2 (2,4,5-Trichlorophenoxy) propionic acid (2,4,5-TP); CASRN 93-72-1

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 2,4,5-TP

File First On-Line 08/22/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/07/1988
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	08/22/1988

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — 2 (2,4,5-Trichlorophenoxy) propionic acid (2,4,5-TP)
CASRN — 93-72-1
Last Revised — 09/07/1988

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
Histopathological changes in the liver **Dog Chronic Oral Bioassay** **Mullison, 1966; Gehring and Betso, 1978**	NOEL: 30 ppm in diet (0.75 mg/kg/day) LOAEL: 100 ppm in diet (2.5 mg/kg/day)	100	1	8E-3 mg/kg/day

*Conversion Factors: 1 ppm = 0.025 mg/kg/day (assumed dog food consumption)

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

Mullison, W.R. 1966. Some toxicological aspects of silvex. In: Proc. 19th Ann. Meet., Southern Weed Conference, Jacksonville, FL. p. 420-435.

Gehring, P.J. and J.E. Betso. 1978. Phenoxy acids: Effects and fate in mammals. In: Chlorinated Phenoxy Acids and Their Dioxins, Vol. 27, C. Ramel, Ed. Ecol. Bull., Stockholm. p. 122-133.

Groups of four male and four female dogs received Kurosal SL at doses of 56, 190, or 560 ppm of diet for 2 years. Since this formulation contains the potassium salt of silvex equivalent to approximately 53% of the acid form of silvex, these dietary levels are 30, 101 and 297 ppm of the acid equivalent of silvex. Using standard assumptions, these adjusted dietary levels are equivalent to doses of 0, 0.75, 2.5 and 7.4 mg/kg/day. The parameters monitored in this study included weekly body weight, food consumption, hematology, serum biochemistry and histopathology of target organs. The only observed adverse effects were dose-related histopathological changes in the livers of female dogs receiving the high dose and in males

receiving the mid and high dose. No adverse effects on growth, food consumption, hematological parameters, or other tissues were observed. Thus, 0.8 mg/kg/day was the NOEL. By applying an uncertainty factor of 100 to this NOEL, an RfD of 0.008 mg/kg/day was derived.

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

UF — The UF of 100 includes a factor of 10 each for uncertainty of interspecies conversion and to protect sensitive individuals.

MF — None

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

Mullison (1966) described a 2-year study in which groups of 25 male and 25 female rats were fed diets containing 0, 10, 30, or 100 ppm Kurosal SL. No effects on general appearance, food consumption, hematological parameters, blood chemistry, or gross and microscopic appearance of tissues were observed. Slightly retarded growth and increased relative kidney weights were the only adverse effects observed, and they occurred only at 100 ppm. No adverse effects occurred at 30 ppm or less, equivalent to 2.6 mg/kg/day of the acid form of silvex. This NOAEL is almost the same as the dog LOAEL. Dogs may be especially sensitive to silvex because of their relatively poor capacity for renal excretion of organic acids (Gehring and Betso, 1978).

Silvex appears to be teratogenic and fetotoxic in mice and rats. Limited information was provided by NAS (1977). Cleft palate was observed in the offspring of mice treated orally at 379 mg/kg/day during gestation (Courtney, 1977). Reduced pup weights and incomplete skull ossification occurred in rats at dosages of 50 mg/kg/day or greater, and 25 mg/kg/day was considered to be a NOAEL for fetotoxic effects (NAS, 1977). The CBI (Confidential Business Information) file contained additional information on rats and hamsters supporting the NOAEL and indicated that an RfD protective of chronic toxicity and fetotoxicity would also protect against teratogenicity.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

Confidence in the study is medium because it was well-designed and defined a NOEL in a sensitive species that was lower than chronic NOAELs in other species, but had a limited number of animals. Confidence in the database is medium because of the limited availability of

additional data, including chronic rat, fetotoxicity and teratogenicity studies, to support the NOEL. Therefore, confidence in the RfD is rated medium.

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

Source Document — U.S. EPA, 1985

Extensive peer review and agency-wide review.

Other EPA Documentation — None

Agency Work Group Review — 01/06/1987, 10/15/1987, 01/21/1988

Verification Date — 01/21/1988

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 (2,4,5-Trichlorophenoxy) propionic acid 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 (2,4,5-Trichlorophenoxy) propionic acid (2,4,5-TP)
CASRN — 93-72-1

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 2 (2,4,5-Trichlorophenoxy) propionic acid (2,4,5-TP)
CASRN — 93-72-1
Last Revised — 08/22/1988

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

NOTE: Commercial 2,4,5-TP contains as a contaminant 2,3,7,8-tetrachloro- dibenzo-p-dioxin, a known animal carcinogen.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — D; not classifiable as to human carcinogenicity.

Basis — Human data are not available and the available animal cancer bioassay studies are considered to be inadequate.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Inadequate. There are only two studies of commercial 2,4,5-TP available for review. Innes et al. (1969) reported that tumor incidences were not increased at any site in B6C3F1 or B6AKF1 mice (18/sex/strain) that were treated orally by gavage from 7-28 days of age with 46.4 mg/kg bw/day of 2,4,5-TP in 0.5% gelatin, and subsequently maintained for 76-77 weeks on a diet that contained 121 ppm 2,4,5-TP. If it is assumed that mice consume 13% of their weight in feed each day, the estimated daily TWA dose of 2,4,5-TP is 17.2 mg/kg/day. Elevated incidences of tumors were also not observed at any specific sites in the same strains of mice (18/sex/strain) 18 months after single s.c. injections of 215 mg/kg 2,4,5-TP (in dimethyl sulfoxide) on day 28 of age. Complete necropsies that included gross and histological examination of major organs and tissues were performed on all treated and control animals. Male B6C3F1 mice that were treated orally or by s.c. injection did show a higher incidence of total tumors (8/17 and 7/18 in treated vs. 22/79 and 2/24 in controls, respectively), but this was not apparent in female B6C3F1 or B6AKF1 mice of either sex.

Gehring and Betso (1978) reported that the Dow Chemical Company (unpublished studies) found no increased incidence of tumors in male or female Wistar rats that were fed 2,4,5-TP potassium salt at levels of 0, 0.26, 0.8, 2.6 or 7.9 mg acid equivalent/kg bw/day for 2 years. Thirty animals of each sex were initially treated at each dose level, and 3-5 rats/sex/dose were selected for interim sacrifices at 12 and 18 months, reducing the final total to <20/sex/dose.

These two studies are judged insufficient to assess the carcinogenicity of 2,4,5-TP, due to inadequacies of design; that is, small number of animals, duration of exposure, and no evidence of MTD dosing.

II.A.4. Supporting Data for Carcinogenicity

The mutagenicity of 2,4,5-TP for Salmonella typhimurium was evaluated in one study (spot test) and found to be negative (Anderson et al., 1972). 2,4,5-TP is not metabolized extensively; 93% of the administered oral dose was excreted in urine by rats.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1985

The Drinking Water Criteria Document received Agency and external review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 12/02/1987

Verification Date — 12/02/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for 2 (2,4,5-Trichlorophenoxy) propionic acid 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.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

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).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — 2 (2,4,5-Trichlorophenoxy) propionic acid (2,4,5-TP)
CASRN — 93-72-1

VI.A. Oral RfD References

Courtney, K.D. 1977. Prenatal effects of herbicides: Evaluation by the Prenatal Development Index. Arch. Environ. Contam. Toxicol. 6: 33-46.

Gehring, P.J. and J.E. Betso. 1978. Phenoxy acids: Effects and fate in mammals. In: Chlorinated Phenoxy Acids and Their Dioxins, Vol. 27, C. Ramel, Ed. Ecol. Bull., Stockholm. p. 122-133.

Mullison, W.R. 1966. Some toxicological aspects of silvex. In: Proc. 19th Ann. Meet., Southern Weed Science Society, Raleigh, NC p. 420-435.

NAS (National Academy of Sciences). 1977. Drinking Water and Health, Vol. 1. NAS, Washington, DC.

U.S. EPA. 1985. Drinking Water Criteria Document for 2 (2,4,5- trichlorophenoxy) Propionic Acid (2,4,5-TP). Prepared by the Office of Health and Environmetnal Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. EPA-600/X- 84-183-1.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Anderson, K.J., E.G. Leighty and M.T. Takahashi. 1972. Evaluation of herbicides for possible mutagenic properties. J. Agric. Food Chem. 20(3): 649-656.

Gehring, P.J. and J.E. Betso. 1978. Phenoxy acids: Effects and fate in mammals. In: Chlorinated Phenoxy Acids and Their Dioxins, C. Ramel, Ed. Ecol. Bull. (Stockholm). 27: 122-133.

Innes, J.R.M., B.M. Ulland, M.G. Valerio, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. J. Natl. Cancer Inst. 42(6): 1001-1114.

U.S. EPA. 1985. Drinking Water Criteria Document for 2 (2,4,5- trichlorophenoxy) Propionic Acid (2,4,5-TP). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water. EPA-600/X-84-183-1.

VII. Revision History

Substance Name — 2 (2,4,5-Trichlorophenoxy) propionic acid (2,4,5-TP)
CASRN — 93-72-1

Date	Section	Description
08/22/1988	II.	Carcinogen summary on-line
09/07/1988	I.A.	Oral RfD summary on-line
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — 2 (2,4,5-Trichlorophenoxy) propionic acid (2,4,5-TP)
CASRN — 93-72-1
Last Revised — 08/22/1988

- 2 (2,4,5-Trichlorophenoxy) Propionic Acid
- 93-72-1
- ACIDE 2-(2,4,5-TRICHLORO-PHENOXY) PROPIONIQUE
- ACIDO 2-(2,4,5-TRICLORO-FENOSSI)-PROPIONICO
- ALPHA-(2,4,5-TRICHLOROPHENOXY)PROPIONIC ACID
- PROPANOIC ACID, 2-(2,4,5-TRICHLOROPHENOXY)-

- PROPIONIC ACID, 2-(2,4,5-TRICHLOROPHENOXY)-
- Silvex
- 2,4,5-TP
- 2-(2,4,5-TRICHLOOR-FENOXY)-PROPIONZUUR
- 2,4,5-TRICHLOROPHENOXY-ALPHA-PROPIONIC ACID
- (+/-)-2-(2,4,5-trichlorophenoxy)propanoic acid
- 2-(2,4,5-TRICHLOROPHENOXY)PROPIONIC ACID
- 2,4,5-TRICHLOROPHENOXYPROPIONIC ACID
- Trichlorophenoxy Propionic Acid, 2 (2,4,5-
- 2-(2,4,5-TRICHLOR-PHENOXY)-PROPIONSAEURE