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Provisional Peer Reviewed Toxicity Values for

Tetramethylcyclohexane
(CASRN 30501-43-0)

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
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 TETRAMETHYLCYCLOHEXANE (CASRN 30501-43-0)

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.

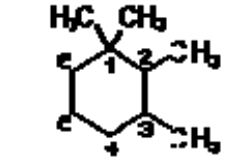
It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the 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

Tetramethylcyclohexane (TMCH) exists in many isomeric forms. One example is shown below:



1,2,3-Tetramethyl-cyclohexane

No chronic or subchronic RfDs, RfCs or cancer assessment for TMCH are available on IRIS (U.S. EPA, 2007), the Drinking Water Standards and Health Advisory list (U.S. EPA, 2006) or in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 1997). No documents for TMCH are included in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA 1991a, 1994). Neither the Agency for Toxic Substances and Disease Registry (ATSDR, 2007) nor the International Agency for Research on Cancer (IARC, 2007) has published documents on the toxicity or carcinogenicity of TMCH. The World Health Organization (WHO) has not published an Environmental Health Criteria Document for TMCH. The National Toxicology Program (NTP, 2007) has not performed toxicity or carcinogenicity assessments for TMCH, nor is TMCH listed on the 11th Report on Carcinogens (NTP, 2005). The Occupational Safety and Health Administration (OSHA, 2007), the National Institute of

Occupational Safety and Health (NIOSH, 2007) and the American Conference of Governmental Industrial Hygienists (ACGIH, 2007) do not list occupational exposure values for TMCH.

To identify toxicological information relevant to the derivation of provisional toxicity values for TMCH, literature searches were conducted on July 1, 2007 using the following databases: MEDLINE (1960s – July 2007), TOXLINE (1960s – July 2007), BIOSIS (1974 – July 2007), DART/ETIC (1960s – July 2007), TSCATS/TSCATS2, CCRIS, GENETOX, HSDB, RTECS and Current Contents (prior 6 months). Except where noted, the literature searches were not limited by date.

REVIEW OF PERTINENT DATA

Human Studies

No studies regarding the acute, subchronic or chronic toxicity of TMCH to humans were located.

Animal Studies

Groups of 15 male and 15 female rats (Sprague-Dawley, age not specified) were fed TMCH (1:1 ratio of *cis*, *trans*-1,1,3,5- and *cis*, *trans*-1,2,3,4- isomers), in standard Purina Rat Chow, at concentrations of 0, 3000, 10,000 or 30,000 ppm, for 90 days (Johannsen and Levinskas, 1987). The authors estimated that these dietary concentrations provided doses of approximately 0, 300, 1000 or 3000 mg/kg-day, respectively. Endpoints assessed in the study included: clinical signs and mortality (daily); body weight (day one and weekly intervals, thereafter); food consumption (5 rats/sex/group, weekly); hematology, serum chemistry and urinalysis (5 rats/sex/group, controls and high-dose only; 45 and 84 days post-treatment-initiation); gross examination, organ weights (brain, gonads, heart, kidneys, liver, spleen) and histopathology at termination (10 rats/sex[1]; brain, adrenals, aorta, ceacum, colon, esophagus, eyes, gonads, heart, kidneys, liver, lungs, lymph nodes, muscle, optic nerve, pancreas, parathyroid, pituitary, prostate, salivary glands, sciatic nerve, small intestine, trachea, thyroid, urinary bladder and uterus; additional kidney sections from 10/sex from the two lower dose groups). Statistical analyses included Dunnett's test for multiple comparisons. Tests yielding p-values less than or equal to 0.05 were considered to be significant.

No effects on survival, clinical signs, body weight, food consumption, hematology, serum chemistry, or urinalysis were found. Organ weight and histopathology changes were observed in male rats, but not females. High-dose males had a statistically significant decrease in absolute liver weight ($p<0.01$, data not shown) that was not accompanied by changes in relative organ weight or histopathology, and was therefore considered not to be treatment-related by the researchers. Other changes in male rats were restricted to the kidneys. A statistically significant increase in absolute kidney weight was observed in all treated male groups, relative to controls

[1] Although not clearly stated in the study report, it appears that histopathological examination was restricted to the control and high-dose groups, with the exception of the kidney, which was examined in males and females of all dose groups.

(Table 1). The differences from control were small (approximately 10%) and did not increase with dose. The ratios of kidney-to-body weight and kidney-to-brain weight were higher than controls in all treated groups, but the difference from controls was statistically significant only at the 3000 mg/kg-day dose for the former and the 1000 mg/kg-day dose for the latter (Table 1). Histopathological evaluation revealed kidney lesions in all TMCH-treated males examined. The primary renal lesion consisted of protein droplets in the cytoplasm of the epithelial cells lining the proximal convoluted tubules in the cortex. These droplets were stained with eosin dye and variable in size. The authors reported further that some sections had changes indicative of regeneration of the tubular epithelium (foci of tubules lined with enlarged basophilic staining cells). The authors also noted that the histopathologic changes observed in the kidneys of male rats were dose-related in terms of severity and degree of parenchymal involvement and considered to be degenerative, but that no signs of necrosis or inflammation were observed.

Table 1. Kidney Effects in Male Rats Exposed to Tetramethylcyclohexane in the Diet for 90 Days[a]

Effect	Dose (mg/kg-day)			
	0 (Control)	300	1000	3000
Absolute Kidney Weight (grams ± SD)	3.56 ± 0.35	3.90 ± 0.35[b]	3.94 ± 0.41[b]	3.89 ± 0.28[b]
Kidney-to-Body Weight	0.717	0.759	0.783	0.797[c]
Kidney-to-Brain Weight	1.689	1.824	1.861[b]	1.822

[a] Source: Johannsen and Levinskas, 1987
[b] $p<0.05$
[c] $p<0.01$

The kidney effects observed in this study are consistent with alpha-2u-globulin nephrotoxicity commonly observed in male albino rats (U.S.EPA, 1991b). Hyaline droplet nephropathy in male rats likely is related to the binding of chemicals to α_{2u}-globulin and the formation of complexes that are resorbed, but not degraded in kidney tubules. Because the α_{2u}-globulin protein is not found in humans, these lesions are unlikely to be predictive of health effects in humans (U.S. EPA, 1991b).

The EPA Risk Assessment Forum Technical Panel Report (U.S. EPA, 1991b), discussed three categories of information and histopathology criteria required for demonstrating that the α_{2u}-globulin process may be a factor in any observed renal effects in male rats. The first criterion is an increase in the number and size of hyaline droplets in the renal proximal tubule cells of treated male rats. Hyaline (protein) droplets were observed in proximal tubule epithelium of male rats from the Johannsen and Levinskas (1987) study. The second criterion is accumulation of α_{2u}-globulin protein in the hyaline droplets, in order to rule out a nonspecific response to protein overload. In a personal communication to Dr. Lisa Ingerman at Syracuse Research Corporation in November 1991, Dr. Johannsen stated that Monsanto dropped the investigation after the subchronic study was completed and that further investigations were not conducted to determine whether the observed lesions were caused by α_{2u}-globulin accumulation. Therefore, the second criterion has not been addressed. The third criterion is the presence of additional aspects of the pathological sequence of lesions associated with α_{2u}-globulin nephropathy (e.g. single-cell necrosis, exfoliation of epithelial cells into the proximal tubular lumen, formation of granular casts, linear mineralization of papillary tubules, and tubule hyperplasia). Additional pathological lesions associated with α_{2u}-globulin nephropathy were

observed in the Johannsen and Levinskas (1987) study (e.g., foci of tubules lined with enlarged basophilic staining cells, suggesting regenerative changes in the tubular epithelium).

In conclusion, two of the three criteria for α_{2u}-globulin nephropathy in male rats were met by the results of the Johannsen and Levinskas (1987) study and the third was not addressed (no data available). Considering that two α_{2u}-globulin nephropathy criteria were met in male rats and that no kidney lesions were observed in female rats or dogs of either sex in subchronic studies (see below), the weight of evidence indicates that the observed kidney effects in male rats reported in Johannsen and Levinskas (1987) likely are associated with male rat-specific α_{2u}-globulin nephropathy which is not relevant to humans. If the kidney effects in male rats are not considered, then the study of Johannsen and Levinskas (1987) identified a free-standing NOAEL of 3000 mg/kg-day in rats. A LOAEL was not identified.

In the dog study, Johannsen and Levinskas (1987) exposed groups of dogs (purebred Beagles; 5 months of age; 4 per sex/group) to mixed isomers of TMCH (1:1 ratio of *cis*, *trans*-1,1,3,5- and *cis*, *trans*-1,2,3,4- isomers; same composition as for rat study) at dietary concentrations of 0, 100, 300 or 1000 ppm for 90 days. The study authors estimated doses of approximately 0, 2.5, 7.5 or 25 mg/kg-day. Food was available initially for 6 hours per day, then continuously as the study ensued (specifics not given). Dogs were examined daily for clinical signs. Other endpoints included: hematology, serum chemistry and urinalysis (study days 0, 42 and 84); gross necropsy; organ weights (adrenals, brain, gonads, heart, kidneys, liver, pituitary, spleen, thyroid); and histopathology (adrenals, aorta, bone marrow, brain, caecum, colon, esophagus, gall bladder, gonads, heart, kidneys, liver, lungs, lymph nodes, muscle, pancreas, pituitary, prostate, salivary glands, sciatic nerve, small intestine, spinal cord, spleen, stomach, trachea, thyroid, uterus and urinary bladder). Statistical analyses included Dunnett's test for multiple comparisons. No treatment-related statistically significant effects were observed for any endpoint. A slight, transient decrease in body weight gain was noted only for male dogs (dose groups not specified) during the first week of the study. "Recovery to normal weight," presumably in comparison with controls, was observed within the following week. On the basis of these findings, 25 mg/kg-day is identified as a NOAEL for dogs in this study.

Johannsen and Levinskas (1987) also reported the results of acute lethality studies with TMCH isomers in rats. These studies were also described by IBT (1974). Groups of "young" male and female rats (five per sex, Sprague-Dawley, Charles River strain) were exposed via gavage to undiluted analytically pure (>99%, verified by gas chromatogram) TMCH isomers (*cis*-1,1,3,5; *trans*-1,1,3,5; 1:1 ratio mixture of *cis*-1,1,3,5 and *trans*-1,1,3,5; *cis, trans*-1,2,3,4; *cis, trans*-1,2,3,5; *cis, trans*-1,2,4,5) at doses of 0, 4556, 6834, 10,250 or 15,800 mg/kg. Due to limited quantities of test material, groups of one rat per sex were treated with the *cis, trans*-1,1,2,3 isomer at the same doses. Rats were housed individually following intubation and were observed for 14 days.

Only three deaths were reported, and all in males. Those occurred within 5 to 15 minutes post-administration of 6834, 10,250 and 15,380 mg/kg of the *cis*-1,1,3,5-TMCH isomer. Convulsions and prostration preceded death (IBT, 1974). The animals that died had chemical burns in the gastrointestinal tract, pale livers and hemorrhagic lungs. Animals in all groups treated with TMCH presented with signs of neurotoxicity and duress following treatment:

hyperactivity, salivation, excessive grooming, muscle incoordination, abnormal stance, hiccups and hypoactivity were noted within one minute of treatment; labored breathing, ruffed fur, muscular weakness, ptosisis, diarrhea, hyperactivity, hemorrhagic rhinitis, and hypoactivity were noted 10 minutes to three hours after treatment and persisted for as much as 2 days. Diuresis was also noted in some, but not all groups; no specific pattern is obvious upon examination of the IBT (1974) data. Based on these results, IBT (1974) reported LD_{50} values of >15,380 mg/kg for each isomer and isomer combination tested.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR TETRAMETHYLCYCLOHEXANE

The database for assessing the potential toxicity of TMCH to humans is incomplete. There are no human data. The animal database consists solely of the acute oral study with rats and 90-day dietary studies with rats and dogs (Johannsen and Levinskas, 1987; IBT, 1974). There are no developmental or reproductive toxicity studies.

Results from the acute oral studies suggest that the *cis*-1,1,3,5 isomer of TMCH may be more toxic than the other isomers tested, given that the only mortalities observed were among three male rats treated with 1,1,3,5-TMCH at concentrations of 6834 mg/kg and higher. However, the reported LD_{50} for all isomers tested, including 1,1,3,5-TMCH, is greater than 15,360 mg/kg (IBT, 1974). Based on these values, all isomers of TMCH are considered "practically non-toxic" (LD_{50} >5000 mg/kg) for acute oral toxicity under the classification scheme used by U.S. EPA's Office of Prevention, Pesticides and Toxic Substances (OPPTS) and the Organization for Economic Cooperation and Development (OECD) (U.S.EPA, 1998). Thus, any differential acute toxicity among the isomers is likely confined to higher doses well beyond those tested normally under currently accepted guidelines (U.S. EPA, 1998) and, therefore, not of practical interest in terms of assessing acute toxicity to humans. The subchronic studies (Johannsen and Levinskas, 1987) used mixed isomers (equal ratio of *cis*, *trans*-1,1,35 and *cis*, *trans*-1,2,3,4-TMCH). Therefore, no conclusions regarding the differential toxicity of TMCH isomers are possible for subchronic toxicity.

In the acute oral studies, there were a number of sublethal effects observed among all treated rats, regardless of dose or isomer tested. These effects included behavioral signs of neurotoxicity, respiratory effects and gastroenteritis. However, some of these effects are likely associated with the stress of receiving an undiluted bolus of pure compound in high concentration. Given that no clinical signs, other than a slight transient weight gain depression in dogs, were seen in the subchronic dietary studies with rats and dogs, it is likely that TMCH is neither neurotoxic nor disruptive of the digestive tract or lungs, following subchronic dietary exposure at lower sub lethal doses.

As discussed previously, the only effects associated with subchronic dietary exposure in rats were effects on the kidneys of treated males. These effects are likely associated with alpha-2u-nephrotoxicity specific to male albino rats and not relevant to human health risk assessment (U.S. EPA, 1991b). There were no other treatment-related effects in male rats and no treatment-related effects of any kind in female rats. Other than a transient depression in body weight gain

in TMCH-treated males at the beginning of the study, there were no treatment-related effects on dogs (Johannsen and Levinskas, 1987). The effect levels from these studies are summarized in Table 2.

Table 2. Effect Levels from 90-Day Dietary Toxicity Studies with Tetramethylcyclohexane[a]

Species	Sex	mg/kg-day			Adverse Treatment-Related Effects
		Doses Tested	NOAEL	LOAEL	
Rat	M, F	0, 300, 1000, 3000	3000	ND	None (renal effects in males at ≥300 likely associated with male rat-specific α_{2u}-globulin nephropathy)
Dog	M, F	0, 2.5, 7.5, 25	25	ND	None

[a] Source: Johannsen and Levinskas, 1987
ND = Not Determined

The database for derivation of the subchronic and chronic p-RfD is limited to two freestanding 90-day NOAEL values of 25 mg/kg-day in dogs and 3000 mg/kg-day in rats. Although there remains some uncertainty regarding the relevance of the kidney lesions in male rats to humans (i.e., studies to identify the protein in the observed hyaline droplets were not conducted) and the relative sensitivity of the dog compared to the rat for potential adverse responses, the NOAEL of 3000 mg/kg-day from the rat study is chosen as the basis for the subchronic p-RfD.

The **subchronic p-RfD of 3 mg/kg-day** is calculated by applying a composite uncertainty factor of 1000 to the subchronic rat NOAEL of 3000 mg/kg-day, as follows:

$$\begin{aligned} \text{Subchronic p-RfD} &= \text{NOAEL} \div \text{UF} \\ &= 3000 \text{ mg/kg-day} \div 1000 \\ &= 3 \text{ mg/kg-day} \end{aligned}$$

The composite UF of 1000 was composed of the following:

- A default UF of 10 was applied for interspecies extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between rats and humans.
- A default UF of 10 for intra-species differences was used to account for potentially susceptible individuals in the absence of information on the variability of potential adverse response in humans.
- A full UF of 10 was applied for uncertainty in the database. A LOAEL was not identified in either of the available studies; therefore, it is not clear whether the free-standing NOAELs did represent the true NOAELs in those animal species. There are no reproductive or developmental toxicity studies. In addition, the lack of definitive data on accumulation of α_{2u}-globulin protein in the hyaline droplets further supports the use of a full UF of 10 for the database deficiency.

No **chronic p-RfD** is derived due to an unacceptable level of uncertainty.

Confidence in the critical study (Johannsen and Levinskas, 1987) is medium. The study is reported in a peer-reviewed journal and methods and results are adequately described given the age of the study. The numbers of animals used in the subchronic study were adequate, though somewhat small (15 rats per sex per group; 4 dogs per sex per group) and the range of doses selected is supported by the acute studies. The decision to test mixed isomers also seems adequate based on results of the acute studies, as discussed previously. There is some uncertainty about the actual doses tested in both rats and dogs. Johannsen and Levinskas (1987) only present "approximate" doses (unclear as to how they arrived at these values) and do not present body weight data and measured dietary concentrations from which to calculate actual doses. There is some uncertainty about whether the observed nephrotoxicity in male rats is of the type specific to male albino rats (alpha-2u-globulin nephrotoxicity) or a more general form of nephrotoxicity. Adverse effect levels were not identified in either species. Confidence in the database is low. The only observed effect (kidney effects in male rats) probably is not relevant to humans. No chronic toxicity data are available. In addition, there are no reproductive or developmental toxicity studies, though no untoward effects on sex organs were noted in the 90-day dietary studies. There is some uncertainty regarding gender sensitivity, which is not addressed by the existing data. Although the numbers are small, the three deaths that occurred following high-dose acute exposures to 1,1,3,5-TMCH were all males. Also, the transient depression in body weight gain seen in the dog study (not considered an adverse effect) occurred only in treated males. The kidney effects observed in the rat study affected only the males, although this effect is species-specific. Overall, confidence in the subchronic p-RfD value is low.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR TETRAMETHYLCYCLOHEXANE

No human or animal inhalation studies of TMCH were located, precluding derivation of subchronic or chronic p-RfC values for this chemical.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR TETRAMETHYLCYCLOHEXANE

Weight-of-Evidence Descriptor

Studies evaluating the carcinogenic potential of oral or inhalation exposure to TMCH in humans or animals were not identified in the available literature. No genotoxicity data were located. Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), inadequate information is available to assess the carcinogenic potential of TMCH.

Quantitative Estimates of Carcinogenic Risk

There are no data upon which to base quantitative estimates of cancer risk for TMCH.

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