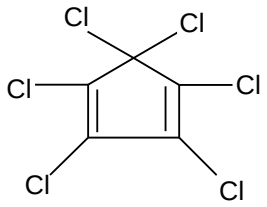
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	77-47-4
Chemical Name	Hexachlorocyclopentadiene (HCCP)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The exact oral absorption figure of HCCP cannot be derived, although the minimal amount of oral absorption ranges from approximately 18% to 39% after a single gavage administration (7 - 61 mg/kg bw dose), and from 5.5% to 12.2% when applied via the diet for 30 days. No studies on the kinetics of HCCP following dermal application were available. However, HCCP is absorbed via the dermal route as is indicated by toxic responses reported in acute dermal toxicity studies. From the inhalation studies, it is concluded that complete respiratory absorption cannot be excluded.
After oral administration, kidneys and liver, and in some studies fat, gonads and lungs were the major sites of residue deposition. In urine, at least four metabolites of HCCP were present. Both rats and mice were capable of extensively degrading HCCP, with no intact HCCP found in excreta or tissues. The faeces were found to be the primary route of elimination.

The 4-hr inhalation LC_{50} ranged from 0.018-0.041 mg/l for rats; the 3.5-hr LC_{50} for rabbits was <0.0158 mg/l. Effects of HCCP in the acute inhalation studies included ocular and nasal discharge, irregular breathing and damage to the respiratory tract. The dermal LD_{50} for rabbits ranged from <200-780 mg/kg bw; for rats this value was >2000 mg/kg bw. In both species HCCP caused marked effects on the skin. Furthermore, in all skin irritation studies, mortality was observed in rabbits. The oral LD_{50} ranged from 505-1500 and 679 mg/kg bw for rats and mice, respectively. Upon acute oral exposure, clinical signs included diarrhoea, lethargy and decreased respiration.
Mortality was also observed in all tested animals (4 male and female rabbits) in the eye irritation study in which 0.1 ml of HCCP was placed into the conjuctival sac of the right eye.

HCCP is irritating and corrosive to the skin and eyes and irritating to the respiratory tract in animal studies and workers. HCCP may also cause sensitisation by skin contact.

The overall NOAEC for local and systemic effects after semichronic inhalatory exposure is 0.45 mg/m^3 (observed in mice after 13 weeks of exposure). After inhalatory exposure to dose levels of 1.67 mg/m^3 and higher, decreased absolute body weight and squamous metaplasia of the larynx or trachea in mice were observed. An overall NOAEC for chronic inhalatory exposure could not be established since the lowest dose tested still induced treatment related local effects (LOAEC: 0.11 mg/m^3). This LOAEC is derived from a two 2-year chronic inhalation toxicity study with rats and mice. Concentrations of $\geq$ 0.11 mg/m^3 HCCP caused toxicity to the respiratory tract, i.e. an increase in the incidence of pigmentation of the respiratory epithelium of the nose, trachea, and the bronchi and bronchioles of the lung in both rats and mice. In addition, in rats a significantly higher incidence of squamous metaplasia of the laryngeal

epithelium of females exposed to concentrations of ≥ 0.11 mg/m^3 HCCP was observed. No increased incidence in neoplasms was found. The NOAEC for systemic effects after chronic exposure is 0.11 mg/m^3. This NOAEC is based on the higher incidences of suppurative ovarian inflammation in mice exposed to 0.56 and 2.28 mg/m^3.
Two 13-week oral (gavage) toxicity studies with rats (doses 0, 10, 19, 38, 75 and 150 mg/kg bw/day) and mice (doses 0, 19, 38, 75, 150 and 300 mg/kg bw/day) were performed. The local and systemic NOAEL for rats was 10 mg/kg bw/day based on effects in the forestomach and increased relative kidney weight, respectively. The systemic LOAEL of 19 mg/kg bw in mice was also based on relative kidney weight. The local NOAEL in mice based on effects in the forestomach was 10 mg/kg bw/day.

HCCP does not appear to be a bacterial mutagen and does not induce gene mutations in mammalian cells in vitro. HCCP did induce chromosome aberrations in mammalian cells in vitro, though under conditions of clear toxicity. No induction of sex-linked recessive lethal mutations was noted in germ cells of treated male Drosophila Melanogaster. In mice no micronucleated erythrocytes were found after 13 weeks of inhalation exposure to various doses of HCCP including a maximally tolerated dose. HCCP is considered not to have mutagenic activity under in vivo conditions.

Based on a 2-year chronic inhalation study with rats and mice, HCCP is not considered to be a carcinogenic compound for this route. Data on carcinogenic effects of HCCP after dermal or oral exposure are lacking. Due to the absence of mutagenic activity of HCCP in vivo and the absence of carcinogenic potential in rats and mice after chronic inhalation exposure, it is concluded that HCCP is not likely to be a carcinogenic substance.

No specific inhalation and dermal studies on toxicity of HCCP for reproduction are available. In several inhalation repeated dose studies (rats and mice exposed for 13 weeks up to at least 4.46 mg/m^3; rats and monkeys exposed fro 14 weeks up to 2.28 mg/m^3; rats exposed for 30 weeks up to 6.34 mg/m^3; rats and mice exposed for 2 years up to 2.28 mg/m^3) male and female reproduction organs were histopathologically examined, but no biologically relevant histopathological treatment related effects with regard to fertility were observed. Therefore, the inhalation NOAEC for fertility effects was established at 6.34 mg/m^3.
No standard oral studies on toxicity of HCCP for reproduction are available. In an oral repeated dose study (13 weeks; rats exposed up to 150 mg/kg bw and mice exposed up to 300 mg/kg bw), male and female reproduction organs were also histopathologically examined. No biologically relevant histopathological treatment related effects were observed. Therefore, the oral NOAEL for fertility effects was established at 150 mg/kg bw for rats and 300 mg/kg bw for mice.
In oral teratogenicity studies with mice and rats, no teratogenic effects were found. The overall NOAEL for maternal and developmental toxicity is concluded to be 25 mg/kg bw/day based on the study with rabbits. In rabbits, one minor skeletal variation (13 rib(s)) was seen more frequently among the foetuses of rabbits given 75 mg/kg/day, in the presence of significant maternal toxicity (severe diarrhoea and death).

Environment

HCCP is a pale, yellow-green liquid with a melting point of -9°C and a boiling point of 239°C. The vapour pressure is 10 Pa at 25°C. The Henry's Law Constant is determined to be 2.7E-02 atm m3/mol at 25°C. The substance has a measured water solubility of 1.03-1.25 mg/l at 22°C ± 1°C. In a shake-flask experiment the log Kow was measured to be 5.04. The bioconcentration factor of HCCP in the fathead minnow was 29 and <11. In ^{14}C studies higher BCF-values were reported (323 and 1297 in Goldfish and 1230 in the Mosquitofish). The lower BCF values reported represent the steady-state bioconcentration factor that was measured in 30-day flow through exposures to constant levels of HCCP, and the higher values that are derived from ^{14}C studies are based on total radioactivity and so may include persistent metabolites.

HCCP will be removed via reaction with photochemically-generated hydroxyl radicals in the atmosphere (estimated rate constant is 5.6 x 10^{-13} cm^3 /molecule x sec and corresponding to a half-life of 29 days.). Based on the highly chlorinated structure of HCCP, it is expected that reaction of this compound with ozone molecules in the atmosphere would be too slow to be environmentally significant. Degradative processes for removal of HCCP from water include

photolysis, hydrolysis and biodegradation. Hydrolysis of HCCP in water occurs much more slowly than photolysis and the half-life in water seems to be dependent on pH. In shallow or flowing waters, photolysis is the predominant fate process; in deeper waters hydrolysis and biodegradation may be more important environmental fate processes. A hydrolysis half-life of HCCP of 3.3 days was found at pH 7 and 30°C. The calculated half-life for photolysis in water is 10.7 minutes. HCCP strongly adsorbs to organic carbon and is considered to be immobile in soil (measured Koc for HCCP is 4265). These available dataset for biodegradation did not give definitive results because their designs could not easily differentiate removal or degradation via abiotic processes (adsorption, volatilisation, hydrolysis, photolysis) from that via biodegradation. However, results suggest that HCCP will biodegrade at a slow to moderate rate in aqueous environments and is therefore considered to be inherently biodegradable on the basis of a weight of evidence approach. Under anaerobic conditions dehalogenation will occur and one or more chlorinated metabolites will be formed. The persistence of HCCP in soil is low, with degradation of >90% of applied HCCP to non-polar products within approximately 7 days. Based on Level III distribution modeling using EPISUITE (assuming equal and continuous releases to air, water and soil), it is estimated that the majority of HCCP released to the environment will partition into soil (74.1%) and sediment (19.5%) with smaller amounts to water (3.68%) and air 2.66%. The SimpleBox model (v2.0), a Mackay level III model, can be used to estimate the percentage of distribution to soil, air or water when 100% of the substance will initially be emitted to one of these compartments.

	Air	Water	Soil
Receiving compartment			
Air	91.7	2.5	5.8
Water (incl. sediment)	1.7	98.3	0
Soil	0.5	0	99.5

The 96 h-LC_{50} values for freshwater fish range from 7-240 µg/l, of which the lowest 96 h-LC_{50} of 7µg/l (measured) was found for the freshwater fish *Pimephales promelas*. The marine 96-h LC_{50} values varied from 37-48µg/l. The 48 h-LC_{50} values for freshwater invertebrates range from 39-52.2µg/l. In marine species 96-h LC_{50} values range from 7 - 371 µg/l. In freshwater and marine algae species, growth was reported to be inhibited by 50% at exposure levels ranging from 3.5 to 240µg/l.
In a 30-day early-life stage flow-through toxicity test with fathead minnows using 1 day old larvae the 96-h LC_{50} value was 7µg/l (reached within 4 days). Based on the toxicity and growth data it can be concluded that 3.7µg/l is the highest concentration of HCCP that produces no adverse effects (NOEC) on fathead minnow larvae. For *Daphnia magna* a 21-day NOEC of 9µg/l was found. For marine invertebrate species (*Mysidopsis bahia*) a NOEC of 0.3µg/l (reproduction) was found.

A 0.5 h EC_{50} > 100 mg/l HCCP was found for activated sludge micro-organisms.

The toxicity of HCCP to lettuce (*Lactuca sativa*) was determined in soil and nutrient solution. The EC_{50} of HCCP on growth was 10 mg/kg d.w., based on nominal concentrations.

Exposure

World-wide production volume was estimated to be approximately 15,000 tonnes in 1988, shared almost equally between the United States and The Netherlands. Production of HCCP is currently thought to be limited to only one company in the United States.

HCCP is used as an intermediate in the production of many chlorinated cyclodiene pesticides like dieldrin, aldrin, endrin, endosulfan, chlordane, Mirex and Pentac. It is also used as an intermediate in the production of chlorendic acid (HET-acid) or its anhydride (chlorendic anhydride) which are used as a copolymer to produce flame retardant and corrosion proof polyesters and alkydresins. HCCP is also used to produce Dechlorane Plus, which is an additive in the production of flame retardant plastics. Minor HCCP applications are its use as an intermediate in the production of dyes and pharmaceuticals. In Europe only two major applications of HCCP are relevant. HCCP is used as an intermediate in the production of endosulfan and it is used in the synthesis of HET-acid. In the year 2000 a maximum of 6000 tonnes HCCP was imported into Europe.

Environmental release of HCCP may occur during industrial use as an intermediate in the production of cyclodiene pesticides and HET-acid. Hexachlorocyclopentadiene may also be released during pesticide application and from the

production and industrial use of flame-retardant polymers and paints. The total estimated environmental release of HCCP resulting from residual amounts of HCCP in processed HET-acid (resins and paints) are found to be very low. In the case of endosulfan the residual content of HCCP is about 0.1%.

Occupational exposure is possible in chemical industries where HCCP is used as an intermediate during the manufacturing of pesticides and flame retardants. These products are produced in closed systems and occupational exposure may occur during connecting and disconnecting of transfer lines. Occupational exposure may also occur when products containing HCCP are added to chemical processes (e.g. containing flame retardants in unsaturated polyesters, paints and thermoplastics). Unintentional exposure to HCCP as a reaction product is possible in the semiconductor industry through drumming of waste products and maintenance activities. It might be possible that in some workplaces adequate worker protection measures are already being applied. Occupational Exposure Limits (OEL values) are available, but not harmonized.

The expected consumer exposure to HCCP in the use as an intermediate (in the production of pesticides and in the production of flame retardant chemicals) can be considered negligible.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (acute toxicity, corrosive to skin and eyes, respiratory tract irritation, sensitization, repeated dose toxicity). Therefore, member countries are invited to perform an exposure assessment for workers and if indicated a risk assessment.

Note: A risk assessment to be performed in the context of the EU Existing Substances Regulation (793/93/EEC) in the European Union is in progress.

Environment: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity to freshwater and marine aquatic organisms below 1 mg/l). However, based on data presented by the Sponsor country (which relates to the use in several OECD countries) emissions to the environment are low. Countries may wish to investigate any exposure scenarios for the environment that were not presented by the Sponsor Country.

Note: A risk assessment to be performed in the context of the EU Existing Substances Regulation (793/93/EEC) in the European Union is in progress.