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Provisional Peer Reviewed Toxicity Values for

2-Chloropropane

(CASRN 75-29-6)

Superfund Health Risk Technical Support Center
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Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level

MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	**provisional inhalation unit risk**
p-OSF	**provisional oral slope factor**
p-RfC	**provisional inhalation reference concentration**
p-RfD	**provisional oral reference dose**
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	**Provisional Peer Reviewed Toxicity Value**
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

8-22-2005

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 2-CHLOROPROPANE (CASRN 75-29-6)

Background

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

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

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

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

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

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

Because science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions or the EPA Headquarters Superfund Program sometimes request that a frequently used PPRTV be reassessed. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

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

Questions Regarding PPRTVs

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

INTRODUCTION

The HEAST (U.S. EPA, 1997) lists subchronic and chronic RfC values for 2-chloropropane of 1E+0 and 1E-1 mg/m^3, respectively. The source document for this assessment was a Health and Environmental Effects Document (HEED) for 2-Chloropropane (U.S. EPA, 1987). The RfC values in the HEAST are based on liver effects observed in a four week inhalation study in rats (Gage, 1970). The HEAST does not include an RfD assessment for 2-chloropropane; the HEED included no oral studies for this chemical. 2-Chloropropane is not listed on IRIS (U.S. EPA, 2005a) or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). The CARA list (U.S. EPA, 1991, 1994) includes only the previously mentioned HEED. ATSDR (2003) has not published a Toxicological Profile for 2-chloropropane, and no Environmental Health Criteria Document is available (WHO, 2003).

ACGIH (2003), NIOSH (2003), and OSHA (2003) have not developed occupational exposure limits for 2-chloropropane.

A cancer weight-of-evidence classification for 2-chloropropane is not listed in the HEAST (U.S. EPA, 1997) or on IRIS (U.S. EPA, 2005a). The HEED (U.S. EPA, 1987) assigned 2-chloropropane to U.S. EPA (1986) weight-of-evidence Group D (not classifiable as to human carcinogenicity) due to a lack of human and animal data. Neither IARC (2003) nor NTP (2003) have evaluated the carcinogenicity of 2-chloropropane. Literature searches were conducted from 1986 through 2003 for studies relevant to the derivation of provisional toxicity values for 2-chloropropane. Databases searched included: TOXLINE (supplemented with BIOSIS and NTIS updates), MEDLINE, CANCERLIT, TSCATS, RTECS, CCRIS, DART/ETICBACK, EMIC/EMICBACK, HSDB, and GENETOX. An additional literature search was conducted by NCEA-Cincinnati through December 2004.

REVIEW OF PERTINENT DATA

Human Studies

2-Chloropropane has been used as an anaesthetic in humans (Elam and Newhouse, 1951). A high incidence of circulatory and cardiac irregularities were observed in patients given anesthesia with 2-chloropropane, and one case of complete circulatory failure was reported (Elam and Newhouse, 1951; Buhr, 1953).

Animal Studies

Acute inhalation exposure to high concentrations of 2-chloropropane in the air produced anaesthetic and cardiac effects in animals, as in humans. Rats exposed to a saturated atmosphere of 2-chloropropane were anaesthetized within 3 minutes and died within 6 minutes (Dow Chemical, 1953). Rats exposed to 2-chloropropane in a 4-hour study showed signs of central nervous system depression at 8000 ppm. Dogs exposed to an anaesthetic concentration of 2-chloropropane (694,000 mg/m^3) for 3-5 minutes experienced decreased arterial blood pressure, increased venous blood pressure, increased respiratory rate, and decreased respiratory volume (Enders and Koner, 1952). Coronary blood flow was decreased 50% and electrocardiograms showed significant damage to the heart muscle.

Only limited data were located regarding longer-term inhalation exposure of laboratory animals to 2-chloropropane. In one study, groups of 4 male and 4 female Alderly Park SPF rats (weighing ≈200 g at start of experiment) were exposed to 2-chloropropane vapor at concentrations of 250 or 1000 ppm 6 hours per day, 5 days per week for 4 weeks (Gage, 1970). Body weight, condition, and behavior were monitored daily. Urine was collected for

biochemical tests overnight after the last exposure. Rats were sacrificed the following day. At that time, blood was collected for hematological tests, the organs were examined grossly, and sections of lung, liver, kidney, spleen, and adrenals were collected for microscopic examination. A concurrent control group was not included in the study. No clinical signs of toxicity were seen at either exposure level, including signs of irritation or central nervous system depression. Blood and urine tests were normal. Histopathological examination revealed extensive vacuolation and necrosis in the liver of rats exposed to 1000 ppm (incidence not reported by the researchers). No lesions were seen in the liver or other organs of rats exposed to 250 ppm.

A longer study was conducted in which rats (20/sex/group), mice (10 females/group), guinea pigs (8/sex/group), rabbits (2/sex/group), and monkeys (2 females per group) were exposed to 0 or 1000 ppm of 2-chloropropane for 7 hours/day, 5 days a week for a total of 181 days (approximately 6 months) (Dow Chemical, 1958; Betso, 1987; Torkelson and Rowe, 1981). 2-Chloropropane did not affect behavior, appearance, growth, mortality, or final organ or body weights. Histopathological changes in the liver, kidney, and lung were observed following repeated inhalation exposure to 2-chloropropane. Liver histopathology was characterized by necrosis of the parenchymal cells in the portal area; liver effects were seen in every species tested. In the kidney, tubule degeneration of the epithelium and some necrosis were noted; kidney effects were observed in guinea pigs, rabbits, and monkeys. Lung edema or pneumonitis was observed in female rabbits and monkeys. Torkelson and Rowe (1981) also reported that Dow Chemical performed an experiment in which rats, guinea pigs, rabbits, and dogs were exposed to 500 ppm of 2-chloropropane 7 hours/day, 5 days per week for 6 months, with no effects on appearance, growth, hematology, clinical chemistry, organ weight, or gross or histopathological examination. However, Dow Chemical no longer has any record of this study (Betso, 1987).

Other Studies

Few genotoxicity studies for 2-chloropropane were located. 2-Chloropropane was mutagenic in *Salmonella typhimurium* strain TA100 in the presence of an S9 liver activation system, when tested in a desiccator (Simmon et al., 1977). The chemical was not genotoxic in the *E. coli* SOS chromotest without metabolic activation (Szegedi, 1989).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 2-CHLOROPROPANE

In the absence of subchronic or chronic data on the oral toxicity of 2-chloropropane in humans or animals, derivation of provisional subchronic or chronic RfD values is precluded.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 2-CHLOROPROPANE

The inhalation data for 2-chloropropane are inadequate to support derivation of an RfC. Dow Chemical (1958) found lesions in the liver of rats exposed to 1000 ppm of 2-chloropropane for 6 months, but also found lesions in the kidneys and lungs of some of the other species tested under the same conditions. This study examined only one dose level, rendering it inadequate for RfC derivation. The only study that included multiple dose levels was that of Gage (1970). This study found fatty and necrotic liver lesions in rats exposed to 1000 ppm for 4 weeks, but not those exposed to 250 ppm. Although this study investigated a fairly broad array of endpoints, there was only limited examination of the respiratory tract (clinical signs of irritation, lung histopathology) and CNS (gross clinical signs of depression), and no examination of cardiac or circulatory endpoints. Effects on the CNS and the heart and circulation are known from clinical trials in humans and acute studies in animals with 2-chloropropane. The Gage (1970) study was also limited by small group sizes, short exposure duration, lack of a concurrent control group, and incomplete and qualitative reporting of the data.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2-CHLOROPROPANE

Data on the carcinogenicity of 2-chloropropane in humans or animals are not available. Very limited genotoxicity testing produced both positive and negative results. As the available data are insufficient to assess carcinogenic potential in animals or humans, they are consistent with the hazard descriptor, *"inadequate information to assess carcinogenic potential,"* as specified by the U.S. EPA (2005b) Guidelines for Carcinogen Risk Assessment.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2003. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 2003. Internet HazDat-Toxicological Profile Query. Online. http://www.atsdr.cdc.gov/toxpro2.html

Betso, J. 1987. Dow Chemical Company. Personal communication to P. Goetchius, Syracuse Research Corp. (Cited in U.S. EPA, 1987).

Buhr, G. 1953. Effect of isopropyl narcosis on the human heart and circulation. Der Anaesthesist. 2: 180-83.

Dow Chemical. 1953. Results of some range finding toxicological tests on isopropyl chloride. EPA Doc. No. 86-870002157. Fiche No. OTS0515947.

Dow Chemical. 1958. Results of repeated vapor exposure of laboratory animals to isopropyl chloride at a concentration of 1000 ppm. EPA Doc. No. 86-870002156. Fiche No. OTS0515946.

Elam, J.E. and M.L. Newhouse. 1951. An investigation of the properties of isopropyl chloride. Br. Med. J. 1: 13-14.

Enders, A. and F.R. Koner. 1952. The influence of isopropyl chloride on heart and circulation. Der Anaesthesist. 1: 113-5.

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

IARC (International Agency for Research on Cancer). 2003. Search IARC Monographs. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

NIOSH (National Institute for Occupational Safety and Health). 2003. Online NIOSH Pocket Guide to Chemical Hazards. Online. http://www.cdc.gov/niosh/npg/npgdcas.html

NTP (National Toxicology Program). 2003. Management Status Report. Online. http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html

OSHA (Occupational Safety and Health Administration). 2003. OSHA Standard 1910.1000 Table Z-1. Part Z, Toxic and Hazardous Substances. Online. http://www.osha-slc.gov/OshStd_data/1910_1000_TABLE_Z-1.html

Simmon, V.F., K. Kauhanen and R.G. Tardiff. 1977. Mutagenic activity of chemicals identified in drinking water. Dev. Toxicol. Environ Sci. 2: 249-58.

Szegedi, M. 1989. Genotoxic activities of 3-chloropropionic acid and related compounds. Env. Mol. Mutagen. 196. (Abstract)

Torkelson, T.R. and V.K. Rowe. 1981. Halogenated aliphatic hydrocarbons containing chlorine, bromine, and iodine. In: Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol IIB, G.D. Clayton and F.E. Clayton, Ed., John Wiley and Sons, Inc. p. 3433-3601.

U.S. EPA. 1986. Guidelines for Carcinogen Risk Assessment. September 24, 1986. Federal Register. 51 (185): 33992-340003.

U.S. EPA. 1987. Health and Environmental Effects Document for 2-Chloropropane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April 1991.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December 1994.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS PB97-921199.

U.S. EPA. 2002. 2002 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. Summer 2002. EPA 822-R-02-038. Online. http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf

U.S. EPA. 2005a. Integrated Risk Information System (IRIS). Office of Research and Development. National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris/

U.S. EPA. 2005b. Guidelines for Carcinogen Risk Assessment. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. EPA/630/P-03/001F.

WHO (World Health Organization). 2003. Online catalogs for the Environmental Health Criteria Series. Online. http://www.who.int/dsa/cat97/zehc1.htm