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Provisional Peer Reviewed Toxicity Values for

1,3-Dichloropropane

(CASRN 142-28-9)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
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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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PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 1,3-DICHLOROPROPANE (CASRN 142-28-9)

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.

This document has passed the STSC quality review and peer review evaluation indicating that the quality is consistent with the SOPs and standards of the STSC and is suitable for use by registered users of the PPRTV system.

INTRODUCTION

The 1997 HEAST (U.S. EPA, 1997) does not list subchronic or chronic RfD or RfC values for 1,3-dichloropropane (1,3-DCP), noting that data were inadequate for quantitative risk assessment, or any cancer assessment for the chemical. A Health and Environmental Effects Profile (HEEP) for Dichloropropanes (U.S. EPA, 1985), which was listed in the HEAST as a reference for subchronic and chronic toxicity, reported no pertinent data regarding the subchronic or chronic toxicity or carcinogenicity of the chemical. 1,3-DCP is not listed on IRIS (U.S. EPA, 2002), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2000). No

relevant documents, other than the previously mentioned HEEP, were located in the CARA list (U.S. EPA, 1991, 1994). ACGIH (2002), NIOSH (2002), and OSHA (2002a,b) have not assessed the toxicity of 1,3-DCP. Neither ATSDR (2002), IARC (2002), nor the WHO (2002) have written a toxicological review document on 1,3-DCP. 1,3-DCP is not included in the NTP Management Status Report (2002). Literature searches were conducted from 1985 thru 2001 for studies relevant to the derivation of provisional toxicity values for 1,3-DCP. Databases searched included: TOXLINE, MEDLINE, CANCERLIT, TSCATS, RTECS, CCRIS, DART, EMIC/EMICBACK, HSDB and GENETOX.

REVIEW OF PERTINENT DATA

Human Studies

No studies were located regarding the subchronic or chronic toxicity or carcinogenicity of 1,3-DCP in humans.

Animal Studies

A single study investigated subchronic oral toxicity of 1,3-DCP in the rat (Terrill et al., 1991). 1,3-DCP dissolved in corn oil was administered by oral gavage at doses of 0 (corn oil vehicle only), 200, 600 or 1800 mg/kg-day, 7 days/week, for 14 days and, based on results of the 14-day study, at 50, 200 or 800 mg/kg-day, 7 days/week, for 90 days to male and female Sprague-Dawley-derived rats (10/sex/group). Signs of toxicity, body weight, and food consumption were monitored. Ophthalmoscopic examinations (90-day study only) and hematological and clinical chemistry determinations were performed on all animals at termination. All animals underwent gross necropsy. Histopathological examinations were performed on the liver and kidney of all animals, and on a comprehensive collection of tissues, including stomach, from all mid- and high-dose animals and from 5 control animals per sex.

In the 14-day range-finding study, all high-dose, but no animals in other treatment groups, died within the first week (Terrill et al., 1991). Clinical signs in the high-dose group included languid behavior, salivation and tremors after dosing. No clinical signs were reported for the other treatment groups. Because of the early deaths of high-dose animals, no comparisons for body weight, food consumption, hematology, clinical chemistry, organ weights or histopathology were made between the high-dose and control animals. For mid-dose and low-dose animals, no treatment-related differences were apparent in body weight, food consumption or hematological data. Organ weight, clinical chemistry and urinalysis data point toward the liver and kidney as target organs of 1,3-DCP toxicity. The most notable findings were statistically significant increases in absolute and relative liver weights ($\geq$21%) in mid-dose males and females and absolute and relative kidney weights ($\geq$11%) in mid-dose males. Other potentially relevant

findings were small, statistically significant decreases in urine pH in low- and mid-dose males and mid-dose females, and small, statistically significant increases in serum albumin (mid-dose group) and total protein (low- and mid-dose groups) in females. No gross or microscopic lesions attributable to treatment were found in either males or females.

In the 90-day study, no treatment-related deaths occurred (Terrill et al., 1991). The only clinical observation was urine-stained fur in high-dose females. Food consumption was comparable in treated and control animals. Body weight data were unremarkable in treated females and low- and mid-dose males. In high-dose males, however, body weight was progressively reduced throughout the study, with the deficit from controls reaching a statistically significant 17% at termination. Ophthalmoscopic and hematologic evaluations did not reveal any treatment-related effects. Clinical chemistry changes of note included significant increases in alkaline phosphatase (high-dose males and females) and slight, but statistically significant, increases in alanine aminotransferase and bilirubin (high-dose males), albumin (mid- and high-dose males and mid-dose females) and protein (mid-dose females). Urine pH was significantly decreased in mid- and high-dose males, but not in females. Absolute and/or relative liver weights were significantly increased in a dose-related fashion in mid- and high-dose males and low-, mid- and high-dose females. Absolute and/or relative kidney weights were significantly increased in high-dose males and in relation to dose in mid- and high-dose females. Other statistically significant organ weight changes, which occurred primarily in high-dose males where they were secondary to significantly reduced body weight, were not considered related to treatment. Postmortem evaluations did not reveal any gross treatment-related lesions.

Microscopic examination revealed minimal-to-slight centrilobular hypertrophy of the liver in mid- (1/10) and high-dose (10/10) males and high-dose (9/10) females, but not in controls or lower-dose animals (Terrill et al., 1991). The lesion was characterized by decreased eosinophilia and cytoplasmic enlargement of hepatocytes surrounding the central vein. Early chronic progressive kidney nephropathy, characterized by multifocal tubular cell regeneration and minimal mononuclear cell infiltration, was found in 0/10, 0/10, 3/10 and 7/10 males and 0/10, 1/10, 0/10 and 3/10 females in the control, low-, mid- and high-dose groups, respectively. In a few cases, tubules were slightly dilated and contained proteinaceous casts. While chronic progressive nephropathy is a common finding in mature Sprague-Dawley rats, the early appearance of this lesion in this study was considered treatment-related by the researchers. No stomach abnormalities were noted, indicating a lack of portal-of-entry adverse effects. This study identifies the liver and kidney as the critical target organs of 1,3-DCP toxicity, based on histopathological lesions and increased weights in both organs, and potentially related urinalysis and serum chemistry changes, including small increases in serum alkaline phosphatase, alanine aminotransferase, bilirubin, albumin and protein, and decreased urine pH. These effects were seen primarily in males and females of the mid- and high-dose groups, and generally increased in severity in relation to dose. The only observations in the low dose group were increased absolute, but not relative, liver weight in females, and minimal nephropathy in 1/10 females. It is

not clear, however, that nephropathy in this individual was related to treatment: 1) none of the 10 females at the next higher dose were affected and no males at the same dose were affected, even though males overall appeared to be more sensitive for this endpoint, and 2) although not present in any controls in this study, this is a spontaneously occurring lesion in aging rats. The increase in absolute liver weight at the low dose appears to have been a treatment-related effect, but was not of sufficient magnitude to increase relative liver weight and was not accompanied by lesions or other evidence of toxicity; therefore, the increase in liver weight at the low dose level is not considered to be adverse. It is concluded that the low dose of 50 mg/kg-day represents a NOAEL, and the mid-dose of 200 mg/kg-day a LOAEL, for hepatic and renal effects in this study.

One other relevant toxicity study was located. In a study to assess the acute toxicity of 1,3-DCP with respect to testicular changes, the chemical was administered by oral gavage in arachis oil vehicle to male albino Wistar rats (10/treated group, 20 in vehicle control group) at dose levels of 0, 100 or 400 mg/kg-day for 14 days (Shell Oil, 1979a). Macro- and microscopic examinations revealed no significant differences between treated and control animals in the testes, epididymides, ductuli efferentes, vasa deferentes or kidneys.

Genotoxicity studies of 1,3-DCP have produced mixed results. 1,3-DCP did not show any mutagenic potential in selected *Escherichia coli* strains or in the Ames assay in *Salmonella typhimurium* frameshift strains TA98, TA1537 and TA1538, or base-pair strain TA100, with or without metabolic activation; in base-pair strain TA1535, 1,3-DCP produced weak positive results only in the presence of S9 (Dean et al., 1985; Granville et al., 2001; Shell, 1979b; Stolzenberg and Hine, 1980). 1,3-DCP was weakly mutagenic without S9 in the *E. coli* prophage-induction assay (Granville et al., 2001). 1,3-DCP was inactive in SOS chromotests with *E. coli* (von der Hude et al., 1988; Mersch-Sundermann et al., 1994), but active in the *Bacillus subtilis* microsome rec-assay with, but not without, S9 (Matsui et al., 1989). 1,3-DCP did not induce mitotic gene conversion in the yeast *Saccharomyces cerevisiae* with or without S9 (Dean et al. 1985), and did not increase mitotic chromosome segregation rates in the fungus *Aspergillus nidulans* (Crebelli et al., 1995). 1,3-DCP produced negative results in an assay for forward mutations in mouse lymphoma cells (Henry et al., 1998). 1,3-DCP did not induce an increase in the frequency of chromosome aberrations in rat liver RL4 cells without S9 (Shell Oil, 1979b), but did induce an increase in sister chromatid exchange in Chinese hamster V79 cells *in vitro* with or without S9 (von der Hude et al., 1987). In isolated human lymphocytes, 1,3-DCP exhibited clastogenic activity in the micronucleus and Comet assays (Tafazoli and Kirsch-Volders, 1996; Tafazoli et al., 1998). 1,3-DCP induced significant increases in micronuclei in selected, but not all, human B lymphoblastoid cell lines; protection was apparently provided by the activities of various cytochrome P450 isoenzymes and/or microsomal epoxide hydrolase (Doherty et al., 1996). *In vivo*, 1,3-DCP was mutagenic in the eye *w*/*w*+ assay in *Drosophila melanogaster* (Rodriguez-Arnaiz, 1998), but was inactive in a sex-linked recessive lethal assay in

D. melanogaster when administered by inhalation for 6 hours at 2400 mg/m^3 or 96 hours at 990 mg/m^3 (Kramers et al., 1991).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 1,3-DICHLOROPROPANE

The subchronic rat study by Terrill et al. (1991) identified the liver and kidney as critical targets for 1,3-DCP. Effects included histopathological lesions (minimal-to-slight centrilobular hypertrophy in the liver, minimal chronic progressive nephropathy in the kidney) and increased weights in both organs, and potentially related urinalysis and serum chemistry changes, including small increases in serum alkaline phosphatase, alanine aminotransferase, bilirubin, albumin and protein, and decreased urine pH. The NOAEL for these effects was 50 mg/kg-day, and the LOAEL was 200 mg/kg-day. Support for these findings comes from the associated 14-day range-finding study, which found similar effects (increased liver and kidney weights, increased serum albumin and protein, and decreased urine pH), primarily at 600 mg/kg-day. Subchronic and chronic p-RfD values for 1,3-DCP can be derived from the subchronic study, as detailed below.

A **subchronic p-RfD of 0.2 mg/kg-day** is derived by applying an uncertainty factor of 300 (10 to extrapolate from rats to humans, 10 to protect sensitive individuals and 3 for database limitations, including lack of reproductive or developmental studies) to the NOAEL of 50 mg/kg-day, as follows:

subchronic p-RfD = NOAEL / UF
= 50 mg/kg-day / 300
= 0.2 mg/kg-day or 2E-1 mg/kg-day

A **chronic p-RfD of 0.02 mg/kg-day** is similarly derived by applying to the NOAEL of 50 mg/kg-day an uncertainty factor of 3000 (10 for use of a subchronic study, 10 to extrapolate from rats to humans, 10 to protect sensitive individuals and 3 for database limitations, including lack of reproductive or developmental studies), as follows:

p-RfD = NOAEL / UF
= 50 mg/kg-day / 3000
= 0.02 mg/kg-day or 2E-2 mg/kg-day

Confidence in the principal study is medium. The study provided sufficient detail of methods and results, examined an adequate array of endpoints (including portal-of-entry tissues), and identified sensitive target organs and critical effect levels. Group sizes, however, were only minimally adequate, limiting the power of the study to detect treatment-related changes. Confidence in the oral database is low. The only supporting data come from the 14-day range-

finding experiment associated with the key study. Chronic, developmental and reproductive studies are lacking. Low-to-medium confidence in the subchronic and chronic p-RfDs results.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 1,3-DICHLOROPROPANE

Subchronic or chronic inhalation p-RfC values for 1,3-DCP cannot be derived because human and animal toxicity data following subchronic or chronic inhalation exposure to 1,3-DCP are lacking.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1,3-DICHLOROPROPANE

There are no human or animal carcinogenicity data for 1,3-DCP. Genotoxicity assays of 1,3-DCP have yielded mixed responses in bacteria, fruit flies and mammalian cells. Under the proposed U.S. EPA (1999) cancer guidelines, the available data are inadequate for an assessment of human carcinogenic potential.

Derivation of quantitative estimates of cancer risk for 1,3-DCP is precluded by the absence of carcinogenicity data for 1,3-DCP.

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