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# Provisional Peer Reviewed Toxicity Values for

# 2,3,6-Trichlorotoluene

(CASRN 2077-46-5)

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 |

9-22-2005

# PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 2,3,6-TRICHLOROTOLUENE (CASRN 2077-46-5)

## 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 2,3,6-trichlorotoluene based on a LOAEL of 0.5 ppm (0.05 mg/kg-day) for mild lesions of the liver, kidney, and thyroid in 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 2,3,6-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 that includes 2,3,6-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 2,3,6-trichlorotoluene. Neither IARC

(2003) nor NTP (2003) have evaluated the carcinogenicity of 2,3,6-trichlorotoluene. Literature searches were conducted from 1987 through August, 2003 for studies relevant to the derivation of provisional toxicity values for 2,3,6-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 2,3,6-trichlorotoluene in humans were not located.

### Animal Studies

Chu et al. (1984) fed several trichlorotoluene isomers, including 2,3,6-trichlorotoluene, to Sprague-Dawley rats (10/sex/dose) at dietary concentrations of 0, 0.5, 5, 50, or 500 ppm for 28 days (the trichlorotoluene isomers were dissolved in corn oil and then mixed with food to achieve appropriate concentration). 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, except for a slight increase in serum SDH (sorbitol dehydrogenase) in males at 5 ppm (35 ±125 mIU/mL vs. 19 ±4.8 mIU/mL for control). SDH was apparently not increased in the 50 or 500 ppm males (data not included in study report). Significant increases in absolute liver weight were observed in males fed 5 or 500 ppm as compared to control (13.8 ±1.4 g and 14.1 ±1.6 g vs. 11.8 ±2.4 g, respectively), but apparently not males fed 50 ppm (data not included in study report). Relative weights were not reported. Weights of other major organs were not affected.

The researchers observed mild histopathological lesions in the liver, kidney, and thyroid of rats exposed to 2,3,6-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 2,3,6-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. Histological alterations in the thyroid resulting from exposure to 2,3,6-trichlorotoluene included mild 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 2,3,6-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. Histopathologic lesions in the thyroid, bone marrow, kidney, and liver were observed in exposed dams (doses not specified). Fetal weight was reduced in the 400 mg/kg-day pups. 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 genotoxicity of 2,3,6-trichlorotoluene were not located.

## DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 2,3,6-TRICHLOROTOLUENE

No relevant data were located regarding the toxicity of 2,3,6-trichlorotoluene to humans following oral exposure. Animal toxicity studies of 2,3,6-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 RfD values for 2,3,6-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 2,3,6-TRICHLOROTOLUENE

In the absence of subchronic or chronic data on the inhalation toxicity of 2,3,6-trichlorotoluene in humans or animals, derivation of provisional subchronic or chronic RfC values is precluded.

## DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2,3,6-TRICHLOROTOLUENE

Data on the carcinogenicity of 2,3,6-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 2,3,6-trichlorotoluene.

## REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2003. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 2003. Internet HazDat-Toxicological Profile Query. Online. http://www.atsdr.cdc.gov/toxpro2.html

Chu, I., S.Y. Shen, D.C. Villeneuve et al. 1984. Toxicity of trichlorotoluene isomers: a 28-day feeding study in the rat. J. Environ. Sci. Health. B19(2): 183-191.

IARC (International Agency for Research on Cancer). 2003. Search IARC Monographs. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

NIOSH (National Institute for Occupational Safety and Health). 2003. Online NIOSH Pocket Guide to Chemical Hazards. Index by CASRN. Online. http://www.cdc.gov/niosh/npg/npgdcas.html

NTP (National Toxicology Program). 2003. Management Status Report. Online. http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html

OSHA (Occupational Safety and Health Administration). 2003. OSHA Standard 1910.1000 Table Z-1. Part Z, Toxic and Hazardous Substances. Online. http://www.osha-slc.gov/OshStd_data/1910_1000_TABLE_Z-1.html

Ruddick, J.A., D.C. Villeneuve, V.E. Secours and V.E. Valli. 1982. A transplacental and teratological evaluation of three trichlorotoluene congeners in the rat. Teratology. 25(2): 72A-73A. (Cited in U.S. EPA, 1987)

U.S. EPA. 1987. Health and Environmental Effects Document for Selected Chlorinated Toluenes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS PB97-921199.

U.S. EPA. 2002. 2002 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. Summer 2002. EPA 822-R-02-038. Online. http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf

U.S. EPA. 2005a. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris/

U.S. EPA. 2005b. Guidelines for Carcinogen Risk Assessment. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. EPA/630/P-03/001F.

WHO (World Health Organization). 2003. Online catalogs for the Environmental Health Criteria Series. Online. http://www.who.int/dsa/cat97/zehc1.htm