I. IDENTIFICATIONS
Chemical Name: 2,3,5,6-tetrachloropyridine
Synonyms: Pyridine, 2,3,5,6-tetrachloro-; SymTet
CAS Number: 2402-79-1
Molecular Formula: C₅HCl₄N
Structural Formula:

II. CHEMICAL AND PHYSICAL PROPERTIES
Physical State: solid (white crystals)
Odor description and Threshold: camphor-like
Molecular Weight: 216.87
Conversion Factors: 1 mg/m³ = approx., 0.11 ppm; 1 ppm = approx. 8.9 mg/m³
Melting Point: 91°C (195.8°F)
Boiling Point: 251°C (483°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 Kow: 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. Dow Chemical Company is the sole producer within Organization for Economic Cooperation and Development (OECD) member countries.

IV. ANIMAL TOXICOLOGY DATA
A. Acute Toxicity and Irritancy
1. Lethality Data

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>LD₅₀ or LC₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse (female)</td>
<td>Intraperitoneal</td>
<td>1150 mg/kg</td>
</tr>
<tr>
<td>Rat (male)</td>
<td>Oral</td>
<td>1414 mg/kg</td>
</tr>
<tr>
<td>Rat (female)</td>
<td>Oral</td>
<td>1182 mg/kg</td>
</tr>
<tr>
<td>Rat (male)</td>
<td>Inhalation (7 hr)</td>
<td>&gt;0.056 mg/m³</td>
</tr>
</tbody>
</table>

2. Eye Irritation
Very slight conjunctival irritation when instilled in the eye of a rabbit, with or without washout.

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. Skin Sensitization
No data available.

6. Inhalation Toxicity
LC₅₀ (male Spague Dawley, 7 hr) > 0.056 mg/ m³ (approx. 6300 ppm). No signs of toxicity were observed at this level. 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-tetrachloropyridine/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 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-1 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-tetrachloropyridine would be occupational exposure via dermal
contact or inhalation of aerosols. 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 \textit{in vitro} and \textit{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 WEEIL 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 WEEIL GUIDE

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

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

VIII. REFERENCES

(1) Hazardous Substance Database (HSBD). \textit{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.


(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. \textit{The Toxicologist} 1993, 13, 77.