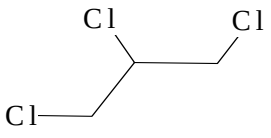
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	96-18-4
Chemical Name	1,2,3-Trichloropropane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

A Concise International Chemical Assessment Document (CICAD) number 56 is available for 1,2,3-trichloropropane (TCP). In addition, an Integrated Risk Information System (IRIS) assessment has been conducted. This case is being evaluated under the OECD HPV Chemicals Programme to ensure that the SIDS required endpoints have been addressed and that robust summaries have been prepared on the relevant studies.

Human Health

The potential human exposure to 1,2,3-trichloropropane is expected to be principally *via* inhalation or ingestion. This compound was rapidly absorbed from the gastrointestinal tract, metabolized and excreted (within 60 hours) via urine (50-65%), faeces (15-20%) and breath as carbon dioxide (20%). Metabolism appears to occur faster in mice than in rats. In rats after oral administration, the major urinary metablites after 6h is a mercapturic acid conjugate (N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine). After 24h a second metabolite, a cysteine conjugate (S-(3-chloro-2-hydroxypropyl)-L-cysteine) was determined. ^{14}C activity was still found in the target organs (liver, kidney and forestomach) 60h after oral administration of [^{14}C] 1,2,3-trichloropropane. After intravenous injection in rats, one major metabolite in the bile was 2-(S-glutathionyl)malonic acid. In mice, the profile of urinary metabolites was more complex than in rats, in that the biotransformation appears to involve both conjugation with glutathione and oxidation.. One proposed pathway in the liver is the mixed-function oxidase-catalysed oxygenation of 1,2,3-trichloropropane on a terminal carbon to yield a chlorohydrin, followed by additional reactions that result in formation of the observed metabolites. A second pathway in the liver may involve the GSH transferase-catalysed formation of GSH conjugates, which either undergo additional biotransformation in the liver or are excreted in bile or plasma. Dermal absorption of 1,2,3-trichloropropane can also occur based on the results of acute dermal toxicity studies; a single prolonged exposure may result in the material being absorbed in harmful amounts.

In acute oral studies rats the LD_{50} range was from 120 to 205 mg/kg bw. Results revealed LD50 values of 205 mg/kg bw (male) and 170 mg/kg bw (female); and 120 mg/kg bw (males) and 188 mg/kg bw (females) the combined LD50 from these studies were 190 and 151 mg/kg bw, respectively. Rabbit dermal LD50 values ranged between 523 and 880 mg/kg (sexes combined). A 4-h inhalation toxicity study with rats at a concentration of 4800 mg/m^3 revealed no deaths and no significant findings at necropsy. However, other 4-h studies with rats and mice revealed an LC_{50} of about 3000 mg/m^3. The primary effects observed were irritation of the eye and nose mucosa along with liver and kidney damage. Due to the volatility of 1,2,3-trichloropropane, excessive vapor concentrations are readily attainable and may cause serious adverse effects, even death. Direct contact of 1,2,3-trichloropropane with the skin causes slight irritation or strong irritation if confined to the skin. In rabbits (24-h occlusive, intact skin) 1,2,3-trichloropropane indicated mild reversible irritation with comparable results also reported for intact and abraded skin of rabbits with a

primary index of 1.63. In contrast, in another study 1,2,3-trichloropropane was severely irritating in rabbits (24h occlusive, intact and abraded skin). In rabbits, two different standard eye irritation tests revealed that the substance was moderately irritating to the eyes of rabbits with slight variation between the two studies. Effects in one study included conjunctival irritation, conjunctival necrosis, clouding of the cornea and iris damage with all effects reversible in 2-7 days. In sensitization tests using guinea pigs, 1,2,3-trichloropropane was determined to be non-sensitizing (two acceptable studies) to very mildly sensitizing (one acceptable study).

Short and longer-term duration repeated dose inhalation studies were conducted in rats and mice. Two 9-day studies were conducted in rats and mice at 0, 80, 240 or 780 and 6, 18 and 61 mg/m^3. The primary effects in rats and mice are microscopic degeneration and inflammatory changes in the nasal olfactory mucosa. Besides nasal exudates at the lowest dose in both species, degeneration of the epithelium was observed in rats and 80 mg/m^3 and mice at 240 mg/m^3. Further nasal exostosis and fibrotic changes were detectable in rats at 780 mg/m^3, whereas mice showed nasal exostosis from 240 mg/m^3. Concentration-dependent adverse effects on nose tissues were more severe in rats than mice. In a 13-week study, male and female rats were exposed to concentrations of 0, 28, 92 and 300 mg/m^3. Body weight decreases were noted in both the mid and high dose females only. In addition, increases in liver weights were observed in males (all dose groups) and females (mid and high dose groups). Signs of respiratory tract irritation were reported at 92 mg/m^3 and higher. Hepatocellular hypertrophy was observed in male rats at all doses. Dose related focal peribronchial lymphoid hyperplasia was found primarily in males whereas splenic extramedullary haematopoiesis was observed only in females at all 1,2,3-trichloropropane concentrations. In a similar 13-week study with doses up to 9.2 mg/m^3 (1.5 ppm) reported effects include signs of irritation of mucous membranes (increase of lacrimal discharge), even at the lowest concentration of 3.1 mg/m^3 (0.5 ppm). At the highest dose an increase in lung and ovary weights was found without corresponding microscopic findings.

Repeated oral doses to laboratory animals by intubation directly into the stomach (called gavage) for up to 120 days, produced adverse effects to the forestomach, liver, kidney, spleen, nasal tissues and blood. More severe effects were found when 1,2,3-trichloropropane was administered by gavage than were observed at comparable doses with continuous exposure *via* the drinking water. The lowest observed effect levels (LOELs) for increased liver weight following 17 weeks of dosing by gavage were 8 mg/kg/day in male rats and 16 mg/kg/day in female rats; the LOELs in mice were 63 and 125 mg/kg/day for males and females, respectively. The LOELs for increased relative liver and kidney weights in the study where 1,2,3-trichloropropane was administered for 90 days to rats *via* the drinking water were higher, 17.6 and 113 mg/kg/day for males and females, respectively.

At a dose of 120 mg/kg/day, 1,2,3-trichloropropane was shown to impair the fertility of female mice in studies where the dose was given by intubation directly into the stomach. The NOAEL for a reduction in fertility was 60 mg/kg/day. 1,2,3-Trichloropropane was negative in studies examining the potential to produce birth defects or fetal death when injected into the peritoneal cavity of pregnant rats at doses up to 37 mg/kg.

Long term gavage administration of 1,2,3-trichloropropane caused cancer in multiple tissues in both rats and mice. In rats, an increased incidence of cancer was found in non-glandular stomach (no analog of this tissue exists in humans) and the oral mucosa in both sexes. Increased incidence of cancer was also found in the mammary gland in female rats, the pancreas and kidney in male rats as well as the preputial gland and clitoral gland in males and females, respectively. In mice, the main targets of carcinogenic action were the non-glandular stomach, the liver and the Harderian gland. Significant increases in tumor incidence were observed at 3 mg/kg/day and 6 mg/kg/day in rats and mice, respectively.

In vitro genotoxicity studies have demonstrated a genotoxic potential for 1,2,3-trichloropropane in the presence of metabolic activation systems. *In vivo*, DNA damage was detectable with the alkaline elution method after intraperitoneal injection of 1,2,3-trichloropropane. The major DNA adduct, *S*-[l-(hydroxymethyl)-2-(*N*7-guanyl)ethyl]glutathione, and other DNA adducts were identified in preneoplastic and neoplastic lesions of target organs.

Environment

1,2,3-Trichloropropane is a clear, colourless liquid with a boiling point of -14.7 °C and melting point of 156-157 °C. At 20 °C the relative density is 1.4 g/cm^3. The vapour pressure of 1,2,3-trichloropropane is 0.492 kPa, while the

water solubility is 1.75 g/l. The log K_{ow}, based on calculated and measured data, ranged between 1.98 and 2.54. In Mackay level I fugacity modeling, the predominant target compartment for 1,2,3-trichloropropane in the environment is air (85%) followed by water (11%). Whereas, level III fugacity modeling results with equal distribution to air, water and soil indicate the primary distribution compartment to be soil (46.7%) followed by water (34.9%), air (18.3%) and sediment (0.122%). 1,2,3-Trichloropropane released into the environment is neither hydrolysed nor readily biodegraded and might therefore remain present for extended periods. However, it can be removed from aquatic systems by evaporation and might be leached from soil into groundwater, which is due to the low soil sorption coefficients reported for this compound. Based on the low octanol/water partition coefficient and the volatility of 1,2,3-trichloropropane it is unlikely to bioaccumulate. The half-life of 1,2,3-trichloropropane in the troposphere was calculated to be 30.5 days based on reaction with hydroxyl radicals.

The acute toxicity of 1,2,3-trichloropropane was tested using a variety of aquatic species from different trophic levels. Standard guideline studies were done with algae (*Selenastrum capricornutum*) and water fleas (*Daphnia magna*) in closed test systems to assure exposure. Based on measured concentrations the EC50 values for biomass and immobility were 50 and 20 mg/l, respectively. A flow-through fish test with fathead minnow (*Pimephales promelas*) revealed an LC50.96h value of 66.5 mg/l based on effective (measured) concentrations. No data were identified on the toxic effects of this substance upon terrestrial invertebrates or higher plants.

Exposure

Based on the available information 1,2,3-trichloropropane is only manufactured as a byproduct of the production of other chlorinated compounds including epichlorohydrin. Less than about 50 000 metric tons of 1,2,3-trichloropropane is produced annually, globally, as a byproduct of epichlorohydrin. There are about 20-30 epichlorohydrin-producing facilities in North America, Europe and Asia.

The majority (>80%) of the 1,2,3-trichloropropane produced as a byproduct of epichlorohydrin is incinerated on-site. 1,2,3-Trichloropropane is used as an intermediate for the synthesis of other chemicals (e.g. pesticides) in closed systems and is used as crosslinking agent in the production of polymers such as polysulfides and hexafluoropropylene. To the best of our knowledge, TCP is no longer marketed for use in consumer product applications.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for human health and the environment. Based on data presented by the Sponsor country, exposure to humans and the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by Sponsor countries.