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Provisional Peer Reviewed Toxicity Values for

Tetrahydrothiophene
(CASRN 110-01-0)

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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
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
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

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR TETRAHYDROTHIOPHENE (CASRN 110-01-0)

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 new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. 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

Computer searches of the following databases were conducted to 2007 to identify studies regarding the oral toxicity of tetrahydrothiophene: TOXLINE, TOXLINE65, RTECS, TSCATS, DART, ETIC and GENETOX. Other sources of information that were consulted include the CARA data base (U.S. EPA, 1991, 1994), IRIS (U.S. EPA, 2007), the HEAST (U.S. EPA, 1997) and the Drinking Water Regulations and Health Advisories list (U.S. EPA, 2006), the updated National Toxicology Program Status Reports (NTP, 2007), the Merck Index (Merck and Company, 1989) and Sax's Dangerous Properties of Industrial Materials (Sax, 1984). No ATSDR Toxicological Profile for this compound was available (2007).

Occupational exposure limits for tetrahydrothiophene were not adopted by ACGIH (2007), OSHA (2007) or NIOSH (2005).

REVIEW OF PERTINENT DATA

Human Studies

No toxicity or epidemiology data in humans were identified.

Animal Studies

Atochem North America, Inc. (1992) reported a skin irritation study in rabbits, in which 0.5 mL of tetrahydrothiophene was applied to an occluded, 1-square-inch area of the skin of six rabbits for 4 hours, produced tissue destruction at the application site (necrosis and eschar formation) in four of the six rabbits within 7 days of exposure. RTECS (1994) listed a mouse inhalation LC50 of 27 g/m^3 from a Czechoslovakian report.

The German Deutsche Forschungsgemeinschaft (DFG, 2005) reported an 8-hour time-weighted-average workplace airborne exposure limit (MAK) of 180 mg/m^3. However, at this writing, the basis for this value was unavailable.

The International Toxicology Estimates of Risk (ITER) database (TERA, 2007) and Vermeire, 1993 noted that unpublished data from a German language report (Glaser, 1990) served as the basis for a Dutch tolerable concentration in air (TCA) of 0.65 mg/m^3 (Vermeire, 1991). Berg, 1997 reported that the Dutch oral tolerable daily intake (TDI) of 0.18 mg/kg-day was based on the TDI for tetrahydrofuran. However, Baars et al. (2001) corrected this by noting that the TDI was based on extrapolation from the inhalation data.

In a 12-week inhalation study, Glaser (1990) identified a 6-hour/day, 5-day/week NOAEL of 3660 mg/m^3 for adrenal effects in rats. Vermeire (1991) adjusted this value for duration of exposure, as follows:

$$3660\ mg/m^3 \times \left(\frac{6\ hr/day}{24\ hr/day}\right) \times \left(\frac{5\ days/wk}{7\ days/wk}\right) = 654\ mg/m^3$$

to determine a point of departure. Uncertainty factors of ten each were applied to account for inter- and intraspecies variability and for the apparent species differences in severity of effects on the central nervous system following inhalation exposure to the primary metabolite sulfolane, for which monkeys were more sensitive than dogs and dogs more sensitive than rodents (Andersen et al., 1977). No attempt to calculate a human effective concentration (HEC) was reported. TERA (2007) reported no other study details, including other dose levels, numbers of animals, specific adrenal effects observed, or frequency of effects.

The European Commission (EC), 2000 compiled toxicology data for tetrahydrothiophene in its IUCLID dataset. Of special interest were two industry reports, apparently in English, from the Pennwalt Corporation (1988a,b). EC (2000) noted that both studies followed good laboratory practices (GLP). However, the dataset also noted that data reported in IUCLID datasets have not undergone evaluation by the EC.

In Pennwalt, 1988a, Sprague-Dawley rats were exposed via inhalation, 6 hours/day, 5 days/week for 90 days, to tetrahydrothiophene, at concentrations of 50, 275, and 1500 ppm. These airborne concentrations are equivalent to exposures at approximately 180, 1000, and 5400 mg/m^3. The NOAEL reported was 180 mg/ m^3 for mild irritation. The EC (2000) reported that no other significant toxic effects were observed.

In Pennwalt 1988b, pregnant Sprague-Dawley rats were exposed 6 hours per day via inhalation to 250, 750, and 2000 ppm tetrahydrothiophene, on days 6 through 15 of gestation. These concentrations were equivalent to approximately 900, 2700, and 7200 mg/ m^3. The NOAEL for unspecified maternal effects was 900 mg/m^3. EC (2000) reported that no teratogenic or embryogenic effects were observed.

Tetrahydrothiophene is structurally similar to tetrahydrofuran (S replaces O in the furan ring), a compound for which there was considerable toxicological information (ACGIH, 2001b). However, there was insufficient information regarding the behavior of tetrahydrothiophene in biological systems to conclude that the toxicity of these compounds may be similar.

DERIVATION OF PROVISIONAL RfDs FOR TETRAHYDROTHIOPHENE

The absence of oral toxicity data precluded derivation of p-RfDs for tetrahydrothiophene.

DERIVATION OF PROVISIONAL RfCs FOR TETRAHYDROTHIOPHENE

EC (2000) reported that Pennwalt, 1988a identified a 90-day inhalation NOAEL of 180 mg/m^3 for irritation in rats and that Pennwalt, 1988b identified a 20-day inhalation NOAEL of 900 mg/m^3 for maternal toxicity. It also reported that Pennwalt, 1988b identified a developmental NOAEL of >900 mg/m^3, although the EC (2000) description implied that no effects were seen in developing pups when dams were exposed to concentrations as high as 7200 mg/m^3. Although EC (2000) reported that both of these Pennwalt studies followed GLP, the original data were not available to the author of this PPRTV document. In addition, the EC (2000) secondary source for these data indicated that the studies had not been peer reviewed and provided few study details. For these reasons, the PPRTV author deemed these data to be insufficient for deriving inhalation toxicity values.

In its ITER database, TERA (2007) reported that unpublished data from Glaser (1990) was used by the Netherland National Institute of Public Health & Environmental Protection (RIVM) to derive an inhalation tolerable concentration in air (TCA) of 0.65 mg/m^3, based on a duration–adjusted NOAEL of 650 mg/m3 for unspecified adrenal effects. Although it seems likely that RIVM peer-reviewed the Glaser (1990) study report before selecting it as the basis for its TCA, we could not verify this because the original RIVM derivation paper (Vermeire, 1991), in Dutch or a translation, was not available to the author of this PPRTV document. Because the Glaser (1990) data were available only in a tertiary source, the PPRTV author deemed these data to be insufficient for deriving inhalation toxicity values.

The authors of this PPRTV report will continue attempts to obtain the Glaser (1990) and Pennwalt (1988a,b) reports. If they become available, derivation of p-RfCs will be reconsidered.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR TETRAHYDROTHIOPHENE

A cancer classification of "*Inadequate Information to Assess Carcinogenic Potential*" was appropriate, since no data pertinent to the possible carcinogenicity of the compound were available.

In the absence of tumor data, derivation of p-OSF or p-IUR values for carcinogenicity was precluded.

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