2,3,4,6-Tetrachlorophenol; CASRN 58-90-2

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 2,3,4,6-Tetrachlorophenol

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	03/01/1988
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 — Substance Name — 2,3,4,6-Tetrachlorophenol
CASRN — 58-90-2
Last Revised — 03/01/1988

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
Increased liver weights and centrilobular hypertrophy **Rat oral subchronic study** **U.S. EPA, 1986**	NOAEL: 25 mg/kg/day LOAEL: 100 mg/kg/day	1000	1	3E-2 mg/kg/day

*Conversion Factors: none

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

U.S. EPA. 1986. 2,3,4,6-Tetrachlorophenol. 90-Day subchronic oral toxicity study in rats. Office of Solid Waste, Washington, DC.

Sprague-Dawley rats (30/sex/dose) were gavaged daily with 0, 25, 100 or 200 mg/kg/day 2,3,4,6-tetrachlorophenol in olive oil. Body weight gain, food consumption, clinical signs of toxicity and mortality were recorded throughout the study. Clinical pathology was performed on 10 rats/dose/sex both at 44-45 day interim sacrifice interval and after 90 days; gross pathology was performed on all animals sacrificed at interim or final sacrifice and on all animals found dead or sacrificed moribund. Histopathological evaluations were also conducted in animals sacrificed at 90 days as well as in the cases of unscheduled death. Results of this study indicated that at 200 mg/kg/day dose male rats showed progressive depression of body weights 3 weeks after the onset of dosing; these body weight depressions were significantly different from controls during week 4, and weeks 8 through 12. No such difference was observed in females. Liver and kidney weights and relative liver and kidney weights (ratio to body and brain weight) were significantly higher than controls both in males and females at the time of sacrifice. Centrilobular hypertrophy was observed histopathologically in 15 males and 6 females at this

dose (200 mg/kg), compared with none seen in control. Females in the 200 mg/kg group had significantly reduced platelet count (increased alkaline phosphatase levels), and increased BUN levels at 100 and 200 mg/kg; whereas males in the high-dose group had increased SGPT levels and an A/G ratio. Both males and females had significantly reduced Cl levels at 200 mg/kg, and females (200 mg/kg) and males (100 and 200 mg/kg) had increased total protein and albumin levels.

Rats administered 100 mg/kg/day tetrachlorophenol were found to have statistically significant elevations in liver weights (net and relative) in both males and females. In females, both absolute and relative kidney weights were also elevated. Centrilobular hypertrophy in livers was seen (with lower incidence than in the 200 mg/kg dosage group) in 12 males and 1 female. Based on the results discussed above, the 25 mg/kg/day dosage represents the NOAEL and the 100 mg/kg/day is the LOAEL for 2,3,4,6-tetrachlorophenol in this oral subchronic study.

A reproductive study (Schwetz et al., 1974) and a 55-day oral gavage study (Hattula et al., 1981) provided a NOEL of 10 mg/kg/day in rats; however, inadequate study designs (few animals per group) and impurities associated with the commercial grade tetrachlorophenol used in these studies raised some concerns for the validity of the database to derive an RfD. These concerns prompted the Office of Solid Waste to sponsor a 90-day oral study (U.S. EPA, 1986) and a teratology study (Research Triangle Institute, 1986) in rats. Both the studies used purified 2,3,4,6-tetrachlorophenol (99% pure) suspended in olive oil.

In the teratology study, pregnant rats were administered by gavage with 0, 25, 100 or 200 mg/kg/day 2,3,4,6-tetrachlorophenol in olive oil daily on days 6-15 of gestation. Body weight gain, food consumption and clinical signs of toxicity were recorded during the gestation period. Rats were sacrificed on gestation day 20; gross pathology, liver and gravid uterine weight and status of uterine contents were recorded. Fetuses were removed, weighed and examined for malformations.

Results of this study indicated the only statistically significant adverse effect in the high-dose group (200 mg/kg/day): reduced maternal weight gain (corrected to exclude weight of uterine contents) as contrasted with controls. No significant maternal effects were noted at 25 or 100 mg/kg/day dosage group. Embryo-fetal growth and prenatal viability were not adversely affected by tetrachlorophenol exposure, nor was there any definitive evidence of an effect of the compound on fetal morphological development.

Based on data presented above, the 25 mg/kg/day dosage represents the subchronic NOAEL for 2,3,4,6-tetrachlorophenol; by applying an uncertainty factor of 1000 to this NOAEL, an RfD of 0.025 mg/kg/day or 0.03 mg/kg/day can be derived.

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

UF — 1000: 10 interspecies and 10 for intraspecies 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)

Previously an RfD of 0.01 mg/kg/day was verified on 7/8/85 based on a 55-day oral study (Hattula et al., 1981) in which Wistar rats were administered daily with 0, 10, 50 and 100 mg/kg/day 2,3,4,6-tetrachlorophenol by gavage (10 rats/group). This study reported body weight changes and organ histopathology at doses higher than 10 mg/kg; the NOAEL identified in this study was 10 mg/kg/day. This study, however, used commercial grade compound which contains substantial proportion of contaminants such as pentachlorophenol and dioxins. Additionally, this study used few number of animals and the duration of the study was only 55 days.

Schwetz et al. (1974) evaluated potential effects of both commercial grade and purified 2,3,4,6-tetrachlorophenol on embryo-fetal development following gavage dosing of pregnant Sprague-Dawley rats on gestational days 6 through 15. Based upon an earlier range finding study, doses of 10 and 30 mg/kg/day of both grades of tetrachlorophenol were examined in this teratology study. Administration of either grade of the compound resulted in no evidence of maternal toxicity, resorptions, fetal body weight or fetal crown-rump length. The only fetal anomaly that was increased at 30 mg/kg/day was delayed ossification of the skull bones, an effect that was interpreted as a developmental delay, not teratogenicity. The lower dose (10 mg/kg/day) in this study produced subcutaneous edema in exposed fetuses that was considered a chance alone incidence. The subcutaneous edema was not observed in the high-dose group. The issues related to both these studies, discussed above, call into question the validity of the data to derive an RfD.

I.A.5. Confidence in the Oral RfD

Study — High
Database — Medium
RfD — Medium

The critical study is a very well-designed oral study with adequate toxicological endpoints and a higher than average number of animals/sex/dose; therefore, a high confidence was recommended. The database provided adequate supporting subchronic oral studies and reproductive studies; therefore, a medium confidence was recommended. The RfD was

supported by subchronic toxicity and teratology studies; however, until additional chronic toxicity data are available a medium confidence is recommended.

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 — U.S. EPA, 1986

Agency Work Group Review — 07/08/1985, 08/13/1987

Verification Date — 08/13/1987

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 2,3,4,6-Tetrachlorophenol conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to 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 — 2,3,4,6-Tetrachlorophenol
CASRN — 58-90-2

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 2,3,4,6-Tetrachlorophenol
CASRN — 58-90-2

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 — 2,3,4,6-Tetrachlorophenol
CASRN — 58-90-2

VI.A. Oral RfD References

Hattula, M.L., V.M. Wasenius, R. Krees, A.U. Arstila and M. Kihlstrom. 1981. Acute and short-term toxicity of 2,3,4,6-tetrachlorophenol in rats. Bull. Environ. Contam. Toxicol. 26: 795-800.

RTI (Research Triangle Institute). 1986. Teratologic evaluation of 2,3,4,6- tetrachlorophenol (CAS No. 58-90-2) administered to CD rats on gestational days 6 through 15. Chemistry and Life Sciences, RTI, Research Triangle Park, NC.

Schwetz, B.A., P.A. Keeler and P.J. Gehring. 1974. Effect of purified and commercial grade Tetrachlorophenol on rat embryonal and fetal development. Toxicol. and Appl. Pharmacol. 28: 146-150.

U.S. EPA. 1986. 2,3,4,6-Tetrachlorophenol. 90-Day subchronic oral toxicity study in rats. Office of Solid Waste, Washington, DC.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — 2,3,4,6-Tetrachlorophenol
CASRN — 58-90-2

Date	Section	Description
12/23/1987	I.A.	RfD withdrawn pending further review
03/01/1988	I.A.	Revised Oral RfD summary added - RfD changed
12/03/2002	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — 2,3,4,6-Tetrachlorophenol
CASRN — 58-90-2
Last Revised — 01/31/1987

- 58-90-2
- DOWICIDE 6
- PHENOL, 2,3,4,6-TETRACHLORO-
- RCRA WASTE NUMBER U212
- TCP
- 2,3,4,6-Tetrachlorophenol
- 2,4,5,6-TETRACHLOROPHENOL
- Tetrachlorophenol, 2,3,4,6-