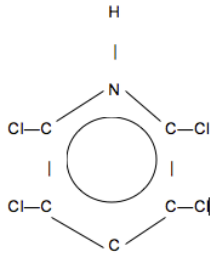
WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

OARS WEEL

1,3,5,6-Tetrachloropyridine (2016)

I. IDENTIFICATIONS

Chemical Name: 2,3,5,6-tetrachloropyridine
Synonyms: Pyridine, 2,3,5,6-tetrachloro-; SymTet
CAS Number: 2402-79-1
Molecular Formula: C_5HCI_4N
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1–3]

Physical State: solid (white crystals)
Odor description and Threshold: camphor-like
Molecular Weight: 216.87
Conversion Factors: 1 mg/m^3 = approx., 0.11 ppm; 1 ppm = approx. 8.9 mg/m^3
Melting Point: 91°C (195.8°F)
Boiling Point: 251°C (483.8°F)
Vapor Pressure: 0.02 mm Hg at 25°C (77°F); 1.0 mm Hg at 74°C (165.2°F); 8.20 mm Hg at 112°C (233.6°F)
Saturated Vapor Concentration: 26.3 ppm (25°C) (77°F)
Flammability Limits: No data available
Flash Point: No data available
Autoignition Temperature: No data available
Specific Gravity: No data available
Solubility: approx. 30 mg/L at 25°C (77°F)
Reactivity: No data available log K_{ow}: 3.32 at 25°C (77°F)

II. USES

2,3,5,6-Tetrachloropyridine is a commercially important derivative that is used in the manufacture of pesticides. In particular, it is an intermediate for the insecticide chlorpyrifos and the herbicide triclopyr.[1] Dow Chemical Company is the sole producer within Organization for Economic Cooperation and Development (OECD) member countries.[3]

IV. ANIMAL TOXICOLOGY DATA

A. Acute Toxicity and Irritancy

1. Lethality Data

Species	Route	LD_{50} or LC_{50}
Mouse (female)	Intraperitoneal	1150 mg/kg[2]
Rat (male)	Oral	1414 mg/kg[4]
Rat (female)	Oral	1182 mg/kg[4]
Rat (male)	Inhalation (7 hr)	>0.056 mg/m^3[6]

2. Eye Irritation

Very slight conjunctival irritation when instilled in the eye of a rabbit, with or without washout.[5]

3. Skin Absorption

No data available.

4. Skin Irritation

Tetrachloropyridine was applied 10 times to intact rabbit skin. The study does not report if the site was occluded, the amount of test material applied, or the frequency of application. Slight redness appeared following the fourth application, which disappeared within a week.[5]

5. Skin Sensitization

No data available.

6. Inhalation Toxicity

LC_{50} (male Spague Dawley, 7 hr) > 0.056 mg/ m^3 (approx. 6300 ppm). No signs of toxicity were observed at this level.[6] The vapors were generated by bubbling air at a rate of 2 ml/min through the test material heated to 100°C (212 °F).

B. Subacute Toxicity

No data available.

C. Subhronic Toxicity

1. Inhalation Toxicity

No data available.

2. Oral Toxicity

2,3,5,6-Tetrachloropyridine was evaluated for subchronic and reproductive toxicity in a screening assay conducted as part of the OECD SIDS program for high production volume chemicals. Groups of 15 adult Sprague-Dawley rats of each sex were dosed by oral gavage with 0, 5, 25, or 150 mg/kg/day for 2 weeks prior to breeding, and throughout gestation and lactation. Dosing of both sexes continued throughout the gestation and lactation period. Parental toxicity included slight to severe renal tubular epithelial cell degeneration and inflammation of the renal papillae in females at 150 mg/kg/day, and protein droplet nephropathy in males at 25 and 150 mg/kg/day. The protein droplet nephropathy observed in male rats was considered to be specific to the male rat and thus of limited relevance for human health risk assessment. The authors set the no observable adverse effect level (NOAEL) for subchronic systemic toxicity at 150 mg/kg/day in males and 25 mg/kg/day in females.[3,7]

Groups of 10 Sherman rats of each sex were fed diets at target doses of 0, 1, 3, 10, 30, or 100 mg 2,3,5,6-terachloropyridine/kg/day for 91 days. Males in the 100 and 30 mg/kg/day groups had increased absolute and relative kidney weights. Histopathological examination revealed dose-related hyaline droplet nephropathy at the 10, 30, and 100 mg/kg/day levels. The protein droplet nephropathy observed in male rats was considered to be specific to the male rat, and thus of limited relevance for human health risk assessment. The absolute and relative weights of livers in the 100 mg/kg/day male rat group were significantly elevated versus the controls; however, there were no histopathological changes noted at any treatment level. Absolute and relative liver and spleen weights in female rats at the 30 and 100 mg/kg/day level were significantly elevated compared to the control group. The authors considered these effects to be treatment-related, although there was no evidence of histopathologic changes in either organ at these treatment levels. There were no kidney weight changes or histopathology evident in females at any dose. The authors set the no observable effect level (NOEL) at 10 mg/kg/day based on relative liver and spleen weight changes in females.[8]

D. Chronic Toxicity/Carcinogenicity

No data available.

E. Reproductive/Developmental Toxicity

2,3,5,6-Tetrachloropyridine was evaluated for reproductive and developmental toxicity in a screening assay conducted as part of the OECD SIDS program for high production volume chemicals. Groups of 15 adult Sprague-Dawley rats of each sex were dosed by oral gavage with 0, 5, 25, or 150 mg/kg/day prior to breeding, during gestation and lactation. No effects attributed to treatment were observed on fertility indices, litter size, neonatal growth or survival, testes or epididymis weights, or gross/histopathologic changes of the ovaries or testes at any dose level. The authors set the NOAEL for reproductive and developmental toxicity at 150 mg/kg/day.[7]

F. Genotoxicity/Mutagenicity

1. In vitro

Tetrachloropyridine was evaluated in the Ames test using a pre-incubation modification of the standard assay. Tester strains TA98, TA100, TA1535, and TA1537 were exposed to concentrations of 0.5-50 µg/plate without S-9 activation and 1.67-166.7 µg/plate with S-9 activation. The test material did not induce a mutagenic response in any of the tester strains and was classified as negative in the Ames assay.[3]

2. In vivo

Tetrachloropyridine was also evaluated in the mouse micronucleus assay. Groups of CD-I mice were dosed once by gavage with 0, 22.5, 75, or 225 mg/kg (males) or 0, 93, 310, or 930 mg/kg (females). Mice treated with 120 mg/kg cyclophosphamide served as positive controls. Five mice/sex were sacrificed 24, 48, and 72 hr after dosing. One thousand polychromatic erythrocytes (PCE) were evaluated from each surviving animal and the frequencies of micronucleated PCE's was determined. There were no significant increases in micronucleated PCE's at any of the tetrachloropyridine dose levels used in the study, and it was judged negative.[3]

G. Metabolism/Pharmacokinetics

No data available.

V. HUMAN USE AND EXPERIENCE

The most probable human exposure to 2,3,5,6-tetra-chloropyridine would be occupational exposure via dermal

contact or inhalation of aerosols.[1] The substance is used solely as an intermediate in the synthesis of pesticides.

VI. RATIONALE

The available acute data for 2,3,5,6-tetrachloropyridine in rats and mice suggest a low order of acute toxicity. The available irritancy data for 2,3,5,6-tetra-chloropyridine suggest that it produces slight eye and skin irritation. It was negative in both *in vitro* and *in vivo* genotoxicity assays. No long-term toxicity data are available via the dermal or inhalation routes. The lowest NOAELs for repeated oral exposure to 2,3,5,6-tetrachloropyridine were 10 mg/kg/day based on increased relative liver and spleen weights in rats and 25 mg/kg/day based on nephrotoxicity in female rats. Given the high boiling point and low vapor pressure for 2,3,5,6-tetrachloropyridine, inhalation exposures are expected to occur only when dust is generated from the solid or when mists are formed from spraying, agitating, or heating solutions of the material. Based on a review of the available toxicological data and the absence of human effects attributable to 2,3,5,6-tetrachloropyridine exposures in industrial use, this material is not believed to present a significant health hazard in the workplace environment. A WEEL Guide of 5 mg/m^3 is considered to provide an acceptable level of worker protection from all known hazards of 2,3,5,6-tetrachloropyridine.

VII. RECOMMENDED WEEL GUIDE

8-hr time-weighted average (TWA): 5 mg/m^3

This WEEL value was originally established in 2000. No significant new literature was identified since 2000 that supports a change to the recommended WEEL value.

VIII. REFERENCES

(1) Hazardous Substance Database (HSBD). *HSDB: 2,3,5,6-Tetrachloropyridine (2402-79-1)*; U.S. National Library of Medicine, National Institutes of Health, Health & Human Services: Bethesda, MD, 2002.

(2) Gehring, P. J.; Torkelson, T. R.; Oyen, F. A Comparison of the Lethality of Chlorinated Pyridines and a Study of the Acute Toxicity of 2-Chloropyridine. *Toxicol. Appl. Pharmacol.* **1967**, *11*, 361–371.

(3) OECD. *OECD SIDS Initial Assessment Profile for 2,3,5,6-Tertachloropyridine.* Organization for Economic Cooperation and Development (OECD), UNEP Publications: Paris, France, 1992.

(4) The Dow Chemical Company. *Initial Submission: Tetrachloropyridine: Acute Oral Toxicity Study in Fischer 344 Rats with Cover Letter Dated 072492. EPA Doc. ID 88-920005644, NATIS/OTS0544427.* U.S. Environmental Protection Agency (EPA): Washington, DC, 1987.

(5) Sexton, A. R.; Hendrick, C. L.; Olson, K. J. *Toxicological Properties and Industrial Handling Hazards of 2,3,5,6-Tetrachloropyridine. T35.12-32358-1*. The Dow Chemical Company: Midland, MI, 1965.

(6) The Dow Chemical Company. *Dow Chemical Company: Acute Inhalation Toxicity Evaluation of 2,3,5,6-Tetrachloropyridine in Rats. HET K-32358-(5).* Midland, MI, 1978.

(7) Zielke, G.; Yano, B.; Breslin, W. 2,3,5,6-Tetrachloropyridine: Combined Repeat Dose and Reproductive/Developmental Toxicity Screen in Sprague-Dawley Rats. 32nd Annual Meeting of the Society of Toxicology Abstract #200. *The Toxicologist* **1993**, *13*, 77.

(8) McCollister, S. B.; Sparaschu, G. L. *Results of a 91-Day Dietary Feeding Studies of 2,3,5,6-Tetrachloropyridine in Rats. BCT35.12-32358-3.* The Dow Chemical Company: Midland, MI, 1969.