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SIDS INITIAL ASSESSMENT PROFILES AGREED IN THE COURSE OF THE OECD COOPERATIVE CHEMICALS ASSESSMENT PROGRAMME IN 2011

Series on Testing & Assessment
No. 242

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SIDS INITIAL ASSESSMENT PROFILES AGREED IN THE COURSE OF THE OECD COOPERATIVE CHEMICALS ASSESSMENT PROGRAMME IN 2011

IOMC
INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
Paris 2017

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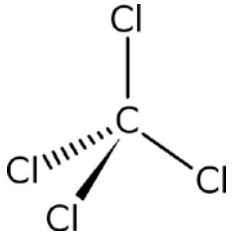
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	56-23-5
Chemical Name	Tetrachloromethane (carbon tetrachloride)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Tetrachloromethane (IUPAC name) is listed in many national and regional databases as well as in regulatory frameworks under its industrial common name carbon tetrachloride. Therefore carbon tetrachloride (CTC) is used in this assessment.

Physical-chemical properties

Carbon tetrachloride (CTC) is a colourless liquid with a melting point of -22.6 °C, a boiling point of 76.8 °C, a relative density of 1.59 at 20 °C and a measured vapour pressure of 12 kPa at 20 °C. The measured octanol-water partition coefficient (log K_{ow}) is 2.83, and the measured water solubility is 846 mg/L at 20 °C.

Human Health

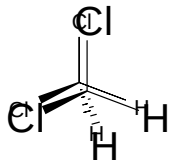
Carbon tetrachloride is rapidly absorbed by all routes of exposure. Oral absorption is estimated to be 85% of which the majority is expired to air. Inhalation absorption is estimated to be 60% from studies in rodents and in monkeys. Carbon tetrachloride diffuses from the blood to the liver, kidney, brain, and other organs and accumulates in adipose tissue. Carbon tetrachloride is mainly metabolised by cytochrome P-450 enzymes, with the production of the trichloromethyl radical, which by aerobic metabolism may eventually form phosgene, which undergoes hydrolytic cleavage to form carbon dioxide. The radical can undergo anaerobic reactions to form chloroform, hexachloroethane or carbon monoxide, or directly bind covalently to lipids, proteins, and DNA. Both haloalkylation and lipid peroxidation by metabolites contribute to the loss of cellular functions and subsequent cell death. Unmetabolised carbon tetrachloride is primarily exhaled in air and excreted in faeces, and relatively minimal amounts are retrieved from urine. No human data on metabolism are available.

Acute data are all based on a weight of evidence approach of studies with limited information. The oral LD_{50} value was 2500 mg/kg bw in rats and the dermal LD_{50} value (for an unspecified duration of exposure) was > 2130 mg/kg bw in guinea pigs. The lowest inhalation (6-h) LC_{50} value was 46260 mg/m^3 in rats. Clinical signs included narcosis and somnolence after inhalation exposure. After acute oral or dermal exposure no clinical signs were reported. Non-lethal toxicity in the form of hepatic injury was evident after inhalation and oral exposure.

Based on the limited information available from animal studies, carbon tetrachloride is slightly irritating to skin and eyes. Neat carbon tetrachloride gave evidence of weak skin sensitization in a Local Lymph Node assay (OECD TG 429) in mice.

In all repeated dose studies liver toxicity was observed. In a 90-day study (OECD TG 413) 10 rats/sex/concentration were exposed by inhalation to 0, 64, 192, 576, 1728 or 5184 mg/m^3 for 6 hours/day, 5 days per week. The lowest level of 64 mg/m^3 was determined to be a LOAEC based on increased liver weight and

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 ≥ 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, 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 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 ≥ 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 ≥ 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 ≥ 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.

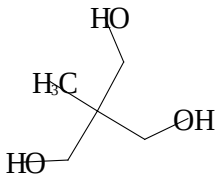
The Scientific Committee on Occupational Exposure Limits (SCOEL) recommends for dichloromethane an occupational exposure limit (OEL, 8h time-weighted average) of 100 ppm [353 mg/m^3] and a short-term exposure limit (STEL, 15 min) of 200 ppm [706 mg/m^3].

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	77-85-0
Chemical Name	1,1,1-TRIS(HYDROXYMETHYL)ETHANE
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical properties

1,1,1-Tris(hydroxymethyl)ethane is a white powder with no odour at standard temperature. Melting point and boiling point are 204 °C and 286.7 °C, respectively. Vapour pressure is 1.82 x 10^{-5} Pa at 25 °C, extrapolated from the experimental value. The measured partition coefficient between octanol and water (log K_{ow}) is -0.95 and the measured water solubility is more than 300 g/L at 20 °C.

Human Health

No specific study on toxicokinetics, metabolism and distribution has been identified. The slight liver toxicity seen in rats given 1000 mg/kg bw/day (in the combined repeated dose and reproductive/developmental toxicity screening test) indicates that 1,1,1-tris-(hydroxymethyl)ethane is absorbed through the gastrointestinal tract to some degree.

In an acute oral study conducted in accordance with OECD TG 401, no deaths or signs of toxicity were observed at 2,000 mg/kg bw in rats. Therefore, the oral LD_{50} value of 1,1,1-tris(hydroxymethyl)ethane was concluded to be > 2,000 mg/kg bw. Data on acute dermal toxicity were not available. The limited information on dermal toxicity in the rat of the structurally similar analogue of tris(hydroxymethyl)propane (CAS 77-99-6, assessed at SIAM 1) suggests that the LD_{50} for 1,1,1-tris(hydroxymethyl)ethane may be greater than 500 mg/kg bw. . Data on inhalation toxicity were not available. The limited information on inhalation studies in rats, mice, rabbits and guinea pigs of the structurally similar analogue tris(hydroxymethyl)propane suggests that the LC_{50} for 1,1,1-tris(hydroxymethyl)ethane is higher than 0.29 mg/L/4h.No reliable studies were available on skin irritation or sensitisation. The limited information on skin irritation in rabbits of the structurally similar analogue of tris(hydroxymethyl)propane suggests that there is no irritation.

There is one reliable study for repeated dose toxicity of 1,1,1-tris(hydroxymethyl)ethane. This study was conducted in accordance with OECD TG 422 except for the limited haematological and clinical chemistry examination in males only. The substance was administered via gavage to 13 rats/sex/dose at 0, 100, 300 or 1,000 mg/kg bw/day for 42 days (starting from 14 days before mating) in males and and for 49 days (the 14-day pre-mating, mating and gestation periods and the days until day 3 of lactation) in females. No treatment-related effects were observed in clinical signs, food consumption, hematology (examined only in males), organ weight and the histopathological appearance of tissues from the major organs including the liver. In clinical chemistry (examined only in males), significant but slight increases in GOT and GPT, reflecting an effect on liver function, and a slight decrease in glucose were observed at 1,000 mg/kg bw/day. Based on no histopathological changes in the liver, these changes in clinical chemistry were not considered to be toxicologically important. A significant but slight decrease in body weight gain was observed in pregnant females at 1,000 mg/kg bw/day. However this change was observed only in the late period of pregnancy. Based on the above findings, the NOAEL was considered to be 1000 mg/kg bw/day in both sexes.

In an Ames test with multiple strains of *Salmonella typhimurium* and *Escherichia coli* [OECD TG 471 and 472], 1,1,1-tris(hydroxymethyl)ethane was negative both with and without metabolic activation. An *in vitro* chromosome aberration test using cultured Chinese hamster lung (CHL/IU) cells [OECD TG 473], 1,1,1-tris(hydroxymethyl)ethane was negative both with and without metabolic activation. Based on these results, 1,1,1-tris(hydroxymethyl)ethane is considered non genotoxic *in vitro*.

No data were available for the carcinogenicity of 1,1,1-tris(hydroxymethyl)ethane.

The reproductive toxicity of the 1,1,1-tris(hydroxymethyl)ethane has been investigated in the above-mentioned combined repeated oral gavage dose toxicity study with the reproductive/developmental toxicity screening test in rats (OECD TG 422). No adverse effects on reproductive parameters (copulation, fertility, gestation and delivery index, etc.) and on reproductive organ (weight or histopathological changes) were observed, and therefore the oral NOAEL for reproductive toxicity was the maximum tested dose of 1,000 mg/kg bw/day. For developmental effects, there were no treatment-related changes in the number of live pups born, viability index on postnatal day 4, body weight on postnatal day 0 and day 4, and number of external anomalies. The NOAEL for developmental toxicity was considered to be 1,000 mg/kg bw/day (the highest dose).

1,1,1-tris(hydroxymethyl)ethane has a low hazard profile for human health. Adequate screening level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

In the atmosphere, 1,1,1-tris(hydroxymethyl)ethane is expected to be degraded by hydroxyl radicals. A calculated half-life time of 0.85 days was obtained by AOPWIN (version 1.92a) for the indirect photo-oxidation by reaction with hydroxyl radicals in air.

1,1,1-Tris(hydroxymethyl)ethane is not hydrolysed due to the lack of hydrolysable functional groups. A hydrolysis test according to OECD TG 111 showed no hydrolysis of 1,1,1-tris(hydroxymethyl)ethane in water at pH 4, 7 and 9 in 50 °C after five days.

An OECD TG 301C test was conducted with 1,1,1-tris(hydroxymethyl)ethane with activated sludge for four weeks. The concentration of the test substance was 100 mg/L and the concentration of the activated sludge was 30 mg/L as suspended solid matters. The test result showed 3-6 % degradation by BOD. According to the result, 1,1,1-tris(hydroxymethyl)ethane is considered to be not readily biodegradable.

No information was available on the bio-concentration on 1,1,1-tris(hydroxymethyl)ethane. Using an octanol-water partition coefficient (log K_{ow}) of -0.95, a bio-concentration factor of 3.2 was calculated with BCFBAF (version 3.00). This chemical is not expected to bioaccumulate.

Fugacity level III calculations show that 1,1,1-tris(hydroxymethyl)ethane is mainly distributed to the soil compartment (61.0 %) and water compartment (38.7 %) if equally and continuously released to the air, soil and water. A Henry's law constant of 1.13×10^{-3} Pa.m^3/mole at 25 °C suggests that 1,1,1-tris(hydroxymethyl)ethane is non volatile from water. A soil adsorption coefficient of Log K_{oc} = -0.4 indicates 1,1,1-tris(hydroxymethyl)ethane has low adsorption to soil and sediment.

The following acute and prolonged toxicity test results have been determined for aquatic species;

Fish [*Oryzias latipes*, OECD TG 203]:	96 h LC_{50} > 100 mg/L (nominal)
Fish [*Oryzias latipes*, OECD TG 204]:	14 d LC_{50} > 99.8 mg/L (nominal)
	14 d NOEC > 99.8 mg/L (nominal)
Daphnid [*Daphnia magna*, OECD TG 202]:	48 h EC_{50} > 1000 mg/L (nominal)
Algae [*Pseudokirchneriella subcapitata*, OECD TG 201]:	
	72 h ErC_{50} > 1000 mg/L (nominal, growth rate)
	72 h EbC_{50} > 1000 mg/L (nominal, area under growth curve)

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

Daphnid [*Daphnia magna*, OECD TG 211]:	21 d NOEC > 88.5 mg/L (measured)
Algae [*Pseudokirchneriella subcapitata* OECD TG 201]:	
	72 h NOErC and 72 h NOEbC > 1000 mg/L (nominal)

1,1,1-tris(hydroxymethyl)ethane does not present a hazard to the environment due to its low hazard

profile. Although this chemical is considered not to be readily biodegradable, it has a low bioaccumulation potential. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Exposure

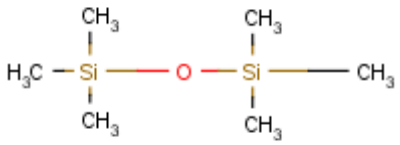
Currently, no production of 1,1,1-tris(hydroxymethyl)ethane is reported in Japan (sponsor country) and import volume in Japan is between 100 and 1,000 tonnes/year. Production and/or import volume of 1,1,1-tris(hydroxymethyl)ethane in the United States was between 1 million and 10 million pounds (454,000 - 4,540,000 tonnes) during 2006 according to the U.S. Inventory Updated Reporting. Worldwide production volume was not available.

1,1,1-Tris(hydroxymethyl)ethane is produced by aldol condensation of propionaldehyde with formaldehyde, followed by reaction of the intermediate 2,2-bis(hydroxymethyl)propanal with excess formaldehyde in the presence of sodium hydroxide or lime as a basic component. 1,1,1-Tris(hydroxymethyl)ethane is used as a conditioning agent, manufacture of varnishes, alkyd and polyester resins, synthetic drying oils. This substance is also used as a coating agent for titanium dioxide pigment. According to the U.S. Inventory Updated Reporting, 1,1,1-tris(hydroxymethyl)ethane is included in consumer products such as paints and coatings.

Occupational inhalation exposure scenarios indicate that this exposure route is of low concern taking into account the very low vapour pressure of this chemical.

As 1,1,1-tris(hydroxymethyl)ethane may be included in consumer products such as paints and coatings, consumer exposure is anticipated. However, no detailed information is obtained for the consumer exposure.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-46-0
Chemical Name	Hexamethyldisiloxane (HMDS)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical properties

Hexamethyldisiloxane (HMDS) is a liquid with a measured melting point of -68.2°C and a measured boiling point of 100.5°C at 1013 hPa. The measured vapor pressure is 44.51 hPa at 20 ºC. The measured water solubility is 0.93 ± 0.63 mg/L at 23 ºC. The measured log K_{ow} of HMDS is 5.20 at 20 ºC. Estimated log K_{oc} values using EPISuite v 4.10 range from 2.5 (MCI method) to 4.5 (Kow method). As Episuite does not contain fragments for siloxanes for log K_{oc} predictions, these values should be treated with caution. The potential for hydrolysis of the test substance may have influenced the determination of partition coefficient and water solubility.

Human Health

The toxicokinetics of HMDS has been investigated; *in vivo* distribution in rats following nose only inhalation and *in vitro* percutaneous absorption in human skin have been evaluated. The primary route of elimination is in expired volatiles. The absorption of HMDS through the human skin is very low (0.023%). The major metabolites of HMDS identified in rat urine were $Me_2Si(OH)_2$; $HOMe_2SiCH_2OH$; $HOCH_2Me_2SiOSiMe_2CH2OH$ (predominant); $HOCH_2Me_2SiOSiMe_3$; $HOMe_2SiOSiMe_3$; Me_3SiOH. The presence of $Me_2Si(OH)_2$ and $HOMe_2SiCH_2OH$ clearly establish some demethylation at the silicon-methyl bonds. Considering the effective removal of HMDS through metabolism and exhalation, accumulation in the body after repeated exposures is unlikely despite its high lipophilicity.

HMDS has been tested for acute toxicity by the inhalation, dermal and oral routes of exposure. The 4-hour LC_{50} of HMDS in rats is 15,956 ppm (106 mg/L; OECD TG 403). The dermal LD_{50} (24 hours) of HMDS ranges from greater than 2000 mg/kg bw in rats to 12,160 mg/kg bw in rabbits (similar to OECD TG 402). The oral LD_{50} of HMDS is greater than 2000 mg/kg bw in rats (similar to OECD TG 401). Undiluted HMDS produced no significant persistent irritation in several skin and eye (similar to OECD TG 405) irritation studies in rabbits. HMDS was not a skin sensitizer in studies in guinea pigs or humans. A positive control was not included in the guinea pig study.

HMDS has been tested for repeated dose toxicity using inhalation, dermal and oral routes of exposure in rats. Test durations ranged from 28-days up to 2 years and measured concentrations provided a range from 0.14 mg/L to 59.2 mg/L (inhalation), 100 to 1000 mg/kg bw/day (dermal) and 10 to 1000 mg/kg bw/day (oral). In a 4 week nose-only vapor inhalation study in rats, test substance-related changes were noted in clinical chemistry and target organs included lung, liver, ovaries, and kidney (male-specific). A NOAEC could not be determined as clinical chemistry and pathologic changes in the lungs occurred at all doses from 0.67 to 67 mg/L; the LOAEC was 0.67 mg/L. In a 13 week whole-body exposure in rats, minor alterations were noted in hematological and clinical chemistry but these were not considered toxicologically relevant; target organs included kidney (male-specific changes) and testes. The NOAEC for male and female rats was reported to be 1.3 mg/L and 33.1 mg/L, respectively. Because the effects observed in male rats were considered to be alpha-2µ-globulin mediated and

therefore not relevant to humans, the NOAEC for systemic toxicity is considered to be 33.1 mg/L. In another study, rats were exposed via nose-only inhalation exposure for 3 months to HMDS vapor (OECD TG 413) and a subset of animals was retained for a one month recovery period. Occult blood was observed in males of the two highest exposure groups and target organs included testes, lung, adrenal gland, vagina and kidney. Based on organ weight and histopathological changes in the lungs and testes, the NOAEC was not achieved in this study; the LOAEC for systemic toxicity was 0.14 mg/L. In a two-year combined chronic toxicity/carcinogenicity whole body vapor inhalation study in rats (OECD TG 453), the target organs were kidney, nasal cavity and testes. Effects in the kidneys were considered to be mediated by an alpha-2u-globulin mediated mechanism which is not relevant to humans. Effects in the nasal cavity were considered to be irritative. The no observed adverse effect level (NOAEL) for a 28-day repeated dose dermal toxicity study in rats (OECD TG 410) was 500 mg/kg bw/day in male rats based on reduced kidney and liver weights; there were no such effects in females. Based on a mechanistic study performed by the oral route to evaluate the alpha-2u-globulin induction, a NOAEL for specific kidney effects was < 10 mg/kg bw/day in male rats and > 1000 mg/kg bw/day in females. In a one-generation reproduction inhalation toxicity study (OECD TG 415), the parental NOAEC was 33.1 mg/L based on increased lung and liver weights. In a two-generation reproduction inhalation toxicity study with rats (OECD TG 416), the NOAEC for parental toxicity was 2.7 mg/L, based on the liver effect (pigment accumulation, chronic inflammation, bile duct hyperplasia).

HMDS did not induce chromosome damage in a rat bone marrow chromosome aberration test *in vivo*. HMDS did not induce gene mutations in bacteria (with and without metabolic activation) *in vitro* and, excepting one assay (a positive response without a dose-response relationship was observed in mouse lymphoma L5178Y cells only in the presence of metabolic activation), was not mutagenic with or without metabolic activation in a variety of *in vitro* mammalian assays. HMDS is not expected to be genotoxic. In the two-year combined chronic toxicity and oncogenicity whole-body inhalation study in Fischer 344 rats, there were no neoplastic effects. The target organs of HMDS were kidney, nasal cavity and testes. Effects in the kidneys were considered species-specific (alpha-2µ globulin-mediated mechanism). Effects on the testes (Leydig cell tumors) were increased following exposure to all concentrations, but they are considered to be spontaneous findings as they are common to Fischer 344 rats and were also observed in control animals. It was thought that HMDS might accelerate progression to this common tumor.

In a one-generation reproduction inhalation toxicity study (OECD TG 415), the NOAEC for maternal and reproductive/developmental toxicity of HMDS in the rat via whole body inhalation exposure was 33.1 mg/L and the paternal NOAEC was 33.1 mg/L based on increased lung and liver weights in parental males. In a two-generation reproduction inhalation toxicity study with rats (OECD TG 416), the NOAEC for parental toxicity was 2.7 mg/L, based on the liver effect (pigment accumulation, chronic inflammation, bile duct hyperplasia). The NOAEC for reproductive toxicity was 33.1 mg/L (the highest concentration tested). The NOAEC for developmental toxicity was 2.7 mg/L due to decreased offspring weights at 10.6 and 33.1 mg/L. In the same study, developmental landmarks (balanopreputial separation and vaginal patency) were evaluated for the selected F1 and F2 rats. The NOAEC for developmental neurobehavioral endpoints was 10.6 mg/L. The NOAEC for neuropathologic endpoints was 33.1 mg/L (the highest concentration tested). There were no gross anomalies in pups. Based on decreased offspring weights, the NOAEC for developmental toxicity was 2.7 mg/L.

Hexamethyldisiloxane may possess properties indicating hazard for human health (based on repeated dose toxicity and developmental toxicity at high concentrations). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Not all programs within EPI Suite have been validated for chemicals that contain the element Si, but recent upgrades to the Kow and water solubility modules, found in the current version of EPI Suite (v4.10), may improve estimates for silanes and siloxanes. However, there is still uncertainty associated with the calculated values and they should be used with caution whenever they are reported, specifically, the Koc estimate.

HMDS is hydrolytically unstable over a range of environmentally relevant pH and temperature conditions (OECD TG 111), and results in the production of trimethylsilanol. The silanols condense to siloxane oligomers under certain conditions; this condensation of silanols is affected by both concentration and pH, and since both change over time it is not feasible to isolate specific silanols for analysis other than trimethylsilanol (the structures continue to evolve until they either reach equilibrium or precipitate out of solution). At environmentally relevant concentrations, condensation is not expected to occur. Basic pH accelerates condensation of silanols. The hydrolysis half-lives were 1.5, 120 and 12 h at pH 5, 7 and 9 and at 25 °C, respectively. HMDS in air undergoes indirect photolysis through hydroxyl radical oxidation. The dominant photochemical loss process of HMDS in the atmosphere is by gas-phase reaction with OH radicals. By use of a

tropospheric OH radicals concentration of 7.7 x 10^5 molecule/cm^3 over a 24h period, a half-life of 7.5 days is calculated. The O_3 reactions are of negligible importance as a tropospheric removal process for HMDS, and that the NO_3 radical reactions are, at most, of minor significance. Level III Fugacity modeling, using equal releases to air, soil, and water (loading rates of 1000 kg/hour to each medium), shows the following percent distribution of HMDS: air = 48.5%, soil = 0.62%, water = 50.1%, and sediment = 0.72%. The log Koc used for the modeling is 2.5 (KOCWIN MCI method). There is a range of estimated and measured Koc values and this uncertainty in the selected Koc may affect the results of the distribution modeling. In addition, the expected hydrolysis rate of HMDS in natural waters could be reduced due to absorption to sediments. However, due to the range and uncertainty of Koc estimates the significance of this effect of absorption for HMDS is not known. The estimated Henry's Law constant of 5.1x10^5 Pa m^3/mole at 20°C, suggests that volatilization from the water phase for HMDS is expected to be high. In two studies, HMDS achieved a breakdown rate of 0-4% and 0-2% after 28 days, indicating that it is is not readily biodegradable. In one biodegradation study, 20% of the parent substance was converted into trimethylsilanol, which is expected to reflect hydrolysis of HMDS rather than biodegradation. HMDS has a measured BCF in carp of approximately 776-1660 for exposure at 0.004 mg/L for 10 weeks and a BCF of 1290-2410 was calculated for exposure at 0.040 mg/L for 8 weeks (OECD TG 305C). These studies indicate that HMDS has the potential to bioaccumulate.

Due to the hydrolysis of HMDS, the aquatic organisms are likely exposed to a mixture of the parent and its hydrolysis products. The following acute toxicity test results with HMDS have been determined for aquatic species:

Fish [*Oncorhynchus mykiss*]	96-h LC_{50}= 0.46 mg/L (flow-through; measured)
[*Pimephales promelas*]	14-d LC_{50} >0.093 mg/L (flow-through; not specified)
Algae [*Pseudokirchneriella subcapitata*]	70-h E_rC_{50} >0.55 mg/L (measured), NOEC = 0.10 mg/L (nominal)
Algae [*Pseudokirchneriella subcapitata*]	95-h E_rC_{50},> 0.55 mg/L (measured); 95-h NOEC growth rate = 0.15 mg/L (measured) 95- E_bC_{50} = 0.22 mg/L (measured); 95- LOEC growth rate = 0.28 mg/L (measured)

Where: E_bC_{50} = EC_{50} based on biomass; E_rC_{50} = EC_{50} based on growth rate

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

Invertebrate [*Daphnia magna*]	21-d EC_{50} = 0.45 mg/L (semi-static; measured) NOEC = 0.25 mg/L (mortality) NOEC = 0.08 mg/L (reproduction) LOEC = 0.14 mg/L (reproduction) NOEC = 0.25 mg/L (condition) LOEC = 0.44 mg/L (condition)

Hexamethyldisiloxane possesses properties indicating a hazard for the environment (acute and chronic aquatic toxicity values below 1 mg/L). HMDS is not readily biodegradable and has the potential to bioaccumulate. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

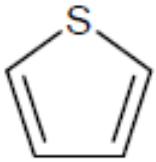
Exposure

The 2010 production and import volumes in the United States (sponsor country) were 9072 tonnes and 454 to 4536 tonnes, respectively. The 2010 production and import volumes in Europe were 8210 tonnes and 45 to 454 tonnes, respectively. The 2010 production and import volumes in Japan were 227 to 680 tonnes and 227 to 680 tonnes, respectively. HMDS is used as a chemical intermediate in the production of monomers and polymers, and also in personal care applications (cosmetics), in insulating materials, and as part of construction material additives.

In production, this material is handled in closed systems. Necessary engineering controls during production include local ventilation. HMDS is stored on site in large outside storage tanks connected by piping to the manufacturing facility. Worker exposure may occur via inhalation or dermal exposure which can be mitigated through the use of personal protective equipment (PPE), particularly during drum transfers.

Consumer exposure can occur through the use of HMDS in personal care products; concentrations are generally less than 10 percent. Environmental exposure through the use of consumer products is likely.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	110-02-1
Chemical Name	Thiophene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical properties

Thiophene is a colourless liquid at standard temperature and pressure with slight aromatic odour resembling that of benzene. Melting point and boiling point are -38.3 °C and 84.4 °C, respectively. The measured partition coefficient between octanol and water (log Kow) is 1.81. The measured vapour pressure is 1.06×10^4 Pa at 25 °C. The measured water solubility is 3015 mg/L at 25°C. Thiophene has no dissociable group.

Human Health

Nose-only inhalation exposure to [^{14}C] thiophene at 8000 ppm for 1 h showed that at least 16.3% of the inhaled thiophene was absorbed from the respiratory system in rats. At 72-h after exposure, concentrations of thiophene were in the following order: blood cells > liver > kidney, heart, and lung > brain, fat, and skeletal muscles. Within 72 h following exposure, 73.9% of the absorbed thiophene was excreted in expired air, 24.8% in urine, 0.6% in feces, and 0.8% in the cage wash. Excretion primarily occurred within the first 8 h. In rats, orally administered thiophene (240–300 mg/kg bw) was partly excreted unchanged in expired air (32%) and feces (<1%), and partly (40%) in urine as two mercapturic acids within 6 h. The result indicated that the absorption via oral exposure could be more than 70 % in rat. In rabbits, 38% of orally administrated thiophene (150–225 mg/kg bw) was excreted in urine as two mercapturic acids (same metabolites as in rats). No increase in the excretion of glucuronic acid or ethereal sulfate was observed. By intraperitoneal administration, the major metabolite of thiophene (30% of the administered dose) excreted in rat urine was dihydrothiophene sulfoxide mercapturate, which suggests that thiophene undergoes S-oxidation and glutathione conjugation.

The oral LD_{50} has been reported as more than 2000 mg/kg bw in female rats (OECD TG 423). At the lower test dose used in this study, 300 mg/kg bw, the rats showed drooping eyelids, salivation and soiled perineal region. Additional effects seen at 2000 mg/kg bw included decreased locomotor activity, smudges around the mouth and nose, unkempt fur, and a temporary reduction in body weight (evident at 4 days but not at 8 days). Macroscopic examination revealed no abnormal changes. The inhalation LC_{50} was reported to be 4525 ppm (15.6 mg/L) for a 6 h exposure in rats. The dermal LDL_0 was determined to be >3160 mg/kg after single doses of the undiluted test material applied to the closely clipped, intact skin of albino rabbits.

Thiophene caused low to moderate skin and eye irritation in rabbits. Occlusive dermal application for 24 h caused severe irritation in guinea pigs. Although no reliable information for skin sensitization is available,the limited data suggests no skin sensitization in guinea pigs.

In a repeated-dose oral toxicity study in rats (OECD TG 422 except for the limited haematological and clinical chemistry examination in only males), thiophene was administered via gavage to 13 animals/sex/dose at 0, 25, 100, or 400 mg/kg bw/day for 7 days/week. The male rats were dosed from 14 days before mating to the day before necropsy (including the mating period; 42 days in total) and the female rats from 14 days before mating to day 3 of lactation (including the mating period, gestation period, and delivery; 53 days in total). Incomplete eyelid opening, irregular respiration, decrease in locomotor activity, abdominal position and leaning position

were observed in males at 100 and 400 mg/kg bw/day and in females at 400 mg/kg bw/day. Three females showed ataxia and one of them showed tonic convulsions in the lactation period at 400 mg/kg bw/day. Decreases in food consumption and body weight gain were observed in the 400 mg/kg bw/day groups in both sexes. At necropsy, hypertrophy of hepatocytes was observed in the groups given 100 mg/kg bw/day or more in both sexes. In males of the 400 mg/kg bw/day group, infiltration of macrophages, necrosis of hepatocytes, and homogenous or vesicular cytoplasmic change of hepatocytes in the central zones were observed. In addition, pyknosis/necrosis of granular cells (male: 1/13; female: 8/13) and necrosis in the laminae albae (female: 7/13) in the cerebella were observed in the 400 mg/kg bw/day group. Pyknosis/necrosis of granular cells was also observed in one female at a dose of 100 mg/kg bw/day. Increase in relative liver weights were observed in males of the 100 mg/kg bw/day or more group and in females of the 400 mg/kg bw/day group. Decrease in glucose and ALP and increase in inorganic phosphorus was observed in males of the 100 mg/kg bw/day or more groups. Vacuolar degeneration of the tubular epithelium in the kidney was observed in females of the 100 mg/kg bw/day or more group.

Based on hepatic toxicity in both sexes together with histopathological changes in the cerebella and kidneys in females and clinical changes in males at 100 mg/kg bw/day, the no observed adverse effect level (NOAEL) for toxicity of thiophene administered repeatedly under conditions of this study was determined to be 25 mg/kg/day for both sexes. Some case reports for the therapeutic use of thiophene indicated that the liver injury with jaundice and pruritus was caused after the repeated doses for 3 to 10 days.

In a summary report of a subacute inhalation toxicity study (5 male rats/concentration at 0 (air), 1600, or 3200 ppm (0, 5.52 or 11.04 mg/L, respectively) for 6 h/day, for 12 exposures over a 15-day period), the sites of toxic action were the liver, kidney, thymus, nasal passages, and central nervous system. The NOAEL could not be determined in this study.

In a bacterial reverse mutation assay (Ames test) with multiple strains of *Salmonella typhimurium* and *Escherichia coli* (OECD TG 471; Guidelines for Screening Mutagenicity Testing of Chemicals, Chemical Substances Control Law of Japan), thiophene was negative both with and without metabolic activation. In addition, an *in vitro* chromosomal aberration test using cultured Chinese hamster lung cells (OECD TG 473) was also negative both with and without metabolic activation. In a mouse lymphoma mutagenicity assay, positive findings were obtained with and without S9, but only at a concentration that decreased survival below 10%. No information is available on *in vivo* genotoxicity testing. Based on these results, thiophene is considered to be non genotoxic *in vitro*.

No data were available on the carcinogenicity of thiophene.

The reproductive toxicity of thiophene was investigated in a study that combined repeated-dose toxicity with reproductive or developmental toxicity screening in rats (OECD TG 422, see above). In that study, there were no adverse effects on copulation, ovulation, and fertility in any thiophene-treated group. Three females showed ataxia and one of them showed tonic convulsions in the lactation period at 400 mg/kg bw/day. Extinction of nursing and/or lactation was observed in 1, 2, and 3 animals at 25, 100, and 400 mg/kg bw/day doses, respectively. No adverse effects on pup viability on postnatal day 0 or the sex ratio were detected in any thiophene-treated group. In the 400 mg/kg bw/day group, pup weights at birth and on postnatal day 4, along with their viability, were decreased, but these changes were statistically insignificant and considered to be secondary effects of maternal toxicity. No morphological abnormalities associated with the administration of thiophene were found in any pup. Based on abnormal lactation and cessation of nursing, the LOAEL for reproductive toxicity in females is considered to be 25 mg/kg bw/day and the NOAEL for fertility and developmental toxicity is considered to be 400 mg/kg bw/day (the highest dose). The parental NOAEL was considered to be 25 mg/kg bw/day (see repeated dose toxicity).

Thiophene possesses properties indicating a hazard for human health (repeated-dose toxicity, eye and skin irritation, and reproductive toxicity (abnormal lactation and cessation of nursing)). Adequate screening-level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

Thiophene entering in the atmosphere is expected to be degraded by hydroxyl radicals. Using AOPWIN (version 1.92), a calculated half-life time of 1.12 days and a rate constant of 9.53×10^{-12} cm^3/molecule-sec are obtained for

the indirect photo-oxidation of thiophene by reaction with hydroxyl radical in air. Concentration of hydroxyl radicals was assumed to be 1.5×10^6 OH/cm^3 and the time frame of hydroxyl radicals was 12 hours/day.

Thiophene is not expected to undergo hydrolysis in the environment due to the lack of hydrolysable functional groups. A study according to the equivalent protocol of OECD TG 111 showed no hydrolysis of thiophene in water at pH 4, 7 and 9 in 50 °C after five days.

A test similar to OECD TG 301C was conducted with thiophene with activated sludge for two weeks. The concentration of the test substance was 100 mg/L and the concentration of the activated sludge was 30 mg/L as suspended solid matters. The test results showed 0% degradation by BOD. Thiophene is not readily biodegradable according to a protocol similar to OECD TG 301C.

The aerobic biodegradation of thiophene was studied in microcosm experiments using groundwater microorganisms as inoculum. The inoculum used was an aerobic, free-living enrichment culture that originated from the ground water at a creosote-contaminated site. Thiophene was not used as a sole source of carbon. However, it was completely biodegraded aerobically with benzene and toluene as primary substrates in 18 days, and to 80% with ethylbenzene. Some 5-20% biodegradation of thiophene was observed in 18 days when *p*-xylene, *o*-xylene, *m*-xylene, naphthalene, and 1-methylnaphthalene were the primary substrates. These results show that thiophene can be degraded concomitantly under aerobic conditions by adapted microorganisms by co-metabolism.

In a study performed according to a protocol similar to OECD TG 305 with carp exposed to thiophene, bio-concentration factors of less than 9.0 were obtained for the concentration of 15 µg/L for six weeks exposure period. In this test, the lipid content value of the test fish was 4.8 %. Taking into account the octanol-water partition coefficient, a bio-concentration factor can be calculated as 7.265 according to a log Kow of 1.81 by BCFBAF, version 3.00. Thiophene is not expected to bioaccumulate.

Fugacity modeling (level III) for thiophene was conducted using EPISUITE, version 4.0. Input parameters were water solubility of 3015 mg/L, boiling point of 84.4 °C, melting point of -38.3 °C, log Kow of 1.81, vapour pressure of 9.68×103 Pa, Henry's law constant of 2.97×10^2 Pa.m3/mole. When equal and continuous release to air, water and soil is assumed, thiophene is mainly distributed in water and soil compartments. If released to the water compartment only, thiophene mostly stays in the water compartment. A Henry's law constant of 2.97×10^2 Pa.m3/mole (2.93×10-3 atm.m3/mole) at 25 °C suggested that volatilization of thiophene from water is moderate. A soil adsorption coefficient of log Koc = 1.903 indicated thiophene has low adsorption to soil and sediment.

The following acute and prolonged toxicity test results have been determined for aquatic species;

Fish [*Oryzias latipes*, OECD TG 203]: 96 h LC_{50} = 31 mg/L (measured)
Fish [*Oryzias latipes*, OECD TG 204]: 14 d LC_{50} > 30 mg/L (measured)
14 d NOEC = 12 mg/L (behaviour, nominal)
Daphnid [*Daphnia magna*, OECD TG 202]: 48 h EC_{50} = 21 mg/L (measured)
Algae [*Pseudokirchneriella subcapitata*, OECD TG 201]:
72 h ErC_{50} = 113 mg/L (measured, growth rate)
72 h EbC50 = 106 mg/L (measured, area under growth curve)

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

Daphnid [*Daphnia magna*, OECD TG 211]: 21 d LOEC = 8.1 mg/L (measured)
21 d NOEC = 2.8 mg/L (measured)
Algae [*Pseudokirchneriella subcapitata* OECD TG 201]:
72 h NOErC and 72 h NOEbC 12 mg/L (measured)

Thiophene possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 10 and 100 mg/L for fish and invertebrates). This chemical is considered not readily biodegradable and is not expected to have bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the Cooperative Chemicals Assessment Programme.

Exposure

Production volume and/or import volume of thiophene in Japan (sponsor country) was probably less than 100 tonnes in 2009. Information of the current production volume in other areas is not available.

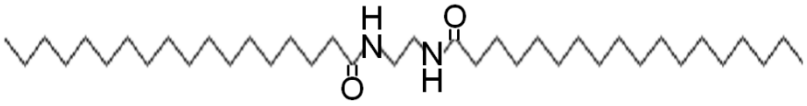
Thiophene is synthesized from heating sodium succinate with phosphorus trisulfide. Thiophene is made available in commercial quantities by a process utilizing the dehydrogenation of butane with sulfur as the dehydrogenating agent, followed by cyclization with sulfur to form the thiophene ring.

Thiophene is used as a solvent similar to benzene and as raw materials for resins. Thiophene is also used as raw materials for dyes or pharmaceuticals. Thiophene is used as an intermediate for medicines/pesticides/dyes and a chemical reagent in Japan. Thiophene is found in coal tar, in coal gas, and in technical benzene. According to monitoring data in Japan in 1985, thiophene was present in sediments at 0.0002 - 0.0015 μg/g dry weight. However it was not detected in surface water at the detection limit of 0.005 μg/L. Information on the processing site in a Japanese company is available. In this company, exhaust gas from ventilations and reactors is cleaned by using tail gas scrubber. Then, this exhaust gas is discharged into the atmosphere. The waste water from washing scrubber is disposed by an industrial waste disposer. There is little potential for environmental exposure in the sponsor country.

Occupational exposure through inhalation of vapour and via the dermal route is anticipated.

Thiophene becomes another material at the stage of processing. Therefore, thiophene is not expected to be included in consumer products. It is expected that there is no consumer exposure potential.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	110-30-5
Chemical Name	1,2-Bis(stearoylamino)ethane
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address only the following endpoint(s): Human Health: acute toxicity, repeated dose toxicity and *in vitro* mutagenicity. It cannot be considered as a full SIDS Initial Assessment. Nevertheless, the conclusions for the endpoints addressed have been agreed by member countries and may be used for hazard and risk assessment. Results on other endpoints may be relevant for hazard and risk assessment but have not been addressed in the assessment.

Rationale for targeting the assessment

Under the Japanese Chemical Substances Control Law, hazard assessment of existing chemical substances via environmental exposure has been conducted. If a chemical substance is evaluated as "not biodegradable (persistent)" and "not highly bioaccumulative", at least, a 28-day repeated dose toxicity and two *in vitro* mutagenicity studies are required as screening studies for hazard evaluation regarding human health. If a chemical is evaluated as having potential of long-term toxicity for human health, the chemical is classified as a Type II Monitoring Chemical Substance. If not, the chemical is of low priority for further action. Type II Monitoring Chemical Substances undergo risk-based management; at first, annual production volumes of those substances are monitored.

1,2-Bis(stearoylamino)ethane was evaluated as "not biodegradable (persistent)" and "moderately bioaccumulative" by the METI (Ministry of Economy, Trade and Industry, Japan). Biodegradation and bioaccumulation are not part of the targeted assessment and therefore not presented in the ITAP. In order to determine whether this chemical is classified as a Type II monitoring chemical substance, the initial hazard assessment of 1,2-bis(stearoylamino)ethane was conducted for the acute toxicity, repeated dose toxicity and mutagenicity by MHLW (Ministry of Health, Labour and Welfare, Japan) in January 2005.

This targeted assessment document was originally based on the material from the chemical assessment council of MHLW, and the toxicological profile was re-assessed for the OECD Cooperative Chemicals Assessment Programme.

Physical-chemical properties

1,2-Bis(stearoylamino)ethane is a dry powder at standard temperature and pressure. Melting point and boiling point are 149 °C and 260 °C, respectively. Vapour pressure is calculated to be 0.116 Pa at 25 °C by MPBPWIN. Partition coefficient between octanol and water (log K_{ow}) is calculated to be 13.98 by KOWWIN. Water solubility is calculated to be 1.099×10^{-10} mg/L at 25 °C by WSKOWWIN. 1,2-Bis(stearoylamino)ethane has no dissociable group.

Human Health

An acute oral toxicity study was conducted under OECD TG 401. The oral LD_{50} value was more than 2000 mg/kg bw for both sex in rats. No treatment-related deaths or clinical signs of toxicity were observed.

A repeated dose oral toxicity study in rats was conducted following a Guideline for 28-Day Repeated Dose Toxicity Test in Mammalian Species (Chemical Substances Control Law of Japan). In this study, 1,2-

bis(stearoylamino)ethane was administered via gavage at 0 (vehicle control: corn oil), 100, 300 or 1000 mg/kg bw/day for 28 days. Ten animals/sex (in the control and top-dose group) and 5 animals/sex (in the low and medium-dose groups) were used. There were no treatment-related deaths and no toxicological effects in either sex. Based on the findings, the NOAEL for this 28-day repeated dose toxicity study is considered to be 1000 mg/kg/day (the highest dose tested) for both sexes.

In bacterial mutation studies using several strains of *Salmonella typhimurium* and one strain of *Escherichia coli*, 1,2-bis(stearoylamino)ethane was negative with or without metabolic activation. In an *in vitro* chromosome aberration test using CHL/IU cells, 1,2-bis(stearoylamino)ethane was also negative with or without metabolic activation. Based on these results, 1,2-bis(stearoylamino)ethane is not considered to be genotoxic *in vitro*.

Agreed hazard conclusions

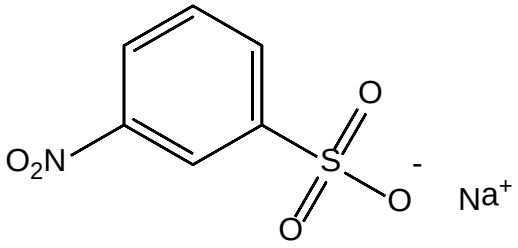
This chemical has a low hazard profile for the human health endpoints (acute toxicity, repeated dose toxicity and gene mutations and chromosomal aberrations) targeted in this assessment. Toxicity studies via relevant routes of consumer and occupational exposure were not identified in this targeted assessment.

Available Exposure information

Production volume and/or import volume of 1,2-bis(stearoylamino)ethane in Japan (sponsor country) was between 1,000 and 10,000 tonnes in 2007. Information of the production volume in other areas is not obtained.

1,2-Bis(stearoylamino)ethane is used in plastics and metal powder lubricants, varnishes, lacquers, defoamers, and resistant antiblock paints. Dermal and inhalation exposure of consumers and workers is expected.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	127-68-4
Chemical Name	Sodium 3-nitrobenzenesulfonate
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address only the following endpoint(s): Human Health: acute toxicity, repeated dose toxicity and *in vitro* mutagenicity. It cannot be considered as a full SIDS Initial Assessment. Nevertheless, the conclusions for the endpoints addressed have been agreed by member countries and may be used for hazard and risk assessment. Results on other endpoints may be relevant for hazard and risk assessment but have not been addressed in the assessment.

Rationale for targeting the assessment

Under the Japanese Chemical Substances Control Law, hazard assessment of existing chemical substances via environmental exposure has been conducted. If a chemical substance is evaluated as "not biodegradable (persistent)" and "not highly bioaccumulative", at least, a 28-day repeated dose toxicity and two *in vitro* mutagenicity studies are required as screening studies for hazard evaluation regarding human health. If a chemical is evaluated as having potential of long- term toxicity for human health, the chemical is classified as a Type II Monitoring Chemical Substance. If not, the chemical is of low priority for further action. Type II Monitoring Chemical Substances undergo risk-based management; at first, annual production volumes of those substances are monitored.

Sodium 3-nitrobenzenesulfonate was evaluated as "not biodegradable (persistent)" and "moderately bioaccumulative" by the METI (Ministry of Economy, Trade and Industry, Japan). Biodegradation and bioaccumulation are not parts of the targeted assessment and therefore not presented in the ITAP. In order to determine whether this chemical is classified as a Type II monitoring chemical substance, the initial hazard assessment of sodium 3-nitrobenzenesulfonate was conducted for the repeated dose toxicity and mutagenicity by MHLW (Ministry of Health, Labour and Welfare, Japan) in September 2005.

This targeted assessment document was originally based on the material from the chemical assessment council of MHLW, and the toxicological profile was re-assessed for the OECD Cooperative Chemicals Assessment Programme.

Physical-chemical properties

Sodium 3-nitrobenzenesulfonate is a pale yellow powder at standard temperature and pressure. Melting point and boiling point are 52.30 °C and 217.50 °C, respectively. Vapour pressure is calculated to be 10.3 Pa at 25 °C by MPBPWIN. The partition coefficient between octanol and water (log K_{ow}) is calculated to be -3.13 by KOWWIN. Water solubility is calculated to be 1.0×10^6 mg/L at 25 °C by WSKOWWIN. It is considered that sodium ion of this chemical is dissociated from sulfonate group in water.

Human Health

No reliable information was found on the acute toxicity of sodium 3-nitrobenzenesulfonate. However, as no treatment related mortality or no clinical signs of toxicity were found up to 1000 mg/kg bw/day at the beginning of dosing in a 28-day repeated oral gavage toxicity study, it is assumed that the LD_{50} value is more than 1000

mg/kg bw. Less reliable information indicates an oral LD_{50} value of 11 g/kg bw in rats.

A repeated dose oral toxicity study in rats was conducted following Guideline for 28-Day Repeated Dose Toxicity Test in Mammalian Species (Chemical Substances Control Law of Japan). In this study, sodium 3-nitrobenzenesulfonate was administered via gavage at 0 (vehicle control: corn oil), 100, 300 or 1000 mg/kg bw/day for 28 days. Ten animals/sex (in the control and top-dose group) and 5 animals/sex (in the low and medium-dose groups) were used. There were no deaths and no treatment-related toxicological effects in either sex. As for the possibility of the methemoglobin formation, in contrast, the levels of methemoglobin at 1000 mg/kg bw/day in both sexes tended to decrease. No related changes were observed. Based on the findings, the NOAEL for this 28-day repeat dose toxicity study is considered to be 1000 mg/kg bw/day (the highest dose tested) for both sexes.

In a bacterial mutation study using four strains of *Salmonella typhimurium* and one strain of *Escherichia coli*, sodium 3-nitrobenzenesulfonate was negative with or without metabolic activation. In an *in vitro* chromosome aberration test using CHL/IU cells, sodium 3-nitrobenzenesulfonate was also negative with or without metabolic activation. Based on these results, sodium 3-nitrobenzenesulfonate is not considered to be genotoxic *in vitro*.

Agreed hazard conclusions

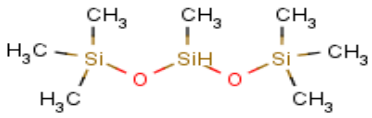
This chemical has a low hazard profile for the human health endpoints (repeated dose toxicity and gene mutations and chromosomal aberrations) targeted in this assessment. Toxicity studies via relevant routes of occupational exposure were not identified in this targeted assessment.

Available Exposure information

Production volume and/or import volume of sodium 3-nitrobenzenesulfonate in Japan (sponsor country) was between 100 and 1,000 tonnes in 2007. Production and/or import volume of sodium 3-nitrobenzenesulfonate in the United States was between 1 million and 10 million pounds (454,000 - 4,540,000 tonnes) during 2006 according to the U.S. Inventory Update Reporting. Information of the production volume in other areas was not obtained.

Sodium 3-nitrobenzenesulfonate is used as a dye intermediate, dyeing aid and plating remover in Japan. Dermal and inhalation exposure of workers is expected.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1873-88-7
Chemical Name	1,1,1,3,5,5,5-Heptamethyltrisiloxane (HMTS)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Justification

Octamethyltrisiloxane (L3; CAS No. 107-51-7) is used as an analogue to address the potential for chronic aquatic toxicity of 1,1,1,3,5,5,5-heptamethyltrisiloxane (HMTS). L3 has previously been assessed in the OECD HPV programme. Chronic toxicity data are not feasible for HMTS due to hydrolytic instability, low water solubility and high volatility. L3 is an appropriate analogue based on (1) the measured octanol-water partition coefficient (log K_{ow}) of 6.60 at 24.1 °C, (2) the measured water solubility of 0.0345 mg/L at 23 °C, which is within the same order of magnitude as the solubility value for HMTS, and (3) similarities in structure between L3 and HMTS.

Physical-Chemical Properties

HMTS is a liquid with a measured melting point of less than -20.2 °C, a measured boiling point of 140.85 to 142.85°C at 1008.8 to 1027.9 hPa and a measured vapour pressure of 8.47 hPa at 25 °C. The measured octanol-water partition coefficient (log K_{ow}) is 7.84 at 25 °C, and the measured water solubility is 0.02 mg/L at 22.0 °C (pH of 4.0). The water solubility and log K_{ow} values may not be applicable because the substance is hydrolytically unstable.

Human Health

No toxicokinetics data are available for HMTS. Based on reported toxicity following repeated oral exposure (gavage), HMTS is systemically absorbed and then distributed, at least in part, to the liver and kidney.

The oral (gavage) LD_{50} value was >2000 mg/kg bw in female rats [OECD TG 425]. Clinical signs included ruffled fur, sedation, poor coordination, hunched posture and ventral recumbency.

No irritation or sensitization data are available for HMTS.

The repeated-dose toxicity of HMTS has been investigated in one study. In a combined repeated-dose/reproductive/developmental toxicity screening test in rats [OECD TG 422], HMTS was administered via gavage to 10 rats/sex/dose at 0, 50, 200 or 800 mg/kg bw/day during pre-mating, mating (males and females), gestation and lactation day 4 (females). Males were dosed for 5 weeks and females 6-8 weeks. No mortality was seen. There were no treatment-related clinical signs of toxicity. In males, food consumption (800 mg/kg bw) and body weight/body weight gain (at 200 mg/kg bw/day and higher) were statistically significantly reduced. Clinical chemistry changes were limited to males at 800 mg/kg bw/day (cholesterol was increased; total bilirubin was reduced). Absolute and relative weights of liver and kidney were increased in males at 800 mg/kg bw/day. At 200 mg/kg bw/day and higher, absolute and relative liver weight were increased in females. At 800 mg/kg bw/day,

enlarged kidneys were observed in two males and the renal pelvic dilation which occurred in one male correlated with renal tubular lesions observed microscopically. Microscopically, test substance-related lesions were seen in the liver, kidney and thyroid gland. Centrilobular hypertrophy was noted in females at 200 mg/kg bw/day and higher; this was accompanied by extramedullary hematopoiesis in a single female at 800 mg/kg bw/day. The liver cell hypertrophy was considered to be an adaptive response due to metabolism of the test substance. There was increased protoporphyrin within portal bile ducts accompanied by reactive bile duct hyperplasia and perilobular fatty change in 800 mg/kg bw/day males, characteristic features of hepatic protoporphyrin accumulation. In the kidneys, focal or multifocal tubular degeneration/regeneration was increased in all males at 200 mg/kg bw/day and higher, and in some males at 800 mg/kg bw/day; this lesion was associated with tubular simple dilation or hyaline casts. These tubular lesions in males were accompanied by an increase in pelvic dilation, causing macroscopic renal enlargement and pelvic dilation in some males at 800 mg/kg bw/day. Furthermore, the test substance induced an increase in hyaline droplets/granules in males at 200 mg/kg bw/day and higher, and along with increased tubular degeneration/regeneration, may be interpreted as alpha 2u-globulin nephropathy. Diffuse follicular cell hypertrophy (thyroid) and an increase in extramedullary hematopoiesis (spleen) were observed in females at 200 mg/kg bw/day and in all animals at 800 mg/kg bw/day; these were considered adaptive effects. Based on effects at 200 and 800 mg/kg bw/day which included microscopic findings in the kidneys and liver (protein droplet nephropathy and hepatic protoporphyrin accumulation) in males and a statistically significant increase in liver weight in females, the No Observed Adverse Effect Level (NOAEL) for systemic toxicity was 50 mg/kg bw/day.

In bacterial reverse mutation assays with multiple strains of *Salmonella typhimurium* and *E. coli* [OECD TG 471] HMTS was negative both with and without metabolic activation. In an *in vitro* cytogenetic assay in Chinese hamster V79 cells [OECD TG 473] HTMS did not induce chromosomal aberrations with or without metabolic activation. Based on these results, HTMS is not considered to be genotoxic *in vitro*.

No data are available for the carcinogenicity of HMTS.

The reproductive and developmental toxicity of HTMS has been investigated in a repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422]. In this study, HTMS was administered via gavage to 10 rats/sex/dose at 0, 50, 200 or 800 mg/kg bw/day during pre-mating, mating (males and females), gestation and lactation day 4 (females). No mortality was seen. There were no test substance-related effects on any fertility parameter; the NOAEL for effects on fertility was 800 mg/kg bw/day, the highest dose tested. A statistically significantly higher postnatal loss and lower pup weight gain were noted at 800 mg/kg bw/day. As described above, maternal toxicity was seen at and above 200 mg/kg bw/day. The NOAELs for maternal and developmental toxicity were considered to be 50 mg/kg-bw/day and 200 mg/kg bw/day (in the presence of maternal toxicity), respectively.

1,1,1,3,5,5,5-Heptamethyltrisiloxane possesses properties indicating a hazard for human health (repeated-dose and developmental toxicity following oral exposure). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Not all programs within EPI Suite have been validated for chemicals that contain the element Si, but recent upgrades to the Kow and water solubility modules, found in the current version of EPI Suite (v4.10), give reasonable estimates for silanes and siloxanes.

HMTS has low water solubility (0.02 mg/L). A hydrolysis study with HMTS was not conducted due to its high volatility and low water solubility. These properties make it very difficult to devise an appropriate experimental setup to test for hydrolysis [OECD TG 111] because losses due to hydrolysis are very hard to distinguish from losses due to volatilization. Significant test substance losses were often found in the extensive pre-experiments, but no hydrolysis product was observed. As a result, a hydrolysis test with HMTS was not performed because no experimental setup, together with an accurate and sensitive analytical method, could be devised. At pH 9 and greater, the hydrolysis of HMTS is expected to be rapid (t½ in minutes to hours; ignoring its low water solubility, basic pH is a catalyst for hydrolysis of HMTS). At pH 7, hydrolysis is expected to be slow (2-3 days) and at pH 4, hydrolysis is expected to occur in hours to days. These estimates are based solely on best professional judgment. HMTS is expected to hydrolyze to 1 mole of hydrogen gas for each mole of 1,1,1,3,5,5,5-heptamethyl-3-trisiloxanol. The trisiloxanol condenses to disiloxane dimers; this condensation of silanols is affected by both concentration and pH (as basicity increases, condensation of silanols increases), and since both change over time

it is not feasible to isolate specific silanols for analysis (the structures continue to evolve until they either reach equilibrium or precipitate out of solution). The Si-O bond may also be susceptible to hydrolysis, resulting in the formation of two moles of trimethylsilanol and one mole of methylhydridyldisilanol. If HMTS is slowly released such that the concentration of the resulting trisiloxanol is not high enough to result in polymerization, the trisiloxanol will exist largely as a monomer. Thus, there is some uncertainty about the environmental fate of the parent substance and potential hydrolysis products. The estimated log Kow and water solubility for the trisiloxanol are 3.39 and 7.53 mg/L at 25 ^{o}C, respectively. In the atmosphere, indirect photo-oxidation by reaction of HMTS with hydroxyl radicals is predicted to occur with an estimated half-life of 10.2 days. The biodegradation of HMTS was determined in the CO_2 headspace test [OECD TG 310]; HMTS was not readily biodegradable (0 % after 28 days).

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments estimated that HMTS will distribute mainly to water (66%) compartment with lesser distribution to air (26.7%) and soil or sediment compartments (5.71 and 1.52%, respectively). The estimated Henry's Law constant of 3.07 x10^4 Pa-m^3/mole (Bond Estimate) suggests that volatilization from the water phase for HMTS is expected to be high. Note that the Henry's Law constant based on calculated vapour pressure and water solubility is 9.4 x 10^6 Pa-m3/mole; this is the value used for distribution modelling.

The estimated BCF value for HMTS is 5157 L/kg wet-wt indicating a potential for bioaccumulation; the log BAF (Arnot-Gobas upper trophic) was estimated to be 6.41 for HMTS and the BAF was 2.56E+006 L/kg wet-wt. The BCF of the immediate hydrolysis product (1,1,1,3,5,5,5-heptamethyl-3-trisiloxanol) is 630 L/kg wet-wt.

The following acute toxicity test results with a single, nominal concentration of 0.2 mg/L HMTS have been determined for aquatic species:

Fish [*Brachydanio rerio*]	96 h EC_{50} > 0.108 mg/L(OECD TG 203; semi-static; measured)
Invertebrate [*Daphnia magna*]	48 h EC_{50} > 0.030 mg/L(OECD TG 202; semi-static; measured)
Algae [*Pseudokirchneriella subcapitata*]	72-h E_yC_{50}, E_bC_{50} > 0.019 mg/L (OECD TG 201; measured)

Aquatic toxicity tests were conducted in closed systems to avoid loss of the substance through volatilization. Fish and Daphnid studies also included 24 hour substance renewals.

The following chronic toxicity test results are from the analogous substance, CASRN 107-51-7 Octamethyltrisiloxane (L3):

Chronic	
Invertebrate [*Daphnia magna*]	
21-day EC_{50} (mortality/immobility and reproduction)	> 0.015 mg/L (flow-through)*
21-day NOEC (for survival, reproduction and growth)	= 0.015 mg/L*
21-day LOEC (for survival, reproduction and growth)	> 0.015 mg/L*
Sediment	
Invertebrate [*Lumbriculus variegatus*]	
28-day EC50 (survival/reproduction/growth)	> 17 mg/Kg*
28-day NOEC (survival/reproduction)	= 1.1 mg/Kg
28-day LOEC (survival/reproduction)	= 1.6 mg/Kg
28-day NOEC (growth)	= 17 mg/Kg*
28-day LOEC (growth)	> 17 mg/Kg*
Invertebrate [*Chironomus riparius*]	
28-day LC50 (mortality)	= 166 mg/Kg
28-day NOEC (development time/emergence ratio)	= 84 mg/Kg
28-day LOEC (development time/emergence ratio)	= 210 mg/Kg
28-day NOEC (development rate)	= 84 mg/Kg
28-day LOEC (development rate)	= 39mg/Kg

*These results reflect the highest measured concentration tested and the functional limit of solubility under the conditions of administration (no effects at saturation).

HMTS possesses properties indicating a low hazard profile to the aquatic pelagic environment (at the limit of water solubility), the substance hydrolyzes, has potential to bioaccumulate and is not readily

biodegradable. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

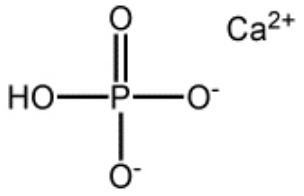
In the United States (sponsor country), production volume in 2005 was approximately 1043 tonnes. HMTS is produced in North America, Europe (<227 tonnes) and Japan (< 227 tonnes). Uses are the same in the US, Europe and Japan. The substance is used only as an intermediate for manufacturing other surfactants.

There is no intentional release of HMTS to the environment.

The substance is manufactured in closed systems. Open systems may be used for sampling only. Use of engineering controls at the manufacturing site includes general ventilation, closed sample loops, kettle house ventilation and local vent drops, Bailey Controls process system with process interlocks, metered feed and transfer systems, and grounded equipment. Personal protective equipment includes chemical-resistant gloves, glasses/goggles, chemical and fire resistant clothing, hard hat, steel-toed shoes, and respirator. Potential routes of exposure during routine operations (such as sampling operations) at the manufacturing site include dermal and inhalation.

HMTS is not used in consumer products.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7757-93-9
Chemical Name	Calcium hydrogenorthophosphate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical and chemical properties

Calcium hydrogenorthophosphate is an odourless, tasteless, white crystalline powder, with melting point of >450° C . It has a density of 2.92 g/cm^3 and water solubility of 153 mg/L at 20°C, pH 6.5 and is insoluble in ethanol. The boiling point, vapour pressure, dissociation constants and partition coefficients are not applicable to an inorganic salt like calcium hydrogenorthophosphate.

Human Health

Calcium and phosphate play a key role as an essential structural component of the skeleton. Calcium is absorbed from the gastrointestinal (GI) tract in a two-step process. Absorption occurs rapidly from the gut lumen into mucosal cells, and is then extruded into the interstitial fluid, with the first step faster than the second. 1,25-Dihydroxyvitamin D (1,25(OH)2D, the active form of vitamin D) is required for both steps in calcium transport. Fractional calcium absorption varies inversely with dietary calcium intake. During calcium deficiency, the absorption of calcium from diet increases, as a result of serum parathyroid hormone and 1,25(OH)2D action. Calcium in the bloodstream is predominantly associated with albumin. Unabsorbed ingested calcium is excreted in the feces. Renal calcium excretion is a function of the filtered load and the efficiency of reabsorption; the latter of these is regulated by parathyroid hormone. A high sodium diet increases the renal excretion of calcium, as both compete for reabsorption at the same sites in the renal tubules.

About 85% of the roughly 500 to 700 g of phosphate in the body is contained in bone, where it is an important constituent of carbonated hydroxyapatite. In soft tissues, phosphate is mainly found in the intracellular compartment. Inorganic phosphate is a major intracellular anion, but it is also present in plasma. Like calcium, gastrointestinal phosphate absorption is also enhanced by vitamin D. Renal phosphate excretion roughly equals GI absorption to maintain net phosphate balance. Phosphate depletion can occur in a variety of disease states and results in conservation of phosphate by the kidneys. Bone phosphate serves as a reservoir, which can buffer changes in plasma and intracellular phosphate.

The oral LD_{50} values were higher than 2,000 mg/kg bw for female rats [OECD TG 423]. The substance did not cause relevant clinical effects or findings at necropsy. Normal body weight gains were obtained in all animals for the 2nd step of the acute oral study, but there was temporary loss of body weight in one animal for the 1st step and that was recovered on 7 days after administration.

Neat calcium hydrogenorthophosphate was not irritating to rabbit skin. Two older *in vivo* studies indicated that dicalcium phosphate (anhydrous or the dihydrate) was not irritating to the rabbit eye.

Although no good-quality sensitisation studies were found for calcium hydrogenorthophosphate itself, the presence of these ions in large amounts in the body, structural considerations, existing data on other calcium and

phosphate salts, as well as a good-quality LLNA study on the sodium salt, indicate that calcium hydrogenorthophosphate is highly unlikely to possess any significant sensitisation potential.

In a repeated dose oral toxicity study in rats [OECD TG 407], calcium hydrogenorthophosphate was given by gavage at dose levels of 0, 250, 500 or 1,000 mg/kg bw/day to rats. Ten animals/sex (in the control and top-dose group) and 5 animals/sex (in the low and medium-dose groups) were used. There were no treatment-related changes in clinical signs, body weight, food consumption, urinalysis, hematology, serum biochemistry, necropsy finding and organ weights. Based on these results, it was concluded that the oral administration of calcium hydrogenorthophosphate to rats resulted in no toxicologically significant changes in all items examined. Therefore, under the present experimental conditions, the NOAEL of the test item is considered to be 1,000 mg/kg bw/day for both sexes of rats in this 28-day repeated dose oral toxicity study.

In a bacterial reverse mutation assay [OECD TG 471] with multiple strains of *Salmonella typhimurium* and one strain of *Escherichia coli*, calcium hydrogenorthophosphate was negative both with and without metabolic activation. In an *in vitro* chromosomal aberration test [OECD TG 473], it was also negative with and without metabolic activation. Based on these results, calcium hydrogenorthophosphate is considered to be non genotoxic *in vitro*. In addition, tricalcium phosphate, a similar substance to calcium hydrogenorthophosphate was not mutagenic in bacteria and did not cause chromosome aberration in hamster lung cells.

No data were available for the carcinogenicity of calcium hydrogenorthophosphate.

Calcium hydrogenorthophosphate has been investigated in a reproductive and developmental toxicity screening test [OECD TG 421]. Rats (13/sex/dose) were treated by gavage at doses of 0, 250, 500 or 1,000 mg/kg bw/day. Males were dosed once daily for two weeks each prior to, during and post mating, and females were dosed once daily for two weeks prior to mating, throughout gestation and four days after delivery. During the observation period, there were no dose related effects on clinical signs, body weights, food consumption, mating, gestation, delivery, organ weights, necropsy and histopathology in parents. No dose-related changes in clinical signs, body weights, viability index, external malformations and sex ratios were noted in pups. Based on the results of this study, no dose-related effects were noted in reproductive function of parents and in pups in the 1,000 mg/kg bw/day dosed group. The reproductive and developmental NOAEL was considered to be 1,000 mg/kg bw/day for parents of both sexes and pups, respectively.

Calcium hydrogenorthophosphate has a low hazard profile for human health. Adequate screening-level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

Environmental fate analysis based on log Kow and log Koc is not applicable to inorganic substances such as calcium hydrogenorthophosphate. Photodegradation and biodegradation are not applicable to inorganic substances. The current state of science does not allow for the unambiguous interpretation of the significance of various measures of bioaccumulation (e.g., BCF, BAF) for inorganic substances.

The substance has a significant eutrophication potential, similar to that of inorganic phosphate.

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

Fish [*Oryzias latipes*] 96 h LC_{50} >100 mg/L (nominal) [pH 7.18 to 7.97]
> 13.5 mg/L (highest concentration measured in solution)
Invertebrate [*Daphnia magna*] 48 h EC_{50} >100 mg/L (nominal) [pH 7.80 to 8.14]
> 2.9 mg/L (highest concentration measured in solution)
Algae [*P. subcapitata*] 72 h E_rC_{50} >100 mg/L (growth rate, nominal) [pH 8.30 to 9.06]
> 4.4 mg/L (growth rate, highest concentration measured in solution)
72 h E_yC_{50} >100 mg/L (yield, nominal) [pH 8.30 to 9.06]
> 4.4 mg/L (yield, highest concentration measured in solution)

Calcium hydrogenorthophosphate has a low hazard profile for the environment. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the Cooperative Chemicals

Assessment Programme.

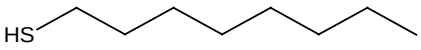
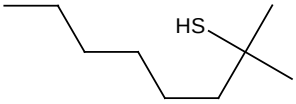
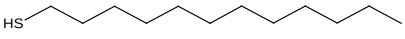
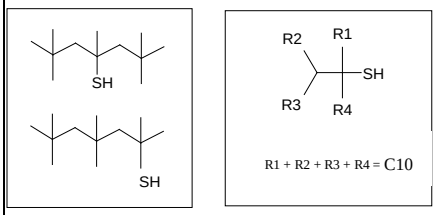
Exposure

In the Republic of Korea (sponsor country), the production, use and import volumes of calcium hydrogenorthophosphate were 1,292, 796 and 20,292 tonnes in 2006, respectively. In European Nordic countries estimated use volumes of calcium hydrogenorthophosphate were approx. 400, 6,500 and 3,600 tonnes in 2007, 2008 and 2009, respectively.

Calcium hydrogenorthophosphate is mainly used as a disinfectant in toothpaste products, in pharmaceuticals, pigments, paints, and as ink additives and food/foodstuff additives in the sponsor country. It is also used for control of acidity in powdered drink mixes and as a leavening agent in bread, cake mixes, and self-rising flour. The general public may be exposed to small quantities of calcium hydrogenorthophosphate by the consumption of food and some food/foodstuff additives.

In use facilities of the sponsor country, calcium hydrogenorthophosphate is handled in closed systems. No monitoring data were available for the workplace. Occupational exposure is managed with local ventilation systems and personal protective equipment such as dust masks, gloves and goggles. Occupational exposure is considered to be negligible in the sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

Category Name	C8-C12 Aliphatic Thiols Category
CAS No.	111-88-6 25360-10-5 112-55-0 25103-58-6
Chemical Names	1-Octanethiol 1,1-Dimethyl-heptanethiol 1-Dodecanethiol Tertiary-Dodecanethiol
Structural Formulae	 1-Octanethiol (*n*-Octyl Mercaptan)  1,1-Dimethyl-heptanethiol (*t*-Nonyl Mercaptan)  1-Dodecanethiol (*n*-Dodecyl Mercaptan)  Tertiary-Dodecanethiol (*t*-Dodecyl Mercaptan) Various Isomers

SUMMARY CONCLUSIONS OF THE SIAR

The members of the C8-C12 Aliphatic Thiols category are straight or branched aliphatic carbon chains containing a sulfhydryl functional group. The members of this category are all high molecular weight aliphatic thiols with a carbon number of C8 through C12. The representative structures (see above) represent the predominant isomer (> 95%) associated with each category member. With respect to ***t*-dodecyl mercaptans**, the predominant species is $C_{12}H_{25}SH$; however, there are also C10-C13 isomers (<2%) present because the commercial production process does not result in a single isomer. It is a complex mixture of 100+ structural isomers. The prevalent isomer will be highly branched and vary depending on product type but remains predominantly C12 rich. Similarly, ***t*-nonyl mercaptan** represents many different branched, C9 mercaptan isomers.

The category is based on the presumed common metabolism of alkyl thiols. It is generally recognized that thiols are metabolized via several different pathways in vertebrates that include: S-methylation, resulting in a methyl thioether that undergo S-oxidation; reaction with glutathione to form mixed disulfides (the likely form in circulation); oxidation forming sulfenic acids that undergo further metabolism yielding sulfinic and sulfonic acids, and finally oxidative desulfuration. Each of these cellular pathways would provide supporting evidence of the likely metabolism for the members of this category. Trends in physicochemical properties (e.g. increasing log K_{ow} with increasing carbon chain) and similar stability in water support the grouping of these chemicals. Available data for human health suggest that a range of acute local effects are observed, and for repeated exposures, both local and systemic effects may be seen. Therefore, read-across from one category member to another may only be appropriate for systemic toxicity (see below). A trend for acute ecotoxicity is expected. However the low water

solubility and the high degree of branching of some of the category members may cause deviation from the trends. For **n-octyl mercaptan,** the predicted value for acute toxicity to fish is close to the measured value.

Data availability used for human health endpoints for the C8-C12 Aliphatic Thiols Category

Substance	**CAS No.**	**Repeated-Dose Toxicity**	**Effects on Fertility**	**Developmental Toxicity**	**Gene Mutations**	**Chromo-somal Aberrations**
n-Octyl Mercaptan	111-88-6	**X**	**X**	**X**	**X**	**X**
t-Nonyl Mercaptan	25360-10-5	**O**	**O**	**O**	**X**	**O**
n-Dodecyl Mercaptan	112-55-0	**X**	**O**	**X**	**X**	**O**
t-Dodecyl Mercaptan	25103-58-6	**X**	**O**	**X**	**X**	**X**

X = data available; O = experimental data not available

Data availability used for ecotoxicity endpoints for the C8-C12 Aliphatic Thiols Category

Substance	**CAS No.**	**Acute Toxicity to Fish**	**Acute Toxicity to Aquatic Invertebrates**	**Toxicity to Aquatic Plants**
n-Octyl Mercaptan	111-88-6	**X**	**X**	**X**
t-Nonyl Mercaptan	25360-10-5	**O**	**O**	**O**
n-Dodecyl Mercaptan	112-55-0	**O**	**X**	**X**
t-Dodecyl Mercaptan	25103-58-6	**O**	**X**	**O**

X = data available; O = experimental data not available

Physico-chemical Properties

The C8-C12 mercaptans (***n*-octyl, *t*-nonyl, *n*-dodecyl, and *t*-dodecyl**) are liquids at room temperature. The respective measured (and EPISuite v 4.1 calculated) melting points are -49.2 (-28.3), -43.2 (-21.4), -8.0 (15.7), and ≤-20ºC (11.9); the measured (and calculated) boiling points are 199.1 (195.1), 188 (195.1), 274 (268.4), and 156ºC (251.4); the measured (and calculated) vapour pressures are 0.57 (0.46), 0.71 (0.87), 0.01 (0.01), 0.2 (4.0) hPa (all at 25ºC); the measured water solubility values are 4 at 25ºC (22.6 at 25ºC calculated), 9.6 at 25ºC (calculated), < 1 at 22ºC (0.3 at 25ºC calculated), 0.25 at 20ºC (0.3 at 25ºC calculated) mg/L; the octanol log K_{ow} values are 4.21 (calculated), 4.59 (calculated), > 6.2 (measured), > 6.2 (measured), respectively. The calculated Henry's law constants are 0.019, 0.025, 0.059, and 0.059 atm·m^3/mol.

Human Health

No toxicokinetic, metabolism or distribution studies were identified for any of the C8-C12 Aliphatic Thiols. A description of the likely metabolism of the C8-C12 Aliphatic Thiols is summarized above in the category rationale.

Acute toxicity data are available for the inhalation, dermal and oral routes of exposure. In rats, the inhalation 4-hour LC_{50} values range from > 40 ppm (0.24 mg/L) [***n*-octyl mercaptan]** to > 1074 ppm (7.04 mg/L) [***t*-nonyl mercaptan**]. Clinical signs included signs of irritation during exposure and ataxia, lethargy, salivation, lacrimation and piloerection following exposure. The dermal LD_{50} value following 24-hour exposure is greater than 1700 mg/kg bw in rabbits [***n*-octyl mercaptan**] and greater than 2000 mg/kg bw in rats [***n*-octyl**, ***t*-nonyl** and ***n*-dodecyl mercaptans]**. Erythema and induration were observed in one study with ***n*-octyl mercaptan**. In rats, the oral LD_{50} values are 1293 mg/kg bw [***n*-octyl mercaptan]**, 5550 mg/kg bw [***t*-nonyl mercaptan**] and greater than 5000 mg/kg bw [***n*-dodecyl mercaptan**]. Clinical signs included abnormal posture, decreased activity, ataxic gait, tremors and lacrimation [***n*-octyl mercaptan**].

***n*-Octyl mercaptan** and ***t*-nonyl mercaptan** are, at most, slightly irritating to rabbit skin. ***t*-Dodecyl mercaptan and *n*-dodecyl mercaptan** are irritating and corrosive to rabbit skin, respectively. ***n*-Octyl** and ***t*-nonyl**

mercaptans are slightly irritating to the eyes of rabbits. Based on the available data, the C8-12 Aliphatic Thiols category members are irritating to rabbit skin and eyes. Respiratory irritation was observed after repeated inhalation exposure of rats to ***n*-dodecyl mercaptan.** In addition, the C8-C12 Aliphatic Thiols category members are considered to be weak to moderate skin sensitisers in guinea pigs and humans. Repeated-dose toxicity studies are available via the inhalation route for ***n*-dodecyl mercaptan** and ***t*-dodecyl mercaptan** and via the oral route for ***n*-octyl mercaptan**.

Systemic Toxicity: In a 4-week inhalation toxicity study (comparable to OECD TG 407), rats were exposed (whole body) to nominal concentrations of 0, 0.5 (0.004 mg/L), 2.0 (0.016 mg/L), or 7.0 ppm (0.058 mg/L) (measured 0, 0.44, 1.7, or 7.7 ppm, respectively) ***n*-dodecyl mercaptan** for six hours/day, five days/week. Signs of respiratory and dermal irritation were observed at the high concentration more frequently as the exposure period progressed. Body weight reduction in males (7.0 ppm; 0.058 mg/L) and reduced food consumption in both sexes (2.0 and 7.0 ppm; 0.016 and 0.058 mg/L, respectively) were observed. At 7.0 ppm (0.058 mg/L), both sexes showed increased AST and ALT levels; males also had increased urea nitrogen levels. However, there were no microscopic changes in the liver or kidneys. Macroscopic changes in the 7.0 ppm (0.058 mg/L) group consisted of skin irritation and enlargement of superficial lymph nodes. At 7.0 ppm (0.058 mg/L), the most marked microscopic findings were as follows: acanthosis (10/10 males and females), hyperkeratosis (10/10 males and females), and chronic active inflammation in the skin (8/10 males and 9/10 females) and secondary changes in regional lymph nodes in a few animals (3/10 males and 1/10 females). The NOAEC for systemic toxicity was 2.0 ppm (0.016 mg/L).

Local Effects: There was no evidence of respiratory damage; however, ***n*-dodecyl mercaptan** did appear to be a skin irritant at 7.0 ppm (0.058 mg/L). Similar exposure to dogs resulted in skin irritation but no other evidence of toxicity; the NOAEC was 2.0 ppm (0.016 mg/L). Similar exposure to mice resulted in death of all mice at 7.0 ppm (0.058 mg/L) by week 3. No exposure-related effects were observed at 0.5 (0.004 mg/L) or 2.0 ppm (0.016 mg/L); the NOAEC was 2.0 ppm (0.016 mg/L).

Systemic Toxicity: In another 4-week inhalation study (comparable to OECD TG 407), rats were exposed to nominal concentrations of 0, 26 (0.22 mg/L) or 98 ppm (0.81 mg/L) (the high concentration was a saturated vapour) ***t*-dodecyl mercaptan** for six hours/day, five days/week. Body weight reduction in males (98 ppm; 0.81 mg/L) with a corresponding reduction in food consumption was observed. High-dose males showed an increase in creatinine, and liver weights showed an exposure-related increase. Male rats at both concentrations exhibited mild renal tubular degeneration and granular cysts which were consistent with species-specific hydrocarbon nephropathy. High-dose female rats exhibited hydronephrosis. The LOAEC was 26 ppm (0.22 mg/L). Similar exposure to dogs (25 and 109 ppm; 0.22 and 0.90 mg/L, respectively) resulted in increases in alanine aminotransferase and reductions in blood urea nitrogen in females. Both sexes showed increases in alkaline phosphatase and exposure-related increases in liver weights with microscopic hepatocellular hypertrophy observed at the high dose for both sexes. The LOAEC was 25 ppm (0.21 mg/L). Similar exposure to mice (25 and 109 ppm; 0.21 and 0.90 mg/L, respectively) resulted in death of one male and one female at the high concentration. At the high concentration, reductions in erythrocyte counts and hematocrit, and increases in MCH and MCHC levels were observed at termination and females exhibited dermal inflammation, acanthosis, and hyperkeratosis, and showed increases in alanine aminotransferase and blood urea nitrogen, and decreased alkaline phosphatase values. These females also had decreased ovary weights, and histopathological evaluation revealed either an absence of, or few, corpora lutea. Low-concentration females showed statistically significant increases in blood glucose. Liver weights revealed exposure-related increases; both sexes showed liver enlargement, discoloration and hepatocellular hypertrophy at both concentrations. The LOAEC for systemic toxicity was 25 ppm (0.21 mg/L); the NOAEC was not established.

Systemic Toxicity: In the combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422), rats were administered ***n*-octyl mercaptan** in olive oil by gavage at 0, 10, 50 or 250 mg/kg bw/day for 35 days (males) or from 14 days prior to mating until 4 days post-parturition (females). Treatment-related clinical signs observed at 250 mg/kg bw/day included salivation and a decrease in locomotor activity (both sexes), and abnormal gait (females). Effects at 250 mg/kg bw/day included: decreased body weight and body weight gain (both sexes); decreased food consumption (females); decreased red blood cells (both sexes), hemoglobin concentration (males) and MCHC (both sexes); increased MCV and reticulocyte ratio (both sexes); increased MCH (females). Effects at 250 mg/kg bw/day on organ weights included: for males, increased spleen weight and increased relative (to bw) heart, liver (also for 50 mg/kg bw/day), spleen, and kidney weights; for females included increased liver, spleen and adrenal weights and increased relative (to bw) liver, spleen, kidneys and adrenal weights. Histopathological findings for both sexes at 250 mg/kg bw/day included several findings consistent with stomach irritation/corrosion, congestion, extramedullary hematopoiesis and hemosiderin deposition in the spleen, and increased erythropoiesis in the bone marrow. In addition, atrophy of the thymus was noted in females. The NOAEL for systemic toxicity was 50 mg/kg bw/day.

The C8-12 Aliphatic Thiol category members were negative in bacterial mutagenicity assays [OECD TG 471] *in*

vitro. ***n*-Octyl mercaptan** was negative in a chromosomal aberration assay [OECD TG 473] *in vitro*; the results for ***t*-dodecyl mercaptan** were equivocal. ***n*-Octyl, *n*-dodecyl** and ***t*-dodecyl mercaptans** were negative in the sister chromatid exchange [OECD TG 479] and mouse lymphoma assays [OECD TG 476] *in vitro*. ***n*-Dodecyl mercaptan** was negative in the *in vivo* mouse micronucleus test [OECD TG 474]. The C8-12 Aliphatic Thiol category members are not considered to be genotoxic *in vitro* or *in vivo*.

No carcinogenicity studies were identified for the C8-C12 Aliphatic Thiols.

Data are available for reproductive/developmental toxicity for ***n*-octyl mercaptan** via the oral route and developmental toxicity for ***n*-dodecyl mercaptan** and ***t*-dodecyl mercaptan** via the inhalation route. In a combined repeated-dose/reproductive/developmental toxicity test in rats via the oral route, ***n*-octyl mercaptan** showed no effects on fertility but showed potential for developmental toxicity (post implantation loss) at 250 mg/kg bw/day (highest dose tested). The NOAEL for reproductive toxicity was 250 mg/kg bw/day (highest dose tested). The NOAEL for developmental toxicity was 50 mg/kg bw/day. In prenatal developmental toxicity studies via the inhalation route in rats and mice, ***n*-dodecyl mercaptan** showed maternal toxicity in rats at 7.4 ppm (0.06 mg/L) or greater; development was unaffected. The NOAEC for maternal toxicity was not established (< 7.4 ppm; 0.06 mg/L). The NOAEC for developmental toxicity was 7.4 ppm (0.06 mg/L) (highest concentration tested). In rats and mice exposed via inhalation to ***t*-dodecyl mercaptan**, no treatment-related maternal or developmental toxicity was observed at concentrations up to 88.6 ppm (0.73 mg/L). Based on available data, the C8-C12 Aliphatic Thiols show maternal toxicity at low exposure concentrations (<0.1 mg/L); however, they do not elicit developmental effects at the concentrations tested in reliable studies via the inhalation route. However a reproductive study showed the potential for developmental toxicity via the oral route (i.e. post implantation loss at the highest dose tested).

These chemicals possess properties indicating a hazard for human health (skin sensitisation, repeated-exposure toxicity and potential for developmental toxicity via the oral route). The local effects (skin, eye and respiratory irritation, are chemical specific; n-dodecyl mercaptan is corrosive to rabbit skin while the other members of the category are considered irritants to skin and eyes. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

The C8-C12 Aliphatic Thiols do not react with water; the only functionality other than carbon-hydrogen bonds is the sulfhydryl group. Predicted Atmospheric Oxidation half lives for these chemicals are 2.6 hours (***n*-octyl mercaptan**), 3.2 hours (***t*-nonyl mercaptan**), 2.3 hours (***n*-dodecyl mercaptan**), and 3.0 hours (***t*-dodecyl mercaptan**). There are no photoreactive groups in these molecules and, therefore, direct photolysis is not expected.

The level III fugacity model calculation with equal and continuous release to air, water, and soil show similar results for the category members with main distributions to water and soil and less significant distributions to air and sediment. All of the C8-C12 Aliphatic Thiols have been evaluated in biodegradation studies conducted according to OECD TG 301D or 301F. The 28-day degradation for ***t*-nonyl**, ***n*-octyl**, ***n*-dodecyl** and ***t*-dodecyl mercaptan** is 0%, 10%, 39.2% and 10.4%, respectively; therefore, C8-C12 Aliphatic Thiols are not readily biodegradable.

Volatilization of these chemicals from the water phase is expected to be high based on the Henry's law constant presented in the following table. For bioaccumulation, no reliable studies for the C8-C12 Aliphatic Thiols were identified. Based on BCF values estimated using the BCFBAF model (v. 3.01) presented below, bioaccumulation potentials are expected to be low except for highly branched **t-dodecyl mercaptan**.

Substance CAS No.	*n*-Octyl Mercaptan 111-88-6	*t*-Nonyl Mercaptan 25360-10-5	*n*-Dodecyl Mercaptan 112-55-0	*t*-Dodecyl Mercaptan 25103-58-6
Henry's law constant (atm m^3/mol)	0.019 (Calculated – Bond Estimate)	0.025 (Calculated – Bond Estimate)	0.059 (Calculated – Bond Estimate)	0.059 (Calculated – Bond Estimate)
Half-life (12 hr day; 1.5E06 OH/cm^3)	2.6 hours	3.2 hours	2.3 hours	3.0 hours

Overall OH Rate Constant (cm^3/molecule-sec)	5.0 x 10^{-11}	4.0 x10^{-11}	5.5 x 10^{-11}	4.4 x 10^{-11}
BCF[a]	11.8	499	234	198[b] 3338[c]

[a]BCF estimates based on the EPA BCFBAF model (v 3.01)

[b]Estimate for structure that is not highly branched

[c] Estimate for highly branched structure

The following acute toxicity test results have been determined for the members of this category:

Fish [*Oryzias latipes*]
96 h LC_{50} = 0.326 mg/L (measured) for **n-octyl mercaptan**.
96 h LC_{50} = 0.160 mg/L (estimated; ECOSAR v.1.00a) for **n-octyl mercaptan**
96 h LC_{50} = 0.096 mg/L (estimated; ECOSAR v.1.00a) for **t-nonyl mercaptan**
96 h LC_{50} = 0.01 mg/L (estimated; ECOSAR v.1.00a) for **n-dodecyl mercaptan**
96 h LC_{50} = 0.01 mg/L (estimated; ECOSAR v.1.00a) for **t-dodecyl mercaptan**

Invertebrate [*Daphnia magna*] 48 h LC_{50} = 0.024, 1-10 and 0.16 mg/L (measured) to 0.42 mg/L (measured) for **n-octyl**, ***n*-dodecyl** and ***t*-dodecyl mercaptans**, respectively. Some values provided are above the water solubility limit for **n-** and **t-dodecyl mercaptans**.

Algae [*Pseudokirchneriella subcapitata*] 72 h ErC_{50} = 0.039 and < 0.0145 mg/L (measured) for ***n*-octyl** and ***t*-dodecyl mercaptans**, respectively

The following chronic toxicity test results have been determined (aquatic invertebrates/OECD TG 211):

[*Daphnia magna*] 21-d, NOEC = 0.0011 and 0.0108 mg/L (measured) **n-octyl** and ***t*-dodecyl mercaptans**, respectively.

These chemicals possess properties indicating a hazard for the environment (acute toxicity values lower than 1 mg/L for fish, aquatic invertebrates, and algae, and chronic toxicity values lower than 0.1 mg/L for aquatic invertebrates; not readily biodegradable). The chemicals have the potential to bioaccumulate: *t*-dodecyl mercaptan is being further investigated within the framework of the EU. These chemicals are not readily biodegradable. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

In the United States (Sponsor country) in 2006, companies produced or imported between 450-4500 metric tons of ***n*-octyl** and ***t*-nonyl mercaptan**, between 4500-22,500 metric tons of ***n*-dodecyl mercaptan** and between 22,500 and 45,000 metric tons of ***t*-dodecyl mercaptan**. The total annual global production estimates by the Mercaptans/Thiols Council, for the C8-C12 Aliphatic Thiols is approximately 100 million pounds (45,000 metric tons).

***n*-Octyl mercaptan** is produced by the reaction of hydrogen sulfide with octene-1, followed by purification by distillation. ***t*-Nonyl mercaptan** is produced by the addition of H_2S to propylene trimer under acid catalysis conditions, followed by distillation to remove light and heavy components. ***n*-Dodecyl mercaptan** is produced by the reaction of hydrogen sulfide with dodecene-1, followed by purification by distillation. ***t*-Dodecyl mercaptan** is produced by the reaction of hydrogen sulfide with propylene tetramer over catalysts with elevated temperature, followed by purification by distillation.

Thiols possess a sulfhydryl group (-SH) that is instrumental in introducing a sulfur group into various biologically active molecules in the pharmaceutical and agrochemical industries. Thiols in the C8-C12 carbon range are commonly used as intermediates in the organic synthesis and as polymerization chain transfer agents. ***t*-Dodecyl mercaptan** may also be used directly as an end product in ore collection operations.

***n*-Octyl**, ***t*-nonyl** and ***t*-dodecyl mercaptans** are primarily used in closed systems and environmental exposure is expected to be very limited during manufacturing of the mercaptans. There are no deliberate releases to the environment during manufacture; however, certain applications of *t*-dodecyl mercaptan use aqueous processing

which may result in environmental exposure. Residual mercaptans in finished products are low (e.g., the odour threshold for ***n*-dodecyl mercaptan** is 0.5 ppb and for t-dodecyl mercaptan is <0.5 ppm) because of the processes used and the need to remove the thiols due to odour and customer acceptability.

In the Sponsor country, workplace exposure values are in place for ***n*-octyl mercaptan** [NIOSH ceiling is 0.5 ppm (3.0 mg/m^3) 15-min] and ***n*-dodecyl mercaptan** [NIOSH ceiling is 0.5 ppm (4.1 mg/m^3) (15-min); ACGIH TLV 0.1 ppm TWA (8-h)], and t-dodecyl mercaptan (NIOSH ceiling is <0.5 ppm). Due to very low odour thresholds, even low concentrations of the aliphatic thiols can be detected and mitigated to avoid odour complaints. Although mercaptans are handled in closed systems and engineering controls limit potential exposure, proper personal protective equipment (PPE) should always be worn in accordance with the recommendations of the manufacturers.

The C8-C12 Aliphatic Thiols are substances manufactured and used for chemical processing at very low concentrations during polymerization. The resulting polymers undergo several transformations before being used for the production of final consumer products. If there are any residual thiols, they are expected to be trapped in the articles and no release is expected to occur under normal or reasonably foreseeable conditions of use. However, due to the high affinity of these substances for organic matter, the amount volatilized may not be representative of the amount remaining in the polymer.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	**C_{14}-C_{20} Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category**
Chemical Names and CAS Registry Numbers	**Substance Name** — **CAS Number** ***n-Paraffins Subcategory*** n-Tetradecane — 629-59-4 Pentadecane — 629-62-9 Hexadecane — 544-76-3 Paraffins, petroleum, normal C_{5-20} — 64771-72-8† Alkanes, C_{14-16} — 90622-46-1† Alkanes, C_{14-17} — 90622-47-2† ***Iso-Paraffins Subcategory*** Alkanes, $C_{13-16,}$ iso- — 68551-20-2† Distillates, petroleum, alkylate — 64741-73-7† ***Multi-constituent Subcategory*** Raffinates, petroleum, sorption process — 64741-85-1† Distillates, petroleum, solvent-refined middle — 64741-91-9† Distillates, petroleum, hydrotreated middle — 64742-46-7† Distillates, petroleum, hydrotreated light — 64742-47-8†
Structural Formula and CAS Registry Numbers	**Structural Formula** — **CAS Number** ***n-Paraffins Subcategory*** CH_3-$(CH_2)_{12}$-CH_3 — 629-59-4 CH_3-$(CH_2)_{13}$-CH_3 — 629-62-9 CH_3-$(CH_2)_{14}$-CH_3 — 544-76-3 CH_3-$(CH_2)_8$-CH_3 to CH_3-$(CH_2)_{16}$-CH_3 — 64771-72-8† CH_3-$(CH_2)_{12}$-CH_3 to CH_3-$(CH_2)_{14}$-CH_3 — 90622-46-1† CH_3-$(CH_2)_{12}$-CH_3 to CH_3-$(CH_2)_{15}$-CH_3 — 90622-47-2† ***Iso-Paraffins Subcategory*** CH_3 CH_3 CH_3-CH-CH_2-CH_2-$(CH_3)_6$ CH_3 Various isomers of primarily C_{13}, C_{14}, C_{15}, and C_{16} alkyl-branched hydrocarbons — 68551-20-2† Various isomers of primarily C_{11}, C_{12}, C_{13}, $C_{14,}$ C_{15}, C_{16} and/or C_{17} alkyl-branched hydrocarbons — 64741-73-7† ***Multi-constituent Subcategory**** UVCB† substances containing aliphatic (linear, branched, and/or cyclic paraffins) molecules of carbon and hydrogen, predominantly in the C_{14} to C_{20} range — 64741-85-1†, 64741-91-9†, 64742-46-7†, 64742-47-8 Individual category member substances are comprised of aliphatic hydrocarbon molecules whose carbon numbers range between C14 and C20; approximately 80% of the aliphatic constituents for a given substance fall within the C14-C20 carbon range. * It should be noted that other substances defined by the same CAS RNs may have boiling ranges outside the range of 220-350 degrees Celsius and that these substances are not covered by the category.

	† Denotes a UVCB substance. UVCBs are defined as chemical substances of unknown or variable composition, complex reaction products or biological materials.
	The category has been defined for members with specific constituents/component profiles or composition as outlined in the full SIDS Initial Assessment Report and the SIDS Dossiers. The C_{14}-C_{20} Aliphatic (≤2% aromatic) Hydrocarbon Solvents Category contains some multi-constituent substances (UVCBs) that have a variable composition due to their chemistries and method of manufacturing. The substances in this category contain >99% hydrocarbons. The C_{14}-C_{20} Aliphatic (≤2% aromatic) Hydrocarbon Solvents typically contain < 2% aromatics; a few members contain up to 2% total aromatics (either one- or 2-ring molecules). Benzene is intentionally removed to levels less than 0.01% and sulfur and nitrogen compounds are removed by the refining process. As complex hydrocarbon substances, some of the category members share CAS RNs with some petroleum process streams. This assessment only applies to CAS RNs with the constituent profiles and compositions described within this assessment. Consequently, the conclusions of this assessment do not specifically apply to petroleum process streams with the same CAS numbers as those belonging to the C_{14}-C_{20} Aliphatic (≤2% aromatic) Hydrocarbon Solvents Category.

Identification of chemicals defined by processing procedures	Typical Carbon Number Range (%)										
	< C11	**C12**	**C13**	**C14**	**C15**	**C16**	**C17**	**C18**	**C19**	**C20**	**C21+**
n-Tetradecane (CAS RN 629-59-4)				>99							
Pentadecane (CAS RN 629-62-9)					>99						
Hexadecane (CAS RN 544-76-3)						>99					
Paraffins, petroleum, normal C5-20 (CAS RN 64771-72-8) Boiling Range ~35-345°C	~2		~10	~31	~25	~14	~9	~4			
Alkanes, C14-16 (CAS RN 90622-46-1)				~ 63	~ 28	~ 9					
Alkanes, C14-17 (CAS RN 90622-47-2)				~ 27	~ 50	~ 19	~ 3	~ 1			
Alkanes, C13-16, iso- (CAS RN 68551-20-2)	~ 1	~ 6	~ 13	~ 47	~ 32	~ 1					
Distillates, petroleum, alkylate (CAS RN 64741-73-7) Boiling Range ~205 - 320°C	~1	~3	~14	~38	~30	~14					
Raffinates, petroleum, sorption process (CAS RN 64741-85-1) Boiling Range ~35 - 400°C			~1	~3	~6	~9	~17	~20	~15	~11	~18
Distillates, petroleum, solvent-refined middle			~1		~8	~18		~21		~7	~4

(CAS RN 64741-91-9) Boiling Range ~15 - 345°C				~6			~24		~11		
Distillates, petroleum, hydrotreated middle (CAS RN 64742-46-7) Boiling Range ~ 205 - 400°C			~ 0.5	~ 3	~ 11	~ 19	~ 28	~ 25	~ 8	~ 5	~ 0.5
Distillates, petroleum, hydrotreated light (CAS RN 64742-47-8) Boiling Range ~150 - 290°C			~ 5	~ 29	~ 24	~ 18	~ 14	~ 7	~ 2	~ 1	

SUMMARY CONCLUSIONS OF THE SIAR

Category Definition/Justification

The C_{14}-C_{20} Aliphatic (≤2% aromatic) Hydrocarbon Solvents Category is comprised of 12 CAS registry numbers (CAS RNs) that are associated with pure and multi-constituent aliphatic hydrocarbon solvent commercial chemicals, which typically contain <2% aromatics with a few members containing up to approximately 2% total aromatics (toluene and xylene). Benzene is intentionally removed to levels less than 0.01% and sulfur and nitrogen compounds are removed by the refining process. Substances in the C_{14}-C_{20} Aliphatic Hydrocarbon Solvents (≤2% aromatics) Category contain >99% hydrocarbons. Carbon (C) numbers and initial boiling points (IBPs) are typically used to physically characterize substances in this category. The constituent C numbers range primarily from 14 to 20. Although the CAS definitions for some category members suggest that a wider C number range exists, the narrower C_{14} to C_{20} range is confirmed by the distillation temperature for category members, which range from approximately 220 to 350°C (428 to 662°F) for the category.

Assignment of CAS RNs to hydrocarbon substances is generally based on a hierarchy of considerations including hydrocarbon type(s), carbon number and/or range, distillation temperature and/or range, and last processing step in the production process. One documented source of criteria for assignment of CAS RNs for multi-constituent hydrocarbon substances is provided by the U.S. EPA on proceedings for development of the TSCA inventory for U.S. chemicals. These criteria, however, may allow the same CAS RN to be applied to differing hydrocarbon and petroleum-derived substances (hydrocarbon streams) with somewhat different compositions and applications (e.g., solvents, fuels, lubricants, etc.). Similarly, different CAS RNs can be applied to substances of similar composition and application.

Members in the C_{14}-C_{20} Aliphatic Hydrocarbon Solvents (≤2% aromatics) Category are fully saturated hydrocarbons and have or are expected to have similar toxicokinetics, mammalian and ecological toxicological properties. No acute toxicity was noted at the limit doses, no irritation was noted in ocular or skin (semi-occlusive) irritation studies, minimal to no toxicity was noted in read-across studies for repeated dose and reproductive/developmental studies, and the substances (or read-across substances) were not mutagenic in *in vitro* and *in vivo* studies. In the environment, the toxic mode of action of the aliphatic constituents is non-polar narcosis, which results in disruption of the biological membrane. The critical body residue (CBR) is the internal concentration of a substance that causes adverse effects. Only substances with sufficient water solubility to reach the CBR will demonstrate toxicity. Category members do not demonstrate suitable water solubility to reach the CBR in acute and chronic aqueous exposure studies.

Category Member Conventional Naming

The naming convention used to identify category members is based on their general compositions (predominant carbon number range and hydrocarbon type, specifically aromatics) and is intended to identify hydrocarbon solvent substances manufactured by various companies that are sufficiently similar with regard to composition such that their physical and biological properties would exhibit similar if not identical values. The naming convention as applied to hydrocarbon solvents was seen as a means to provide an immediate understanding of the type of solvent and its composition to allow for an accurate grouping of hydrocarbon substances within categories. As UVCBs, some of the hydrocarbon solvent category members share CAS RNs with some petroleum process streams, which have broader boiling ranges and consequently are compositionally more complex.

Production of C_{14}-C_{20} Aliphatic (≤2% aromatic) Hydrocarbon Solvents Category is differentiated from other refinery streams such as gasoline and diesel fuel by additional processing steps leading to finished substances with narrower distillation ranges, removal of sulfur- and nitrogen-containing compounds, and low color.

Category members (CAS RN 64741-85-1, 64741-91-9, 64742-46-7 and 64742-47-8) meet the criteria for UVCB substances because they contain a relatively large number of discrete chemical constituents and the exact composition of some of the constituent chemicals may be unknown. However, linear C14 paraffin, n-tetradecane (CAS Registry Number (RN) 629-59-4), linear C15 paraffin, n-pentadecane (CAS RN 629-62-9), and linear C16 paraffin, n-hexadecane (CAS RN 544-76-3) have specific molecular formulas and so they are not considered UVCBs. The general naming convention guidance was developed and used for category members as follows:

"Hydrocarbons", the first part of the name, recognizes the specific chemical class.

The carbon number range typically identifies at least 80% of the chemical constituents in the substance.

The structures are identified by the types of hydrocarbons present: n-paraffins (n-alkanes), iso-paraffins (isoalkanes), cyclic-paraffins or naphthenics (cyclics), and aromatics. The first three are mentioned when present in the substance at a level between 10 and 80%. Aromatics will be indicated as per the High Production Volume category and when present as a smaller fraction, identified at levels less than or greater than 2%.

Components with specific toxicology or classification will be mentioned, using the classification cut-off as an indication level (according to EU DSD [Dangerous Substances Directive] and GHS [Global Harmonized System of Classification and Labeling of Chemicals] guidance).

Based on structure and composition, the category has been divided into three subcategories to more accurately characterize member physico-chemical and environmental endpoints. Sub-categorisation was not needed for human health endpoints and therefore in the human health sections the whole category is evaluated. CAS RNs and a general description of compositions of subcategory members are as follows:

n-Paraffins Subcategory - 6 CAS RNs, three are composed of a single, normal paraffin

629-59-4	linear C_{14} paraffin, n-tetradecane
629-62-9	linear C_{15} paraffin, n-pentadecane
544-76-3	linear C_{16} paraffin, n-hexadecane
64771-72-8†	linear C_{5-20} paraffin, a complex combination of n-paraffins, paraffins, petroleum, normal C_{5-20}
90622-46-1†	a multi-constituent substance that can be composed predominantly of linear C_{14-16} normal paraffins, Alkanes C_{14-16}
90622-47-2†	a multi-constituent substance that can be composed predominantly of linear C_{14-17} normal paraffins, Alkanes C_{14-17}

Iso-Paraffins Subcategory - 2 CAS RNs, composed of a range of isoparaffins predominantly in the C_{13} to C_{16}, or C_{11} to C_{17} range

68551-20-2†	alkyl-branched C_{13} to C_{16} isoparaffin, Alkanes, C_{13-16}, iso-
64741-73-7†	a multi-constituent substance that can be composed predominantly of branched C_{11} through C_{17} isoparaffin isomers, Distillates, petroleum, alkylate

Multi-constituent Subcategory - 4 CAS RNs composed of paraffins predominantly in the C_{14} to C_{20} range with varying concentrations of normal paraffins, isoparaffins, and/or cycloparaffins, that can include members and constituents from the normal and isoparaffin subcategories

- 64741-85-1† raffinates, petroleum, sorption process
- 64741-91-9† distillates, petroleum, solvent-refined middle
- 64742-46-7† distillates, petroleum, hydrotreated middle
- 64742-47-8† distillates, petroleum, hydrotreated light

For the environment, ECOSAR and read-across approaches have been used to address and support the data gaps for the category members. The available toxicology data show that the C_{14}-C_{20} Aliphatic Hydrocarbon Solvents have similar levels of toxic potency under a variety of experimental conditions.

The category has been defined for members with specific purity/impurity profiles or composition as outlined in the full SIDS Initial Assessment Report and the SIDS Dossiers.

The conclusions of this assessment do not necessarily apply to substances with the same CAS number but different purity/impurity profiles or compositions.

† Denotes a UVCB substance.

Read-Across Substance Identification

In addition to the available physical and biological data for substances in this category, data for the following analogues are also presented, as necessary, to support the characterization of selected endpoints:

CAS RN 124-18-15; n-decane

CAS RN 1120-21-4; Undecane

CAS RN 112-40-3; n-dodecane

CAS RN 1921-70-6; pristane; (2, 6, 10, 14-tetramethylpentadecane, an iso- (branched) alkane)

CAS RN 64742-48-9; Hydrocarbons, C9-C11, n-alkanes, isoalkanes, cyclics, < 2% aromatics

CAS RN 90622-57-4; Hydrocarbons, C_{10}-C_{12}, isoalkanes, <2% aromatics

CAS RN 64741-65-7; Hydrocarbons, C10-C12, isoalkanes, < 2% aromatics

CAS RN 64742-48-9; Hydrocarbons, C10-C13, n-alkanes, isoalkanes, cyclics, < 2% aromatics

CAS RN 64742-47-8; Hydrocarbons, C12-C16, n-alkanes, isoalkanes, cyclics, < 2%

CAS RN 60908-77-2; Isohexadecane

CAS RN 8008-20-6; Jet-A and JP-8 (having a carbon range of 8-16 carbons)

CAS RN 64742-54-7; C20-C50 hydrotreated oil

CAS RN 52845-07-5; Iso-eicosane

CAS RN 64771-72-8; hydrocarbons, C10-C13, n-alkanes, <2% aromatics

CAS RN 93924-07-3; C10-C13, n-, iso-, cycloalkanes, <2% aromatics

The nine of the read-across substances form a physical-chemical continuum with the C_{14}-C_{20} Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category and contain a range of carbons and physical-chemical properties that are either immediately above or below the range specified for the C_{14}-C_{20} Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category.

The read-across candidates have comparable toxicities to those of the C_{14}-C_{20} Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category. Hydrocarbon absorption is inversely related to the number of carbon atoms; that is to say that the lower the number of carbons in a substance, the greater is its potential to be absorbed in the intestine. While hydrocarbon molecules in the range of C9 to C14 are absorbed from the intestinal tract, they are poorly absorbed through the skin. The C9 to C14 aliphatic hydrocarbons are orally absorbed at a greater rate than hydrocarbon molecules with C14 to C20. The read-across substances above are fully saturated hydrocarbons. Minimal to no toxicity was noted in read-across studies for repeated doses, reproductive/developmental studies, in *in vitro* and *in vivo* studies. Since no toxicity was observed in these substances, using a read-across strategy, substances in the C_{14}-C_{20} Aliphatic (≤2% aromatic) Hydrocarbon Solvents Category would be interpolated to have similar properties.

The Jet-A, Jet-8, and C20-C50 hydrotreated oil substances are wide cut hydrocarbon streams and are less refined than the hydrocarbon solvents. Typically, Jet-A, Jet-8, and C20-C50 hydrotreated oil contain more aromatics than the C_{14}-C_{20} Aliphatic (≤2% aromatic) Hydrocarbon Solvents Category and are not as severely refined. Test results from these substances could be considered a "worst-case" scenario when using the data to read-across to the C_{14}-C_{20} Aliphatic (≤2% aromatic) Hydrocarbon Solvents Category.

Data for the following analogues are also presented to support the characterization of selected endpoints.

Analogue (CAS RN)	**Composition**	**Endpoint(s) Characterized**
124-18-5	n-decane	*In vivo* mutagenicity Reproductive toxicity
112-40-3	n-dodecane	*In vivo* mutagenicity
1120-21-4	n-undecane	Reproductive toxicity
1921-70-6	2, 6, 10, 14-	Toxicokinetics, metabolism, and

	tetramethylpentadecane	distribution
8008-20-6	Jet A, JP8, JP(100)	Acute toxicity (dermal) Reproductive toxicity (oral)
60908-77-2	Isohexadecane	Acute toxicity (oral) Irritation (dermal, eye) *In vitro, in vivo* mutagenicity
52845-07-5	iso-eicosane	Irritation (dermal)
64742-54-7	C20-C50 hydrotreated oil	Repeat dose toxicity (inhalation)
64741-65-7	hydrocarbons, C10-C12, isoalkanes, <2% aromatics	Subchronic toxicity (inhalation)
64771-72-8	hydrocarbons, C10-C13, n-alkanes, <2% aromatics	*In vivo* mutagenicity
64742-48-9	hydrocarbons, C9-C11, n-alkanes, isoalkanes, cyclics, <2% aromatics	*In vivo* mutagenicity
93924-07-3	C10-C13, n-, iso-, cycloalkanes, <2% aromatics	*In vivo* mutagenicity
90622-57-4	C_{10}-C_{12}, isoalkanes, <2% aromatics	Acute fish and invertebrate toxicity Alga toxicity Biodegradation *In vivo* mutagenicity

Substances in the C_{14}-C_{20} Aliphatic Hydrocarbon [≤2% aromatics] Solvents Category can be composed of a single chemical or a range of hydrocarbons that can include n-paraffinic, isoparaffinic, and/or cycloparaffinic (naphthenic) structures that fall predominantly within a C number range of 14 to 20. As a result, some category member's physicochemical properties can be characterized by a range of values as a function of composition because a single value is not possible. For example, a multi-constituent hydrocarbon substance will not exhibit a single P_{ow} value, but rather a range based on its composition. This would be the case regardless of whether the data were measured using a standard testing procedure or calculated based on the individual constituent chemicals.

For some properties, the value range is based on a series of representative hydrocarbons that were selected by industry, based on hydrocarbon process (distillation) knowledge, to accurately characterize category members. The hydrocarbons selected include paraffins from C_{14} to C_{20} (see the following list). Chemicals with single multi-carbon chains and/or multiple methyl groups were chosen to provide the most comprehensive range of expected values.

Chemical Name	**CAS RN**
n-tetradecane	629-59-4
n-pentadecane	629-62-9
n-hexadecane	544-76-3
n-octadecane	593-45-3
eicosane	112-95-8
2,5,6,9-tetramethyldecane	n/a
2,5,8-trimethyl-tridecane	n/a
2,5,6,9,11-pentamethyl-tridecane	n/a
2,3,6,7-tetramethyldecalin	n/a
1,6-di-n-propyldecalin	n/a
1,6-di-n-pentyldecalin	n/a

n/a = not available

Physical-chemical Properties

The members of the C_{14}-C_{20} Aliphatic Hydrocarbon Solvents [≤2% aromatics] Category are liquids at room temperature. The melting point values range from -42 to -69 °C. The boiling points range from 170 to 335 °C. The vapor pressure values range from <0.001 to 0.78 hPa at 25 °C. Water solubility values range from <0.001 to 0.13 mg/L (at 25 °C) with a relative density range of 0.70 to 0.86 g/cm^3 (at 15 to 20 °C). The log K_{ow} values for the category members range from 5.9 to 10.2 (at 25 °C). Physical-chemical properties for category members include both measured and calculated values.

Human Health

Toxicokinetics, Metabolism, and Distribution

It is estimated that ~ 50% (37% - 61%) of a C14-C20 hydrocarbon solvent would be absorbed when ingested. C14-C20 aliphatic, <2% aromatic hydrocarbon fluids are typically metabolized by side chain oxidation to alcohol and carboxylic acid derivatives. These metabolites can be glucuronidated and excreted in the urine or further metabolized before being excreted. The majority of the metabolites are expected to be excreted in the urine and to a lower extent, in the feces. Excretion is expected to be rapid with the majority of the elimination occurring within the first 24 hours of exposure. This is supported in repeated dose studies with analogue substances (see table above) where hypertrophy of the liver was observed; this is an adaptive change in order to metabolize the test material.

There have not been any *in vivo* dermal absorption studies of C14 - C20 aliphatic, <2% aromatic hydrocarbon fluids, but there have been *in vitro* studies of similar constituents, including one category member, hexadecane (CAS RN 544-76-3). Dermal absorption of hexadecane was determined to be only 0.18% of the applied dose; other constituents are expected to have similarly low dermal absorption rates.

Acute Toxicity Summary

The available acute toxicity data demonstrate that hydrocarbon solvent substances tested in the C14-C20 Aliphatic Hydrocarbon Solvents (≤2% aromatics) Category did not demonstrate acute toxicity at the limit dose by the oral, dermal, and inhalation routes of exposure.

Acute Inhalation Toxicity

Acute inhalation LC_{50} values in rats for C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) (C14-C16 n-Paraffins, CAS RN 90622-46-1) ranged from >5266 to >5800 mg/m^3 (aerosol, the highest achievable concentration). Concentrations were dependent on the inherent physical-chemical properties of the test material, e.g., volatility, thus limiting the study design to the maximum achievable saturated vapor/aerosol concentration.

Acute Dermal Toxicity

Three acute dermal toxicity studies were conducted on commercial C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) products. All studies were conducted similarly to OECD TG 402 without GLP compliance. The dermal LD_{50} in rabbits was greater than 2000 mg/kg bw (Hydrocarbons, C14-C17, n-alkanes, <2% aromatics, CAS RN 90622-47-2; C14-C16 n-Paraffins, 90622-46-1). No data were available for the other subcategories.

Acute Oral Toxicity (gavage administration)

The acute 14-day, single dose, oral gavage, toxicity studies were conducted in rats on commercial C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics). The LD_{50} results of the oral studies in rats ranged from >5.0 to 36.0 g/kg bw (CAS RN 90622-46-1, 64771-72-8, and 60908-77-2). However, these C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) products may be an aspiration hazard based on their viscosities. Chemicals with a viscosity of <20.5 mm^2/sec at 40°C should also be considered an aspiration hazard (the accidental inhalation of fluids into the lungs).

Irritation and Sensitisation

Irritation studies were conducted in rabbits on commercial C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) (CAS RN 64742-47-8, 64742-46-7, 90622-47-2, 60908-77-2 (analogue), 90622-46-1, and 52845-07-5 (analogue)). In dermal irritation tests, the average erythema score (24, 48, 72 hours) results were 0.0 to 1.11, but generally below 1.0. The average edema score (24, 48, 72 hours) results were 0.0 to 1.0, but generally 0.0, suggesting that these solvents produce no to minimal irritation to rabbit skin. One study (CAS

90622-46-1) used a prolonged 24 hour exposure and an occlusive dressing. The average erythema score (24, 48, 72 hours) of 3.0 and the average edema score (24, 48, 72 hours) of 1.4 indicate that under prolonged, occluded exposure, hydrocarbons can display an irritancy potential. One study examined the relative irritancy potential of n-tetradecane (CAS RN 629-59-4), n-pentadecane (CAS RN 629-62-9), and n-hexadecane (CAS RN 544-76-3). This study used an occlusive dressing and a 96 hour continuous exposure; under these conditions n-tetradecane was the most irritating substance. Due to the occlusive nature of the dressing, these conditions are not anticipated to be encountered outside of experimental settings.

Several eye irritation studies were conducted in rabbits on commercial C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) (CAS RN 64742-47-8, 90622-47-2, 90622-46-1and 60908-77-2 [analogue]). The average conjunctivae score (24, 48, 72 hours) results were 0.0 to 0.33. The average chemosis score (24, 48, 72 hours) results were 0.0 to 0.1; all iritis and cornea opacity scores were 0 for all studies. These results suggest that these solvents produce no to minimal irritation to the eyes of rabbits.

Seven studies were available on the irritation and/or sensitisation potential of several types of hydrocarbon solvents in human volunteers (n-alkane UVCB substances: 64771-72-8; n-alkane, iso-alkane, and cyclic alkane UVCB substances:CAS RN: 64742-47-8 and 64742-46-7). Clinical tests were conducted with populations ranging from 24 to 112 patients. N-alkanes did not cause a sensitisation or irritation effect; the mixed aliphatics did not cause a sensitisation or irritation effect. Based on these data, the C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) substances are not expected to be sensitizers or skin irritants.

Mild irritation was noted at 75% concentration of Paraffins, petroleum, normal C_{5-20} (CAS RN 64771-72-8; alternative name C14-C17, n-alkane <2% aromatics) under occlusive conditions; one volunteer had a minimal reaction on rechallenge, but when retested, did not develop any reaction. Under occlusive conditions at ≥75%, the Paraffins, petroleum, normal C_{5-20} was determined to be a mild skin irritant. No irritation or sensitisation was noted in a 21-day cumulative patch test on human volunteers when Paraffins, petroleum, normal C_{5-20} (CAS RN 64771-72-8) was applied at 25% concentration under occlusive conditions. Hydrocarbons, C14-C18, n-alkanes, isoalkanes, cyclics, <2% aromatics (CAS RN: 64742-47-8) tested using an occlusive patch at 75% w/w, demonstrated some irritation potential, but did not demonstrate any sensitization potential in the volunteers. When evaporation is prevented through the use of occlusive dressings, the physical properties of the dermis are altered and hydrocarbons can display an irritancy potential. However, this scenario is unlikely to occur during normal use of hydrocarbons.

Based on the data presented above, the category members are not expected to be eye irritants; the category members are not expected to cause skin irritation under semi-occlusive conditions. No toxicological studies have demonstrated skin defatting (which may result in cracking of the skin) but it is a well known property of organic solvents. Category members are not expected to have the potential to cause skin sensitization.

Repeated Dose Toxicity (Inhalation)

No inhalation repeated dose studies were located for the C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) Category. Using a read-across approach, a repeated dose inhalation study was conducted in a C9-C14 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) Category substance. Hydrocarbons, C10 - C12, isoalkanes, < 2% aromatics (CAS RN 64741-65-7, analogue) was administered via inhalation to rats at concentrations of 0, 2600, 5200 or 10400 mg/m^3 (vapor) for 6 hours/day; five days/week for 13 weeks (similar to OECD TG 413). No adverse effects were observed at 10400 mg/m^3. Based on these observations, the repeat inhalation concentration NOAEC is 10400 mg/m^3 (10.4 mg/L) for C9-C14 aliphatic, < 2% aromatic hydrocarbon fluids.

In a second study, data on a C20-C50 hydrotreated oil (CAS RN 64742-54-7; average carbon number C35, analogue) can be used as read-across to demonstrate minimal toxicity at the upper bound carbon number range. A C20-C50 hydrotreated oil (HO) with 2.4% aromatics is a less refined UVCB than the C14-C20 Aliphatic, ≤ 2% Aromatics Hydrocarbon Solvents and showed minimal toxicity in rats at exposures up to 1000 mg/m^3, aerosol (MMAD 1.1 + 0.1 µm; GSD 1.9 + 0.1). The exposure was conducted for 28 days at aerosol concentrations at 0, 50, 210 or 1000 mg/m^3 for 6 hours per day, 5 days per week (similar to OECD TG 412). The only treatment-related changes were increased lung weight and an increased in associated lymph nodes weight. Increases in lung weights may have been related to the increased numbers of alveolar macrophages and other cells and/or the presence of residual oil. These findings are consistent with other published studies that showed a progressive accumulation of alveolar macrophages as a result of an increased deposition of aerosolized oil particles. The authors of this paper concluded that the NOEC (No Observed Effect Concentration) was 220 mg/m^3 (analytical) based on the accumulation of macrophages in the lungs; the systemic NOAEC was determined to be 980 mg/m^3 (analytical) based on the lack of any observed systemic toxicity. Mild accumulation of alveolar macrophages is not expected to be an adverse effect in a C14-C20 Aliphatic, ≤ 2% Aromatics Hydrocarbon Solvent due to their lower carbon number, molecular weight, and

higher vapor pressure and expected metabolism; these physical-chemical properties would result in increased clearance from the lungs. This study was included to demonstrate the lack of systemic toxicity of higher molecular weight and less refined UVCBs. Based on the read-across data and a weight of evidence approach, substances in the C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) Category are expected to have minimal systemic inhalation toxicity.

Repeated Dose Toxicity (Oral)

No oral repeated dose studies were located for the C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) Category. One available read-across study from the structurally analogous test material Hydrocarbons, C10-C13, n-alkanes, isoalkanes, cyclics, < 2% aromatics (CAS RN 64742-48-9, analogue) was analyzed. All tests were performed in a manner similar or equivalent to currently established OECD TG 408. Exposures were conducted for 90 days by oral gavage in rats at concentrations of 5000 mg/kg bw/day (actual ingested), 2500 mg/kg bw/day (actual ingested), or 500 mg/kg bw/day (actual ingested). Several changes were noted in clinical chemistry, hematological, and organ weights; these effects were considered to be adaptive in response to the administration of the test material and were not considered to be biologically adverse. Except for the α2μ-globulin effects noted in the kidneys in male rats, all effects were reversible in the recovery group. Nephropathy due to α2μ-globulin is a phenomenon well documented in male rats that are exposed to hydrocarbons; it is not relevant to human health. The systemic NOAEL was determined to be higher than 5000 mg/kg bw/day in rats.

No data were available on neurotoxicity.

Based on the analogue data above, the C14-C20 Aliphatic Hydrocarbon Solvents (≤2% aromatics) Category members are expected to have similar or lower toxicity via the oral route than the analogue substances due to predicted lower absorption.

Mutagenicity

Materials in the C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) were evaluated in several *in vitro* genotoxicity assays. The results of the Ames Reverse Mutation Assays (OECD TG 471) using the test materials: Hydrocarbons, C14-C18, n-alkanes, isoalkanes, cyclics, <2% aromatics (CAS RN 64742-47-8), Isohexadecane (CAS RN 60908-77-2), and C14-C17, n-alkanes <2% aromatics (CAS RN 64771-72-8) were negative both with and without metabolic activation. An *in vitro* mammalian chromosome aberration test (OECD TG 473), conducted with the structurally analogous test material, Hydrocarbons, C12-C16, n-alkanes, isoalkanes, cyclics, < 2% (CAS RN 64742-47-8, analogue), was negative with and without metabolic activation.

There were no *in vivo* mutagenicity studies located for materials in the C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) Category. However, substances in the C9-C14 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) Category were evaluated in a mouse micronucleus assay and in a dominant lethal assay. The substance Hydrocarbons, C10-C12, isoalkanes < 2% aromatics (CAS RN 90622-57-4, analogue) was found to be not genotoxic in a dominant lethal assay up to 900 ppm (inhalation) (OECD TG 478). Similarly, Hydrocarbons, C9-C11, n-alkanes, isoalkanes, cyclics, < 2% aromatics (CAS RN 64742-48-9, analogue) was not genotoxic in a dominant lethal assay up to 900 ppm (inhalation) (OECD TG 478, analogue). The read-across test materials, Hydrocarbons, C10-C13, n-alkanes, < 2% aromatics (CAS RN 64771-72-8) and Hydrocarbons, C10-C13, n-alkanes, isoalkanes, cyclics, < 2% aromatics (CAS RN 64742-48-9, analogue), were not clastogenic in two micronucleus assays (OECD TG 474). DNA adduct formation was not observed in an *in vivo* study conducted using the read-across test materials n-decane (CAS RN 124-18-15, analogue) and n-dodecane (CAS RN 112-40-3, analogue).

As there was no evidence of clastogenicity or genotoxicity in any of the assays, based on a weight of evidence approach, substances in the C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) Category are not expected to be genotoxic.

Reproductive and Developmental Toxicity

There are no studies for reproductive effects conducted with C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) Solvents Category products; however, there are data available in three read-across substances; decane, undecane, and JP-8 fuel. A C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) Category product was tested for developmental toxicity.

There are two reproductive studies available on products from the read-across material from the C9-C14 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics). Undecane (CAS RN 1120-21-4, analogue) was examined in rats in a one generation reproduction study. No effects to reproductive performance or to developmental

endpoints were observed at the highest dose tested (NOAEL =1000 mg/kg bw/day). A Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test similar to OECD TG 422 was conducted using decane (CAS RN: 124-18-5, analogue). No effects to reproductive performance or to developmental endpoints were observed at the highest dose tested; the NOAEL = 1000 mg/kg bw/day.

Lower carbon chain molecules are predicted to be absorbed to a greater extent than higher carbon chain molecules when administered orally; decane and undecane are predicted to be absorbed approximately 72 to 77%. It is estimated that ~ 50% (37% - 61%) of a C14-C20 hydrocarbon solvent would be absorbed when ingested. Since the studies for decane and undecane demonstrated no reproductive toxicity and were absorbed to a greater extent than the C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) Solvents Category products, substances in this category are unlikely to cause reproductive toxicity.

The read-across test material JP-8(CAS RN: 8008-20-6, analogue) was examined in two, one-generation reproduction studies. JP-8 is a UVCB with an aliphatic carbon range of C8-C16 and may contain up to 25% aromatics.

In the first study, male rats were given 0, 750, 1500 or 3000 mg/kg neat JP-8(CAS RN: 8008-20-6; an aliphatic carbon range of C8-C16, aromatics ≤25%) daily by gavage for 70 days prior to mating with naive females to assess fertility and sperm parameters (similar to OECD TG 415). Males were allowed to mate while continuing to receive treatment. Aside from a decrement in male body weight in the 3000 mg/kg bw/day dose group, no clinical signs were observed. There were no statistical differences noted in any reproductive parameter measured. The reproductive NOAEL = 3000 mg/kg bw/day for male rats.

In the second study, female rats were dosed by gavage at 0, 325, 750 or 1500 mg/kg bw/day with neat JP-8 (CAS RN: 8008-20-6; an aliphatic carbon range of C8-C16, aromatics ≤25%) for a total of 21 weeks (90-day plus mating with naive males, gestation and lactation periods) in an effort to assess general toxicity, fertility and reproductive endpoints (similar to OECD TG 415). The NOAEL was 1500 mg/kg bw/day for female fertility, the highest dose tested. The NOAEL for the pup was 750 mg/kg bw/day based on a decrease in body weight which correlated with a decrease in maternal body weight at 1500 mg/kg bw/day.

A C14-C20 Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) Category product was tested for developmental toxicity and showed no evidence of causing embryonic or teratogenic effects in rats. Hydrocarbons, C16-C20, n-alkanes, isoalkanes, cyclics, <2% aromatics (CAS RN 64742-46-7) were studied in rats in a Prenatal Developmental Toxicity Study (OECD TG 414). The maternal systemic toxicity NOAEL = 1000 mg/kg bw/day; the developmental toxicity NOAEL = 1000 mg/kg bw/day, the highest dose tested.

In summary, no developmental effects were observed in the category member at the highest dose tested (1000 mg/kg bw/day). No effects to fertility were noted in the read-across substances decane, undecane, and JP-8 fuel up to 3000 mg/kg bw/day. Based on this data, the C14-C20 Aliphatic Hydrocarbon Solvents (≤2% aromatics) Category members are not expected to be reproductive or developmental toxicants.

Carcinogenicity

No carcinogenicity studies for C_{14}-C_{20} Aliphatic Hydrocarbon Solvents (≤2% aromatics) Category members were located in the scientific literature.

The C_{14}-C_{20} Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) Category substances may possess properties indicating hazard for human health (aspiration and possible skin defatting with repeated exposure). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Members of the C_{14}-C_{20} Aliphatic Hydrocarbon Solvents (≤2% aromatics) Category have a low potential to volatilize from surface waters, based on Henry's Law constants (HLC) representing volatility for category members that range from 1.8×10^4 to 4.6×10^6 Pa-m^3/mole. In the air, category members have the potential to degrade through indirect photolytic processes mediated primarily by hydroxyl radicals ($^{\bullet}OH$) with calculated degradation half-lives ranging from 3.8 to 7.6 hours or 0.31 to 0.63 days, based on a 12-hr day and a $^{\bullet}OH$ concentration of 1.5×10^6 $^{\bullet}OH/cm^3$. These chemicals are unlikely to degrade by hydrolysis as they lack a functional group that is hydrolytically reactive.

Determining the biodegradation potential of UVCBs can be challenging. The result for each multi-constituent substance (UVCB) characterizes the biodegradability of that substance as a whole, but it does not suggest that each constituent of the UVCB is equally biodegradable. As with all ready biodegradation test guidelines, the

test system and study design used with these substances (OECD TG 301F) is not capable of distinguishing the relative contribution of the substances' constituents to the total biodegradation measured (constituents with higher branching/cyclic structures may degrade to a lesser extent than linear and less branched structures). The n-paraffins sub-category members have the potential to biodegrade rapidly based on results that support their characterization as readily biodegradable. In comparison, members of the iso-paraffins subcategory are expected to demonstrate a slower rate of biodegradation based on results for one of the multi-constituent isoparaffinic substances, which was shown not to be readily biodegradable, but did demonstrate a moderate extent of biodegradation (25%) over an extended period of time (37 days). Multi-constituent subcategory members are not expected to be readily biodegradable.

Mackay Level III fugacity modeling indicates that category member constituents partition mostly to the sediment and soil compartments when an equal emission rate (1000 kg/hr) to the air, water, and soil compartment is assumed. When release occurs only to either the air or soil compartment, members are indicated by the model to partition largely to the compartment to which they are released. When release occurs only to the water compartment, members are indicated in the modeling to partition to the soil and sediment compartments.

When released primarily to the air compartment, the primary mode of removal would be via photodegradation. Although the substances and their chemical constituents demonstrate a range of water solubility with most constituents having relatively low solubility, wet deposition of category chemical constituents is not likely to play a significant role in their atmospheric fate because of their rapid photodegradation. Volatilization to the air can contribute to the loss of category chemical constituents from aqueous and terrestrial habitats.

Category members are expected to sorb to organic matter in soil, sediment, and wastewater solids based on log K_{oc} values ranging from 5.1 to 8.8. Category members have a potential to bioaccumulate, based on measured and calculated BCF values (based on the GHS criteria of >500). Determining the bioaccumulation potential of UVCBs can be challenging. BCF values for n-paraffins, iso-paraffins, and cycloparaffins can be different due to differences in metabolism in aquatic organisms. Constituents with higher branching/cyclic structures may therefore bioaccumulate to a greater extent than linear and less branched structures. It should be noted that for highly lipophilic constituents uptake through the diet may exceed the direct uptake through water.

Sufficient data are available to characterize the fish, invertebrate, and algae acute toxicity of the C_{14}-C_{20} Aliphatic Hydrocarbon Solvents [≤2% aromatics] Category. Category members are not expected to exhibit acute toxic effects to aquatic organisms at or below the limit of water solubility. High treatment loading water-accommodated-fractions from substances in this category, as well as analogue substances from the C_9-C_{14} Aliphatic Hydrocarbon Solvents (≤2% aromatics) Category, fail to cause acute mortality and/or effects to both freshwater and marine fish, invertebrates, and algae (at nominal loadings >1000 mg/l). Chronic studies with a substance in the C10-C12 isoparaffinic range indicated an effect (NOEC = 0.025mg/l), but isoparaffins in the C11-C13 range did not. In chronic invertebrate studies, no effects were observed up to 1 and 5 mg/l (highest loading tested) for the C11-C13 and C13-C16 carbon ranges (CAS RN: 90622-58-5, 64742-47-8) respectively. The lack of acute or chronic aquatic toxicity, for the C14-C20 carbon range, is likely due to the low water solubility of their constituent chemicals.

Chemicals in this category do not possess properties indicating a hazard for the aquatic pelagic environment (no observed acute or chronic toxicity at the limit of water solubility). Category members have a potential to bioaccumulate. n-Paraffin category members are readily biodegradable, while isoparaffinic and multi-constituent members are not. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Production/Use/Exposure

Production

As reported to the U.S. Environmental Protection Agency for the year 2006, companies produced or imported the following volumes of C_{14}-C_{20} hydrocarbon solvents:

- n-Tetradecane, CAS RN 629-59-4: 4500-22,500 metric tons (10 million to < 50 million pounds)
- Pentadecane, CAS RN 629-62-9: 450-4500 metric tons (1 million to < 10 million pounds**)**
- Hexadecane, CAS RN 544-76-3: 450-4500 metric tons (1 million to < 10 million pounds**)**
- Paraffins, (petroleum), normal C5-20, CAS RN 64771-72-8: 45,000-225,000 metric tons (100 to <500

million pounds) †
- Alkanes, C_{14}-$_{16}$, CAS RN 90622-46-1: 4500-22,500 metric tons (10 million to < 50 million pounds) †
- Alkanes, C_{14}-$_{17}$, CAS RN 90622-47-2: No data†
- Alkanes, C_{12}-$_{14}$, CAS RN 129813-67-8: No data†
- Alkanes, C_{12}-$_{14}$-iso-, CAS RN 68551-19-9: 450-4500 metric tons (1 million to < 10 million pounds) †
- Alkanes, C_{13}-$_{16}$-iso-, CAS RN 68551-20-2: 450-4500 metric tons (1 million to < 10 million pounds) †
- Distillates, (petroleum), alkylate, CAS RN 64741-73-7: 450,000 or greater metric tons (1 billion pounds or greater) †
- Raffinates, (petroleum), sorption process, CAS RN 64741-85-1: 450,000 or greater metric tons (1 billion pounds or greater) †
- Distillated, (petroleum), solvent-refined middle, CAS RN 64741-91-9: 45,000-225,000 metric tons (100 to <500 million pounds) †
- Distillates, (petroleum), hydrotreated middle, CAS RN 64742-46-7: 450,000 or greater metric tons (1 billion pounds or greater) †
- Distillates, (petroleum), hydrotreated light, CAS RN 64742-47-8: 450,000 or greater metric tons (1 billion pounds or greater) †

† Denotes a UVCB substance.

Use

Hydrocarbon solvents in the C_{14}-C_{20} range with aromatic contents of less than or equal to 2% have relatively low volatility and are odorless. They are sold for many uses, i.e., ink oils, consumer substances, mineral seal oil, and as light lubricants. The predominant commercial uses of C_{14}-C_{20} aliphatic ≤2% aromatic hydrocarbon solvent substances are in lubrication, ink transfer, insecticide carrier base, and specialized metalworking solvents. This information is based on a survey of the industry sponsors and represents the commercial applications in which these products are sold, which includes the US, European and Japanese markets. Further information was not available.

Exposure

The sources for potential environmental exposure to C_{14}-C_{20} Aliphatic Hydrocarbon Solvents (≤2% aromatics) Category substances could include releases from chemical and petroleum manufacturing/processing facilities, releases from facilities that use C_{14}-C_{20} Aliphatic Hydrocarbon Solvents (≤2% aromatics) Category substances, and releases from industrial products that include C_{14}-C_{20} Aliphatic Hydrocarbon Solvents (≤2% aromatics) Category substances.

Hydrocarbon solvents in the C_{14}-C_{20} Aliphatic Hydrocarbon Solvents (≤2% aromatics) Category are generally used in coatings, cleaning agents, agricultural chemicals, fuel, lubricants, and functional fluids. Exposure includes occupational exposure and consumer use.

large fatty droplets in hepatocytes. In a mouse study using the same exposure regime, the LOAEC of 64 mg/m^3 was based on large fatty droplets and cytoplasmic globules in hepatocytes. In a combined chronic toxicity/carcinogenicity study, 50 rats/sex/concentration were exposed by inhalation to 0, 32, 160 or 800 mg/m^3 for 6 hours/day, 5 days/week for 2 years. A LOAEC of 32 mg/m^3 was established based on an increased incidence of elevated urinary protein level (which was combined with an increase of chronic nephropathy in females at higher dose levels). Histopathological effects in the liver were seen at 160 mg/m^3. A NOAEC of 32 mg/m^3 was found in mice exposed under the same conditions, based on reduced survival, reduced body weight gain, increased liver weight, liver histopathology and the associated increased enzyme activities indicative of liver toxicity at 160 and 800 mg/m^3. Oral exposure of rats and mice (weight of evidence approach of studies with limited information) showed also that liver effects were the most critical as indicated by increased enzyme activities (LDH, AST, ALT), increased liver weight and histopathological effects (hepatocytic centrilobular vacuolization, hepatocytomegaly) and decreased liver excretion function. From a 12-week study in male rats given 0, 1, 10 or 33 mg/kg bw/day a NOAEL of 1 mg/kg bw/day was established. Increased enzyme activities indicative of liver toxicity and abnormal liver histopathology resulted from doses of 10 mg/kg bw/day and above. In an epidemiological study among chemical plant workers there was some indication of an effect on liver function in those exposed to 6.2 – 75 mg/m^3 carbon tetrachloride. Suppression of immune function has been seen in mice after oral repeated dosing, but not in rats.

The majority of in vitro mutagenicity studies were negative. Ambiguous or positive results have been obtained in some Salmonella tests, and studies in fungi were consistently positive. *In vitro* genotoxicity assays in mammalian cells gave mixed results. Evidence of gene mutations is in general not found in *in vivo* tests, including in transgenic mice. There is some evidence that carbon tetrachloride administration results in DNA breakage and fragmentation in the liver of treated mice and rats; however, extensive hepatotoxicity was seen in each of the studies where DNA damage has been reported. While some of the damage may be due to reactive species formed during carbon tetrachloride metabolism and lipid peroxidation, much of the observed damage appears to be more related to a cytotoxic response associated with cell death rather than to a genotoxic response leading to mutation. There was no evidence of activity when carbon tetrachloride was tested in conventional assays for chromosomal damage in the rat or mouse bone marrow. There is some evidence that following high cytotoxic doses of carbon tetrachloride, increases in chromosome breakage and loss can occur in the rat liver. The increases that have been observed have occurred exclusively at hepatotoxic doses. Carbon tetrachloride did induce DNA adduct formation via reactive oxygen species and lipid peroxidation products in the liver of rodents. No unscheduled DNA synthesis was noted in livers of carbon tetrachloride-treated rats or mice even when tested under conditions producing significant hepatotoxicity.

Based on overall weight of evidence, carbon tetrachloride is not considered to be a mutagen *in vivo*. Genotoxic effects observed *in vivo* occur in the presence of overt cytotoxicity as a response to cell damage as well as oxidative stress.

Preneoplastic lesions of hepatocarcinogenesis, i.e. altered cell foci, recognized as glutathione-S-transferase placental form positive foci, and increased mitosis were seen in a 90-day study in rats at 576 mg/m^3 and higher. Preneoplastic lesions of hepatocarcinogenesis were also seen at 800 mg/m^3 in the 2-year rat study. In the above mentioned combined chronic toxicity/carcinogenicity in rats and mice, the incidence of hepatocellular adenomas and carcinomas and/or combined was increased. Multiple occurrence of hepatocellular tumours and metastasis to the lung was noted. For rats, a NOAEC of 160 mg/m^3 was established based on hepatocellular adenomas and carcinomas combined. For mice, a LOAEC of 32 mg/m^3 was established based on hepatocellular adenomas. At higher concentration levels, phaeochromocytomas in the adrenal gland in mice were noted. Rats exposed for 6 weeks to 0, 6.4, 32, 160 or 800 mg/m^3 of carbon tetrachloride after being initiated with diethylnitrosamine also showed a concentration-related increase in pre-neoplastic liver lesions at the end of treatment with a NOAEC of 32 mg/m^3. After oral exposure to doses as low as 20 mg/kg bw/day 4 days apart, mice showed a marked increase of liver tumours in the presence of marked toxicity. Hamsters exposed orally to 20 mg/kg bw weekly had an increased incidence of liver tumours in the presence of overt toxicity. Overall, inhalation and oral exposure to carbon tetrachloride resulted in tumours in the liver of rodents, generally in the presence of hepatotoxicity. Benign tumours in the adrenal gland occurred in mice exposed by inhalation. No reliable dermal carcinogenesis study was available. In humans, there is inadequate evidence for the carcinogenicity of carbon tetrachloride as concluded by IARC.

Toxicity to reproduction was examined in a very limited manner during a 2-year feeding study where rats given

estimated doses of 0, 5-8 or 15-25 mg/kg bw/day of carbon tetrachloride were mated 5 times at 2-month intervals. A NOAEL of 15-25 mg/kg bw/day for parental toxicity and reproductive toxicity was claimed. In addition, in 90-day and chronic inhalation studies in rat and mouse no histological effects were found in sexual organs. As effects on luteinizing hormone were seen in a developmental study (see below) there is an uncertainty that carbon tetrachloride may cause an adverse effect on reproductive performance at higher doses. Exposure of female rats to 0, 2137 or 6425 mg/m^3 for 6 hours/day on days 6 to 15 of pregnancy according to OECD TG 414 (1981), resulted in a LOAEC of 2137 mg/m^3 for maternal and developmental toxicity. At this dose level, maternal body weight and food consumption were reduced and liver effects were observed; foetal body weight and crown-rump length were decreased. Pregnant rats were given 0, 25, 50 or 75 mg/kg bw/day during gestation days 6-15 by gavage and dams were allowed to deliver and sacrificed 6 days after parturition. A NOAEL of 25 mg/kg bw/day for maternal and developmental toxicity was established based on decrease of maternal body weight and full litter resorption. The latter was associated with reduced luteinizing hormone levels. In conclusion carbon tetrachloride has demonstrated developmental toxicity only at doses that are also maternally toxic.

Carbon tetrachloride possesses properties indicating a hazard for human health (acute toxicity (liver), slight skin and eye irritation, skin sensitization, repeated dose toxicity (liver, kidney), carcinogenic effects in experimental animals (principally liver tumours in the presence of hepatotoxicity), developmental toxicity at maternally toxic doses and neurotoxicity). Adequate screening-level data are available to characterise the hazard to human health for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

The primary sink of carbon tetrachloride is photodissociation in the stratosphere, but also losses by surface ocean uptake and uptake by soil are relevant. Estimates of the total atmospheric lifetime (the overall persistence of CTC in the troposphere and the stratosphere combined, taking into consideration the losses to the stratosphere, oceans, and soil) range from 20 to 35 years, with 26 years being the most recently refined value. The partial lifetime of CTC with respect to its loss to the stratosphere was derived to be 44 to 50 years.

CTC is little susceptible towards indirect photolysis by hydroxyl radicals in the troposphere (its estimated tropospheric half-life exceeds 330 years). Ultimately it diffuses upward into the stratosphere where it is photodegraded (185-225 nm) to form the trichloromethyl radical and chlorine atoms. Direct photolysis under stratospheric conditions is very efficient and the DT50 values range in the order of minutes. However the migration time from the troposphere to the stratosphere is very long and the migration time limits the dissipation. The rate of photodissociation begins to become important at altitudes >20 km, and increases with altitude. CTC and other reactive species formed by photodecomposition of CTC in the stratosphere catalyse reactions that deplete stratospheric ozone.

CTC is a greenhouse gas with a Global Warming Potential (GWP) of 1380 relative to CO_2.

Based on the available data, hydrolysis is not a relevant process for carbon tetrachloride degradation under environmental conditions as the rate of hydrolysis is extremely slow, with a calculated half-life of 7,000 years at a concentration of 1 ppm.

CTC seems to be toxic to aquatic microorganisms in concentrations higher than 10 mg/L. In water, under aerobic conditions, a negative result has been reported for a ready biodegradability test according to OECD TG 301C (MITI(I) test method), but at the high concentration used in the test, toxicity to bacteria may have prevented biodegradation. In another aerobic study a significant primary biodegradation of 80-87% in 7 days and 100% in subcultures after another 7 days at 5 and 10 mg/L has been observed (abiotic controls registered between 5 and 23% evaporation losses at 25°C for test substance concentrations of 5 and 10 mg/L, repectively). Under anaerobic conditions, several studies have reported metabolization and mineralisation of CTC under denitrifying as well as under methanogenic conditions (about 70% conversion after 3 weeks to mainly carbon dioxide under denitrifying conditions with non-adapted bacteria; complete degradation to carbon dioxide in 3 weeks under methanogenic conditions with adapted bacteria). However, CTC would not be expected to serve as a sole source of carbon and energy for heterotrophic bacterial growth. It can be concluded that CTC may be rapidly biodegraded under anoxic conditions by co-metabolism, provided that the specific requirements (redox potential, pH, absence of toxic metals) for the microorganisms are fulfilled. Under laboratory conditions it has been observed that the acetogenic

bacteria *Acetobacterium woodii* and *Clostridium thermoaceticum* in fructose/salts and glucose/salts media, respectively, degraded CTC completely within three days. Depending on the particular conditions chloroform, methylene chloride and chloromethane can be generated from CTC as transient intermediates.

Low bioconcentration factors (BCF) have been determined in aquatic species. In freshwater fish, BCF values have been measured in rainbow trout (40) and bluegill sunfish (30). In rainbow trout (*Salmo gairdneri* Richardson) bioconcentration in muscle was 17.7 ± 2.4.

Carbon tetrachloride has a moderate potential for adsorption in soil and will according to fugacity model level I partition for more than 99% to the atmosphere. Level III fugacity modelling (EPI Suite 4.1) with equal emissions to air, water and soil compartments indicate that CTC will partition predominantly to air (49%) and water (48%) with only minor parts to soil and sediment. If released to air only, carbon tetrachloride will remain almost completely in this compartment (>99%) with negligible partitioning to water, soil, and sediment. A Henry's law constant of 2370 $Pa.m^3$/mole at 20 °C suggests that volatilization from the water phase is expected to be high. A weighted mean K_{oc} value of 115.2 for two soil types (silt loam and sandy loam) was determined experimentally and indicates a moderate potential for adsorption in soil.

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

Taxon	Test species	Endpoint	Result [mg/l]	Comments
Fish, freshwater	*Danio rerio*	96h-LC_{50}	24 (m)	flow though (OECD TG 203)
Fish, freshwater	*Oryzias latipes*	96h-LC_{50}	7.6 (m, mortality)	semi-static (OECD TG 203)
Invertebrates, freshwater	*Daphnia magna*	48h-EC_{50}	8.1 (m, immobility)	semi-static (OECD TG 202)
Aquatic plants	*Pseudokirchnerella subcapitata*	72h-ErC_{50}	20 (m, growth rate)	static, closed system without headspace (OECD TG 201)

m: measured

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

Taxon	Test species	Endpoint	Result [mg/l]	Comments
Invertebrates, freshwater	*Daphnia magna*	21d-NOEC	3.1 (m, growth and reproduction)	semi-static, closed system without headspace (OECD TG 211)
	Daphnia magna	21d-EC50 21d-NOEC	1.8 mg/l (m, inhibition of reproduction) 0.49 (m, inhibition of reproduction)	semi-static (OECD TG 211)
Aquatic plants	*Pseudokirchnerella subcapitata*	72h-NOEC	2.2 (m, growth rate)	static, closed system without headspace (OECD

				TG 201)
Microorganisms	*Pseudomonas putida*	16h-TT	30	no guideline study

m: measured; TT: toxicity threshold

The toxicity of CTC on embryo-larval stages was tested on the amphibian *Rana temporaria*, *Rana pipiens*, *Ambystoma gracile* and *Xenopus laevis* using a covered flow-through test system. LC_{50} was calculated at 0 days and 4 days beyond hatching. The values are 4.56 mg/L and 1.16 mg/L respectively for *Rana temporaria*, 6.77 mg/L and 1.64 mg/L respectively for *Rana pipiens*, 9.01 mg/L and 1.98 mg/L respectively for *Ambystoma gracile* and > 27 mg/L and 22.42 mg/L respectively for *Xenopus laevis*.

Carbon tetrachloride possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L). In addition chlorine radicals and other reactive species formed by photodecomposition of CTC in the stratosphere catalyze reactions that deplete stratospheric ozone. CTC is not readily biodegradable under aerobic conditions, but is rapidly biodegraded under anaerobic conditions by cometabolism. CTC has no significant bioaccumulation potential. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the Cooperative Chemicals Assessment Programme.

Exposure

Chloroform, methylene chloride and carbon tetrachloride, are coproduced with chlorination of methyl chloride or methane with chlorine. Depending on the operating conditions the proportions of the three chloromethanes can be adapted to the market demand. Methylene chloride, chloroform and carbon tetrachloride are separated by distillation.

A global production volume (for all applications including feedstock) of 156,000 tonnes of CTC was reported to UNEP for the year 2008 (UNEP, 2010). Most of this production is used as feedstock, i.e. raw material, which is fully converted to other products except for residues, e.g., in the manufacture of chlorofluorocarbons (CFCs, e.g. CCl_3F, CCl_2F_2), hydrochlorofluorocarbons (HCFCs), hydrofluorocarbons (HFCs) and other chemicals.

Actual production volumes in the EU, excluding all imports from outside the EU and all purchases from other EU based producers, but including authorised production under the Montreal Protocol, decreased from 58,000 tonnes in 1989 to 15,700 tonnes in 2008.

In the US, since 1996, practically all carbon tetrachloride produced has been exported for use in feedstock and other uses permitted under the Montreal Protocol. The total CTC exported from the US (considered equal to total production) was greater than 10,000 metric tonnes in 2006 and earlier but have fallen to below 500 metric tonnes per annum in 2010.

The uses of carbon tetrachloride are restricted by the Montreal Protocol on Substances that Deplete the Ozone Layer, implemented in the EU by the Regulation (EC) No 1005/2009. The main authorized use for CTC is as feedstock, the minor solvent uses are limited to specific industrial process agents (e.g. to separate the residual chlorine from the inert vapours present in the chlorine gas and recover it in a usable form) and essential laboratory and analytical applications.

Environmental exposure

Major sources of carbon tetrachloride in the environment are fugitive losses from industrial production and the permitted uses. Despite a significant reduction in the last 20 years, CTC accounted for 359 ppt (about 11%) of total tropospheric chlorine from long-lived chemicals (~3.4 parts per billion [ppb] in 2008). The global mean surface mixing ratio of CTC have decreased since a peak in about 1990. By 2008, the surface mean CTC concentration was approximately 90 ppt and had decreased during 2007-2008 at a rate of -1.1 to -1.4 ppt/yr. Maximum CTC concentrations in the atmosphere have been measured below 10 km in altitude with volume mixing ratio values of 100–130 ppt. Nine-year (1995-2004) averaged surface fluxes from industrial sources of CTC were estimated to be between 45,500 tonnes/year (industry-based data) and 74,100±4,300 tonnes/year (calculated based on atmospheric CTC measurements from two networks and a 3D chemical transport model).

There is a discrepancy between CTC emissions derived from data reported to UNEP and emissions derived from measured global mixing ratios which cannot be explained by scaling the lifetime or by uncertainties in the atmospheric trends.

CTC is produced by marine algae in the oceans, from biomass burning and abiotically by volcanoes; further it is contained in rocks and ores. Mining activities and wheathering of rocks release CTC among other organohalogens. Estimated global emissions of CTC from volcanic sources account for 3.4±1.0 tonnes/year. The amount emitted from marine algal production is not known. The potassium salt mining industry accounts for the liberation of 100-150 tonnes CTC per year.

Quantitative data on both emissions to air and releases to water from IPPC installations have been reported for five activities, mostly from industrial scale production of basic organic compounds, covering 50 facilities in 14 EU Member States: 63 tonnes emissions to air in 2008 and 0.5 tonnes releases to water.

Chlorine radicals and other reactive species formed by photodissociation of CTC in the stratosphere can catalyze reactions that deplete stratospheric ozone. As the manufacture of chlorofluorocarbons from CTC is phased out according to the Montreal Protocol, the impact of CTC on atmospheric ozone and global warming is likely to decrease.

Human exposure

In the EU the use of CTC (as pure substance or in mixtures of more than 0.1 % CTC) is restricted since 1996 by the former directive 76/769/EEC (so-called Marketing and Use Directive) now succeeded by the REACH regulation (Regulation [EC] 1907/2006), for only industrial uses or for laboratory uses by professionals. Therefore no direct consumer exposure is expected in the EU since 1996.

In addition, CTC is even more restricted by the Montreal Protocol, implemented in the EU by regulation (EC) No. 1005/2009 on substances that deplete the ozone layer (so-called ODS regulation), which foresees only the use in industry as intermediate or solvent in individual named processes in closed installations with tight emission controls. Also the use as laboratory agent is restricted to specific uses by laboratory professionals.

The European Scientific Committee on Occupational Exposure Limits (SCOEL) recommends for CTC an 8 hour time weighted average exposure limit of 1 ppm [6.4 mg/m^3] and a short term exposure limit (15 min) of 5 ppm [32 mg/m^3].

Use of CTC in “dispersive” applications such as metal cleaning, dry-cleaning, solvent extraction etc. ceased in the US by 1970 following recognition of hepatotoxicity, and use of CTC as a feedstock for manufacture of CFCs ended in 1996.

The 2006 EPA Inventory Update Report (IUR, accessed via www.epa.gov) is based on 2005 production and use of CTC. The public information shows that CTC production was between 45,4455 and 227,273 metric tonnes. The number of production, processing and use sites was between 100 – 999 involving 1,000 or more workers. It may be assumed that these values include situations where CTC is generated as a by-product and destroyed. As expected, no consumer uses of CTC were reported.