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Provisional Peer Reviewed Toxicity Values for

α-2,6-Trichlorotoluene

(CASRN 2014-83-7)

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

9-23-2005

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR α,2,6-TRICHLOROTOLUENE (CASRN 2014-83-7)

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) lists a subchronic oral RfD of 5E-5 mg/kg-day for α,2,6-trichlorotoluene based on a LOAEL of 0.5 ppm (0.05 mg/kg-day) for mild lesions of the liver, kidney, and thyroid from a 28-day dietary study in Sprague-Dawley rats (Chu et al., 1984). The source document for this assessment was a HEED for Selected Chlorinated Toluenes (U.S. EPA, 1987). IRIS (U.S. EPA, 2005a) does not report an RfD, RfC, or cancer assessment for α,2,6-trichlorotoluene, and this chemical 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 no relevant documents other than the HEED. ATSDR (2003) has not published a Toxicological Profile for α,2,6-trichlorotoluene, and no Environmental Health Criteria Document is available for this chemical (WHO, 2003). ACGIH (2003), NIOSH (2003), and OSHA (2003) have not developed occupational exposure limits for α,2,6-trichlorotoluene. Neither IARC (2003) nor

NTP (2003) have evaluated the carcinogenicity of α,2,6-trichlorotoluene. Literature searches were conducted from 1987 through August, 2003 for studies relevant to the derivation of provisional toxicity values for α,2,6-trichlorotoluene. Databases searched included: TOXLINE (supplemented with BIOSIS and NTIS updates), MEDLINE, CANCERLIT, TSCATS, RTECS, CCRIS, DART/ETICBACK, EMIC/EMICBACK, HSDB, and GENETOX. Additional literature searches from August 2003 through September 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

Studies examining the toxicity or carcinogenicity of α,2,6-trichlorotoluene in humans were not located.

Animal Studies

Chu et al. (1984) fed several isomers of trichlorotoluene, including α,2,6-trichlorotoluene, to Sprague-Dawley rats (10/sex/dose) at dietary concentrations of 0, 0.5, 5, 50, or 500 ppm for 28 days (the chemicals were dissolved in corn oil and then mixed with food). Doses were estimated by the researchers to be 0.048 - 46 mg/kg-day in males and 0.053 - 53 mg/kg-day in females. The study evaluated the toxicity of these chemicals based on general appearance, weekly body weight and food consumption, hematology and serum chemistry, liver enzyme activity, gross tissue pathology, organ weights, and histopathology. No clinical signs of toxicity were observed and all animals survived to the end of exposure. Body weight and food consumption were unaffected. Hematology and clinical chemistry investigations were unremarkable. Male rats fed 500 ppm of α,2,6-trichlorotoluene exhibited increased activities of hepatic microsomal amino-pyridine-N-demethylase as compared to control (62 ±9.2 vs. 47 ±7.2 nmole HCHO/hr-mg protein, respectively). There was no effect on weight of the liver or other major organs.

The researchers observed mild histopathological lesions in the liver, kidney, and thyroid of rats exposed to α,2,6-trichlorotoluene (Chu et al., 1984). Histopathological changes in the liver consisted of mild regular and irregular lobular patterns. Hepatocytes had mild anisokaryosis associated with pyknosis, and occasionally necrotic hepatocytes. Cytoplasmic vacuolization and increased eosinophilia were seen in portal areas of the hepatic lobule. In the kidney, the authors report mild, but significant changes associated with exposure to α,2,6-trichlorotoluene. The renal changes included accumulation of eosinophilic intracytoplasmic inclusions in the epithelium of proximal tubules associated with focal glomerular adhesions and interstitial scarring due to aging. The hepatic and renal effects resulting from exposure to α,2,6-trichlorotoluene were more pronounced than those seen with the other trichlorotoluene isomers tested. Histological

alterations in the thyroid resulting from exposure to α,2,6-trichlorotoluene were mild and consisted of reductions in follicular size and colloid density. The epithelial cells were columnar and thickened, with focal and multifocal angular collapse of follicles. In addition, focal and multifocal papillary proliferations and focal vacuolizations were observed. Although the incidence and severity of lesions was reported to increase with increasing dose, the authors did not specify the incidence of lesions in any tissue by dose. Because the specific doses at which lesions were produced were not identified, NOAEL and LOAEL values could not be identified.

The same group of researchers conducted a developmental toxicity study that was reported only as an abstract (Ruddick et al., 1982). Gravid rats were given 0, 100, 200, or 400 mg/kg-day of α,2,6-trichlorotoluene by gavage on gestation days 6-15. Maternal toxicity was assessed by weight gain, organ weight, hematology, serum chemistry, and histopathology. Litter size, fetal weight, skeletal and visceral examination, and microscopic examinations were used to evaluate developmental toxicity. Treatment with α,2,6-trichlorotoluene resulted in statistically significant reductions in maternal weight gain at 200 and 400 mg/kg-day. Histopathologic lesions in the thyroid, bone marrow, kidney, and liver were observed in exposed dams (doses not specified). Liver lesions were observed in pups (doses not specified), with the most severe effects in the 400 mg/kg-day group. The available abstract provides insufficient information to evaluate the study.

Other Studies

Pertinent data concerning the mutagenicity of α,2,6-trichlorotoluene were not located.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR α,2,6-TRICHLOROTOLUENE

No relevant data were located regarding the toxicity of α,2,6-trichlorotoluene to humans following oral exposure. Animal toxicity studies of α,2,6-trichlorotoluene were limited to a 28-day feeding study (Chu et al., 1984) and a developmental toxicity study (Ruddick et al., 1982), neither of which was presented in sufficient detail to identify critical effect levels or permit independent evaluation. Derivation of subchronic or chronic oral p-RfD values for α,2,6-trichlorotoluene is, therefore, precluded. The subchronic RfD in the HEED (U.S. EPA, 1987) and HEAST (U.S. EPA, 1997) was derived by assuming, without any supporting information, that lesions were found at all dose levels in the Chu et al. (1984) study.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR α,2,6-TRICHLOROTOLUENE

In the absence of subchronic or chronic data on the inhalation toxicity of α,2,6-trichlorotoluene in humans or animals, derivation of provisional subchronic or chronic RfC values is precluded.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR α,2,6-TRICHLOROTOLUENE

Data on the carcinogenicity of α,2,6-trichlorotoluene in humans or animals are not available. No genotoxicity testing results were located. Under the cancer guidelines (U.S. EPA, 2005b) the data provide inadequate information to assess the carcinogenic potential of α,2,6-trichlorotoluene.

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