1,2,4,5-Tetrachlorobenzene; CASRN 95-94-3

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR 1,2,4,5-Tetrachlorobenzene

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	01/31/1987
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — 1,2,4,5-Tetrachlorobenzene
CASRN — 95-94-3
Last Revised — 01/31/1987

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Kidney lesions **Rat Oral Subchronic Study** **Chu et al., 1984**	NOAEL: 5.0 ppm of diet or 0.34 mg/kg/day LOAEL: 50 ppm of diet or 3.4 mg/kg/day	1000	1	3E-4 mg/kg/day

*Conversion Factors: Dose conversions were reported by the authors.

I.A.2. Principal and Supporting Studies (Oral RfD)

Chu, I., D.C. Villeneuve, V.E. Valli and V.E. Secours. 1984. Toxicity of 1,2,3,4-, 1,2,3,5- and 1,2,4,5-tetrachlorobenzene in the rat: Results of a 90- day feeding study. Drug Chem. Toxicol. 7: 113-127.

Groups of 15/sex weanling Sprague-Dawley rats were fed diets containing 0, 0.5, 5.0, 50, and 500 ppm of 1,2,4,5-tetrachlorobenzene (TCB) for 13 weeks. The corresponding dose range in mg/kg bw/day was given as 0.034-34. Dose- related increases in the frequency and severity of kidney lesions for male rats were observed at 1,2,4,5-TCB dose levels of 5.0 ppm and greater. The severity of effects was considered significant only at the 50 and 500 ppm levels because of a high incidence of mild kidney lesions in the controls. Liver lesions were observed for female rats at 500 ppm.

A 28-day feeding study of 1,2,4,5-TCB in rats (10/sex/group) showed dose- related effects for liver and kidney pathology at 3.4 and 32 mg/kg bw/day (Chu et al., 1983). Liver lesions were reported as mild to moderately severe, while kidney lesions were judged to be mild. Relative liver weight was significantly increased (20-30%) at 32 mg/kg/day. Hepatic microsomal enzymes were induced 2- to 12-fold at 32 mg/kg/day. Males were more susceptible than females for all criteria. Adverse effects were not observed at two lower doses (0.04 and 0.4 mg/kg/day).

Higher doses (50, 100, and 200 mg/kg/day) were associated with mortality (200 mg/kg/day only), elevated serum cholesterol, increased organ weights, and liver enzyme induction when administered to pregnant rats for 10 days (Ruddick et al., 1981).

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Braun et al. (1978) reported a NOAEL for dogs of 5 mg/kg bw/day for 1,2,4,5- TCB administered in the diet for 2 years. Increased serum alkaline phosphatase activity and increased liver weights were reported at 10 mg/kg bw/day in a separate 144-day dog study referred to in Braun et al. (1978). Both studies were unpublished and were judged inadequate for risk assessment. The 2-year study was designed for other purposes and did not employ adequate controls or timely histopathologic analysis.

A Russian study (Fomenko, 1965) reported impaired liver function and learning response for rats and rabbits dosed orally for 8 months with 1,2,4,5-TCB at 0.005 or 0.05 mg/kg bw/day. A NOAEL of 0.001 mg/kg/day was established. The study was judged unsuitable because of the lack of itemized data and detailed study protocol.

NTP testing is in progress.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Low
RfD — Low

The principal study, although of short duration, is excellent in most respects (dose range, toxicologic criteria, data presentation, range of effects) except for the high incidence of kidney lesions in the control animals and a subsequent uncertainty in interpretation of effects. Thus, the confidence in the study is rated medium. The principal supporting study is of similar high quality, although shorter in duration. Effect levels are mutually supportive. However, the

database lacks a bona fide chronic study and adequate reproductive and teratology bioassays. Thus, the database rates a low confidence. Low confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 10/09/1985, 11/06/1985

Verification Date — 11/06/1985

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for 1,2,4,5-Tetrachlorobenzene conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — 1,2,4,5-Tetrachlorobenzene
CASRN — 95-94-3

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 1,2,4,5-Tetrachlorobenzene
CASRN — 95-94-3

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

VI. Bibliography

Substance Name — 1,2,4,5-Tetrachlorobenzene
CASRN — 95-94-3

VI.A. Oral RfD References

Braun, W.H., L.Y. Sung, D.G. Keyes and R.J. Kociba. 1978. Pharmacokinetic and toxicological evaluation of dogs fed 1,2,4,5-tetrachlorobenzene in the diet for two years. J. Toxicol. Environ. Health. 4: 727-734.

Chu, I., D.C. Villeneuve, V.E. Valli and V.E. Secours. 1984. Toxicity of 1,2,3,4-, 1,2,3,5- and 1,2,4,5-tetrachlorobenzene in the rat: Results of a 90-day feeding study. Drug Chem. Toxicol. 7: 113-127.

Chu, I., D.C. Villeneuve and V.E. Secours. 1984. Comparative toxicity of 1,2,3,4-, 1,2,4,5- and 1,2,3,5-tetrachlorobenzene in the rat: Results of acute and subacute studies. J. Toxicol. Environ. Health. 11: 663-677.

Fomenko, V.N. 1965. Determination of the maximum permissible concentratin of tetrachlorobenzene in water basins. Gig. Sanit. 30: 8-15.

Ruddick, J.A., D.C. Villeneuve, I. Chu, S. Kacew and V.E. Valli. 1981. Transplacental and teratological evaluation of tetrachlorobenzene isomers in the rat. Teratology. 23: 59A.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — 1,2,4,5-Tetrachlorobenzene
CASRN — 95-94-3

Date	Section	Description
12/03/2002	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — 1,2,4,5-Tetrachlorobenzene
CASRN — 95-94-3
Last Revised — 01/31/1987

- 95-94-3
- BENZENE, 1,2,4,5-TETRACHLORO-
- RCRA WASTE NUMBER U207
- 1,2,4,5-Tetrachlorobenzene
- Tetrachlorobenzene, 1,2,4,5-