value of <0.05, unless otherwise noted. The most common routes of exposure to toxic levels of 2-chloroethanol are expected to be dermally or by inhalation (NTP, 1985a,b,c). 2-Chloroethanol is quite stable and persistent and has been found in foods, medical supplies, and medical devices (Andrews et al., 1983).

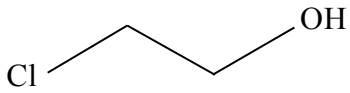

Figure 1. 2-Chloroethanol Structure

Table 1. Physicochemical Properties Table for 2-Chloroethanol (CASRN 107-07-3)[a]

Property (unit)	Value
Boiling point (ºC)	128−130
Melting point (ºC)	−67.5
Density (g/cm^3 at 20ºC)	1.197
Vapor pressure (mm Hg at 20ºC)	4.9
Solubility in water (g/L at 25ºC)	infinitely
Relative vapor density (air = 1)	2.78
Molecular weight (g/mol)	80.51
Octanol/water partition coefficient (log K_{ow}, unitless)	−0.06

[a]Values were obtained from HSDB (2005).

No RfD, RfC, or cancer assessment for 2-chloroethanol is included on EPA's Integrated Risk Information System (IRIS) (U.S. EPA, 2012b) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2006). No RfD or RfC values were reported in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 2012a). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994) does not include a Health and Environmental Effects Profile (HEEP) for 2-chloroethanol. The toxicity of 2-chloroethanol has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2008) or the World Health Organization (WHO, 2010). The California Protection Agency (CalEPA, 2008) has not derived toxicity values for exposure to 2-chloroethanol.

Regulatory standards are reported in the Hazardous Substance Data Bank (HSDB, 2005) for 2-chloroethanol (CASRN 107-07-3). The OSHA Permissible Exposure Limit (PEL) for general, construction, and maritime industries is a 5-ppm (16 mg/m^3) 8-hour time weighted average (OSHA, 2010). The American Conference of Governmental Industrial Hygienists (ACGIH) has set a Ceiling Threshold Limit Value (TLV-C) to skin of 1 ppm (3.3 mg/m^3) (ACGIH, 2010, 2001). The NIOSH recommended exposure limit is a ceiling value of 1 ppm (3.3 mg/m^3) to skin (NIOSH, 2010). The NIOSH Immediately Dangerous to Life or Health Concentration (IDLH) is 7 ppm. The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994) does not include any health and environmental assessment documents for 2-chloroethanol.

Literature searches were conducted on sources published from 1900 through November 2011 for studies relevant to the derivation of provisional toxicity values for 2-chloroethanol (CASRN 107-07-3). Searches were conducted using EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for health information: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides information for all of the potentially relevant studies. Entries for the principal studies are bolded.

Table 2. Summary of Potentially Relevant Data for 2-Chloroethanol (CASRN 107-07-3)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical effects at LOAEL	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
1. Oral (mg/kg-day)[a]								
Subchronic	None							
Chronic	None							
Developmental	None							
Reproductive	None							
Cancer	None							
2. Inhalation (mg/m^3)[a]								
Subchronic	None							
Chronic	None							
Developmental	None							
Reproductive	None							
Cancer	2174 males, occupational epidemiological study, mean duration and follow-up not reported	Not known	Increased risk for leukemia and pancreatic cancer with increasing time on the job	Not applicable	Not run	Not applicable	Greenberg et al. (1990)	PR
Cancer	278 males, occupational epidemiological study, mean duration 5.9 years, mean follow-up 36.5 years	Not known	Increased risk for total cancer, pancreatic cancer, all lymphatic and hematopoietic cancers, and leukemia with increasing time on the job	Not applicable	Not run	Not applicable	Benson and Teta (1993)	PR
Cancer	1361 males, occupational epidemiological study, duration 0.1−35 years, follow-up 8−44 years	Not known	No increased risk for pancreatic, lymphopoietic, and hematopoietic cancers	Not applicable	Not run	Not applicable	Olsen et al. (1997)	PR

Table 2. Summary of Potentially Relevant Data for 2-Chloroethanol (CASRN 107-07-3)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical effects at LOAEL	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Animal								
			1. Oral (mg/kg-day)[a]					
Subchronic	**25/25 FDRL rat, 6 weeks administered daily in diet followed by 12 weeks daily gavage**	**0, 30, 45, or 67.5**	**Increased moribundity, decreased body weight, and death (17/25 males, 19/25 females) at the high dose**	**45**	**Not run**	**67.5**	**Oser et al. (1975a)**	**PS, PR**
Subchronic	5 male, strain not specified rat, daily in diet, 220 days	0, 9, 18, 36, 72, 108, 144, or 216 , (calculated by U.S. EPA, 1988)	Decreased body-weight gain	72	Not run	108	Ambrose (1950)	PR
Subchronic	4/4 beagle dog, administered daily in diet, 15 weeks	Estimated at 13.3, 18.3, and 18.4 in males and 16.9, 19.3, and 20.3 in females	Severe emesis prevented consistent dose retention in all but the lowest doses in males and females	13.3/16.9 in males/ females	Not run	Not identified	Oser et al. (1975b) ; no adverse effects observed in any dose group, but severe emesis complicates dosimetry	PR
Subchronic	2/2 Rhesus monkey, administered daily in diet, 12 weeks	0, 30, 45, or 62.5 mg/kg-day	None observed	62.5	Not run	Not identified	Oser et al. (1975c)	PR
Chronic	None							
Developmental	12 female CD-1 mouse, gavage, administered on GDs 6−16	0, 50, 100, or 150; additional control group treated with 86.5 ethanol	Dams: decreased body-weight gain Fetuses: decreased body weight	50 50	Not run	100 100	Courtney et al. (1982a)	PR

Table 2. Summary of Potentially Relevant Data for 2-Chloroethanol (CASRN 107-07-3)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical effects at LOAEL	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Developmental	Dose groups included 16, 3, 3, 4, and 13 female CD-1 mice, drinking water, administered on GDs 6−16	0, 16, 43, 77, or 227	Dams: none observed Fetuses: none observed	227 227	Not run	Not identified	Courtney et al. (1982b)	PR
Reproductive	None							
Carcinogenic	None							
2. Inhalation (mg/m^3)[a]								
Subchronic	None							
Chronic	None							
Developmental	None							
Reproductive	None							
Carcinogenic	None							

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-day) for oral noncancer effects. All long-term exposure values (4 weeks and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure.
[b]PS = principal study, NPR = not peer reviewed, PR = peer reviewed.

HUMAN STUDIES

Oral Exposures

No oral studies on the subchronic, chronic, developmental, or reproductive toxicity or on the carcinogenicity of 2-chloroethanol in humans were identified.

Inhalation Exposures

No inhalation studies were found on the subchronic, chronic, developmental, or reproductive toxicity of 2-chloroethanol in humans. The carcinogenic potential of 2-chloroethanol was evaluated in three epidemiological studies (Greenberg et al., 1990; Benson and Teta, 1993; Olsen et al., 1997). None of the three studies determined exposure levels of 2-chloroethanol. Further, the studies do not conclusively identify the causative agent, thus precluding their use in a quantitative assessment.

Greenberg et al. (1990) performed a retrospective cohort study examining mortality in 2174 men, potentially exposed to 2-chloroethanol at two chemical production plants between 1940 and 1978. These workers had duties in a department that used or produced ethylene oxide, a known alkylating agent that is genotoxic and carcinogenic in rats and mice. The study cohort was drawn from a pool of 29,139 male workers who had ever been employed at either of the two production facilities and an associated technical center during the same period. There were no statistically significant increases in deaths due to any cause; however, 7 deaths were attributed to leukemia with 3.0 deaths expected, and 7 deaths were attributed to pancreatic cancer with 4.1 deaths expected. Investigations revealed that four of the seven leukemia victims and six of the seven pancreatic cancer victims had worked in the "chlorohydrin department," an area that produced ethylene chlorohydrin (2-chloroethanol) and/or propylene chlorohydrin. Further, the relative risk of death from these diseases was "strongly related to duration of assignment to that department." Potential exposure to ethylene oxide in this department was low, suggesting an association between exposure to ethylene chlorohydrin and/or propylene chlorohydrin and increased death due to leukemia and pancreatic cancer.

Benson and Teta (1993) subsequently performed a 10-year update on 278 men who had worked in the "chlorohydrin unit" to verify the increases in mortality due to leukemia and pancreatic cancer observed by Greenberg et al. (1990). Standardized mortality ratios (SMRs; the relative measure of the difference in risk between exposed and unexposed populations in a cohort study) were calculated, and duration-response trends were assessed for this group. Two additional cases of pancreatic cancer were noted, along with cases of non-Hodgkin's lymphoma and multiple myeloma. The authors concluded that "pronounced increases in risk were seen for total cancer, pancreatic cancer, all lymphatic and hematopoietic cancers, and leukemia with increasing durations of assignment to the "chlorohydrin unit." However, there were insufficient data to conclusively identify the causative agent(s).

Olsen et al. (1997) performed another epidemiological study on a cohort of 1361 men who worked at chemical manufacturing facilities at different locations than in the previous two studies to determine whether a similar increased risk in mortality from pancreatic, lymphopoietic, and hematopoietic cancers occurred. The subjects were exposed during their employment to ethylene chlorohydrin and propylene chlorohydrin. Calculation of the SMR did not indicate an increased risk of the previously reported cancers; however, the authors did conclude that "an additional five to ten years of follow-up of the cohort are necessary to ensure

comparable latency periods" with the previous studies. No follow-up studies were identified in the literature search for this assessment.

In summary, these epidemiological studies were not able to determine a causative agent, and there are no conclusive data to support that 2-chloroethanol is carcinogenic in humans at this time.

ANIMAL STUDIES

Oral Exposure

The effects of oral exposure of animals to 2-chloroethanol have been evaluated in subchronic (Oser et al., 1975a,b,c; Ambrose, 1950) and developmental (Courtney et al., 1982a,b) studies. Oser et al. (1975) is a journal article containing studies performed on three different species (i.e., rat, dog, and monkey). To differentiate between the studies, the designation of Oser et al. (1975a) is used for the rat study, Oser et al. (1975b) is used for the dog study, and Oser et al. (1975c) is used for the monkey study. Courtney et al. (1982a,b) is a journal article containing the results of studies performed using two routes of exposure; Courtney et al. (1982a) is used for the gavage study, and Courtney et al. (1982b) is used for the drinking water study.

Subchronic Studies

The study by Oser et al. (1975a) is selected as the principal study for deriving the subchronic and chronic p-RfDs. In a peer-reviewed study, Oser et al. (1975a) administered 2-chloroethanol (purity not provided) in the diet to 25 FDRL rats/sex/dose group at concentrations intended to provide 0, 30, 45, or 67.5 mg/kg-day daily for 6 weeks. After 6 weeks, the method of administration was changed to gavage due to a lack of stability of the compound in the diet. At this point, body-weight gains were similar in all groups and in both sexes, and no differences were noted in the clinical signs. Thereafter, the rats were fasted overnight, allowed a 1-hour feeding period, and dosed by daily gavage for an additional 12 weeks (10-mL/kg dose volume) with freshly prepared aqueous solutions at 0, 30, 45, or 67.5 mg/kg-day. Food (Purina Laboratory Chow) remained available until the end of each work day; water was provided ad libitum. The rats were housed individually in raised-bottom cages (no further husbandry information was provided). At Weeks 6 and 12 from the start of gavage dosing, urine was collected from 10 rats/sex/dose group for urinalysis; blood was collected from these rats and analyzed for hemoglobin, hematocrit, total and differential leukocyte counts, prothrombin time, blood urea nitrogen, blood glucose, serum glutamic-oxaloacetic transaminase, and serum alkaline phosphatase. The rats were sacrificed and necropsied after 12 weeks of gavage treatment. The liver, kidneys, heart, gonads, adrenals, thyroids, and pituitary were weighed. Tissue samples were taken from 26 organs (i.e., liver, kidney, lung, heart, and other organs unspecified in the report) from 10 rats/sex/dose in the control and 67.5-mg/kg-day groups and evaluated histologically. Additionally, tissue samples from the liver and kidney were evaluated for all dose groups. This study was conducted prior to the adoption of Good Laboratory Practice (GLP) standards (40 CFR Part 160; November 29, 1983). Statistical analyses were not performed, and insufficient data were provided to allow the reviewers to perform statistical analyses. It was not stated whether the stability of the compound in the aqueous solutions was verified, although solutions were prepared fresh prior to dosing. However, the following information is known from the Hazardous Substance Data Bank (HSDB, 2005): the test compound is miscible with water and degrades in water at high temperature (100°C); the National Fire Protection Association (NFPA) Hazard Classification of reactivity for 2-chloroethanol is 0 (it is not reactive with water); the aquatic fate of the compound when

released into water may be biodegradation; 2-chloroethanol is not expect to volatize from surface waters, adsorb to sediment, bioconcentrate in fish, photolyze, or hydrolyze. A National Toxicology Program (NTP, 1985a,b,c) study demonstrated the stability of the compound in 70% aqueous ethanol for 21 days at room temperature. Thus, together, this information suggests that 2-chloroethanol may be stable in water at room temperature. Consequently, risk assessment proceeds on the assumption that the test compound is stable in water. Considering that the actual dose received during the first 6 weeks (dietary formulations) is unknown due to test compound instability, total exposure of these animals is also unknown.

During the first 3 weeks after gavage administration was begun, food consumption was decreased (see Table B.1), and labored breathing was observed in the majority of the 67.5-mg/kg-day rats (Oser et al., 1975a). These animals became moribund and were sacrificed; only 8 of 25 males and 6 of 25 females survived to the end of the 12-week dosing period. Overall (Weeks 1−12 of gavage dosing) body-weight gain was decreased by 34% in the surviving 67.5-mg/kg-day males. No other adverse effect was reported for any examined parameter, except in the decedents. The following gross pathological findings were noted in the decedents: dark livers with alternate pale and granular areas; reddened and/or bloody gastrointestinal tissues; hemorrhagic adrenal and pituitary glands; and red or dark red lungs. The following qualitative histological findings were noted in the decedents: subacute myocarditis (frequently, both sexes), colloid depletion in the thyroid (one male, four females), fatty changes in the liver (one male, five females), thyroid congestion (four males), and congestive pulmonary changes (frequently, both sexes). Based on a lack of observed toxicological effects, the study authors defined 45 mg/kg-day as the NOAEL. Frank effects (i.e. moribundity) were observed in rats treated at the next (highest) level (67.5 mg/kg-day). Consequently, the LOAEL is also the study FEL (Frank Effects Level).

Ambrose (1950) administered 2-chloroethanol in the diet at concentrations of 0, 0.01, 0.02, 0.04, 0.08, 0.12, 0.16, or 0.24% (equivalent to 0, 9, 18, 36, 72, 108, 144, or 216 mg/kg-day, respectively, calculated by the U.S. EPA [1988]) daily to five male rats/dose group (strain not specified) for approximately 220 days. Stability of the test compound in the diet was not reported. Because the stability of the test compound in the diet is unknown in this study and 2-chloroethanol was shown to be unstable in the diet (Oser et al., 1975), this study is considered unacceptable for calculating a p-RfD and is only briefly summarized. Body-weight gain was decreased at doses of 108 mg/kg-day and above, and food consumption was decreased at doses of 144 mg/kg-day and above. Autopsy and histological examination revealed no treatment-related effects. The study authors did not define a NOAEL or LOAEL. Rats dosed at 72 mg/kg-day showed no treatment-related effects; therefore, this dose level is considered the NOAEL. The LOAEL is 108 mg/kg-day, based on decreased body-weight gain.

Oser et al. (1975b) administered 2-chloroethanol (purity not provided) in the diet to four beagle dogs/sex/dose group for up to 15 weeks at estimated daily mean doses of 13.3, 18.3, and 18.4 mg/kg-day in males and 16.9, 19.3, and 20.3 mg/kg-day in females. Approximately 20 mg/kg-day seemed to be the maximum dose tolerated without a severe emetic response. Doses were administered initially as a wet mash at concentrations up to 1350 ppm (4445 mg/kg), but these concentrations were reduced in several stages to ensure retention. The levels of 2-chloroethanol were gradually increased as long as the doses were retained; however, only the lowest dose was consistently retained. Husbandry and study design/methodology were the same as previously described in Oser et al. (1975a). Stability of the compound in the diet was not

reported, but it was stated that the diets were freshly prepared. It was unclear how the estimated daily mean dose could be accurately determined due to the reported emetic response. The mid- and high-dose groups received approximately the same dose. Statistical analyses were not reported. No adverse effects were reported for any dose group. The study authors did not define a NOAEL or LOAEL; however, the highest dose that was consistently retained by the dogs (13.3/16.9 mg/kg-day in males/females) showed no effects; therefore, the 13.3/16.9 mg/kg-day is considered a NOAEL in males and females, respectively, and a LOAEL is not identified.

Oser et al. (1975c) administered 2-chloroethanol (purity not provided) orally by syringe in an apple sauce vehicle to two Rhesus (*Macaca mulatta*) monkeys/sex/dose group for up to 12 weeks at daily doses of 0, 30, 45, or 62.5 mg/kg-day. Dose formulations were "freshly prepared," but stability of the compound in the vehicle was not reported. Each animal was housed individually in a raised-bottom cage and was fed Rockland Farms Monkey Chow and fresh fruit (no further husbandry information was provided). The study design/methodology was the same as previously described in Oser et al. (1975a). No adverse effects were reported for any dose group, and an *n* of 2 precludes meaningful statistical analyses. The study authors did not define a NOAEL or LOAEL; however, the highest dose (62.5 mg/kg-day) showed no effects. Thus, 62.5 mg/kg-day is considered a NOAEL; a LOAEL is not identified.

Chronic Studies

No studies regarding the effects of chronic oral exposure to 2-chloroethanol in animals were identified.

Developmental and Reproduction Studies

In a developmental toxicity study, Courtney et al. (1982a) administered 2-chloroethanol (99% purity) in water by gavage to 12 presumed pregnant CD-1 mice/dose group at doses of 0, 50, 100, or 150 mg/kg-day in a volume of 0.1 mL/mouse/day on Gestation Days (GDs) 6−16. Doses were calculated based on GD 6 body weights. It was not stated whether the test compound stability was confirmed in the vehicle, and frequency of preparation of the dosing solutions was not provided. All mice were sacrificed on GD 17. Upon sacrifice, the fetuses were weighed as a litter and examined, and half of each litter was stored in Bouin's solution until examined by dissection. The remaining fetuses were stained with alizarin red S for skeletal examination. In addition, the fetuses selected for alizarin staining were weighed individually, and their livers were removed and weighed. Parameters reported also included maternal body-weight gain, relative liver weight, implants/litter, fetus mortality, fetuses/litter, fetal weight, number and type of anomalies, fetal liver weight (absolute and relative), placenta weight, and number of litters and fetuses. At 150 mg/kg-day, 75% of the maternal mice died, usually after 2−4 treatments, and the remaining 25% were not pregnant. At 100 mg/kg-day, maternal body-weight gain was decreased ($p \leq 0.05$) by 61%, and fetal body weight was decreased ($p \leq 0.05$) by 14%. At 100 mg/kg-day, absolute and relative liver weights of the fetuses were decreased ($p \leq 0.05$) by 19% and 9%, respectively. These findings were considered to reflect the decreased fetal body weight. A minor decrease ($p \leq 0.05$) of 6% was also noted in relative liver weight in the 50-mg/kg-day fetuses; this finding was not considered biologically relevant. The study authors did not define a NOAEL or LOAEL. Maternal mice dosed at 50 mg/kg-day showed no treatment-related effects; therefore, this dose level is considered the maternal NOAEL. The maternal LOAEL is 100 mg/kg-day, based on decreased maternal body-weight gain. Fetuses dosed at 50 mg/kg-day showed no treatment-related effects; therefore, this dose

level is considered the developmental NOAEL. The developmental LOAEL is 100 mg/kg-day, based on decreased fetal body weight.

In a companion developmental toxicity study, Courtney et al. (1982b) administered 2-chloroethanol (99% purity) in the drinking water of presumed pregnant CD-1 mice at nominal doses of 0, 10, 25, 50, or 200 mg/kg-day on GDs 6−16. Actual intake, reported by the study authors, was 0, 16, 43, 77, or 227 mg/kg-day, and the numbers of pregnant mice for which data were reported were 16, 3, 3, 4, and 13 per dose group, respectively. It was not stated whether the test compound stability was confirmed in the vehicle, and frequency of preparation of the dosing solutions was not provided. All mice were sacrificed on GD 17. Upon sacrifice, the fetuses were weighed as a litter and examined, and half of each litter was stored in Bouin's solution until examined by dissection. The remaining fetuses were stained with alizarin red S for skeletal examination. Total liver triglycerides of the dams in the high-dose group and the concurrent control mice were determined. Parameters reported also included maternal body-weight gain, relative liver weight, implants/litter, fetus mortality, fetuses/litter, fetal weight, and number and type of anomalies. There were no significant differences in the maternal or fetal parameters at any dose level in the drinking water, and no teratogenic effect could be attributed in either group to the compound. The gavage arm of the study (Courtney et al., 1982a) probably produced higher transient blood levels of the compound than did the drinking water study (Courtney et al., 1982b), possibly resulting in more severe effects. The study reviewers identified a maternal and developmental NOAEL of 227 mg/kg-day (the highest dose tested); a LOAEL is not identified.

Reproductive Studies

No studies regarding the effects of oral exposure to 2-chloroethanol on reproduction in animals were identified.

Carcinogenic Studies

No studies regarding the effects of oral exposure to 2-chloroethanol on carcinogenicity in animals were identified.

Inhalation Exposure

No inhalation studies on the subchronic, chronic, developmental, or reproductive toxicity or carcinogenicity of 2-chloroethanol in animals were identified.

OTHER STUDIES

Short-Term Toxicity Studies

Human Studies

Several studies detailing the acute or short-term toxicity of 2-chloroethanol in humans were found (Deng et al., 2001; Miller et al., 1970; Bush et al., 1949; Goldblatt and Chiesman, 1944). Because the effects in humans are of particular concern, these studies are detailed below (and in Table 3), even though the information cannot be used to quantify subchronic or chronic RfD or RfC values.

Deng et al. (2001) conducted a retrospective analysis to evaluate patients with 2-chloroethanol poisoning reported to the Taiwan Poison Control Center during 1985−1998. There were 17 patients (11 male and 6 female) ranging from 2−70 years of age. Five patients attempted or committed suicide, nine patients were exposed unintentionally, and three patients were occupationally exposed. Ingestion via the mouth was the most common route of exposure (14 patients), while three patients were exposed through the dermal and/or oral route, and one

patient was exposed by inhalation. Seven out of 17 patients died within 24 hours after exhibiting severe symptoms such as metabolic acidosis, respiratory failure, shock, and/or coma. The estimated dose resulting in patient death was in excess of 330 mg/kg. An estimated dose of 742 mg/kg-day resulted in severe toxicity to a 7-year-old male; however, this patient improved upon receiving ethanol therapy soon after admission and for the next 4 days. Although shown to have a protective effect on 2-chloroethanol toxicity (Bonitenko et al., 1981), ethanol therapy was insufficient to rescue a 2-year-old male who ingested an estimated 396−792 mg/kg dose. The benefit of ethanol therapy was unclear for two other cases where only mild or moderate toxicity was observed. Doses of less than 100 mg/kg resulted in mild toxicity (transient signs and symptoms). All but one patient developed symptoms within 2 hours after exposure. Patients with mild-to-moderate poisoning had mild gastrointestinal, cardiovascular, respiratory, or neurologic effects (nine patients); vomiting (five patients); tachycardia, tachypnea, and weakness/lethargy (three patients); nausea, transient confusion, and sore throat/oral discomfort (two patients); and dizziness, chest tightness, transient hypertension, chilliness, hypokalemia, and slightly impaired renal function (one patient). See the *Metabolism and Toxicokinetic Studies* section and Figure 2 for additional information on mechanism of ethanol therapy.

Miller et al. (1970) presented a case study in which a 23-month-old male patient ingested approximately 2 mL of Cinecol, a photographic film cement containing 1−2 mL of chloroethanol. The patient became pale and cyanotic and showed respiratory difficulty. General convulsions, fluctuating systolic blood pressure, and varying pulse rate were observed 5−7 hours later. His temperature and pulse rate increased, while his blood pressure decreased. The patient vomited, became apnoeic, and had a cardiac arrest resulting in his death in less than 12 hours after ingestion. At necropsy, the following findings were noted: edematous and congested lungs; pulmonary hemorrhage; petechiae in the subepicardium, thymus, and beneath the liver capsule; toxic follicular pattern in the spleen; and agonal intussusceptions in the small bowel. Microscopically, early necrosis of the liver parenchyma with nuclear vacuolation, cytoplasmic swelling, and small foci of polymorph infiltration, kidney tubular swelling, widespread neuronal enlargement in the brain, damaged Purkinje cells, and swollen endothelial lining of some cerebral blood vessels were observed. Neither 2-chloroethanol nor chloroacetic acid were found in the blood or tissues.

Bush et al. (1949) described the poisoning of employees at a large seed potato supply firm in Bakersfield, CA. Exposure of seed Irish potatoes to 2-chloroethanol can reduce their dormancy period from 90 days to only a few days. Workers were exposed by both the dermal and inhalation routes. One worker suffered nausea and dizziness followed by vomiting, abdominal pain, weakness, and diminished vision. He seemed to recover an hour and a half after the symptoms were first noticed; however, he collapsed and became comatose after two more hours. He was deeply cyanotic, his heart tones were imperceptible, his skin was cold and clammy, and his blood pressure could not be measured. He was treated with caffeine and sodium benzoate, atropine sulfate, morphine sulfate, picrotoxin, nikethamide solution, methylene blue, and epinephrine. He died 8 hours after the initial onset of symptoms. Findings in the patient included albuminuria, fatty infiltration of the liver, brain edema, lung congestion/edema, dilatation of the chambers of the right side of the heart, spleen congestion, cloudy swelling and hyperemia of the kidneys, fatty degeneration of the myocardium, swollen and hyperemic renal glomeruli, swollen epithelial cells occluding the renal convoluted tubules, pulmonary alveoli dilated and filled with blood, and hyperemia in the spleen. These findings may have been confounded by the drugs that were administered therapeutically. Five coworkers survived but

suffered from nausea, vomiting, and dizziness. There were varying complaints of "burning sensation of the nose, irritation of the eyes, diminished vision, and numbness of the hands and fingers." A significant fall in blood pressure was noticed in two patients. One patient required 76 days for complete recovery, while a second patient required almost a month. The other three patients recovered within hours to days after exposure.

Eleven cases of poisoning observed in workers involved in the manufacture of 2-chloroethanol were described by Goldblatt and Chiesman (1944). In two of these cases, the patient died. A foreman was exposed to high concentrations of 2-chloroethanol and ethylene dichloride (quantitative dose unknown) for approximately 1.5 hours. The findings included vomiting, restlessness, unsteadiness, weak pulse, pupils varying in size, sluggish tendon reflexes, blood pressure immeasurable, profuse perspiration, petechial hemorrhages in the pericardium, cerebral cortex congestion, cerebral hemisphere edema, lung collapse and edema, extravasation of blood into the alveoli, areas of degenerative change in the liver, fatty degeneration in the liver, loss of cellular outlines and nuclei disappearance in liver, and cross striations in heart not visible. The author stated that the second mortality may be attributed to individual susceptibility (idiosyncratic response). This patient was exposed for some 2 months to concentrations (quantity unknown) of 2-chloroethanol (probably mixed with some sym-dichloroethane) and died 11 weeks and 2 days after starting work. The patient would collapse while walking in the street. He complained of headache, dizziness, and vomiting. His mental condition was called "very muddled." At autopsy, the following findings were noted: congested, slightly hyperplastic spleen, congested kidney, damaged renal convoluted tubules, and degenerative changes and edema of the basal ganglia.

A summary of the signs and symptoms in the nine nonfatal cases of human exposure described by Goldblatt and Chiesman (1944) included

- *digestive system—nausea, epigastric pain, repeated vomiting (bile may appear), and bulky offensive stools;*
- *circulatory system—depressor action on the circulation, and signs of shock in severe cases;*
- *nervous system—headache, giddiness, incoordination, confusion, and mild narcotic effects;*
- *urinary system—slight albuminuria (disappearing on recovery) and polyuria;*
- *respiratory system—cough may be present and rhonchi; and*
- *skin—erythema on skin of arms and trunk in severe cases.*

The authors further stated that "symptoms and signs were worse in men of poor physical standard. Recovery in these nonfatal cases was complete; and in all except one, it was rapid."

From the nature of the work (Goldblatt and Chiesman, 1944), it is certain that the route of absorption was the respiratory tract. The vapor absorbed was a mixture of 2-chloroethanol and ethylene dichloride, but the very minor narcotic effects observed lead the authors to believe that the latter was not the principal cause of the symptoms. The possibility of summation of toxic effects cannot be ruled out, and the contribution of ethylene dichloride to the observed toxicity is not known. Concentrations of 2-chloroethanol and ethylene dichloride were measured at seven different sampling points during the night shift, and steps were taken to effectively reduce these concentrations. Concentrations of 2-chloroethanol ranged from 2−49 ppm (mean of 21 ppm or

69 mg/m^3), and concentrations of ethylene dichloride were 2−152 ppm (mean of 70 ppm or 230 mg/m^3). When these concentrations were lowered to 0−5 ppm (mean of 2.5 ppm or 8 mg/m^3) 2-chloroethanol and 12−48 ppm (mean of 30 ppm or 99 mg/m^3) ethylene dichloride, there was also a corresponding decrease in symptoms in the workers.

Animal Studies

The NTP (1985a,b,c) study is subdivided for clarity. The NTP (1985a) section addresses acute toxicity of 2-chloroethanol in a variety of species. The NTP (1985b) section addresses chronic dermal toxicity and carcinogenicity in rats while the NTP (1985c) refers to similar studies with mice. Only a brief synopsis is presented because these data are not pertinent to deriving subchronic and chronic RfD or RfC values. The LD_{50} is 1357 and 1813 mg/kg in male and female Swiss mice, and the LD_{50} is 395 mg/kg) in both male and female F344/N rats. "2-Chloroethanol is highly irritating to mucous membranes but produces little if any reaction upon contact with rabbit skin. It is not a sensitizer in the guinea pig test. Toxic amounts can be absorbed through the skin without causing dermal irritation."

Studies Involving Exposure Routes Other Than Oral or Inhalation

While not useful for deriving provisional toxicity values, the following studies may be helpful under some circumstances. Chronic toxicity/carcinogenicity studies were performed by dermal exposure in rats (NTP, 1985b) and mice (NTP, 1985c). Carcinogenicity studies were performed in mice by intravenous injection (Homburger, 1968), rats by subcutaneous injection (Mason et al., 1971), and mice by subcutaneous injection (Dunkelberg, 1983a,b). A subchronic study was performed in rats by intraperitoneal injection (Lawrence et al., 1971). Cardio toxicity was examined in rat heart tissue (Chen et al., 2011) and developmental studies were performed in mice (Jones-Price et al., 1985a) and rabbits (Jones-Price et al., 1985b) by intravenous injection.

In a dermal chronic toxicity/carcinogenicity study (NTP, 1985b), 2-chloroethanol in 70% aqueous ethanol was applied to the shaved skin of 50 F344N rats/sex/dose at dose levels of 0, 50, or 100 mg/kg-day, 5 days/week during a 103-week period. No adverse effects were reported, and no evidence of carcinogenic potential was noted. In a companion dermal chronic toxicity/carcinogenicity study (NTP, 1985c), 2-chloroethanol in 70% aqueous ethanol was applied to the shaved skin of 50 Swiss CD-1 mice/sex/dose at dose levels of 0, 7.5, or 15 mg/kg-day daily for 5 days/week during a 104-week period. In males, survival at 15 mg/kg-day was 12/50 compared to 26/50 in the controls. In the mice that died, local inflammation and ulceration were observed, as well as lung congestion, inflammation, or hemorrhage. No evidence of carcinogenic potential was found. The results of these studies were confounded by the use of ethanol as a vehicle. Bonitenko et al. (1981) demonstrated that the simultaneous administration of ethanol provides a protective effect against 2-chloroethanol toxicity regardless of route (oral or dermal), increasing the LD_{50}, reducing the incidence of hepatic and renal necrotic lesions, and raising the blood concentration of 2-chloroethanol. Blair and Vallee (1966) demonstrated that 2-chloroethanol is a substrate for the purified cytoplasmic alcohol dehydrogenase of human liver, and Sood and O'Brien (1994) showed that 2-chloroacetaldehyde (CAA)-induced cytotoxicity in isolated hepatocytes was enhanced markedly if hepatocyte alcohol- or aldehyde-dehydrogenase were inhibited prior to CAA administration. Despite the confounding factor that the choice of vehicle introduces, it is noteworthy that male mice were treated with up to toxic levels (as indicated by increased

mortality) without evidence of carcinogenic potential (NTP, 1985c). See the *Metabolism and Toxicokinetic Studies* section and Figure 2 for additional information.

Homburger (1968) evaluated tumor incidence in mice over a 12-month period following a single 1.2-mg intravenous dose of 2-chloroethanol. No increase in tumor incidence was observed; however, a small increase in alveolar/bronchiolar adenomas (5/18 treated vs. 2/18 controls) was noted when the same dose was administered once per month for 7 months.

Mason et al. (1971) evaluated tumor incidence in F344 rats following subcutaneous injections of 2-chloroethanol in saline at dose levels of 0, 0.3, 1, 3, or 10 mg/kg-day twice each week for 52 weeks followed by observation without treatment for 26 weeks. It was stated that pituitary gland adenomas were observed in 7/100 female rats dosed with 2-chloroethanol (all dose groups combined) compared to 1/50 controls. Data were not presented to allow verification of a dose-dependent effect. This study is considered inappropriate for the development of chronic toxicity values due to the route of administration, and dosing only twice a week.

Dunkelberg (1983a) evaluated tumor incidence in female NMRI mice following weekly subcutaneous injection of 0.3, 1, or 3 mg of 2-chloroethanol in tricaprylin for approximately 70 weeks. No carcinogenic effect was noted. In the companion arm of the study, Dunkelberg (1983b) also evaluated tumor incidence in rats (number, strain, and sex not specified in abstract) following a single gavage dose at 2.5 or 10.0 mg/kg in salad oil; no carcinogenic effect was noted. Both studies were presented in German, and an English translation was unavailable for review.

Lawrence et al. (1971) administered 2-chloroethanol to groups of 12 male Sprague-Dawley rats by intraperitoneal injection at dose levels of 0, 12.8, or 32.0 mg/kg-day three times per week for 12 weeks. Six of the 12 rats dosed at 32.0 mg/kg-day and four of the 12 rats dosed at 12.8 mg/kg-day died early in the study. The study was repeated with doses of 6.4 and 12.8 mg/kg-day; all rats survived. A third phase, in which 12 rats/dose group were administered daily doses of 2-chloroethanol at 0, 6.4, or 12.8 mg/kg-day for 30 days, was conducted. Seven of 12 rats given daily doses of 12.8 mg/kg-day died during the study.

Chen et al. (2011) compared the ability of both 2-chloroethanol and chloroacetaldehyde (CAA) to cause cardiotoxicity in vitro in heart tissue (atria) from male Sprague-Dawley rats. A trial tissue was isolated from groups of 5 rats and cultured with 2-chloroethanol or 2-CAA (0, 1, 5, and 10 mM), and the contractile tension was measured for 60 minutes with a force displacement transducer. Cardiotoxicity was measured by the ability of the chemicals to reduce or arrest tension in the atrial tissue. 2-Chloroethanol significantly reduced atrial tension in a dose-dependent manner but did not induce (cardiac) arrest after 60 minutes. 2-CAA also significantly reduced the atrial tension but to a greater (2-fold) degree and caused tension arrest in the tissues after approximately 23 minutes. The authors concluded that the CAA metabolite of 2-chloroethanol was likely responsible for the observed cardiotoxicity in humans (Deng et al., 2001) or cardiac arrest reported by Miller et al. (1970). In a developmental toxicity study (Jones-Price et al., 1985a), 2-chloroethanol in 5% dextrose was administered daily by intravenous injection in a volume of 1 mL/kg body weight to timed-pregnant CD-1 mice at doses of 0, 60, or 120 mg/kg-day on GDs 4−6, 6−8, 8−10, or 10−12. At sacrifice on GD 17, a total of 34−54 dams (i.e., confirmed-pregnant females) per treatment group from each exposure period were evaluated. Administration at 60 mg/kg-day did not result in any statistically significant

expression of maternal toxicity, regardless of the period of administration. Evidence of embryotoxicity in the 60-mg/kg-day group was observed only following exposure on GDs 8−10, a treatment that significantly decreased the average fetal body weight per litter. No statistically significant change in the incidence of malformed fetuses per litter was observed for any exposure period at 60 mg/kg-day. At 120 mg/kg-day, decreased maternal and fetal body weights were noted, as well as increased maternal mortality. An increase in the incidence of malformed fetuses was only seen at one exposure period (GDs 8−10). In a companion developmental toxicity study (Jones-Price et al., 1985b), 2-chloroethanol in 5% dextrose was administered daily by intravenous injection in a volume of 0.3 mL/kg of body weight to artificially inseminated New Zealand white rabbits at doses of 0, 9, 18, or 36 mg/kg-day on GDs 6−14. At sacrifice on GD 30, a total of 15 to 21 does (i.e., confirmed-pregnant females) per treatment group were evaluated. There was no evidence of a fetotoxic or teratogenic effect at any dose.

Genotoxicity Studies

The genotoxicity of 2-chloroethanol was reviewed and summarized in the NTP (1985a,b,c) study. It was found that the compound can cause gene mutations in *Salmonella typhimurium*, *Klebsiella pneumonia*, *Escherichia coli*, and *Aspergillus nidulans*. It is a direct-acting base-pair substitution mutagen in *S. typhimurium* strains TA1530, TA1535, and TA100, and the addition of rat liver S9 enhances the mutagenic effect. It can cause DNA damage to *Escherichia coli* and human fibroblasts, and it causes chromosome aberrations in *Allium* and rat bone marrow. However, no genotoxicity was noted in many other eukaryote tests. No evidence of genotoxicity was noted in the following tests: gene mutation in *Schizosaccharomyces pombe*, *Drosophila melanogaster*, mouse lymphoma, or Chinese hamster (V79); chromosomal aberrations in *Saccharomyces cerevisiae* or *Glycine max*; DNA damage in human (HeLa); and micronucleus, heritable translocations, and dominant lethal tests in the mouse. Since this report was published, 2-chloroethanol has been shown to be genotoxic in other tests. For example, it causes the induction of prophage lambda in *E. coli* (DeMarini and Brooks, 1992).

Kitchin et al. (1992) developed an assay using battery of short-term in vitro tests to predict carcinogenicity in 111 chemicals. The complementary tests were designed to detect cytotoxicity, promotion, and carcinogenesis in Sprague-Dawley rats that were treated with 2-chloroethanol at doses of 18 or 54 mg/kg-day. The first dose was given 21 hours before sacrifice, and the second dose was given 4 hours before sacrifice by an unreported route of administration. Rat serum alanine aminotransferase activity (a measure of cell damage), hepatic DNA damage as determined by alkaline elution (potential carcinogenesis), hepatic ornithine decarboxylase activity (possible promotion), and hepatic cytochrome P450 content (possible promotion) were measured. This study evaluated 111 chemicals of known rodent carcinogenicity (49 carcinogens and 62 noncarcinogens). Using data from these short-term assays, the suggested technique achieved 73% concordance with its predicted carcinogenic potential for these chemicals and the known carcinogenic potential of these chemicals. The sensitivity of the technique was 56%, and the specificity was 84%. This concordance ratio is superior to the Ames test (51%) and structural alerts (46%). This study predicts that 2-chloroethanol is carcinogenic, which is noteworthy in the absence of a suitable animal carcinogenicity study.

Allavena et al. (1992) developed another battery of in vivo assays to confirm the results of in vitro assays or as an alternative to in vitro assays to predict carcinogenic potential. These

tests included the micronucleus assay, induction of unscheduled DNA synthesis (UDS), and induction of rat hepatocyte DNA damage. Two protocols were used. The first protocol involved administration of 2-chloroethanol in 1% aqueous carboxymethylcellulose by gavage to male Sprague-Dawley rats at one-half the LD_{50} value 20 hours after a two-thirds hepatectomy. The animals were sacrificed 48 hours later, and micronucleated cells in the liver and bone marrow were assayed. In the second protocol, rats were administered 2-chloroethanol 30 and 6 hours before termination. "The bone marrow was examined for the frequency of micronuclei in polychromatic erythrocytes; hepatocyte primary cultures were prepared from the liver for the subsequent evaluation of the amount of DNA fragmentation, carried out at 4 and 20 hours, and of UDS, measured 20 hours after seeding." The results of these tests indicated that 2-chloroethanol was not genotoxic.

Rannug et al. (1976) evaluated potential mutagenicity by testing the ability of 2-chloroethanol, and other metabolites of vinyl chloride, to directly cause base-pair substitution in *Salmonella typhimurium* TA1535 bacteria without S-9 metabolic activation. No effects were observed at 0, 0.1, 0.5, or 1.5 mM (0.008, 0.043, or 0.128 mg/L). 2-Chloroethanol was retested at higher concentrations of 0, 1 mM, and 1 M (0, 80.5 mg/L, and 80.5 g/L). 2-Chloroethanol was only faintly toxic (details not reported for the highest doses) and only weakly mutagenic (data not available). The authors concluded that the mutagenicity observed for vinyl chloride could not be attributed to 2-chloroethanol.

McCann et al. (1975) evaluated the potential mutagenicity of 2-chloroethanol by testing its ability to cause the reversion of *S. typhimurium*, strains TA100 and TA1535 with and without S-9 activation, using S-9 fraction from both rat liver microsomes and also human liver extracts. 2-Chloroethanol was weakly mutagenic in the TA1535 strain but showed clear activity (1 revertant colony per 0.6 µM) in the TA100 strain with S-9 activation. The testing of chloroacetaldehyde yielded similar results using S-9 activation with strains TA100 and TA1535. The authors suggest that chloroacetaldehyde may be the active metabolite of 2-chloroethanol, which supports the hypothesis that chloroacetaldehyde may cause the toxicity attributed to 2-chloroethanol (Johnson, 1967).

In summary, 2-chloroethanol is known to be genotoxic in some tests, particularly in bacterial systems. It has only sometimes been shown to be genotoxic in eukaryote systems. Conflicting data exist in short term in vivo assays regarding its genotoxicity; however, one system, which may correctly predict carcinogenic potential 73% of the time, suggests that 2-chloroethanol may be carcinogenic.

Metabolism and Toxicokinetic Studies

The NTP (1985a,b,c) summarized the proposed metabolic pathway of 2-chloroethanol as follows (see Figure 2):

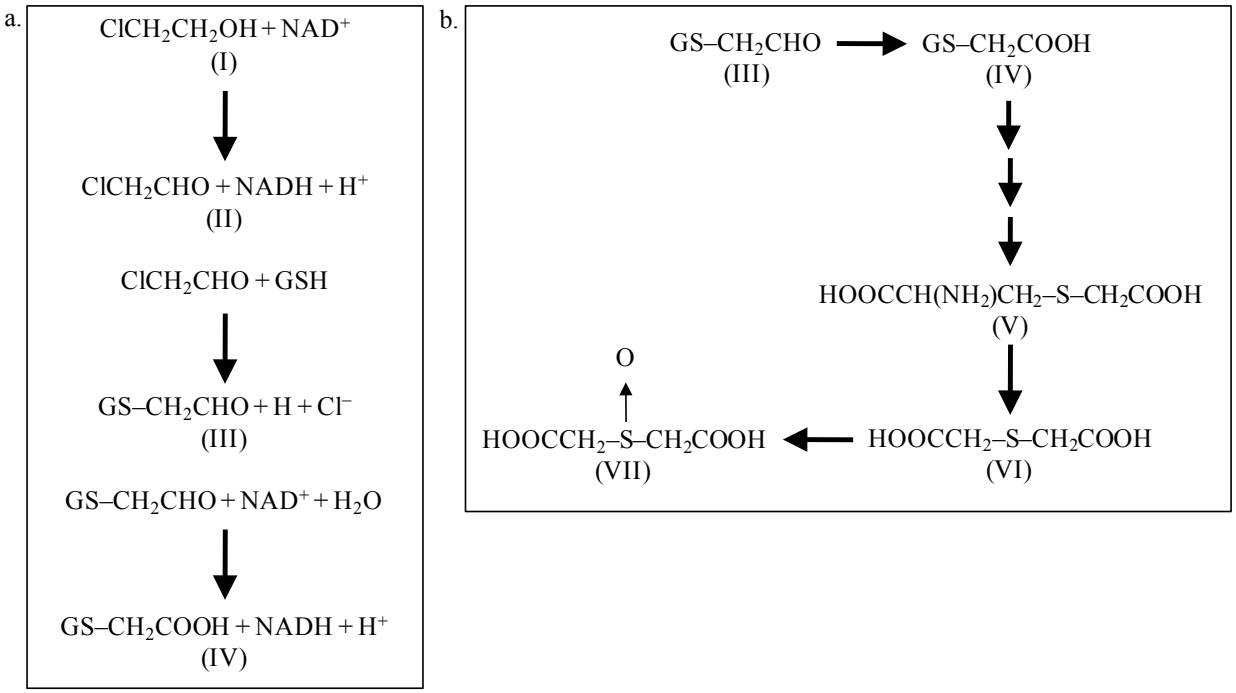

Figure 2a,b. Metabolic Pathway of 2-Chloroethanol
Source: NTP (1985a,b,c).

Johnson (1967) suggested that the toxicity of 2-chloroethanol (I) was due to the formation of chloroacetaldehyde (II) by the test animal in amounts greater than could be detoxified by glutathione (GSH). Both ethanol and 2-chloroethanol are known to be substrates for the purified cytoplasmic alcohol dehydrogenase of human liver, rat liver, or yeast. Co-administration with ethanol reduces the toxicity of 2-chloroethethanol, presumably by competition for the alcohol dehydrogenase. Johnson (1967) demonstrated the in vivo and in vitro formation of S-carboxymethyl-GSH (IV) in livers of rats dosed with 2-chloroethanol; S-carboxymethyl-GSH (IV) is presumably formed from GSH and chloroacetaldehyde, the dehydrogenation product of 2-chloroethanol; S-formylmethyl-GSH is the presumed intermediate. Grunow and Altmann (1982) reported finding thiodiacetic acid (VI) and thionyldiacetic acid in the urine of rats given an oral dose of 2-chloroethanol; both these compounds are derivable from S-carboxymethylcysteine, the hydrolysis and deamination product of S-carboxymethyl-GSH. Thiodiacetic acid has been shown to be a metabolite of compounds that have the general property of being converted to chloroacetaldehyde (II); these compounds include vinyl chloride, 1,2-dichloroethanol, and vinylidene chloride.

Chen et al. (2010) performed a metabolism study in male Sprague-Dawley rats (group size not reported) injected once intraperitoneally with saline or 120 mg/kg of 2-chloroethanol. Thirty minutes before 2-chloroethanol administration, the animals were treated with saline, 5-mg/kg fomepizole (an inhibitor or alcohol dehydrogenase with very high affinity), or 75-mg/kg disulfiram (an inhibitor of acetaldehyde dehydrogenase). Another group was treated with

400-mg/kg-day *N*-acetylcysteine (used to augment glutathione reserves) for 4 days, followed by one dose of 5 mg/kg of fomepizole and 120 mg/kg of 2-chloroethanol. Animals were sacrificed 1 hour after 2-chloroethanol treatment, and blood, liver, and kidneys were collected. Chloroacetaldehyde was measured in the plasma, and glutathione was measured in the liver and kidneys. The study authors also determined LD_{50} values for 2-chloroethanol. The addition of fomepizole reduced the conversion of 2-chloroethanol to chloroacetaldehyde (CAA) and the resulting toxicity of 2-chloroethanol was reduced. Treatment with disulfiram increased the concentration of CAA with an increase in 2-chloroethanol toxicity. Glutathione levels were significantly less than the control group in the liver after treatment with 2-chloroethanol. This research corroborates the proposed metabolic pathway described above.

Hung et al. (2006) evaluated 4-methylpyrazole (4-MP) as an antidote to 2-chloroethanol toxicity by pretreatment of rats (number and strain not specified) with 4-MP or saline control followed by ip injection with several doses (not specified) of 2-chloroethanol. 4-MP is a potent inhibitor of alcohol dehydrogenase which catalyses the conversion of 2-chloroethanol to CAA. The blood concentration of CAA in the treated group was 42.7% lower than in the untreated controls. Treatment with 4-MP also increased the LD_{50} from 58 mg/kg (control value) to 180 mg/kg. The Hung et al. (2006) study is available only as an abstract with few details.

Bonitenko et al. (1981) demonstrated that the simultaneous administration of ethanol provides a protective effect against 2-chloroethanol toxicity regardless of route (oral or dermal), increasing the LD_{50}, reducing the incidence of hepatic and renal necrotic lesions, and raising the blood concentration of 2-chloroethanol. Blair and Vallee (1966) demonstrated that 2-chloroethanol is a substrate for the purified cytoplasmic alcohol dehydrogenase of human liver, and Sood and O'Brien (1994) showed that 2-chloroacetaldehyde (CAA)-induced cytotoxicity in isolated hepatocytes was enhanced markedly if hepatocyte alcohol or aldehyde dehydrogenase were inhibited prior to CAA administration. Consequently, ethanol has been used as a specific treatment for 2-chloroethanol toxicity (Deng et al., 2001).

Grunow and Altman (1982) conducted a toxicokinetic study in which male Wistar rats were dosed orally by gavage using [1,2-^{14}C]-chloroethanol (99% radiochemical purity) in water. The study was conducted in three parts: elimination studies, distribution studies, and identification of urinary metabolites. In the elimination study, six rats received single doses of approximately 5 mg/kg, and three rats received doses of about 50 mg/kg. After dosing, the animals were placed in metabolism cages. Urine and feces were collected separately at 24-hour intervals. Expired air was also collected. After 4 days, the animals were euthanized. Blood and select organs (adipose tissue, adrenal, bone, brain, heart, intestine, kidney, liver, lung, muscle, skin, spleen, stomach, testes, and thyroid) were collected. In a distribution study, single doses of 5 mg/kg were given to eight rats, and these animals were sacrificed after 0.5, 1, 2, 4, 6, or 8 hours. Radioactivity was determined in the blood, liver, and kidney. For the isolation and identification of urinary metabolites, unlabelled 2-chloroethanol was administered in doses of 50 mg/kg.

The authors described the results as follows:

> *At both dose levels, the radioactivity was rapidly eliminated, mainly in the urine. On the first day after application of 5 mg/kg, 77.2% of the dose was found in the urine, 1.7% in the feces, and 1.0% as carbon dioxide in the expired air. Only*

2.8% were [sic] *excreted by these routes during the following 3 days. The residual radioactivity remaining in the tissues after 4 days was almost equally distributed and amounted to about 0.4% of the dose in the liver and 3% in the whole organism. At the higher dose level, excretion rates and tissue concentrations were similar. Examination of the urine by anion exchange chromatography on DEAE-Sephadex revealed two metabolites which were identified by GC/MS analysis as thiodiacetic acid and thionyldiacetic acid. These metabolites represented almost all of the urinary radioactivity. They were excreted in approximately equal amounts at the low dose whereas the thiodiacetic acid predominated with about 70% of the urinary radioactivity at the high dose.*

Thiodiacetic acid can be formed from the GSH conjugate of chloroacetaldehyde or chloroacetic acid by hydrolysis and subsequent deamination and decarboxylation of the intermediate product S-carboxymethylcysteine. Thionyldiacetic acid is formed by oxidation of thiodiacetic acid.

Mode-of-Action and Mechanistic Studies

Friedman et al. (1982) evaluated the effects of 2-chloroethanol on rat tissue following in vitro and in vivo exposure in a series of eight tests. 2-Chloroethanol (99% purity) in 0.9% saline was administered by gavage to Osborne-Mendel (FDA strain) rats (4−8/sex/dose group depending on the experiment). In Test 1, rats (6 males/dose group) were treated with 2-chloroethanol at 0 or 54.8 mg/kg, and the GSH concentrations were determined in the liver and red blood cells. In Test 2, rats (7 males/dose group) were treated with 0, 5, 10, 20, or 40 mg/kg 2-chloroethanol. After 2 hours, they were given [^{14}C]orotic acid (12.5 µCi/kg) and [^{3}H]leucine (50.0 µCi/kg) via i.p. injection and sacrificed 1 hour later. The amount (mg/g) of RNA and protein and the radioactivity (dpm/mg × 10^3) were quantified, as were concentrations of DNA (mg/g) and GSH (µmol/g). In Test 3, rats (8 males/dose group) were treated with 2-chloroethanol at 0, 10, 20, or 50 mg/kg. After 2 hours, they were given [^{14}C]leucine (12.5 µCi/kg) and [^{3}H]leucine (50 µCi/kg) and sacrificed 1 hour later. Protein synthesis was measured by quantifying [^{3}H]leucine and [^{14}C]leucine. In Test 4, rats (8 males/dose group) were treated with 2-chloroethanol at 0, 10, 20, or 40 mg/kg. After 2 hours, they were given [^{14}C]glycine (19.2 µCi/kg) and [^{3}H]leucine (76.9 µCi/kg) and sacrificed 1 hour later. Unincorporated radioactivity (^{3}H and ^{14}C) and protein synthesis ([^{3}H]leucine and [^{14}C]glycine) were measured. In Test 5, rats (6 males/dose group) were treated with 2-chloroethanol at 30 mg/kg. At either 0, 1, 2, 3, 5, or 6.5 hours after treatment, the rats were given [^{3}H]leucine (50 µCi/kg) and sacrificed 30 minutes later. RNA, DNA, fat, and protein were quantified (mg/g), as was GSH (µmol/g). In Test 6, rats (7/sex/dose group) were treated with 2-chloroethanol at 0, 15, 20, or 30 mg/kg. After 2 hours, they were given [^{14}C]orotic acid (12.5 µCi/kg) and [^{3}H]leucine (25.0 µCi/kg) and sacrificed 1 hour later. Liver samples were taken from both sexes, and kidney samples were taken from males. GSH was measured in the liver (µmol/g), and RNA and protein levels were determined by measuring radioactivity (dpm/mg × 10^3). In Test 7, one male rat was administered [^{14}C]leucine (12.5 µCi/kg) intraperitoneally 2 hours before sacrifice. The liver was removed, rapidly prepared, and incubated with 2-chloroethanol at 0, 1.5, 3, 6, 12, 24, or 48 mg/mL in triplicate. The liver slices were homogenized, and protein was isolated and analyzed for radioactivity. In Test 8, rats (6 males/dose group) were treated with 2-chloroethanol by gavage at 0 or 20 mg/kg immediately after receiving saline, cysteine HCl (200 mg/kg), or diethyl maleate (1000 mg/kg) by intraperitoneal injection. After 2 hours, they were given [^{3}H]leucine (30 µCi/kg) and sacrificed

1 hour later. Protein synthesis (dpm/mg × 103) and GSH (µmol/g) were quantified, and the percentage change was reported. Further details of the methodology, including the preparation of samples and their analysis, are provided in the cited report. This series of experiments provides insight on several modes of action of 2-chloroethanol, briefly summarized as follows:

> *At concentrations as low as 2.5 mg/ml, protein synthesis in liver slices was inhibited; at concentrations of 25 mg/ml and above, RNA synthesis and respiration were also impaired. Single oral doses of 2-chloroethanol to young adult rats at doses of 15−40 mg/kg body weight depressed liver nonprotein sulfhydryl (GSH) concentration and liver protein but not RNA synthesis. Liver lipid was increased by 7 hr after a single oral dose of 30 mg/kg. The time courses and dose-response relationship for GSH depletion and restoration and for protein synthesis inhibition and recovery were similar. The livers of female rats were more sensitive than the livers of male rats to the effects of 2-chloroethanol. Protein synthesis was also depressed in kidneys of 2-chloroethanol-treated male rats but at higher doses than those needed for this effect to occur in livers of the same animals. Liver polysome disaggregation also occurred after oral 2-chloroethanol doses of 20 mg/kg and greater. The effects of 2-chloroethanol on ribosome profiles and protein synthesis were at least partially reversed by concurrent intraperitoneal administration of cysteine.*

Andrews et al. (1983) evaluated the effects of 2-chloroethanol on fatty acid synthesis. Cornish × White Rock crossbred chicks (6−8/dose group) received a gavage dose of 60-mg/kg 2-chloroethanol (99% purity) as a 10% aqueous solution, 200-mg/kg ethanol as a 10% aqueous solution, or 200-mg/kg undiluted carbon tetrachloride. Another group of 6−8 chicks was treated with eight consecutive daily doses of 40-mg/kg-day 2-chloroethanol as a 10% aqueous solution. Control groups received gavage treatment with water. Eighteen hours after the last treatment, blood samples were collected, the chicks were sacrificed, and the livers were harvested. The chicks and livers were weighed. Livers were homogenized. Fatty acid synthesis, mitochondrial fatty acid elongation, protein content, cytochrome c oxidase activity, isocitrate dehydrogenase activity, and tissue triglyceride levels were measured in the homogenates. Plasma trigyceride levels were also measured. Histological examination of the liver tissue was also performed. Further details of the procedures used in quantifying the parameters are detailed in the cited publication. Briefly, the results were reported as follows:

> *Mitochondrial elongation of fatty acids was decreased significantly while fatty acid sythetase activity was not significantly affected by 2CE treatment. Cytochrome c oxidase activity in fresh whole liver homogenate was significantly higher in chicks subjected to acute exposure with 2CE when compared to the controls. Upon freezing and thawing of homogenates, cytochrome c oxidase activity increased significantly in the control group, but was unchanged in the 2CE group, which suggests that the mitochondrial membrane integrity is compromised by 2CE treatment. Serum and liver triglyceride levels were significantly elevated in both the single and multiple 2CE dose groups. Liver to body weight ratios were significantly higher in both treatment groups when compared to their controls. Histological examination of the liver of the 2CE chicks showed cytoplasmic clearing of the cells, but no vacuolization or*

centrilobular necrosis. Serum isocitrate dehydrogenase levels were significantly higher in the multiple treatment 2CE group than in the control group.

Greater than 70% inhibition of mitochondrial fatty acid elongation activity was observed in this study. This inhibition could have a serious impact on organs, such as the heart, which relies entirely on this synthetic system for fatty acid production.

Feuer et al. (1977) evaluated the effect of 2-chloroethanol on hepatic microsomal enzymes in the rat. 2-Chloroethanol in saline was given by daily subcutaneous injection (sc) to rats at a dose level of 0 or 20 mg/kg-day in females and 0, 3, 10, or 20 mg/kg-day in males for 7 days. The rats were sacrificed after the last dose. One additional group of males was given a single subcutaneous dose of 50 mg/kg and sacrificed 3 hours later. Liver homogenates and postlysosomal fractions containing microsomes were prepared. Activities of aminopyrine *N*-demethylase, coumarin 3-hydroxylase, glucose 6-phosphatase, and inosine diphosphatase were assayed, and protein content was determined. Enzyme levels were determined in homogenates to obtain the total and in microsomes to identify the localization of the enzyme in this fraction. 2-Chloroethanol caused an impairment of microsomal drug-metabolizing enzymes and phosphatases in the liver of rats. Briefly, the results were reported as follows:

A significant reduction in activities of drug-metabolizing enzymes (aminopyrine N-demethylase, coumarin 3-hydroxylase) and a marked decrease of glucose 6-phosphatase were seen in both sexes given dose levels of 20 mg/kg sc daily for 7 days. Inosine diphosphatase activity remained unaltered. In male rats given 3 or 10 mg/kg, a trend in the inhibition of drug metabolism was found. A single dose of 50 mg/kg caused no apparent change in the activities of the enzymes measured.

Kaphalia and Ansari (1989) treated Sprague-Dawley male rats (4/dose group) with a single daily gavage dose of 2-chloroethanol (purity not reported) in mineral oil at 0 or 50 mg/kg-day for 5 days. The rats were then sacrificed. Hepatic microsomal lipids were extracted, and the fatty acid esters were separated by thin-layer chromatography. The ester fraction was further purified by HPLC and analyzed by ammonia chemical ionization mass spectrometry. 2-Chloroethyl palmitate, 2-chloroethyl oleate, and 2-chloroethyl stearate were isolated. The authors concluded that the administration of 2-chloroethanol could cause hepatic fatty acid conjugation.

Bhat et al. (1991) investigated the effect of 2-chloroethanol on rat liver mitochondrial respiration. Rat liver mitochondria were isolated, and mitochondrial respiration was determined with an oxygen electrode. The results were as follows:

With succinate as the respiratory substrate and using chloroethanols (purity = 99%; 150 mM), 2-chloroethanol stimulated respiration by 28% and 2,2-dichloroethanol by 203%. 2-Chloroethanol showed maximum stimulation at 600 mM (98%). Respiratory stimulation was independent of mitochondrial protein concentration. Chloroethanols (optimal concentrations for respiratory stimulation with succinate) inhibited mitochondrial respiration when glutamate-malate was used as the respiratory substrate. Estimation of ATP showed that chloroethanols inhibited the synthesis of ATP. These results indicate

that chloroethanols stimulate mitochondrial respiration by uncoupling oxidative phosphorylation and that the uncoupling potency is proportional to the extent of chlorination at the β-position of haloethanol.

In summary, these studies demonstrate cardiotoxicity as well as the following findings in the liver that result from 2-chloroethanol treatment: inhibited protein synthesis, impaired RNA synthesis and respiration, depressed nonprotein sulfhydryl (GSH) concentration, increased lipid levels, polysome disaggregation, decreased mitochondrial elongation of fatty acids, increased cytochrome c oxidase activity, compromised mitochondrial membrane integrity, elevated triglyceride levels, increased liver-to-body-weight ratios, cytoplasmic clearing of the cells, hepatic fatty acid conjugation, stimulation of mitochondrial respiration by uncoupling oxidative phosphorylation, and decreased aminopyrine *N*-demethylase, coumarin 3-hydroxylase, and glucose 6-phosphatase activities. The livers of female rats were more sensitive than the livers of male rats to at least some of these effects.

Table 3. Other Studies for 2-Chloroethanol (CASRN 107-07-3)

Tests	Materials and Methods	Results	Conclusions	References
Short-Term Toxicity Studies				
Human poisoning cases	Poison cases of 11 males and 6 females (ages from 2 to 70 years) were detailed. Exposure route was typically oral.	Signs and symptoms ranged from mild gastrointestinal and neurologic effects to metabolic acidosis, respiratory failure, and death.	The compound is acutely toxic and potentially fatal to humans.	Deng et al. (2001)
Toddler ingestion case	23-Month-old male ingested approximately 1−2 mL of 2-chloroethanol	Signs included cyanosis, respiratory difficulty, convulsions, shock, and death. Necropsy findings were also reported.	The compound can be fatal in small doses to children.	Miller et al. (1970)
Employee poisoning cases	Six workers were exposed dermally and by inhalation while working at a large seed potato supply firm.	Signs and symptoms ranged from mild gastrointestinal and neurologic effects to coma and death. Necropsy findings were also reported. Recovery for survivors was usually within a few days.	Following OSHA mandates is needed to protect workers.	Bush et al. (1949)
Employee poisoning cases	Eleven cases of poisoning observed in workers involved in the manufacture of the compound are described. The exposure route was by inhalation.	The compound has effects on the digestive, circulatory, nervous, urinary, and respiratory systems, as well as the skin. Effects can be fatal; otherwise, recovery is typically rapid and complete.	Following OSHA mandates is needed to protect workers.	Goldblatt and Chiesman (1944)
Acute dermal toxicity in animals	LD_{50}, and other acute effects from single dose skin painting exposure are very briefly reported for rats and mice.	The LD_{50} is approximately 395 mg/kg in both male and female F344/N rats and the LD_{50} is approximately 1357 mg/kg in male- and 1813 mg/kg in female Swiss CD-1 mice.	The compound is acutely toxic.	NTP (1985a)

Table 3. Other Studies for 2-Chloroethanol (CASRN 107-07-3)

Tests	Materials and Methods	Results	Conclusions	References
Studies Involving Exposure Routes Other Than Oral or Inhalation				
Chronic toxicity/ carcinogenicity study-dermal exposure	2-Chloroethanol was applied in 70% aqueous ethanol to the shaved skin of 50 F344/N rats/sex/dose at dose levels of 0, 50, or 100 mg/kg-day, 5 days/week during a 103-week period.	No adverse effect was observed.	The results of this study were confounded by the vehicle used.	NTP (1985b)
Chronic toxicity/ carcinogenicity study-dermal exposure	2-Chloroethanol was applied in 70% aqueous ethanol to the shaved skin of 50 Swiss CD-1 mice/sex/dose at dose levels of 0, 7.5, or 15 mg/kg-day, 5 days/week during a 104-week period.	Increased mortality was observed at 15 mg/kg-day, but no evidence of carcinogenic potential was observed.	The results of this study were confounded by the vehicle used.	NTP (1985c)
Carcinogenicity study	Mice were injected intravenously with a single 1.2-mg dose, and evaluated for tumors after one year.	No effect on tumor incidence was observed.	Study is not useful for this assessment.	Homburger (1968)
Carcinogenicity study	Rats were injected subcutaneously at dose levels of 0, 0.3, 1, 3, or 10 mg/kg twice each week for 12 months and observed untreated for an additional 6 months.	A possible increase in pituitary adenomas in females was noted, but could not be confirmed.	Study is not useful for this assessment.	Mason et al. (1971)
Carcinogenicity study	Mice were injected subcutaneously once weekly at dose levels of 0.3, 1, or 3 mg/kg in tricaprylin.	No carcinogenic effect was noted.	Study is not useful for this assessment. Article is in German	Abstract only. Dunkelberg (1983a,b)
Subchronic study	Rats were treated by intraperitoneal injection 3 times weekly at doses of 0, 6.4, 12.8, and 32 mg/kg-day for 12 weeks. In a second experiment, rats received 0, 6.4, and 12.8 mg/kg-day daily for 30 days.	No adverse effect was observed.	Study is not useful for this assessment.	Lawrence et al. (1971)
Cardiotoxicity	Cardiotoxicity was demonstrated in isolated Sprague-Dawley rat atrial tissue exposed to 2-chloroethanol or CAA in vitro.	Spontaneous atrial tissue tension was significantly reduced in a dose-dependent manner by 2-chloroethanol after 60 minutes. Chloroacetaldehyde also caused a dose-dependent reduction approximately 2-fold greater than 2-chloroethanol and caused tension arrest after 23 minutes.	Chloroacetaldehyde treatment resulted in greater cardiac toxicity in isolated heart tissue than 2-chloroethanol.	Chen et al. (2011)

Table 3. Other Studies for 2-Chloroethanol (CASRN 107-07-3)

Tests	Materials and Methods	Results	Conclusions	References
Developmental study	Mice were treated by daily intravenous injections of 0, 60, or 120 mg/kg-day in 5% dextrose on GDs 4−6, 6−8, 8−10, or 10−12.	Evidence of embryotoxicity in the 60-mg/kg-day group was observed only following exposure on GDs 8−10, a treatment that significantly decreased the average fetal body weight per litter. At 120 mg/kg-day, decreased maternal and fetal body weights were noted, as well as increased maternal mortality. An increase in the incidence of malformed fetuses was seen only at GDs 8−10.	Study is not useful for this assessment.	Jones-Price et al. (1985a)
Developmental study	Rabbits were treated by daily intravenous injections of 0, 9, 18, or 36 mg/kg-day in 5% dextrose on GDs 6−14.	There was no evidence of a fetotoxic or teratogenic effect at any dose.	Study is not useful for this assessment.	Jones-Price et al. (1985b)
Genotoxicity Studies				
Review of genetic toxicity	Provides an overview of genetic toxicity studies up to 1985.	The compound is mutagenic in bacteria. Other forms of genotoxicity were also noted. The compound demonstrated genotoxicity in some eukaryote cell tests, but not in others.	There is evidence that the compound is genotoxic, particularly in bacteria.	NTP (1985a,b,c)
Genotoxicity study	Evaluated whether the compound causes induction of prophage lambda in *E. coli*.	Induction of prophage lambda was observed.	The compound is genotoxic in *E. coli*.	DeMarini and Brooks (1992)
Genotoxicity study	A battery of short-term in vitro tests (DNA damage and enzyme assays) in rats was used to predict carcinogenicity. This study evaluates 111 chemicals for carcinogenicity using the test battery and achieved a 73% concordance with in vivo rodent tests.	This study predicted 2-chloroethanol is a carcinogen.	This test battery could be useful as a replacement or a supplementary study to the Ames Assay.	Kitchin et al. (1992)
Genotoxicity study	A battery of short-term in vivo tests in rats was used to predict carcinogenicity. These tests included the micronucleus assay, induction of unscheduled DNA synthesis, and induction of DNA damage.	No significant difference from controls.	These tests suggest that the compound may not be genotoxic in rats.	Allavena et al. (1992)

Table 3. Other Studies for 2-Chloroethanol (CASRN 107-07-3)

Tests	Materials and Methods	Results	Conclusions	References
Genotoxicity study	Ames bacterial assay using *Salmonella typhimurium* strain TA1535 for base-pair substitution mutagenesis at concentrations of 0.1 mM to 1 M (0.008 mg/L to 80.5 g/L).	Chloroethanol was weakly mutagenic at the highest dose	Weak mutagenic activity supports potential carcinogenicity.	Rannug et al. (1976)
Genotoxicity study	Ames bacterial assay using *Salmonella typhimurium* strains TA100 (histidine reversion) and TA1535 (frameshift mutations) with and without S-9 activation at concentrations of 0, 1, 5, and 21 mg/plate.	S-9 activated chloroethanol is clearly mutagenic at the high dose (TA100) but weakly mutagenic in TA1535.	Mutagenic activity supports potential carcinogenicity. Results with 2-chloroethanol were similar to results with chloroacetaldehyde and supports conclusion (Johnson, 1967) that toxicity associated with 2-chloroethanol is caused by chloroacetaldehyde.	McCann et al. (1975)
Genotoxicity study	The Bhas 42 cell transformation assay is a short-term system using a clone of the BALB/c 3T3 cells transfected with an oncogenic murine *ras* gene (v-Ha-*ras*) that detects initiators and also promoters. Cells exposed to 0, 10, 30, 100, 300, 1,000 mM of 2-chloroethanol with MCA used as initiator and TPA as a promoter.	Cells were not transformed by 2-chloroethanol after initiation nor were cells promoted by TPA.	2-chloroethanol was not an initiator or a promoter in this assay.	Sakai et al. (2010)
Genotoxicity study	2-chloroethanol vs Chloroacetaldehyde (CAA) tested in vitro for ability to cause chromosome aberrations in CHO cells at 0, 5, 7.5, and 10 mM. In vivo tests with ICR mice given 0, 10, 20, and 40 mM 2-chloroethanol or CAA via i.p. injection for ability to induce micronucleus formation.	Neither chemical caused chromosome aberrations without S-9 activation. With S-9, CAA caused aberrations while 2-chloroethanol did not. CAA did but 2-chloroethanol did not induce micronuclei in mice.	CAA but not 2-chloroethanol caused chromosome aberrations and micronucleus formation. Supports the hypothesis that 2-chloroethanol metabolite, CAA, is responsible for the observed mutagenicity of 2-chloroethanol	Liao et al. (2011)
Metabolism and Toxicokinetic Studies				
Metabolism study	This study summarizes what is known concerning the metabolism of the compound.	The compound is a substrate for alcohol dehydrogenase. Glutathione is used in the metabolism of the compound. The ultimate products of the metabolism are thiodiacetic acid and thionyldiacetic acid.	As with other alcohols, the metabolism of this compound is affected by the availability of alcohol dehydrogenase.	NTP (1985a,b,c)

Table 3. Other Studies for 2-Chloroethanol (CASRN 107-07-3)

Tests	Materials and Methods	Results	Conclusions	References
Metabolism study	This study investigated the effects of fomepizole (alcohol dehydrogenase inhibitor), disulfiram (an inhibitor of acetaldehyde dehydrogenase) and *N*-acetylcysteine (to augment glutathione reserves) on 2-chloroethanol toxicity.	*N*-acetylcysteine slightly decreased toxicity. Fomepizole significantly decreased toxicity. The two agents combined were even more effective. Disulfiram increased the toxicity of 2-chloroethanol thus confirming CAA as the toxic metabolite of 2-chloroethanol.	Supports the pathway detailed in the NTP study above.	Chen et al. (2010)
Metabolism study	This study investigated the effect of 4-methylpyrazole (aldehyde dehydrogenase inhibitor) on 2-chloroethanol toxicity.	4-Methylpyrazole decreased toxicity of 2-chloroethanol.	Supports the pathway detailed in the NTP study above.	Abstract only Hung et al. (2006)
Metabolism study	The effect of simultaneous administration of ethanol with 2-chloroethanol was compared to the administration of 2-chloroethanol only.	Ethanol increases the LD_{50}, reduces the incidence of hepatic and renal necrotic lesions, and raises the blood concentration of 2-chloroethanol.	Ethanol has a protective effect against 2-chloroethanol toxicity.	Bonitenko et al. (1981)
Metabolism study	Human liver alcohol dehydrogenase catalytic activity was tested in vitro on several substrates including 2-chloroethanol	Demonstrated that 2-chloroethanol is a substrate for the purified cytoplasmic alcohol dehydrogenase of human liver	Supports the pathway detailed in the NTP study above.	Blair and Vallee (1966)
Metabolism study	The effect of ethanol or aldehyde dehydrogenase inhibition in isolated hepatocytes on 2-chloroacetaldehyde-induced cytotoxicity was examined.	Ethanol or aldehyde dehydrogenase inhibition markedly enhanced 2-chloroacetaldehyde-induced cytotoxicity. Hepatocyte glutathione and ATP depletion was noted, as well as enhanced lipid peroxidation. 2-Chloroacetaldehyde metabolites were less toxic than the parent.	Alcohol or aldehyde dehydrogenase inhibition increases the toxicity of 2-chloroethanol. 2-Chloroacetaldehyde can result in oxidative stress and its cytotoxicity depends on cellular redox homeostasis and cellular energy supply.	Sood and O'Brien (1994)

Table 3. Other Studies for 2-Chloroethanol (CASRN 107-07-3)

Tests	Materials and Methods	Results	Conclusions	References
Toxicokinetic study	Male Wistar rats were dosed orally by gavage using [1,2-^{14}C]-chloroethanol in water. In elimination studies, 6 rats received single doses of approximately 5 mg/kg, and 3 rats received doses of about 50 mg/kg. After dosing, animals were placed in metabolism cages. Urine and feces were collected separately at 24-hour intervals. Expired air was also collected. After 4 days, the animals were terminated. Blood and selected organs were collected. In a distribution study, single doses of 5 mg/kg were given to 8 rats, and these animals were sacrificed after 0.5, 1, 2, 4, 6, and 8 hours. Radioactivity was determined in the blood, liver, and kidney. For the isolation and identification of urinary metabolites, unlabelled 2-chloroethanol was administered in doses of 50 mg/kg. Radioactivity was quantified through liquid scintillation counting, and metabolites were identified by GC-MS.	At both dose levels, the radioactivity was rapidly eliminated, mainly in the urine. On the first day after application of 5 mg/kg, 77.2% of the dose was found in the urine. The residual radioactivity remaining in the tissues after 4 days was almost equally distributed and amounted to about 3% in the whole organism. Two urinary metabolites were identified as thiodiacetic acid and thionyldiacetic acid, and they represented almost the whole urinary radioactivity.	Elimination is rapid, through the urine, and mainly as thiodiacetic acid and thionyldiacetic acid. The identification of these metabolites supports the metabolic pathway proposed above.	Grunow and Altman (1982)
Mode-of-Action and Mechanistic Studies				
Mode/mechanistic action study	A series of tests were conducted to elucidate the mode of action and provide insight into the mechanism of action of 2-chloroethanol. In male and female rats.	There was a dose-related decrease in RNA, protein synthesis, GSH, in male and female liver slices and an increase in fat content.	These studies demonstrated that, in the liver, 2-chloroethanol can inhibit protein synthesis, impair respiration, depress nonprotein sulfhydryl (GSH) concentration, increase lipid levels, and result in polysome disaggregation. The livers of female rats were more sensitive than the livers of male rats to at least some of these effects.	Friedman et al. (1982)

Table 3. Other Studies for 2-Chloroethanol (CASRN 107-07-3)

Tests	Materials and Methods	Results	Conclusions	References
Mode of action study	Chicks were treated by gavage, and their livers were collected, weighed, and homogenized. Fatty acid synthesis, mitochondrial fatty acid elongation, protein content, cytochrome c oxidase activity, isocitrate dehydrogenase activity, and tissue triglyceride levels were measured in the homogenates. Plasma triglyceride levels were measured, and histological examination of the liver tissue was performed.	2-Chloroethanol decreased mitochondrial elongation of fatty acids, increased cytochrome c oxidase activity, compromised mitochondrial membrane integrity, elevated triglyceride levels, increased liver-to-body-weight ratios.	Inhibition of mitochondrial fatty acid elongation activity could have serious impact on organs, such as the heart, which relies entirely on this synthetic system for fatty acid production	Andrews et al. (1983)
Mode of action study	2-Chloroethanol in saline was given by daily subcutaneous injection to rats at various doses for 7 days or as a single dose. Liver homogenates and postlysosomal fractions containing microsomes were prepared. Activities of aminopyrine *N*-demethylase, coumarin 3-hydroxylase, glucose 6-phosphatase, and inosine diphosphatase were assayed, and protein content was determined.	2-Chloroethanol treatment decreased aminopyrine *N*-demethylase, coumarin 3-hydroxylase, and glucose 6-phosphatase activities.	2-Chloroethanol decreases the activity of microsomal drug-metabolizing enzymes and phosphatases in the liver of rats.	Feuer et al. (1977)
Mode of action study	Male rats were treated by gavage and sacrificed, hepatic microsomal lipids were extracted, and fatty acid esters were isolated and identified.	2-Chloroethyl palmitate, 2-chloroethyl oleate, and 2-chloroethyl stearate were identified.	2-Chloroethanol can cause hepatic fatty acid conjugation.	Kaphalia and Ansari (1989)
Mechanistic study	Rat liver mitochondria were isolated and used in vitro to evaluate mitochondrial respiration following 2-chloroethanol treatment. Succinate or glutamate maleate were used as respiratory substrates.	2-Chloroethanol stimulates respiration with succinate and inhibits respiration with glutamate maleate. 2-Chloroethanol inhibits ATP synthesis.	2-Chloroethanol stimulates mitochondrial respiration by uncoupling oxidative phosphorylation.	Bhat et al. (1991)

DERIVATION OF PROVISIONAL VALUES

Table 4 presents a summary of noncancer reference values. Table 5 presents a summary of cancer values.

Table 4. Summary of Noncancer Reference Values for 2-Chloroethanol (CASRN 107-07-3)

Toxicity Type (Units)[a]	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD	UFc	Principal Study
Subchronic p-RfD (mg/kg-day)	Rat/MF	Absence of any toxicological effects and frank effects	2×10^{-1}	NOAEL	45	300	Oser et al. (1975a)
Chronic p-RfD (mg/kg-day)	Rat/MF	Absence of any toxicological effects and frank effects	2×10^{-2}	NOAEL	45	3000	Oser et al. (1975a)
Subchronic p-RfC (mg/m^3)	None						
Chronic p-RfC (mg/m^3)	None						

ND = Not Determined

Table 5. Summary of Cancer Values for 2-Chloroethanol (CASRN 107-07-3)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	None			
p-IUR	None			

DERIVATION OF ORAL REFERENCE DOSE

Derivation of Subchronic and Chronic Provisional RfDs

There are four subchronic-duration and two developmental studies involving oral exposure to 2-chloroethanol (see Table 2). The subchronic-duration rat study by Oser et al. (1975a) is selected as the principal study for derivation of a subchronic p-RfD. In this study, the study authors administered 2-chloroethanol (0, 30, 45, and 67.5 mg/kg-day) to male and female FDRL rats, 25/sex/dose, for 6 weeks in the diet followed by 12 weeks of gavage treatment at the same doses. The study authors conducted urinalysis, hematology, and histology of tissues from 26 organs (though incompletely reported). The highest dose (67.5 mg/kg-day) caused high mortality (17/25 males; 19/25 females), thus constituting a FEL in both sexes. There were no observed effects of treatment at the next lower dose (45 mg/kg-day). This study was reported in a peer-reviewed journal and was performed prior to implementation of GLP standards. However, this study generally met the standards of study design and performance with regard to numbers of animals, examination of potential toxicity endpoints, and presentation of information. The selected study had some minor deficiencies, particularly in the reporting of the results. These details are provided in the "Review of Potentially Relevant Data" section. Benchmark dose (BMD) analysis is not appropriate because the highest dose is a FEL, and there were no observed effects at the next lower dose. The other acceptable studies performed in dogs and

monkeys (also reported in the publication by Oser et al., 1975a) did not identify any toxicological effects at the highest doses tested (20.3 and 62.5 mg/kg-day, respectively).

The developmental toxicity study by Courtney et al. (1982a) could possibly be used to derive p-RfDs. In that study, pregnant CD mice (12/dose group) were administered 0, 50, 100, or 150 mg/kg-day of 2-chloroethanol on GDs 6−16 followed by sacrifice on GD 17. The study authors examined litter and fetus weight, implants/litter, fetus mortality, number of fetuses/litter, and the number and type of fetal anomalies. The maternal NOAEL was 50 mg/kg-day based on a decrease in maternal body weight at a dose of 100 mg/kg-day. The fetal NOAEL was 50 mg/kg-day based on a biologically significant reduction in relative (9%) and absolute (19%) fetal liver weight and a 14% reduction in body weight at 100 mg/kg-day. Although the Courtney et al. (1982a) study provides a NOAEL and a LOAEL, the NOAELs (50 mg/kg-day, fetal and maternal) are greater than that from Oser et al. (1975a). Thus, based on the absence of any observable toxicological effects, the rat study by Oser et al. (1975a) provides the lowest POD (a NOAEL of 45 mg/kg-day) for developing a subchronic p-RfD.

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

Adjusted for daily exposure:

The following dosimetric adjustments were made for each dose in the principal study for dietary treatment.

$$\begin{aligned} NOAEL_{ADJ} &= NOAEL_{\text{Oser et al., 1975a}} \times [\text{conversion to daily dose}] \\ &= 45 \text{ mg/kg-day} \times (\text{days of week dosed} \div 7 \text{ days in week}) \\ &= 45 \text{ mg/kg-day} \times 7 \div 7 \\ &= 45 \text{ mg/kg-day} \end{aligned}$$

The subchronic p-RfD for 2-chloroethanol, based on the NOAEL of 45 mg/kg-day (POD) in male and female rats (Oser et al., 1975a), is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= NOAEL_{ADJ} \div UF_C \\ &= 45 \text{ mg/kg-day} \div 300 \\ &= \mathbf{2 \times 10^{-1} \text{ mg/kg-day}} \end{aligned}$$

Table 6 summarizes the uncertainty factors (UFs) for the subchronic p-RfD for 2-chloroethanol.

Table 6. Uncertainty Factors for Subchronic p-RfD of 2-Chloroethanol (CASRN 107-07-3)[a]

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans.
UF_D	3	A UF_D of 3 is applied because the database includes two acceptable developmental studies in mice but no acceptable two-generation reproduction studies. Additionally, neurotoxicity studies may be relevant based on data in humans (short-term exposure).
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a NOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study (Oser et al., 1975a) was utilized as the principal study.
UF_C	300	

[a]Oser et al. (1975a).

Derivation of Chronic Provisional RfD (Chronic p-RfD)

The study by Oser et al. (1975a) is selected as the principal study for derivation of a chronic p-RfD in the absence of an acceptable chronic toxicity test in animals. The selection of this study is detailed under the "Derivation of Subchronic p-RfD." Similar to the subchronic p-RfD, the POD is a NOAEL of 45 mg/kg-day.

Adjusted for daily exposure:

The following dosimetric adjustments were made for each dose in the principal study for dietary treatment.

$$\begin{aligned} NOAEL_{ADJ} &= NOAEL_{\text{Oser et al., 1975a}} \times [\text{conversion to daily dose}] \\ &= 45 \text{ mg/kg-day} \times (\text{days of week dosed} \div 7 \text{ days in week}) \\ &= 45 \text{ mg/kg-day} \times 7 \div 7 \\ &= 45 \text{ mg/kg-day} \end{aligned}$$

The chronic p-RfD for 2-chloroethanol, based on the NOAEL of 45 mg/kg-day (POD) in male and female rats (Oser et al., 1975a), is derived as follows:

$$\begin{aligned} \textbf{Chronic p-RfD} &= NOAEL_{ADJ} \div UF_C \\ &= 45 \text{ mg/kg-day} \div 3000 \\ &= \mathbf{2 \times 10^{-2} \text{ mg/kg-day}} \end{aligned}$$

Table 7 summarizes the UFs for the chronic p-RfD for 2-chloroethanol.

Table 7. Uncertainty Factors for Chronic p-RfD of 2-Chloroethanol (CASRN 107-07-3)[a]

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans.
UF_D	3	A UF_D of 3 is applied because the database includes 2 acceptable developmental studies in mice but no acceptable two-generation reproduction studies. Additionally, neurotoxicity studies may be relevant based on data in humans (short-term exposure).
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a NOAEL.
UF_S	10	A UF_S of 10 is applied because a subchronic-duration study (Oser et al., 1975a) was utilized as the principal study.
UF_C	3000	

[a]Oser et al. (1975a).

DERIVATION OF INHALATION REFERENCE CONCENTRATION

Derivation of Subchronic or Chronic Provisional RfCs (Subchronic or Chronic p-RfCs)

No published studies investigating the effects of subchronic or chronic inhalation exposure to 2-chloroethanol in humans or animals were identified that were acceptable for use in derivation of subchronic or chronic p-RfCs.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 8 identifies the cancer WOE descriptor for both oral and inhalation exposure to 2-chloroethanol as "*Inadequate Information to Assess Carcinogenic Potential*." No carcinogenicity dose-response studies in humans via the oral or inhalation routes were found. Three epidemiological studies investigating the potential for 2-chloroethanol to cause cancer in humans were located; however, the results were contradictory. Furthermore, these epidemiological studies were insufficient to establish a causal relationship due to human exposure to multiple chemical compounds. No animal carcinogenicity studies (oral or inhalation) were located, regardless of route of administration. The most informative study available was NTP (1985b,c), in which rats and mice were treated with 2-chloroethanol by dermal application; however, this study was confounded because the 2-chloroethanol was applied in a 70% aqueous ethanol vehicle. Ethanol protects against 2-chloroethanol toxicity. It is noteworthy that male mice in this study were exposed to a FEL (increased mortality) without any evidence of increased neoplastic incidence. Consequently, the WOE for carcinogenicity is "*Inadequate Information to Assess Carcinogenic Potential*."

Table 8. Cancer WOE Descriptor for 2-Chloroethanol (CASRN 107-07-3)			
Possible WOE Descriptor	**Designation**	**Route of Entry (Oral, Inhalation, or Both)**	**Comments**
"Carcinogenic to Humans"	Not Selected	N/A	No definitive human studies are available.
"Likely to be Carcinogenic to Humans"	Not Selected	N/A	There are no animal carcinogenicity studies via oral or inhalation routes.
"Suggestive Evidence of Carcinogenic Potential"	Not Selected	N/A	There are no animal carcinogenicity studies via oral or inhalation routes.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**There is inadequate human and animal evidence of carcinogenicity via the oral or inhalation route. Available epidemiological studies provide conflicting results regarding the possible involvement of 2-chloroethanol in increased cancer risk. Case studies do not provide evidence to inform the assessment of carcinogenic potential. There are no animal carcinogenicity studies via the oral or inhalation route.**
"Not Likely to be Carcinogenic to Humans"	Not Selected	N/A	

MODE OF ACTION

There are insufficient data to determine the mode of carcinogenic action.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

No human or animal studies examining the carcinogenicity of 2-chloroethanol following oral exposure were identified. Therefore, derivation of a p-OSF is precluded.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

No human or animal studies examining the carcinogenicity of 2-chloroethanol following inhalation exposure were identified. Therefore, derivation of a p-IUR is precluded.

APPENDIX A. DERIVATION OF SCREENING VALUES

No screening values are presented.

APPENDIX B. DATA TABLES

Table B.1. Mean Body-Weight, Food Efficiency, and Survival in Rats Exposed to 2-Chloroethanol via Gavage for 12 Weeks[a,b]

Parameter	Exposure Group (mg/kg-day)			
	0	**30**	**45**	**67.5**
Males				
Mean body weight (g)	111	91	94	73
Food Efficiency (BWG in g/100 g food)	5.8	5.9	6.6	5.4
Survival (%)	100	100	100	32
Females				
Mean body weight (g)	51	49	49	46
Food Efficiency (BWG in g/100 g food)	3.7	4.3	4.0	4.0
Survival (%)	96	100	96	24

[a]Oser et al. (1975a). Data were obtained from Table 1 on page 314 of the cited publication.
[b]Means only, variations were not reported; statistical analyses were not performed.

BWG = body-weight gain.

APPENDIX C. BMD MODELING OUTPUTS FOR 2-CHLOROETHANOL

There are no BMD modeling outputs for 2-chloroethanol.

APPENDIX D. REFERENCES

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