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ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR CHLOROETHANE

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
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1. ATSDR internal clearance process review.

ADDENDUM for Chloroethane
Supplement to the 1998 Toxicological Profile for Chloroethane

Background Statement

This addendum to the Toxicological Profile for Chloroethane supplements the Toxicological Profile for Chloroethane that was released on December 1998.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986, which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund.) CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" (Title 42, Chapter 103, Subchapter I, § 9604 [i] [1] [B]).

This addendum is a non-peer–reviewed supplement containing scientific data that were published in the open peer-reviewed literature since the release of the toxicological profile in 1992.

Chapter numbers in this addendum coincide with the Toxicological Profile for Chloroethane (1998). This document should be used in conjunction with the profile. It does not replace it.

2. HEALTH EFFECTS

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.1 Inhalation Exposure

2.2.1.1 Death

Broussard et al. (2000) studied the case of a 30-year-old white male found dead in a locked apartment with a rag held loosely in his mouth. Cans labeled as VCR head cleaner (chloroethane) were found next to the body. The concentrations of chloroethane in the tissues and body fluids of the deceased were

- blood - 423 mg/L,
- urine - 35 mg/L,
- vitreous - 12 mg/L,
- brain - 858 mg/kg, and
- lungs - 86 mg/kg.

Phenylpropanolamine, and low therapeutic levels of diazepam (64 µg/L) and nordiazepam (126 µg/L) were detected during toxicological analysis.

Based on a literature search, the authors believe that this is the first report of chloroethane levels in tissue (Broussard et al. 2000).

Holder (2008) analyzed the toxicity of chloroethane and compared it to that of bromoethane. He observed, based on references cited therein, that

- chloroethane is not very toxic as illustrated by LC_{50s} of 60,000 to 70,000 ppm, and
- acute mortality in humans does not occur at concentrations below 50,000 ppm when chloroethane is inhaled as a recreational street-drug.

2.2.1.4 Neurological Effects

A 41-year-old African American male presented to the emergency department due to mental status changes and an inability to walk. After the blood alcohol and urine drug screen returned with negative results, a family member revealed that the patient frequently abused an inhalant containing the volatile solvent chloroethane.

The authors state that inhalants should be included in the differential diagnosis of patients presenting with acute mental status changes and neurologic impairment that resolve over less than one week (Finch and Lobo 2005).

2.2.1.7 Genotoxic Effects

Holder (2008) analyzed the toxicity of chloroethane and compared it to that of bromoethane. He observed, based on references cited therein, that

- significant genotoxicity is not observed below 40,000 ppm.

2.2.1.8 Cancer

There are animal studies that differ by species in terms of carcinogenic outcomes (from inhalation exposure to chloroethane) making it difficult to ascertain or predict human health effects with certainty.

Picut et al. (2003) reevaluated the pathology and incidence data of the National Toxicology Program (NTP 1989) inhalation studies because of the dramatically high rates of uterine neoplasms (induced by chemicals given by the inhalation route) and metastases. The NTP study had found that chloroethane induces endometrial neoplasms in the uterus of B6C3F1 mice following an inhalation route of exposure. The NTP's chronic bioassays resulted in an unusually high incidence of 86% uterine epithelial neoplasms in B6C3F1 mice (NTP 1989).

In the Picut study, the uterine neoplasms were classified as adenocarcinomas for chloroethane. The adenocarcinomas were invasive into the myometrium and the serosa, and metastasized to a wide variety of organs. Metastatic sites included most commonly the lung, lymph nodes, and ovary at unusually high rates of metastases (79% for chloroethane).

Picut et al. (2003) confirmed the earlier NTP (1989) results and concluded that the mechanism of uterine carcinogenesis by chloroethane is unclear.

Holder (2008) analyzed the carcinogenicity of chloroethane and compared it to that of bromoethane (a structural analogue). He observed, based on references cited therein, that

- chloroethane is generally not toxic to test rodents except for B6C3F1 female mice at very high exposure concentrations (15,000 ppm CE gas for 6 hr/day, 5 day/week for 100 weeks) resulting in uncommon to rare uterine malignant tumors, and
- although the true chloroethane dose –response function is not yet known, the data for test rodents (i.e. rats) indicating lack of adverse health effects is consistent with findings in many reports of environmental chloroethane exposures in humans.

Holder (2008) contrasted the relative low toxicity of chloroethane with the fact that the inhalation of 15,000-ppm chloroethane gas in air produced the highest incidence of an

uncommon-to-rare endometrial cancer in female mice, but not in rats. Bromoethane produced results similar to chloroethane.

The question then becomes, which of the two models, the mouse or the rat, apply to humans. This remains an unanswered question.

Female mice, but not female rats, develop uterine cancer when exposed to high concentrations (15,000 ppm) chloroethane (NTP 1989). Gargas et al. (2008) expanded an existing PBPK model for rats and developed chloroethane PBPK models for mice and humans to facilitate species comparisons. They developed and validated models of chloroethane absorption, disposition, metabolism, and elimination for mice, rats, and humans. They calculated GSH-conjugation rates for the liver, kidney, brain, ovary, adrenal gland, and uterus (Gargas et al. 2008). The PBPK modeling results reported here are consistent with the hypothesis that a GSH-derived metabolite of chloroethane, possibly in association with acetaldehyde, is involved with the mode of action for uterine tumors in mice.

2.2.3 Dermal Effects

2.2.3.2 Systemic Effects

Ocular effects

Rodriguez andAscaso (2012) described a case where a patient suffered an acute burn of the ocular surface following chloroethane spray exposure. The patient had undergone excision of a papilloma on his superior right eyelid after slight freezing with the chloroethane spray.

2.2.4 Other Routes of Exposure

2.2.4.4 Neurological Effects

According to Holder (2008), chloroethane has over the years been used as a

- cryoanalgesic,
- cryoanesthetic for topical surgery, and
- as a human and animal general anesthetic in exposures lasting 0−2 hours.

Physicians often use chloroethane as a local refrigerant spray anesthetic. There are also reports describing its use in touch stimulus assessment. For example, Walsh et al. (2010) studied the use of a Neuropen monofilament vs. ethyl chloride for assessing loss of touch sensation during combined spinal-epidural anesthesia for caesarean section. Both touch stimulus modalities were found to be equivalent.

Researchers have also studied chloroethane (ethyl chloride)

- as a topical refrigerant spray for pediatric venipuncture for outpatient surgery (Schlieve and Miloro 2015),
- for prevention of pruritus (severe itching of the skin) in a skin prick test (Gal-Oz et al. 2015),
- for pain relief during needle electromyography in flexor carpi radialis (a muscle of the human forearm) (Moon and Kim 2014),
- as a trigger of malignant hyperthermia (Hopkins 2011),
- for its acute reversible neurotoxicity associated with inhalation (Demarest et al. 2011; Senussi and Chalise 2015), and
- for its adverse effects as a topical anesthetic for tail biopsy of preweanling mice (Braden et al. 2015).

2.3 TOXICOKINETICS

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Female mice, but not female rats, develop uterine cancer when exposed to high concentrations (15,000 ppm) chloroethane (NTP 1989). Gargas et al. (2008) expanded an existing PBPK model for rats and developed chloroethane PBPK models for mice and humans to facilitate species comparisons. They developed and validated models of chloroethane absorption, disposition, metabolism, and elimination for mice, rats, and humans. They calculated GSH-conjugation rates for the liver, kidney, brain, ovary, adrenal gland, and uterus (Gargas et al. 2008). The PBPK modeling results reported here are consistent with the hypothesis that a GSH-derived metabolite of chloroethane, formed via oxidation by cytochrome P-450 (likely producing acetaldehyde) and conjugation with glutathione (GSH) (Gargas et al. 2008), is involved with the mode of action for uterine tumors in mice.

2.8 Interactions with Other Chemicals

Chloroethane in mammalian tissues is:

- oxidatively dechlorinated in an NADPH-and O_2-dependent reaction, P450-dependent metabolism, resulting in the formation of acetaldehyde (Fedtke et al. 1994a), or
- conjugated with glutathione (GSH) in a reaction catalyzed by GSHS-transferases (Fedtke et al. 1994b)

3. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.3 USE

According to Holder (2008), chloroethane has over the years been used as a

- cryoanalgesic,
- cryoanesthetic for topical surgery, and
- as a human and animal general anesthetic in exposures lasting 0−2 hours.

Cho andAndrews (2013) determined the infrared spectra of manganese insertion, vinyl, and cyclic complexes prepared in reactions of laser-ablated Mn atoms with ethyl chloride, among other substances.

Talamo et al. (2012) used chloroethane to study the degree of pain experienced by patients undergoing a bone marrow aspiration and biopsy (BMAB), and to evaluate the effectiveness of several strategies aimed at reducing the pain score.

4.4 DISPOSAL

The dechlorinating activity of a methanogenic granular sludge from a methanol-fed up-flow anaerobic sludge blanket reactor was investigated with chlorinated ethanes. The results revealed that

- this unadapted methanogenic consortium degraded all chloroethanes tested, and

- reductive hydrogenolysis and dichloroelimination were important dechlorinating mechanisms (van Eekert et al. 1999).

5. POTENTIAL FOR HUMAN EXPOSURE

5.3 ENVIRONMENTAL FATE

5.3.2. Transformation and Degradation

5.3.2.3 Sediment and Soil

Nitrifying activity was stimulated to study cooxidation of monohalogenated hydrocarbons by native populations of NH_3-oxidizing bacteria. These slurries actively degraded chloroethane at maximum rates of 20-30 nmol/ml/hr that could be sustained for approximately 12 hours (Duddleston et al. 2002).

Hommes et al. (1998) examined the influence of soil upon the cooxidation of a variety of halogenated and nonhalogenated hydrocarbons by *Nitrosomonas europaea*. Small quantities of Willamette silt loam (organic carbon content, 1.8%; cation-exchange capacity, 15 mmol/kg of soil) were suspended with *N. europaea* cells in a soil-slurry-type reaction mixture. The oxidations of ammonia and chloroethane were compared to results for controls in which no soil was added. Findings included that the modifying effects of soil on nitrite production and on the cooxidation of chloroethane could be circumvented by raising the ammonium concentration in the reaction mixture from 10 to 50 mM (Hommes et al. 1998).

5.3.2.4 Sludge

The dechlorinating activity of a methanogenic granular sludge from a methanol-fed up-flow anaerobic sludge blanket reactor was investigated with chlorinated ethanes. Findings revealed that

- this unadapted methanogenic consortium degraded all chloroethanes tested, and
- reductive hydrogenolysis and dichloroelimination were important dechlorinating mechanisms (van Eekert et al. 1999).

Wu et al. (2013) found that a *Bacillus* strain capable of degrading chloroethane (ethyl chloride) showed the best growth for biodegradation at a pH value of 7.0, immobilized microorganism ratio of 5%, and temperature of 30℃.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Barletta et al. (2009) identified chloroethane (ethyl chloride) among a suite of tracer gases (OCS, CH_3Cl, 1,2-dichloroethane, ethyl chloride, and Halon-1211) that scientists can use to trace contaminants originating in China to determine if they might be moving with wind currents into the U.S., becoming a source of U.S. population exposure.

6. ANALYTICAL METHODS

6.1 BIOLOGICAL SAMPLES

Chloroethane, also known as ethyl chloride, can be confused with ethanol during the analyses of blood samples. Chloroethane can coelute with ethanol when headspace gas chromatography is used to try to separate both substances (Laferty 1994). Tarnovski et al. (2009) found similar results when researching a case of sexual asphyxia with drug and volatile substance abuse. They used GC-FID analysis for alcohol.

Kaleemullah et al. (2011) developed and validated a gas chromatography method for low-level detection of residual ethyl chloride in ziprasidone hydrochloride, a psychotropic agent used to treat mental diseases such as schizophrenia.

7. REGULATIONS AND ADVISORIES

Immediately Dangerous To Life or Health (IDLH). The original (SCP) IDLH for chloroethane (ethyl chloride) was 20,000 ppm, based on human exposure data reported by Davidson (1925) in which 13,000 ppm caused no difficulty in walking or balancing after 21 minutes, but 19,000 ppm caused weak analgesia and slight dizziness after 12 minutes (NIOSH 2011). The revised IDLH for ethyl chloride is 3,800 ppm based strictly on safety considerations, *i.e.*, being 10% of the lower explosive limit of 3.8% (NIOSH 2014).

TABLE 7-1. Regulations and Guidelines Applicable to Chloroethane

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 3[a]	IARC (1991), IARC (1999)
NATIONAL			
Regulations:			
a. Air:			
OSHA	Permissible Exposure Limit (PEL) -Time Weighted Average (TWA)	1,000 ppm (2,600 mg/m^3)	OSHA (2015)
b. Other:			
EPA	Reportable Quantity	45.4 kg (100 lb)	EPA (2015b)
	Required Reporting Under Title III SARA	Yes	EPA (2015c)
	Designated as a hazardous substance	No	EPA (2015a)
Guidelines:			
a. Air:			
ACGIH	TLV-TWA (skin)	100 ppm (264 mg/m^3)	ACGIH (2016) TOXLINE (2001)
	Carcinogenic Classification	Group A3[b]	ACGIH (2016) TOXLINE (2001)
EPA	RfC (inhalation)	10 mg/m^3 (4 ppm)	EPA (1991)
b. Water:			
EPA	MCLG	None listed	(EPA 2016)
	MCL	None listed	(EPA 2016)
	Health Advisories:		(EPA 2016)
	1-day (child)	None listed	
	10-day (child)	None listed	
	Longer Term (child and adult)	None listed	
	Lifetime	None listed	
	DWEL	None listed	(EPA 2016)
b. Other:			
ACGIH	Biological Exposure Index	None listed	ACGIH (2016) TOXLINE (2001)
EPA	RfD (oral)	None listed	EPA (2016)
STATE			
Regulations:			
a. Air:			
California	8-hour TWA (ST) STEL, (C) Ceiling	(C) 25 ppm	Cal/OSHA (2015)

[a]IARC - Chloroethane *is not classifiable as to its carcinogenicity to humans* (Group 3)
[b]ACGIH Group A3: Animal carcinogen of unknown relevance to humans
ACGIH = American Conference of Governmental Industrial Hygienists
DWEL = Drinking Water Equivalent Level
EPA = Environmental Protection Agency
IARC = International Agency for Research on Cancer
MCL = Maximum Contaminant Level
MCLG = Maximum Contaminant Level Goal
NATICH = OSHA = Occupational Safety and Health Administrations
RfC = Reference concentration
RfD = Reference Dose
SARA = Superfund Amendments and Reauthorization Act
TLV-TWA = Threshold Limit Value-Time-Weighted Average

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