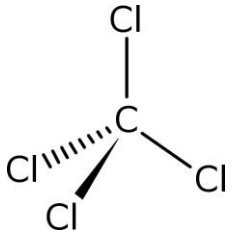
SIDS INITIAL ASSESSMENT PROFILE

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 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.