SIDS INITIAL ASSESSMENT PROFILE

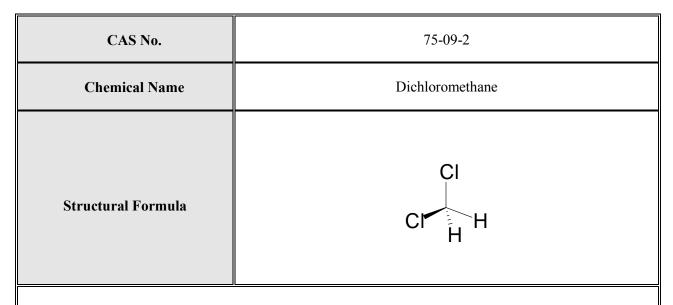| CAS No.	75-09-2
Chemical Name	Dichloromethane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical properties

Dichloromethane (also known as Methylene chloride) is a colourless liquid with a melting point of -95 °C, a boiling point of 40 °C and a measured vapour pressure of 58,400 Pa at 25 °C. The measured octanol-water partition coefficient (log K_{ow}) is 1.25, and the measured water solubility is 13,200 mg/L at 25 °C.

Human Health

Dichloromethane is rapidly and extensively absorbed from the lungs into the systemic circulation (uptake in humans 70-75%) and is well absorbed from the gastrointestinal tract of animals (uptake 97%). Dichloromethane can be absorbed via the skin (absorption rate in mice 6.6 mg/cm^2/h). However, due to its high volatility this route of exposure is of less significance than other routes of exposure under non-occlusive conditions. Dichloromethane is distributed to many organs, including liver, kidney, lungs, brain, muscle and adipose tissue, after respiratory and oral exposure. Dichloromethane is quite rapidly excreted after oral exposure, mostly via the lungs in the exhaled air. It can cross the blood-brain barrier and be transferred across the placenta, and small amounts can be excreted in urine or in milk. At high doses, most of the absorbed dichloromethane is exhaled unchanged. The remainder is metabolized to carbon monoxide, carbon dioxide and inorganic chloride, whereby two routes of oxidative metabolism have been identified, one mediated by cytochrome P450 (predominantly in humans) and the other by glutathione-S-transferase (especially in mice). The oral and 24-hour dermal LD$_{50}$ values were >2,000 mg/kg bw in rats and the inhalatory 7-h LC$_{50}$ value was 49,000 mg/m^3 in mice. Clinical signs included laboured respiration, twitches and/or convulsions and uncoordinated movements, narcosis and paralysis after oral and inhalation exposure. CNS effects were seen in guinea pigs, dogs and rodents at $\geq$ 14,400 mg/m^3. Inhalation exposure of humans showed increased carboxyhaemoglobin levels and decreased tracking performance and a decline in response time in the visual-peripheral component of dual-tasking at 200 ppm (= 695 mg/m^3) for 4 hours.

Based on the available information from animal studies (OECD TG 404), dichloromethane is a skin and eye irritant. Based on human data dichloromethane might be irritating to the respiratory tract at high concentrations.

There is no direct indication that dichloromethane is a sensitizer of any practical significance in humans. The neat liquid gave no evidence of sensitizing potential in a Local Lymph Node (OECD TG 429) assay in mice.

Dichloromethane was found to be mutagenic in bacteria (OECD TG 471), and not mutagenic in mammalian cells *in vitro* (no guideline followed). It was found to be clastogenic *in vitro* (OECD TG 473). In general,

1

dichloromethane tested negative for genotoxicity in standard *in vivo* studies in rats and mice. The increase in chromosomal damage (aberrations and micronuclei) seen in B6C3F1 mice is thought to be related to this strain`s high rate of metabolism of dichloromethane by the glutathione transferase. Overall, the data indicate that dichloromethane is not genotoxic *in vivo*.

In a 2-year combined chronic inhalation toxicity/carcinogenicity study rats were exposed to 0, 174, 695 or 1740 mg/m^3 dichloromethane for 6 hours/day, 5 days/week. The 2-year NOAEC for chronic inhalation toxicity in rats was 695 mg/m^3 based on histopathological changes in the liver. CO-haemoglobin levels were measured in 4-5 rats per sex per group. Increases in CO-haemoglobin levels were seen at all concentrations. These measurements did not show accumulation with time and had no impact on chronic toxicity. Repeated inhalation of high concentrations (≥ 17 g/m^3) showed CNS depression after 3-6 months in a broad range of species including rats and dogs. Liver effects were observed in rodents and dogs whereas changes in renal tubules have only been observed in dogs. From epidemiological studies it can be concluded that no effects on the CNS, cardiac or physiological parameters were attributable to chronic exposure to dichloromethane up to a time-weighted average of 1650 mg/m^3.

In a combined oral chronic toxicity/carcinogenicity study rats were exposed to dichloromethane via drinking water at 0, 5, 50, 125 or 250 mg/kg bw/day during 24 months (actual average male/female doses: 6, 55, 131, 249 and 251 (recovery) mg/kg bw/day, respectively). The 2-year NOAEL for oral toxicity was 6 mg/kg bw/day in rats, based on increased haematological parameters and increased foci/areas of cellular alteration and fatty changes in the liver. A similar 2-year study in mice resulted in a NOAEL of 185 mg/kg bw/day based on histopathological changes in the liver.

In an inhalation carcinogenicity study (OECD TG 451), rats were exposed (whole body) to 0, 3,475, 6,950 or 13,900 mg/m^3 for 6 hours/day, 5 days/week, for 102 weeks. Dichloromethane induced increased incidences of mammary gland neoplasms in both male and female rats at 6,950 mg/m^3 and higher. In addition, there was a marginal increase in the incidence of subcutaneous tissue fibromas in the region of the mammary chain in male rats. Since these fibromas were all found in the axillary and inguinal areas, they probably arose from mammary tissue. Increased incidences of mammary tumours in both sexes were confirmed by another study.

In an inhalation carcinogenicity study (OECD TG 451), B6C3F1 mice were exposed (whole body) to 0, 6,950 or 13,900 mg/m^3 for 6 hours/day, 5 days/week, for 102 weeks. The survival was reduced in all exposed groups. A concentration-related, increased incidence of alveolar/bronchiolar adenomas in both male and female mice was observed compared to the controls. Also concentration-related increases in the incidences of exposed animals bearing multiple lung tumours were noted. No control animal had more than one lung tumour, whereas 38% of all exposed male mice and 42% of all exposed female mice had multiple lung tumours. Lung tumour multiplicity included both alveolar/bronchiolar adenomas and carcinomas. Cytological degeneration of the liver was seen at 13,900 mg/m^3 in males (22/49) and females (21/48) and in females at 6,950 mg/m^3 (23/48). An increased incidence of hepatocellular carcinomas and of adenomas or carcinomas (combined) in males at 13,900 mg/m^3 was observed. In female mice, dichloromethane induced concentration-related increases in the incidences of both hepatocellular adenomas and hepatocellular carcinomas. The incidence of animals with multiple hepatocellular tumours was increased in both males and females in a concentration-related manner. Hepatocellular tumour multiplicity was found in 4% of the male control mice and in none of the female controls, whereas 28% of all exposed males and 32% of all exposed females had multiple liver tumours.

Mechanistic studies have shown that glutathione-S-transferase-mediated metabolism of dichloromethane - producing reactive intermediates that are considered responsible for the liver and lung tumour formation- is expressed to a greater extent in mouse tissues than in rat, hamster or human tissues, explaining the development of liver and lung tumours in mice. Mechanistic studies in rats demonstrating dichloromethane-induced elevation of serum prolactin provide evidence that mammary tumours found in rats are plausibly related to hyperprolactinaemia.

From occupational studies, it was concluded that no strong or consistent finding for any site of cancer was apparent despite several studies of large occupational cohorts of workers potentially exposed to high concentrations of dichloromethane. Sporadic and weak associations were reported for cancers of the pancreas, liver and biliary passages, breast and brain. The results of human studies cannot completely rule out the possibility of carcinogenic effects caused by dichloromethane and there is some evidence from animal studies

2

that it may cause cancer, based either on a metabolism less relevant for humans or by a non-genotoxic, threshold-mediated mode of action.

In a two-generation reproduction toxicity study (OECD TG 416) (1983), male and female rats were exposed whole-body to 0, 350, 1,770 or 5,300 mg/m^3 for 6 hours/day, 5 days/week for 14 weeks up to mating and for 7 days/week during mating, gestation and lactation. Determinations on estrous cycle, sperm parameters, sexual maturation, organ weights and histopathology of reproductive organs as required by OECD TG 416 (2001) were not performed. F1 and F2 offspring showed no effects on viability, clinical signs or body weight, gross pathology or histopathology. The NOAEC for parental toxicity, reproduction toxicity and developmental toxicity was established to be $\geq$ 5,300 mg/m^3. In a developmental study, female rats and mice were exposed to 4,300 mg/m^3 for 7 hours/day on gestation days 6-15. This level was shown to be a LOAEC for maternal toxicity based on increased carboxyhaemoglobin levels and increased absolute liver weights. Only minor visceral and skeletal variations were observed in the foetuses. These variations have not been confirmed in other oral or inhalation studies in rats performed at higher dose or concentration levels. Overall, the available data do not indicate that dichloromethane causes effects on fertility or induces developmental toxicity.

At concentrations below 7,000 mg/m^3 dichloromethane does not induce neurological effects in rats. The NOAEC for immunotoxicity in rats is $\geq$ 17,340mg/m^3.

Dichloromethane possesses properties indicating a hazard for human health (skin and eye irritation, possibly respiratory irritation at high concentrations, liver toxicity, increased CO-Hb levels). There is sufficient evidence that dichloromethane is carcinogenic in experimental animals; however, the relevance to humans may be limited. No clear evidence for carcinogenicity was derived from the available epidemiological studies. Adequate screening-level data are available to characterise the hazard to human health for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

Dichloromethane can be hydrolysed slowly under environmental conditions and the hydrolysis half-life is $\geq$ 1.5 years at 25° C. Photolysis is not likely to be a significant removal process for dichloromethane in water.

Since dichloromethane does not absorb light above 290 nm, it will not degrade by direct photolysis in the troposphere. The most important removal process for dichloromethane from the atmosphere is the reaction with hydroxyl radicals in the troposphere. Dichloromethane is photochemically oxidized by hydroxyl radicals abstracting H atoms. The calculated half life of dichloromethane due to this reaction at 25°C is 107 days using an OH radical concentration of 1.5E06 OH/cm^3 for 12 hrs/day, the corresponding OH-rate constant is 1.0E-13 cm^3 molecule^{-1} s^{-1}.

Dichloromethane is mineralized by various microbial mixed consortia and isolated single bacterial strains both under aerobic and anaerobic conditions. In sewage treatment, biodegradation will not be a significant sink due to the volatility of dichloromethane. Dichloromethane was degraded at a concentration of 3.3 mg/L in the aqueous phase of natural sediment. The corresponding half-life is 10.9 days. No suitable guideline test data on ready biodegradation (OECD TG 301 series) of dichloromethane is available. However, based on results of studies on biodegradation of dichloromethane by pre-adapted mixed cultures and isolated strains of bacteria, dichloromethane is considered to be rapidly biodegraded once the microorganisms are adapted to utilize the substance as a carbon and energy source. Aerobic degradation of dichloromethane was observed in a variety of (sub) surface soils (a sand, a sandy loam, a sandy clay loam and a clay soil). Degradation was also observed in sandy loam soil under anaerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that dichloromethane will distribute to the air (56.5%), water (35.5%) and soil (8%) compartments with negligible distribution to the sediment compartment. If released only to the water compartment, dichloromethane stays mainly in the water compartment (81.5%) and the remaining part will partition to air (18.4%) with negligible amounts in sediments and soil. A measured Henry's law constant of 222 Pa.m^3/mole at 24.8 °C suggests that volatilization from the water phase is expected to be high. A K$_{oc}$ of 46.8 was estimated based on the log K$_{ow}$ and indicates a low potential for accumulation in soil.

The bioaccumulation potential seems to be low based on the low log K$_{ow}$ value of 1.25 and BCF values ranging

from 0.91 to 40 L/kg.

The following acute toxicity test results have been determined for aquatic species:

Taxon	Test species	Endpoint	Result [mg/L]	Comments
Fish, freshwater	*Pimephales promelas*	96h-LC50 96h-LC50 96h-LC50	193 (m) 502 (m) 330 (m)	Flow-through Method ASTM E729-80 -
Fish, marine	*Fundulus heteroclitus*	48h-LC50	97 (m)	-
Invertebrates, freshwater	*Daphnia magna*	48h-LC50	27 (n)	Static
Invertebrates, marine	*Palaemonetes pugio*	48h-LC50	109 (m)	Static, closed system
Aquatic plants	*Chlamydomonas sp.*	3h-EC50	1478-2292 (n)	Flasks closed with cotton wool

m: measured; n: nominal

The following chronic toxicity test results have been determined for aquatic species:

Taxon	Test species	Endpoint	Result [mg/L]
Fish, freshwater	*Pimephales promelas*	28d-NOEC	142 (m, mortality, larval survival), 83 (m, body weight)

m: measured; n: nominal; TT: toxicity threshold

The lowest acute E(L)C50 value has been observed with *Daphnia magna*. However, no chronic toxicity data are available for daphnia. To reduce the uncertainty of the hazard assessment for the environment, the missing long-term NOEC for *Daphnia magna* was predicted by using three independent QSARs (QSAR Toolbox v.2.2.1.1120 based on mode of action and structural analogs, and ECOSAR 1.0). A 21d-NOEC for daphnids between 6.2 mg/L and 13.3 mg/L was estimated.

The toxicity of dichloromethane to activated sludge was evaluated by a simple respirometric procedure set up on the basis of OECD TG 209. A 40min-EC_{50} value of 2590 mg/L was derived from this study.

No reliable data were available for sediment organisms.

Various studies were performed with *Eisenia fetida* (earthworm) and various higher plants. However, they were either not relevant for the endpoint or the original study could not be found and the available information was not sufficient. Incubation of soil for 2 months with 1-10 mg/kg (dry weight) dichloromethane reduced the activity of ß-glucosidase, ß-acetylglucosaminidase and proteinase during the first 28 days, with recovery after 2 months; no effect was observed at 0.1 mg/kg.

With a photochemical ozone creation potential (POCP) of 0.009, dichloromethane is not a precursor of tropospheric ozone.

Dichloromethane possesses properties indicating a hazard for the environment (acute aquatic toxicity values for invertebrates between 10 and 100 mg/L). Dichloromethane is not readily biodegradable. It is not expected to bioaccumulate. Adequate screening-level data are available to characterize the hazard for the

environment for the purposes of the Cooperative Chemicals Assessment Programme.

Exposure

Dichloromethane is sold with an annual volume of 100,000 tonnes in Europe in 2009. Worldwide production volume was in the range from 764,000 to 814,000 metric tonnes per year from 2005 to 2010. Dichloromethane is produced together with other chloromethanes methyl chloride, chloroform and carbon tetrachloride by the Stauffer process, in which methanol is reacted with hydrogen chloride to form methyl chloride. In a second step, methyl chloride is chlorinated with chlorine to heavier chloromethanes through thermal, catalytic, or photolytic chlorination. Direct chlorination – either thermal or catalytic – of methane is also used.

The major use of dichloromethane is as a solvent in the pharmaceutical and chemical industry for chemical reactions, purification and isolation of intermediates or products. Other uses of dichloromethane include use as feedstock for the production of HCFC 32 (R32), as a blowing agent in foam blowing, for plastics processing, as an extraction solvent in the food industry, in metal cleaning (cold and vapour degreasing), in paint and varnish removers, in aerosol formulations (hairsprays, adhesives, cleaning and degreasing products), in paints, sealants and adhesives, as laboratory chemical, as a heat transfer fluid and for removal of photoresistant coatings in the production of printed circuit boards.

Quantitative data are available on both emissions to air and releases to water from large industrial installations: 6 activities covering 208 facilities in 18 EU Member States (2,682 tonnes released to air in 2008 and 12 tonnes releases to water). In Switzerland (sponsor country), 15 industrial facilities reported annual mean emissions of 25 tonnes to air and 0.19 tonnes to water in the period 2007-2009. The quantity of dichloromethane in the global environment due to contribution from oceans is estimated between 190,000 and 200,000 tonnes per year. Another source of contribution refers to biomass burning with an estimated release of 59,000 tonnes per year.

The Scientific Committee on Occupational Exposure Limits (SCOEL) recommends for dichloromethane an occupational exposure limit (OEL, 8h time-weighted average) of 100 ppm [353 mg/m^3] and a short-term exposure limit (STEL, 15 min) of 200 ppm [706 mg/m^3].

Typical worker exposure estimates for the activities associated with the uses of dichloromethane range between 0.004 and 318 mg/m^3 (long term exposure) and 0.07 and 636 mg/m^3 (short term exposure).

Typical consumer exposure estimates for the activities associated with the uses of dichloromethane have been assessed and the inhalation mean concentration on day of exposure for the consumer uses are between 0.04 and 56 mg/m^3.

Indirect exposure of humans via the environment appears via intake media such as fish, root crops, leaf crops, meat, milk, drinking water and air but exposure concentrations are very low.