SIDS INITIAL ASSESSMENT PROFILE

CAS No.	74-87-3
Chemical Name	Chloromethane (Methyl chloride)
Structural Formula	H_3C-Cl

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Chloromethane is a gas, unless it is under pressure. Inhalation is the major route of exposure in the occupational setting. Most inhaled chloromethane is metabolized and rapidly excreted via urine and expired CO_2. Because of high volatility and rapid metabolism, chloromethane does not accumulate in the tissues. The blood clearance is rapid and biphasic. Chloromethane metabolism involves conjugation with reduced glutathione in the ultimate transformation to formate and CO_2.

Chloromethane exhibits low acute toxicity by the oral and inhalation routes. The rat oral LD_{50} is 800 mg/kg bw. Studies illustrate species, strain and sex differences in sensitivity following acute inhalation, such that male mice appear to be most susceptible (6-hour LC_{50} = 4500-4600 mg/m^3), followed by rats (4-hour LC_{50} = 5300-5400 mg/m^3), and then female mice (6-hour LC_{50} = 17,000-17,500 mg/m^3).

In a 90-day inhalation study with rats and mice exposed to 375, 750 and 1500 ppm (750, 1500 and 3000 mg/m^3) the NOAEL and LOAEL were 750 ppm (1500 mg/m^3) and 1500 ppm (3000 mg/m^3), respectively. The LOAEL is based on the observation of significant increases in SGPT activity (male mice) with histological hepatic changes, hepatic infarction (one male mouse and one female rat), increased liver weights, and lower body weights (male and female rats.) In a two-year, inhalation bioassay, rats and mice were exposed to 50, 225 and 1000 ppm (100, 450, 2000 mg/m^3) with interim sacrifices at 6, 12 and 19 months. The NOAEL and LOAEL for systemic effects in rats and mice were 225 ppm (450 mg/m^3) and 1000 ppm (2000 mg/m^3), respectively. In rats, at 1000 ppm (2000 mg/m^3), increased relative heart weights (males and females), relative kidney and liver weights (males), decreased absolute and relative testes weights and decreased absolute liver weights (females) were seen. Histopathology of testes showed bilateral and diffuse generation and atrophy of the seminferous tubules at 6 months and their severity increased until the 18-month sacrifice. Mice were more affected than rats, severe effects were seen at 1000 ppm. Effects at 1000 ppm included: neurofunctional impairment (females); depressed growth, clinical signs suggestive of CNS disturbance, significantly elevated SGPT levels, and increased relative heart weights (males and females); increased relative liver weights (females); decreased absolute brain weights (males and females); and decreased absolute and relative testes weights. In addition, hepatocellular degeneration (males and females); renal tubule epithelial hyperplasia, and cerebellar lesions characterized by degeneration and atrophy of the cerebellar granular cells occurred at 1000 ppm and was treatment related (males). Splenic atrophy and lymphoid depletion were noted at 1000 ppm (males and females). In a 12-day inhalation study in rats (4000, 7000 or 10000 mg/m^3) and mice (1000, 2000 or 4000 mg/m^3), deaths occurred in both rats and mice at the highest concentration tested. Primary effects were CNS related with lesions also occurring in the liver, kidney and brain. Rats were evaluated for testicular degeneration in which a clear exposure-concentration related response was observed. Lesions did not affect all seminiferous tubules equally with the principle affects being a reduction in late-stage spermatids, separation of spermatocytes and early-stage spermatids, with sloughing of the cells into the lumen, formation or irregular, apparently membrane-bound vacuoles in the germinal epithelium and variable formation of the giant cells. In a 93-95 day multi-species inhalation study, CNS, liver, kidney and testes were evaluated in dogs, rats and mice. No specific target organ toxicity or unequivocal toxic manifestations of chloromethane were observed in rats, mice and dogs exposed to concentrations as high as 800 mg/m^3. The NOAEL for the study was determined to be 800 mg/m^3

(the highest dose tested). In an a-typical repeated dose inhalation study, female mice were continuously exposed (22 hrs/day for 11 days) to 15, 50, 100, 150, 200 or 400 ppm (30, 100, 200, 300, 400 or 800 mg/m^3), the NOAEL was determined to be 100 mg/m^3 (50 ppm) and the LOAEL = 200 mg/m^3 (100 ppm) based on the presence of cerebellar lesions. In the same study, female mice were intermittently exposed (5.5 hrs/day for 11days) to 150, 400, 800, 1600 or 2400 ppm (300, 800, 1600, 3200 or 4800 mg/m^3) the NOAEL and LOAELs were 300 mg/m^3 (150 ppm) and 800 mg/m^3 (400 ppm), respectively.

The weight of evidence indicates that chloromethane, at high concentrations, is a direct-acting mutagen in bacteria and human cells in culture (*in vitro*) however, *in vivo* genotoxic effects were not seen due to cytotoxicity occuring at high doses. Existing information indicates that chloromethane exposure does not result in DNA alkylation.

In a 2-year bioassay, there were no statistically significant increases in tumors in rats exposed to 100, 450 or 2000 mg/m^3. A similar exposure in mice caused increased mortality at 2000 mg/m^3, and an increased incidence of kidney tumors in male mice only. Male mice exposed to 450 mg/m^3 had a slightly increased incidence of kidney tumors. Exposure of 100 mg/m^3 did not cause any increases in the tumor incidence in either sex of mice.

In a two-generation reproduction study in rats, repeated 6-hour exposures to 3000 mg/m^3 (1500 ppm) resulted in sterility (decreased spermatogenesis) that is consistent with the testicular degeneration and granulomas seen in the epididymis of male rats after seven weeks. Exposures to 950 mg/m^3 (475 ppm) also caused a decrease in fertility, but no effects were seen in rats exposed daily to 300 mg/m^3 (150 ppm) for two generations. Exposures of 300 mg/m^3 did not cause inflammation of the epididymis and did not effect reproduction in rats. The NOAEL was 300 mg/m^3 for both adults and offspring. Teratological studies have shown possible differences between species. In rats, severe maternal toxicity was seen at 3000 mg/m^3 (1500 ppm), but no teratological response was observed following repeated 6-hour daily exposures to 200, 1000, or 3000 mg/m^3 (100, 500 or 1500 ppm) during gestation. In two studies, an increased incidence of heart malformations in mice were reported at exposures that were not maternally toxic. In both studies, the NOAELs for maternal toxicity were 1000 mg/m^3 (500 ppm.) The NOAELs for developmental toxicity in these studies were 200 mg/m^3 (100 ppm) and 500 mg/m^3 (250 ppm).

In humans, the most common consequence of single or repeated exposures $\geq$ 400 mg/m^3 is functional changes in the CNS, which can involve unsteadiness, dizziness, etc. The liver, kidney, testes, epididymis and lungs can also be affected by these exposures, but most of these effects are secondary, as pronounced CNS changes occur in the presence of these effects being observed.

Environment

Chloromethane has a vapor pressure of 4800 hPa at 20^{o}C, a melting point of -97.7^{0}C, a boiling point of -24.22^{0}C (at 1013 hPa), a log K_{ow} of 0.91 and a water solubility of 4800 to 5325 mg/l at 25^{0}C. Chloromethane's atmospheric residence time is estimated to be about 1 year. The major removal process for chloromethane is reaction with hydroxyl radicals with an estimated half-life of approximately one year. Natural environmental levels are about 700 parts per trillion in ambient air. The stratospheric steady-state ozone depletion potential (ODP) of methyl chloride has been determined to be 0.02 relative to CFC 11 (ODP=1). Hydrolysis of chloromethane in water is relatively slow (does not readily hydrolyze) with a half-life of about 1.1 years at pH 7 and 25^{o}C. Considering its solubility, volatility and resultant Henry's Law Constant, chloromethane is expected, under equilibrium conditions, to exist principally in the air and is not expected to be present in the aquatic or terrestrial compartments. Fugacity (Level III) modeling performed based upon release data to the respective compartments, indicates that about 99.8% of the total, steady state mass of chloromethane will reside in the air compartment and about 0.1% will reside in each of the soil and water compartments. However, when chloromethane is released only to the water compartment it is predicted to remain primarily in that compartment (80% water and 20% air). Chloromethane is not readily biodegradable but may be degraded by adapted bacteria and under anaerobic conditions. The calculated BCF ranges from 2.98 to 3.16.

Based on the chemical's volatility, results based on nominal concentrations may be considered an underestimation of the actual toxicity; however, this may be mitigated by the chemical's high water solubility and dependent upon test conditions. The LC_{50} from the 96-hr fish study using nominal concentrations is 270 mg/L. In daphnia, the 48-hr reported EC_{50} based on nominal concentrations is 200 mg/L. The algal toxicity thresholds of 550 and 1450 mg/L were 7 day tests using nominal concentrations. Due to the possibility that the algae may not have been in the

exponential growth phase throughout the tests, the ECOSAR predicted 96-hour EC_{50} value of 231 mg/L is preferred. In addition, the predicted acute toxicity of chloromethane (ECOSAR; version 0.99g) is in good agreement with the experimental data as indicated above for green algae along with acute toxicity for fish (96-h LC_{50} = 396 mg/L) and daphnia (48-h LC_{50} = 394 mg/L.). In combination with the chemicals environmental fate characteristics, the chemical is considered to be a low concern for the environment.

Exposure

Chloromethane is used almost entirely as a chemical intermediate to make other chloromethanes, silicone intermediates, pesticides, quaternary amines and surfactants, and as a methylation reactant for various other processes. The various uses of chloromethane were estimated at the following percentages in 1987: 74% silicones, 7% agricultural chemicals, 6% methyl cellulose, 5% quaternary amines, 2% butyl rubber, 2% miscellaneous, 4% exports. These estimates do not recognize captive use for other chloromethane production. Most chloromethane is released to the air from non-anthropogenic sources (forest fires and releases from the ocean). The natural levels of chloromethane are about 700 parts per trillion in ambient air. Monitoring near non-industrial anthropogenic sources have shown much higher levels. Chloromethane has been observed at low concentrations (< 222 ng/l) in water. The total global production from sources other than manufacture is estimated at about 4.5×10^9 tonnes. The 1997 global manufactured production of chloromethane was estimated at 1.54×10^6 tonnes. This estimate is based on the assumption that the U.S. produces 35-45% of the total global estimate and the 1997 U.S. production volume of 6.3×10^5 tonnes. Under the US EPA Toxic Release Inventory, 109 U.S. facilities reported in 1998, that approximately 1.2×10^6 kgs were released to air, representing approximately 90% of the total on-and of-site releases of chloromethane. People who smoke or use wood as a heat source are likely exposed to much higher than normal background concentrations of chloromethane. Higher exposures may also occur in or near industrial plants producing or using this chemical. Individuals engaged in chloromethane production may be exposed to concentrations greater than background; however, most U.S. industries have maintained their worker-exposure levels well below the ACGIH guideline of 50-ppm TWA, which was adopted by OSHA in 1989. Chloromethane is not used in any commercial product currently manufactured.

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. 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 a low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.