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Provisional Peer Reviewed Toxicity Values for

2-Chlorobutane

(CASRN 78-86-4)

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

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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 HQ 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) reports that data are inadequate for quantitative risk assessment of 2-chlorobutane. The source document for this assessment was a HEED for Monochlorobutanes (U.S. EPA, 1988). IRIS (U.S. EPA, 2003) does not report an RfD or RfC for 2-chlorobutane, and lists 2-chlorobutane in carcinogenicity group D (not classifiable as to human carcinogenicity). 2-Chlorobutane is not included in the Drinking Water Standards and Health Advisories List (U.S. EPA, 2002). The CARA list (U.S. EPA, 1991, 1994) includes the previously mentioned HEED, as well as a HEEP for Monochlorobutanes (U.S. EPA, 1983). ATSDR (2003) has not published a Toxicological Profile for 2-chlorobutane, 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-chlorobutane. Neither IARC (2003) nor NTP (2003) have evaluated the carcinogenicity of 2-chlorobutane.

Literature searches were conducted from 1987 through October, 2003 for studies relevant to the derivation of provisional toxicity values for 2-chlorobutane. Databases searched included: TOXLINE (supplemented with BIOSIS and NTIS updates), MEDLINE, TSCATS, RTECS, CCRIS, DART, EMIC/EMICBACK, HSDB, GENETOX, and CANCERLIT. In addition, the available reviews were tree-searched to locate other potentially relevant references.

REVIEW OF PERTINENT DATA

Human Studies

Studies examining the toxicity or carcinogenicity of 2-chlorobutane in humans were not located.

Animal Studies

In a study designed to look only for lung tumors after short-term, high-level exposure, Poirier et al. (1975) gave groups of 10 male and 10 female strain A/Heston mice a total of 13 intraperitoneal injections (3 injections/week) of 7, 17.5, or 35 mmol/kg (648, 1620, or 3240 mg/kg) of 2-chlorobutane in tricaprylin; the study originally intended to administer 24 injections, but was altered due to early mortality. Untreated and tricaprylin-treated mice were used as negative controls, and urethane-treated mice were used as positive controls. Survival of animals in the low-, mid-, and high-dose groups was 75, 75, and 50%, respectively. In the untreated and vehicle controls and urethane-treated group, survival was >90%. Surviving animals were sacrificed 24 weeks after the first injection. Treatment with 2-chlorobutane resulted in a dose-related increase in the average number of lung tumors per mouse; this increase attained statistical significance, relative to controls, in the 35 mmol/kg (3240 mg/kg) group. Urethane-treated animals also showed a significant increase, relative to controls, in gross lung tumor formation. Other organs examined for abnormalities were the kidney, intestine, liver, thymus, spleen, and salivary and endocrine glands. Additional details of the toxicity of 2-chlorobutane were not reported.

Other Studies

2-Chlorobutane (4 μL/dessicator) was mutagenic in *Salmonella typhimurium* strain TA100 in the absence of hepatic homogenates when tested in a dessicator (Simmon, 1981).

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

In the absence of subchronic or chronic data on the oral toxicity of 2-chlorobutane 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-CHLOROBUTANE

In the absence of subchronic or chronic data on the inhalation toxicity of 2-chlorobutane in humans or animals, derivation of provisional subchronic or chronic RfC values is precluded.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2-CHLOROBUTANE

Data on the carcinogenicity of 2-chlorobutane in humans are not available. No long-term studies of the carcinogenicity of 2-chlorobutane in animals are available; the only available study consisted of a short-term carcinogenesis screening assay that reported positive results, but is insufficient for determining possible carcinogenic effects of 2-chlorobutane. Limited genotoxicity testing also produced positive results. Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), 2-chlorobutane has *inadequate information to assess carcinogenic potential* because there is no data on the carcinogenicity of 2-chlorobutane in humans and inadequate data in animals.

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