European Union Risk Assessment Report

HEXACHLOROCYCLOPENTADIENE

CAS No: 77-47-4

EINECS No: 201-029-3

RISK ASSESSMENT

July 2007

FINAL APPROVED VERSION

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Final report, July 2007

The Netherlands

Rapporteur for the risk assessment of Hexachlorocyclopentadiene is the Ministry of Housing, Spatial Planning and the Environment (VROM) in consultation with the Ministry of Social Affairs and Employment (SZW) and the Ministry of Public Health, Welfare and Sport (VWS). Responsible for the risk evaluation and subsequently for the contents of this report, is the rapporteur. The scientific work on this report has been prepared by the Netherlands Organization for Applied Scientific Research (TNO) and the National Institute for Public Health and the Environment (RIVM), by order of the rapporteur.

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Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.
The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.
The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Health and Environmental Risks (SCHER) which gives its opinion to the European Commission on the quality of the risk assessment.
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.
The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992 and confirmed in the Johannesburg Declaration on Sustainable Development at the World Summit on Sustainable Development, held in Johannesburg, South Africa in 2002.
This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.

[1] O.J. No L 084, 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT[4]

CAS Number: 77-47-4
EINECS Number: 201-029-3
IUPAC Name: Hexachlorocyclopentadiene

Environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all environmental compartments, both at the local and regional scale. The RCRs for the aquatic compartment for the impurity of HCCP in endosulfan application are also below 1.

Human health

Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) is reached because:

- adverse local and systemic health effects cannot be excluded after repeated inhalation exposure in the occupational scenarios 'Production of pesticides and flame retardants' and 'Use of product containing residual HCCP';
- adverse systemic health effects cannot be excluded after repeated dermal exposure in the occupational scenarios 'Production of pesticides and flame retardants' and 'Unintentional occurrence of HCCP in the semiconductor industry'.

It might be possible that in some workplaces adequate worker protection measures are already being applied.

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

[4] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Humans exposed via the environment

Conclusion (**ii)** There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Human health (physico-chemical properties)

Conclusion (**ii)** There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

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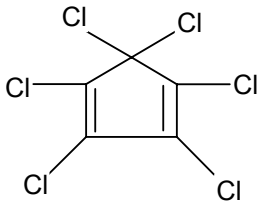
TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 77-47-4
EINECS Number: 201-029-3
IUPAC Name: hexachlorocyclopentadiene
Molecular formula: C_5Cl_6
Structural formula:



Molecular weight: 272.77
Synonyms: hexachloro-1,3-cyclopentadiene; perchlorocyclopentadiene; hexachloro-1,3-cyclopentadiene; 1,2,3,3,4,5-hexachloro-1,4-cyclopentadiene; HCCP

1.2 PURITY/IMPURITIES, ADDITIVES

The nature and levels of HCCP contaminants vary with the method of production (WHO, 1991). HCCP made by the chlorination of cyclopentadiene by alkaline hypochlorite at 40 °C, followed by fractional distillation, is only 75% pure, and contains many lower chlorinated cyclopentadienes and other contaminants (e.g., hexachlorobenzene and octachlorocyclopentene). Purities above 90% have been obtained by thermal dechlorination of octachlorocyclopentene at 470-480 °C. The current specification for HCCP produced by the Velsicol Chemical Corporation at Memphis, Tennessee, USA, which is used internally and sold to other users, has a minimum purity of 97%. The major contaminants found in an industrial preparation of HCCP from Velsicol were octachlorocyclopentene (0.68%), hexachloro-1,3-butadiene (1.11%), tetrachloroethane (0.09%), hexachlorobenzene (0.04%), and pentachlorobenzene (0.02%). A preparation from Shell International Petroleum (1982) contained up to 1.5% of octachlorocyclopentene and approximately 0.2% of hexachloro-1,3-butadiene (WHO, 1991). Analysis results from another company (Company C, 2003) indicated the following impurities: lights (boiling point less than 234 °C): 0.1%, hexachlorobutadiene: 0.1%, octochlorocyclopentane: 0.3% and others (primarily penta and hexa chloro compounds related to hexachlorocyclopentadiene): 0.2%.

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1-1 Summary of physico-chemical properties

Property	Value	Reference/comment
Physical state	Liquid	Pale, yellow-green (Callahan, 1979,; WHO, 1991)
Melting point	-9 °C / -10 °C	Callahan, 1979; US Coast guard, 1984; Velsicol Chemical Co., 1997
Boiling point	234 °C / 239 °C	WHO, 1991
Relative density	1.70 at 20 °C	Callahan, 1979; US Coast guard, 1984; Velsicol Chemical Co., 1997; WHO, 1991
Vapour pressure	10 Pa at 25 °C	WHO, 1991
Water solubility	1.03 – 1.25 mg/l at 22 °C	WHO, 1991
Water reactivity	HCCP reacts slowly with water to form hydrochloric acid.	NIOSH, 2005
Partition coefficient n-octanol/water (log value)	3.99 – 5.51	Callahan, 1979; Wolfe et al, 1982; US Coast guard, 1984; Weast Chem.Handb.,1988; HSDB, EPIWIN, ClogP
Granulometry		Particle size distribution is not relevant for liquids
Conversion factors	1 ppm = 11.3 mg/m^3; 1 mg/m^3 = 0.088 ppm at 20 °C and 101.3 kPa	WHO, 1991
Flash point	-	Taking into account the structural formula and the thereof-derived thermokinetics, no flashpoint is to be expected and the determination of the flashpoint is considered superfluous in view of decomposing properties
Autoflammability	-	Taking into account the structural formula and the thereof-derived thermokinetics, no autoflammability is to be expected
Flammability	-	Taking into account the structural formula and the thereof-derived thermokinetics, no water incompatibility is to be expected; Taking into account the structural formula and the thereof-derived thermokinetics, no pyroforic properties are to be expected
Explosive properties	-	Taking into account the structural formula and the thereof-derived thermokinetics, no explosive properties are to be expected
Oxidizing properties	-	Taking into account the structural formula and the thereof-derived thermokinetics, no oxidising properties are to be expected
Henry's constant	2.7*10^{-2} atm m^3/mol at 25 °C	Callahan, 1979; Wolfe, 1982
Surface tension	37.5 mN/m at 20 °C	Callahan, 1979; US Coast guard, 1984; Weast Chem.Handb.,1988
Heat of vaporisation	1.76*10^{-5} J/kg	WHO, 1991

[1] A further evaluation of the log Kow value is given below:

Log Kow value	Method	Reference
3.99	No information	Cited in HSDB
4.6	Calculated	EPIWIN
5.04	Calculated	ClogP
5.04	Measured, shake-flask method	Wolfe et al. (1982)
5.51	Calculated	Not assignable

In the shake-flask experiment, three 10 mg samples of HCCP were dissolved in 2 ml of 1-octanol and equilibrated with 40 ml of water (octanol saturated) and shaken for 15 min. One ml of the aqueous layer was extracted with 10 ml of isooctane and analysed by GLC. One-half ml of the octanol layer was diluted to 10 ml in hexane and analysed by GLC. The Kow was measured to be $1.1 \pm 0.1 \times 10^5$ at 28ºC. This value is comparable to a study in which LC was used, from which a Kow of 1×10^5 was obtained (McDuffie, 1981 cited in Wolfe et al., 1982). With ClogP the log Kow value of 5.04 was confirmed. Given the uncertainties of the lower (3.99) and upper (5.51) values and because the log Kow value of 5.04 is a measured value from a reliable study, comparable to a OECD guideline study, this value will be used for the environmental risk assessment. For pragmatic reasons a value of 4.99 is used in EUSES 2.0.

1.4 CLASSIFICATION

1.4.1 Current classification

T+; R26
T; R24
Xn; R22
C; R34
N; R50-53

1.4.2 Proposed classification

Environmental aspects: N: R50/53; S60/61

Human health aspects:

T+; R26
T; R24
Xn; R22
C; R34
R43
T; R48/23

Symbols: T+
R-phrases: 22, 24, 26, 34, 43, 48/23
S-phrases: (2), 26, 28, 36/37/39, 38, 45, 53

Specific concentration limits:

C ≥25% T+; R22-24-26-34-43-48/23
10% ≤ C <25% T+; R21-26-34-43-48/23
7% ≤ C < 10% T+; R21-26-36/37/38-43-48/20
5% ≤ C < 7% T; R21-23-36/37/38-43-48/20
3% ≤ C <5% T; R21-23-43-48/20
1% ≤ C < 3% T; R23-43-48/20
0.1% ≤ C < 1% Xn; R20-43
0.001% ≤ C < 0.1% R43

In addition, based on mortality which occurred in the eye irritation study with HCCP, it is noted that under the new EU regulation on classification and labelling of chemicals (based on GHS), the sentence 'EUH070 - Toxic through eye' will be applicable.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

2.1.1 Production processes

Manufacturing processes of hexachlorocyclopentadiene (HCCP) can be based on three different synthesis pathways: 1) synthesis from polychlorinated C1-C3-hydrocarbons, 2) chlorination of C5-alkanes with subsequent cyclisation and 3) chlorination of cyclopentadiene. The various routes of HCCP production are shortly described below.

2.1.1.1 Synthesis from polychlorinated C1-C3-hydrocarbons

HCCP can be synthesised from polychlorinated hydrocarbons via two different reaction pathways. One is the catalytic reaction of hexachloropropene with cis-1,2-dichloroethene in methylene dichloride to form 1,1,2,3,3,4,5,5,-octachloropentene-1. HCCP is then formed after two steps. In each step hydrochloric acid is separated off. The second synthesis route is the production of HCCP via the catalytic reaction of trichloroethene with carbon tetrachloride and subsequent pyrolysis of the reaction products at 500 ºC. Another pyrolysis route is the pyrolysis of octachlorocyclopentene which is obtained as a result of Prins technology-based 5 stage reaction of tetrachloroethene, chloroform and trichloroethene as well via the reaction of trichloroethene with chloroform in the presence of $AlCl_3$ (BUA, 1988).

2.1.1.2 Chlorination of C5-alkanes

The production takes place in a two-stage process. In the first stage, C5-alkanes are photochemically chlorinated in the liquid phase, resulting in a polychloropentane. At the second stage, thermal chlorination and ring closure occurs in the vapour phase. This is followed by pyrolytic dechlorination of octachlorocyclopentene that has been formed intermediately.

Another chlorination process is the direct two step chlorination of cyclopentadiene. In the first stage, liquid cyclopentadiene is chlorinated into tetrachlorocyclopentane. Further direct chlorination yields octachlorocyclopentane, which is then thermally dechlorinated into HCCP. Purification is subsequently carried out by means of distillation (BUA, 1988).

2.1.1.3 Chlorination of cyclopentadiene

In petroleum ether cyclopentadiene reacts with an aqueous alkaline solution of either potassium hypochlorite or sodium hypochlorite. HCCP is separated from the reaction mixture by carrying out fractionated distillation. In view of the formation of low chlorinated compounds, which diminish the yield, and of the difficulty in separating off HCCP at the level of purity needed for further reactions, this process is of only limited technical significance (BUA, 1988).

2.1.2 Production capacity

Production of HCCP is currently thought to be limited to only one company in the Western World. Velsicol Chemical Corporation in Memphis, Tennessee in the United States is the only production company since Shell Nederland Chemie BV ceased production of HCCP. Velsicol and Shell were reported as the only manufacturers in the Western world in the 1980s (BUA, 1988). But, currently there are no known producers in the European Union (Silberhorn and Smith, 2001), leaving Velsicol as the only manufacturer in the Western world.

World-wide production volume was estimated to be approximately 15,000 tonnes in 1988, shared almost equally between the United States (Velsicol) and The Netherlands (Shell). The 1983 production was stated to be 9,130 tonnes in the United States (BUA, 1988).

2.2 USES

2.2.1 Introduction

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 (hexachloroendomethylenetetrahydro-phthalic acid (HET-acid)) which is 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. Dechlorane Plus is not produced within the European Union. 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 by Aventis CropScience GmbH in Germany and it is used in the synthesis of HET-acid by Durez Europe (former Occidental Chemical) in Belgium. In the year 2000 Aventis imported between 1000 and 5000 tonnes HCCP and Durez Europe imported less than 1000 tonnes. Chemical Innovations Limited (CIL) in England imported less than 20 tonnes of HCCP from the United States in the year 2000 for its use as an intermediate in the production of a speciality coating (Silberhorn and Smith, 2001).

2.2.2 Production of cyclodiene pesticides

One of the two major applications of HCCP is its use as an intermediate in the production of so-called cyclodiene pesticides. Many of these pesticides are synthesised via the Diels-Alder reaction of the diene-group with an unsaturated compound as dienophile. Other pesticides like Kepone and Mirex are synthesised via dimerisation and dechlorinating dimerisation. Of these products endosulfan has maintained considerable significance as an insecticide. Two ways of manufacturing have been elaborated. In the preferred method, Thiodandiol is obtained by means of saponification of the addition product from HCCP and cis-1,4-diacetoxybutene-2. The other method is a direct reaction with cis-1,4-butenediol according to the Diels-Alder reaction. Reaction with thionyl chloride then provides the active ingredient. Xylene, toluene or tetrachloromethane can be used as solvents for both stages (BUA, 1988).

2.2.3 Production of HET-acid

HET-acid is synthesised through the Diels-Alder reaction of HCCP with maleic anhydride to form HET-anhydride. HET-anhydride finally is hydrolysed to form HET-acid. The solution is cooled and the HET-acid crystallises out. After filtration and washing the HET-acid is dried in a hot inert gas stream to produce anhydrous HET-acid (Durez, 2001).

2.2.4 Production of specialty coatings

HCCP is used by a site located in the United Kingdom for the production of speciality coatings (Silberhorn and Smith, 2001). HCCP is not expected to be used in coating formulations as such, unless it is used as an UV-hardener. At the UK site HCCP is reacted with a high molecular weight polymer in solution, using a Diels-Alder reaction, to produce speciality coatings. Organic solvents are used and no water is involved in the whole process (CIL, 2002).

2.3 USE OF HET-ACID, DECHLRORANE PLUS AND PESTICIDES

The use of HET-acid, Dechlorane Plus and pesticides are treated in this section, because HCCP is present as an impurity in these products. As a result emissions may occur from processing these substances.

2.3.1 Use of HET-acid

HET-acid is used as a reactive substance (flame-retardant) in both the production of unsaturated polyesters from which for example transparent corrugated sheets are made and the production of flame-resistant, anti-rust and anti-corrosive paints based on alkyd and polyester resin, for instance internal coating of chemical reactor tank. HET-acid contains up to 0.005% of HCCP (Company B, 2002). In Western Europe HET-acid is almost exclusively used, for about 90%, in unsaturated polyester resins and 10% goes into paints (BUA, 1988). The Western European market is about 620 ton in 2001. Of this 620 ton about 95% is used in the production of unsaturated polyester resins and the remaining 5% is used in paints (Durez, 2002). These latter values will be used for the exposure assessment.

2.3.2 Use of Dechlorane Plus

Dechlorane Plus together with a few analogous Dechlorane brands is used as an non-reactive and non-plasticising flame resistant additive in mostly thermoplastic materials like polyethylene, polyvinyl acetate and polypropylene in for instance electronic applications and wire and cable applications. The Dechlorane Plus contents range from 5-35%. It is also used in polyester and epoxy resins, for example self-extinghuising phenolic resin laminated paper, but these are minor applications. The amount used in Western Europe was reported to be about 800 tonnes per year in 1981 (BUA, 1988). More recent figures indicate that sales to Europe were still about 800 tonnes in 2000 (Durez, 2002). The level of HCCP in dechlorane plus is about 0.005%.

2.3.3 Use of Cyclodiene pesticides

Cyclodiene pesticides are still used, but within the European Union many of these pesticides are banned or their use is severely restricted. **Table 2-1** gives more detailed information on legislation, trade and use of most known cyclodiene based pesticides in the European Union from various sources (EU (2002) reference year 2001 (table note 8), Pesticide News (1998) reference year unknown (table notes 6 and 7), information on import/export, production and use, table notes 1-5 from ECB (2002a,b) reference year unknown).

Table 2-1 Use, trade and legislation of cyclodiene based pesticides.

Substance	CAS nr.	AUT	BEL	DNK	FIN	FRA	GER	GRC	IRL	ITA	LUX	NLD	PRT	ESP	SWE	GBR
Aldrin	309-00-2	1	1,2	1,2	1	1,2	1	1	1	1,2	1	1,2,5	1	1,2	1,3	1
Alodan	2550-75-6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bromodan	1715-40-8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chlordane	57-74-9	1	1,2	1,2	1,3	1,2	1	1	1	1,2	1	1,2	1	1,2	1,3	1
Dieldrin	60-57-1	1	1,2	1,2	1	1,2	1	1	1	1,2	1	1,2	1	1,2	1,3	1
Endosulfan	115-29-7	?	8	6	7	?	4,6	8	8	4,8	?	6	8	8	6	7
Endrin	72-20-8	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Heptachlor	76-44-8	1	1,2	1,2	1,2	1,2	1	1	1	1,2	1	1,2	1	1,2	1,3	1
Isobenzan	297-78-9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Isodrin	465-73-6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kelevan	4234-79-1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kepone	143-50-0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mirex	1385-85-5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pentac	2227-17-0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

1) It is prohibited to use or place on the market all plant protection products containing this chemical

2) for uses other than plant protection, written authorisation is required for import

3) for uses other than plant protection no consent

4) imported or produced HPVC

5) imported or produced LPVC

6) banned

7) severely restricted

8) in use

-) no information

Use of cyclodiene pesticides in the European Union is mainly limited to endosulfan. Other cyclodiene pesticides like drins, chlordane and heptachlor are either not imported or produced in the European Union. Additionally, their use as a plant protection agent is prohibited or otherwise severely restricted. For many other pesticides listed in Table 2.1 there is no information on limitations with regard to use, import or production. Endosulfan is still used in several countries within the European Union as an insecticide or acaricide in agriculture on fruits, vegetables, cereals and oilseed. In some countries it is widely used, in other countries use is limited to some single crops (FAO, 1993).

Both endosulfan and aldrin are reported to be either produced or imported into some countries. Aldrin was produced by Shell Nederland Chemie till 1990. The last stocks were sold in 1991 and since then Shell Nederland Chemie is not importing or exporting aldrin anymore (SNC, 2002). The only producer of endosulfan in the European Union is located in Germany (Aventis/Bayer CropSience). Italy is also reported to be either an importer or a producer (ECB, 2002a). It may provisionally be concluded that Italy only imports endosulfan. Total imported quantity in the European Union is about 200 tonne per year. The total annual quantity used within the EU is estimated to be about 550 tonne (Aventis, 2002). The residual content of HCCP in endosulfan is about 0.1% (Aventis, 2001 and BUA, 1988).

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

3.1.1.1 Environmental releases

Environmental release of hexachlorocyclopentadiene may occur during industrial use of HCCP as an intermediate in the production of cyclodiene pesticides and HET-acid, as described in Chapter 2. Industrial use is the only relevant stage for HCCP in the European Union, since Shell Netherlands ceased production. Hexachlorocyclopentadiene may also be released during pesticide application and from the production and industrial use of flame-retardant polymers and paints.

3.1.1.2 Release from production

There is no production of hexachlorocyclopentadiene within the European Union.

3.1.1.3 Release from industrial/professional use

Hexachlorocyclopentadiene is only used as an intermediate in the chemical industry (life cycle stage II). The corresponding industrial category is Chemical industry, IC-3 and the corresponding use category is Intermediates, UC-33 according to the TGD (EC, 2003). Based on submitted information for both applications, i.e., synthesis of endosulfan and HET-acid, main category Ic applies, isolated intermediates processed off-site with controlled transport.

Production of endosulfan (site IIa)

Based on the reported annual emissions for the production site of endosulfan (Aventis, 2002) the emission factor to air is 1.9 g per tonne of HCCP used. The production process of endosulfan is stated to be free of water and no water is used for cleaning operations (Aventis, 2002). Therefore it is assumed that there are no emissions to wastewater.

Production of HET-acid (site IIb)

HET-acid is produced at one site in Belgium. Based on the reported annual emissions for the production of HET-acid (Durez, 2000) the emission factor to air is 0.03 g per tonne. Process water containing HCCP is treated in an on-site wastewater treatment facility, which discharges to a public sewage treatment plant. Measured concentrations in the effluent of the on-site wastewater treatment installation were reported to be below the detection limit of 0.02 $\mu g.l^{-1}$. Measured influent concentrations to the wastewater treatment facility were about 20 $\mu g.l^{-1}$. The wastewater treatment facility consist of a suspended solids filter and two active carbon filters (Durez, 2001). Silberhorn and Smith (2001) estimated the emission to wastewater by assuming an effluent concentration of half the detection limit. This corresponds to a removal efficiency of almost 90% and an annual emission of about 0.3 kg. The producer itself reported a removal efficiency of the wastewater treatment facility of 75% (Durez, 2000),

which corresponds to a concentration in the effluent of the local wastewater treatment facility equal to the detection limit and an emission rate of 0.6 kg per year.

As reasonable worst case, the effluent concentration in the wastewater treatment installation is assumed to be 0.02 $\mu g.l^{-1}$ (detection limit; arbitrary choice). This results in an annual release of 0.002 kg to the public wastewater treatment plant.

Production of speciality coatings (site IIc)

The production of speciality coatings is stated to be free of water and there is no wastewater from any of the production processes on site (CIL, 2002). The process is designed to minimise any emissions to air of either solvents or HCCP. A default emission factor for air of 10 g per tonne (EC, 2003) for this application is used and emissions to waste water are assumed not to occur. Formulation is also a relevant stage for site II-c, because the produced resin is applied during the formulation of the paint. Emissions from this stage are not accounted for since emissions are considered to be negligible (2 gram/year).

Default release estimation

According to the default emission tables from the TGD (EC, 2003), the emission factor for industrial use of HCCP in closed systems with controlled transport is 10 g per tonne to air for all sites. The release factor for wastewater is 7 kg per ton for site IIa and 20 kg per tonne for site II-b and II-c.

Table 3-1 Input data for the local exposure assessment for water and air at industrial use (II). Site specific information is presented in bold

	II-a	**II-b**	**II-c**
Processing tonnage (t/y)	**4000-5000**	**<1000**	**<20**
IC/UC	3/33	3/33	3/33
Number of days	**Conf.**	**Conf.**	20
Release to air (%), generic	0.001	0.001	0.001
Release to waste water (%), generic	0.7	2	2
Emission to air (kg/y), generic 1)	50	10	0.2
Emission to waste water (kg/y), generic 1)	35,000	20,000	400
Emission to air (kg/y), site-specific	**9.5**	**0.027**	n.r. 2)
Emission to waste water (kg/y), site-specific	**0**	0.002	**0**
STP flow (m^3/d)	2,000	**66,000**	2,000
Receiving water flow (m^3/s)	**188**	0.8	2.1
Dilution factor	8,100	1	10

1) based on the default emission factors from the Technical Guidance Document (EC, 2003)

2) not relevant: emission to air are not reported, default emission factor is used.

Site specific release factors for both sites II-a and II-b are much lower than the default release factors. The rapporteur considers the reported site-specific emission factors to be acceptable,

given the process descriptions, emission abatement measures and reported data of site II-a, II-b, and II-c. Therefore site-specific release factors will be used in the risk assessment. The atmospheric releases from site II-c are not reported and are estimated by using default emission factors (EC, 2003).

3.1.1.4 Other releases of hexachlorocyclopentadiene

3.1.1.4.1 Releases of HCCP during industrial use of HET-acid and Dechlorane Plus

Polymers industry (III-a and III-c)
HET-acid or the anhydride, is used to add flame-retarding properties to unsaturated polyesters and paints. It contains 0.005% (Durez, 1995) up to 0.01% (maximum for high grade Chlorendic Anhydride) hexachlorocylcopentadiene (Velsicol, 2002). HET-acid or its anhydride are both used as a reactive intermediate. It is assumed that only HET-acid is used in the European Union and there is no import of chlorendic anhydride from outside the European Union.

For the stage of processing HET-acid in unsaturated polyesters, possible release of HCCP might result from two processing steps and a formulation step, i.e. the polymerisation process (the making of the pre-polymer), mixing of the pre-polymer with reactive monomer and polymer processing (the thermo-setting). The pre-polymer is produced by esterification (polycondensation). During processing of the resin, the pre-polymers and the reactive monomer are mixed with an initiator to establish the radical polymerisation reaction (thermo-setting). The relevant industrial and use categories, process or reaction types and the A-tables from the EC (2003) are given in Table 3.2.

Besides HET-acid, Dechlorane Plus is also used as a flame-retardant additive to plastics, usually thermoplastics. Dechlorane Plus is still used as a flame-retardant additive to plastics within the European Union in an amount of 800 tonnes in 2000. Hexachlorocyclopentadiene emissions might occur during processing (extrusion) of the thermoplastic. This is the stage at which Dechlorane Plus is added to the plastic. It is assumed that Dechlorane Plus contains 50 ppm of hexachlorocyclopentadiene as a reasonable worst case. Specifications on the MSDS give concentrations of HCCP in Dechlorane Plus that are in the range of 5-50 ppm. However, recent data show that actual measurements indicate an average concentration of 5 ppm (Durez, 2002). The corresponding industrial and use categories are given in Table 3.2.

Paints, lacquers and varnishes industry (IIIb)
Production, formulation and processing (industrial use) are the relevant stages for the use of HET-acid in alkyd resin or unsaturated polyester resin based paints. The first step is the processing of HET-acid in the production of a pre-polymer. The next step in the production of the paint is the formulation. Here, pre-polymers are mixed with other paint constituents. During processing of the paint, the pre-polymers are mixed with an initiator which is kept separate (two component systems) to establish the radical polymerisation reaction (thermo-setting).

Consumer use of these types of paints is assumed to be not relevant, because it concerns speciality paints, which will only be applied in a limited number of applications referred to as

non-dispersive or industrial use. Table 3.3 lists the appropriate industrial and use categories and A-tables from the TGD (EC, 2003).

Hexachlorocyclopentadiene is also used in LPVC amounts in the United Kingdom, where it is used in the production of a speciality coating. It is not likely that HCCP is used as such in paint. It is more likely that HCCP is used as an intermediate to produce chemical, like HET-acid, which in its place is used in paints. Its use as a flame retardant in paints is already believed to be covered by the present HET-acid scenarios for paint (see above).

Table 3-2 Industrial and use categories and relevant life cycle stages for the application of HET-acid and Dechlorane Plus.

	IC	UC	Process type	Chemical type	Table (TGD) [1)]
III-a. Use of HET-acid in polyester resins					
Processing step 1 (production of pre-polymer)	11	55/43	B (other, wet)	I	A3.10
Formulation step (mixing polyester with reactive monomer)	11	55			A2.1
Processing step 2 (application resin, thermo-setting)	11	55	B	I	A3.11
III-b. USE of HET-acid in paint					
Production of resin	14	55	B (other, wet)	I	A3.10
Formulation of paint	14	55	MC-1b		A2.1
Application of paint	14	55	solvent based		A3.15
III-c. Use of Dechlorane Plus in thermo plastics					
processing of polymer	11	55/22	A	I	A3.11

1) EC (2003)

The calculated emissions (Table 3.4) are based on the consumed amount of HET-acid and Dechlorane Plus. The amounts of HET-acid used in the production of resins and paints are respectively 589 tonnes/year (95% of use) and 29 tonnes/year (5% of use) (Table 3.3). The use of Dechlorane Plus for the production of flame-retardant plastics is assumed to be about 800 tonnes in the European Union. The emission factors resulting from the A-tables (EC, 2003) were corrected for the HCCP content in the processed substances. The used concentration of HCCP in HET-acid and Dechlorane Plus is 0.005% (see also Table 3.3).

Table 3-3 Applied emission factors and relevant tonnage for the use of HET-acid and Dechlorane Plus in various applications.

	Tonnage [tonnes/yr]	Substance	HCCP content	Emission factor TGD [1] (A-tables)	Effective Emission factor
III-a. Use of HET-acid in polyester resins	589	HET-acid	0.005%		
Processing step 1 (production of pre-polymer)					
Air				1E-03	5E-08
Water				1E-05	5E-10
Soil				0	0
Formulation step (mixing with monomer)					
Air				0.001	5E-08
Water				0.003	1.5E-07
Soil				0	0
Processing step 2 (application resin					
Air				0	0
Water				0	0
Soil				0	0
III-b. USE of HET-acid in paint	29	HET-acid	0.005%		
Production of resin					
Air				1E-03	5E-08
Water				1E-05	5E-10
Soil				0	0
Formulation of paint					
Air				1E-03	5E-08
Water				3E-03	1.5E-07
Soil				1E-04	5E-09
Application of paint					
Air				1E-03	5E-08
Water				1E-03	5E-08
Soil				5E-03	2.5E-07
III-c. Use of Dechlorane Plus in thermo plastics	800	Dechlorane Plus	0.005%		
processing of polymer					
Air				2.5E-03	2.5E-05
Water				5E-04	5E-06
Soil				1E-04	1E-06

1) EC (2003)

The total emissions to air for the release scenarios III-a, III-b and III-c are 0.06, 0.0045 and 0.10 kg per year, respectively (Table 3.4). The estimated total annual emissions to waste water are 0.09, 0.006 and 0.02 kg, respectively. The total estimated environmental release of HCCP resulting from residual amounts of HCCP in processed HET-acid (resins and paints) are thus found to be very low. For this reason no further (PEC) calculations will be carried out for these three emission scenarios (III-a, III-b and III-c).

Table 3-4 Emissions [kg/year] from residual amounts of HCCP in processed HET-acid and Dechlorane Plus.

Classification	Emission air	Emission STP	Emission soil
III-a. Use of HET-acid in polyester resins	**0.06**	**0.09**	**0**
Processing step 1 (production of pre-polymer)	0.03	0.0003	0
Formulation step (mixing with reactive monomer)	0.03	0.0885	0
Processing step 2 (application resin, thermo-setting) 1)	0	0	0
III-b. Use of HET-acid in paint	**0.0045**	**0.006**	**0.008**
Production of resin	0.0015	0.000015	0
Formulation of paint	0.0015	0.0045	0.00015
Application of paint	0.0015	0.0015	0.0075
III-c. Use of Dechlorane Plus in thermoplastics	0.1	**0.02**	**0.004**
processing of polymer	0.1	0.02	0.004

1) no emission expected during application of two-component resin. In addition residual amount of HCCP present in resin may be released during service live of the material. This step of the live cycle is not yet incorporated in the A-tables for this application.

3.1.1.4.2 Releases of HCCP during application of pesticides

Pesticides may contain residues of the initial product, hexachlorocyclopentadiene. In the case of endosulfan the residual content of HCCP is about 0.1% (Aventis, 2001 and BUA, 1988). Because of the limited use of cyclodiene pesticides other than endosulfan in the European Union, only hexachlorocyclopentadiene release through endosulfan application is considered in the exposure assessment (see Chapter 2).

Three local emission scenarios are conducted with USES 3.0 (RIVM, 1999) to estimate the potential releases of HCCP during agricultural application of endosulfan. Two scenarios were based on high application rates and one scenario based on a relatively low application rate. The two high application scenarios consider the use of endosulfan on cabbage and citrus fruits in a Mediterranean setting and the low one resembles the use on tomatoes also in a Mediterranean setting. The scenario choice is based on registered use rates and patterns in various European countries provided by the main manufacturer (GAP data) (FAO, 1993) (see Appendix B).

USES 3.0 is a tool for evaluating the human and environmental risks of crop protection chemicals. It is developed especially for The Netherlands and, consequently, reflects the (typical) Dutch situation with regard to environmental characteristics and the typical agricultural situation at the local scale. Therefore some environmental parameters were

adjusted to values, which more adequately represent the Mediterranean conditions. Additionally, some scenario choices had to be made to reflect the situation in a typical Mediterranean setting at best. These changed values are assumed to match those typical for the Sahel region and are taken from Linders (2001). See Table 3.5.

Table 3.5 Environmental parameters for local release estimates of HCCP through agricultural application of endosulfan.

Parameter	Reference (Dutch situation)	Adjusted value (Mediterranean situation)	Unit
Environmental temperature	12	20	[°C]
Soil			
Volume fraction water in application soil	0.2	0.1	[-]
Volume fraction air in application soil	0.2	0.3	[-]
Volume fraction solids in application soil	0.6	0.6	[-]
Weight fraction of organic carbon in soil	2.9	1	[-]
Ditch			
Temperature of ditch	10	18	[°C]
Concentration suspended matter in ditch	15	50	[mg.l-1]
Weight fraction of organic carbon in sediment	0.05	0.029	[-]

USES 3.0 has several scenario options to describe the local situation and agricultural operation, like for instance the way of pesticide application, crop and growing stage. It is also possible to indicate whether there is a drainage system present or the soil is ploughed after application. The scenario choices are given in Table 3.6. The drift fraction is determined by crop and way of application and is set to crops resembling citrus trees, cabbage and tomato plants at best and a reasonable worst case situation. This reasonable worst case situation reflects a spraying period where crops have little or no leaves and where sprayed crops are also located near the ditch.

Table 3.6 Scenario choice for the use of endosulfan on citrus fruits, cabbage and tomatoes (HCCP content is 0.1%).

Parameter	Scenario 1 (Citrus)	Scenario 2 (Cabbage)	Scenario 3 (Tomatoes)
Application mode	Sprays	sprays	sprays
Emission to soil			
Crop and growing stage	n.r. 1)	n.r. 1)	n.r. 1)
Fraction of emission to soil	0	0	0
Fraction of emission to air	1	1	1
Emission to water			
Choice of application	fruit trees on ditch edge	full field, sugar beets	full field, maize
Fraction of drift related to application	0.325 (0.17/0.07) 2)	0.18	0.024 (0.17/0.07) 2)
Drainage	No	No	No
Mixing with soil	No	No	No
Number of applications [-]	1	3	3
Application interval [days]	n.r.	7 3)	7 3)
Dosage[kg.ha^{-1}]	6.3	2.45	0.098
Amount of spraying liquid used [l.ha-1]	400 4)	400 4)	400 4)

1) Crop and growing stage is not relevant. The emission to soil is calculated from the emission to air and the fraction intercepted by the crop. The fraction to air, which depends on the vapour pressure is one for HCCP, according to USES 3.0

2) Between brackets the drift factor for fruit trees, without and with leaves, is given. These values are from USES 4.0

3) Default application interval for pesticides (USES 3.0) was assumed for endosulfan

4) A default amount of spraying liquid of 400 l.ha^{-1} (USES 3.0) is chosen

3.1.1.5 Regional and continental exposure assessment (emissions)

To estimate the continental emissions of HCCP through application of endosulfan, country specific emissions were calculated for those countries within the EU where the use of endosulfan is allowed (See table 2.1). Country and crop specific use rates and patterns (application rates and number of applications) provided by the main manufacturer (FAO, 1993) were used in combination with grown crop area for the year 2000 (FAO, 2002) to calculate the total amount of endosulfan applied in agriculture. The reported use rates and patterns are based on the figures from 1993 and only those countries allowing the use of endosulfan are considered. Furthermore it was assumed to be likely that there are other pesticides in use, which serve the same agricultural purpose as endosulfan. Therefore arbitrarily one tenth of the area was assumed to be treated with endosulfan. A total amount of endosulfan for agricultural use of 1068 tonnes per year was estimated this way for the whole European Union. This is approximately two times higher than the reported amount of endosulfan used on the European market in 2001 (Industry information; see section 2.3.3). - The residual amount of hexachlorocyclopentadiene is 0.09% (Aventis, 2001) giving an emission of HCCP through agricultural use of endosulfan of 961 kg/year. From the USES 3.0 calculations it is shown that during application of endosulfan, by far most of the HCCP is emitted indirectly to air within 24 hours after application. Emission of HCCP to adjoining

ditches (drift) is assumed to be only 1% of the applied amount. This is the drift factor for full field applications as used in pesticide evaluation in The Netherlands (See USES 3.0). This standard drift factor of 1% does not correspond with the drift factors used in the local scenarios for the agricultural use of endosulfan (Table 3.6). Because of the many different drift factors for the various applications on various crops, the standard drift factor for full field applications is used as default for calculating the continental HCCP emissions from endosulfan usage.

The total continental release (including regional) of HCCP resulting from the local emission sources, i.e. processing HCCP, the release through agricultural use of endosulfan and the processing of HET-acid and Dechlorane Plus, are presented in Table 3.7. The continental emissions from the non-agricultural scenarios are derived from Tables 3.1 and 3.4. The total continental emission to air is 962 kg/year and the release to water is 10.4 kg/year.

Table 3.7 Total continental release of HCCP (kg/year). Total release includes both continental and regional emissions Generic emission data from site II-c are not included [1].

Parameter	Air	Waste water
HCCP processing	9.53	0.002
Agricultural use of endosulfan	951.59	9.61 [2]
Residual amounts in HET-acid and Dechlorane Plus	0.23	0.21
Total	962	10.37

1) Continental emissions as they should be used in EUSES are the total emissions in the EU region excluding regional emissions.

2) emission to surface water

Regional emissions of hexachlorocyclopentadiene were calculated assuming the 10% rule, i.e., regional emissions are assumed to be about 10% of the total continental emissions. The use of the 10% rule seems to be justified here as the major emission source, i.e. the agricultural use of endosulfan, is distributed over a number of countries. Regional emissions to air and water therefore amount to 96.2 kg/year and 1.0 kg/year, respectively. The release to water includes emissions to waste water of 0.08 kg/year.

3.1.2 Environmental fate

3.1.2.1 Degradation in the environment

For the degradation in the environment physico-chemical data have been used, which were on the one hand experimentally derived and on the other hand estimated using structure-activity relationships. The following table gives an overview of experimental (source IUCLID) and estimated data (EPIWIN). The effect of the use of either data on environmental degradation will be discussed in the next chapter. The experimentally derived data will be used in EUSES.

Table 3.8 Experimentally derived and with QSARs estimated physico-chemical characteristics of HCCP

Parameter	Unit	Experimentally derived	Estimated with QSARs
Melting point	[°C]	-9	55
Boiling point	[°C]	239	242
Vapour pressure	[Pa] at 25°C	10	2.8
Octanol-water partition coefficient	[log Kow]	3.99-5.04	4.63
Water solubility	[mg/l] at 25°C	1.14	0.88

3.1.2.1.1 Atmospheric degradation

Chemical reactions that are important for atmospheric removal of organic substances include reactions with the hydroxyl radical (OH), the nitrate radical (NO_3), and ozone (O_3), as well as photolysis. HCCP is expected to be degraded rapidly by photolysis. The atmospheric half-life of HCCP by reaction with hydroxyl radicals varies from less than 1 day to about 29 days, based on different quantitative structure-activity relationships. These QSARs show a great discrepancy in the removal of HCCP by reaction with ozone. Estimated half-life values range from 50 minutes to more than 9 years.

The rate constant for the reaction of HCCP vapour with photochemically generated hydroxyl radicals in the atmosphere has been estimated to be $5.6 \cdot 10^{-13}$ $cm^3.molecule^{-1}.sec^{-1}$ at 25°C. Assuming an average ambient hydroxyl radical concentration of $5 \cdot 10^5$ molecule/cm^3 the half-life for this reaction has been estimated to be 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 (HSDB, 2001). This result was confirmed using the US-EPA AOPWIN model. With this model an overall hydroxyl rate constant of $3.9 \cdot 10^{-13}$ cm^3 $molecule^{-1}$ sec^{-1} at 25°C was estimated. The half-life for a 12-hour day (hydroxyl radical concentration of $1.5 \cdot 10^6$ molecule/cm^3) is estimated to be 27 days. For ozone the overall rate constant with this model was estimated to be $3.4 \cdot 10^{-21}$ cm^3 $molecule^{-1}$ sec^{-1} at 25°C, which corresponds to an atmospheric half-life of about 9 years (ozone concentration of $7 \cdot 10^{11}$ mol/cm^3).

In another study on quantitative structure-activity relationships, with the ionisation potential employed as physical parameter, reaction rates with hydroxyl, nitrate radicals and ozone radicals were estimated. Corresponding values were $9.3 \cdot 10^{-11}$ cm^3 $molecule^{-1}$ sec^{-1}, $2.5 \cdot 10^{-12}$ cm^3 $molecule^{-1}$ sec^{-1} and $4.5 \cdot 10^{-16}$ cm^3 $molecule^{-1}$ sec^{-1}, respectively. Based on the estimated reaction rate and an atmospheric concentration of 10^6 OH molecule/cm^3, the half-life of HCCP in air is estimated to be less than 1 day. Considering an atmospheric ozone concentration of 100 ppb, the estimated half life of HCCP is estimated to be 50 minutes (Grosjean, 1990).

Other estimates of reaction rates with hydroxyl and nitrate radicals and ozone are available. Based on estimation reaction rates of the chemical with hydroxyl radicals and ozone of $5.9 \cdot 10^{-11}$ and $8 \cdot 10^{-18}$ cm^3 $molecule^{-1}$ sec^{-1}, respectively, the tropospheric residence time was estimated to be 5 hours (Cuppitt, 1980 cited in US-EPA, 1984).

When solved in cyclohexane, HCCP strongly absorbs UV light in the environmentally significant range ($\lambda > 290$ nm) (HSDB, 2001). Strong absorption of UV light wavelength and

observed rapid photolysis in aqueous solution suggests that direct photolysis would probably be the dominant removal process in the atmosphere and on soil surfaces. When adsorbed onto silica gel, the substance underwent 46.0% photomineralization when irradiated with UV light (> 290 nm) for 17 hours. These data indicate that HCCP adsorbed onto sunlight-exposed particles (e.g. dust, soil surfaces) may be subject to rapid photodegradation.

The results indicate that HCCP will not persist in the atmosphere as it will be removed via reaction with photochemically-generated hydroxyl radicals. Since HCCP is known to photolyse rapidly (half-life < 10 minutes) in water (Atallah et al., 1981, Butz et al., 1982, Wolfe et al., 1982), atmospheric photolysis is also expected. However, no estimate of the reaction rate for atmospheric photolysis is available. Furthermore, 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. Therefore, as a realistic worst-case approach, an atmospheric half-life of 29 days, based on QSAR estimation, will be used in EUSES.

3.1.2.1.2 Aquatic degradation (incl. sediment)

Degradation processes for removal of HCCP from water include photolysis, hydrolysis and biodegradation. In shallow or flowing waters, photolysis is expected to be the predominant fate process. In deeper waters hydrolysis and biodegradation may be more important environmental processes (US-EPA, 1984).

Abiotic degradation

Photolysis
HCCP photolyses rapidly in water when exposed to sunlight or a mercury-vapour light source (Butz et al., 1982, Chou et al., 1987, Wolfe et al., 1982). The half-life values ranged from less than 2 minutes (Wolfe et al., 1982) to 4 minutes in natural sunlight (Chou et al., 1987) and less than 1 minute when irradiated with a mercury-vapour light source (Butz et al., 1982).

Zepp et al. (1979) and Wolfe et al. (1982) furthermore studied the direct photo-reaction of HCCP in water under controlled conditions in the laboratory using a monochromatic light (313 nm) isolated by filters from a mercury lamp. Photo-transformation rate constants, computed for the study location (Athens, GA, 34°N latitude), agreed with those observed in the sunlight experiments described above. Rate constants were also computed for various times of day at 40°N latitude. The near surface photo-transformation rate constant of HCCP at this latitude on cloudless days (averaged over both light and dark periods for a year) was 3.9 hr^{-1}, which corresponds to a half-life of 10.7 minutes. The presence of natural suspended sediments had virtually no influence on the photolysis rate as compared with the photolytic degradation in distilled water. It was deduced from this result that a photo-sensitizing effect by means of dissolved or suspended substances can be excluded and that light-induced processes do not play a dominant role in view of rapid direct photolysis.

More recently, Podowski and Khan (1996) reported that HCCP was photolysed rapidly as a solution in acetone (half-life < 1 day) to apolar, polar and hydrophilic products. The 15-day photolysis mixture contained no HCCP. The reported photodegradation products included three primary products (2,3,4,4,5-pentachloro-2-cyclopentenone, hexachloro-2-cyclopentenone, and hexachloro-3-cyclopentenone) and three secondary products (pentachloro-cis-2,4-pentadienoic acid, Z- and E-pentachlorobutadiene, and

tetrachlorobutyne) (Chou et al., 1987). Dimerization of 2,3,4,4,5-pentachloro-2-cyclopentenone to form a higher molecular weight compound such as hexachloro-indenone may be a minor degradation pathway. This indicates that degradation of HCCP in water does not always produce lower molecular weight, less toxic products (Butz et al., 1982, Chou et al., 1987). Pentachlorocyclopentenone has been reported to be the primary photolysis product by Butz et al. (1982) and the dimerization has been proposed as being an artefact. However, more recent work by Podowski and Khan (1996) rejected the idea that the dimer is an artefact as they could not produce the dimer compound by injecting pentachlorocyclopentenone into the GC at 190°C. The authors also reported that the dimer, with a proposed molecular formula of $C_9C_{18}O$, was not mirex or chlordecone as judged by its GC behaviour, indicating that HCCP may not form at least the latter stable chemicals.

Hydrolysis

Hydrolysis of HCCP in water occurs much more slowly than photolysis. In a study of the transformation pathways of HCCP in aquatic systems, the reported average hydrolysis rate constant over a pH range of 3-10 was $1.5 \cdot 10^{-6}$ sec^{-1} at 30°C (Wolfe et al., 1982), which corresponds to a half-life of 5.35 days (US-EPA, 1984). At pH 7 and 30°C a hydrolytic half-life of 3.3 days was found. The addition of natural sediments sufficient to adsorb up to 92% of the compound caused the rate constant to vary by less than a factor of 2. It was therefore concluded that sorption to sediments would not significantly affect the rate of hydrolysis. In this study also a preliminary investigation was conducted to determine the products from hydrolysis. The hydrolysis reaction was conducted at 60-70°C in 40% acetonitrile-water at 10^{-4} M HCCP and proceeded through approximately two half-lives. After extraction and concentration of the lipophilic reaction products, analysis by GC/MS showed nine major peaks in the chromatogram. Several of these were high molecular weight compounds, however an identification was not possible.

Some variability of hydrolysis rate with changes in pH was demonstrated by Yu and Atallah (1977). They studied the stability of ^{14}C-HCCP in water at pH 3, 6, 9 and 12 at 25°C and 45°C, under dark conditions. HCCP was relatively unstable at alkaline pH. At 25°C, the half-lives were 11.4, 11.4 and 6.0 days at pH 3, 6 and 9, respectively, and <2 hours (0.1 day) at pH 12. At 45°C the half-lives at pH 3, 6 and 9 were 9.2, 10.6 and 4.4 days, respectively. Degradation of HCCP resulted in water-soluble products, and based upon their chromatographic behaviour, the hydrolysis products appear to be polyhydroxy compounds, with CO_2 as a minor hydrolysis product.

More recently, Podowski and Khan (1996) reported that the time it took for HCCP to reach 50, 10 and 5% of its initial concentration in water (7 ppb) was 4, 27 and 40 days, respectively.

Biodegradation

Biodegradation of HCCP occurs in water under laboratory conditions. In a static laboratory culture, 100% of HCCP was lost within 7 days from both 5 mg/l and 10 mg/l solutions (Tabak et al., 1981). Volatilisation was not reported to occur under the test conditions.

In an evaluation of the potential for biodegradation as a spill-clean up technique, HCCP was reported not to be directly accessible to micro-organisms in aquatic media (Thuma et al., 1983). The reported degradation of HCCP ranged from 16 to 40% after 7 days, and from 35 to

60% after 14 days. Addition of methanol as a solubiliser increased the rate of biodegradation in 3 of 7 test cultures, with degradation up to 76%. These results are significant because controls were used to account for losses of HCCP by means other than biodegradation, so abiotic losses can be ruled out.

When activated sludge from a municipal sewage works (1 g dw/l) was exposed at 25°C to a concentration of 50 μg/l, more than 75% of HCCP applied was degraded after five days. About 49% of the HCCP applied was found in the activated sludge in the form of metabolites and 26.4% was converted to products that were soluble in water. The vast majority (89.1%) of the conversion products contained in the activated sludge was not extractable (Freitag et al., 1982). The carbon dioxide formed was less than 0.1% of the amount of HCCP applied (Freitag et al., 1985).

Experiments were carried out on the removal of HCCP from leachates from an industrial waste landfill. In an experimental procedure simulating the biological purification stage of a sewage works and using activated sludge from a municipal sewage works, the removal rate at concentrations of 124 to 255 μg/l was over 99% (Goltz et al., 1983).

During a study of biodegradability in a static test over five days using activated sludge from an industrial sewage plant (1 g dw/l) the elimination rate was found to be over 90%. The test solution contained 64 mg of dissolved and finely dispersed HCCP per litre, which was in accordance with a determination of the content of organic carbon. The test substance was already eliminated for 90% after 3 hours (Hoechst, 1979).

In examining the effect of a 500 mg/l concentration of HCCP on anaerobic micro-organisms under anaerobic conditions at 37°C, Johnson and Young (1983) detected a significant biodegradation of HCCP after an incubation period of 15 days. The test solution had a chlorine content which corresponded to a loss of four chlorine atoms per molecule, i.e. the level of mineralization was over 66%.

Atallah et al. (1981) examined the biodegradability of ^{14}C-labelled HCCP in the course of 28 days under aerobic conditions. They used an adapted mixed inoculum from the effluent of a municipal sewage works and several strains of *Pseudomonas putida*. HCCP, together with vitamin traces, was applied as the sole source of carbon in concentrations of 4.5 and 45.3 mg/l. After one day, more than 80% of the radioactivity had volatilised out of the aqueous medium as volatile, organic compounds. After a 4-week incubation period, the speed of conversion to $^{14}CO_2$ in relation to the radiocarbon content dissolved in the test medium in the inoculated and the non-inoculated samples was 3% and 1% CO_2 respectively per week.

The majority of these tests do not characterise the biodegradation of HCCP in surface water, but are screening tests with activated sludge. These tests 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 (Thuma et al., 1978).

3.1.2.1.3 Degradation in soil

If released to soil, HCCP will be immobilised by strong adsorption to organic matter. Significant losses on soil surfaces may occur via photolysis. Below the soil surface, photolysis

would not be a significant fate process due to light attenuation. Volatilisation from soil surfaces is expected to be of minor importance. In moist soil, HCCP will be subject to chemical hydrolysis (half-life hours to weeks) and biodegradation under aerobic and anaerobic conditions (HSDB, 2001).

Biodegradation of HCCP by soil micro-organisms is an important process in its environmental degradation. Soil degradation is rapid under non-sterile aerobic and anaerobic conditions, with indirect evidence for microbial involvement reported by Rieck (1977b,c).

Volatilisation from soil was examined in another experiment (Rieck, 1977c). In a 14-day study, radiocarbon volatilised from non-sterile, ^{14}C-HCCP-treated soil was trapped and assayed. Over the study duration, a total of 20.2% of the applied ^{14}C was trapped; 11.2% in hexane and 9.0% in ethanolamine-water. Most of the hexane fraction (9.3% of applied ^{14}C) was trapped during the first day, probably representing volatilised HCCP. However, the ethanolamine-water fraction, considered to represent evolved CO_2, was released gradually over the 14-day period. In the soil analysis, non-polar (extractable) and polar (extractable and unextractable) material accounted for 3.4 and 40% of the dose, respectively, during the 14 days; thus, total recovery was only 63.6% including volatilisation. No metabolic products were identified in either study by Rieck (1977b,c). In these studies, HCCP was degraded to polar material in both sterile and non-sterile soils, indicating the occurrence of an abiotic degradation process such as hydrolysis by soil water and possibly some photolysis. Since degradation occurred more quickly in non-sterile soils, biodegradation evidently was also occurring. Volatilisation of HCCP occurred mainly during the first day, and apparently represented no more than 11.2% of the total amount applied, although the low total recovery in this experiment decreases the reliability of this figure.

Thuma et al. (1978) studied the feasibility of using selected pure cultures to biodegrade spills of hazardous chemicals on soils, including HCCP. They tested 23 organisms and found that 2-76% of the HCCP had been removed from the aqueous culture medium within 14 days. Seven of the 23 organisms degraded more than 33% of the HCCP within 14 days. Losses of HCCP, other than biodegradation, were accounted for by the use of controls.

3.1.2.1.4 Summary of environmental degradation

Atmosphere

The results indicate that HCCP will not persist in the atmosphere as it will be removed via reaction with photochemically-generated hydroxyl radicals. Furthermore, 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. Therefore, as a realistic worst-case approach, a atmospheric half-life of 29 days will be used in EUSES. It should be noted that this value is only an estimation of the photodegradation of the substance in the vapour phase and not of adsorbed substance on airborne particles. The importance of this can not be quantified in EUSES.

Aquatic compartment

Degradative processes for removal of HCCP from water include photolysis, hydrolysis and biodegradation. Hydrolysis of HCCP in water occurs much more slowly than photolysis. In shallow or flowing waters, photolysis is the predominant fate process; in deeper waters hydrolysis and biodegradation may be more important environmental fate processes (US-EPA, 1984).

In the study from Wolfe et al. (1982) a hydrolysis half-life of 3.3 days was found at pH 7 and 30°C. For risk assessment purposes for fresh water a pH of 7 and a temperature of 12°C will be established which is in conformity with the standard environmental parameters. The hydrolysis half-life reflecting an average EU outdoor temperature can be recalculated by the equation:

DT50(X°) = DT50(t) • e(0.08.(T-X))
DT50(12°C) = 3.3 (days) • e(0.08.(30-12))
DT50(12°C) = 3.3 (days) • 4.2 = 13.9 days

The half-life for hydrolysis can be converted to a pseudo first-order rate constant:

khydrwater = ln 2/DT50 hydrwater = ln 2/13.9 = 5.0E-02 d^{-1}

From the study from Wolfe et al. (1982) a photo-transformation rate constant of HCCP was computed to be 3.9 hr-1. The presence of natural suspended sediments had virtually no influence on the photolysis rate as compared with the rate of photolytic degradation in distilled water. The half-life for photolysis in water can be calculated using the equation:

DT50 photowater = ln 2/kphotowater = ln 2/93.6 (d-1) = 7.0E-03 days = 10.7 minutes
kphotowater = 3.9 hr-1

HCCP can be biodegraded in aquatic media under laboratory conditions as was seen in the study from Atallah et al. (1981), although evidence is considered to be weak. However, another study on the fate of HCCP found biodegradation to be a relatively unimportant process in aquatic systems, based on the observation that there was no detectable difference in hydrolysis rates between sterile and non-sterile studies and measured numbers of micro-organisms (Wolfe et al., 1982). It is difficult to differentiate removal or degradation via abiotic processes (adsorption, volatilisation, and hydrolysis) from that via biodegradation.
HCCP is a volatile, hydrophobic substance, which will be metabolised, strongly adsorbs to organic carbon and will not be mineralised aerobically. Under anaerobic conditions dehalogenation will occur and one or more chlorinated metabolites will be formed. HCCP will hydrolyse to some extent.

On the basis of the available data on aquatic biodegradation, HCCP is considered to be inherently biodegradable, not fulfilling specific criteria (rate constant 0 h^{-1}). This is a rather worst case assumption, but adequate data are lacking to make a more balanced decision on this issue. The rate constant k will be greater than 0 h^{-1} under some conditions (expert judgement).

Terrestrial compartment
The persistence of HCCP in soil is low, with degradation of >90% of applied HCCP to non-polar products within approximately 7 days. Factors contributing to this loss include abiotic and biotic degradation processes and volatilisation, although the relative importance of each is difficult to quantify given the limited information available. As no half-life in soil can be derived from the experimental data presented, the use of screening data may be considered. Degradation half-life classes for soil, partly based on K_p can be used. As HCCP has a K_{psoil} of lower than 100 l/kg and the substance is considered to be inherently biodegradable, a half-life of 300 days is chosen (EC, 2003)

In the following table the selected values for environmental degradation are summarised. These values will be put into the EUSES model to calculate PECs in different environmental media.

Table 3.9 Overview of environmental degradation data used as input data in EUSES

Compartment		Rate constant	DT50	Based on
Water	Hydrolysis	5.0E-02 d^{-1}	13.9 days	Experimental data
	Photolysis	3.9 hr^{-1}	10.7 minutes	Experimental data
	Biodegradation	0 hr^{-1}	∞	TGD* default/expert judgement
Atmosphere		5.6E-13 cm^3/molecules/sec	29 days	QSAR estimation
Sediment		2.31E-04 d^{-1}	3000 days	TDG default
Soil		2.31E-03 d^{-1}	300 days	TGD default

* (EC, 2003)

In the previous sections the environmental degradation of HCCP has been addressed. Despite a number of uncertainties in the various breakdown routes of HCCP in the environment several metabolites of HCCP have been identified (esp. photolysis products). Given the very low environmental release of HCCP the need for any further characterisation (e.g. PBT potential) of these (and possibly other) metabolites is considered to be low.

3.1.2.2 Distribution

Using a vapour pressure of 10 Pa (WHO, 1991) and a water solubility of 1.25 mg/l (WHO, 1991) a Henry's law constant of 2.18E03 $Pa.m^3$/mol is calculated.

Because HCCP has a vapour pressure of about 10 Pa at 25°C, when released to the atmosphere, it will exist almost entirely in the vapour phase (see SimpleBox calculation below). Detection of HCCP in ambient air downwind of a hazardous waste site indicates that atmospheric transport of HCCP may occur (US-EPA, 1984). However, transported distance will be limited by the high reactivity of the chemical in the atmosphere.

HCCP introduced into water bodies may be transported in undissolved, dissolved or adsorbed forms. In its undissolved form, HCCP will tend to sink because of its high specific gravity and may then become concentrated in deeper waters, where photolysis and volatilisation would be precluded. Some HCCP may be dissolved in water and then be dispersed with water flow. HCCP tends to adsorb onto organic matter because of its lipophilic nature and may then be transported with water flow in a suspended form. Transport to air may occur by volatilisation. However, suspended solids in surface water may be a major factor in reducing volatilisation.

Volatilisation is most likely to occur from moving water bodies, with estimated removal of about 15% of the HCCP in a turbid river compared with less than 5% removal from a lake or pond (Callahan et al., 1979). The volatilisation rate from aquatic systems depends on specific conditions, including adsorption to sediments, pH of the medium and airflow rate. In a laboratory study, 5.87% of ^{14}C-HCCP per ml of evaporated water volatilised during the first

hour (Kilzer et al., 1979). Data from the same study indicated that volatilisation is much lower from soils. Volatilisation was highest from the sand and lowest from the humus. Volatilisation was greater in soils with low organic content. The results indicate that HCCP evaporation to air occurred mainly during the first day following application and was probably associated with the soil surface only.

HCCP in soils is predicted to be tightly adsorbed to organic matter and relatively resistant to leaching by soil water. Thus, the primary routes of transport for soil applied HCCP are by movement of particles to which it is adsorbed or by volatilisation.

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.

Table 3.10 SimpleBox estimation of theoretical distribution of HCCP to different 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

Soil adsorption properties of HCCP can be predicted from their soil organic carbon-water partition coefficients. EPIWIN calculations predict an organic carbon-water partition coefficient (Koc) for HCCP of 1667 and with EUSES the Koc is estimated to be 15,000 l/kg. Substances with Koc values > 1000 are tightly bound to soil components and are immobile in soils. The measured Koc for HCCP is 4265 (Chou and Griffin, 1983). HCCP, released to the water, will partition rapidly to sediment and suspended solids in the water column. The proportion remaining dissolved in solution and available for biological uptake will therefore be small.

More sorption data were found in literature for an experimentally flooded soil. Weber (1979) reported that an average of 68% of applied HCCP was adsorbed to Cape Fear loam soil present in aqueous solutions. From this data it was suggested that HCCP is very strongly adsorbed by organic colloids because of its hydrophobic character.

The following partition coefficients will be used as input in the EUSES model:

K_{oc} 4265 l/kg (experimental value)
Kp_{susp} 427 (Foc_{susp} = 0.1)
Kp_{sed} 213 (Foc_{sed} = 0.05)
Kp_{soil} 85 (Foc_{soil} = 0.02)
$K_{soil\text{-}water}$ 128
$K_{susp\text{-}water}$ 108
$K_{sed\text{-}water}$ 107

3.1.2.2.1 Distribution in wastewater treatment plants

The SimpleTreat model of EUSES can be used to estimate the distribution of HCCP in a STP. This distribution is given below.

Table 3.11 SimpleTreat estimation of distribution of HCCP in an STP

	EUSES
Air [%]	69.6
Water [%]	5.4
Sludge [%]	25
Biodegradation [%]	0

The EPIWIN estimation (below) shows a more or less identical percentage for total STP removal (95%), but some differences are found with SimpleTreat for the underlying removal processes. These can be explained by different default settings for the sewage treatment plant of both models.

Table 3.12 EPIWIN estimation of removal of HCCP in an STP

	EPIWIN
Total removal [%]	94.9
Total biodegradation [%]	0.3
Total sludge adsorption [%]	55.8
Total to air [%]	38.9

In order to determine the accumulation of HCCP in activated sludge from a municipal sewage works, activated sludge (1 g dw/l) was exposed for five days to a concentration of 50 µg 14C-HCCP per litre of water. The accumulation factor as a quotient of HCCP-equivalent concentrations in activated sludge measured in µg/g dry weight and in water in µg/ml amounted to 2350 (Kotzias et al., 1980; Freitag et al., 1982) and 2400 respectively (Freitag et al., 1985).

3.1.2.3 Accumulation and metabolism

The log Kow of HCCP has been experimentally determined to be 3.99-5.04 (Geyer et al., 1984; Wolfe et al., 1982), which would indicate a substantial potential for bioconcentration, bioaccumulation and biomagnification. With EPIWIN a BCF of 1516 was estimated (log Kow 5.04) and with EUSES the BCF would amount to 3800. Actual determinations indicate that HCCP does not seem to accumulate to a great extent (Podowski and Khan, 1979), mainly because it is metabolised rapidly (studies described in more detail below).

In the following section bioconcentration factors (BCF) and bioaccumulation factors (BAF) are reported. Bioconcentration implies that tissue residues result only from exposure to the ambient environment (e.g. air for terrestrial or water for aquatic species). Bioaccumulation considers all exposures (air, water and food) of an individual organism as the source of tissue residues.

Podowski and Khan (1979, 1984) conducted several experiments concerning the uptake, bioaccumulation and elimination of ^{14}C-HCCP in goldfish and concluded that the species eliminated absorbed HCCP rapidly. In one experiment, fish were transferred daily into fresh solutions of ^{14}C-HCCP for 16 days. This transfer of three fish/jar resulted in accumulative exposure of 240 µg of HCCP. Nominal HCCP concentrations of 10 µg/l resulted in measured water concentrations in the range of 3.4-4.8 µg/l, because of rapid volatilisation of the compound. Radioactivity accumulated rapidly in fish tissue, reaching a maximum on day 8 corresponding to 6 mg HCCP/kg. Since an undetermined amount of the radioactivity was present as metabolites, no reliable bioconcentration factor can be calculated. From day 8 to day 16, tissue levels declined in spite of daily renewal of exposure solutions, indicating that excretion of HCCP and/or its metabolites was occurring more rapidly than uptake. In a static exposure to an initial measured HCCP concentration of 5 µg/l, radioactivity was taken up by the fish to a level corresponding to 1.6 mg HCCP/kg on day 2, accompanied by a slight decrease of HCCP in the water. By day 4, approximately 50% of the absorbed activity had been excreted, and the water level increased. Over the following 12 days, radioactivity in both water and fish declined slowly.

Podowski and Khan (1979, 1984) also studied elimination, metabolism and tissue distribution of HCCP injected intraperitoneally into goldfish and concluded that goldfish eliminate injected HCCP both rapidly and linearly (biological half-life approx. 9 days). Fish (27-45 g) were injected with 39.6 µg of ^{14}C-HCCP and analysed 3 days later. Of the 97% of the radiolabelled dose accounted for, the fish eliminated approx. 18.9%, leaving a residual of 78.1%. Of the residue found in the fish, 47.2% was extractable in organic solvent; 10.6% was water-soluble metabolites, and 20.3% was unextractable. None of the metabolites were identified. Biphasic elimination was observed, rapid at first, followed by a slower phase. Based on a study of goldfish injected with ^{14}C-HCCP, the elimination of HHCP occurs in multiple stages, with a reported half-life in the organism of 7 days and predicted clearance of 90 to 95% of the chemical after 162 and 211 days, respectively (Podowski et al., 1991).

Veith (1979, cited in US-EPA, 1984) determined the BCF for HCCP to be 29 in the fathead minnow. In a 32-day flow-through study, 30 fish were exposed to HCCP at a mean concentration of 20.9 µg/l and were sacrificed five at a time for residue analysis at 2, 4, 8, 16, 24 and 32 days. The study was conducted using Lake Superior water at 25ºC (pH 7.5, dissolved oxygen >5.0 mg/l and hardness 41.5 mg/l as $CaCO_3$). On the basis of its estimated octanol/water partition coefficient alone (log P = 5.51; value from Veith!), a BCF of circa 9600 would have been predicted. However, HCCP did not bioconcentrate substantially, and therefore deviated from the log P:log BCF relationship shown for most of the 29 chemicals tested.

Spehar et al. (1979) conducted a 30-day early-life stage, flow-through toxicity test at 25°C with the fathead minnow. HCCP residues in the fish after 30 days of continuous exposure to HCCP were <0.1 mg/kg for all concentrations tested (0.78-9.1 µg/l), and the BCF was <11 (0.1 mg/kg in fish divided by 9.1 µg/l in water).

Kotzias et al. (1980) and Freitag et al. (1982, 1984, 1985) examined the bioaccumulation of ^{14}C-HCCP in the goldfish. Following 24 hours of exposure to a concentration of 50 µg/l under static conditions at 20 to 25°C a bioaccumulation factor of 308 (Kotzias et al., 1980) was recorded and of 1230 after three days of exposure (Freitag et al., 1982, 1984, 1985). There is apparently no equilibrium between uptake and elimination after 24 hours. In this investigation

no account was taken of a potential metabolism since only the radioactivity in the fish and in the water respectively was measured in order to determine the concentrations of HCCP.

Lu et al. (1975) studied the fate of HCCP in a model terrestrial-aquatic ecosystem maintained at 26.7°C with a 12-hour photoperiod. They also studied the metabolism of HCCP by the organisms present in the model terrestrial-aquatic ecosystem. They reported that unmetabolized HCCP represented large percentages of the total extractable ^{14}C, being 33% in algae, 50% in snail, 46% in mosquito and 41% in fish. Percent biotransformation was calculated for each organism: 4% for the algae, 10% for the snail, 2% for the mosquito and 27% for the fish. However, these values may underestimate the extent of metabolism, since acetone extractable polar compounds were not considered in the calculations.

Results on the bioaccumulation potential of HCCP by the green alga (*Chlorella fusca*) were reported by Geyer et al. (1984) and Freitag et al. (1982, 1984, and 1985). The concentrations of HCCP in the alga and in water were determined after 24 hours of exposure under static conditions at 20 to 25°C to a concentration of 50 µg/l. The bioaccumulation factor (BAF) for algae was 1090.

In a different study (Kotzias et al., 1980), the bioaccumulation factor in the green alga, *Chlorella fusca*, obtained under the same experimental conditions was given as 1140.

Discussion of bioaccumulation data

Based on the experimentally derived octanol/water partition coefficient of 5.04, HCCP would be predicted to have a BCF of about 1516 (EPIWIN calculations). The TGD QSAR predicts a value of 3800. Investigations on the bioconcentration factor of HCCP, however, show much lower values. Veith et al. (1979) found that HCCP does not follow the log Kow:log BCF relationship and measured a BCF of 29 in the fathead minnow. Spehar et al. (1979) reported also a low BCF (<11) in the same species under comparable conditions (flow-through study, test duration about 30 days, no use of radiolabelling).

In ^{14}C studies higher BCF-values were reported (323 and 1297 in Goldfish, Podowski and Khan, 1979, 1984 and 1230 in the Mosquitofish, Freitag et al., 1982, 1984, 1985). Since the body residues as well as the radioactivity in water included products other than HCCP, the calculated bioconcentration ratios (BCF), based on total radioactivity, may not give the precise estimate of bioconcentration of HCCP. If the BCFs were based on parent HCCP and not total extractable radioactivity, the BCFs would likely be smaller. Furthermore, the studies of the biotransformation of HCCP in goldfish are complicated by the fact that HCCP and its metabolites are very reactive, many being very volatile and extremely lipophilic.

Although QSAR estimates for the BCF point to a significant bioaccumulation potential, HCCP was found to be rapidly metabolised and eliminated in a number of studies. This is reflected in relatively low experimental BCFs. US-EPA concluded to use the BCF of <11 and adjusted it for lipid content. The weighted average BCF for the edible portion of freshwater and estuarine aquatic organisms was calculated and found to be 4.34 (ATSDR, 1999). However, as the photodegradation half-life of HCCP in the aquatic compartment was found to be around 11 minutes, the ^{14}C present in the fish in many of the studies may represent metabolites. These metabolites could be formed by photolysis of the substance in solution rather than metabolism in the organisms itself. The ^{14}C studies may therefore have actually determined the uptake of degradation products rather than the parent compound. Podowski and Khan (1979) showed relatively long 90 and 95% clearance times of the ^{14}C-label of 162

and 211 days, respectively, which could be an indication that persistent metabolites may have been formed. To deal with this uncertainties BCF values of both less than 11, representing the steady-state bioconcentration factor that was measured in 30-day flow through exposures to constant levels of HCCP, and a realistic worst case value of 1297, covering persistent metabolites, will be used in EUSES.

Accumulation in earthworms

No experimental data are available on accumulation in earthworms. Therefore, the BCF is estimated according to the following QSARs given in the revised TGD:

$BCF_{earthworm} = 0.84 + 0.012\ K_{ow}/RHO_{earthworm}$

Where for $RHO_{earthworm}$ by default a value of 1 ($kg_{ww} \cdot L^{-1}$) can be assumed.

$BCF_{earthworm} = 1.32E03\ l/kg_{wet\ earthworm}$

The formula for the $BCF_{earthworm}$ in kg_{soil}/kg_{worm} then becomes:

$(0.84 + 0.012\ K_{ow} * RHO_{soil})/(K_{soil\text{-}water} * CONV_{water})$

Using a logKow of 5.04 this leads to a BCF_{worm} of 17.5 kg/kg.

3.1.2.4 Calculation of predicted environmental concentrations (PEC_{local})

3.1.2.4.1 Calculation of PEC_{local} for industrial/professional use

Predicted Environmental Concentrations (PEC values) in the environmental compartments have been calculated with EUSES 2.0.1 (EC, 2004) for the three processing sites, using the input data from Table 3.1. The resulting local PEC values are listed in Table 3.13. It is emphasised that the local PEC values are the sum of the local concentration (C_{local}) calculated from the site specific emissions and the regional background concentration ($PEC_{regional}$).

Table 3.13 Local PEC values in the various environmental compartments for processing of HCCP.

Compartment	II-a	II-b	II-c
STP (mg/l)	0	2.4E-08	0
Water (mg/l)[1]	7.69E-12	2.42E-08	7.69E-12
Sediment (mg/kg_{wwt})	7.19E-10	2.26E-06	7.19E-10
Air ($\mu g/m^3$)	7.32E-03	2.83E-05	1.60E-04
Soil (mg/kg_{wwt})	1.04E-06	3.19E-07	2.26E-08

[1] $PEC_{local} = C_{local} + PEC_{regional}$

The calculated STP effluent concentration for site II-b is in line with the results of an analysis of the STP effluent in 2002, which indicated an effluent concentration below the detection limit of 0.02 µg/l (Durez, 2002). The calculated sediment concentration for site II-b is in line with the results of an analysis of the sediment near the STP. The concentration HCCP was below the detection limit of 0.01 mg/kg dw, with a dry weight content of 62% (Durez, 2003).

Based on wet weight the concentration HCCP was found to be below 0.016 mg/kw wwt. Because only a measured value below the detection limit is available, the estimated $PEC_{sediment}$ will be used as input in EUSES. It should be realised that the latter value is also based on a detection limit value (for effluent), but it is founded on a series of measurements. The sediment monitoring refers to only a very limited number of measurements. Both approaches indicate, however, that local HCCP levels are expected to be negligible.

3.1.2.4.2 Agricultural use of endosulfan

Local PEC values for HCCP in ditches surrounding agricultural fields are calculated using USES 3.0 (RIVM, 1999), using input data from Tables 3.5 and 3.6 (Table 3.14). These concentrations are the result of the agricultural field application of endosulfan in which HCCP is present as an impurity.

Table 3.14 Local PEC values for HCCP in surface water for agricultural use of endosulfan (USES 3.0 calculation).

Compartment	Citrus fruits	Cabbage	Tomatoes
Ditch, yearly average concentration (μg /l)	1.67E-05	1.95E-06	1.04E-07
Ditch, 21 day average concentration (μg /l)	6.13E-03	4.03E-04	2.15E-05
Ditch, maximum concentration (μg/l)	9.18E-01	1.98E-02	1.05E-03

Following current pesticide regulations from The Netherlands only the average water concentrations are being used in pesticide risk assessments (long term effects). The average concentration is calculated for the same exposure period as the lowest ecotoxicity test (key study) takes. For that reason only the average HCCP concentrations are being used for this pesticide scenario for endosulfan in the risk characterisation (21/28 day average).

3.1.2.5 Measured levels

There are no measured data available for HCCP.

3.1.3 Secondary poisoning

The concentration of HCCP in food (fish) or fish-eating predators ($PECoral_{predator}$) is calculated from the PEC for surface water, the measured range of BCF values for fish (11 and 1297) and the biomagnification factor (Table 3.15).

Table 3.15 Calculation of predicted environmental concentration in food

Site	BCF_{fish} [$l/kg_{wet\ fish}$]	PEC_{water} [mg/l]	BMF	$PECoral_{predator}$ [$mg/kg_{wet\ fish}$]
IIa	11	7.69E-12	1	8.46E-11
	1297	7.69E-12	1	1E-08
IIb	11	2.42E-08	1	2.92E-08
	1297	2.42E-08	1	3.44E-06
IIc	11	7.69E-12	1	8.46E-11
	1297	7.69E-12	1	1E-08

PEC_{water}: scenario where 50% of the diet comes from a local area (annual average PEClocal) and 50% of the diet comes from a regional area (annual average PECregional) (EC, 2003)

BMF: a biomagnification factor of 1 was used as the BFCfish is below 2000 (EC, 2003)

For the assessment of secondary poisoning via the terrestrial food chain the $PECoral_{predator}$ is equal to the total concentration of HCCP in worm as a result of bioaccumulation in worm tissues and the adsorption of the substance to the soil present in the gut. As no experimental $BCF_{earthworm}$ is available this was estimated with a QSAR model (EC, 2003).

Table 3.16 Calculation of predicted environmental concentration in food

Site	$BCF_{earthworm}$ [l/kg$_{wet\ earthworm}$]	$PECoral_{predator}$ [mg/kg$_{wet\ earthworm}$]
IIa	1.32E03	7.29E-06
IIb	1.32E03	7.76E-07
IIc	1.32E03	1.66E-07

3.1.4 Calculation of $PEC_{regional}$

The regional PEC values resulting from calculations with EUSES 2.0.1 (EC, 2004), using the regional emissions as reported in Section 3.1.1.5 are presented in Table 3.17.

Table 3.17 Regional PEC values.

Compartment	PEC regional
Surface water (μg/l)	7.74E-09
Sediment (mg/kg$_{wwt}$)	1.26E-09
Air (μg/m^3)	7.55E-06
Agricultural soil (mg/kg$_{wwt}$)	1.02E-09
Natural soil (mg/kg$_{wwt}$)	1.01E-09

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT ASSESSMENT)

3.2.1 Aquatic compartment (incl. sediment)

3.2.1.1 Toxicity test results

3.2.1.1.1 Criteria for validation

Ecotoxicity data are checked on their reliability and relevance. For HCCP, a great number of the ecotoxicity tests were not performed according to internationally recognised guidelines. Furthermore, some relevant data originates from secondary literature (especially US-EPA, 1984). These data have not been re-evaluated. As the substance is susceptible to photodegradation in solution (half-life is estimated to be around 11 minutes), it is important to consider possible photodegradation in the interpretation of the ecotoxicity data. Furthermore, it is possible that some loss through volatilisation could have occurred in some of the studies. From the available studies it can not be concluded if volatilisation and photodegradation were taken into account. In most of the studies only nominal or measured (mother compound) concentrations were given. It is emphasised that for the PNEC derivation only measured data (key studies) were used thereby largely circumventing these uncertainties. Furthermore, the possibility that toxic effects may have been caused by certain HCCP metabolites is reasonably rebutted by the fair match between experimental results and QSAR outcomes (see section 3.2.1.2.1).

3.2.1.1.2 Fish

Acute toxicity

Table 3.18 Acute toxicity to freshwater and marine fish species

Species	Method	Duration [h]	Criterion	Value [µg/l]	Comments	Reference
Freshwater species						
Fathead minnow (larvae, <0.1 g) (*Pimephales promelas*)	FT, M	96	LC50	7	soft water, 25°C	Spehar et al. (1977, 1979)
Rainbow trout *(Salmo gairdneri)*	FT	6.5	LC100	130	12°C	Sinhaseni (1982, 1983)
	S	4	LC100	120	14°C	Sinhaseni (1982)
Bluegill *(Lepomis macrochirus)*	S, N	96	LC50	25000	water aerated, 25°C	Shell (1984)
Largemouth bass *(Micropterus salmoides)*	S, N	96	LC50	20000	water aerated, 25°C	
Leuciscus idus melanotus	DIN 38412, part 15	48	LC50	240 (160-320)	20°C	Hoechst (1979)

Species	Method	Duration [h]	Criterion	Value [µg/l]	Comments	Reference
Fathead minnow (*Pimephales promelas)*	S, N	96	LC50	180 (160-220)	soft water, 22°C	Buccafusco and LeBlanc (1977)
Channel catfish *(Ictalurus punctatus)*	S, N	96	LC50	97 (81-120)		
Bluegill *(Lepomis macrochirus)*	S, N	96	LC50	130 (110-170)		
Goldfish *(Carrasius auratus)*	NR	96	LC50	78	NR	[1]Podowski and Khan (1979)
Fathead minnow (*Pimephales promelas)*	S, N	96	LC50	104 78 59	hard water, acetone sol. soft water, acetone sol. hard water, emulsion	cited in US-EPA (1984)
Marine species						
Sheepshead minnow *(Cyprinodon variegatus)*	S, N	96	LC50	45 (34-61)		cited in US-EPA (1984)
Pinfish *(Lagodon rhomboids)*	S, N	96	LC50	48 (41-58)		cited in US-EPA (1984)
Spot *(Leiostomus xanthurus)*	S, N	96	LC50	37 (30-42)		cited in US-EPA (1984)

S = static; FT = flow-through; N = nominal concentrations; M = measured concentrations; NR = Not reported
[1] only abstract

The 96 h-LC50 values for freshwater range from 7-240 µg/l. The lowest value is from a study with measured concentrations. HCCP is slightly soluble in water (solubility of 1.02-1.25 mg/l) and can be considered as volatile (vapour pressure is 10.7 Pa at 25 °C). The lower LC50-values obtained in the study from Spehar are probably the result of the utilisation of intermittent-flow exposure systems and/or the use of the most sensitive life stages of development for testing. The recovery of HCCP from 12 spiked samples in this test was 94%.

For the effect assessment for freshwater vertebrates the lowest reported LC50 value of 7 µg/l will be used (Spehar et al., 1977 and 1979). The extremely high results from Shell (1984) are not taken into account, because the reported values are above the water solubility limit of the substance. Furthermore, since the test water was aerated during the test, volatilisation of the test compound can not be excluded.

The acute toxicity values for HCCP were comparable for each of the three marine fish species tested. The static 96-hour LC50 values based on nominal concentrations for spot, sheepshead minnow and pinfish varied from 37-48 µg/l.

Long-term toxicity

Table 3.19 Long-term toxicity to fish

Species	Method	Duration [days]	Criterion	Value [µg/l]	Endpoint	Reference
Fathead minnow (larvae, <0.1 g) (*Pimephales promelas)*	FT, M	30	NOEC	3.7	survival	Spehar et al. (1977, 1979)

S = static; FT = flow-through; N = nominal concentrations; M = measured concentrations

In a 30-day early-life stage flow-through toxicity test with fathead minnows using 1 day old larvae the 96-h LC50 value was 7 µg/l (measured concentrations; see section 3.2.1.1.3). The

lowest concentration causing 50% mortality was reached within 4 days. Furthermore, HCCP residues found in fathead minnows at the end of the 30-day exposure period were low (< 0.1 µg/g), and a BCF value of < 11 was reported. Based on the toxicity and growth data it can be concluded that 3.7 µg/l is the highest concentration of HCCP that produces no adverse effects on fathead minnow larvae. It should be noted, that this fish study only investigated the survival and growth of larvae and as such is not directly comparable with the long-term fish tests currently recommended in the TGD.

3.2.1.1.3 Aquatic invertebrates

Acute toxicity

In the next table the acute toxicity data for invertebrates are shown.

Table 3.20 Acute toxicity to freshwater and marine invertebrates

Species	Method	Duration [h]	Criterion	Value [µg/l]	Comments	Reference
Freshwater species						
Daphnia magna	DIN 38412, part 11	24	EC50	210	Closed system	Kühn et al. (1989)
Daphnia magna	S, N	24 48	LC50 LC50	93 (79-110) 52.2 (44.8-60.9)	soft water, 17°C	Vilkas (1977)
Daphnia magna	S, N	24 48	LC50 LC50	130 (68-260) 39 (30-52)	soft water, 22°C	Buccafusco and LeBlanc (1977)
Marine species						
Mysid shrimp *(Mysidopsis bahia)*	S, N FT, N FT, M	96 96 96	LC50 LC50 LC50	32 (27-37) 12 (10-13) 7 (6-8)		cited in US-EPA (1984)
Grass shrimp *(Palaemonetes pugio)*	S, N	96	LC50	42 (36-50)		cited in US-EPA (1984)
Polychaete *(Neanthes arenaceodentata)*	S, N	96	LC50	371 (297-484)		cited in US-EPA (1984)

S = static; FT = flow-through; N = nominal concentrations; M = measured concentrations

The 48 h-LC 50 values for freshwater invertebrates, resulting from two static tests with nominal concentrations, range from 39-52.2 µg/l (Vilkas, 1977 and Buccafusco and LeBlanc, 1977).

In marine species 96-h LC50 values range from 7 to 371 µg/l (US-EPA, 1984). The lowest value obtained is from a study with measured concentrations. Except where indicated, these results were obtained from static tests with nominal concentrations of HCCP. The highest LC50 by far was for the polychaete *Neanthes arenaceodentata*, which is an infaunal organism living in the sediment. The two shrimp species tested were more sensitive to HCCP by a factor of 10 or more. The static LC50 value for the grass shrimp was slightly higher than that

for the mysid shrimp. However, the LC50 for the mysid shrimp was considerably lower in a flow-through test than in the static test. Similarly, the LC50 value was lower when calculated from measured concentrations of HCCP as the value based on nominal concentrations. Although, the results for marine invertebrates are obtained from cited studies, they will be used for effect assessment purposes as these tests were performed according to EPA standard methods and the important test conditions are known (flow-through, measured concentrations).

Long-term toxicity

The following table shows the chronic toxicity data for invertebrates.

Table 3.21 Long-term toxicity to freshwater and marine invertebrates

Species	Method	Duration [days]	Criterion	Value [µg/l]	Endpoint	Reference
Freshwater species						
Daphnia magna	UBA (1984)	21	NOEC	9	Reproduction	Kühn et al. (1989)
Marine species						
Mysid shrimp (*Mysidopsis bahia)*	FT, M	28	NOEC	0.3	Reproduction	cited in US-EPA (1984)

S = static; FT = flow-through; N = nominal concentrations; M = measured concentrations

Kühn et al. (1989) reported a 21-day NOEC of 9 µg/l for Daphnia magna, based on nominal concentrations.

In the unpublished study from US-EPA, groups of 40 mysid shrimp were exposed for 28 days in a flow-through system. Measured concentrations were found to be about one-half of the nominal ones. Mortality occurred in all concentrations except the control, but showed no consistent dose-response relationship. Reproduction, however, was more clearly related to dose (NOEC of 0.3 µg/l). First significant effects on mortality started occurring at the same concentration as for the reproduction endpoint. At higher doses there is a poor dose response relationship for mortality.

3.2.1.1.4 Algae

Acute/long-term toxicity

In the next table the acute toxicity data for algae are shown.

Table 3.22 Acute toxicity to freshwater and marine algae

Species	Method	Duration [h]	Criterion	Value [µg/l]	Comments	Reference
Freshwater species						
Scenedesmus subspicatus	DIN 38412, part 9	48	EC50 EC50	80 240	Biomass Growth rate	Kühn and Pattard (1990)
Selenastrum capricornutum		96	EC50	190	Growth rate	Shell (1984)
Marine species						
Dunaliella tertiolecta	Walsh (1980)	168	EC50	100	Growth rate	cited in US-EPA (1984)
Skeletonema costatum	Walsh (1980)	168	EC50	6.6	Growth rate	cited in US-EPA (1984)

Isochrysis galbana	Walsh (1980)	168	EC50	3.5	Growth rate	cited in US-EPA (1984)
Porphyridium cruentum	Walsh (1980)	168	EC50	30	Growth rate	cited in US-EPA (1984)
Skeletonema costatum	NR	48	LC4	25	Mortality	Walsh (1983)

S = static; FT = flow-through; N = nominal concentrations; M = measured concentrations; NR = not reported

In freshwater and marine algae species, growth was reported to be inhibited by 50% at exposure levels ranging from 3.5 to 240 µg/l. Other tests with S. costatum indicated that the direct, algicidal effect of HCCP was less pronounced than its effect on growth. After 48 hours of exposure to HCCP at 25 µg/l mortality was only 4%. Some of the studies were carried out over 168 hours rather than the more usual 72 hours. From the studies it cannot be concluded if algae were still undergoing exponential growth at the end of the study, as these are unpublished data.

3.2.1.1.5 Microorganisms

The effects of HCCP on micro-organisms in aqueous systems have been tested. In an activated sludge micro-organisms toxicity study, according to OECD guideline 209, 6 and 13% inhibition of the respiration rate was found at a concentration of 100 mg/l. Therefore, it can be concluded that HCCP is very slightly toxic to waste water micro-organisms at a concentration of 100 mg/l. Since HCCP is poorly soluble in water, the test substance was added quantitatively to the test vessels. Many of the aqueous concentrations in the other tests exceeded the maximum water solubility (1.25 mg/l). In these tests organic solvents were used to overcome this problem. The environmental significance of these results should, however, be interpreted with care.

Table 3.23 Effects of HCCP on micro-organisms

Species	Test conditions	Duration [h]	Criterion	Value [mg/l]	Reference
Activated sludge micro-organisms	OECD209	0.5	EC50 EC10	>100 100	Desmares-Koopmans (2003)
Desulfovibrio desulfuricans	Inhibition of anaerobic substrate reduction	3 24	EC100 LC100 EC100	500-1000 50-1000 1-10	Atallah et al. (1981), Butz and Atallah (1980)
Anaerobic bacteria from STP	ETAD fermentation tube method	24		No effect	Hoechst (1979)
Anaerobic microorganisms	Inhibition gas formation	5	EC8 EC35	1 10	Kahn et al. (1981)
Anaerobic microorganisms	Inhibition gas formation	5	EC76 EC82	50 100	Kahn et al. (1981)
Anaerobic microorganisms	Inhibition gas formation	285	EC0 EC10 EC9	10 50 100	Kahn et al. (1981)
Trichoderma longibrachiatum (fungi)		168	EC50	1.1	cited in US-EPA (1984)
Trichoderma longibrachiatum (fungi)		48	EC50	0.2	cited in US-EPA (1984)

3.2.1.2 Calculation of Predicted No Effect Concentration (PNEC)

3.2.1.2.1 Aquatic compartment

No clear distinction can be made between the sensitivity for freshwater and marine organisms. Therefore, the $PNEC_{freshwater}$ will be derived from the entire data set and will be used for the risk assessment of the freshwater compartment. As no quantitative risk assessment for the marine compartment will be made, no $PNEC_{marine}$ is derived.

Freshwater data
Estimations of the toxicity for freshwater species have also been made with ECOSAR (input physical chemical parameters: log Kow 5.04, water solubility 1.25 mg/l and melting point -9°C).

Table 3.24 Overview of toxicity data for freshwater organisms

	Acute toxicity [µg/l]	Chronic toxicity [µg/l]	QSAR [µg/l]
Fish	7 (96-h LC50)	3.7 (30 days NOEC)	57 (96-h LC50)
Invertebrates	39 (48-h LC50)	9 (21 days NOEC)	42 (48-h LC50)
Algae	190 (96-h EC50)	-	245 (96-h EC50)

From these results it can be concluded that available NOECs ranged from 3.7-9 μg/l and that fish seems the most sensitive and algae being the least sensitive species. QSAR calculations are more or less of the same order of magnitude, being (slightly) higher than the test data.

Marine data
The following table contains the marine data.

Table 3.25 Overview of toxicity data for marine species for derivation of PNEC

	Acute toxicity [μg/l]	Chronic toxicity [μg/l]
Fish	37 (96-h LC50)	-
Invertebrates	7 (48-h LC50)	0.3 (28 days NOEC)
Algae	3.5 (96-h EC50)	25 (48 h LC4)

From the data it can be concluded that NOECs ranged from 0.3-25 μg/l, with shrimp being the most sensitive and aquatic plants being the least sensitive species.

Calculation of $PNEC_{freshwater}$ when lumping data on freshwater and marine organisms

Table 3.26 Calculation of $PNEC_{aqua}$ when lumping data on freshwater and marine organisms

	Acute toxicity [μg/l]	Chronic toxicity [μg/l]
Fish	7 (96-h LC50)	3.7 (30 days NOEC)
Invertebrates	7 (48-h LC50)	0.3 (28 days NOEC)
Algae	3.5 (96-h EC50)	25 (48 h LC4)

When all freshwater and marine toxicity data are considered together, three long-term values are available. An assessment factor of 10 can then be used for calculating the $PNEC_{freshwater}$. Based on the lowest NOEC of 0.3 μg/l for shrimp, the PNEC becomes:

$PNEC_{freshwater}$: 3.0 x 10^{-5} mg/l

3.2.1.2.2 Sewage treatment plants

For deriving the $PNEC_{micro\text{-}organisms}$ short-term measurements in terms of hours (e.g. 10 h) are preferred, in accordance with the retention time in a STP. Also the information available on the toxicity for micro-organisms has to be relevant for the endpoint considered, i.e. microbial degradation activity in a STP.

In a respiration inhibition test according to OECD 209, 6 and 13% inhibition of the respiration rate was found at a concentration of 100 mg/l. The 0.3 h-IC50 is >100 and an EC10 of 100 mg/l can be derived. Applying an assessment factor of 10 on the EC10 the $PNEC_{micro\text{-}organisms}$ becomes:

$PNEC_{micro\text{-}organisms}$: 10 mg/l

3.2.1.3 Toxicity test results for sediment organisms

There are no studies available on sediment-dwelling organisms exposed via sediment.

3.2.1.4 Calculation of Predicted No Effect Concentration (PNEC) for sediment organisms

HCCP is expected to adsorb to and persist in the sediment. A provisional PNEC will be calculated using the equilibrium partitioning method.

$PNEC_{sediment}$ = $K_{sediment\text{-}water}/RHO_{sediment}$ x $PNEC_{aqua}$ x 1000
= 108/1150 x 3.10^{-5} x 1000
= 2.81 x 10^{-3} mg/kg ww

The tentative PNEC for the sediment compartment is 2.81 µg/kg ww. However, the ingestion of the sediment-bound substance by sediment dwelling organisms may not be sufficiently explained by this relationship for substances with a log Kow greater than 5. The TGD suggests that in such cases the PEC/PNEC ratio is increased by a factor 10. However, as HCCP has a measured log Kow range of 3.99-5.04 it is felt to be a borderline case. Furthermore, the measured Koc value (4,265 l/kg) indicates that the substance is not adsorbed to the extent that would be expected from the Kow value (calculated Koc of 15,000 l/kg). For these reasons the factor of 10 will not be applied here.

$PNEC_{sediment}$ = 2.81 µg/kg ww

3.2.2 Terrestrial compartment

3.2.2.1 Toxicity test results

The effects of HCCP on plants and micro-organisms in soil systems have been tested.

Table 3.27 Overview of toxicity data on terrestrial organisms

Species	Test parameter	Duration [days]	Criterion	Value [mg/kg d.w.]	Reference
Lactuca sativa	Growth according to OECD 208	14	EC50	10	Hulzebos et al. (1993)
Soil microorganisms	^{14}C-determination	14	EC50	1374	Atallah et al. (1981), Butz and Atallah (1980)
Soil microorganisms	^{14}C-determination	1	EC50	104	Atallah et al. (1981), Butz and Atallah (1980)
Soil microorganisms		1	SG[1]	≥ 10	Rieck (1977a) cited in Bell et al. (1978)

[1] Schaedlichkeitsgrenze

The toxicity of HCCP to lettuce (*Lactuca sativa*) was determined in soil and nutrient solution. The EC50 of HCCP on growth was 10 mg/kg d.w., based on nominal concentrations (Hulzebos et al, 1993).

In the study from Rieck (1977a) no effects were found on natural populations of bacteria, actinomycetes, or fungi after a 24-day incubation of a sandy loam soil treated with 1 or 10 mg HCCP/kg d.w. It is concluded that no significant effects on microbial populations would result from contamination of soils with these levels of HCCP. However, adsorption onto soil particles may also account for the lack of toxicity in this study.

In the studies from Atallah and Butz the EC_{50} increased from 104 mg/kg at day 1 to 1374 mg/kg at day 14. It is suggested that the low toxicity and its decrease over time in this experiment may have been due to adsorption of the toxicant onto soil particles, as well as to potential adaptation by the organism.

HCCP was reported to be non-toxic to plants in concentrations at which it was an effective fungicide (Yowell, 1951). Test solutions were prepared by adding HCCP at various proportions to attaclay and a wetting agent, and the mixture was then mixed with water. The concentrations of HCCP applied to plants as an aqueous spray were 0.1, 0.2, 0.5 and 1.0%. Slight injury (unspecified) to *Coleus blumei* was reported at 1.0% HCCP, whereas lower concentrations were not harmful. Similarly, HCCP was added to horticultural spray oil and an emulsifier at various proportions and then mixed with water. The concentrations of HCCP in the prepared spray were 0.25 and 0.5%. No injury to *Coleus blumei* was observed at these concentrations.

3.2.2.2 Calculation of Predicted No Effect Concentration (PNEC)

A $PNEC_{soil}$ using assessment factors can be calculated by using the acute value measured in plants (EC50 = 10 mg/kg d.w.). An assessment factor of 1000 should be applied (EC50 from the acute plant test).

PNECsoil = 10 µg/kg d.w.

The PNECsoil can also be derived using the equilibrium partitioning method. For this calculation the PNECaqua for all aquatic organisms is used.

$PNEC_{soil} = K_{soil\text{-}water}/RHO_{soil} \times PNEC_{aqua} \times 1000$
$= 128/1700.26 \times 3.10^{-5} \times 1000$
$= 2.26 \times 10^{-3}$ mg/kg d.w.

$PNEC_{soil}$ = 2.26 µg/kg d.w.

The experimental PNEC is slightly higher than the one derived with the equilibrium partitioning method. It should be noted that experimental toxicity data are based on nominal concentrations. Furthermore, there is a significant potential for this substance to be removed from the soil by volatilisation, degradation and photolysis, and the available results may underestimate the actual toxicity of HCCP. Results presented by Atallah and Butz (1980 and 1981) showed decreasing toxicity to soil micro-organisms with time. Therefore, the equilibrium partitioning approach will be used for the risk characterisation. Similar arguments

as used in section 3.2.1.4 (sediment) can be brought forward here for not using the additional factor of 10 in the soil risk characterisation.

3.2.3 Atmosphere

Organic chemicals, which contain F and/or Cl or Br and are gaseous or a volatile liquid with a vapour pressure greater than or equal to 100 Pa should immediately be subjected to a first qualitative assessment of the ozone depletion potential (ODP). The following steps are then conducted:

- estimation of how long the substance will exist in the atmosphere
- if the life-time is equal or longer than 1 year the ODP will be calculated as described in De Leeuw (1993)

HCCP is a liquid with a vapour pressure of 10 Pa at 25ºC. The results on atmospheric degradation indicate that HCCP will not persist in the atmosphere as it will be removed via reaction with photochemically-generated hydroxyl radicals. Since HCCP is known to photolyse rapidly (half-life < 10 minutes) in water (Atallah et al., 1981, Butz et al., 1982, Wolfe et al., 1982), atmospheric photolysis is also expected. However, no estimate of the reaction rate for atmospheric photolysis is available. Furthermore, 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. An atmospheric half-life of 29 days has been derived from these data. As the estimated life-time of the substance in the atmosphere is < 1 year the substance is not expected to reach the stratosphere and therefore has no significant ozone depletion potential.

3.2.4 Secondary poisoning

3.2.4.1 Effect data

One oral repeated dose toxicity study with HCCP was available. In this 13 week oral (gavage) toxicity studies with rats and mice, no NOAEL could be established for rats, based on the toxicological relevant dose related increase in female kidney:body weight ratio at all dose levels compared to the control animals (LOAEL is 10 mg/kg bw). Furthermore, no NOAEL could be established for mice, based on the toxicological relevant increase in female liver:body weight and kidney:body weight ratio at all dose levels compared to the control animals (LOAEL is 19 mg/kg bw).

It should be noted that the batch of HCCP used in this study was contaminated with hexachloro-1,3-butadiene (0.51%), which is a known nephrotoxin in rodents. In the ATSDR (1994), a study of the NTP (1991) is mentioned in which a LOAEL of 0.2 mg/kg bw (0.51% of 38 mg/kg bw ≈ 0.2 mg/kg bw) was derived for hexachloro-1,3-butadiene based on the presence of kidney damage in female mice). Nevertheless, the oral LOAEL of 10 mg/kg bw, based on an increase in kidney:body weight ratio in female rats, is taken forward for the $PNEC_{oral}$ derivation.

3.2.4.2 Calculation of PNECoral

A LOAEL of 10 mg/kg bw was established from a 19 week oral gavage toxicity study with rats. For derivation of the $NOEC_{food}$ a NOAEL for mammals is needed. Given the used doses in the 13 week toxicity study (0, 10, 19, 38, 75, 150 mg/kg bw/day) and the observed (marginal) effects (increase in female kidney:body weight ratio at all dose levels) an assessment factor of 3 is used to derive the NOAEL for mammals. Using a conversion factor of 20 for rats (>6 weeks) to come from the NOAEL to the $NOEC_{food}$ will lead to a $NOEC_{food}$ of 66.6 mg/kg food. The $PNEC_{oral}$ is then derived from the $NOEC_{food}$ applying an assessment factor of 90, which is proposed by the TGD (2003) for a 90 day toxicity study with mammals. The $PNEC_{oral}$ will then become:

$PNEC_{oral}$ = 0.74 mg/kg_{food}

3.3 RISK CHARACTERISATION [5]

In Table 3.28 the PEC/PNEC ratios are shown for all relevant scenarios.

Table 3.28 Local risk characterisation ratios (PEC/PNEC values)

	WATER	SOIL	SEDIMENT	STP	FISH-EATING PREDATORS[1]	WORM-EATING PREDATORS
II-a processing facility	2.56E-07	4.76E-04	2.56E-07	0	1.14E-10 – 1.35E-08	9.85E-06
II-b processing facility	8.05E-04	1.41E-04	8.05E-04	2.43E-09	3.95E-08 – 4.65E-06	1.05E-06
II-c processing facility	2.56E-07	9.96E-06	2.56E-07	0	1.14E-10 – 1.35E-08	2.24E-07
Application of endosulfan						
Scenario 1 (Citrus)	2.04E-01		Not calculated [2]			
Scenario 2 (Cabbage)	1.34E-02		Not calculated [2]			
Scenario 3 (Tomatoes)	7.17E-04		Not calculated [2]			

[1] For fish eating predators BCF values of 11 and 1297 were used.
[2] Not calculated with USES 3.0, but PEC/PNEC sediment (equilibrium partitioning) would equal PEC/PNEC water.

[5] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Table 3.29 contains the PEC/PNEC ratios for the regional scenario.

Table 3.29 Regional risk characterisation ratios (PEC/PNEC values)

	water	SOIL	SEDIMENT
Regional scenario	2.56E-07	4.49E-07	4.48E-07

3.3.1 Aquatic compartment (incl. sediment)

Conclusions to the risk assessment for the aquatic compartment:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all local sites, endosulfan application and the regional scenario, as all the PEC/PNEC ratios for surface water and sediment are below 1.

3.3.1.1 Marine compartment

A marine risk assessment for HCCP was performed by Silberhorn and Smith (2001). A complete risk assessment according to the TGD (EC, 2003) for the marine compartment is not performed in this report. Based on the very low water and sediment PEC/PNEC ratios for the regional compartment (inland zone), there seems to be a negligible risk of HCCP for the regional marine environment . A local marine risk assessment is not relevant for processing sites IIa and IIb as those sites are not located near the coast. Site IIc does not discharge any HCCP to the aquatic environment due to characteristics of the applied production process. The agricultural scenario (endosulfan use) is considered not relevant for a marine risk assessment. The HCCP releases to air from endosulfan use are estimated to be around 1 t/y at a continental scale (see Table 3.9), but the atmospheric persistence of HCCP is assumed to be rather low as indicated in section 3.1.1.2.1. Therefore the potential of HCCP for long-range transport is considered to be low.

3.3.2 Terrestrial compartment

Conclusions to the risk assessment for the terrestrial compartment:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all sites, as the soil PEC/PNEC ratios for all local scenarios and the regional scenario are below 1.

3.3.3 Atmosphere

Because of its physical and chemical characteristics it is not expected that a great amount of HCCP will persist in the atmosphere. Additionally, there are no indications for either biotic or abiotic effects of HCCP in the atmospheric compartment.

Conclusions to the risk assessment for the atmosphere:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all sites, because of its physical and chemical characteristics it is not expected that a great amount of HCCP will persist in the atmosphere. Additionally, there are no indications for either biotic or abiotic effects of HCCP in the atmospheric compartment. The ozone depleting potential of HCCP is considered to be not significant.

3.3.4 Secondary poisoning

Conclusions to the risk assessment for secondary poisoning:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all sites, as all PEC/PNEC ratios for worm- and fish-eating predators are below 1.

PBT-assessment

The PBT assessment is conducted according to the TGD (EC, 2003).

Persistence
HCCP is considered to be inherently biodegradable in the risk assessment with a rate constant of 0 h^{-1} and should be regarded as potentially persistent.

When using the three models of BIOWIN, HCCP is predicted to be not fastly biodegradable with the non-linear model and not readily biodegradable with the MITI non-linear model. The ultimate biodegradation timeframe model does not support these results. Only when all three models give the same result a prediction of the biodegradability can be made. Based on this model the biodegradability of HCCP is unclear.

The current information on the abiotic degradation of HCCP, hydrolysis in particular, is insufficient to draw a conclusion on the 'real situation' in the marine environment.

HCCP is potentially persistent. As the B criterion is not met (see below) further testing on P is not considered necessary.

Bioaccumulation
Based on the log Kow-value of 5.04, HCCP would be considered to potentially fulfil the B-criterion. However, as BCF-values of less than 11 for the steady-state and 1297 from ^{14}C

studies are derived from experimental data, the substance is not expected to fulfil the B-criterion, as the BCF value does not exceed the trigger value of 2000.
HCCP does not meet the B-criterion of the PBT-criteria.

Toxicity
The lowest NOECs for freshwater and marine organisms were found to be 0.0037 and 0.0003 mg/l, respectively. This is clearly under the cut-off value of 0.01 mg/l.

HCCP meets the T-criterion in the PBT-assessment.

Overall, HCCP does not meet the PBT criteria. It should be noted that HCCP has an impurity of 0.1% hexachlorobutadiene, which is considered to be a PBT substance.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

HCCP is a liquid with a low vapour pressure of approximately 10 Pa at 25 °C.

Production of HCCP does not take place in the EU. HCCP for use as an intermediate in the chemical industry is imported in 20 tonnes rail tanks or marine portable tanks.

4.1.1.2 Occupational exposure

HCCP is mainly used in the production of pesticides, e.g. mirex, kepone, endosulfan and pentac (Bell et al., 1978; Company C, 2003), and flame retardant chemicals, e.g. chlorendic acid and dechlorane plus (Klingenberg, 1988).
HCCP derived chlorinated organic flame retardants are used for unsaturated polyesters with fire retarding or corrosion-resistant properties, for building materials, and the use in transporting and chemical process industries. Furthermore, dechlorane plus is used in the production of nylon for electrical uses, e.g. in switches (Klingenberg, 1988).
Some sources give information on the occurrence of HCCP both in solid chemical waste and in sewage water from the chemical industry, which causes inhalation exposure to workers in the waste- and sewage-processing branch (Grisham, 1986; D'Appolonia, 1982; Kominsky et al., 1980). The exposure of these workers is assumed to take place very infrequently, only after accidental large spills or dumps in the chemical industry. Therefore this scenario is not addressed in this exposure assessment.
Furthermore, HCCP is formed in the production of semiconductors, during the aluminium plasma etching process (Bauer et al., 1995; Schmidt et al., 1995). In plasma etching processes the controlled removal of layers of material from the surface of a silicon wafer is realised using halogen containing process gasses (no HCCP). Upon radiation with radio frequency energy, the gases are dissociated and ionised to create ions and free radicals. As a result, complex mixtures of halogenated hydrocarbons and inorganic chlorides are formed, among which HCCP. The substance was found in contaminated vacuum pump oil and in some gas pipelines (Bauer et al., 1995; Schmidt et al., 1995).
HCCP is also reported to be formed during oxidative degradation (fire) of a flame retardant (Company B, 2001). This unintentional release of HCCP during fires indicates the potential occupational exposure of fire fighters and professional clean up workers.

Occupational exposure in the EU is possible in industries where HCCP is used as an intermediate, such as in the pesticide producing industry and the flame retardant producing industry. Since there is a residue concentration of HCCP in flame retardants, the use of these substances may also cause occupational exposure. The possible occupational exposure caused by the use of pesticides is not evaluated in this report since this is covered by different legislation. Furthermore, occupational exposure may occur when HCCP is formed in a process (e.g. in the semiconductor industry) or is present as a contaminant (e.g. chemical

waste and sewage water from the chemical industry; not addressed in this exposure assessment).
Inhalation and dermal contact are the most obvious routes of exposure to workers. Ocular exposure is possible due to hand-eye contact.
HCCP is a labelled corrosive substance. For the handling of corrosive substances and formulations, immediate dermal contacts occur only accidentally and it is assumed that repeated daily dermal exposure can be neglected. Therefore according to the revised TGD (section 2.2.5.3) dermal exposure to pure HCCP will not be assessed. Dermal exposure to dilutions of HCCP that do not warrant labelling for corrosivity (dilutions containing <7% HCCP, see classification and labelling), will be taken into account. Repeated dermal exposure cannot be neglected for these substances and formulations.

The use of HCCP as an intermediate and the handling of substances or objects where HCCP is present as a (unintentional) contaminant may include:
- Transfer of liquids by means of transfer line and pumping
- Automated or manual adding to the chemical process
- Drumming of (waste) products
- Cleaning and maintenance of production systems
- Fire fighting and clean up after fires

Relevant populations potentially exposed are workers in the chemical industry, workers in the semiconductor industry, and fire fighters and clean up workers, specifically those workers that may have more or less direct contact with HCCP in the above mentioned activities.

The exposure is assessed using the available information on substance, processes and work tasks. Industry only provided information on the process and measured data for the use of HCCP as an intermediate in the chemical industry.
More detailed information on the various exposure scenarios may lead to a more accurate exposure assessment.

In this part of the assessment, external (potential) exposure is assessed using relevant models and other available methods in accordance with the Technical Guidance Documents and agreements made at official Meetings of the Competent Authorities. Internal dose depends on external exposure and the percentage of the substance that is absorbed (through the skin and via the respiratory system).

The exposure is assessed without taking account of the possible influence of personal protective equipment (PPE). If the assessment as based on potential exposure indicates that risks are to be expected, the use of personal protective equipment may be one of the methods to decrease actual risks, although other methods (technical and organisational) are to be preferred. This is in fact obligatory following harmonised European legislation.
Knowledge of effectiveness of PPE in practical situations is very limited. Furthermore, the effectiveness is largely dependent on site-specific aspects of management, procedures and training of workers. A reasonably effective use of proper PPE for skin exposure may reduce the external exposure with 90%. For respiratory protection the efficiency depends largely on the type of protection used. Without specific information, a tentative reduction efficiency of 90% may be assumed, equivalent to the assigned protection factors for supplied-air respirators with a half mask in negative pressure mode (NIOSH, 1987). Better protection devices will lead to higher protection. Imperfect use of the respiratory protection will lower the practical protection factor compared to the assigned factor. These estimations of reduction are not

generally applicable "reasonable worst case" estimations, but indicative values based on very limited data. They will not be used directly in the exposure and risk assessment. Furthermore, the reduction of external exposure does not necessarily reflect the reduction of absorbed dose. It has to be noted, that the use of PPE can result in a relatively increased absorption through the skin (effect of occlusion), even if the skin exposure is decreased. This effect is very substance-specific. Therefore, in risk assessment it is not possible to use default factors for reduction of exposure as a result of the use of PPE.

For occupational exposure assessment, the following data (if available) are used:
- physico-chemical data of HCCP and products containing the substance: physical appearance, vapour pressure at room temperature, percentage of HCCP in products;
- data regarding methods of use and use pattern of the substance and products potentially containing HCCP and exposure control pattern in the relevant industries (from the HEDSET or other sources);
- exposure data for HCCP from the HEDSET and other sources (literature, exposure databases);
- results from exposure models if applicable (EASE model); in the exposure models the above mentioned types of data are used.

For the occupational exposure assessment the exposure situations can be clustered into 4 scenarios based on the occurrence of HCCP. In the first scenario use of HCCP as an intermediate in the chemical industry is considered. The second scenario assesses the use of HCCP containing flame retardants in unsaturated polyesters, paints and thermoplastics. The third scenario considers the unintentional occurrence of HCCP as a reaction product in the semiconductor industry. The fourth scenario describes the unintentional release of HCCP during fires as a degradation product of a flame retardant.

Occupational scenario 1	Use of HCCP as an intermediate in the chemical industry
Occupational scenario 2	Use of products containing residual HCCP
Occupational scenario 3	Unintentional occurrence of HCCP in the semiconductor industry
Occupational scenario 4	Unintentional release of HCCP during fire

In this report for each occupational exposure scenario first a general description of dermal and inhalation exposure will be presented. Subsequently, measured data (if available), and results from similar substances in comparable exposure scenarios will be presented. This will be followed by data derived using suitable inhalation models. The methods of estimation for inhalation exposure will be compared using expert judgement and a choice for the best applicable estimates will be made. Dermal exposure will be described and assessed by means of the EASE model and will be compared to measured data (if available) using expert judgement.

The following parameters of exposure are assessed for each (sub)scenario:
- *full shift reasonable worst case inhalation exposure level*: the inhalation exposure level considered representative for a high percentile (90 to 95 percentile) of the distribution of full shift exposure levels;
- *short term reasonable worst case inhalation exposure level*: the inhalation exposure level considered representative for a high percentile (90 to 95 percentile) of the distribution of short term exposure levels; short term exposure is for this purpose considered to be exposure for up to one hour, with typical duration of approximately 15 minutes;

- *typical inhalation exposure level*: the inhalation exposure level considered representative for the mean of the distribution of full shift exposure levels;
- *reasonable worst case dermal exposure level*: the dermal exposure level considered representative for a high percentile (90 to 95 percentile) of the full shift dermal exposure levels.

4.1.1.2.1 Scenario 1: Use of HCCP as an intermediate in the manufacture of pesticides and flame retardants

General description

HCCP is used as an intermediate in the chemical industry for the batch wise manufacturing of pesticides and flame retardants. In the EU one company provided information on the production of endosulfan (a pesticide; Company A, 2000) and another one on the production of chlorendic acid (a flame retardant; Company B, 2000).

HCCP is delivered in tanks and is pumped into storage tanks using transfer lines. During connecting and disconnecting of transfer lines for unloading of transport tanks a full face mask, gloves, boots and protective clothing is worn. HCCP is loaded into the process reactors through a closed system with fixed pipe lines, automatically driven pumps and mass flow meters are used to measure the added quantity of HCCP. In one company the HCCP is circulated over a cartridge filter and a sample is taken with a closed (septum) sampling system before loading the reaction vessel. During changing of the cartridge filters, which is done 4 to 5 times per year, a full face mask, chemical suit, rubber gloves and boots are worn by the worker. (Company A, 2000; 2003; Company B, 2000; 2004).

The pesticide is formed in a 'Diels Alder reaction' with butenediol and forms a substance called "HET-diol" in toluene in a closed system with nitrogen blanketing. HET-diol is separated from residual HCCP by filtration and washed with toluene in the same closed system. The washed HET-diol is then reacted in the next connected closed vessel to form endosulfan. A part of the separated toluene and residual HCCP is used for the next batch, a part is recovered by distillation in a separate closed vessel. Recovered materials are also recycled into the process. Distillation residues containing 2% HCCP (Company A, 1997) are transferred to drums and sent for incineration. In all cleaning steps only toluene is used, which is stored and fed back into the process (Company A, 2000). The end product, endosulfan, which contains a maximal residual concentration of 0.1% HCCP, is then transferred to storage tanks and is further transported via tank cars (Company A, 2001; 2003).

The flame retardant is produced by reacting HCCP and maleic anhydride in a closed system at 160°C in the presence of monochlorobenzene to a substance called "HET-anhydride". The molten batch is dropped to a crystalliser where it is added to water with agitation. At the proper temperature, the HET-anhydride quickly hydrolyses to chlorendic acid. The batch is then cooled and the chlorendic acid crystallises out. The crystals are fed continuously to a filter (closed system), washed with monochlorobenzene and then water. The wet crystals are discharged continuously to a closed rotary tray dryer in a current of hot inert gas to produce anhydrous chlorendic acid. The dried chlorendic acid is conveyed to two blenders, from which it is packaged in paper bags of 30 kg or big bags of approximately 950 kg. The residual concentration of HCCP in chlorendic acid is up to 50 ppm (company B, 2002). The filtrate and wash mediums are pumped to a decanter where the monochlorobenzene separates from the water and is collected for recovery by distillation. Liquid waste containing up to 20% HCCP is transferred from the storage tanks to tank cars once per production run (4 or 5 times per year). The operator wears a full face mask with cartridge, chemical suit, rubber gloves and boots.

Exposure to HCCP is expected to take place during connecting and disconnecting of transport tanks, sampling of the pure HCCP, changing of cartridge filters, drumming of product and distillation residues and maintenance.

It should be noted that, Grisham (1986) reported the use of HCCP as a chemical intermediate in the manufacture of dyes, pharmaceuticals, and resins. However, it is not known whether these uses are at present in practice in the EU and whether residual amounts of HCCP are present in these products.

Inhalation exposure

Measured data

The measured data, provided by industry and from databases are reported in Table 4-1. The databases NEDB (UK), COLCHIC (France), EXPO (Norway) and ATABAS (Denmark) were searched but these contained no exposure data on HCCP. No measured data is available on dermal exposure.

Table 4-1 Measured inhalation exposure levels during manufacture of pesticides and flame retardants

Process or activity	Year	PAS/ STAT	N	Duration of measurements (minutes)	Range µg/m³	AM µg/m³	90th percen tile	Source and remarks
Production	1989	-	-	-	27-119	-	-	Company A, 1997
Production	1991	-	-	-	20-460	-	-	Company A, 1997
Production	1992-1996	-*	7	480	3-39	15	-	Company A, 2000
Production	1998	PAS	2	480	1.4-1.6	1.5	-	Company A, 2000
Production, filling of distillation residue and cleaning	2001	PAS	1	317	3	-	-	Company A, 2001
Process operator	1996-1999	PAS	5	440	0.77-11.03	4.91	13.0	Company B, 2000;2004
Maintenance	1995-1999	-*	2	63-165	3.8-17.8	10.8	-	Company B, 2000;2004
General	1992-1996	STAT	271	120	1.0-54.6	-	-	Company B, 2000
Production of pesticides	1982	PAS	31	8h TWA	55.9-189.0	-	-	WHO, 1991
Production of pesticides	1982	STAT	26	8h TWA	161.6-174.1	-	-	WHO, 1991
Cleaning of filters	1982	-	3	8h TWA	Max 3.36	-	-	WHO, 1991
Disposing of waste product	1982	-	6	8h TWA	Max 222.5	-	-	WHO, 1991
Production of flame retardants	1982	PAS	7	8h TWA	89.5-345.6	-	-	WHO, 1991
Production of flame retardants Control room	1982	STAT	3	8h TWA	11.2	-	-	WHO, 1991
Short term exposure								
Connecting and disconnecting of transfer lines	1996-1999	PAS	5	45	0.59-16.5	4.23	9.56	Company B, 2000; 2004

Process or activity	Year	PAS/ STAT	N	Duration of measurements (minutes)	Range µg/m³	AM µg/m³	90th percen tile	Source and remarks
Cleaning of filters	1982	-	1	15	67.1	-	-	WHO, 1991
Disposing of waste product	1982	-	6	15	5.6	-	-	WHO, 1991

- : unknown
PAS: personal air sampling
STAT: stationary air sampling
N: number of measurements
AM: arithmetic mean
TWA: time weighted average
* measurements are assumed to concern personal air monitoring, though this is not entirely clear from the HEDSET or information from company B (2004).

Modelled data

During production of chemicals in closed systems, assuming no breaching, exposure is estimated with EASE (version 2.0 for Windows) to be 0 to 0.1 ppm (0-1.1 mg/m^3).
Since the hazards of HCCP are well known and the use of LEV is generally present in the chemical industry, changing of cartridge filters and drumming of distillation residues are assumed to take place in the presence of LEV. The exposure during changing of cartridge filters is estimated to be 0.5-1 ppm (5.6-11.1 mg/m^3), assuming no aerosol formation, non-dispersive use, and LEV. With an HCCP concentration in the pesticide product of 0.1% and in the distillation residue of 2% (Company A, 1997) and in the flame retardant of 0.005% (Company B), the partial vapour pressure of HCCP is calculated to be 0.01 Pa, 0.2 Pa and 0.0005 Pa, respectively. Exposure during drumming or bagging of product and distillation residue is estimated with EASE to be 0 to 0.1 ppm (0-1.1 mg/m^3), assuming a very low vapour pressure (partial vapour pressures are below 1 Pa) and non dispersive use.
Connecting and disconnecting of transfer lines transporting the pure substance is assumed to take place outdoors, therefore no LEV is assumed to be present. The exposure is estimated with EASE to be 10-20 ppm (111.5-223 mg/m^3), assuming a vapour pressure of 10 Pa (pure substance), no aerosol formation, non-dispersive use and dilution ventilation.

Summary/statement of the exposure level

The measured inhalation data from the WHO (1991), as presented in Table 4-1, are from a production company outside the EU. These data originate from measurements performed in 1982, and do not represent the current exposure levels as the company indicates that worker exposures have been reduced by about a factor 10 since the early eighties (Company C, 2002). Compared to the measured data provided by industry, the modelled data seem to overestimate the exposure during production. Therefore the measurement data provided by companies A and B are given more weight in the exposure assessment.
Because workers are protected with full face masks, gloves, protective clothing and boots during production, when handling pure HCCP, the exposure levels for this production scenario are assessed for both the protected and the unprotected worker as prescribed in the TGD.

Company A (1997) reported a change of process in 1991, which can be noticed in Table 4-1 by a decrease in the exposure level. When the earlier data are ignored, the data provided by industry are all in the same order of magnitude, with the highest stationary measurement being 55 µg/m^3 (total n=271) and the highest personal exposure level during production being 16.7 µg/m^3 (total n=15). For 7 measurements, with the highest exposure level being 39 µg/m^3,

it is unknown whether they represent personal or stationary air sampling. Comparing the measured data to the modelled data, EASE seems to overestimate the exposure during all production activities. Since ample data are provided by industry and databases, more weight is given to the measured data. Because there are only a limited number of personal exposure levels and the stationary levels are in the same order of magnitude, the total set of data (personal, stationary and unknown) is used as a basis for the estimation of the reasonable worst case level. For inhalation exposure, a reasonable worst case full shift exposure level of 50 μg/m^3 for the unprotected worker will be taken forward to the risk characterisation. A full face mask provides a reduction of the actual exposure level by a factor of 20 (British Standard Institution, 1997). The reasonable worst case inhalation exposure level for protected workers is therefore estimated to be 2.5 μg/m^3. The estimates are based on a data set of in total 288 measurements, provided by the sole two companies in the EU using HCCP for the purpose of producing flame retardant and pesticides. The fact that stationary measurements form the vast majority of the total data set gives some uncertainty to the estimates, however since there are no specific indications that these are not relevant they are used to give a broader foundation to the concluded estimates. The overall uncertainty of the concluded reasonable worst case estimates is considered to be relatively low.

The typical exposure is generally represented by the mean exposure level. Unfortunately, only few of the data sets provided enough information to calculate mean values. The arithmetic mean values range from 1.5 to 15 μg/m^3. The mean of the individual measurements of the data sets is calculated to be 10.7 μg/m^3. As a typical exposure level, 10 μg/m^3 will be taken forward to the risk characterisation for the unprotected worker. With a full face mask, providing a reduction factor of 20 (British Standard Institution, 1997), the typical inhalation exposure level of a protected worker amounts to 0.5 μg/m^3. These values are based on measurements (n=17) performed in the sole two EU companies and can therefore be regarded as estimates with a relatively low uncertainty.

For short term inhalation exposure one company reported 5 personal measurements during connecting of transfer lines, with the highest value 16.5 μg/m^3, measured over 45 minutes. WHO (1991) reported rather limited data on cleaning of filters and disposing of waste products containing HCCP. No information is provided whether these measurements concerned personal or stationary air samples. Furthermore the latter data do not represent current exposure levels. The measured data do not provide enough basis for the derivation of a short term exposure value. Therefore, as a rule of thumb, for short term exposure is estimated to be two times the level of the full shift reasonable worst case exposure, thus 100 μg/m^3 (TWA 15 minutes) (expert judgement). Given the measured data, this may be an overestimation of the short term exposure level. Personal protection in the form of a full face mask will reduce the actual exposure with a factor of 20 (British Standard Institution, 1997), to a level of 5 μg/m^3. Because the estimate is based on a combination of limited measured data and expert judgement the uncertainty is moderate.

Dermal exposure

Because pure HCCP is a corrosive substance, effective control measures are expected to be in place to prevent dermal exposure to the pure substance. Furthermore protective clothing and gloves are considered to be used consistently when handling corrosive substances. Both production companies report the use of protective gloves, suits and boots while handling pure HCCP. Repeated daily dermal exposure to the pure substance (during production or coupling of transfer lines) is therefore neglected.

Dilutions of HCCP containing less than 7% of the substance do not have corrosive properties. Therefore dermal exposure is assessed for scenarios where formulations or products containing less than 7% HCCP are handled.

Measured data

No measured data are available.

Modelled data

The estimated exposure for drumming or bagging of product and distillation residues is 0.1-1 mg/cm^2/day, assuming non dispersive use, direct handling, and intermittent contact. Considering an exposed area of 210 cm^2 (palm of one hand) and a HCCP concentration of 0.1% in the pesticide product, 0.005% in the flame retardant and 2% in the distillation residues the exposure level amounts 0.021-0.21 mg/day, 0.001-0.011 mg/day and 0.42-4.2 mg/day respectively.

Summary/statement of the exposure level

Repeated dermal exposure to pure HCCP is expected to be negligible because, due to the corrosive properties of HCCP, adequate exposure controls and protective equipment will be used consistently. Dermal exposure may take place during handling of products and distillation residues containing less than 7% HCCP. The reasonable worst case exposure level for this scenario is therefore based on the upper range of the EASE estimate for drumming of distillation residue, containing a worst case percentage of 2% HCCP, and amounts to 0.02 mg/cm^2/day (1 mg/cm^2/day * 2%), which calculates to a daily exposure level of 4.2 mg (assuming non dispersive use, direct handling, incidental contact, exposed area 210 cm^2). Both production companies indicate the use of eye protection and protective gloves and clothing when there is potential for contact with HCCP containing products. This may reduce the exposure with 90% (TGD guideline) to 0.002 mg/cm^2/day (0.42 mg/day).Because the dermal exposure data are all based on modelling, the uncertainty in the reasonable worst case exposure level that was derived for this scenario is rather high.

Production of pesticides and flame retardants is reported to take place up to 300 days/year and up to 70 days/year, respectively, both on a 24 hours/day basis (Company A, 2000; Company B, 2004). For risk assessment purposes it is estimated that exposure may take place up to 300 days/year. The number of workers involved in these processes is approximately 45 in total (Company A, 2000; Company B, 2004).

4.1.1.2.2 Scenario 2: Use of products containing residual HCCP

General description

HET acid, which contains up to 0.005% residual HCCP (Company B, 2002), is used as a flame retardant in unsaturated polyesters and paints. Dechlorane Plus, containing up to 50 ppm (0.005%) HCCP, is also used as a flame retardant additive, mainly in thermoplastics. Though not much is known on the actual tasks performed during the production, exposure is assumed to be highest during adding of the HCCP containing products to the products. Therefore inhalation and dermal exposure during this scenario is assessed and taken forward to the risk characterisation.

Inhalation exposure

Measured data

No measured data are available on exposure to residual HCCP while handling HET acid or Dechlorane Plus.

Modelled data

As a reasonable worst case scenario addition of the HCCP containing products is assumed to take place manually from bags or drums. The partial vapour pressure of HCCP at 25°C in HET acid and in Dechlorane Plus is 0.0005 Pa (0.005% * 10 Pa). Inhalation exposure during adding is estimated by EASE to be 0-0.1 ppm (0-1.1 mg/m^3), assuming no aerosol forming activities and a partial vapour pressure of 0.0005 Pa.

Summary/statement of the exposure level

There are no measured data available. Furthermore, from scenario 1 it appears that EASE may largely overestimate the inhalation exposure, because of the very low partial vapour pressure of HCCP in products. As these routes of estimation are considered to give a very high uncertainty to the exposure assessment in this scenario, the saturated vapour concentration is calculated using the partial vapour pressure of HCCP in the products. This saturated vapour concentration gives an approximation of the maximum range of the exposure level. The saturated vapour concentration for a partial vapour pressure of 0.0005 Pa is 54 µg/m^3 (general gas law). This value is rather close to the reasonable worst case exposure estimate in scenario 1 (50 µg/m^3). In scenario 1 pure HCCP is handled and therefore in the present scenario a lower exposure would be expected when handling flame retardants that contain a minor amount of HCCP. However, not much information is available on the way the flame retardants are handled and it may be assumed that there are less exposure control measures in place than in scenario 1. The reasonable worst case estimate taken forward to the risk characterisation will therefore be the saturated vapour concentration of 54 µg/m^3 (expert judgement). The typical exposure value is estimated to be similar to scenario 1, thus 10 µg/m^3 (expert judgement). The short term exposure level is calculated to be 108 µg/m^3, by multiplying the reasonable worst case full shift exposure level by two (expert judgement).
The estimated inhalation exposure levels have a relatively high uncertainty because of the lack of information on use patterns and relevant measured exposure values and the fact that the estimates are based on use of the saturated vapour concentration and expert judgement.

Dermal exposure

Measured data

No measured data are available on exposure to residual HCCP while handling HET acid or Dechlorane Plus.

Modelled data

Dermal exposure during loading of the substance is assumed to involve non-dispersive use, direct handling, intermittent contact level, and a maximum concentration of 0.005% HCCP in the product, leading to an estimated exposure by EASE of 0.005-0.05 μg/cm^2/day. Considering an exposed area of 420 cm^2 (half of two hands) the exposure level amounts to 0.0021-0.021 mg/day respectively.

Summary/statement of the exposure level

Since there are no measured data available for dermal exposure the upper value of the EASE estimate 0.05 μg/cm^2/day (0.021 mg/day) is taken forward to the risk characterisation as reasonable worst case exposure level. Because the dermal exposure value is based on modelling, the uncertainty in the reasonable worst case exposure level that was derived for this scenario is rather high.

4.1.1.2.3 Scenario 3: Unintentional occurrence of HCCP in the semiconductor industry

General description

The technology of plasma etching with chlorine-containing gas mixtures in semiconductor chip production can generate very complex mixtures of highly chlorinated waste products.
In plasma etching processes the controlled removal of layers of material from the surface of a silicon wafer is realised using halogen containing process gasses (HCCP is not one of the etching gases). Upon radiation with radio frequency energy (usually at 13.56 MHz), the gasses are dissociated and ionised to create ions and free radicals. The product of the etch reaction is typically a halogenated compound of the material being etched. Due to the reactivity of the ions and radicals, side reactions can be expected between the feed gases, the carrier gas (nitrogen), and organic photoresist masks that define the areas on the wafer to be etched. As a result, complex mixtures of halogenated hydrocarbons and inorganic chlorides are created (Bauer et al., 1995; Schmidt et al., 1995).

In a toxicology study 3 samples were collected from contaminated vacuum pump oil (1 sample) and from the solid wastes from the gas pipeline behind the vacuum pump of a Plasma Therm C 2800 etching reactor (2 samples). In these samples a HCCP content of 1.26 mg/kg oil in the vacuum pump sample and 38.16 and 19.32 mg/kg solid in the solid waste samples were found (Schmidt et al., 1995). Potentially, workers that come into contact with these waste products, assumed to be mainly maintenance workers, are exposed to HCCP by the inhalation route (although not probable when solely exposed to the pump oil) as well as the dermal route (expert judgement).

Unfortunately, no information is available on the amount of waste product present in the process, the activities that may cause contact with the waste products, and the frequency and exposure level of contacts.

Inhalation exposure

Measured data

No measured data are available.

Modelled data

Inhalation exposure is estimated to be higher during removing of the solid waste than during maintenance of vacuum pumps, because the solid is assumed to become airborne more easily. Assuming that exposure only takes place during maintenance work, EASE estimates the inhalation exposure to the solid waste product to be 5-50 mg/m^3 of dust (non-fibrous dust, dry manipulation, no LEV, no aggregation of particles). Assuming a content of 38.16 mg HCCP per kg solid waste, the exposure level ranges from 0.19 to 1.9 µg/m^3. The reasonable worst case full shift exposure level is estimated to be 1.9 µg/m^3, based on the upper range of the EASE estimation.

Summary/statement of the exposure level

The reasonable worst case estimate for full shift inhalation exposure is 1.9 µg/m^3. The typical inhalation exposure level is estimated to be the mean of the upper and lower range of the EASE estimate. For inhalation exposure the typical exposure is calculated to be 1 µg/m^3. The concluded data are based on EASE estimations, no measured exposure data, and no detailed descriptions of the activities of the exposure scenario are available. Therefore these estimates that are taken forward to the risk characterisation are considered to be rather uncertain and have to be interpreted with substantial caution.

No information is available on the frequency of maintenance and the number of workers involved in this activity in the semiconductor industry. It is assumed that the maintenance takes place on a monthly basis, therefore the estimated frequency of exposure is 10-20 days/year. No estimation can be made of the number of workers involved as there is no information available on the number of semiconductor manufacturing industries in the EU.

Dermal exposure

Measured data

There are no measured data available.

Modelled data

Assessing dermal exposure for the same situation leads to an EASE estimate of 1-5 mg/cm^2/day (solid is dusty, non dispersive use, direct handling, extensive contact). Assuming a content of 38.16 mg/kg solid waste, the exposure level ranges from 0.038 to 0.19 µg/cm^2/day. The reasonable worst case exposure level is estimated to be 0.19 µg/cm^2/day, based on the upper range of the EASE estimation. Assuming an exposed skin surface area of 1300 cm^2 (both hands and part of the forearms) this leads to an exposure of 0.25 mg/day.

Summary/statement of the exposure level

The reasonable worst case estimate for full shift dermal exposure 0.19 µg/cm^2/day, calculated to 0.25 mg/day. The concluded data are based on EASE estimations, no measured exposure data, and no detailed descriptions of the activities of the exposure scenario are available. Therefore these estimates that are taken forward to the risk characterisation are considered to be rather uncertain and have to be interpreted with substantial caution.

No information is available on the frequency of maintenance and the number of workers involved in this activity in the semiconductor industry. It is assumed that the maintenance takes place on a monthly basis, therefore the estimated frequency of exposure is 10-20 days/year. No estimation can be made of the number of workers involved as there is no information available on the number of semiconductor manufacturing industries in the EU.

4.1.1.2.4 Scenario 4: Unintentional release of HCCP during fire

The components evolving during the oxidative degradation (fire) of HET-acid, a flame retardant, were identified in an experimental setting. It appeared that during heating of the substance up to 800°C, HCCP appeared as one of the degradation products (Company B, 2001). This unintentional release of HCCP during fires indicates the potential occupational exposure of fire fighters and professional clean up workers. The occupational exposure for this scenario can not be assessed, because of a lack of information on e.g. the amount of HCCP that is released per amount of HET-acid, the amount of HET-acid used in fire retarding products, and the amount of these products used in buildings.

4.1.1.2.5 Summary of occupational exposure

In Table 4-2 the conclusions of the exposure assessment are summarised.

Table 4-2 Conclusions of the exposure assessment

Scenario	Activity	Frequency days/year	Exposed workforce	Duration	Inhalation exposure Reasonable worst case		Inhalation exposure Typical case		Dermal exposure Reasonable worst case	
					µg/m³	Method	µg/m³	Method	mg/cm²/day	Dose (mg/day)
1) Production of pesticides and flame retardants	General production	300	42	8h TWA	50 (2.5 with PPE)	Measured data	10 (0.5 with PPE)	Measured data	0.02 (0.002 with PPE)	4.2 (0.42 with PPE)
				15 min TWA	100 (5 with PPE)	Expert judgement	-	-	-	-
2) Use of product containing residual HCCP	Addition of flame retardants			8h TWA	54	SVC and expert judgement	10	EASE	0.00005	0.021
				15 min TWA	108	SVC and expert judgement				
3) Unintentional occurrence of HCCP in the semiconductor industry	Maintenance	20	-	8h TWA	1.9	EASE	1	EASE	0.19	0.25
4) Unintentional release of HCCP during fire	-	-	-	-	-	-	-	-	-	-

TWA: time weighted average
SVC: saturated vapour concentration
PPE: personal protective equipment

4.1.1.3 Consumer exposure

HCCP is used as an intermediate in the production of pesticides (Bell et al., 1978), and as an intermediate in the production of flame retardant chemicals (Klingenberg, 1988). The expected consumer exposure to intermediates is so low that it can be neglected further in the risk characterisation.

Literature (TOXLINE and Current Contents was searched from 1989- January 2001) and Internet (with Google, CAS number, November 2002) was searched but no consumer exposure was identified. A search in the Scandinavian product registers did not give any products that contain HCCP.

Therefore the exposure of consumers to HCCP can be considered negligible.

4.1.1.4 Humans exposed via the environment

The environmental emissions of HCCP for the industrial uses II-a, II-b and II-c, and the application of HET-acid and Dechlorane Plus are given in Tables 3.1 and 3.4 (both sections 3.1.1), respectively. On the basis thereof the estimated HCCP concentrations in air, drinking water and food resulting from industrial uses II-a, II-b and II-c are presented in **Table 4-3** (EUSES calculation). Because of the uncertainties of the BCF value (see section 3.1.2.3) two different BCF values are used as input. A BCF value of 11, representing the steady-state bioconcentration factor measured in a 30-day flow through exposure to constant levels of HCCP, and a realistic worst case value of 1297, covering persistent metabolites. This results in 2 estimates for the HHCP levels in wet fish for each scenario. **Table 4-3** shows that the concentrations in air, drinking water and food are all very low (ng-range). The upper concentration in wet fish is about 118 times higher than the lower concentration, but still in the ng-range. The concentrations for the application of HET-acid and Dechlorane Plus will be even lower than those for industrial uses II-a, II-b and II-c (not shown in **Table 4-3**). Also the residual HCCP concentration from endosulfan application in air (considering the field as a point source) and water (tables 3.6 and 3.14, respectively) is much lower than for the industrial scenarios. Therefore these scenarios will only be considered if a concern is indicated in the risk characterisation for any of the industrial scenarios II.

Table 4-3 HCCP concentrations in various environmental compartments relevant for exposure man indirectly via the environment (local scale; industrial use II).

	II-a	**II-b**	**II-c**
Emission to air (kg/y), site-specific	**9.5**	**0.027**	0.2
Concentration in air μg/m^3	7.32e-3	2.83e-5	< II-b
Emission to waste water (kg/y), site-specific	**0**	0.002	**0**
Concentration in drinking water (mg/l)	1.37e-8	1.45e-9	< II-b
Concentration in wet fish (mg/kg)	8.46e-11[1] - 9.96e-9[2]	5.83e-8[1] - 6.88e-6[2]	< II-b
Concentration in root tissue (mg/kg)	1.08e-5	1.14e-6	< II-b
Concentration in leaves (mg/kg)	5.33e-6	2.06e-8	< II-b
Concentration in meat (mg/kg)	3.08e-6	1.21e-8	< II-b

Concentration in milk (mg/kg)	9.74e-7	3.83e-9	< II-b

[1] BCF VALUE OF 11 USED; [2] BCF VALUE OF 1297 USED

Table 4-4 Daily intake of HCCP via various environmental compartments relevant for exposure man indirectly via the environment (local scale; industrial use II).

Intake (in mg/kg bw/day)	**II-a**	**II-b**	**II-c**
Intake via air	2.09e-6	8.09e-9	< II-b
Intake via drinking water	3.91e-10	4.14e-11	< II-b
Intake via wet fish	1.39e-13[1] - 1.64e-11[2]	9.58e-11[1] - 1.13e-8[2]	< II-b
Intake via root tissue	5.92e-8	6.25e-9	< II-b
Intake via leaves	9.14e-8	3.53e-10	< II-b
Intake via meat	1.32e-8	5.20e-11	< II-b
Intake via milk	7.81e-9	3.07e-11	< II-b
Total daily intake	2.26e-6[1,2]	1.49e-8[1] - 2.61e-8[2]	< II-b

[1] BCF VALUE OF 11 USED; [2] BCF VALUE OF 1297 USED

Air concentrations of local scenario II-a will be brought forward to the risk characterisation as this scenario shows the highest air concentrations (7.3E-03 μg/m^3). This scenario also resulted in higher concentrations in leaves, meat and milk compared to scenario II-b. Therefore, scenario II-b will be used as the next lower intake value for man exposed. Though the environmental exposure for man for scenario II-b depends on which BCF is used this does not change the overall lower intake compared to scenario II-a. The total daily intake via food (= total daily intake – daily intake via air) is 1.7E-7 mg/kg bw/day for scenario II-a and 1.8E-08 mg/kg bw/day for scenario II-b. These figures will be taken forward to the risk characterisation. Scenario II-c will not be further taken into account due to its low emissions.

The regional PEC in air (total) calculated with EUSES is 7.55E-06 μg/m^3. For the regional situation, air is the main source of exposure to man (93%): daily intake via air is 2.16E-09 mg/kg bw/day, as compared to 2.33E-09 mg/kg bw/day for the total daily intake. This leaves only 1.70E-10 mg/kg bw/day for the total regional daily intake via food (including drinking water). Variation of the BCF-value, as was done for the local situation, has no impact on the regional situation. Compared to local intakes, regional intakes via air and food are orders of magnitude lower.

4.1.1.5 Combined exposure

Humans can be exposed to HCCP at the workplace and via the environment. In theory, exposure to a combination of these two sources is possible. However, since exposure to HCCP via the environment is very low compared to exposure to HCCP at the workplace, HCCP exposure via the environment will not lead to an increased exposure for workers. Therefore, there is no need to perform a combined exposure assessment.

4.1.2 Effects assessment: Hazard identification and dose (concentration)-response (effect) assessment

General remark:

The toxicity studies performed at the laboratory of the firm Industrial Bio-Test (IBT) are not included because of the infamous case of fraud which occurred at this laboratory in the late 1970s. The studies with regard to HCCP were performed in 1975 and 1977. The result of the fraud investigation forced the retesting of literally thousands of industrial chemicals.

4.1.2.1 Toxicokinetics, metabolism and distribution

4.1.2.1.1 Studies in animals

In vivo studies

Route comparison
Dorough (1980) made a comparative study of the uptake, disposition, and elimination of HCCP after administering radiolabelled ^{14}C-HCCP by inhalation (exposure concentrations not specified, the retained doses were reported to be 7 and 24/28 µg/kg bw), gavage (7 µg/kg bw and 6 mg/kg bw), and by intravenous injection (5/7 µg/kg bw) to Sprague-Dawley rats weighing between 175 and 250 g. The same study was later described by Lawrence and Dorough (1981 and 1982). It was noted that while doses in the microgram range were useful for monitoring the urinary and faecal excretion of HCCP, much higher doses were necessary to obtain levels in the principal organs that could be measured with any precision. Indeed, the doses administered orally were some 215-860 times the inhaled and intravenous doses, respectively. The individual studies are described in more detail in the separate route sections.

Inhalation
Groups of female SD rats (number of animals not reported) were exposed nose-only to vapours of ^{14}C-HCCP for 1 hour. The animals were exposed to ^{14}C-HCCP vapour in a specially designed, single animal inhalation exposure system. The exposure concentrations were not reported. Each animal was exposed to the vapours in a rodent respirator, with the exhaust vapours from the system passing through a filter pad made from expanded polyurethane foam. The flow rate and concentration of HCCP was measured prior to and after passing through the respirator containing the exposed animal. The difference between the amounts of HCCP in the input and output was assumed to be equivalent to the retained dose. Immediately after 1 hour, rats exposed to HCCP vapours which resulted in low retained doses (0.19 to 0.57 µg) and much higher retained doses (5.0-9.9 µg) retained 90.6% and 87.4% of the inhaled dose, respectively. Less than 1% of the administered radiocarbon was eliminated as ^{14}C-HCCP in the 0-24 hour expired air. No $^{14}CO_2$ was detected. The 24-, 48- and 72-hour fate of radiocarbon following inhalation exposure which resulted in retained doses of 7 and 24 or 28 µg/kg bw ^{14}C-HCCP is presented in **Table 4-5** and **Table 4-6**. Tissue distribution of radiocarbon after 7 µg/kg bw is not reported (Dorough, 1980; published by Lawrence and Dorough, 1981 and 1982).

Inhaled ^{14}C-HCCP (at air concentration of both 7 and 24 µg/kg bw) was, within 72 h, primarily excreted in the urine (33.1% of the dose) and faeces (23.1% of the dose). After 72 h, 12.9% of the administered radioactivity was still present in the body. After a vapour exposure

to 28 µg/kg bw HCCP, the trachea and lungs were the tissues of highest residue concentration. The concentration of HCCP equivalents was 8 times higher in kidneys than in liver. However, the liver contained about half as much total radioactivity as kidneys because of its larger size. Fat was not a site of residue accumulation.

Table 4-5 Disposition of radioactivity from ^{14}C-HCCP in rats exposed by the inhalation route (Dorough, 1980; Lawrence and Dorough, 1981).

Matrix	Cumulative percent of dose [a] retained dose of 7 µg/kg bw			retained dose of 24 µg/kg bw		
	24 h	48 h	72 h	24 h	48 h	72 h
Urine	29.7±4.5 [a]	32.5±5.1	33.1±4.5	ND	ND	33.1±4.5
Faeces	17.0±7.5	21.0±7.5	23.1±5.7	ND	ND	23.1±5.7
Body	ND	ND	12.9±4.7	ND	ND	12.9±4.7
Total	ND	ND	69.7±9.6	ND	ND	69.0±9.6

[a] all values are the mean ± SD of three replicate animals. [b] ND: not determined.

The disposition data described by Dorough (1980) and Lawrence and Dorough (1981) are confusing; details are lacking. For two different retained doses after inhalation exposure (7 µg/kg bw and 24 µg/kg bw) the same cumulative percent of dose found in the urine, faeces and body (72 h) are reported. Furthermore, referring to the total recovery of 69.0-69.7%, it has to be noted that 30.3-31% of the inhaled dose was not accounted for. However, since 87.4 - 90.6% of the inhaled dose was apparently retained immediately after exposure, the low recovery may be caused by release of volatile metabolites of HCCP.

Table 4-6 Tissue distribution of radiocarbon 72 hours after inhalation exposure to ^{14}C-HCCP in rats (Dorough, 1980)

Matrix	retained dose of 28 µg/kg bw	
	% of dose	µg/kg tissue[a]
Trachea	0.32	107.1
Lungs	1.99	71.5
Liver	0.43	3.6
Kidneys	0.78	29.5
Fat	NR	1.1
Carcass[b]	7.85	1.3
Total	11.37±2.51	-

[a] All values are the mean ± SD of three replicate animals.
[b] Carcass includes total homogenate of body excluding tissue shown.
NR: not reported.

In a study by SRI (El Dareer *et al.*, undated; also published by El Dareer *et al.*, 1983), rats were exposed by inhalation to vapours of ^{14}C-HCCP for 2 h. The exposure concentration was not reported. The authors calculated the systemic retained dose from the total amounts of radioactivity recovered in each rat (excluding that in the fur), in the exhaled CO_2, and in the urine and faeces (no further details were specified). The systemic retained dose for rats killed 6 hours after exposure was 1.3±0.2 mg/kg bw; for rats killed 72 hours after exposure, the systemic retained dose was 1.8±0.3 mg/kg bw. After 6 and 72 hours of exposure, 28.9% and 11.5% remained in the tissues of male F344 rats, respectively (mean values of three rats). No detectable amount of intact ^{14}C-HCCP was present in the lungs or kidneys of the exposed rats. Only about 1% was converted to $^{14}CO_2$. The results are presented in **Table 4-7**.

Table 4-7 Disposition of radioactivity from ^{14}C-HCCP in rats exposed by inhalation (El Dareer *et al.*, undated; El Dareer *et al.*, 1983).

Matrix	Inhalation[b]	
	6 h[c]	72 h[c]
	retained dose of 1.3 mg/kg/ bw	retained dose of 1.8 mg/kg)/bw
Urine	41.0±4.8[a]	40.0±6.6
Faeces	28.7±4.3	47.5±6.4
Tissues	28.9±1.6	11.5±0.8
Blood (2 ml)	1.7±0.1	1.3±0.1
Liver	1.7±0.3	0.8±0.2
Skin (ears)	0.5±0.0	0.1±0.0
Kidneys	3.6±0.1	1.7±0.1
Brain	0.1±0.0	<0.1
Tail section	-	-
Intestine	1.7±0.3	0.2±0.0
Lungs	4.5±0.5	1.6±0.0
Carcass	15.1±0.6	5.6±0.6
CO2	1.4±0.3	1.0±0.5
Other volatile	-	-
Total recovery	(100)	(100)

[a] The values represent the mean % of dose ± SD of three rats.
[b] Exposure period was 2 h.
[c] Time after exposure.

Dermal

No studies on the kinetics of HCCP following dermal application were found, but systemic toxic responses reported after dermal application suggest that HCCP is absorbed via the dermal route (WHO, 1991).

Oral

Four male SD rats received ^{14}C-HCCP by a single oral intubation (1 µCi per animal, 5 µmol ≈ 0.3 mg/kg bw) as 0.2 ml of a solution in corn oil. An average of approximately 33% of the administered dose was excreted in the urine after 7 days (Mehendale, 1977). About 87% of that was eliminated during the first 24 hours after the administration. Faecal excretion accounted for about 10% within 7 days of which nearly 60% within 24 hours. Tissues retained only trace amounts after 7 days. Kidney retained 0.5% of the dose and the liver contained less than 0.5%. The nature of the radioactivity excreted in urine was examined for possible metabolites. The results suggest that at least four metabolites of HCCP were present. These metabolites have not been identified and characterised in this study. It should be noted that recovery was only approximately 44% after oral administration, rendering the study less suitable for evaluation.

When ^{14}C-HCCP (7 µg/kg bw and 6 mg/kg bw) was administered by gavage to female SD rats (Dorough, 1980; published by Lawrence and Dorough, 1981 and 1982), the faeces were found to be the primary route of elimination (68.2 and 63.3% of the dose, respectively within

72 hours). Radiocarbon excreted in the urine was equivalent to 24.4% and 15.3% of the dose, respectively. Only trace amounts of radioactivity remained in the tissues after the 72-hour period. The deposition of radioactivity is summarised in **Table 4-8**.

Table 4-8 Disposition of radioactivity from ^{14}C-HCCP in rats dosed by gavage (Dorough, 1980; Lawrence and Dorough, 1981).

Matrix	Cumulative percent of dose [a]					
	7 µg/kg bw			6 mg/kg bw		
	24 h	48 h	72 h	24 h	48 h	72 h
Urine	22.2±1.8	24.0±1.9	24.4±1.9	13.5±3.7	15.0±3.2	15.3±3.3
Faeces	62.2±8.0	67.7±5.1	68.2±5.1	17.4±9.8	61.8±9.8	63.6±8.5
Body	ND	ND	0.2±0.2	ND	ND	2.8±1.1
Total	ND	ND	92.8±4.7	ND	ND	81.7±6.7

[a] all values are the mean ± SD of three replicate animals.
ND: not determined.

After a gavage dose of 6 mg/kg bw ^{14}C-HCCP, the kidneys and liver were the major sites of residue deposition. The concentration of radiocarbon in the kidneys was about 6 times as large as in the liver, but the total amount of radioactivity was only slightly higher in the kidneys. The lungs were also a site of residue deposition following dosing by gavage, with the concentration of HCCP equivalents being only slightly lower in the lungs than in the liver. The fat was not a site of residue accumulation. The tissue distribution of radiocarbon 72 hours after oral exposure to 6 mg/kg bw ^{14}C-HCCP is summarised in **Table 4-9**.

Table 4-9 Tissue distribution of radiocarbon 72 hours after oral exposure (gavage) to ^{14}C-HCCP in rats (Dorough, 1980)

Matrix	6 mg/kg bw	
	% of dose	Mg/kg tissue[a]
Trachea	0.01	290
Lungs	0.07	422
Liver	0.39	535
Kidneys	0.47	3271
Fat	NR	311
Carcass	1.87	58
Total	2.81±1.10	-

[a] All values are the mean ± SD of three replicate animals.
[b] Carcass includes total homogenate of body excluding tissue shown.
NR: not reported.

SD rats (6 males and 18 females) were administered a single gavage dose of ^{14}C-HCCP (ranging from 8.5 to 25.6 mg/kg bw in corn oil) (Yu and Atallah, 1981). Radiocarbon administered by gavage was eliminated mainly in faeces (70%) and also in urine (17%) within 48 hours. The maximum concentration in the blood after oral administration was reached between 2-8 h after administration. Little sex differences were observed. The kidneys, liver, blood, and fat generally had higher residue levels than muscle, brain and heart. The amount of radioactivity present in the lung was 0.02% of the dose after 48 hours. HCCP was rapidly degraded in the rat body. No intact HCCP was detected in excreta or tissues. It is not explicitly reported by the authors in which manner it was determined that no intact HCCP was present. Most degradation products were polar. The body burden and the area under the curve for blood of orally administered rats was about 1/10 and 1/70 respectively of the rats exposed via i.v. administration (also investigated in this study). These results indicated that only a fraction of the orally administered radiocarbon was absorbed in the GI tract of rats.

Adult SD rats and mice received a single dose (2.5 or 25 mg/kg bw) ^{14}C-HCCP by gavage or as a component of the diet (1, 5 or 25 ppm; equal to 0.07, 0.33 and 1.67 mg/kg bw/day for rats and 0.16, 0.82 and 4.1 mg/kg bw/day for mice, respectively) for a maximum of 30 days (Dorough and Ranieri, 1984). Continuous feeding was based on an average consumption rate of 15 g of feed per day for rats and 5 g per day for mice. The number of animals analysed per dose group is mentioned in **Table 4-10** and **Table 4-12**.
Furthermore, bile excretion of HCCP in 3 SD rats was investigated. After 24 hours, without food, the rats were cannulated. Six hours thereafter, a single oral dose of 1.67 mg/kg bw HCCP was administered in 3 ml corn oil. Bile samples were collected hourly and analysed for radioactivity.

Female SD rats and mice dosed with 2.5 mg/kg bw ^{14}C-HCCP had excreted an average of 16.4% of the dose in the urine after 7 days, while the average faecal elimination after 7 days was 63.3%. Animals administered 25 mg/kg bw HCCP had eliminated an average of 15.8% of the dose in the urine and 75.2% of the dose in the faeces after 7 days, indicating linear kinetics between 2.5-25 mg/kg bw. Tissue residue levels were reduced by at least 70% after 7 days in female mice and rats at both dose levels as compared to levels at day 1. The results are shown in **Table 4-10**. In the study report no detailed information was given on total recovery of radioactivity.

Table 4-10 Tissue residues and elimination of radiocarbon following treatment of rats and mice with single oral gavage doses (2.5 and 25 mg/kg bw in corn oil) of ^{14}C-HCCP (Dorough and Ranieri, 1984).

Animal, sex and days after treatment	mg/kg tissue ^{14}C-HCCP equivalents						Cum. % of dose	
	Liver	Kidneys	Fat	Muscle	Brain	Gonads	Urine	Faeces
Females	*2.5 mg/kg bw*							
1-rats	0.38[a]	1.87	0.18	0.05	0.09	0.23	12.4	65.2
7-rats	0.07	0.53	0.10	0	0	0.08	15.0	71.7
1-mice	1.01	0.33	0.10	0.03	0.01	0.07	13.8	42.1
7-mice	0.15	0.06	0.01	0	0	0	17.8	54.9
Females	*25 mg/kg bw*							
1-rats	4.37	34.38	2.42	0.24	0.41	11.60	10.2	58.1
3-rats	1.31	25.73	1.05	0.11	0.25	0.98	12.9	69.1
7-rats	0.75	10.26	0.81	0	0	0.06	14.9	70.8
1-mice	9.47	4.67	1.58	0.53	0.37	3.84	11.1	62.4
3-mice	4.46	3.40	0.53	0.15	0.34	0.42	14.9	73.9
7-mice	1.68	0.76	0.44	0.09	0.05	0.50	16.6	79.7
Males								
3-rats	3.12	19.42	1.58	0.25	0.78	0.32	13.4	73.6
3-mice	3.04	1.09	0.29	0.09	0.10	0.13		

[a] Data are the mean of 2 animals. Limit of sensitivity = 0.01 µg/g.

In **Table 4-11** the excretion results from the continuous feeding study are shown. The total cumulative excretion by the animals ranged from 61 to 79% of the consumed ^{14}C-HCCP. On the average, excretion patterns were the same for rats and mice, male and female, at all levels of ^{14}C-HCCP after 30 days on treatment. In every case, very little additional radiocarbon was excreted after the animals were returned to a normal diet for another 30 days. The average excretion of radiocarbon in the faeces at the end of the experiment was 64.2% of the total consumed ^{14}C-HCCP when all animals were considered. For the urine, the average excretion was 8.4% of the consumed radiocarbon. The extraction data on the urine and faeces strongly indicated that rats and mice were capable of extensively degrading HCCP when applied orally, and that the metabolites formed were of a nature (polar) that favoured faecal elimination. One possible explanation was that HCCP was metabolised in the liver, the

metabolites returned to the intestine via the bile and were then excreted in the gut. Another possibility was that HCCP was largely metabolised in the gut, probably by microorganisms, to products which were not absorbed and, consequently, were voided in the faeces. Collecting the bile from male rats treated with a single oral dose of ^{14}C-HCCP showed that only 16% of the dose (1.67 mg/kg bw) was excreted in the bile. Still, 66% of the dose was voided in the faeces and 9% in the urine. Based upon these data, it was concluded that the majority of orally consumed HCCP is metabolised in the gut, that the metabolites formed are not absorbed, and that a relatively small fraction of the orally administered radiocarbon was absorbed in the GI tract of rats.

Table 4-11 Elimination of radiocarbon from animals fed 1, 5, and 25[a] ppm ^{14}C-HCCP as component of the diet (animals returned to normal diet for 30 days after 30 days of treatment) (Dorough and Ranieri, 1984).

Animal, sex and time	Estimated cumulative percent of dose[b]								
	1 ppm			5 ppm			25 ppm		
	Urine	Faeces	Total	Urine	Faeces	Total	Urine	Faeces	Total
Female rats									
30 days on	6.4	69.4	75.8	8.5	69.9	78.4	8.9	61.5	70.4
+ 30 days off	6.6	67.2	76.7	8.5	71.1	79.6	9.0	63.4	72.4
Male rats									
30 days on	8.4	67.2	75.6	5.4	64.0	69.4	7.5	68.2	75.7
+ 30 days off	8.5	69.0	77.5	5.5	64.8	69.3	7.6	68.5	76.1
Female mice									
30 days on	12.0	66.1	78.1	7.3	54.0	61.3	8.0	56.4	64.4
+ 30 days off	12.2	67.0	79.2	7.4	54.4	61.8	8.3	57.1	65.4
Male mice									
30 days on	8.1	68.1	76.2	6.8	55.4	62.2	11.0	60.3	71.3
+ 30 days off	8.3	68.5	76.8	6.9	55.7	62.6	12.0	60.7	72.7

[a] 1, 5 and 25 ppm: equal to 0.07, 0.33, and 1.67 mg/kg bw per day for rats and equal to 0.16, 0.82, and 4.1 mg/kg bw per day for mice, respectively. [b] Number of animals analysed for these results were not reported; throughout the study, urine and faeces were collected every 24 hours.

Three animals at each dietary HCCP level were sacrificed at each interval of feeding in order to examine tissues for radioactive residues. Female animals fed the 25 ppm diet were sacrificed after being on treatment for 1, 3, 7, 12, 15 and 30 days. The kidney, liver, ovaries and fat were the major sites of deposition of ^{14}C-HCCP equivalents (**Table 4-12**). As with the other tissues, an apparent equilibration was attained after about 15 days of feeding. In rats, the kidneys contained the highest levels of residues, whereas in mice the residues in the liver exceeded those in the kidneys. It should be noted that data on concentrations of ^{14}C-HCCP in the lungs and carcass are lacking. On the average, excretion patterns were the same for rats and mice, male and female, at all dose levels within both treatments (single and continuous dosing).

Table 4-12 Comparative level of radioactive residues in tissue of female and male rats and mice after 15 days on diet containing 1, 5, and 25 ppm[a] ^{14}C-HCCP (Dorough and Ranieri, 1984).

		^{14}C-HCCP equivalents (ppm)[b]					
Tissue	Animal	Females			Males		
		1 ppm	5 ppm	25 ppm	1 ppm	5 ppm	25 ppm
Kidney	rats	0.32	1.31	5.77	0.11	0.71	4.91
	mice	0.07	0.40	1.85	0.02	0.29	1.80
Liver	rats	0.05	0.25	1.78	0.03	0.19	1.30
	mice	0.16	0.74	4.30	0.09	0.59	2.29
Fat	rats	0.21	0.59	3.73	0.07	0.31	3.01
	mice	0.31	1.08	4.10	0.15	1.27	4.19
Muscle	rats	0	0.01	0.42	0	0.02	0.39
	mice	0	0.02	0.60	0	0.02	0.43

Brain	rats	0	0.01	0.10	0	0	0.12
	mice	0	0.05	0.21	0	0	0.24
Gonads	rats	0.09	0.27	2.17	0.01	0.02	0.09
	mice	0.34	0.61	3.09	0	0.30	0.35

[a] 1, 5 and 25 ppm: equal to 0.07, 0.33, and 1.67 mg/kg bw per day for rats and equal to 0.16, 0.82, and 4.1 mg/kg bw per day for mice, respectively. [b] Data are the mean of 3 animals. Limit of detection = 0.01 µg/g.

After dosing of male F344 rats once by a gavage dose of 4.1 or 61 mg/kg bw ^{14}C-HCCP (in ethanol and water; three rats per dose group), the amount of the radioactivity remained in the tissues after 72 h was only 2.4% (El Dareer *et al.*, undated; published by El Dareer *et al.*, 1983). Most of the radioactivity excreted in urine appeared in the first 24 h; considerable faecal excretion of radioactivity occurred in the second 24 h period. Only about 1% was converted to $^{14}CO_2$. A summary of the disposition and distribution of ^{14}C-HCCP is given in **Table 4-13**.

Table 4-13 Disposition of radioactivity from ^{14}C-HCCP (expressed as % of dose) in rats dosed by gavage (El Dareer *et al.*, undated; published by El Dareer *et al.*, 1983).

Matrix	**Gavage[a]**	
	4.1 mg/kg bw	**61 mg/kg bw**
Urine	35.5±2.5	28.7±4.2
Faeces	79.5±2.8	65.3±6.9
Tissues	2.4±0.6	2.4±0.1
Blood (2 ml)	0.1±0.0	0.1±0.0
Liver	0.6±0.0	0.4±0.0
Skin (ears)	<0.1±0.0	<0.1
Kidneys	0.7±0.0	0.5±0.1
Brain	<0.1	<0.1
Tail section	-	-
Intestine	-	-
Lungs	-	-
Carcass	1.1±0.6	1.4±0.1
CO2	0.8±0.0	0.6±0.0
Other volatile	0.2±0.0	0.3±0.0
Total recovery	118±3	97±7

[a] At 72 h after (single) dose.

Some ^{14}C excreted in the faeces of rats was volatile. The chemical reactivity of HCCP with biological materials was evident in *in vitro* experiments, also carried out in this study, in which HCCP became bound to components of whole blood, plasma, liver homogenates, faecal homogenates, and intestinal contents.

Intravenous administration

In male SD rats (number of rats not reported), after i.v. administration of approximately 1 µCi (5 µmol ≈ 0.3 mg/kg bw) of ^{14}C-HCCP, approximately 9% of the administered dose was excreted in the bile in one hour (Mehendale, 1977). The nature of the ^{14}C material in the bile has not been examined. Biliary excretion of ^{14}C-HCCP and the blood concentration decay curve for ^{14}C-HCCP were unaltered after pre-exposure to 50 mg/kg bw HCCP per day for 3

days. After 60 minutes, examination of the subcellular tissue of animals which received i.v. ^{14}C-HCCP, showed that the kidneys contained higher concentrations than the liver, although by virtue of the size, liver contained more ^{14}C-HCCP. Kidney cytosol fraction contained over 93% of the radioactivity. Most of the radiolabel in the liver (68%) was also present in the cytosol fraction. Pre-exposure with HCCP resulted in an increased (approximately doubled) concentration in the kidneys after a single challenge of ^{14}C-HCCP. Despite the larger size of the liver, kidneys retained similar amounts of ^{14}C-HCCP material in terms of total quantity after pre-exposure with HCCP. The hepatic concentration of ^{14}C-HCCP was unaltered by pre-exposure to HCCP.

After a single intravenous exposure of 5 µg/kg bw HCCP to female SD rats (**Table 4-14**), 22.1% (mean value of three animals) of the dose was excreted in the urine and 47.4% in the faeces after 72 hours; 15.7% of radioactivity remained in the body (Dorough, 1980; published by Lawrence and Dorough, 1981 and 1982). After i.v. exposure of 7 µg/kg bw in rats the total recovery in tissue and carcass was 19% (**Table 4-15**). Highest residues after i.v. administration were measured in the liver, lungs and kidneys. The fat was not a site of residue accumulation.

Table 4-14 Disposition of radioactivity from ^{14}C-HCCP in rats dosed by intravenous injections (Dorough, 1980; Lawrence and Dorough, 1981)

Matrix	Cumulative percent of dose [a] 5 µg/kg bw		
	24 h	48 h	72 h
Urine	18.3±5.2	20.7±5.6	22.1±5.7
Faeces	21.1±7.1	30.4±1.7	47.4±1.9
Body	-	-	15.7±7.8
Total	-	-	85.2±4.8

[a] all values are the mean ± SD of three replicate animals.
[b] NR: not reported.

Table 4-15 Tissue distribution of radiocarbon 72 hours after i.v. exposure to ^{14}C-HCCP in rats (Dorough, 1980)

Matrix	I.v.[a] (7 µg/kg bw)	
	% of dose	µg/kg tissue
Trachea	0.04	3.3
Lungs	1.46	14.9
Liver	5.06	9.6
Kidneys	2.11	22.3
Fat	NR	2.3
Carcass[b]	10.31	0.5
Total	18.98±1.59	-

[a] All values are the mean ± SD of three replicate animals.
[b] Carcass includes total homogenate of body excluding tissue shown.

Three female SD rats were administered a single i.v. dose (0.7 mg ^{14}C-HCCP/kg bw in Emulphor or in saline) (Yu and Atallah, 1981). Intravenous administered doses were eliminated equally in faeces (21%) and in urine (18%) within 48 hours. The kidneys, liver, blood, and fat had higher residue levels than muscle, brain and heart. The amount of radioactivity present in the lung was 0.7% of the dose after 48 hours. HCCP was rapidly degraded in the rat body. No unchanged HCCP was detected in excreta or tissues. Most degradation products were polar. The biological half-life of HCCP in the blood of rats was approximately 32 hours after i.v. administration.

Following an intravenous dose of ^{14}C-HCCP to three male F344 rats at 0.59 mg/kg bw, 39.0% of the radioactivity remained in the tissues after 72 h (El Dareer *et al.*, undated; published by El Dareer *et al.*, 1983). Most of the radioactivity excreted in urine appeared in the first 24 h; considerable faecal excretion of radioactivity occurred in the second 24 h period. Only about 1% was converted to $^{14}CO_2$. A summary of the disposition and distribution of ^{14}C-HCCP is given in **Table 4-16**.

Table 4-16 Disposition of radioactivity from ^{14}C-HCCP (expressed as % of oral dose) in rats dosed intravenously (El Dareer *et al.*, undated; published by El Dareer *et al.*, 1983).

Matrix	**I.v.**[a]
	0.59 mg/kg bw
Urine	15.8±1.4
Faeces	34.0±1.0[e]
Tissues	39.0±1.0
Blood (2 ml)	2.9±1.3
Liver	13.9±1.5
Skin (ears)	<0.1
Kidneys	1.2±0.1
Brain	0.1±0.0
Tail section	1.4±0.6
Intestine	0.7±0.1
Lungs	0.3±0.1
Carcass	18.4±1.2
CO2	0.1±0.0
Other volatile	0.1±0.0
Total recovery	89±2

[a] At 72 h after (single) dose.

In vitro studies

An *in vitro* study (Yu and Atallah, 1981) indicated that HCCP was rapidly degraded in the gut, faeces and liver of rats.

4.1.2.1.2 Studies in humans

In vitro studies

No data are available.

In vivo studies

Inhalation exposure of a human volunteer (male white, age 28, 70 kg) to about 1.3 mg (=200*10^6 DPM) of ^{14}C HCCP (concentration and duration of exposure not given) resulted in excretion of the inhaled radioactivity in the urine within half an hour after the end of exposure. The bulk of the radioactivity was excreted within 5 days following exposure. The slow phase of excretion continued up to 22 days. No unchanged HCCP was detected in urine. Radioactivity comprised polar metabolites, which could not be identified. Only information on urinary elimination of HCCP was provided (Khan *et al.*, 1981).

4.1.2.1.3 Summary of toxicokinetics, metabolism and distribution

Inhalation
Upon respiratory exposure (1-2 hours) of rats to vapours of HCCP (vapour concentrations not specified) which resulted in low retained doses (7 and 24 µg/kg bw) and high retained doses (1.3-1.8 mg/kg bw) of HCCP, excretion of ^{14}C in the urine and faeces lies between 56.2-87.5% after 72 hours and is approximately equally divided between the urine and faecal excretion route. Excretion of $^{14}CO_2$ or other volatiles was minimal at high retained doses, whereas at low retained doses some volatile metabolites of HCCP must have been released, given the difference in retention between 1 hour and the total recovery at 72 hours. Approximately 11-13% of the administered ^{14}C remains in the body after 72 hours. Most of these residues are found in the kidneys and tissues of the respiratory tract. Fat was not a site of residue accumulation.
From the inhalation studies, it is concluded that complete absorption cannot be excluded. For the risk characterisation, 100% inhalation absorption is assumed (worst-case estimate).

Dermal
HCCP is absorbed via the dermal route as is indicated by toxic responses reported in acute dermal toxicity studies. Absorption data on dermal studies is, however, lacking.

Oral
Data on excretion via urine and faeces strongly indicate that rats and mice were capable of extensively degrading HCCP when applied orally, and that the metabolites formed were of a nature that favoured faecal elimination. The exact oral absorption figure cannot be derived, however, because it is not possible to discriminate between two options, which may both occur:
- HCCP is metabolised in the liver, the metabolites return to the intestine via the bile and are then excreted in the gut, and
- HCCP is largely metabolised in the gut, probably by microorganisms, to products which are not absorbed but voided in the faeces.
In addition, studies showed that HCCP became bound to faecal homogenates, and intestinal contents. Thus, from the available data on oral absorption only the minimum level of systemic availability, and consequently the minimal amount of oral absorption can be derived, i.e. via summing up recovered radiolabel in urine, tissues, and expired air: it ranges from approximately 18% to 39% after a single gavage application (7 - 61 mg/kg bw dose), and from 5.5% to 12.2% when applied via the diet for 30 days (0.07 to 1.67 mg/kg bw/day for rats, 0.16 to 4.1 mg/kg bw/day for mice). Both with single and repeated administration, there was no clear relationship between percentage absorption and dose.
The nature of the radioactivity excreted in urine was examined for possible metabolites. The results suggest that at least four metabolites of HCCP were present. These metabolites have not been identified and characterised.

Intravenous administration
After i.v. dosing of HCCP (5 and 590 µg/kg bw in rats), 50-70% of ^{14}C can be retraced in the urine and faeces in the proportion 1:2 after 72 hours. About 15-40% (respectively low dose and high dose) of the dose remains in the body after 72 h, mainly in the lungs, kidneys and liver (kidney and liver cytosol fraction contained most of the radioactivity). Pre-exposure with HCCP resulted in an increased (approximately doubled) concentration in the kidneys after a single challenge of ^{14}C-HCCP. Despite the larger size of the liver, kidneys retained similar

amounts of ^{14}C-HCCP material in terms of total quantity after pre-exposure with HCCP. The hepatic concentration of ^{14}C-HCCP was unaltered by pre-exposure to HCCP. The biological half-life of HCCP in the blood of rats was approximately 32 hours.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

In vivo studies

Several studies have been carried out exposing rats to HCCP via the oral, dermal and inhalatory route. None of the studies was performed according to OECD guidelines. These studies are summarised in **Table 4-17**.

Table 4-17 Summary of acute toxicity studies.

Route	Species	Endpoint LD_{50} or LC_{50}	Unity	Reference
Inhalation	Rat ♂, adult, Carworth (n = 10/dose)	<2 (4h)	mg/l (aerosol mist)	IRDC, 1972
	Rat, adult, sex and strain unspecified (n = 10)	<2.12 (1h)	mg/l (vapour)	Cannon Laboratories, 1976a
	Rat ♂♀, adult, SD (n = 10/sex/dose)	0.018 (♂) (4h) 0.04 (♀) (4h)	mg/l (vapour)	Huntingdon, 1978; published by Rand *et al.*, 1982a
	Rat ♂♀, adult, Wistar (n = 5/sex/dose)	0.041 (4h, 14 days after exposure); 0.033 (4h, 28 days after exposure)	mg/l (vapour) mg/l (vapour)	Huntingdon, 1987
	Rat, sex and strain unspecified (n = 4/dose)	0.035 (3.5h)	mg/l (vapour)	Treon *et al.*, 1955
	Mouse, sex and strain unspecified (n = 5/dose)	0.024 (3.5h)	mg/l (vapour)	Treon *et al.*, 1955
	Rabbit , sex and strain unspecified (n = 3/dose)	<0.0158 (3.5h)	mg/l (vapour)	Treon *et al.*, 1955
	Guinea pig, sex and strain unspecified (n = 2/dose)	0.080 (3.5h)	mg/l (vapour)	Treon *et al.*, 1955
Dermal	Rabbit ♂♀, adult, New Zealand White (n = 2/sex/dose)	<200 (♂) 340 (♀)	mg/kg bw	IRDC, 1972
	Rabbit, sex unspecified, adult , New Zealand White (n = 12)	<200	mg/kg bw	Cannon Laboratories, 1976d
	Rabbit ♀, adult, strain unspecified (n = 3/dose)	780	mg/kg bw	Treon *et al.*, 1955
	Rat ♂♀, adult, SD (n = 5/sex/dose)	between 2000-3200	mg/kg bw	Gardner, 1986a
Oral	Rat ♂♀, strain unspecified (n = 9,10 or 11/sex/dose)	505 (♂) 690 (♀)	mg/kg bw	Treon *et al.*, 1955
	Rat ♂♀, adult, Spartan (n = 5/sex/dose)	584 (♂♀) 630 (♂) 530 (♀)	mg/kg bw	IRDC, 1972
	Rat ♂♀, adult, Wistar (n = 5/sex)	>50	mg/kg bw	Cannon Laboratories, 1976b
	Rat ♂♀, adult, CFY (SD origin) (n = 5/sex/dose)	1400 (♂♀) 1500 (♂) 1300 (♀)	mg/kg bw	Gardner, 1986b
	Rat ♂♀, weanling, Fischer-344 (number unspecified)	425 (♂) 315 (♀)	mg/kg bw	SRI, 1980
	Rat ♂♀, young adult, Sprague-Dawley (number unspecified)	651	mg/kg bw	Dorough, 1979
	Mouse ♂♀, strain and number unspecified)	>600	mg/kg bw	Dorough, 1979

Route	Species	Endpoint LD_{50} or LC_{50}	Unity	Reference
	Mouse ♂♀, adult, Charles River (n = 5/sex/dose)	679	mg/kg bw	IRDC, 1977
	Mouse ♂♀, weanling, B6C3F1 (number unspecified)	680	mg/kg bw	SRI, 1980
	Rabbit ♀, adult, strain unspecified (n = 3/dose)	640	mg/kg bw	Treon *et al.*, 1955

Inhalation

In an acute inhalation study performed by IRDC (1972), male rats (Carworth CFE) were exposed for 4 hours to atmospheric concentrations of HCCP aerosol mist of 2 and 200 mg/l (10/dose). In both dose groups, signs observed were eye squint, dyspnea, cyanosis, salivation, lacrimation, ocular and nasal porphyrin discharge, erythema followed by blanching and hypoactivity. Necropsy exhibited congestion of the lungs in all low dose animals. In the high dose group, grey coloration of the skin and severe haemorrhage of the lungs (10/10) and hydrothorax (7/10) were observed. All animals died within 48 hours following exposure. The LC_{50} was <2 mg/l.

In an acute inhalation study by Cannon Laboratories (1976a), 10 rats (sex and strain unspecified) were exposed for one hour to 2.12 mg/l HCCP vapour. During exposure lacrimation, salivation, gasping, shovel-nosing, hyperactivity, pallor to hyperaemia to cyanosis of extremities and death at 1 hour (3/10) were observed. Post-exposure, 7/10 animals exhibited gasping. All (10/10) animals were found dead at 18 hours. The LC_{50} was <2.12 mg/l.

In an acute inhalation study performed by Huntingdon (1978; published by Rand *et al.*, 1982a), SD rats were exposed for four hours to 0.28, 1.4, 2.5, 3.1, 3.3, 3.4, 4.0, and 5.8 ppm HCCP vapour (10/sex/dose). Rats exposed to 0.28 ppm gained weight normally, no deaths were observed. Animals in all other dose groups lost weight and mortality occurred. Furthermore, some degree of sedation was noted. At 5.8 ppm, most animals showed lacrimation, salivation and ataxia. Animals surviving exposure to 1.4 ppm and higher exhibited significant pulmonary abnormalities (red focal or diffuse consolidation, progressing to haemorrhage and hepatisation). Some animals exposed to 5.8 ppm also exhibited rhinorrhea and mottling of the liver. The LC_{50} was 1.6 (equivalent to 0.018 mg/l) and 3.5 ppm (equivalent to 0.04 mg/l) for males and females, respectively.

In another acute inhalation study performed by Huntingdon (1987) fifty albino rats (Wistar) were divided into groups (5/sex/dose group). One group acted as a control receiving clean air only for 4 hours. The other 4 groups received 1.7 ppm (≈ 0.019 mg/l), 1.8 ppm (≈ 0.020 mg/l), 3.3 ppm (≈ 0.037 mg/l), or 3.5 ppm (≈ 0.040 mg/l) HCCP vapour for 4 hours. Clinical signs reported during the exposure were (partial) closing of the eyes, an abnormal respiratory pattern and the adoption of an abnormal body posture. A proportion of the rats was unusually active during the first hour of exposure. Gasping was evident in rats exposed to 0.037 mg/l. Rats exposed to 0.040 mg/l were hypoactive during the last 2 hours of exposure. During the observation period exaggerated respiratory movements were evident in all rats. Other signs seen in a proportion of the rats dosed at the four different dose levels included increased respiratory rate, lethargy and a discharge from the eyes. Most of the rats exposed to HCCP at 0.019 mg/l or 0.020 mg/l appeared to recover from the effects of exposure within 2-3 days and normal appearance and behaviour was observed in these groups for several days. Subsequently, signs indicating damage to the respiratory tract reappeared and persisted during the observation period. The rats exposed at higher concentrations had an abnormal respiratory

pattern on most days of the observation period. Signs in these rats indicating damage to the respiratory tract included rales, dark eyes, and a cyanosed appearance of the skin and other signs, associated with deteriorating condition, including pilo-erection, emaciation, lethargy, and hypothermia. The rats which died as a result of exposure to HCCP either lost weight over several days before death or gained weight for a few days following an initial disturbance in weight gain before a subsequent decline and death. Surviving rats failed to gain weight normally during the observation period. High absolute lung weights and a high lung weight to bodyweight ratio were found for the majority of rats. Abnormalities seen in the lungs at any concentration included a swollen and sometimes pale appearance of the lungs; areas of congestion and areas of hepatised appearance involving part or complete lobes of the lungs; and red or grey areas, varying in number and size, on the lungs. Other changes seen in a proportion of animals were small or abnormal appearance of some internal organs and distended gas-filled stomachs. The LC_{50} was estimated to be 0.041 mg/l at 14 days after exposure and 0.033 mg/l at 28 days after exposure.

Treon *et al.* (1955) performed an acute inhalation toxicity study with rats (n=4/dose), mice (n=5/dose), rabbits (n=3/dose), and guinea pigs (n=2/dose). Strain and sex of the different species was not specified. The animals were exposed to different concentrations of HCCP vapour (0.15 ppm up to 78.6 ppm) and different durations (1 hour, 3.5 hours, and 7 hours). The rabbits reacted most sensitively to the vapours of HCCP; mice, rats, and guinea pigs exhibited decreasing susceptibility in that order. The LC_{50} values reported for rabbits, mice, rats, and guinea pigs that had been exposed for 3.5 hours were <15.8 mg/m^3, 24 mg/m^3, 35 mg/m^3, and 80 mg/m^3, respectively.
The vapours caused serious irritation to the mucous membranes which expressed itself in cleaning of the eyes and nose, closure of the eyelids, tear, nasal and saliva secretion. In addition, the animals suffered from irregular breathing and later on from difficulty in breathing, while the mice occasionally experienced tremor. At lower concentrations, irritation of the eyes and difficulty in breathing occurred only after an extended period. The animals that died after a short period of exposure showed necroses of the epithelium of the primary, secondary and tertiary bronchial tubes, whereas the necrotic tissue in the animals that survived was infiltrated by neutrophils, erythrocytes and fibrin. Later on, obliterative bronchitis and bronchiolitis as well as connective tissue proliferations occurred.

Dermal

In a study by Hoechst (1969), Wistar rats were exposed to 200, 320, 500, 800, 1200 and 2000 mg/kg bw HCCP (10 rats/dose; sex not reported). An LD_{50} of 825 mg/kg bw was reported. Death occurred within 1-9 days. In this study, it was not explicitly stated whether diluted or undiluted HCCP was used, no solvents were specified and the amount(s) applied were not specified. As this study also contained oral uptake of HCCP, and no distinction was present for the observations after dermal or oral application, toxic characteristics are not mentioned here. This study is not considered suitable for the evaluation of acute toxicity of HCCP.

When HCCP, it was not explicitly stated whether diluted or undiluted HCCP was used, was applied once to the back of New Zealand White rabbits at a dosage level of 200 or 2000 mg/kg bw HCCP (amount(s) applied not specified; 2/sex/dose group; 24 hours under occlusive dressing; the skin of 1 male and 1 female rabbit in each dosage level group was abraded, no solvent was specified), 2/2 males died in the low dose group (IRDC, 1972). Both females survived, exhibiting body weight loss. The male rabbits which died showed weight loss, cachexis, marked dermal irritation and necrosis, and hypoactivity. The skin at the

application site turned purple. All animals in the high dose group died. No differences were reported in the occurrence of effects between animals with non abraded skin and animals with abraded skin. The LD_{50} was <200 mg/kg bw for male and 340 mg/kg bw for females.

When HCCP was administered dermally (200 mg/kg bw; amount applied not specified; 24 hours under occlusive dressing) to the skin of albino New Zealand White rabbits (sex unspecified), 4/12 animals died in the first 24 hours and 4/8 animals were found dead after 48 hours. The LD_{50} was <200 mg/kg bw (Cannon Laboratories, 1976d). Eschar formation was produced for 48 hours. In this study, it was not explicitly stated whether diluted or undiluted HCCP was used. No solvents were specified.

In a study by Treon *et al.* (1955) 3 female rabbits (strain unspecified) were exposed to HCCP concentrations (undiluted) varying from 430 mg/kg bw up to 6130 mg/kg bw (amount(s) applied not specified). The LD_{50} derived from this study is 780 mg/kg bw. HCCP appeared to be extremely irritating to the skin. Even the lowest dose induced a purplish-black local discoloration and subcutaneous oedema.

In an acute dermal study of Gardner (1986a), 5 ml of HCCP, dissolved in corn oil, was administered to abraded skin of SD rats (dose levels 1600, 2000 and 3200 mg/kg bw; 5/sex/dose group; 24 hours under occlusive dressing). An LD_{50} of >2000 mg/kg bw was reported. There were deaths among both sexes dosed at 2000 (one male and one female rat) and 3200 (four male and two female animals) mg/kg on days 2 to 4. Remarkably, administration of the undiluted test substance (2000 mg/kg bw) caused no death. Autopsy of rats that died revealed renal pallor in females dosed 3200 mg/kg bw and pallor of the liver, spleen and kidneys, congestion of the glandular zone of the stomach and congestion of the blood vasculature of the intestine in two rats dosed at 2000 mg/kg bw. Common clinical signs were hunched posture, waddling, lethargy and, at the two highest dose levels, ptosis, decreased respiration, and pallor of the extremities. Recovery of survivors appeared to be completed by day 3 among rats dosed with the undiluted test material or at intervals from days 5 to 9 among rats treated with 32%-40%-64% w/v (dose levels of 1600, 2000 and 3200 mg/kg bw/day, respectively) HCCP in corn oil. A trial test (dose levels 100, 250, 640, and 2000 mg/kg bw) had already indicated an LD_{50} of >2000 mg/kg bw 100% HCCP. All application sites revealed blackening of the skin and moderate or severe oedema during the first week and in general, recovery during the second week in the low and middle dose group. In the high dose group (diluted as well as undiluted), the majority of the rats developed hardened skin at the application site during the second week.

In addition, in the skin irritation studies, HCCP related mortality, necrosis on test sites and severe weight loss were observed (see section 4.1.2.3.1).

Oral

In a study by Treon *et al.* (1955), rats (9, 10 or 11/sex/dose, strain unspecified) and female rabbits (3/dose) were exposed by gavage to doses ranging from 180 up to 2100 mg/kg bw HCCP (solutions in peanut oil; amounts applied ranged from 0.25-3.60 ml/kg). The LD_{50} values were 505 mg/kg bw for male rats, 690 mg/kg bw for female rats and 640 mg/kg bw for female rabbits. The oral administration of the compound induced diarrhoea, lethargy, and a retarded breathing. The rabbits that died exhibited diffuse degenerations of the heart, liver, brain and adrenals, diffuse degenerations and necroses of the renal tubules and the lungs were severely hyperaemic and oedematous. Fatally exposed rats showed diffuse degeneration of the brain, heart, and adrenal glands, diffuse degeneration and necrosis of the liver and the kidney

tubules, and pulmonary hyperaemia and oedema. In some rats there was an acute necrotizing gastritis in the proximal segment of the stomach.

In a study performed by IRDC (1972) Spartan rats were exposed to HCCP suspended in corn oil at doses of 315, 500, 794, 1250 and 1984 mg/kg bw (5 rats/sex/dose group). Volumes of 10 ml/kg of body weight were administered at all dosage levels. The LD_{50} was 584 mg/kg bw. No clinical signs and no necropsy findings were presented. All surviving rats exhibited normal body weight gains.

A single intubation administration of HCCP was given to one group of ten Wistar rats (5/sex) at a dose of 50 mg/kg bw. The test material was administered as a 10% solution in distilled water. The animals exhibited decreased locomotor activity, but no deaths occurred during the 48 hour observation period (Cannon Laboratories, 1976b).

In a study by Gardner (1986b), CFY (SD origin) rats were orally exposed to 1260, 1600 and 2000 mg/kg bw HCCP (solutions in corn oil) (5/sex/dose group). Volumes of 10 ml/kg of body weight were administered at all dosage levels. The LD_{50} was 1400 mg/kg bw. Death occurred mostly on days 2 and 3 with additional female deaths on days 4 and 12. Low bodyweight gains were recorded on day 8 for all rats that survived the effects of treatment. All rats, which survived, achieved at least the anticipated bodyweight gain during the second week of the observation period. No macroscopic abnormalities were found during autopsy of rats which died. Terminal autopsy findings were normal. Reactions to treatment were pilo-erection, hunched posture, abnormal gait (waddling), lethargy, decreased respiration, ptosis, pallor of the extremities, and diarrhoea.

Dorough (1979) reported LD_{50} values of 651 mg/kg bw in rats (Sprague Dawley, number unspecified) and >600 mg/kg bw in mice (strain and number unspecified). The LD_{50} in young rats (Fischer-344, number unspecified) was 425 mg/kg bw for males and 315 mg/kg bw for females and in young mice (B6C3F1, number unspecified) 680 mg/kg bw (SRI, 1980). It is unknown whether diluted or undiluted HCCP and/or solvents were used in this study.

In a study by IRDC (1977) Charles River mice were exposed by gavage to HCCP suspended in corn oil at doses of 21.5, 46.4, 100, 215, 464, 1000, and 2150 mg/kg bw HCCP (5/sex/dose). Volumes of 10 ml/kg of body weight were administered at all dosage levels. The LD_{50} was 679 mg/kg bw. Diarrhoea was the only observation at 215 mg/kg bw (males only), at 464 mg/kg bw accompanied by hypoactivity, at 1000 mg/kg bw accompanied by decreased limb tone, ataxia, ptosis, and death and at 2150 mg/kg bw accompanied by decreased respiratory rate.

Results from skin and eye irritation studies
In all skin irritation studies, mortality was observed in rabbits (see section 4.1.2.3.1). Mortality occurred already at the lowest tested concentration (0.5 ml) which corresponds with a systemic dose level of 250 mg/kg bw assuming a body weight of 2 kg for rabbits.
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 conjunctival sac of the right eye (see section 4.1.2.3.2).

In vitro studies
No data available.

4.1.2.2.2 Studies in humans

Treon *et al.* (1955) reported that members of a research group conducting toxicity tests developed headaches when they were accidentally exposed to unknown concentrations of HCCP. The HCCP escaped into the room when an aerated exposure chamber was opened. No further details were provided.

4.1.2.2.3 Summary of acute toxicity

Although none of the acute toxicity studies were performed according to OECD-guidelines and some are rather outdated the data are sufficient to fulfil the Annex VII requirements for acute toxicity. After acute inhalatory exposure, the 4-hr 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.
The dermal LD_{50} for rabbits ranged from <200-780 mg/kg bw; for rats this value was between 2000 and 3200 mg/kg bw. Furthermore, in all skin irritation studies, mortality was observed in rabbits (see section 4.1.2.3.1). Mortality occurred already at the lowest tested concentration (0.5 ml) which corresponds with a systemic dose level of 250 mg/kg bw assuming a body weight of 2 kg for rabbits.
With regard to oral exposure, the LD_{50} ranged from 505-1500 mg/kg bw for rats; for mice this value was 679 mg/kg bw. Mortality also occurred in all skin and eye irritation studies. From the available data, it can be concluded that HCCP is harmful after acute oral exposure, toxic after acute dermal exposure and very toxic after inhalatory exposure (T+, R26; R24; R22). Starting points for the risk assessment are the 4-hour inhalation LC_{50} value of 0.018 mg/l (18 mg/m^3) in rats and the dermal LD_{50} of <200 mg/kg bw in rabbits.

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 conjunctival sac of the right eye (see section 4.1.2.3.2).
With regard to mortality following eye exposure: in the absence of a proper R-phrase for this effect, an additional S-phrase (S53) is necessary to draw attention to the risk of direct eye contact. S53 is already present in the current entry of HCCP in Annex I.
It is noted that under the new EU regulation on classification and labelling of chemicals (based on GHS), the sentence 'EUH070 - Toxic through eye' will be applicable.

4.1.2.3 Irritation

The results of the available skin and eye irritation studies are summarised in **Table 4-18**. The black, purple or red-black discolorations observed on the skin of the tested animal in several studies were interpretated as necrosis and/or haemorrhages and considered as corrosive effects. More details are given in the relevant sections. None of the irritation studies were performed according to OECD-guidelines and some are rather outdated.

Table 4-18 Summary of the available irritation studies.

Route	Species	Grading	Result	Reference
Skin	Rabbit, Yellow-Silver strain (sex not reported) (n=5)	*	Corrosive: 10% HCCP in sesam oil, non-occlusive	Hoechst, 1969
	NZW Rabbit (n=3/sex)	see **Table 4-19** and **Table 4-20**	Corrosive: 100% HCCP	IRDC, 1972
	NZW Rabbit (sex not reported) (n=6)	see **Table 4-21**	Corrosive: 100% HCCP	Cannon Laboratories, 1976c
	SD Rat (n=5/sex/dose)	*	Corrosive: 32%, 40% and 64% HCCP in corn oil	Gardner, 1986
	Monkey (sex and strain not reported) (n = 2)	*	Corrosive: >10% HCCP in Ultrasene	Treon *et al*., 1955
	Guinea pig (sex and strain not reported) (n=2)	*	Corrosive: 40%, 60% and 90% HCCP in Ultrasene; No skin reactions: 0.01%, 0.1% and 1% HCCP in Ultrasene	Treon *et al*., 1955
	Guinea pig (n=2/sex/dose; strain not reported)	*	Slightly irritant: 2% HCCP in corn oil; No skin reactions: 1% HCCP in corn oil	Price, 1982
Eye	NZW Rabbit (n=4/sex/dose)	**Table 4-23**	Severe irritant and (probably) corrosive	IRDC, 1972

* No scores given

4.1.2.3.1 Skin

Studies in animals

Dermal reactions were investigated by daily application (five times) of 0.5 and 1.0 ml of HCCP (10% in sesame oil; non-occlusive), respectively, on shaved backs of 5 rabbits (Yellow-Silver strain; sex not reported) (Hoechst, 1969). All rabbits exhibited local red-black discoloration and minor subcutaneous oedema already after the first dose. Both phenomena lasted until termination (3 days after the last application). One animal died after three applications of 1.0 ml and two animals after four doses of 1.0 ml. All animals exhibited severe weight loss (110-485 g).

Three male and three female NZW rabbits were used for application of undiluted HCCP (0.5 ml) to intact and abraded skin on the back (IRDC, 1972). The application area was wrapped with a gauze bandage for 4 h. Subsequently, the area was washed with tepid water and examined. The results are presented in **Table 4-19** and **Table 4-20**. Three of six rabbits used died during the observation period. Death was attributed to the test compound. Rabbits, which died during the study, exhibited respiratory depression and frothy, blood-like nasal discharge. Moderate to severe oedema was observed. Intense purple discoloration of the skin at the application site precluded observation of erythema.

Table 4-19 Summary of the test results of a dermal irritation test performed with three NZW rabbits (IRDC, 1972).

Mean scores observed after on intact and abraded skin	**4 hours**		**24 hours**		**72 hours**	
	intact skin	abraded skin	intact skin	abraded skin	intact skin	abraded skin
Erythema					*	*
Oedema Slight (2) Moderate (3) Severe (4)	 3/3	 2/3 1/3	 2/3 1/3	 2/3 1/3	 1/2 1/2	 1/1
Other: diarrhoea, ataxia, hypoactivity			2/3	1/3	2/2	
Death (24-72 h)					1/3	2/3

* No scores possible due to purple discoloration and deaths

Table 4-20 Summary of the test results for dermal irritation of the study of IRDC (1972).

Mean scores observed after	**24 hours (n=3)**		**72 hours (n=3)**	
	intact skin	abraded skin	intact skin	abraded skin
Erythema	*	*	*	*
Oedema	3.3	3.3	2.5	3.0

* No scores possible due to purple discoloration and deaths

A dermal irritation study on intact skin was performed by Cannon Laboratories (1976c). Six NZW rabbits (sex not reported) were administered to 0.5 ml undiluted HCCP per test site covered by occlusive patches. There were two test sites of intact skin per rabbit. After 4 h, the patches were removed for examination. The skin sites were re-examined and recorded after 24 and 48 h. The observations are presented in **Table 4-21** and are similar on both sites. Dermal corrosion (necrosis) was noted on all 12 test sites at 4 hours and at 8 sites (four animals) at 24 and 48 h. Two animals died within 24 h.

Table 4-21 Summary of the results of a dermal irritation/corrosivity test performed with 6 NZW rabbits (Cannon Laboratories, 1976c).

Mean scores observed after on intact skin		**4 hours**	**24 hours**	**48 hours**
Erythema	Very slight (1)			
	Well defined (2)			
	Moderate to severe (3)	6/6		
	Severe (4)		4/4	4/4
Oedema	Very slight (1)			
	Slight (2)			
	Moderate (3)	6/6	4/4	4/4
	Severe (4)			
Necrosis		6/6	4/4	4/4
Death between 4 and 24 h			2/6	2/6

In an acute toxicity study, Gardner (1986a) dermally exposed SD rats to 5 ml of HCCP, dissolved in corn oil at dosage levels of 1600 (in a concentration of 32 %w/v HCCP), 2000 (40 and 100 %w/v HCCP) and 3200 (64 %w/v HCCP) mg/kg bw (5/sex/dose group; 24 hours under occlusive dressing) (see section 4.1.2.2.1). Examination of the application sites revealed blackening of the skin and moderate to severe oedema after 48 and 72 hours in all dose groups. These reactions generally persisted throughout the first week. The condition of the skin treated with 32% or 40% w/v (1600 and 2000 mg/kg bw) HCCP in corn oil improved

during the second week. By day 15, oedema had partially or completely resolved and slough of the discoloured tissue had commenced or was complete. The majority of the rats treated with 64% w/v (3200 mg/kg bw) HCCP in corn oil or the undiluted HCCP developed hardened skin during the second week. This was not resolved before termination (day 15). Deaths occurred in the 40%, 64%, and undiluted group. The severe results found in this study might be attributed to the long period of exposure.

Treon *et al.* (1955) reported HCCP to be a primary skin irritant in rabbits (strain and sex unspecified) (doses tested: 430, 610, 1020, 2130 and 6130 mg/kg bw). The minimum lethal dose of undiluted 93.3% HCCP (remaining 6.7% is not further specified), when maintained in contact with the intact skin of rabbits according to the 24-hour sleeve method of Draize, Woodard and Calvery is greater than 430 and less than 610 mg/kg bw. Such contact resulted in severe damage to the skin, characterised by hyperaemia, haemorrhages, oedema and necrosis of the skin. Contact of the compound with the intact skin of rabbits resulted in pathologic changes in the tissues of these animals, among which were diffuse degeneration of the brain, heart, and adrenal glands, diffuse degeneration and necrosis of the liver and kidney tubules, and pulmonary hyperaemia and oedema. The skin exhibited acute inflammation, focal ulceration, focal crusting, acanthosis, and hyperkeratosis.
Even the lowest dosage induced a purplish-black local discoloration and subcutaneous oedema. About 12 days later, the skin was hard, encrusted and fissured. This local damage varied in severity and extent with the size of the dose applied. The lesions in the viscera of rabbits that died after application of the compound upon their skin were similar to those associated with oral administration. There were diffuse degenerative changes in the brain, heart, and adrenal glands, diffuse degeneration and necrosis of the liver cells and kidney tubules, and pulmonary hyperaemia and oedema. Two rabbits that died 17 and 20 hours, respectively, after having been given the two highest doses showed severe discoloration of the skin, and two others that died on the second and third days, respectively, after contact with smaller amounts exhibited acute diffuse inflammation, focal ulceration, and focal crusting of the skin. The brains, livers, kidneys, and adrenal glands of six rabbits that survived and were killed 7 to 21 days after the application of the compound on their skin had undergone degenerative changes which still persisted. The skin from these animals showed acanthosis, hyperkeratosis, epilation, and chronic inflammation.
Single applications of diluted HCCP solutions upon five sites on the abdomen of a monkey, at concentrations ranging from 0.001% to 10% in a dosage of 0.01 ml (solvent used: Ultrasene; exposure time not specified) followed by single applications of diluted HCCP from 20% to 90% in a dosage of 0.05 ml (solvent used: Ultrasene; exposure time not specified) 10 days later upon separate areas of the back caused prompt discoloration of the skin: from a concentration of 20%, the colour ranging from a very light to a dark tan as the concentration increased. In another monkey, daily 2-hour applications of 0.05 ml of a 10% HCCP solution/kg bw in Ultrasene for 3 consecutive days produced severe skin irritation and necrosis. Five days after the application, the skin was hard, encrusted, fissured, necrotic, and haemorrhagic. At 13 months after the application, a scar was visible on the injured area, with atrophy and complete absence of hair.
HCCP in a concentration of 0.01%, 0.1% and 1.0% did not induce any alteration of the skin of a guinea pig when applied in a dosage of 0.05 ml (solvent used: Ultrasene; exposure time not specified). The application of 3 more concentrated solutions (40%, 60%, and 90%) in the same dosage of 0.05 ml (solvent used: Ultrasene; exposure time not specified) upon separate areas of the back of another guinea pig resulted in all sites becoming discoloured, hard, encrusted, and necrotic. Based on these data it is concluded that the minimal effect concentration for guinea pigs is greater than 1.0% and less than 40% (Treon *et al.*, 1955).

In the dermal range finding study of the skin sensitisation study by Shell (Price, 1982), two groups of two male and two female guinea pigs (strain not reported) were exposed to 0.3 ml of a 1% or 2% HCCP dilution in corn oil (24 hours under occlusive dressing). The skin of the animals exposed to a 2% HCCP dilution showed slight redness (edges not defined), no skin reactions were observed in the rats exposed to 1% HCCP dilution.

Furthermore, in the acute dermal toxicity studies (see section 4.1.2.2.1) local effects to the skin were observed (discoloration, oedema, marked irritation and/or necrosis).

Studies in humans

In **Table 4-22**, data is given concerning 177 employees with symptoms after accidental exposure to HCCP.

Morse *et al.* (1979) and Kominsky *et al.* (1980) studied the effects of HCCP and octachlorocyclopentene on accidentally exposed sewage treatment plant workers in March 1977 in Louisville, KY. On March 26, 1977, an odoriferous, highly viscous, sticky substance entered a sewage treatment plant in Kentucky and coated the bar screens and grit collectors in the primary area. On March 29, the plant was closed when chemical analysis showed waste water at the plant to be contaminated with large amounts of HCCP and smaller amounts of octachlorocyclopentadiene. Although airborne concentrations of these chemicals at the time of exposure were unknown, subsequent air monitoring showed the relative airborne concentrations of HCCP to be much greater than octachlorocyclopentene. Airborne concentrations of HCCP varied between 40 and 19,000 ppb. Eye irritation (59%), headaches (45%) and throat irritation (27%) were the symptoms reported most frequently by employees. Other symptoms included skin irritation, cough, nausea and abdominal cramps. Detailed information on duration of symptoms was not available, as many persons were still symptomatic at the time of the survey. However, even six weeks after the episode, a follow-up questionnaire of 177 plant employees showed residual symptoms: headache in 18%, fatigue in 15%, chest discomfort in 13%, skin irritation in 10% and eye irritation and cough in 9%. A review of medical records for 90 employees seen by the plant physician from mid-March, 1977 to May 15, 1977 showed symptoms of headache and mucous membrane and respiratory tract irritation. In Table 4.19 the type and frequency of symptoms reported immediately prior to plant closure (March 29, 1977) and symptoms as late as 6 weeks after exposure are presented. It should be noted that octachlorocyclopentene is not a primary skin irritant and is a moderate eye irritant (EPA, 1978).

Table 4-22 Percent of 177 employees with symptoms after accidental exposure to HCCP (Kominsky *et al.*, 1980).

		Persistence after onset		
Symptom	**Last 2 weeks March**	**1 Day**	**1 Week**	**May**
Eye irritation	62	40	25	9
Headache	55	45	28	18
Chest discomfort	34	30	23	13
Fatigue	34	31	26	15
Sore throat	30	25	11	5
Cough	24	21	14	9
Nausea	22	18	13	6
Skin irritation	21	17	13	10

4.1.2.3.2 Eye

Studies in animals

In an eye irritation study (IRDC, 1972), 0.1 ml by volume of HCCP was placed into the conjunctival sac of the right eye of four male and four female NZW rabbits; the left eye served as a control. Five animals (sex not given) were exposed to HCCP for five minutes before washing with water, three animals were exposed to HCCP for 24 h prior to washing. The eyes were examined at 1, 24, 48, and 72 h and at 7, 14, and 21 days after treatment. The latter two examinations were precluded by the death of all rabbits on or before day 9 of the observation period, being attributed to the test compound. Signs seen during the observation period were necrosis, blanching, brown-purple discoloration, purulent discharge, corneal damage (investigated using sodium fluorescein), head tilt, facial swelling, dyspnoea, nasal discharge, vocalisation following instillation, and respiratory congestion. Results are summarised in **Table 4-23**.

Table 4-23 Summary of the test results of an eye irritation test performed with 8 NZW rabbits (IRDC, 1972).

	Group 1 (n=5)					**Group 2 (n=3)**				
Observation	**Hours after wash at 5 min.**				**day**	**hours after instillation (wash after 24 h)**				**day**
	1	24	48	72	7	1	24	48	72	7
Mortality			1[a]		3[b]				1[c]	2[d]
Cornea										
No ulceration or opacity	5/5	4/5	4/4	4/4	1/1	3/3	3/3	3/3	2/2	
Grade 1 opacity		1/5								
Grade 2 opacity										
Grade 3 opacity										
Grade 4 opacity										
Iris										
Normal	5/5	4/5	4/4	4/4	1/1	3/3	3/3	3/3	2/2	
Grade 1 iridal irritation		1/5								
Grade 2 iridal irritation										
Conjunctivae										
Vessels normal	2/5					1/3				
Grade 1 swelling	3/5	5/5		1/4		2/3	3/3	2/3		
Grade 2 swelling			2/4	2/4	1/1			1/3	2/2	
Grade 3 swelling			2/4	1/4						
Chemosis										
No swelling										
Grade 1 swelling										
Grade 2 swelling	1/5					2/3				
Grade 3 swelling	3/5	1/5	1/4	4/4		1/3		1/3	1/2	
Grade 4 swelling	1/5	4/5	3/4		1/1		3/3	2/3	1/2	
Ulceration or necrosis of conjunctivae or nictitating membrane				1/4			1/3	3/3	2/2	

[a] One rabbit died between the 24 h and 48 h observation period; [b] Three rabbits died between the 72 h and 7 day observation period and one rabbit died on the 9th day of the study period; [c] One rabbit died between the 48th hour and the 72nd hour of the study period; [d] Two rabbits died on the 6th day of the study period.

Studies in humans

See section 4.1.2.3.1. Skin irritation.

4.1.2.3.3 Respiratory tract

Studies in animals

See section 4.1.2.2.1. Acute inhalation and in section 4.1.2.6.1 the 2-week inhalation range finding study of Rand *et al.*, 1982a in section 4.1.2.6.1.

In the acute inhalation study by Huntingdon (published by Rand *et al.*, 1982a), SD rats were exposed for 4 hours to 0.28, 1.4, 2.5, 3.1, 3.3, 3.4, 4.0, and 5.8 ppm HCCP for 14 days (10/sex/dose). Animals surviving exposure to 1.4 ppm (equivalent to 0.016 mg/l) and higher exhibited significant pulmonary abnormalities (red focal or diffuse consolidation, progressing to haemorrhage and hepatisation).

In the 2-week inhalation range finding study of Huntingdon (published by Rand *et al.*, 1982a), microscopic examination on rats exposed to 5.7 mg/m^3 revealed lung changes mainly confined to the bronchioles, characterised by epithelial erosion, focal areas of hyperplastic cuboidal and columnar epithelium, focal subepithelial fibroblastic proliferation, inflammatory cell infiltration and/or exudate in the lumen. Minimal atrophy of olfactory epithelium with focal neutrophil infiltration, inflammatory exudates in the lumens, and focal hypertrophy of subepithelial mucous glands occurred in the nasal passages.

Studies in humans

See section 4.1.2.3.1. Skin irritation.

4.1.2.3.4 Summary of irritation

Although none of the irritation studies were performed according to OECD-guidelines and some are rather outdated, the data are sufficient to fulfil the Annex VII requirements for testing of irritation to the skin and eyes.

A case study with 177 plant workers showed that HCCP may be irritating to the skin, eyes and respiratory tract of humans after acute exposure.

Based on the available animal data it can be concluded that HCCP is irritating and corrosive to the skin and eyes and irritating to the respiratory tract. In a skin irritation study with rabbits (Hoechst, 1969), a dilution of 10% HCCP caused local red-black discoloration of the skin which was considered an indication of a corrosive effect. In another study (Price, 1982), a dilution of 2% HCCP induced slight redness (edges not defined) in rats. This finding does not require classification with the risk phrase R38 (well defined erythema).

Furthermore, a remarkable finding, mortality, was reported in all animal skin and eye irritation studies (this finding is taken into consideration in section 4.1.2.2.3 Summary of acute toxicity).

Based on the available data, the TC-C & L meeting (October 2006) specified the following concentration limits for local effects caused by HCCP:

$10\% \leq C \leq 100\%$: C, R34

$5 < C < 10\%$: Xi, R36/37/38

$C \leq 5\%$: -

4.1.2.4 Corrosivity

Corrosivity of HCCP has been discussed under 4.1.2.3: Irritation.

4.1.2.5 Sensitisation

In **Table 4-24** the results of the available skin sensitisation studies are given; one test performed according to Magnusson and Kligman and one test using another method. More details are given below.

Table 4-24 Summary of skin sensitisation studies.

Species	Grading	Result	Method	Reference
Guinea pig	*	sensitising	-	IRDC, 1978a
Guinea pig	see **Table 4-25**	sensitising	Magnusson & Kligman	Price, 1982

* no scores given

In the first sensitisation study, eight male albino guinea pigs (strain not reported) were injected intradermally with pure HCCP or saline on shaved skin areas at different sites on the back and flanks every other day, 3 times each week, until a total of 10 sensitising doses had been given (IRDC, 1978a). The first dose consisted of 0.05 ml, for the remaining nine doses 0.10 ml was used. Two weeks following the tenth sensitising dose, a challenge dose of 0.05 ml was given. Reactions to the sensitising as well as the challenge dose were read at 24 and 48 hours. In the event that the score for a challenge dose was greater than the average score of the ten sensitising doses, the control or test compound was considered to have produced dermal sensitisation. 2,4-Dinitro-1-chlorobenzene was used as a positive control (0.1% in saline). All 8 guinea pigs receiving injections of the test material responded to the challenge dose in the flare reaction, seven of them showing a flare response which was greater than the average for the sensitising injections. Examination of the individual mean values (flare) of the sensitising doses indicates that positive values were obtained throughout the sensitising period. All 4 guinea pigs in the positive control group exhibited a flare and wheal response greater than that obtained in the sensitising doses. Skin reactions in all control animals were negative following sensitising or challenge doses. It was concluded that HCCP is sensitising.

A second skin sensitisation study was performed by Shell according to the method of Magnusson and Kligman (OECD guideline 406) (Price, 1982). The test was conducted using a group of ten male and ten female guinea pigs (strain not reported) together with a control group of five males and five females. Two rows of three intradermal injections were performed, one on each site of the midline (shaved skin). Each row consisted of: one injection of Freund's complete adjuvant (FCA), one injection of the test material in solvent (corn oil), and one injection of the test material in 50:50 FCA/solvent (corn oil). Control animals were treated in the same manner but without injecting the test material. All injections were 0.1 ml. Concentrations were chosen based on a range finding study, i.e. 0.05% (w/v) in corn oil for intradermal induction, 2% (w/v) in corn oil for topical induction and 1% (w/v) in corn oil for topical challenge. One week after induction by the intradermal injections a patch with 0.3 ml of the test material was placed over the site for 48 hours for topical induction. Topical challenge was carried out two weeks after topical induction. A patch moistened with 0.1 ml of test material was placed over the test area. After 24 hours the patch was removed and the site was examined for response immediately and after 24 and 48 hours. All of the twenty test animals showed positive responses at both 24 and 48 hours after removal of the challenge patches. The results of this study are summarised in **Table 4-25**. In this study, it was concluded that HCCP is sensitising.

Table 4-25 Skin reaction in guinea pigs following topical challenge with HCCP (Shell, 1982).

		Response to challenge after:		
Animal number	sex	0 h	24 h	48 h
1	M	tr	(a)	(a)
2	M	+	+	+(b)
3	M	+	+	(a)
4	M	+	+	tr
5	M	+	tr	tr
6	F	+	(a)	(a)
7	F	tr	+	+
8	F	tr	(a)	(a)
9	F	tr	+	(a)
10	F	+	+	tr(b)
11	M	+	+(b)	(a)
12	M	+	tr	+
13	M	tr	tr	tr
14	M	+	+	tr
15	M	+	+	+(b)
16	F	+	+	tr(b)
17	F	+	+	tr
18	F	+	(a)	(a)
19	F	+	+	tr
20	F	++	(a)	(a)
Control animals				
1	M	-	-	-
2	M	-	-	-
3	M	-	-	-
4	M	-	-	-
5	M	tr	-	-
6	F	-	-	-
7	F	-	-	-
8	F	-	-	-
9	F	-	-	-
10	F	-	-	-

-: not different from surrounding skin, tr: slight redness, edges not defined, +: pink/red square with defined edges, ++: beet red square with well defined edges, (a): scab due to self inflicted wound (biting) covering entire challenge site, preventing assessment of degree of erythema-counted as positive response, (b): scab due to self inflicted wound (biting) covering part of challenge site, assessment of degree of erythema not affected.

Respiratory tract
No data available.

4.1.2.5.1 Studies in humans
No data available.

4.1.2.5.2 Summary of sensitisation
Two skin sensitisation tests with HCCP are available; one test performed according to Magnusson and Kligman (OECD guideline 406) and one test using another method. The available data are acceptable to fulfil the Annex VII requirements for sensitisation testing. Based on the available data, it can be concluded that HCCP may cause sensitisation by skin contact. Classification with Xi, R43 is proposed.

In the skin sensitisation studies, effects were observed at relatively low concentrations. It is proposed to establish a specific concentration limit for these effects. A concentration of 0.05% HCCP in corn oil for intradermal induction in combination with the observation that all of the twenty test animals showed positive responses at both 24 and 48 hours after removal of the challenge patches results in a specific concentration limit of 0.001% ('extreme sensitiser') according to ECBI/81/02 Rev.2.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

Inhalation
In **Table 4-26**, a summary of the available inhalation repeated dose studies is presented. More details are given in the following paragraphs. None of the studies were performed according to OECD-guidelines and some are rather outdated.

Table 4-26 Summary of inhalation repeated dose toxicity studies with HCCP.

Exposure period	Species	Exposure concentration (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	Critical effects	Reference
2 weeks	Rat ♂♀ Sprague-Dawley N=10/sex/dose	0, 0.25, 1.25, or 5.7	Systemic: 1.25 Local: 1.25	Systemic: 5.7 Local: 5.7	Body weight loss and mortality Impaired respiratory function and microscopic changes in lung and nasal area	Rand *et al.*, 1982a WHO, 1991
6 weeks	rats (n=4), mice (n=5,) rabbits (n=6), guinea pigs (n=2), strain and sex unspecified	3.7 7h/day, 5 days/wk	Systemic: <3.7 Local: unknown	Systemic: 3.7 Local: unknown	Mortality. Except for the guinea pigs. No other effects than mortality were reported.	Treon *et al.*, 1955
13 weeks	Rat ♂♀ F344/N n=10/sex/dose	0, 0.45, 1.67, 4.46, 11.14, 22.28 6 h/day, 5 days/wk	Systemic and Local; 1.67	Systemic and Local: 4.46	Decreased body weight gain and lower mean body weights, listlessness, higher absolute and relative lung weights, and severe local effects on nose and respiratory tract. All rats in the 11.14 and 22.28 mg/m^3 died.	NTP, 1994
	Mouse ♀♂ $B6C3F_1$ n=10/sex/dose		Systemic: 1.67 Local: 0.45	Systemic: 4.46 Local: 1.67	Decreased absolute body weight and squamous metaplasia of the larynx or trachea. Dose levels of ≥ 4.46 mg/m^3 caused decreased body weight gain and lower mean body weights, listlessness, and severe local effects on nose and on respiratory tract and mortality	

Exposure period	Species	Exposure concentration (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	Critical effects	Reference
14 weeks	Rat, SD n=40/sex/dose Monkey, (Macaca fascicularis) N=6/sex/dose	0.11, 0.57, 2.28 6 h/day, 5 days/wk	Systemic and Local: 2.28 Systemic and Local: 2.28	Systemic and Local: >2.28 Systemic and Local: >2.28	No treatment related effects observed No treatment related effects observed	Huntingdon,1980a; Rand *et al.*, 1982b
30 weeks	Rat ♀♂ Wistar n=18/sex/dose	0, 0.68, 1.58, 6.34 6 h/day, 5 days/wk	Systemic: 0.68 Local: 1.58	Systemic: 1.58 Local: 6.34	Significantly higher mean erythrocyte counts, haemoglobin concentration, haematocrit and absolute numbers of neutrophils, and a significantly lower percentage lymphocyte counts and decreased spleen weights in males	Clark *et al.*, 1982
30 weeks	rats (n=4), mice (n=5,) rabbits (n=6), guinea pigs (n=2), strain and sex unspecified	1.7 7h/day, 5 days/wk	Systemic: <1.7 Local: <1.7	Systemic: 1.7 Local: 1.7	Mortality in mice. Mild degenerative changes in the livers and kidneys in all species. Mice were found to have pulmonary oedema and bronchitis. Some rats and guinea pigs developed pneumonia.	Treon *et al.*, 1955
2 years	Rat ♂♀ F344/N n=60/sex/dose	0, 0.11, 0.56, 2.28 6 h/day, 5 days/wk	Systemic: 2.28 Local: <0.11	Systemic: >2.28 Local: 0.11	No treatment related systemic effects were observed Toxicity to the respiratory tract: increased incidence of pigmentation of the respiratory epithelium of the nose, trachea and lung in both males and females and significantly higher incidence of squamous metaplasia of the laryngeal epithelium of females	NTP, 1994
	Mouse ♂♀ B6C3F1 n=60/sex/dose		Systemic: 0.11 Local: <0.11	Systemic: 0.56 Local: 0.11	Higher incidence of suppurative inflammation of ovaries Toxicity to the respiratory tract: pigmentation of the respiratory epithelium of the nose, trachea, and lung	

In a 2-week inhalation range finding study by Huntingdon Research (published by Rand *et al.*, 1982a) groups of Sprague-Dawley rats (n=10/sex/dose) were exposed to concentrations of HCCP (purity: 97.7%) of 0, 0.25, 1.25, or 5.7 mg/m^3 HCCP, 6 hours/day, 5 days/week, for 2 weeks. In the high-exposure group, 9 male and 2 female animals died during the exposure period. In the low- and mid-exposure groups, no mortality or treatment-related clinical signs

were observed. Males and females exposed to 5.7 mg/m^3 had a significant dose-related decrease in mean body weight compared to controls. Morbidity and death in the high dose group may be caused by body weight loss, severe irritation of the respiratory tract and impairment of respiratory function. In the animals of the high-exposure group, clinical signs observed were dark red eyes, laboured respiration, and paleness of the extremities. Haematological examination revealed increases in haematocrit, haemoglobin level, and erythrocyte count and decreased lymphocyte counts. In the mid-exposure group, males showed a decrease in haematocrit, but an increase in haemoglobin level. In all male exposure groups, there was a dose-dependent increase of serum total protein levels. Absolute liver weights were reduced in males of the low-exposure group and in females of the low- and mid-exposure group. In animals exposed to 5.7 mg/m^3, absolute lung weights were increased and the absolute weights of kidneys, adrenals, and ovaries were decreased, compared with the controls. Data on relative organ weights were not given. The following organs were examined macroscopically in the different dose groups: adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thyroid, and uterus. Tissues from the brain, bone marrow, heart, kidneys, liver, lungs, nasal passages and spleen, as well as any other grossly abnormal tissues, were then examined microscopically. There were no treatment-related abnormalities in macroscopic pathology of rats in the control, low and mid-dose group. The predominant macroscopic abnormality in the high dose group consisted of pale areas of consolidation in the lung. Microscopic examination on rats of the 5.7 mg/m^3 group revealed lung changes mainly confined to the bronchioles, characterised by epithelial erosion, focal areas of hyperplastic cuboidal and columnar epithelium, focal subepithelial fibroblastic proliferation, inflammatory cell infiltration and/or exudate in the lumen. Minimal atrophy of olfactory epithelium with focal neutrophil infiltration, inflammatory exudates in the lumens, and focal hypertrophy of subepithelial mucous glands occurred in the nasal passages. There were no significant treatment-related microscopic changes in the mid- and low-exposure groups compared with the controls. These nasal and lung changes in the high-exposure group were consistent with observed impaired respiratory function, confirming the lung as the main target organ, according to Rand *et al.* In a parallel experiment, groups of rats (n=5/sex/group) were treated similarly, but served as separate recovery groups to observe effects during a 14-day (control, low- and mid-exposure groups) or 21-day (high-exposure group) period without exposure. Rats in the high-exposure group received only 5 exposures, because of the high mortality in the main study (see above). All animals survived during the exposure period, but 3 males in the high-exposure group died within 7 days after the end of exposure. A decrease in mean body weight was observed for both sexes in the high-exposed group. Haematological abnormalities, including serum total protein levels, in the high- and mid-exposure group were reversible during the recovery period, except for increased haemoglobin levels in the males of both groups. Changes in absolute organ weights were not observed in any of the groups at 14 or 21 days after the end of exposure. Microscopic changes of the lung and the nasal area observed in the high-exposure group recovered 2 to 3 weeks after termination of exposure. The NOAEC for local effects in this study was 1.25 mg/m^3 based on impaired respiratory function and microscopic changes in lung and nasal area. The haematologic abnormalities probably reflect a homeostatic response to the impaired respiratory function resulting from pathological changes in the respiratory tract epithelium. Based on the reduced body weight and mortality in the highest dose group, the NOAEC for systemic effects was also established at 1.25 mg/m^3.

In an old inhalation study, small groups of rats (n=4), mice (n=5), rabbits (n=6), and guinea pigs (n=2) were exposed to concentrations of 3.7 mg/m^3 (0.34 ppm) HCCP, 7 hours/day, 5 days/week for 6 weeks. Guinea pigs survived the 30 exposures. Four rabbits died before the

25th exposure and all rats and mice between the 6th and 20th exposure (Treon *et al.*, 1955). The only concentration tested in this study (3.7 mg/m^3) was considered a LOAEC.

Two 13-week semichronic inhalation toxicity studies were performed with 6 groups of young F344/N rats and B6C3F$_1$ mice (10/sex/dose group) (NTP, 1994), respectively. The animals were exposed to atmospheres containing 0, 0.45, 1.67, 4.46, 11.14, and 22.28 mg/m^3 HCCP for 6 hours per day, 5 days per week. Additional rats and mice were exposed to 0, 0.45, 4.46, and 22.28 mg/m^3 HCCP for the same period and evaluated for differences in clinical pathology parameters. With regard to histopathological investigations, in the study reports it is not specified how many levels of cross sections were examined on the different tissues and whether the lesions in the tissues could be associated with different epithelial regions.

Rats

All rats in the 11.14 and 22.28 mg/m^3 groups died during the first 4 weeks of the study. The final mean body weight and mean body weight gain of male rats exposed to 4.46 mg/m^3 were significantly lower than those of the controls. These results were not found for the female rats. No results concerning food consumption and ophthalmological examination were reported. Listlessness was observed in rats exposed to 22.28 mg/m^3 from week 1, in 11.14 mg/m^3 rats from week 2, and in 4.46 mg/m^3 rats during week 3. Rats exposed to 11.14 and 22.28 mg/m^3 also experienced respiratory distress. No chemical-related differences in haematology, clinical chemistry, or urinalysis parameters were observed in male or female rats. Absolute and relative lung weights of 4.46 mg/m^3 male rats were significantly greater than those of the controls. Inflammation (necrotising, chronic, or suppurative) of the nose, larynx, trachea, and lungs was observed in 4.46, 11.14, and 22.28 mg/m^3 male and female rats. In addition, squamous metaplasia of the epithelial lining of the nose of 4.46 mg/m^3 male and 11.14 and 22.28 mg/m^3 male and female rats was observed (**Table 4-27**). The NOAEC for both local and systemic effects in the rat study was established at 1.67 mg/m^3.

Table 4-27 Incidences of selected nonneoplastic lesions of the respiratory tract in rats in a 13-week inhalation study (NTP, 1994).

Exposure concentration (mg/m^3)[a]	**0**	**1.67**	**4.46**	**11.14**	**22.28**
Male					
Nose[b]	10	10	10	10	10
Inflammation, necrotising[c]	0	0	2 (2.0)[d]	10** (2.8)	10** (3.8)
Inflammation, suppurative	0	1 (1.0)	7** (1.4)	0	0
Metaplasia, squamous	0	0	4* (1.8)	5* (1.8)	3 (2.3)
Larynx	10	10	10	10	10
Inflammation, necrotising	0	0	0	6** (2.2)	10** (3.3)
Trachea	10	10	10	10	10
Inflammation, necrotising	0	0	1 (1.0)	10** (2.2)	10** (3.9)
Lung	10	10	10	10	10
Inflammation, necrotising bronchus/bronchiole	0	0	5* (1.2)	10** (3.4)	10** (4.0)
Inflammation, suppurative bronchus/bronchiole	0	0	5* (1.2)	0	1 (3.0)
Haemorrhage, alveolus	0	0	0	9** (2.3)	10** (2.7)

Exposure concentration (mg/m³)[a]	**0**	**1.67**	**4.46**	**11.14**	**22.28**
Inflammation, suppurative, alveolus	0	0	1 (1.0)	7** (2.6)	1 (3.0)
Female					
Nose	10	10	10	10	10
Inflammation, necrotising	0	0	0	10** (2.9)	10** (3.7)
Inflammation, suppurative	1 (3.0)	0	2 (1.0)	0	0
Metaplasia, squamous	1 (3.0)	0	0	1 (3.0)	4 (2.5)
Larynx	10	10	10	10	10
Inflammation, necrotising	0	0	1 (1.0)	9** (1.6)	9** (2.8)
Trachea	10	10	10	10	10
Inflammation, necrotising	0	0	1 (1.0)	10** (2.1)	10** (3.6)
Lung	10	10	10	10	10
Inflammation, necrotising					
bronchus/bronchiole	0	0	3 (1.3)	10** (3.3)	10** (3.9)
Inflammation, suppurative bronchus/bronchiole	0	0	2 (1.0)	0	1 (3.0)
Haemorrhage, alveolus	0	0	0	5* (2.4)	7** (3.1)
Inflammation, suppurative, alveolus	0	1 (1.0)	1 (1.0)	9** (2.7)	2 (3.0)

* Significantly different (P≤0.05) from the control group by Fisher's exact test, ** P≤0.01, [a] Animals in the 0.45 mg/m³ group were not examined, [b] Number of animals with organ examined microscopically, [c] Number of animals with lesion, [d] Average severity of lesions in affected animals: 1= minimal; 2= mild; 3= moderate; 4= marked; 5= severe

Mice

All 22.28 mg/m^3 mice died during the first week of exposure. All 11.14 mg/m^3 mice died during the first 5 weeks of exposure. Five male and two female mice in the 4.46 mg/m^3 group died during the first 2 weeks of exposure. Final mean body weights of males exposed to 1.67 and 4.46 mg/m^3 and the body weight gain of 4.46 mg/m^3 male mice were significantly lower than those of the controls. Final mean body weights and mean body weight gains of the other male and female mice exposure groups with survivors were similar to those of the controls. No results concerning food consumption and ophthalmological examination were reported. Treatment-related clinical findings included listlessness in 4.46 and 11.14 mg/m^3 male and female mice. No chemical-related differences in haematology, clinical chemistry, or urinalysis parameters were observed in male and female mice. Necrosis and inflammation of the nose, larynx, trachea, and lung occurred in mice exposed to 4.46, 11.14, and 22.28 mg/m^3 HCCP. Squamous metaplasia of the larynx or trachea was observed in 1.67, 4.46, and 11.14 male and in 4.46 and 11.14 mg/m^3 female mice (**Table 4-28**). The NOAEC for local effects in the mouse study was established at 0.45 mg/m^3 based on the above mentioned effects. The NOAEC for systemic effects was established at 1.67 mg/m^3 based on mortality and listlessness observed in mice exposed to 4.46 and 11.14 mg/m^3.

Table 4-28 Incidences of selected nonneoplastic lesions of the respiratory tract in mice in a 13-week inhalation study (NTP, 1994).

Exposure concentration (mg/m³)[a]	**0**	**0.45**	**1.67**	**4.46**	**11.14**	**22.28**
Male						
Nose[a]	10	10	10	10	10	10
Necrosis, acute[b]	0	0	0	0	1 (4.0)[c]	10** (4.0)
Inflammation, serous	0	1 (2.0)	2 (2.0)	3 (3.3)	1 (4.0)	0
Inflammation, suppurative	0	0	0	6** (2.0)	8** (2.8)	4* (2.5)
Larynx	9	10	10	10	10	10
Necrosis, acute	0	0	0	0	3 (3.3)	10** (4.0)
Metaplasia, squamous	0	0	0	2 (3.0)	1 (3.0)	0
Trachea	8	10	8	8	7	9
Necrosis, acute	0	0	0	0	3 (3.7)	9** (4.0)
Inflammation, necrotising	0	0	0	0	1 (3.0)	0
Metaplasia, squamous	0	0	1 (2.0)	4* (2.8)	4* (3.3)	0
Lung	10	10	10	10	10	10
Necrosis, acute	0	0	0	0	3 (4.0)	10** (4.0)
Congestion	0	1 (2.0)	0	3 (2.7)	0	9** (2.9)
Female						
Nose	10	10	9	10	10	10
Necrosis, acute	0	0	0	0	0	10** (4.0)
Inflammation, serious	0	0	2 (2.0)	7** (3.1)	1 (4.0)	0
Inflammation, suppurative	0	0	0	2 (2.5)	8** (3.0)	5* (2.6)
Larynx	10	10	9	10	10	10
Necrosis, acute	0	0	0	0	0	9**[d] (4.0)
Metaplasia, squamous	0	0	0	0	7**[d] (2.7)	0
Trachea	8	10	8	7	10	9
Necrosis, acute	0	0	0	0	2 (4.0)	9** (4.0)
Inflammation, necrotising	0	0	0	0	2 (4.0)	0
Metaplasia, squamous	0	0	0	2 (2.0)	7** (3.1)	0
Lung	10	10	9	10	10	10
Necrosis, acute	0	0	0	0	1 (4.2)	10** (4.0)
Inflammation, necrotising	0	0	0	0	9** (3.8)	0
Congestion	0	0	0	0	0	9** (3.1)
Inflammation, suppurative	0	0	0	0	0	1 (3.0)
Adenoma	0	0	1	0	0	0

* Significantly different (P≤0.05) from the control group by Fisher's exact test, ** P≤0.01, [a] Number of animals with organ examined microscopically, [b] Number of animals with lesion, [c] Average severity of lesions in affected animals: 1= minimal; 2= mild; 3= moderate; 4= marked; 5= severe, [d] n=9

In a 14-week inhalation study by Huntingdon Research (1980a, published by Rand *et al.* (1982b) Sprague-Dawley rats (n=40/sex/dose) and Cynomolgus monkeys (n=6/sex/dose) received whole-body exposure to HCCP at concentrations of 0, 0.11, 0.57, or 2.28 mg/m^3 (0, 0.01, 0.05, and 0.2 ppm), 6 hours/day, 5 days/week.

Monkeys

There were no mortalities or adverse clinical signs in monkeys during the study. For monkeys, body weight gain and food consumption were not significantly different between groups. The results of the pulmonary function tests (blood gas analysis, lung mechanics, and lung ventilation) were within normal ranges. There was no evidence from ophthalmoscopic examination that HCCP vapour induced eye lesions. Haematology, clinical chemistry, and urinalysis demonstrated no effect of HCCP exposure. No treatment related abnormalities were observed in organ weights, macroscopic pathology, and histopathology. On this basis, the NOAEC for both local and systemic effects for monkeys was 2.28 mg/m^3, the highest dose tested.

Rats

Four rats died or were killed in extremis (control, 0.11, and 0.57 mg/m^3 groups) during the study; no death was considered to be related to inhalation of HCCP. The only adverse clinical sign observed during exposure was the appearance of dark red eyes in male rats of the 0.57 and 2.28 mg/m^3 groups. This was observed after the 10th exposure and had disappeared from all rats 24 h after the 20th exposure. It was also observed in exposed rats in the range-finding study and was considered related to HCCP exposure. Ophthalmoscopic examination did not reveal chemical induced abnormalities. There were no treatment-related changes in body weight gain, food consumption, or clinical chemical parameters. After 12 weeks of exposure, there was a slight, marginal, occasionally statistically significant increase in haemoglobin level, erythrocyte count and the associated mean corpuscular haemoglobin concentration with a corresponding reduction in mean cell volume in the 0.11 mg/m^3 males, 0.57 mg/m^3 females and 2.28 mg/m^3 males and females. These changes were similar to the changes observed in the range-finding study (Huntingdon Research, published by Rand *et al.*, 1982a) that were considered indicative of impaired respiratory function. The changes observed in the current study may have been manifestations of marginally impaired respiratory function which was insufficiently severe to induce detectable histological changes. All other haematology data were considered normal. The mean liver weight (adjusted for the final body weight) in males and females of all treatment groups was statistically significantly reduced by 3 to 14% (no dose response relationship was indicated), relative to controls, and the mean kidney weight (adjusted for the final body weight) in all treated males was reduced by 10 to 11% (no dose response relationship was indicated), relative to controls. Upon macroscopic and microscopic examination, no treatment-related abnormalities in gross pathology or histopathology were observed. On this basis, the NOAEC for local and systemic effects in rats was 2.28 mg/m^3, the highest dose tested (Rand *et al.*, 1982a). This level was confirmed by the WHO (1991).

In a further study by Huntingdon (1980b, published by Rand *et al.* (1982b) the effects of inhalation of HCCP up to 14 weeks (with identical exposure conditions as the previous study) on the terminal bronchioles of Sprague-Dawley rats (n=3/sex/dose) and Cynomolgus monkeys (n=3/sex/dose) was examined by electron microscopy. Exposed rats elicited dose-dependent abnormalities in the Clara cells of the lungs at 0.11 mg/m^3 and above.

These abnormalities comprised an increase in the mean number of inclusions in the apex and base of the Clara cells, the biological significance of which is unclear. In exposed monkeys no ultra structural changes were observed that could be attributed to the inhalation of HCCP vapour.

In an old inhalation study, small groups of rats (n=4), mice (n=5), rabbits (n=6), and guinea pigs (n=2) were exposed, 7 hours/day, 5 days/week for 30 weeks to HCCP vapour (89.5% pure). All species exposed to 0.15 ppm (equivalent to 1.7 mg/m^3), except 4 of 5 mice, survived and grew normally. At approximately twice this concentration, mice, rats, and most rabbits died by or before the 25th exposure, but guinea pigs survived 30 exposures. The HCCP vapours caused tearing, laboured respiration, and, at high concentrations, tremors. Degenerative changes in the brain, heart, liver, adrenal glands, and kidneys, and pulmonary irritation occurred in all species, even at the lowest concentration of 1.7 mg/m^3. Furthermore, the mice were found to have pulmonary oedema and bronchitis, and some of the guinea pigs and rats had developed pneumonia. For none of the species, the strain and sex were specified (Treon *et al.*, 1955). The lowest concentration tested (1.7 mg/m^3) in this study was a LOAEC for both local and systemic effects.

In a semi-chronic inhalation toxicity study conducted by Shell (Clark *et al.*, 1982), Wistar rats were exposed for 30 weeks. The animals were divided in groups (18/sex/dose group) and exposed to 0, 0.06, 0.14, and 0.56 ppm (equal to 0.68, 1.58, and 6.34 mg/m^3) HCCP for 6 hours per day, for 5 days per week either or not followed by a recovery period (9/sex/dose group) of 14 weeks. Animals were examined for their general health status. Animals exposed to 6.34 mg/m^3 were sneezing and lethargic during the study. Four males and two females in the 6.34 mg/m^3 group died during exposure. No clinical signs of toxicity or deaths were recorded in the 0.68 and 1.58 mg/m^3 groups. Body weights of males at the 6.34 mg/m^3 exposure level were significantly lower than body weights in the control group from week 7 until the end of exposure. Body weights of females showed several instances of significant increases from control during the first 3 weeks of exposure. Males in the 6.34 and 1.58 mg/m^3 groups had significantly higher mean erythrocyte counts, haemoglobin concentration, haematocrit and absolute numbers of neutrophils, and significantly lower percentage lymphocyte counts than control animals. The mean absolute numbers of lymphocytes were lower in females at the exposure level of 6.34 mg/m^3. For food consumption, clinical chemistry parameters and for urinalysis no effects were detected. Animals exposed to 6.34 mg/m^3 showed pulmonary degenerative changes ranging from epithelial hyperplasia, oedema and sloughing of the bronchiolar epithelium of both sexes to epithelial ulceration and necrosis in the males. Degenerative changes in the lungs were absent in the animals exposed to 0.68 and 1.58 mg/m^3 HCCP and absent in the recovery group. The deaths were probably due to bronchopneumonia. Mild degenerative changes were seen in the liver and kidney of some rats exposed to 6.34 mg/m^3 after 30 weeks. Absolute kidney weights were significantly increased in females in the 6.34 mg/m^3 exposure group after 30 weeks. Absolute male heart weights were decreased at 30 weeks in this exposure group. At the end of the recovery period, male mean spleen weights adjusted for terminal body weight were significantly decreased at the exposure levels of 6.34 and 1.58 mg/m^3, and male mean testes weights adjusted for terminal body weight were significantly increased at the exposure level of 6.34 mg/m^3. There were no significant changes in female rats after the recovery period. Ophthalmology was not examined. The NOAEC for systemic effects in this study was established at 0.68 mg/m^3 based on haematological changes in males and on the significantly decreased male mean spleen weights adjusted for terminal body weight at 1.58 mg/m^3. The NOAEC for local effects was established at 1.58 mg/m^3 based on degenerative changes in the lungs observed at the next higher dose level.

Two 2-year chronic inhalation toxicity studies were performed with 4 groups of 60 male and 60 female F344/N rats and B6C3F$_1$ mice of 6-7 weeks old, respectively (NTP, 1994). The

animals were exposed to atmospheres containing 0, 0.01, 0.05 and 0.2 ppm (equal to 0, 0.11, 0.56, and 2.28 mg/m^3) HCCP for 6 hours per day, 5 days per week. Food consumption, clinical chemistry, haematology and ophthalmological effects were not investigated in this study. With regard to histopathological investigations, in the study reports it is not specified how many levels of cross sections were examined on the different tissues and whether the lesions in the tissues could be associated with different epithelial regions.

Rats

Survival rates and mean body weights of exposed rats were similar to those of the controls. No chemical-related clinical findings were observed in male or female rats during the 2-year study. No differences in urinalysis parameters at the 15-month interim evaluation could be attributed to exposure to HCCP. No increase in neoplasm incidences could be attributed to HCCP. Toxicity was limited to the respiratory tract: the incidence of bronchiole and peribronchiolar pigmentation in the lung was increased in male rats at a dose of 2.28 and in female rats from a dose of 0.11 mg/m^3. The incidence of mucosal pigmentation in the nose was increased in male and female rats at doses ≥ 0.11 mg/m^3. The incidence of mucosal pigmentation in the trachea was increased in male rats (female rats not reported) at the dose of 2.28 mg/m^3. The brown pigment observed in the mucosa and submucosa of the respiratory tract was not caused by comparable known respiratory toxicants such as methyl isocyanate, glutaraldehyde and formaldehyde. It appears to be a unique response to this chemical. Lipid peroxidation has been implicated in the pathogenesis of this brown pigment. Whether metabolism of HCCP leads to the generation of intracellular free radicals and peroxides is unknown. HCCP is a highly reactive chemical. It reacts readily with olefinic and aromatic compounds. It also binds to whole blood and plasma and to epithelial lung tissue, extracellular lung lining and bronchiolar Clara cells (NTP, 1994). Exposure to HCCP also caused an increase (not dose-related) in the incidence of squamous metaplasia of the laryngeal epithelium of exposed female rats at all tested doses (not investigated in male rats); the incidences in 0.11 and 2.28 mg/m^3 female rats were significantly higher than that of the controls. Severity of squamous metaplasia was minimal in all exposed and control female rats (**Table 4-29**). In assessing the possible health effects on the respiratory tract, it is known that the interpretation of microscopic observations in the larynx may be difficult due to inconsistent sections as stated by the NTP. However, with regard to HCCP, it is clear from the toxicity studies that the respiratory tract is a target organ. Squamous metaplasia is a consistent finding in both the 2-years and 13-weeks inhalation studies performed by the NTP (NTP, 1994) and should be regarded as an unwanted, and therefore adverse, effect.

In the rat chronic toxicity study, no NOAEC for local effects could be established. The LOAEC for local effects for rats was 0.11 mg/m^3 based on toxicity to the respiratory tract. No systemic effects were reported. Therefore, the NOAEC for systemic effects is equal to or higher than the highest dose tested.

Table 4-29 Summary of a 2-year inhalation study (NTP, 1994).

		Rat, ♂	Rat, ♀	Mouse, ♂	Mouse, ♀
Exposure concentrations		0, 0.11, 0.56, 2.28 mg/m³			
Body weights		similar to controls	similar to controls	high dose lower than controls	high dose lower than controls
2-year survival rates		36/50, 33/50, 45/50, 32/50	28/50, 33/50, 30/49, 30/50	35/50, 33/50, 42/50, 34/50	31/50, 32/50, 30/50, 21/50
Lung	bronchiole pigmentation	0/50, 0/50, 0/50, 49/50	0/50, 25/50, 42/49, 50/50		
	peribronchiolar pigmentation	0/50, 0/50, 2/50, 16/50	3/50, 1/50, 4/49, 27/50		
	mucosal pigmentation			0/49, 2/50, 42/50, 45/50	0/48, 0/50, 27/50, 44/49
Nose	mucosal pigmentation	1/48, 46/50, 48/49, 48/50	0/50, 34/50, 47/49, 48/50	0/50, 45/50, 50/50, 44/50	0/49, 40/50, 48/50, 41/48
	suppurative inflammation			0/50, 0/50, 1/50, 36/50	4/49, 0/50, 3/50, 40/48
Trachea	mucosal pigmentation	0/48, 0/50, 0/48, 5/50		0/50, 29/50, 48/50, 48/50	0/49, 6/50, 43/48, 42/47
Larynx	squamous metaplasia[1]		9/50, 20/50, 15/48, 24/50		
Neoplastic effects		none	none	none	none

[1] Squamous metaplasia of the larynx was investigated in female rats only

Mice

There was a dose-related increase in the incidence of suppurative ovarian inflammation in female mice. The incidences of suppurative ovarian inflammation in the 0.56 and 2.28 mg/m^3 group were significantly greater than that of the controls (0/49, 3/50, 6/50, 17/50). The lesions occurred with marked severity in many of the affected mice. The 2-year survival rate of female mice in the 2.28 mg/m^3 group was marginally lower than that of the controls due to a higher incidence of ovarian inflammation in the 2.28 mg/m^3 female mice. Mean body weights of 2.28 mg/m^3 male (weeks 62 to 103) and female mice (throughout the study) were lower than those of the controls. No clinical findings in male or female mice were attributed to chemical exposure during the 2-year study. There were no chemical-related differences in urinalysis parameters at the 15-month interim evaluation. The incidence of mucosal pigmentation in the lung was increased in male and female mice at doses of ≥ 0.56 mg/m^3. The incidence of mucosal pigmentation in the nose and in the trachea was increased in male and female mice at doses of ≥ 0.11 mg/m^3 (**Table 4-29**). The incidence of suppurative inflammation in the nose was increased in male and female mice at the dose of 2.28 mg/m^3. No increased incidence in neoplasms was found in male or female mice. In the mouse chronic toxicity study, no NOAEC for local effects could be established. The LOAEC for local effects for mice was 0.11 mg/m^3 based on toxicity to the respiratory tract.

With regard to systemic effects, the NTP suggested that the suppurative ovarian inflammation may have been due to the reduced immunity of exposed mice as a result of stress. Furthermore, the NTP stated that this condition was similar to the utero-ovarian infections observed in mice in other NTP studies and was apparently caused by *Klebsiella* species.

For this study, no findings were reported which indicated stress reactions. In addition, it was not reported whether the mice were indeed infected with *Klebsiella* at the start of the

experiment. Suppurative ovarian inflammation occurred in a dose related manner indicating that HCCP may be responsible for this effect. Furthermore, if the mice were indeed infected with *Klebsiella*, it may be that HCCP reduced the immunity of the animals through which they were more susceptible to the effects of *Klebsiella* on the ovaries. Therefore, based on the available data, the NOAEC for systemic effects is established at 0.11 mg/m^3 based on the higher incidences of suppurative ovarian inflammation in the mid and high dose group.

In a separate so called 'stop-exposure' study, groups of male mice (n=50/group) were exposed to HCCP concentrations of 2.28 mg/m^3 for 33 or 66 weeks, or to 5.7 mg/m^3 for 26 or 42 weeks, and then examined at 2 years after the beginning of exposure. Two-year survival rates and mean body weights of 'stop-exposure' groups were similar to that of the controls. No treatment-related clinical abnormalities were observed. Macroscopic and microscopic examination revealed that non-neoplastic respiratory tract lesions were similar to those observed in the above 2-year exposure study. Treatment-related pigmentation and inflammation of the respiratory epithelium were persistent, as indicated by their presence in many mice after recovery periods of 62 to 78 weeks. The incidence and severity of the lesions were related to exposure concentration and duration. This suggests that the pigment could be a reaction product between the chemical and an intracellular component of the respiratory tissues that has a very slow turnover rate, according to the authors of the study. There appears to be a critical burden, below which suppurative inflammation of the trachea and lung does not occur. The critical burden, expressed as a composite unit (concentration x weeks), was estimated at 226 - 237 mg/m^3 x weeks (NTP, 1994).

Dermal

No data are available.

Oral

In **Table 4-30**, a summary of the available oral repeated dose studies is presented.

Table 4-30 Summary of the available oral repeated dose toxicity studies with HCCP.

Exposure period	Species (sex and strain)	Doses (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical effects	Reference
13 weeks (gavage)	F344 rat ♂♀ n=10/sex/dose	0, 10, 19, 38, 75, 150 once daily, 5 days/wk	Systemic: 10 Local: 10 (♀)	Systemic: 19 Local: 19 (♀)	Increased kidney: body weight ratio in males and females Proliferation and inflammatory changes of the epithelia in the forestomach of females	SRI, 1981a; published by Abdo *et al.*, 1984 SRI, 1981b; published by Abdo *et al.*, 1984
	$B6C3F_1$ mouse ♂♀ n=10/sex/dose	0, 19, 38, 75, 150, 300 once daily, 5 days/wk	Systemic: <19 (♀) Local: 19	Systemic: 19 (♀) Local: 38	Increased liver and kidney: body weight ratio in females Proliferation and inflammatory changes of the epithelia in the forestomach of males and females	

Two 13-week oral repeated dose studies were performed by administering HCCP in corn oil by gavage to young F344 rats (10/sex/dose group) at doses of 0, 10, 19, 38, 75, or 150 mg/kg bw and to young $B6C3F_1$ mice (10/sex/dose group) at doses of 0, 19, 38, 75, 150, or 300 mg/kg bw HCCP (SRI, 1981a/b; published by Abdo *et al.*, 1984). The doses were administered once a day, five days a week for 13 weeks. This regime was used to imitate exposure to workers.

Rats

Chemically induced deaths occurred at 150 mg/kg bw in rats (**Table 4-31**). Death, which occurred at lower dosing levels, was considered a gavage error. A significant reduction in mean body weight gain relative to controls was observed in male and female rats receiving ≥38 and ≥75 mg/kg bw, respectively. For male and female rats, the increase in liver:body weight ratio at the dose levels of 10, 19, 38, and 75 mg/kg bw was -23% (decrease), 5%, 18%, 31% and 17%, 4%, 19%, 33%, respectively, compared to the control animals as calculated by the rapporteur. The increase in kidney:body weight ratio for male and female rats at the dose levels of 10, 19, 38 and 75 mg/kg bw was -5% (decrease), 13%, 23%, 39% and 10%, 12%, 30%, 62%, respectively, compared to the control animals as calculated by the rapporteur. Organ:body weight ratios could not be calculated for animals treated at the 150 mg/kg dose level because of excessive deaths prior to the end of the study. Acute kidney tubular necrosis, characterised by proximal tubular dilation, and tubular epithelial changes as cytoplasmic vacuolisation, cytomegaly, karyomegaly and anisokaryosis occurred in male and female rats receiving ≥38 mg/kg bw. HCCP caused proliferation and inflammatory changes of the epithelia in the forestomach of female rats receiving ≥19 mg/kg bw and in male rats receiving ≥38 mg/kg bw.

The endpoints ophthalmology, haematology, clinical chemistry, sensory activity and food consumption were not examined.

Mice

Chemically induced deaths occurred at 300 mg/kg bw in mice (**Table 4-31**). Death, which occurred at lower dosing levels, was considered a gavage error. However, HCCP may have been a contributing factor. A significant reduction in mean body weight gain relative to controls was observed in male and female mice receiving 150 and ≥150 mg/kg bw, respectively. For female mice, the increase in liver:body weight ratio at the dose levels of 19, 38, 75, 150 and 300 mg/kg bw was 8%, 13%, 22%, 33% and 41% compared to the control animals as calculated by the rapporteur. The increase in kidney:body weight ratio for female mice at the dose levels of 19, 38, 75, 150 and 300 mg/kg bw was 19%, 18%, 12%, 22% and 34% compared to the control animals as calculated by the rapporteur. Acute kidney tubular necrosis characterised by proximal tubular dilation, and tubular epithelial changes as cytoplasmic vacuolisation, cytomegaly, karyomegaly and anisokaryosis occurred in female mice receiving ≥ 75 mg/kg bw. This toxic nephrosis was not apparent in male mice. HCCP caused proliferation and inflammatory changes of the epithelia in the forestomach of male and female mice receiving ≥38 mg/kg bw.

The endpoints ophthalmology, haematology, clinical chemistry, sensory activity and food consumption were not examined.

Table 4-31 Dosage and mortality of rats and mice in a 13-week oral study (Abdo *et al.*, 1984).

Dose level (mg/kg bw)	Mortality[a]			
	Male rats	Female rats	Male mice	Female mice
0	3/10 (4, 5)	1/10 (3)	1/10 (2)	0/10
10	1/10 (1)	2/10 (2, 5)	-	-
19	1/10 (3)	2/10 (3)	0/10	0/10
38	1/10 (1)	1/10 (2)	0/10	0/10
75	3/10 (1,3,10)	3/10 (1,3)	0/10	0/10
150	7/10 (1,10,11,12)	5/10 (3,5,8,12)	0/10	0/10
300	-	-	10/10 (1, 2)	3/10 (1, 2)

[a] Number dead/number initially in the group. Numbers in parenthesis indicates week during which deaths occurred.

For the above described studies (SRI, 1981a/b; published by Abdo *et al.*, 1984) with mice and rats, it has to be taken into account that the batch of HCCP used was contaminated with 0.51% hexachloro-1,3-butadiene (HCBD), which is a known nephrotoxin in rodents (WHO, 1994): , a 13 week study of the NTP (1991) for HCBD shows a NOAEL of 0.2 mg/kg bw for induction of tubular degeneration in female mice, corresponding to a dose of 39 mg/kg bw of the batch used in the SRI 1981 study. Therefore, the observed tubular necrosis may be caused by hexachloro-1,3-butadiene. The observed increase in kidney:body weight ratio in female rats (10 mg/kg bw) and in female mice (19 mg/kg bw) in the SRI 1981 study, apparently cannot be caused by this contamination, as the HCBD dose needed for this effect was clearly in excess of the 0.51% dose present (WHO, 1994).

With regard to the 13 week rat study, the female kidney:body weight ratio appeared to be increased at all dose levels compared to the control animals. However, at the lowest dose of 10 mg/kg bw this increase was not statistically significant, nor was the absolute kidney weight increased or the body weight decreased at this dose, or were there histopathological changes in the kidneys. Hence, the NOAEL for systemic effects was established at 10 mg/kg bw for both male and female rats. The NOAEL for local effects was also established at 10 mg/kg bw based on the occurrence of proliferation and inflammatory changes of the epithelia in the forestomach of female rats at dose levels of ≥19 mg/kg bw.

With regard to the 13 week mice study, no NOAEL for systemic effects could be established, based on the toxicological relevant increase in female liver:body weight ratio and kidney:body weight ratio at all dose levels compared to the control animals (LOAEL for systemic effects is 19 mg/kg bw). The NOAEL for local effects was 19 mg/kg bw based on the occurrence of proliferation and inflammatory changes of the epithelia in the forestomach of male and female mice at dose levels of ≥38 mg/kg bw.

4.1.2.6.2 Studies in humans

No data are available.

4.1.2.6.3 Summary of repeated dose toxicity

The repeated dose toxicity of HCCP was tested after inhalation and oral exposure. Although almost none of the repeated dose toxicity studies were performed according to OECD-guidelines and some are rather outdated, the data are considered sufficient to fulfil the Annex VII requirements for repeated dose toxicity. The available data permit the derivation of a N(L)OAEL for repeated dose inhalation and oral toxicity.

No suitable dermal repeated dose toxicity studies are available.

Inhalation repeated-dose toxicity studies with subacute, semi-chronic and chronic exposure to HCCP are available.
The lowest NOAEC for systemic subacute inhalatory toxicity (1.25 mg/m^3) was observed in a 2 week range finding study with rats. At the next higher dose level (5.7 mg/m^3) reduced body weight and mortality were observed. The lowest NOAEC for local subacute inhalatory toxicity (1.25 mg/m^3) was also observed in the 2 week range finding study and based on impaired respiratory function and microscopic changes in lung and nasal area.
The overall NOAEC for local and systemic effects after semichronic exposure is 0.45 mg/m^3 (observed in mice after 13 weeks of exposure). After inhalation 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. In mice and rats, dose levels of ≥ 4.46 mg/m^3 caused decreased body weight gain and lower mean body weights, listlessness, higher absolute and relative lung weights, and severe local effects on nose and respiratory tract (inflammation and in rats also squamous metaplasia of the epithelial lining of the nose). At higher dose levels deaths occurred.
An overall NOAEC for chronic inhalation 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 ≥ 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. The brown pigment observed in the mucosa and submucosa of the respiratory tract of rats and mice appeared to be a unique response to HCCP. It is suggested that the formation of the pigment may have been the result of a direct reaction between HCCP or one of its metabolites and the respiratory tissue. HCCP could, under reductive dehalogenation, form free radicals, which could then react with the respiratory epithelium and causing pigmentation. In addition, it has been shown that the pigmentation is highly persistent. These observations lead to the conclusion that the formation of brown pigment in the respiratory tract should be regarded as an unwanted, and therefore adverse, effect. However, the dose response relationship was not very pronounced. In addition to pigmentation in the respiratory tract, 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.
With regard to systemic effects, concentrations of ≥ 0.56 mg/m^3 caused higher incidences of suppurative ovarian inflammation in mice in the 2-year chronic study by NTP (1994). Suppurative ovarian inflammation occurred in a dose related manner. In the semi-chronic (30 weeks) inhalation toxicity study conducted by Clark *et al.* (1982) lymphocyte suppression and reduced spleen weight were observed. Male rats exposed to 6.34 and 1.58 mg/m^3 HCCP had significantly higher mean erythrocyte counts and absolute numbers of neutrophils, and significantly lower percentage lymphocyte counts than control animals. The mean absolute

numbers of lymphocytes were lower in females at the exposure level of 6.34 mg/m^3. At the end of the recovery period, male mean spleen weights adjusted for terminal body weight were significantly decreased at the exposure levels of 6.34 and 1.58 mg/m^3.
Based on these immunological related effects of HCCP, the NOAEC for systemic effects after chronic exposure to HCCP derived from the 2-year chronic study (NTP, 1994) is 0.11 mg/m^3.

One oral repeated dose toxicity study with HCCP was available. In this 13 week oral (gavage) toxicity studies with rats and mice, the local and systemic NOAEL for rats was 10 mg/kg bw/day based on the toxicological relevant dose related increase in male and female kidney:body weight ratio from 19 mg/kg bw/day onwards. No systemic NOAEL could be established for mice, based on the toxicological relevant increase in female liver:body weight and kidney:body weight ratio at all dose levels compared to the control animals (LOAEL is 19 mg/kg bw).
Based on the occurrence of proliferation and inflammatory changes of the epithelia in the forestomach of female rats and male and female mice, the local NOAELs were 10 and 19 mg/kg bw/day for rats and mice, respectively.

Remark with regard to the NOAEC for inhalation exposure:
It is concluded that the suppurative ovarian inflammation is induced by HCCP, because there clearly is a dose-response relationship, irrespective of whether the animals were infected or not (note that an infection with *Klebsiella* was not reported) supported by immunological effects in other studies, resulting in a NOAEC of 0.11 mg/m^3. However, no such effects were observed in the other semi-chronic studies, even up to high exposures as 6.34 mg/m^3 in the 30 weeks rat study by Clark *et al* (1982). Also, it is not clear whether an animal model possibly infected with *Klebsiella* is relevant to humans. In case suppurative ovarian inflammation is considered to be (mainly) due to infection, the next lowest systemic NOAEC value will be 0.56 mg/m^3, based on decreased mean body weights of male (weeks 62 to 103) and female mice (throughout the study) exposed to 2.28 mg/m^3 (NTP, 1994).

With regard to classification of HCCP for repeated dose toxicity, the available inhalation studies show that HCCP mainly has a local effect. The longest studies are the chronic studies. The limits of classification (2 year) are 0.031 mg/l (0.25/8) for Xn; R48/20 and 0.0031 mg/l for T; R48/23. At 0.00228, which is below the limit for T; R48/23, increases in inflammations of the ovaries (with related early death) and suppurative inflammation of the nose (mice, NTP, 1994) and squamous metaplasia of the larynx (rat, NTP, 1994) were seen. The respiratory tract effects in mice were not reversible. Higher dose levels were not tested in the chronic studies but mortality was increased at dose levels of 0.0045 mg/l in the 90-day mouse study. This dose level is clearly below the limit for T; R48/23 for a 90-day study and just above the limit for a 2-year study. Classification with T; R48/23 is proposed. Mortality was seen in the 13-week studies at dose levels of 0.0045 mg/l and above which is below the lowest inhalatory LC_{50} of 0.018 mg/l, indicating some accumulation of the substance or the effects.

4.1.2.7 Mutagenicity

In **Table 4-32**, the results of the *in vitro* and *in vivo* mutagenicity studies are summarised.

Table 4-32 Summary of the available mutagenicity studies.

Test, species or indicator cells	Method and endpoint	Metabolic activation[1]	Solvent	Result	Reference	Suitable for hazard assessment Yes/No	Remarks
Indicator tests							
B: differential killing *Bacillus subtilis* H17 and M45	D Preincubation	-/+ S9	DMSO	positive	Matsui *et al.*, 1989	Y	-
Mc *in vitro* cell transformation assay Mouse BALB/3T3 cells	Endpoint: miscellaneous	-	DMSO	*	Litton Bionetics, 1977	N	A preliminary cytotoxicity test was performed but not reported. As such, the relevance of the concentration range tested could not be verified.
Bacteria, gene mutation							
Escherichia coli K12 (343/113) *Salmonella typhimurium* TA1535, TA1538	GM: different types of back- and forward mutations Liquid incubation	+ S9	not reported	negative	Goggelmann *et al.*, 1978, Bonse and Goggelmann, 1977, Greim *et al.* 1977	Y	
Salmonella typhimurium TA 98, TA 100, E. coli PQ 37	GM	-/+ S9		*	Raabe *et al.* 1993	N	Only abstract available
Salmonella typhimurium TA98, TA100, TA1535, TA1537	GM Ames test, plate incorporation	-/+ S9	ethanol	negative	Hoechst, 1978	Y	Tested up to toxic dose levels
Salmonella typhimurium TA98, TA100, TA1535, TA1537	GM Ames test, preincubation	-/+ S9	DMSO	negative	NTP, 1994 (Haworth et al 1983)	Y	
Mammalian cells in vitro							
Mouse cell line L5178Y	GM TK assay	-/+ S9	DMSO	negative	Litton Bionetics, 1978a	Y	
Epithelial liver cells (long-term cultures from rat liver)	GM HPRT test	-	NS	* (negative)	Williams, 1978, Williams, 1980	N	No further details
Hepatocyte primary culture (adult rat liver)	D UDS test	-	NS	* (negative)	Williams, 1978, Williams, 1980	N	No further details

Test, species or indicator cells	Method and endpoint	Metabolic activation[1]	Solvent	Result	Reference	Suitable for hazard assessment Yes/No	Remarks
Chinese hamster ovary (CHO) cells	D SCE test	-/+ S9	DMSO	-S9: (weakly) positive +S9: weakly positive	NTP, 1994 (Galloway *et al.*, 1987)	Y	
Rat liver (RL4) cells	CA	NS	NS	* (negative)	Brooks *et al.* 1983	N	Only citation available
Chinese hamster ovary (CHO) cells	CA	-/+ S9	DMSO	-S9: weakly positive +S9:(weakly) positive	NTP, 1994 (Galloway *et al.*, 1987)	Y	
Drosophila melanogaster							
Sex linked recessive lethal mutation	GM feeding and injection	NA	ethanol	negative	NTP, 1994; Zimmering *et al.*, 1985; Mason *et al.*, 1992	Y	
Mammals							
Micronucleus test B6C3F$_1$ mice, peripheral erythrocytes	CA 13 week inhalation study	NA	NA	negative	NTP, 1994	Y	Test design included a maximally tolerated HCCP dose (MTD)
Dominant lethal test CD-1 mice, males	CA daily p.o. (gavage) for 5 days	NA	DMSO	*	Litton Bionetics, 1978b	N	no full report available

[1] Test conducted with (+) and/or without (-) the addition of a metabolic activation system (S9-mix)

*: study not suitable for hazard assessment

Endpoints: D, primary DNA damage; GM, gene mutations, CA, chromosome aberrations; M, miscellaneous

NS: not specified

NA: not applicable

4.1.2.7.1 Studies *in vitro*

HCCP diluted in DMSO was examined for differential killing with and without S9 activation in two strains of *Bacillus subtilis* differing in DNA repair capacity, i.e., the rec+ (H17) and rec- (M45) strains (Matsui *et al.*, 1988). Differences in the 50% survival concentrations of the rec- and rec+ assays were used as indicator for possible DNA damaging capacity effects of HCCP. HCCP showed DNA damaging effects in the absence and in the presence of a metabolic activation system.

The ability of HCCP to induce malignant cell transformation was evaluated in BALB/3T3 cells *in vitro* (Litton Bionetics, 1977). The cells were exposed for 48 hours to the controls and several concentrations of HCCP (0.01, 0.02, 0.039, 0.078, and 0.156 nl/ml in DMSO). The plates were then incubated an additional 3-4 weeks, stained, and examined for the presence of foci. A preliminary cytotoxicity test was performed but not reported. As such, the relevance of the concentration range tested could not be verified. The results did not indicate transformation of the cells due to the administration of HCCP.

HCCP was examined for induction of different types of gene mutations in *Escherichia coli* K12 (343/113) and *Salmonella typhimurium* strains TA 1535 and 1538 in a liquid *in vitro* system (Goggelmann *et al.*, 1978). The bacteria were exposed to two concentrations of HCCP (2.7×10^{-3} and 2.7×10^{-4} M) in the presence but not in the absence of a mouse metabolic activation system. The solvent used was not reported. Concentrations above 10^{-3} M were toxic for the bacteria. No mutagenicity was observed in the presence of the metabolic activation system under the conditions of this study.

HCCP dissolved in ethanol was examined in the Ames test (plate incorporation) using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 as indicator strains and S9-mix prepared from Aroclor-induced rat liver S-9 for metabolic activation. The concentration ranges tested amounted to 0.00004-0.004 and 0.00004-0.010 µl/plate without and with addition of S9-mix respectively. In the absence of S-9 mix the high HCCP doses were clearly toxic for the bacteria. In the presence of S-9 mix signs of toxicity were restricted to a slight decrease in number of revertant colonies at the two highest dose levels. HCCP exposure did not result in treatment-related increases in revertants with any of the indicator strains. It is concluded that HCCP is not a bacterial mutagen under the conditions of this study (Hoechst, 1978).

HCCP dissolved in DMSO was tested by a preincubation protocol using the tester strains TA98, TA100, TA1535, and TA1537 in the presence or absence of rat and hamster liver S9 (NTP, 1994, Haworth *et al.* 1983). Five doses of HCCP were administered ranging from 0.03 to 100 µg/plate. HCCP was not mutagenic in the strains tested under the conditions of this study. Higher levels could not be tested due to excessive toxicity.

HCCP, dissolved in DMSO (1%), was evaluated for gene mutations using L5178Y mouse lymphoma cells at concentrations up to 1.25 µl/l with and without mouse liver S9 (Litton Bionetics, 1978a). It was concluded that HCCP was not mutagenic under the conditions of this study. It should be noted, however, that the concentration range used did not range from high (10-20% survival) to low toxicity, only limited toxicity was observed at the highest concentration tested. Considering the steep toxicity range this is acceptable.

HCCP was examined in a Sister Chromatid Exchange (SCE) test using Chinese Hamster Ovary (CHO) cells as indicator cells (NTP, 1994). The concentration ranges tested were 0.016 - 0.50 µg/ml and 0.16 to 5.0 µg/ml DMSO in the absence and presence of a metabolic activation system respectively. Without S9-mix, HCCP was considered weakly positive to positive. In the presence of S9 mix HCCP was considered weakly positive. No clear dose-response relationship was evident (NTP, 1994). In the highest dose less than the desired 200 cells were available due to clear toxicity, with and without S9.

The ability of HCCP to induce chromosomal aberrations was tested in Chinese hamster ovary cells (NTP, 1994). Concentrations ranging from 0.5 - 3.0 µg/ml DMSO were tested in the absence of S9. In the presence of S9 the concentrations ranged from 1.6 – 10 µg/ml DMSO in the first assay and from 3 – 7.5 µg/ml in the repeat assay. The effects of HCCP to cells without S9 were considered weakly positive. In the presence of S9, HCCP was weakly positive in the first test and positive in the repeat assay. At the highest doses tested, i.e., 3 µg/ml without S9 and 10 µg/ml with S9, due to chemical toxicity less than the desired numbers of 200 cells per dose level were available for scoring.

4.1.2.7.2 Studies *in vivo*

Drosophila melanogaster Canton-S wildtype males not older than 24 hours were placed in feeding vials with 40 ppm HCCP in 10% ethanol and 5% sucrose (NTP, 1994; published by Zimmering *et al.*, 1985). Every 24 hours, mortality was recorded and remaining flies were shaken over to vials with fresh feeding mixture. After 72 h of exposure, the males were removed and mated. Males to be injected were held on regular food for 1-3 days, injected with 0.7% NaCl or peanut oil containing 2000 or 3000 ppm HCCP, observed for 24 hours for recovery, and then mated. The following parameters were observed; induced LD (calculated as the percent of chemically treated males that died minus the percent of solvent-treated males that died during treatment), percent sterility, number of sex-linked recessive lethals in the brood, and the total number of X-chromosomes tested. It was concluded that HCCP exposure did not result in induction of recessive lethal mutations in male *Drosophila melanogaster* either upon feeding or upon injection. Repetition of the above study with 10 ppm in the diet or 900 ppm in 0.7% NaCl by injection showed no genotoxic effects either (NTP, 1994; Mason *et al.*, 1992).

The frequency of micronucleated polychromatic erythrocytes (micronucleated PCEs) in peripheral blood was determined in B6C3F1 mice (10 animals/sex/dose group) exposed to atmospheres containing 0, 0.01, 0.05, or 0.2 ppm (equal to 0, 0.11, 0.56, or 2.28 mg/m^3) HCCP, 6 hours per day, 5 days per week, for 13 weeks (NTP, 1994). The frequency of micronucleated cells was scored in 2000 PCEs/animal and in 10,000 normochromatic erythrocytes (NCEs)/animal. The mice used for the screening of micronucleated PCEs and NCEs formed a part of a mice carcinogenicity study with HCCP. Dose selection for the carcinogenicity study was based on findings in a 13-week mice inhalation study, i.e., 100% mortality in 1 and 2 ppm groups, lower mean body weights, and chemical-related respiratory tract lesions at concentrations ≥ 0.4 ppm.
The frequency of micronucleated erythrocytes and the percentage of PCEs among total erythrocytes (NCE+PCE) were not affected by treatment. There were no statistically significant differences between control and different dose groups (NTP 1994). It is concluded that HCCP did not induce micronuclei in erythrocytes of mice exposed by inhalation up to maximally tolerated HCCP doses.

In a mouse dominant lethal test by Litton Bionetics (1978b) four groups of 10 male CD1-mice were given daily doses of 0, 0.1, 0.3, or 1.0 mg/kg bw HCCP in DMSO for 5 consecutive days by oral intubation. After a 2-day rest period following treatment each male was housed with two virgin females for 7 days, which were replaced weekly with two fresh virgin females for a total period of 7 weeks. Females were examined for dead and life implants, resorption sites and total implants. Selection of dose levels was based on mortality findings in preceding studies, the high dose level representing the calculated LD_5. The results did not point to treatment-related dominant lethality. In the main test no treatment-related adverse effects were reported.

4.1.2.7.3 Summary of mutagenicity

The data submitted are considered acceptable with regard to the basic requirements as specified in Annex VIIA of Directive 67/548/EEC.

Based on the data available, it appears that HCCP is not a bacterial mutagen and does not induce gene mutations in mammalian cells *in vitro*. In cytogenetic assays with cultured Chinese hamster ovary cells an induction of both SCE and chromosomal aberrations with and without S9 was observed. Although no cell cycle delay was evident in either of these studies, toxicity was a problem in the chromosome aberration test where fewer than the desired number of 200 cells could be scored at the positive highest doses tested, with and without S9. In the SCE test, no clear dose-response relationship was evident.
No genetic effects were observed in *in vivo* studies. No induction of sex-linked recessive lethal mutations was noted in germ cells of male *Drosophila Melanogaster* treated with HCCP by feeding or injection. No micronucleated erythrocytes were found in male and female mice after 13 weeks of inhalation exposure to various doses of HCCP including a maximally tolerated dose. From this test it is unclear, however, whether HCCP has reached the bone marrow and therefore no clear conclusion can be drawn from this individual study on the mutagenicity of HCCP. However, as no tumours were formed in any of the exposed organs, including the site of first contact, i.e. the respiratory tract, under the conditions of maximum tolerated dose levels in chronic inhalation studies in both rats and mice, HCCP is considered not to have mutagenic activity under *in vivo* conditions.

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

<u>*In vivo* studies</u>
Inhalation
In a 2-year chronic inhalation toxicity study with male and female F344/N rats and male and female B6C3F1 mice tested at dose levels of 0, 0.11, 0.56 and 2.28 mg/m^3 HCCP, no increased incidence of neoplasms was found (NTP, 1994). For a description of the study see section 4.1.2.6: Repeated dose toxicity.

Dermal
No data available.

Oral
No data available.

4.1.2.8.2 Studies in humans

Several epidemiological studies have been reported on workers engaged in the manufacture of HCCP or in the use of HCCP as an important precursor of chemicals of organochlorine pesticide manufacture, such as chlordane, heptachlor, aldrin, or dieldrin. Only one of these studies dealt with workers who had been engaged in the manufacture of HCCP (Buncher *et al.*, 1980). The other reported epidemiological studies dealt with workers who might have been exposed to HCCP during the production of 'cyclodiene' pesticides chlordane, heptachlor, and aldrin and dieldrin (Brown *et al.*, 1980; Shindell and Associates, 1980 and 1981; Shindell and Ulrich (1986); Wang and MacMahon, 1979).

Shindell and Associates (1980) studied a cohort of 783 current and former workers who had been employed at the Velsicol Chemical Corporation plant at Marshall, Illinois, between 1946 and 1979. Of the study cohort, 97.3% of the males and 98.8% of the females were located and data on morbidity and mortality obtained. The purpose of the study was to evaluate the overall health status of all employees who had been present during the manufacture of chlordane for 3 months or more. There were no significant differences in mortality rates between these employees and the overall USA population. Among the white male employees, the number of deaths from cancer, stroke, trauma and other unknown causes all appear to be somewhat lower than would be expected. No deaths were reported among the small number of non-white male employees in the study cohort. There was, thus, no evidence of any long-term latent effect on health related in any way to employment at the Velsicol Chemical Corporation plant in Marshall for the thirty-four year period in which it has been engaged in the production of chlorinated hydrocarbon insecticides. Shindell and Ulrich (1986) updated their 1980 data set with additional worker data.

Concomitant with the study performed by Shindell and Associates (1980), Wang & MacMahon (1979) conducted a retrospective mortality study of workers employed at the Marshall and Memphis plants, where chlordane and heptachlor were manufactured between 1946 and 1976. They studied 1403 males who had worked at the plants for more than 3 months. There were 113 observed deaths compared with 157 expected deaths, giving a standardised mortality ratio (SMR) of 72. Among the various causes of death, the two highest SMRs were 134 for lung cancer and 183 for cerebrovascular disease, but only the latter figure was statistically significant ($P<0.05$). There was one death from liver cancer. The excess mortality due to cerebrovascular disease was not related to the duration of exposure or to the latency period, and occurred only after termination of employment.

Shindell and Associates (1981) completed another epidemiological study for the Velsicol Chemical Corporation at its Memphis, Tennessee, plant covering the period 1952-1979. This coincided with the manufacture of heptachlor, a pesticide made from HCCP. The researchers studied 1115 current and former employees who had worked for 3 months or more (of the study cohort, 93.1% of the males and 90.0% of the females were located and data on morbidity and mortality obtained). The data indicate that overall mortality was lower (but not significantly) in the male employees than that expected in the comparable segment of the USA population as a whole. This was true also in the case of deaths from heart disease and cancer. There was, thus, no evidence of any long-term latent effect on health related in any

way to employment at the Velsicol Chemical Corporation at its Memphis, Tennessee, for the twenty-eight year period in which it has been engaged in the production of chlorinated hydrocarbon insecticides.

Buncher *et al.* (1980) studied the mortality of workers at a chemical plant that produced HCCP. They examined 341 workers (287 male and 54 female), together with their health records, who had worked at the plant for at least 90 days between 1 October 1953 and 31 December 1974. Their vital status was determined through 1978. The expected numbers of deaths, based on the USA population and specific for sex, age, and calendar year, were calculated. The SMR for all causes of death was 69. Deaths caused by specific cancers, all cancers, and diseases of the circulatory and digestive systems were also fewer than expected. The authors noted that the time that had elapsed since the initial exposure (25 years at most) reduced the power of the study to detect cancers that may have a 10-40 year latent period.

Brown *et al.* (1980) conducted a retrospective cohort study to examine the mortality of workers employed in the manufacture of the chlorinated hydrocarbon pesticides, chlordane, heptachlor, DDT and aldrin/dieldrin/endrin. Four manufacturing plants were selected for study, and each cohort included all workers employed for at least 6 months prior to January 1964. The entire group study group consisted of approximately 2100 individuals. Vital status ascertainment for these cohorts ranged from 90% to 97% complete, the cut-off date for follow-up was December 31, 1976. The standardised mortality ratio (SMR) for all causes in each cohort is below expected (100), ranging from 66 to 82, probably reflecting the healthy worker effect. For all malignant neoplasms, the SMRs range from 68 to 91 and for respiratory cancer from 55 to 132. In the aldrin/dieldrin/endrin cohort, pneumonia and other respiratory diseases were significantly above that expected. The authors recommended that these causes of death need to be examined in more detail. They recommended that the cohorts have to be followed for several more years and the mortality patterns re-examined. In general, there are too few deaths in this study to make any meaningful conclusions.

4.1.2.8.3 Summary of carcinogenicity

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. In addition, several epidemiological studies were performed on workers in manufacturing plants where HCCP was used and/or produced among other chemicals. The studies did not give indications for a difference in the incidence of cancer cases between exposed workers and non-exposed workers compared to the overall USA population. However, information specific to HCCP exposure, either qualitative or quantitative, was not available in any of these studies. In addition, study populations were relatively small, and observation times relatively short. Therefore, the studies are of limited value and do not provide conclusive evidence.

Based on the results in genotoxicity tests, the carcinogenicity tests with rats and mice, and the available epidemiological studies it is concluded that HCCP is of no concern with respect to carcinogenic activity.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Effects on fertility

Inhalation

In two 13-week semichronic inhalation toxicity studies performed by NTP (1994) 6 groups of young F344/N rats and $B6C3F_1$ mice (10/sex/dose group) were administered 0, 0.45, 1.67, 4.46, 11.14, and 22.28 mg/m^3 HCCP for 6 hours per day, 5 days per week. Additional rats and mice were exposed to 0, 0.45, 4.46, and 22.28 mg/m^3 HCCP for the same period and evaluated for differences in clinical pathology parameters (see section 4.1.2.6.1: Studies in animals - inhalation). All rats in the 11.14 and 22.28 mg/m^3 groups died during the first 4 weeks of the study, all mice in the 22.28 groups died during the first week of exposure, and mice in the 11.14 mg/m^3 groups died within the first five weeks of exposure. Histopathological examination of the epididymis, mammary gland, prostate gland, testis, ovary and uterus of all control animals, all animals dying before the end of the study and all animals who survived and were exposed to 4.46 mg/m^3 HCCP was performed. If a lesion was observed in an organ, that organ was examined at the next lower dose level until a dose level was found without the lesion. Histopathological examination revealed no treatment related effects of the epididymis, mammary gland, prostate gland, testis, ovary and uterus. It should be noted that due to early death of the animals exposed to 11.14 and 22.28 mg/m^3 the exposure duration at these concentrations may have been too short for effects to become manifest.

In a 14-week inhalation study by Huntingdon Research (1980a, published by Rand *et al.* (1982b) Sprague-Dawley rats (n=40/sex/dose) and Cynomolgus monkeys (n=6/sex/dose) received whole-body exposure to HCCP at concentrations of 0, 0.11, 0.57, or 2.28 mg/m^3 (0, 0.01, 0.05, and 0.2 ppm), 6 hours/day, 5 days/week (see section 4.1.2.6.1: Studies in animals - inhalation). Histopathological examination of the ovaries, uterus, seminal vesicles, prostate and testes was performed for 5 male and 5 female rats after 4 and 8 weeks of exposure and for 12 male and 12 female rats and 6 male and 6 female monkeys after 13 weeks of exposure. No relevant treatment related effects on these organs were observed.

In a semi-chronic inhalation toxicity study conducted by Shell (Clark *et al.*, 1982), Wistar rats were exposed for 30 weeks. The animals were divided in groups (18/sex/dose group) and exposed to 0, 0.06, 0.14, and 0.56 ppm (equal to 0.68, 1.58, and 6.34 mg/m^3) HCCP for 6 hours per day, for 5 days per week either or not followed by a recovery period (9/sex/dose group) of 14 weeks (see section 4.1.2.6.1: Studies in animals - inhalation). Mean testes weights adjusted for terminal body weight were significantly increased at 30 weeks at the dose of 1.58 mg/m^3, and increased at 44 weeks (recovery group) at the dose of 6.34 mg/m^3. The ovaries, uterus, mammary glands, testes and prostate of all animals surviving to the respective scheduled terminations and of animals dying or killed before their scheduled death, unless this was precluded by autolysis, were examined histopathological. The seminal vesicles were only examined if indicated by clinical or pathological findings. The weight change of the testes was not supported by histopathological changes and no weight change in absolute testes weight was reported. Therefore, this finding was probably not of biological relevance. In addition, the other reproduction organs showed no histopathologically effects.

In two 2-year chronic inhalation toxicity studies performed by NTP (1994) 4 groups of 60 male and 60 female F344/N rats and $B6C3F_1$ mice of 6-7 weeks old were administered 0, 0.11, 0.56 and 2.28 mg/m^3 HCCP for 6 hours per day, 5 days per week (see section 4.1.2.6.1: Studies in animals - inhalation). Histopathological examination of the epididymis, seminal vesicles, prostate gland, testis, ovary, uterus and mammary glands of all control animals, all female animals dying before the end of the studies and all rats and male mice exposed to 2.28 mg/m^3 HCCP revealed no treatment related effects on these organs. There was, though, a dose-related increase in the incidence of suppurative ovarian inflammation in female mice. The incidences of suppurative ovarian inflammation in the 0.56 and 2.28 mg/m^3 groups were significantly higher than in controls (0/49, 3/50, 6/50, 17/50). The lesions occurred with marked severity in many of the affected mice and were a likely cause of early death. The suppurative ovarian inflammation was, however, only seen after 2 years exposure. It was not seen at the interim section of 10 females at the highest dose after 15 months. Also, no effects were seen on the ovaria in the 13-week inhalation toxicity study in mice. This indicates that the suppurative ovarian inflammation is an effect only seen in aged mice and unlikely to be observed in a standard fertility study. Taking into account that quantitative cytological analyses of aging C57BL/6J mouse ovaries revealed that the populations of primordial and growing follicles were nearly exhausted by 13-14 months, the average age of ovulatory failure (Gosden *et al.*, 1983), the ovarian inflammation is unlikely to affect the female fertility because the fertility is already low or absent beyond 15 months. Therefore, the observed suppurative ovarian inflammation is not considered biologically relevant when evaluating effects of HCCP on fertility.

Oral

In two 13-week oral repeated dose studies performed by SRI (1981a/b) and published by Abdo *et al.* (1984), HCCP was administered in corn oil by gavage to young F344 rats (10/sex/dose group) at doses of 0, 10, 19, 38, 75, or 150 mg/kg bw and to young $B6C3F_1$ mice (10/sex/dose group) at doses of 0, 19, 38, 75, 150, or 300 mg/kg bw HCCP. The doses were administered once a day, five days a week for 13 weeks (see section 4.1.2.6.1: Studies in animals - oral). This regime was used to imitate exposure to workers. Histopathological examination of seminal vesicles, prostate and testes or mammary glands, ovaries and uterus was performed at dose levels of 0, 75 and 150 mg/kg bw in rats and 0, 150 and 300 mg/kg bw in mice and on all interim death animals. No relevant treatment related effects were reported.

Dermal

No data are available.

4.1.2.9.2 Developmental toxicity

Studies in animals

Oral

Chernoff and Kavlock (1982 and 1983) tested 28 compounds, including HCCP, by an *in vivo* screening procedure. Sixteen pregnant CD-1 mice (Charles River) received HCCP by gavage in doses of 0 or 45 mg/kg bw/day on gestational day 8-12. It should be noted that according to OECD guideline 414 the animals should be exposed from 6-15 of gestation. There were no differences in maternal weight gain, number of live offspring or average weight between the

HCCP-treated animals and controls. No other endpoints were reported. Using a similar approach, Gray *et al.* (1983) found no effects of HCCP on postnatal growth and behaviour of mice.
Gray and Kavlock (1984) extended the observation period proposed by Chernoff and Kavlock (1982, 1983) to 250 days to determine whether neonatal weight reductions, caused by some of the 28 compounds (but not by HCCP), persisted throughout life and whether other serious abnormalities or mortality resulted from exposure to one of the 28 compounds. Again, no treatment related effects were observed on survival rate, and no macroscopic and microscopic abnormalities were found in the liver, testes, seminal vesicles, or right kidney of male animals exposed to HCCP compared to controls. Gray *et al.* (1986) extended the study of Gray and Kavlock (1984) with studying locomotor activity of the offspring. HCCP had no effects on the locomotor activity. The NOAEL for both maternal and developmental toxicity was 45 mg/kg bw/day, the highest dose level tested.

The teratogenic potential of HCCP (98%) was evaluated in CF-1 mice and NZW rabbits (Murray *et al.*, 1980). In a range finding study, female CF-1 mice (5/dose) and female New Zealand white rabbits (5/dose) were administered 0, 25, 75, 250 or 500 mg HCCP/kg bw/day by gavage. HCCP was given to mice from days 6 to 15 and to rabbits from days 6 to 18 of gestation. All mice and rabbits given 500 mg/kg bw/d died before day 13 of gestation: signs of toxicity in both species included diarrhoea, lethargy, and severe weight loss. At 250 mg/kg bw/d, 3/5 mice and 4/5 rabbits died. At 75 or 25 mg/kg bw, the only sign of maternal toxicity was weight loss in rabbits given 75 mg/kg bw/day. In the main study, bred mice (number unspecified) were given 5, 25, or 75 mg HCCP/kg bw per day by gavage from days 6 to 15 of gestation. Additional mice were given cottonseed oil alone to serve as the vehicle control group. Rabbits (number unspecified) were given the same dose levels by gavage from gestation days 6 to 18. Mice and rabbits were killed with carbon dioxide on days 18 and 29 of gestation, respectively. Numbers of living, dead, and resorbed foetuses were recorded. All foetuses were weighed, measured (length), sexed, and examined for external alterations and cleft palate. One-third of the foetuses from each litter were examined immediately by dissection under a stereomicroscope for soft-tissue alterations. All of the foetuses in each litter were examined for skeletal alterations. It should be noted that according to OECD guideline 414 each rabbit foetus should be examined by careful dissection for visceral abnormalities and not 1/3 of the foetuses from each litter. A decrease in the number of litters was observed for all HCCP-treated rabbits and mice. Mice had 33, 23, 29, and 22 litters with 374, 252, 325, and 249 foetuses for the control and increasing dose groups, respectively. Rabbits had 24, 16, 12, and 13 litters with 171, 95, 78, and 77 foetuses for the control and increasing dose groups (0, 5, 25, 75 mg/kg bw/day), respectively. Thus, no dose-effect relation was observed for this effect. Furthermore, the number of mated mice and rabbits per group was not presented and, therefore, this effect cannot be taken into account with regard to developmental toxicity. No maternal toxicity or embryotoxicity was observed in mice given HCCP. In rabbits, significant toxicity (severe diarrhoea and death) occurred in dams given 75 mg/kg bw/day, but little evidence of embryotoxicity was noted. Compared to the control animals, only one minor skeletal variant occurred significantly more often among the offspring of rabbits given HCCP; specifically, the proportion of foetuses with 13 ribs was significantly increased among the offspring of rabbits given 75 mg/kg bw/day; the incidence of 13 rib(s) among foetuses was 58/171, 33/95, 33/78 and 44/77 at 0, 5, 25 and 75 mg/kg bw/day, respectively (the normal number of pairs of ribs in the rabbit is 12 or 13). The authors concluded that HCCP was not teratogenic at the dose levels tested. However, there was an almost two-fold increase over controls in the proportion of foetuses with 13 ribs at 75 mg/kg bw/day. Therefore, the rapporteur is of the opinion that the skeletal variant should be regarded as a treatment related

effect and conclude that in this study the NOAEL for both maternal and developmental toxicity is 25 mg/kg bw/day (rabbits). The NOAEL for mice for both maternal and developmental toxicity is 75 mg/kg bw/day in this study.

In another study, pregnant Charles River CD rats were used to evaluate the teratogenic potential of HCCP (98.2%) (IRDC, 1978b and published by Root *et al.* (1983)). The compound was administered by gavage at dosage levels of 3, 10, and 30 mg/kg bw per day from days 6 through 15 of gestation (25 pregnant rats/dose). A control group received the vehicle, corn oil, at 10 ml/kg bw per day. During gestation, the females were observed for clinical signs, for mortality, and changes in body weight. Caesarean sections were performed on gestation day 20. The number of viable and nonviable foetuses, early and late resorptions, corpora lutea, and total implantations were recorded. The foetuses were weighted and sexed. Examinations for external, soft tissue and skeletal anomalies and variations were performed. There were no differences in appearance or behaviour in any of the rats attributable to treatment with HCCP at 3 or 10 mg/kg bw per day when compared to the rats in the control group. Staining of the anogenital area was seen in all treated groups, however, it was of longer duration in the rats in the 30 mg/kg bw dosage group. Survival was 100% for all groups. Mean maternal body weights were comparable for rats in the treated groups and the control group. There were no biological meaningful differences in the mean number of implantations, corpora lutea, live foetuses, post implantation losses, mean foetal body weights, male to female sex ratio and the number of litters with malformations between the treated groups and the control group. Developmental and teratogenic foetal variations were comparable for the treated groups and the control group. The NOAEL for both maternal and developmental toxicity was 30 mg/kg bw/day, the highest dose tested.

Studies in humans
No data are available.

4.1.2.9.3 Summary of toxicity for reproduction

Although no study was performed according to OECD-guidelines (some studies were performed before the OECD guidelines came into force), the data are sufficient to fulfil the Annex VII requirements for reproductive toxicity.

Effects on fertility

Inhalation
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 for 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 treatment related effects were observed. Therefore, the inhalation NOAEC for fertility effects was established at 6.34 mg/m^3.

Oral
In one 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 (highest dose tested) for rats and 300 mg/kg bw (highest dose tested) for mice.

Dermal
No data are available.

Developmental toxicity

Inhalation
No data are available.

Oral
In oral teratogenicity studies with mice, rats, and rabbits, no teratogenic effects were found. No maternal or embryotoxicity was observed in mice up to 75 mg/kg bw/day. In rabbits, 75 mg/kg bw/day caused significant maternal toxicity. Little evidence of embryotoxicity was observed after treatment with 75 mg/kg bw/day. Compared to the control animals, 13 ribs were seen more frequently among the foetuses of rabbits given 75 mg/kg/day (the normal number of pairs of ribs in the rabbit is 12 or 13). In all groups of rats staining of the anogenital area was observed after exposure to 3, 10, and 30 mg/kg bw per day HCCP from days 6 through 15 of gestation, however this effect was more significant at 30 mg/kg bw/day. No other treatment related effects were observed up to a dose of 30 mg/kg bw/day. The overall NOAEL for maternal and developmental toxicity is concluded to be 25 mg/kg bw/day (rabbits).

Dermal
No data are available

4.1.3 Risk characterisation [6]

4.1.3.1 General aspects

The human population may be exposed to HCCP at the workplace and indirectly via the environment.

Data on excretion via urine and faeces strongly indicate that rats and mice were capable of extensively degrading HCCP when applied orally, and that the metabolites formed were of a nature that favoured faecal elimination. The exact oral absorption figure cannot be derived, however, because it is not possible to discriminate between two options, which may both occur:
- HCCP is metabolised in the liver, the metabolites return to the intestine via the bile and are then excreted in the gut, and
- HCCP is largely metabolised in the gut, probably by microorganisms, to products which are not absorbed but voided in the faeces.

In addition, studies showed that HCCP became bound to faecal homogenates, and intestinal contents. Thus, from the available data on oral absorption only the minimum level of systemic availability, and consequently the minimal amount of oral absorption can be derived, i.e. via summing up recovered radiolabel in urine, tissues, and expired air: it ranges from approximately 18% to 39% after a single gavage application (7 - 61 mg/kg bw dose), and from 5.5% to 12.2% when applied via the diet for 30 days (0.07 to 1.67 mg/kg bw/day for rats, 0.16 to 4.1 mg/kg bw/day for mice). Both with single and repeated administration, there was no clear relationship between percentage absorption and dose.
The nature of the radioactivity excreted in urine was examined for possible metabolites. The results suggest that at least four metabolites of HCCP were present. These metabolites have not been identified and characterised.
From the inhalation studies, it is concluded that complete respiratory absorption cannot be excluded. For the risk characterisation, 100% inhalation absorption is assumed (worst-case estimate).
HCCP is absorbed via the dermal route as is indicated by toxic responses reported in acute dermal toxicity studies. Absorption data on dermal studies is, however, lacking. In general, it is assumed that dermal absorption will not be higher than oral absorption. However, it is shown that HCCP is extensively metabolised after oral exposure, while no information is available on dermal/skin metabolism of HCCP. Therefore, based on the molecular weight and log P_{ow} of HCCP, dermal absorption is assumed to be 100% (TGD, 2003).

After acute inhalatory exposure, the 4-hr 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.
The dermal LD_{50} for rabbits ranged from <200-780 mg/kg bw; for rats this value was >2000 mg/kg bw. Furthermore, in all skin irritation studies, mortality was observed in rabbits (see section 4.1.2.3.1). Mortality occurred already at the lowest tested concentration (0.5 ml) which corresponds with a systemic dose level of 250 mg/kg bw assuming a body weight of 2 kg for rabbits.

[6] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

With regard to oral exposure, the LD_{50} ranged from 505-1500 mg/kg bw for rats; for mice this value was 679 mg/kg bw. From the available data, it can be concluded that HCCP is harmful after acute oral exposure, toxic after acute dermal exposure and very toxic after inhalatory exposure (T+, R26; R24; R22). Starting points for the risk assessment are the 4-hour inhalation LC_{50} value of 0.018 mg/l (18 mg/m^3) in rats and the dermal LD_{50} of <200 mg/kg bw in rabbits.
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 conjunctival sac of the right eye (see section 4.1.2.3.2).
With regard to mortality following eye exposure: in the absence of a proper R-phrase for this effect, an additional S-phrase (S53) is necessary to draw attention to the risk of direct eye contact. S53 is already present in the current entry of HCCP in Annex I.
It is noted that under the new EU regulation on classification and labelling of chemicals (based on GHS), the sentence 'EUH070 - Toxic through eye' will be applicable.

HCCP is irritating and corrosive to the skin and eyes and irritating to the respiratory tract. In addition to the animal studies, a case study with 177 plant workers showed that HCCP may be skin and eye irritating for humans after acute exposure. HCCP may also cause sensitisation by skin contact.

The lowest NOAEC for systemic subacute inhalation toxicity (1.25 mg/m^3) was observed in a 2 week range finding study with rats. At the next higher dose level (5.7 mg/m^3) reduced body weight and mortality were observed. The lowest NOAEC for local subacute inhalation toxicity (1.25 mg/m^3) was also observed the 2 week range finding study and based on impaired respiratory function and microscopic changes in lung and nasal area. The overall NOAEC for local and systemic effects after semichronic 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 inhalation 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 ≥ 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. Based on the available data, classification of HCCP with R48/23: Toxic: danger of serious damage to health by prolonged exposure through inhalation, is proposed. 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.

One oral repeated dose toxicity study with HCCP was available. In this 13 week oral (gavage) toxicity studies with rats and mice, the local and systemic NOAEL for rats was 10 mg/kg bw/day based on the toxicological relevant dose related increase in male and female kidney:body weight ratio from 19 mg/kg bw/day onwards No systemic NOAEL could be established for mice, based on the toxicological relevant increase in female liver:body weight and kidney:body weight ratio at all dose levels compared to the control animals (LOAEL is 19 mg/kg bw).

Based on the occurrence of proliferation and inflammatory changes of the epithelia in the forestomach of female rats and male and female mice, the local NOAELs were 10 and 19 mg/kg bw/day for rats and mice, respectively.

No suitable dermal repeated dose toxicity studies are available.

HCCP appears to be no bacterial mutagen and does not induce gene mutations in mammalian cells *in vitro*. An increase in SCE was observed in treated mammalian cells *in vitro*, but this was without a clear dose-response relationship. 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, though it remains unclear whether HCCP has reached the bone marrow as target in sufficient amounts and therefore no clear conclusion can be drawn from this individual study on the mutagenicity of HCCP. However, as no tumours were formed in any of the exposed organs, including the site of first contact, i.e. the respiratory tract, under the conditions of maximum tolerated dose levels in chronic inhalation studies in both rats and mice, 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. In addition, several epidemiological studies were performed on workers in manufacturing plants where HCCP was used and/or produced among other chemicals. The studies did not give indications for a different cancer-induced mortality in exposed workers when compared to non-exposed workers or to the overall USA population.
However, information specific to HCCP exposure, either qualitative or quantitative, was not available in any of these studies. In addition, study populations were relatively small, and observation times (25 years at most) relatively short. Therefore, the studies are of limited value and do not provide conclusive evidence. However, due to the absence of mutagenic activity of HCCP and the absence of carcinogenic potential in rats and mice after chronic inhalation exposure, it is concluded that HCCP is not 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 for 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 were observed. Therefore, the inhalation NOAEC was established at 6.34 mg/m^3.

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 (highest dose tested) for rats and 300 mg/kg bw (highest dose tested) for mice.
In oral teratogenicity studies with mice and rats, no teratogenic effects were found. In rabbits, at 75 mg/kg bw/day little evidence of embryotoxicity was observed in combination with significant maternal toxicity. Compared to the control animals, 13 ribs were seen more frequently among the foetuses of rabbits given 75 mg/kg/day (the normal number of pairs of

ribs in the rabbit is 12 or 13). The overall NOAEL for maternal and developmental toxicity is concluded to be 25 mg/kg bw/day based on the study with rabbits.

Table 4-33 Summary of effects

Toxicological endpoint	Inhalation (N(L)OAEC)	Dermal (N(L)OAEL)	Oral (N(L)OAEL)
Acute toxicity	18-41 mg/m³ (LC_{50} in rats); <15.8 mg/m³ (LC50 in rabbits)	<200-780 mg/kg bw (LD_{50} in rabbits); >2000 mg/kg bw for rats	505-1500 mg/kg bw (LD_{50} in rats); 697 mg/kg bw (LD50 in mice)
Repeated dose toxicity (local)	1.25 mg/m³ (subacute NOAEC in rats) 0.45 mg/m³ (semichronic NOAEC in mice) 0.11 mg/m³ (chronic LOAEC in rats and mice)	n.a.	10 mg/kg bw (semichronic NOAEL in rats)
Repeated dose toxicity (systemic)	1.25 mg/m³ (subacute NOAEC in rats) 0.45 mg/m³ (semichronic NOAEC in mice) 0.11 mg/m³ (chronic NOAEC in mice)	n.a.	10 mg/kg bw (semichronic NOAEL in rats)
Fertility impairment	>6.34 mg/m³ (NOAEC in rats)	n.a.	>150 mg/kg bw/day (NOAEL in rats) >300 mg/kg bw/day (NOAEL in mice)
Developmental toxicity	n.a.	n.a.	25 mg/kg bw/day (NOAEL in rabbits)

n.a.: not available

4.1.3.2 Workers

Assuming that oral exposure is prevented by personal hygienic measures, the risk characterisation for workers is limited to the dermal and inhalation routes of exposure.

In the scope of the assessment of existing substances, dermal exposure to corrosive concentrations is not assessed. For the handling of corrosive substances and formulations, it is assumed that daily dermal exposure can be neglected because workers are protected from dermal exposure and immediate dermal contacts occur only accidentally. Techniques and equipment (including PPE) are used that provide a high level of protection from direct dermal contact. Eye protection is obligatory for activities where direct handling of HCCP occurs. These protection measures will also protect to the possible occurrence of mortality after dermal and eye exposure (see acute toxicity after dermal exposure and after exposure to the eyes).
Dermal exposure to dilutions of HCCP, that result in a substance or formulation which has no corrosive labelling (dilutions containing <10% HCCP, according to EU classification and labelling commission), also occurs. Dermal exposure to such non-corrosive dilutions of HCCP cannot be neglected and will be taken into account. Furthermore, acute and repeated inhalation exposure to HCCP cannot be neglected.

4.1.3.2.1 Acute toxicity

HCCP is classified as harmful after oral exposure, as toxic after acute dermal exposure and very toxic after inhalation exposure. For occupational risk assessment the short-term exposure levels are compared with the LD_{50} or LC_{50} values.

Inhalation exposure
Starting-point for the risk assessment of acute inhalation toxicity is the 4-hour LC_{50} value of 0.018 mg/l (equivalent to 18 mg/m^3) for male rats.
The MOSs between the LC_{50} and the estimated inhalation exposure level is presented in **Table 4-34**. The MOSs are evaluated by comparison with the minimal MOS (>>12.5). In **Table A-1** (see appendix A) the assessment factors applicable to establish the minimal MOS are given. There is concern when the MOS is lower than the minimal MOS.

The MOS values between the LC_{50} value and the estimated external inhalation concentrations are calculated to be 180 and 167. It should be noted that systemic effects may occur at lower concentrations than the LC_{50} level. However, comparing the MOS values with the minimal MOS of >>12.5, it is concluded that the MOS values are in excess of the minimal MOS even with regard to possible systemic effects (an additional uncertainty factor of 10 is possible).
Furthermore:
- no case reports were available in literature describing mortality, the effect on which the LC_{50} is based, of humans exposed to HCCP in occupational exposure settings;
- the MOS for acute inhalation toxicity is based on a 4-hour LC_{50} while the exposure duration concerns a 15 min TWA, which may indicate an underestimation of the MOS values.
Taking into account these aspects, it is concluded that there is no concern for workers with regard to the occurrence of adverse effects after short-term inhalation exposure to HCCP (**conclusion ii**).

Table 4-34 Occupational risk assessment for acute inhalation toxicity

	Inhalation			
	Exposure	LC_{50}	MOS	Conclusion
Production of pesticides and flame retardants	100 µg/m^3 (15 min TWA)	18 mg/m^3	180	ii
Use of product containing residual HCCP	108 µg/m^3 (15 min TWA)	18 mg/m^3	167	ii

Dermal exposure
Dermal LD_{50} value of <200, 340 and 780 mg/kg bw are reported for rabbits. In addition, mortality was observed in animals in all skin irritation studies. Mortality occurred already at the lowest tested concentration (0.5 ml) which corresponds with a systemic dose level of 250 mg/kg bw assuming a body weight of 2 kg for rabbits. Starting-point for the risk assessment of acute dermal toxicity is the dermal LD_{50} value of <200 mg/kg bw in rabbits.

The MOS between the LD_{50} and the estimated external dermal exposure level is presented in **Table 4-35**. Since no information is available with regard to single high dermal exposure, the 8h TWA exposure levels are used for determination of the MOS values. The MOSs are evaluated by comparison with the minimal MOS (>>50). In **Table A-2** (see appendix A) the assessment factors applicable to establish the minimal MOS are given. There is concern when the MOS is lower than the minimal MOS.

The MOS values between the LD_{50} value and the estimated external dermal dose are calculated to be <3333, <666667 and <56000. It should be noted that systemic effects may occur at lower concentrations than the LD_{50} level.
Comparing the MOS values with the minimal MOS of >>50, it is concluded that these MOS values are significantly in excess of the minimal MOS even with regard to possible systemic effects. Furthermore, it should be noted that existing controls are applied with regard to dermal exposure to HCCP based on the corrosive and irritating properties of this substance (see section 4.1.3.2.2). Also no human case reports were available in literature describing mortality or other serious health effects after exposure to HCCP in occupational exposure settings after acute dermal exposure. Therefore, there is no concern for systemic effects after acute dermal exposure (**conclusion ii**).

Table 4-35 Occupational risk assessment for acute dermal toxicity

	Dermal			
	Exposure[1]	LD_{50}	MOS	Conclusion
Production of pesticides and flame retardants	4.2 (0.06) mg/day	<200 mg/kg bw	<3333	ii
Use of product containing residual HCCP	0.021 (0.0003) mg/day	<200 mg/kg bw	<666667	ii
Unintentional occurrence of HCCP in the semiconductor industry	0.25 (0.0036) mg/day	<200 mg/kg bw	<55556	ii

[1] Between brackets: the systemic dose due to dermal exposure in mg/kg bw assuming a worker body weight of 70 kg.

Eye exposure
With regard to the available animal eye irritation study, it is noted that all exposed animals died during the study. Based on this result, it is concluded that HCCP is of concern for workers with regard to effects as a result of eye exposure. However, ocular exposure can be excluded as effective use of personal protective equipment for the eyes is assumed in all scenarios based on severely eye irritating properties of HCCP (see section 4.1.3.2.2). Therefore, it is concluded that the substance is of no concern for workers with regard to the occurrence mortality as a result of eye exposure (**conclusion ii**).

4.1.3.2.2 Irritation and corrosivity

Dermal irritation after single and repeated exposure
Given the results of the irritation studies and the results of some acute dermal toxicity studies, it is concluded that HCCP is irritating (concentrations 5%≤C<10%) and corrosive (concentrations ≥10%) to the skin.

Dermal exposure to corrosive concentrations of HCCP is considered to occur only accidentally if the required protection is strictly adhered to. Therefore, **conclusion ii** is justifiable for scenarios in which corrosive concentrations of HCCP are handled.

With regard to dermal exposure to irritating, but non-corrosive, dilutions of HCCP, it is assumed that existing controls (i.e., engineering controls and personal protective equipment based on classification and labelling with R38) are applied. Therefore, it is concluded that HCCP is of no concern for workers with regard to effects as a result of dermal exposure for scenarios in which non-corrosive concentrations of HCCP are handled (**conclusion ii**).

No repeated dose toxicity study with regard to dermal irritation of HCCP is available and thus it is not possible to make a quantitative risk assessment for local effects after repeated dermal exposure.

Eye irritation
In the available animal eye irritation study, HCCP was found to be severely irritating to the eyes. Based on this result, it is concluded that HCCP is of concern for workers with regard to effects as a result of eye exposure. However, ocular exposure can be excluded as effective use of personal protective equipment for the eyes is assumed in all scenarios. Therefore, it is concluded that the substance is of no concern for workers with regard to effects as a result of eye exposure (**conclusion ii**).

Respiratory irritation after single exposure
Given the results of acute inhalation studies, it is concluded that HCCP is irritating to the respiratory tract. As starting point for a quantitative risk assessment for local toxicity, the NOAEC (0.28 ppm; equivalent to 3.2 mg/m^3) derived in the acute inhalation study performed by Huntingdon (1978; published by Rand *et al.*, 1982a) is used. In this study, SD rats were exposed for 4 hours to 0.28, 1.4, 2.5, 3.1, 3.3, 3.4, 4.0, and 5.8 ppm HCCP (10/sex/dose). Animals surviving exposure to 1.4 ppm (equivalent to 0.016 mg/l) and higher exhibited significant pulmonary abnormalities (red focal or diffuse consolidation, progressing to haemorrhage and hepatisation).

The MOS between the NOAEC for respiratory irritation and the estimated exposure level is mentioned in **Table 4-36**. The MOSs are evaluated by comparison with the minimal MOS (12.5). In **Table A-3** (see appendix A) the assessment factors applicable to establish the minimal MOS are given. There is concern when the MOS is lower than the minimal MOS. For acute inhalation exposure to HCCP, there is no concern for workers with regard to the occurrence of respiratory irritation for all occupational scenarios (**conclusion ii**).

Table 4-36 Occupational risk assessment for respiratory tract irritation

	Inhalation			
	Exposure	NOAEL	MOS	Conclusion
Production of pesticides and flame retardants	100 µg/m³ (15 min TWA)	3.2 mg/ m³	32	ii
Use of product containing residual HCCP	108 µg/m³ (15 min TWA)	3.2 mg/ m³	30	ii

4.1.3.2.3 Sensitisation

Dermal sensitisation
Based on the data available, no quantitative risk characterisation for this specific endpoint could be performed. Based on the results of the skin sensitisation studies, a non-threshold approach and the anticipated dermal exposure in different scenarios, it is concluded that HCCP is of concern for workers with regard to skin sensitisation (**conclusion iii**). However, in scenarios where engineering controls and personal protective equipment are effectively used based on the classification and labelling of the substance as a skin sensitiser, the possible occurrence of skin sensitisation will be reduced to a minimum and **conclusion ii** is applicable.

Respiratory sensitisation
There are neither data from animal studies nor indications from the human case study for respiratory sensitisation. In addition, there are no other human reports on respiratory sensitisation available, despite the long and widespread use of HCCP. Therefore, there is no concern for this endpoint (**conclusion ii**).

4.1.3.2.4 Repeated dose toxicity

Inhalation exposure
Starting-point for the risk assessment of inhalation repeated dose toxicity are the LOAEC of 0.11 mg/m³ HCCP for local effects and the NOAEC of also 0.11 mg/m³ for systemic effects both from the 2-year inhalation study.

The MOSs between the LOAEC for local effects and the NOAEC for systemic effects and the estimated inhalation exposure level are mentioned in **Table 4-37**. The MOSs are evaluated by comparison with the minimal MOSs (37.5 and 12.5 for local and systemic effects, respectively). In **Table A-4** (see appendix A) the assessment factors applicable to establish the minimal MOS are given. There is concern when the MOS is lower than the minimal MOS. For inhalation exposure to HCCP, there is concern for workers with regard to the occurrence of local and systemic effects for the occupational scenarios 'Production of pesticides and flame retardants' and 'Use of product containing residual HCCP' (**conclusion iii**).

Dermal exposure

Conclusions regarding the risk characterisation for local effects after repeated exposure to HCCP are described in the section 'irritation and corrosion'.

No suitable dermal repeated dose toxicity studies are available.

Oral to dermal extrapolation is not reliable and valid for HCCP. For HCCP it appears that differences in metabolism after oral and inhalation exposure (no dermal toxicokinetic data is available for HCCP) might explain the observed route specific difference. After oral administration, HCCP is extensively degraded to polar metabolites and the majority of the orally consumed HCCP is not absorbed. This first pass metabolism will not occur after inhalatory exposure (Rennen et al, 2004). Based on this, it appears that HCCP is more toxic after inhalation (and possibly also dermal) exposure. Therefore, inhalation to dermal extrapolation is performed.

Starting-point for the risk assessment of dermal repeated dose toxicity is the inhalation NOAEC of 0.11 mg/m^3 for systemic effects both from the 2-year inhalation study. A dermal NAEL of 0.046 mg/kg bw/day is calculated from this NOAEL of 0.11 mg/m^3 assuming an inhalation volume of 41 ml/min for female mice (daily exposure of 6 hours), a body weight of 0.035 kg for female mice, a respiratory retention of 100% and a dermal absorption of 100%.

The MOSs between the NAEL and the estimated dermal exposure levels are mentioned in **Table 4-37**. The MOSs are evaluated by comparison with the minimal MOS (87.5). In **Table A-5** (see appendix A) the assessment factors applicable to establish the minimal MOS are given. There is concern when the MOS is lower than the minimal MOS. For repeated dermal exposure to HCCP, there is concern for workers with regard to the occurrence of systemic effects for the occupational scenarios 'Production of pesticides and flame retardants' and 'Unintentional occurrence of HCCP in the semiconductor industry' (**conclusion iii**).

Combined exposure

The total body burden (systemic dose) is determined by uptake after dermal as well as inhalation exposure to HCCP. In general, a risk characterisation for systemic effects for combined exposure introduces a lot of uncertainties, e.g., due to differences in build-up of the internal exposure after both exposure routes and due to difficulties in the choice of the most appropriate toxicity study as starting point. In view of the dermal and inhalation exposure estimates, there is concern for systemic effects in all occupational scenarios (**conclusion iii**).

Table 4-37 Occupational risk assessment for repeated dose toxicity

	Inhalation					Dermal			
	Exposure	Systemic NOAEC	Local LOAEC	MOS	Conclusion	Exposure	NAEL	MOS[1]	Conclusion
Production of pesticides and flame retardants	50 µg/m³	0.11 mg/m³	0.11 mg/m³	2.2	iii	4.2 mg/day	0.046 mg/kg bw/day	0.8	iii
Use of product containing residual HCCP	54 µg/m³	0.11 mg/m³	0.11 mg/m³	2	iii	0.021 mg/day	0.046 mg/kg bw/day	153	ii
Unintentional occurrence of HCCP in the semiconductor industry	1.9 µg/m³	0.11 mg/m³	0.11 mg/m³	58	ii	0.25 mg/day	0.046 mg/kg bw/day	13	iii

[1] Calculation based on a worker body weight of 70 kg and an inhalation NOAEC of 11 mg//m³ in female mice.

4.1.3.2.5 Mutagenicity

Given the results from the mutagenic studies and as no tumours were formed in any of the exposed organs, including the site of first contact, i.e. the respiratory tract, under the conditions of maximum tolerated dose levels in chronic inhalation studies in both rats and mice, it is concluded that HCCP is of no concern for workers with regard to mutagenicity (**conclusion ii**).

4.1.3.2.6 Carcinogenicity

Given the results from the mutagenicity studies, the chronic animal (rats and mice) repeated dose/carcinogenicity studies with HCCP, and the available epidemiological studies, it is concluded that there are no reasons for concern for workers with regard to carcinogenicity after inhalation and dermal exposure (**conclusion ii**). Risk characterisation of local carcinogenicity after dermal exposure can only be performed based on chronic dermal toxicity studies.

4.1.3.2.7 Toxicity for reproduction

Inhalation exposure

Effects on fertility

No specific study on fertility effects of HCCP is available. However, in different inhalation repeated dose studies (rats and mice exposed for 13 weeks up to at least 4.46 mg/m^3; rats and monkeys exposed for 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 and no biologically relevant histopathological treatment related effects were observed. When comparing the MOS values of the different exposure scenarios with the minimal MOS of 12.5 (factor 2.5 for interspecies and a factor 5 for intraspecies), **conclusion ii** is derived.

Table 4-38 Occupational risk assessment for effects on fertility

	Inhalation			
	Exposure	NOAEC	MOS	Conclusion
Production of pesticides and flame retardants	50 µg/m^3	6.34 mg/m^3	127	ii
Use of product containing residual HCCP	54 µg/m^3	6.34 mg/m^3	117	ii
Unintentional occurrence of HCCP in the semiconductor industry	1.9 µg/m^3	6.34 mg/m^3	3337	ii

Developmental toxicity

Only oral developmental toxicity studies are available. Based on the uncertainties of oral to inhalation extrapolation (see section 4.1.3.2.4, Repeated dose toxicity, *dermal exposure*), a quantitative risk assessment for developmental toxicity after inhalation exposure cannot be performed. However, given the toxicity profile of the substance, it is not expected that developmental effects will occur at the low concentrations (N(L)OAEC of 0.11 mg/m^3 for) at which local and systemic effects are observed upon inhalation exposure (see repeated dose toxicity). Therefore, a **conclusion ii** is derived.

Dermal exposure

Effects on fertility

No suitable study is available to assess the risk of effects on fertility after dermal exposure. 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 histopathologically examined, and no biologically relevant treatment related effects were observed. However, based on the uncertainties of oral to dermal extrapolation (see section 4.1.3.2.4, Repeated dose toxicity, dermal exposure), an extrapolation from inhalation to dermal is preferred. As in different inhalation repeated dose studies no biologically relevant histopathological treatment related effects were observed up to at least 6.34 mg/m^3 (see inhalation section), **conclusion ii** is reached.

Developmental toxicity

Only oral developmental toxicity studies are available. Based on the uncertainties of oral to dermal extrapolation (see section 4.1.3.2.4, Repeated dose toxicity, *dermal exposure*), a quantitative risk assessment for developmental toxicity after dermal exposure cannot be performed. Given the toxicity profile of HCCP, it is not expected that developmental effects will occur at the low dose level (NAEL of 0.046 mg/kg bw/day) at which systemic effects are expected to occur upon dermal exposure (see repeated dose toxicity). Therefore, a **conclusion ii** is derived.

Combined exposure

Effects on fertility

The available data indicate no concern for effects on fertility: **conclusion ii**.

Developmental toxicity

Based on the above considerations it is concluded that there is no concern for this endpoint: **conclusion ii**.

4.1.3.2.8 Summary of risk characterisation for workers

See **Table 4-39** 'Overview of the conclusions with respect to occupational risk characterisation'.

Table 4-39 Overview of the conclusions with respect to occupational risk characterisation

		Acute toxicity		**Irritation and corrosivity**			**Sensiti sation**	**Repeated dose toxicity Systemic**			**Mutagenicity Carcinogenicity Reproductive toxicity**
		Dermal	Inhalation	Skin	Eye	Respira-tory tract		Dermal	Inhalation	Combined	
Production of pesticides and flame retardants	MOS	<3333	180			32		0.8	2.2		
	mMOS	>>50				12.5		87.5	37.5 (local) 12.5 (systemic)		
	Concl.	ii	ii	ii	ii	ii	ii	iii	iii	iii	ii
Use of product containing residual HCCP	MOS	<33333	167			30		153	2		
	mMOS	>>50				12.5		87.5	37.5 (local) 12.5 (systemic)		
	Concl.	ii	ii	ii	ii	ii	ii	ii	iii	iii	ii
Unintentional occurrence of HCCP in the semiconductor industry	MOS	<56000	n.a.			n.a.		13	58		
	mMOS	>>50						87.5	37.5 (local) 12.5 (systemic)		
	Concl.	ii	n.a.	ii	ii	n.a.	ii	iii	ii	iii	ii
Unintentional release of HCCP during fire	MOS	n.a.	n.a.			n.a.		n.a.	n.a.		
	mMOS										
	Concl.	n.a.	n.a.	ii	ii	n.a.	ii	n.a.	n.a.	iii	ii

n.a.: not applicable

4.1.3.2.9 Occupational limit values

According to EC 1488/94, occupational limit values should be evaluated in view of the outcome of the risk characterisation and to conclude on the necessity to (re)consider these values.

There is currently no limit value for exposure to HCCP at the European level (SCOEL, 2005). Some of the EU member countries have set a limit for HCCP (see **Table 4-40**). Furthermore, the ACGIH, OSHA and NIOSH have set a limit/recommended standard for exposure to HCCP. In Germany, a skin notation is applicable for HCCP.

Table 4-40 Existing Occupational Exposure Limits (OELs) for HCCP

Country / Organisation	Level (mg/m^3)	Time-relation	Remarks
The Netherlands (Health Council of the Netherlands, 2003)	0.01	TWA – value (8 hr)	-
United Kingdom (HSE, 2002)	-	-	-
Denmark (Arbejdstilsynet, 2002)	0.1	TWA – value (8 hr)	-
Germany (TRGS, 2006), (Deutsche Forschungsgemein-schaft, 2005)	0.2	TWA – value (8 hr)	H[1]
Sweden (Swedish National Board of Occupational Safety and Health, 2000)	-	-	-
France (INRS, 2003)	0.1	-	-
Scientific Committee on Occupational Exposure Limits (SCOEL, 2005)	-	-	-
ACGIH (ACGIH, 2001)	0.11	TWA – value (8 hr)	-
OSHA (OSHA, 1989)	0.11	TWA – value (8 hr)	-
NIOSH (NIOSH, 2005)	0.11	TWA – value (8 hr)	-

[1] H: Substances are designated with a 'H' when observance of the established MAC value on its own does not guarantee the prevention of adverse effects on health, that is, when dermal exposure increases the body burden. Substances are not designated with an 'H' if toxic effects are not to be expected under workplace conditions, independent of the ability of the substance to penetrate the skin (Deutsche Forschungsgemein-schaft, 2005).

In the Netherlands, a report of the Dutch Expert Committee on Occupational Standards is available which described the same data as were summarised in the HEDSET (Health Council of the Netherlands, 2003). From these data, the 2-year rat inhalation study (NTP, 1994) (see section 4.1.2.6.1 *Inhalation*) was chosen for using as a starting point for deriving a health-based recommended occupational exposure limit (HBROEL). In this study, squamous metaplasia of the laryngeal epithelium was considered to be the critical effect. A NOAEC could not be established, since at 0.11 mg/m^3 (0.01 ppm), the lowest level tested, these laryngeal lesions as well as pigmentation of the respiratory epithelium of the nose, the bronchiles, and the bronchi were demonstrated. For extrapolation to a HBROEL, an overall assessment factor of 12 was applied covering the absence of a NOAEC, intra- and interspecies variation, and the type of critical effect.

Application of this factor of 12 results in a health- based occupational limit of 0.01 mg/m^3 (0.0009 ppm) for HCCP as an 8-hour time-weighted average (TWA). A skin notation was not deemed necessary because of the local character of the critical effect.
It is noted that the value derived is in agreement with the limit values used for risk characterisation for local effects after repeated exposure.

The American Conference of Governmental Industrial Hygienists (ACGIH, 2001), the Occupational Safety and Health Administration (OSHA, 1989) and the National Institute for Occupational Safety and Health (NIOSH, 2005) have established an occupational exposure limit value of 0.11 mg/m^3. This limit value was based on high order of acute toxicity of HCCP in laboratory animals in the study of Treon *et al.* (1955) (see section 4.1.2.6.1 *Inhalation*). Rabbits, mice, rats, and guinea pigs died from inhaling 89.5% of the vapour in air. In 150 daily exposures of seven hours each, rabbits, rats, and guinea pigs survived concentrations of 0.15 ppm, but a similar exposure was fatal to four of five mice. At approximately twice this concentration, mice, rats, and most rabbits died by or before the 25th exposure, but guinea pigs survived 30 exposures. The HCCP vapours caused tearing, laboured respiration, and, at high concentrations, tremors. Furthermore, degenerative changes in the brain, heart, liver, adrenal glands, and kidneys, and pulmonary irritation occurred in all species, even at the lowest concentration of 0.15 ppm. Pulmonary oedema, hyperaemia, necrotising bronchitis, and bronchiolitis were also observed. Without a specified explanation, based on these animal data, a limit value of 0.11 mg/m^3 (0.01 ppm) is recommended (ACGIH, 2001; OSHA, 1989). According to the available information (ACGIH, 2001; OSHA, 1989), this value should protect for ocular, mucous membrane and upper respiratory tract irritation.

4.1.3.3 Consumers

There is no consumer exposure to HCCP, so no risk characterisation is performed.

4.1.3.4 Humans exposed via the environment

Exposure of man via the environment is primarily by air, and some by food.

4.1.3.4.1 Exposure via air

Repeated dose toxicity
Starting points for the risk characterisation for repeated dose toxicity are the highest estimated local exposure level via air (7.3 ng/m^3) and the systemic NOAEC/local LOAEC of 0.11 mg/m^3 from the chronic inhalation study with rats. The margin of safety between this NOAEC/LOAEC and the estimated exposure level is approximately 15000. This margin of safety indicates no concern for human safety for both systemic and local effects after repeated inhalation, taking into account inter- and intraspecies variation and, for the LOAEC, extrapolation to the NAEC (minimal MOS is 2.5 x 10 = 25 for systemic effects, and 2.5 x 10 x 3 = 75 for local effects). Hence, **conclusion ii**.

The regional exposure is orders of magnitude lower and therefore the margin of safety is also sufficiently high (**conclusion ii**).

Mutagenicity
Given the results from the mutagenicity studies and that no tumours were formed in any of the exposed organs, including the site of first contact, i.e. the respiratory tract, under the conditions of maximum tolerated dose levels in chronic inhalation studies in both rats and mice, it is concluded that HCCP is of no concern for mutagenicity for man exposed via the environment (**conclusion ii**).

Carcinogenicity
Given the results from the mutagenicity studies, the chronic animal (rats and mice) repeated dose/carcinogenicity studies and the available epidemiological studies, it is concluded that HCCP is of no concern for carcinogenicity for man exposed via the environment (**conclusion ii**).

Reproductive effects
No specific study on fertility effects of HCCP is 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 for 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 treatment related effects were observed. For risk characterisation, the highest concentration tested without effects on fertility is used, i.e. 6.34 mg/m^3. The other starting point for the risk characterisation is the highest estimated local exposure via air (7.3 ng/m^3). The margin of safety is approximately $8.7*10^5$. This margin of safety indicates no concern for fertility after inhalation, taking into account intra- and interspecies variation (minimal MOS is 2.5 x 10 = 25) (**conclusion ii**).

4.1.3.4.2 Exposure via food and water

Repeated dose toxicity
Starting points for the risk characterisation are the highest exposures via food (1.7E-7 mg/kg bw/day for scenario II-a and 1.8E-08 mg/kg bw/day for scenario II-b) and the oral NOAEL of 10 mg/kg bw from the 13 week study in rats. The margins of safety for these sites are >5.9 x 10^7 and 5.6 x 10^8, respectively, and indicate no concern for human safety after repeated oral exposure, taking into account inter- and intrapecies variation and exposure duration extrapolation (minimal MOS is 4 x 2.5 x 10 x 2 = 200) (**conclusion ii**).

For the regional scenario, the oral exposure is much lower and can be considered negligible (**conclusion ii**).

Mutagenicity
Given the results from the mutagenicity studies and that no tumours were formed in any of the exposed organs, including the site of first contact, i.e. the respiratory tract, under the conditions of maximum tolerated dose levels in chronic inhalation studies in both rats and mice, it is concluded that HCCP is of no concern for mutagenicity for man exposed via the environment (**conclusion ii**).

Carcinogenicity
Given the results from the mutagenicity studies, the chronic animal (rats and mice) repeated dose/carcinogenicity studies and the available epidemiological studies, it is concluded that HCCP is of no concern for carcinogenicity for man exposed via the environment (**conclusion ii**).

Reproductive effects
Starting points for the risk characterisation are the highest exposure via food (1.7E-7 mg/kg bw/day for scenario II-a and 1.8E-08 mg/kg bw/day for scenario II-b) and the oral NOAEL of 25 mg/kg bw for rabbits for teratogenicity, also including studies on rats and mice with higher NOAELs for fertility. The margins of safety for these sites are >1.5 x 10^8 and 1.4 x 10^9, respectively, and indicate no concern for human safety for reproductive effects, taking into account inter- and intraspecies variation (minimal MOS is 2.4 x 2.5 x 10 = 60) (**conclusion ii**).

For the regional scenario, the oral exposure is much lower and can be considered negligible (**conclusion ii**).

4.1.3.4.3 Summary of risk characterisation for exposure via the environment

For all local and regional exposure scenarios, **conclusions ii** have been reached for all relevant toxicological end points.

4.1.3.5 Combined exposure

As there is no need to perform a combined exposure assessment for HCCP (see section 4.1.1.5), a risk characterisation for combined exposure is not applicable.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

No studies are available on the flammability, explosive properties and oxidizing properties of HCCP. However, taking into account the structural formula and the thereof-derived thermokinetics, HCCP is not expected to be flammable, oxidizing and explosive. There are no indications for classification of HCCP with regard to physico-chemical properties and there is no need for further information and/or testing. HCCP is considered of no concern with regard to physico-chemical properties (**conclusion ii**).

5 RESULTS [7]

5.1 ENVIRONMENT

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all environmental compartments, both at the local and regional scale. The RCRs for the aquatic compartment for the impurity of HCCP in endosulfan application are also below 1.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

5.2.1.1 Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) is reached because:

- adverse local and systemic health effects cannot be excluded after repeated inhalation exposure in the occupational scenarios 'Production of pesticides and flame retardants' and 'Use of product containing residual HCCP';
- adverse systemic health effects cannot be excluded after repeated dermal exposure in the occupational scenarios 'Production of pesticides and flame retardants' and 'Unintentional occurrence of HCCP in the semiconductor industry'.

It might be possible that in some workplaces adequate worker protection measures are already being applied.

5.2.1.2 Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5.2.1.3 Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5.2.2 Human health (risks from physico-chemical properties)

[7] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

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ABBREVIATIONS

[update the list to correspond to the substance RAR]

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw*, *b.w.*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 50 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration

POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

APPENDIX A

Establishment of the minimal MOSs used for the worker risk characterisation

In the tables below calculations of the minimal MOS-values via assessment factors are given. The assessment factors are based upon the draft version of the TGD (2005).

Table A-1: Assessment factors for acute inhalation risk assessment

Aspect	Assessment factors for acute dermal irritation
Interspecies differences[1]	2.5
Intraspecies differences	5
Differences between experimental conditions and exposure pattern of the worker	1
Dose-response / Type of critical effect[2]	>>1
Confidence of the database	1
Overall	>>12.5

[1] For inhalation studies only a factor 2.5 is used, and no correction is made for differences in body size, because extrapolation is based on toxicological equivalence of a concentration of a chemical in the air of experimental animals and humans; animal and humans breathe at a rate depending on their caloric requirements.
[2] It is noted that the MOS values are calculated for a severe effect (lethality). It is expected that other toxic effects after acute exposure might occur at lower concentrations than the lethal concentrations.

Table A-2: Assessment factors for acute dermal risk assessment

Aspect	Assessment factors for acute dermal irritation
Interspecies differences	4*2.5
Intraspecies differences	5
Differences between experimental conditions and exposure pattern of the worker	1
Dose-response / Type of critical effect[1]	>>1
Confidence of the database	1
Overall	>>50

[1] It is noted that the MOS values are calculated for a severe effect (lethality). It is expected that other toxic effects after acute exposure might occur at lower concentrations than the lethal concentrations.

Table A-3: Assessment factors for acute respiratory tract irritation risk assessment

Aspect	Assessment factors for acute respiratory tract risk assessment
Interspecies differences[1]	2.5
Intraspecies differences	5
Differences between experimental conditions and exposure pattern of the worker	1
Dose-response / Type of critical effect	1
Confidence of the database	1
Overall	12.5

[1] For inhalation studies only a factor 2.5 is used, and no correction is made for differences in body size, because extrapolation is based on toxicological equivalence of a concentration of a chemical in the air of experimental animals and humans; animal and humans breathe at a rate depending on their caloric requirements.

Table A-4: Assessment factors for repeated dose inhalation risk assessment

Aspect	Assessment factors for repeated dose inhalation risk assessment (local)	Assessment factors for repeated dose inhalation risk assessment (systemic)
Interspecies differences[1]	2.5	2.5
Intraspecies differences	5	5
Differences between experimental conditions	1	1

and exposure pattern of the worker		
Dose-response / Type of critical effect	3[2]	1
Confidence of the database	1	1
Overall	37.5	12.5

[1] For inhalation studies only a factor 2.5 is used, and no correction is made for differences in body size, because extrapolation is based on toxicological equivalence of a concentration of a chemical in the air of experimental animals and humans; animal and humans breathe at a rate depending on their caloric requirements.
[2] A factor 3 is considered applicable for extrapolation from LOAEC to NAEC.

Table A-5: Assessment factors for repeated dose dermal risk assessment

Aspect	**Assessment factors for repeated dose dermal risk assessment**
Interspecies differences[1]	7*2.5
Intraspecies differences	5
Differences between experimental conditions and exposure pattern of the worker[2]	1
Dose-response / Type of critical effect	1
Confidence of the database	1
Overall	87.5

APPENDIX B

SUBSTANCE			
SUBSTANCE IDENTIFICATION			
GENERAL NAME	HCCP		S
DESCRIPTION	1,2,3,4,5,5-HEXACHLOROCYCLO-1,3-PENTADIENE		S
CAS-NO	77-47-4		S
EC-NOTIFICATION NO.			D
EINECS NO.	2010293		S
PHYSICO-CHEMICAL PROPERTIES			
MOLECULAR WEIGHT	272,77	[G.MOL-1]	S
MELTING POINT	-10	[OC]	S
BOILING POINT	239	[OC]	S
VAPOUR PRESSURE AT TEST TEMPERATURE	10	[PA]	S
TEMPERATURE AT WHICH VAPOUR PRESSURE WAS MEASURED	25	[OC]	D
VAPOUR PRESSURE AT 25 [OC]	0,0107	[KPA]	S
OCTANOL-WATER PARTITION COEFFICIENT	5,04	[LOG10]	S
WATER SOLUBILITY AT TEST TEMPERATURE	1,25	[MG.L-1]	S
TEMPERATURE AT WHICH SOLUBILITY WAS MEASURED	22	[OC]	S
WATER SOLUBILITY AT 25 [OC]	1,14	[MG.L-1]	S
PARTITION COEFFICIENTS AND BIOCONCENTRATION FACTORS			
SOLIDS-WATER			
ORGANIC CARBON-WATER PARTITION COEFFICIENT	4,265E+03	[L.KG-1]	S
BIOCONCENTRATION FACTORS			
HUMAN AND PREDATOR EXPOSURE			
BIOCONCENTRATION FACTOR FOR FISH	11	[L.KGWWT-1]	S
BIOTA-WATER			
FOR REGIONAL/CONTINENTAL DISTRIBUTION			
BIOCONCENTRATION FACTOR FOR AQUATIC BIOTA	11	[L.KGWWT-1]	S
DEGRADATION AND TRANSFORMATION RATES			
CHARACTARIZATION			
CHARACTERIZATION OF BIODEGRADABILITY	INHERENTLY BIODEGR., NOT FULFILLING CRIT.		S
STP			
DEGRADATION CALCULATION METHOD IN STP	FIRST ORDER, STANDARD OECD/EU TESTS		S
WATER/SEDIMENT			
WATER			
RATE CONSTANT FOR HYDROLYSIS IN SURFACE WATER	0,05	[D-1] (12[OC])	S
RATE CONSTANT FOR PHOTOLYSIS IN SURFACE WATER	3,9	[HR-1]	S
RATE CONSTANT FOR BIODEGRADATION IN SURFACE WATER	0	[D-1] (25[OC])	S
AIR			
SPECIFIC DEGRADATION RATE CONSTANT WITH OH-RADICALS	5,6E-13	[CM3.MOLEC-1.S-1]	S
RATE CONSTANT FOR DEGRADATION IN AIR	29	[D] (DT50)	S
RELEASE ESTIMATION			
CHARACTERIZATION AND TONNAGE			
HIGH PRODUCTION VOLUME CHEMICAL	YES		S
VOLUME OF CHEMICAL IMPORTED TO EU	6,02E+03	[TONNES.YR-1]	S
USE PATTERN			
INDUSTRY CATEGORY	3 CHEMICAL INDUSTRY: CHEMICALS USED IN SYNTHESIS		S
USE CATEGORY	33 INTERMEDIATES		S
INDUSTRIAL USE			
EMISSION SCENARIO	NO SPECIAL SCENARIO SELECTED/AVAILABLE		S
MAIN CATEGORY INDUSTRIAL USE	IC DEDICATED EQUIPMENT		S
TONNAGE			
FRACTION OF TONNAGE FOR APPLICATION	0,831	[-]	S
RELEVANT TONNAGE FOR APPLICATION	5E+03	[TONNES.YR-1]	S
REGIONAL TONNAGE OF SUBSTANCE	5E+03	[TONNES.YR-1]	S
USE PATTERN			
INDUSTRY CATEGORY	3 CHEMICAL INDUSTRY: CHEMICALS USED IN SYNTHESIS		S
USE CATEGORY	33 INTERMEDIATES		S

INDUSTRIAL USE			
EMISSION SCENARIO	NO SPECIAL SCENARIO SELECTED/AVAILABLE		S
MAIN CATEGORY INDUSTRIAL USE	IC DEDICATED EQUIPMENT		S
TONNAGE			
FRACTION OF TONNAGE FOR APPLICATION	0,166	[-]	S
RELEVANT TONNAGE FOR APPLICATION	1000	[TONNES.YR-1]	S
REGIONAL TONNAGE OF SUBSTANCE	1000	[TONNES.YR-1]	S
USE PATTERN			
INDUSTRY CATEGORY	3 CHEMICAL INDUSTRY: CHEMICALS USED IN SYNTHESIS		S
USE CATEGORY	33 INTERMEDIATES		S
INDUSTRIAL USE			
EMISSION SCENARIO	NO SPECIAL SCENARIO SELECTED/AVAILABLE		S
MAIN CATEGORY INDUSTRIAL USE	IC DEDICATED EQUIPMENT		S
TONNAGE			
FRACTION OF TONNAGE FOR APPLICATION	3E-03	[-]	S
RELEVANT TONNAGE FOR APPLICATION	20	[TONNES.YR-1]	S
REGIONAL TONNAGE OF SUBSTANCE	20	[TONNES.YR-1]	S
INTERMEDIATE RESULTS			
USE PATTERN 1			
RELEASE FRACTIONS AND EMISSION DAYS [1 ""]			
INDUSTRIAL USE			
EMISSION TABLES	A3.3 (IC-SPECIFIC), B3.2 (GENERAL TABLE)		S
EMISSION DAYS			
FRACTION OF THE MAIN LOCAL SOURCE	1	[-]	S
NUMBER OF EMISSION DAYS PER YEAR	300	[-]	S
REGIONAL AND CONTINENTAL RELEASES [1 ""]			
INDUSTRIAL USE			
REGIONAL			
REGIONAL RELEASE TO AIR	0	[KG.D-1]	S
REGIONAL RELEASE TO WASTE WATER	0	[KG.D-1]	S
REGIONAL RELEASE TO SURFACE WATER	0	[KG.D-1]	S
REGIONAL RELEASE TO INDUSTRIAL SOIL	0	[KG.D-1]	S
CONTINENTAL			
CONTINENTAL RELEASE TO AIR	0	[KG.D-1]	S
CONTINENTAL RELEASE TO WASTE WATER	0	[KG.D-1]	S
CONTINENTAL RELEASE TO SURFACE WATER	0	[KG.D-1]	S
CONTINENTAL RELEASE TO INDUSTRIAL SOIL	0	[KG.D-1]	S
USE PATTERN 2			
RELEASE FRACTIONS AND EMISSION DAYS [2 ""]			
INDUSTRIAL USE			
EMISSION TABLES	A3.3 (IC-SPECIFIC), B3.2 (GENERAL TABLE)		S
EMISSION DAYS			
FRACTION OF THE MAIN LOCAL SOURCE	1	[-]	S
NUMBER OF EMISSION DAYS PER YEAR	80	[-]	S
REGIONAL AND CONTINENTAL RELEASES [2 ""]			
INDUSTRIAL USE			
REGIONAL			
REGIONAL RELEASE TO AIR	0	[KG.D-1]	S
REGIONAL RELEASE TO WASTE WATER	0	[KG.D-1]	S
REGIONAL RELEASE TO SURFACE WATER	0	[KG.D-1]	S
REGIONAL RELEASE TO INDUSTRIAL SOIL	0	[KG.D-1]	S
CONTINENTAL			
CONTINENTAL RELEASE TO AIR	0	[KG.D-1]	S
CONTINENTAL RELEASE TO WASTE WATER	0	[KG.D-1]	S
CONTINENTAL RELEASE TO SURFACE WATER	0	[KG.D-1]	S
CONTINENTAL RELEASE TO INDUSTRIAL SOIL	0	[KG.D-1]	S
USE PATTERN 3			
RELEASE FRACTIONS AND EMISSION DAYS [3 ""]			
INDUSTRIAL USE			
EMISSION TABLES	A3.3 (IC-SPECIFIC), B3.2 (GENERAL TABLE)		S
EMISSION DAYS			
FRACTION OF THE MAIN LOCAL SOURCE	1	[-]	S

NUMBER OF EMISSION DAYS PER YEAR	20	[-]	S
REGIONAL AND CONTINENTAL RELEASES [3 ""]			
INDUSTRIAL USE			
REGIONAL			
REGIONAL RELEASE TO AIR	0	[KG.D-1]	S
REGIONAL RELEASE TO WASTE WATER	0	[KG.D-1]	S
REGIONAL RELEASE TO SURFACE WATER	0	[KG.D-1]	S
REGIONAL RELEASE TO INDUSTRIAL SOIL	0	[KG.D-1]	S
REGIONAL AND CONTINENTAL TOTAL EMISSIONS			
TOTAL REGIONAL EMISSION TO AIR	2,63562E-04	[TONNES.D-1]	S
TOTAL REGIONAL EMISSION TO WASTEWATER	2,08219E-07	[TONNES.D-1]	S
TOTAL REGIONAL EMISSION TO SURFACE WATER	2,63014E-06	[TONNES.D-1]	S
TOTAL REGIONAL EMISSION TO INDUSTRIAL SOIL	5,47946E-09	[TONNES.D-1]	S
TOTAL CONTINENTAL EMISSION TO AIR	2,37151E-03	[TONNES.D-1]	S
TOTAL CONTINENTAL EMISSION TO WASTEWATER	1,86302E-06	[TONNES.D-1]	S
TOTAL CONTINENTAL EMISSION TO SURFACE WATER	2,36987E-05	[TONNES.D-1]	S
TOTAL CONTINENTAL EMISSION TO INDUSTRIAL SOIL	4,65754E-08	[TONNES.D-1]	S
LOCAL			
[1 ""] [INDUSTRIAL USE]			
LOCAL EMISSION TO AIR DURING EPISODE	0,032	[KG.D-1]	S
LOCAL EMISSION TO WASTEWATER DURING EPISODE	0	[KG.D-1]	S
SHOW THIS STEP IN FURTHER CALCULATIONS	YES		S
INTERMITTENT RELEASE	NO		S
[2 ""] [INDUSTRIAL USE]			
LOCAL EMISSION TO AIR DURING EPISODE	3,4E-04	[KG.D-1]	S
LOCAL EMISSION TO WASTEWATER DURING EPISODE	6,9E-03	[KG.D-1]	S
SHOW THIS STEP IN FURTHER CALCULATIONS	YES		S
INTERMITTENT RELEASE	NO		S
[3 ""] [INDUSTRIAL USE]			
LOCAL EMISSION TO AIR DURING EPISODE	0,01	[KG.D-1]	S
LOCAL EMISSION TO WASTEWATER DURING EPISODE	0	[KG.D-1]	S
SHOW THIS STEP IN FURTHER CALCULATIONS	YES		S
INTERMITTENT RELEASE	NO		S
DISTRIBUTION			
SEWAGE TREATMENT			
LOCAL			
[1 ""] [INDUSTRIAL USE]			
INPUT AND CONFIGURATION [1 ""] [INDUSTRIAL USE]			
INPUT			
USE OR BYPASS STP (LOCAL FRESH WATER ASSESSMENT)	USE STP		S
LOCAL EMISSION TO WASTEWATER DURING EPISODE	0	[KG.D-1]	S
CONFIGURATION			
TYPE OF LOCAL STP	WITH PRIMARY SETTLER (9-BOX)		S
CALCULATE DILUTION FROM RIVER FLOW RATE	YES		S
FLOW RATE OF THE RIVER	1,67E+07	[M3.D-1]	S
DILUTION FACTOR (RIVERS)	8,123E+03	[-]	S
OUTPUT [1 ""] [INDUSTRIAL USE]			
CONCENTRATION IN EFFLUENT EXCEEDS SOLUBILITY	NO		S
[2 ""] [INDUSTRIAL USE]			
INPUT AND CONFIGURATION [2 ""] [INDUSTRIAL USE]			
INPUT			
USE OR BYPASS STP (LOCAL FRESH WATER ASSESSMENT)	USE STP		S
LOCAL EMISSION TO WASTEWATER DURING EPISODE	6,9E-03	[KG.D-1]	S
CONFIGURATION			
TYPE OF LOCAL STP	WITH PRIMARY SETTLER (9-BOX)		S
NUMBER OF INHABITANTS FEEDING THIS STP	3,3E+05	[EQ]	S
CALCULATE DILUTION FROM RIVER FLOW RATE	NO		S
DILUTION FACTOR (RIVERS)	1	[-]	S
OUTPUT [2 ""] [INDUSTRIAL USE]			
CONCENTRATION IN EFFLUENT EXCEEDS SOLUBILITY	NO		S
[3 ""] [INDUSTRIAL USE]			
INPUT AND CONFIGURATION [3 ""] [INDUSTRIAL USE]			
INPUT			
USE OR BYPASS STP (LOCAL FRESH WATER ASSESSMENT)	USE STP		S

LOCAL EMISSION TO WASTEWATER DURING EPISODE	0	[KG.D-1]	S
CONFIGURATION			
TYPE OF LOCAL STP	WITH PRIMARY SETTLER (9-BOX)		S
CALCULATE DILUTION FROM RIVER FLOW RATE	NO		S
DILUTION FACTOR (RIVERS)	10	[-]	S
OUTPUT [3 ""] [INDUSTRIAL USE]			
CONCENTRATION IN EFFLUENT EXCEEDS SOLUBILITY	NO		S
REGIONAL, CONTINENTAL AND GLOBAL DISTRIBUTION			
PECS			
REGIONAL			
REGIONAL PEC IN SURFACE WATER (TOTAL)	7,77E-09	[UG.L-1]	O
REGIONAL PEC IN SEA WATER (TOTAL)	7,78E-14	[MG.L-1]	O
REGIONAL PEC IN SURFACE WATER (DISSOLVED)	7,72E-09	[UG.L-1]	O
QUALITATIVE ASSESSMENT MIGHT BE NEEDED (TGD PART II, 5.6)	NO		O
REGIONAL PEC IN SEA WATER (DISSOLVED)	7,77E-14	[MG.L-1]	O
QUALITATIVE ASSESSMENT MIGHT BE NEEDED (TGD PART II, 5.6)	NO		O
REGIONAL PEC IN AIR (TOTAL)	7,56E-06	[UG.M-3]	O
REGIONAL PEC IN AGRICULTURAL SOIL (TOTAL)	1,81E-09	[MG.KGWWT-1]	O
REGIONAL PEC IN PORE WATER OF AGRICULTURAL SOILS	2,4E-11	[MG.L-1]	O
REGIONAL PEC IN NATURAL SOIL (TOTAL)	1,02E-09	[MG.KGWWT-1]	O
REGIONAL PEC IN INDUSTRIAL SOIL (TOTAL)	2E-09	[MG.KGWWT-1]	O
REGIONAL PEC IN SEDIMENT (TOTAL)	1,26E-09	[MG.KGWWT-1]	O
REGIONAL PEC IN SEA WATER SEDIMENT (TOTAL)	1,09E-11	[MG.KGWWT-1]	O
CONTINENTAL			
CONTINENTAL PEC IN SURFACE WATER (TOTAL)	8,15E-13	[MG.L-1]	O
CONTINENTAL PEC IN SEA WATER (TOTAL)	1,29E-16	[MG.L-1]	O
CONTINENTAL PEC IN SURFACE WATER (DISSOLVED)	8,1E-13	[MG.L-1]	O
CONTINENTAL PEC IN SEA WATER (DISSOLVED)	1,29E-16	[MG.L-1]	O
CONTINENTAL PEC IN AIR (TOTAL)	3,19E-09	[MG.M-3]	O
CONTINENTAL PEC IN AGRICULTURAL SOIL (TOTAL)	4,14E-10	[MG.KGWWT-1]	O
CONTINENTAL PEC IN PORE WATER OF AGRICULTURAL SOILS	5,48E-12	[MG.L-1]	O
CONTINENTAL PEC IN NATURAL SOIL (TOTAL)	4,29E-10	[MG.KGWWT-1]	O
CONTINENTAL PEC IN INDUSTRIAL SOIL (TOTAL)	5,25E-10	[MG.KGWWT-1]	O
CONTINENTAL PEC IN SEDIMENT (TOTAL)	1,32E-10	[MG.KGWWT-1]	O
CONTINENTAL PEC IN SEA WATER SEDIMENT (TOTAL)	1,8E-14	[MG.KGWWT-1]	O
GLOBAL: MODERATE			
MODERATE PEC IN WATER (TOTAL)	4,03E-18	[MG.L-1]	O
MODERATE PEC IN WATER (DISSOLVED)	4,02E-18	[MG.L-1]	O
MODERATE PEC IN AIR (TOTAL)	4,99E-10	[MG.M-3]	O
MODERATE PEC IN SOIL (TOTAL)	6,71E-11	[MG.KGWWT-1]	O
MODERATE PEC IN SEDIMENT (TOTAL)	5,64E-16	[MG.KGWWT-1]	O
GLOBAL: ARCTIC			
ARCTIC PEC IN WATER (TOTAL)	4,42E-17	[MG.L-1]	O
ARCTIC PEC IN WATER (DISSOLVED)	4,41E-17	[MG.L-1]	O
ARCTIC PEC IN AIR (TOTAL)	3,18E-10	[MG.M-3]	O
ARCTIC PEC IN SOIL (TOTAL)	1,84E-10	[MG.KGWWT-1]	O
ARCTIC PEC IN SEDIMENT (TOTAL)	6,26E-15	[MG.KGWWT-1]	O
GLOBAL: TROPIC			
TROPIC PEC IN WATER (TOTAL)	4,27E-19	[MG.L-1]	O
TROPIC PEC IN WATER (DISSOLVED)	4,26E-19	[MG.L-1]	O
TROPIC PEC IN AIR (TOTAL)	2,58E-10	[MG.M-3]	O
TROPIC PEC IN SOIL (TOTAL)	1,67E-11	[MG.KGWWT-1]	O
TROPIC PEC IN SEDIMENT (TOTAL)	5,85E-17	[MG.KGWWT-1]	O
STEADY-STATE FRACTIONS			
REGIONAL			
STEADY-STATE MASS FRACTION IN REGIONAL FRESH WATER	2,57E-05	[%]	O
STEADY-STATE MASS FRACTION IN REGIONAL SEA WATER	2,86E-07	[%]	O
STEADY-STATE MASS FRACTION IN REGIONAL AIR	0,28	[%]	O
STEADY-STATE MASS FRACTION IN REGIONAL AGRICULTURAL SOIL	0,0136	[%]	O
STEADY-STATE MASS FRACTION IN REGIONAL NATURAL SOIL	8,57E-04	[%]	O
STEADY-STATE MASS FRACTION IN REGIONAL INDUSTRIAL SOIL	6,26E-04	[%]	O
STEADY-STATE MASS FRACTION IN REGIONAL FRESH WATER SEDIMENT	4,79E-05	[%]	O
STEADY-STATE MASS FRACTION IN REGIONAL SEA WATER SEDIMENT	1,38E-07	[%]	O
CONTINENTAL			
STEADY-STATE MASS FRACTION IN CONTINENTAL FRESH WATER	2,36E-04	[%]	O
STEADY-STATE MASS FRACTION IN CONTINENTAL SEA WATER	8,29E-05	[%]	O
STEADY-STATE MASS FRACTION IN CONTINENTAL AIR	20,5	[%]	O

STEADY-STATE MASS FRACTION IN CONTINENTAL AGRICULTURAL SOIL	0,271	[%]	O
STEADY-STATE MASS FRACTION IN CONTINENTAL NATURAL SOIL	0,0317	[%]	O
STEADY-STATE MASS FRACTION IN CONTINENTAL INDUSTRIAL SOIL	0,0144	[%]	O
STEADY-STATE MASS FRACTION IN CONTINENTAL FRESH WATER SEDIMENT	4,4E-04	[%]	O
STEADY-STATE MASS FRACTION IN CONTINENTAL SEA WATER SEDIMENT	2E-06	[%]	O
GLOBAL: MODERATE			
STEADY-STATE MASS FRACTION IN MODERATE WATER	1,44E-04	[%]	O
STEADY-STATE MASS FRACTION IN MODERATE AIR	35,7	[%]	O
STEADY-STATE MASS FRACTION IN MODERATE SOIL	0,204	[%]	O
STEADY-STATE MASS FRACTION IN MODERATE SEDIMENT	6,96E-07	[%]	O
GLOBAL: ARCTIC			
STEADY-STATE MASS FRACTION IN ARCTIC WATER	1,04E-03	[%]	O
STEADY-STATE MASS FRACTION IN ARCTIC AIR	12,4	[%]	O
STEADY-STATE MASS FRACTION IN ARCTIC SOIL	0,245	[%]	O
STEADY-STATE MASS FRACTION IN ARCTIC SEDIMENT	5,06E-06	[%]	O
GLOBAL: TROPIC			
STEADY-STATE MASS FRACTION IN TROPIC WATER	3,5E-05	[%]	O
STEADY-STATE MASS FRACTION IN TROPIC AIR	30,2	[%]	O
STEADY-STATE MASS FRACTION IN TROPIC SOIL	0,0498	[%]	O
STEADY-STATE MASS FRACTION IN TROPIC SEDIMENT	1,65E-07	[%]	O
STEADY-STATE MASSES			
REGIONAL			
STEADY-STATE MASS IN REGIONAL FRESH WATER	2,8E-05	[KG]	O
STEADY-STATE MASS IN REGIONAL SEA WATER	3,11E-07	[KG]	O
STEADY-STATE MASS IN REGIONAL AIR	0,305	[KG]	O
STEADY-STATE MASS IN REGIONAL AGRICULTURAL SOIL	0,0148	[KG]	O
STEADY-STATE MASS IN REGIONAL NATURAL SOIL	9,33E-04	[KG]	O
STEADY-STATE MASS IN REGIONAL INDUSTRIAL SOIL	6,81E-04	[KG]	O
STEADY-STATE MASS IN REGIONAL FRESH WATER SEDIMENT	5,22E-05	[KG]	O
STEADY-STATE MASS IN REGIONAL SEA WATER SEDIMENT	1,5E-07	[KG]	O
CONTINENTAL			
STEADY-STATE MASS IN CONTINENTAL FRESH WATER	2,57E-04	[KG]	O
STEADY-STATE MASS IN CONTINENTAL SEA WATER	9,02E-05	[KG]	O
STEADY-STATE MASS IN CONTINENTAL AIR	22,4	[KG]	O
STEADY-STATE MASS IN CONTINENTAL AGRICULTURAL SOIL	0,295	[KG]	O
STEADY-STATE MASS IN CONTINENTAL NATURAL SOIL	0,0345	[KG]	O
STEADY-STATE MASS IN CONTINENTAL INDUSTRIAL SOIL	0,0156	[KG]	O
STEADY-STATE MASS IN CONTINENTAL FRESH WATER SEDIMENT	4,79E-04	[KG]	O
STEADY-STATE MASS IN CONTINENTAL SEA WATER SEDIMENT	2,18E-06	[KG]	O
GLOBAL: MODERATE			
STEADY-STATE MASS IN MODERATE WATER	1,57E-04	[KG]	O
STEADY-STATE MASS IN MODERATE AIR	38,9	[KG]	O
STEADY-STATE MASS IN MODERATE SOIL	0,222	[KG]	O
STEADY-STATE MASS IN MODERATE SEDIMENT	7,58E-07	[KG]	O
GLOBAL: ARCTIC			
STEADY-STATE MASS IN ARCTIC WATER	1,13E-03	[KG]	O
STEADY-STATE MASS IN ARCTIC AIR	13,5	[KG]	O
STEADY-STATE MASS IN ARCTIC SOIL	0,266	[KG]	O
STEADY-STATE MASS IN ARCTIC SEDIMENT	5,5E-06	[KG]	O
GLOBAL: TROPIC			
STEADY-STATE MASS IN TROPIC WATER	3,81E-05	[KG]	O
STEADY-STATE MASS IN TROPIC AIR	32,9	[KG]	O
STEADY-STATE MASS IN TROPIC SOIL	0,0542	[KG]	O
STEADY-STATE MASS IN TROPIC SEDIMENT	1,8E-07	[KG]	O
LOCAL PECS [INDUSTRIAL USE]			
ANNUAL AVERAGE LOCAL PEC IN AIR (TOTAL)	7,32E-03	[UG.M-3]	O
LOCAL PEC IN SURFACE WATER DURING EMISSION EPISODE (DISSOLVED)	7,72E-12	[MG.L-1]	O
QUALITATIVE ASSESSMENT MIGHT BE NEEDED (TGD PART II, 5.6)	NO		O
ANNUAL AVERAGE LOCAL PEC IN SURFACE WATER (DISSOLVED)	7,72E-09	[UG.L-1]	O
LOCAL PEC IN FRESH-WATER SEDIMENT DURING EMISSION EPISODE	7,21E-10	[MG.KGWWT-1]	O
LOCAL PEC IN SEA WATER DURING EMISSION EPISODE (DISSOLVED)	7,77E-14	[MG.L-1]	O
QUALITATIVE ASSESSMENT MIGHT BE NEEDED (TGD PART II, 5.6)	NO		O
ANNUAL AVERAGE LOCAL PEC IN SEA WATER (DISSOLVED)	7,77E-14	[MG.L-1]	O
LOCAL PEC IN MARINE SEDIMENT DURING EMISSION EPISODE	7,26E-12	[MG.KGWWT-1]	O
LOCAL PEC IN AGRIC. SOIL (TOTAL) AVERAGED OVER 30 DAYS	1,04E-06	[MG.KGWWT-1]	O
LOCAL PEC IN AGRIC. SOIL (TOTAL) AVERAGED OVER 180 DAYS	1,04E-06	[MG.KGWWT-1]	O
LOCAL PEC IN GRASSLAND (TOTAL) AVERAGED OVER 180 DAYS	1,09E-06	[MG.KGWWT-1]	O

LOCAL PEC IN PORE WATER OF AGRICULTURAL SOIL	1,37E-08	[MG.L-1]	O
LOCAL PEC IN PORE WATER OF GRASSLAND	1,45E-08	[MG.L-1]	O
LOCAL PEC IN GROUNDWATER UNDER AGRICULTURAL SOIL	1,37E-08	[MG.L-1]	O
LOCAL PECS [INDUSTRIAL USE]			
ANNUAL AVERAGE LOCAL PEC IN AIR (TOTAL)	3,01E-04	[UG.M-3]	O
LOCAL PEC IN SURFACE WATER DURING EMISSION EPISODE (DISSOLVED)	5,43E-03	[UG.L-1]	O
QUALITATIVE ASSESSMENT MIGHT BE NEEDED (TGD PART II, 5.6)	NO		O
ANNUAL AVERAGE LOCAL PEC IN SURFACE WATER (DISSOLVED)	1,19E-03	[UG.L-1]	O
LOCAL PEC IN FRESH-WATER SEDIMENT DURING EMISSION EPISODE	5,08E-04	[MG.KGWWT-1]	O
LOCAL PEC IN SEA WATER DURING EMISSION EPISODE (DISSOLVED)	1,04E-06	[MG.L-1]	O
QUALITATIVE ASSESSMENT MIGHT BE NEEDED (TGD PART II, 5.6)	NO		O
ANNUAL AVERAGE LOCAL PEC IN SEA WATER (DISSOLVED)	2,28E-07	[MG.L-1]	O
LOCAL PEC IN MARINE SEDIMENT DURING EMISSION EPISODE	9,71E-05	[MG.KGWWT-1]	O
LOCAL PEC IN AGRIC. SOIL (TOTAL) AVERAGED OVER 30 DAYS	7,08E-05	[MG.KGWWT-1]	O
LOCAL PEC IN AGRIC. SOIL (TOTAL) AVERAGED OVER 180 DAYS	2,37E-05	[MG.KGWWT-1]	O
LOCAL PEC IN GRASSLAND (TOTAL) AVERAGED OVER 180 DAYS	5,12E-06	[MG.KGWWT-1]	O
LOCAL PEC IN PORE WATER OF AGRICULTURAL SOIL	3,14E-07	[MG.L-1]	O
LOCAL PEC IN PORE WATER OF GRASSLAND	6,78E-08	[MG.L-1]	O
LOCAL PEC IN GROUNDWATER UNDER AGRICULTURAL SOIL	3,14E-07	[MG.L-1]	O
LOCAL PECS [INDUSTRIAL USE]			
ANNUAL AVERAGE LOCAL PEC IN AIR (TOTAL)	1,6E-04	[UG.M-3]	O
LOCAL PEC IN SURFACE WATER DURING EMISSION EPISODE (DISSOLVED)	7,72E-09	[UG.L-1]	O
QUALITATIVE ASSESSMENT MIGHT BE NEEDED (TGD PART II, 5.6)	NO		O
ANNUAL AVERAGE LOCAL PEC IN SURFACE WATER (DISSOLVED)	7,72E-12	[MG.L-1]	O
LOCAL PEC IN FRESH-WATER SEDIMENT DURING EMISSION EPISODE	7,21E-10	[MG.KGWWT-1]	O
LOCAL PEC IN SEA WATER DURING EMISSION EPISODE (DISSOLVED)	7,77E-14	[MG.L-1]	O
QUALITATIVE ASSESSMENT MIGHT BE NEEDED (TGD PART II, 5.6)	NO		O
ANNUAL AVERAGE LOCAL PEC IN SEA WATER (DISSOLVED)	7,77E-14	[MG.L-1]	O
LOCAL PEC IN MARINE SEDIMENT DURING EMISSION EPISODE	7,26E-12	[MG.KGWWT-1]	O
LOCAL PEC IN AGRIC. SOIL (TOTAL) AVERAGED OVER 30 DAYS	2,26E-08	[MG.KGWWT-1]	O
LOCAL PEC IN AGRIC. SOIL (TOTAL) AVERAGED OVER 180 DAYS	2,26E-08	[MG.KGWWT-1]	O
LOCAL PEC IN GRASSLAND (TOTAL) AVERAGED OVER 180 DAYS	2,37E-08	[MG.KGWWT-1]	O
LOCAL PEC IN PORE WATER OF AGRICULTURAL SOIL	2,99E-10	[MG.L-1]	O
LOCAL PEC IN PORE WATER OF GRASSLAND	3,14E-10	[MG.L-1]	O
LOCAL PEC IN GROUNDWATER UNDER AGRICULTURAL SOIL	2,99E-10	[MG.L-1]	O
EFFECTS			
INPUT OF EFFECTS DATA			
MICRO-ORGANISMS			
TEST SYSTEM	RESPIRATION INHIBITION, EU ANNEX V C.11, OECD 209		D
EC50 FOR MICRO-ORGANISMS IN A STP	>100	[MG.L-1]	S
EC10 FOR MICRO-ORGANISMS IN A STP	100	[MG.L-1]	S
AQUATIC ORGANISMS			
FRESH WATER			
L(E)C50 SHORT-TERM TESTS			
LC50 FOR FISH	7	[UG.L-1]	S
L(E)C50 FOR DAPHNIA	7	[UG.L-1]	S
EC50 FOR ALGAE	3,5	[UG.L-1]	S
NOEC LONG-TERM TESTS			
NOEC FOR FISH	3,7	[UG.L-1]	S
NOEC FOR DAPHNIA	0,3	[UG.L-1]	S
NOEC FOR ALGAE	25	[UG.L-1]	S
MAMMALS			
REPEATED DOSE			
ORAL			
ORAL NOAEL (REPDOSE)	3,33	[MG.KG-1.D-1]	S
ORAL LOAEL (REPDOSE)	10	[MG.KG-1.D-1]	S
SPECIES FOR CONVERSION OF NOAEL TO NOEC	RATTUS NORVEGICUS (<=6 WEEKS)		D
CONVERSION FACTOR NOAEL TO NOEC	10	[KG.D.KG-1]	O
NOEC VIA FOOD (REPDOSE)	33,3	[MG.KG-1]	O
INHALATORY			
INHALATORY NOAEL (REPDOSE)	5,83E-03	[MG.L-1]	O
INHALATORY LOAEL (REPDOSE)	0,0175	[MG.L-1]	O
DERMAL			
DERMAL NOAEL (REPDOSE)	33,3	[MG.KG-1.D-1]	O
DERMAL LOAEL (REPDOSE)	100	[MG.KG-1.D-1]	O
PREDATOR			
DURATION OF (SUB-)CHRONIC ORAL TEST	28 DAYS		S

NOEC VIA FOOD FOR SECONDARY POISONING	33,3	[MG.KG-1]	O
SOURCE FOR NOEC-VIA-FOOD DATA	NO DATA AVAILABLE, ENTER MANUALLY		S
ENVIRONMENTAL EFFECTS ASSESSMENT			
ENVIRONMENTAL PNECS			
FRESH WATER			
TOXICOLOGICAL DATA USED FOR EXTRAPOLATION TO PNEC AQUA	3E-04	[MG.L-1]	O
ASSESSMENT FACTOR APPLIED IN EXTRAPOLATION TO PNEC AQUA	10	[-]	O
PNEC FOR AQUATIC ORGANISMS	3E-05	[MG.L-1]	O
FRESH WATER SEDIMENT			
PNEC FOR FRESH-WATER SEDIMENT ORGANISMS (EQUILIBRIUM PARTITIONING)	2,47E-03	[MG.KGWWT-1]	O
EQUILIBRIUM PARTITIONING USED FOR PNEC IN FRESH-WATER SEDIMENT?	YES		S
PNEC FOR FRESH-WATER SEDIMENT-DWELLING ORGANISMS	2,47E-03	[MG.KGWWT-1]	O
TERRESTRIAL			
PNEC FOR TERRESTRIAL ORGANISMS (EQUILIBRIUM PARTITIONING)	2,26E-03	[MG.KGWWT-1]	O
EQUILIBRIUM PARTITIONING USED FOR PNEC IN SOIL?	YES		S
PNEC FOR TERRESTRIAL ORGANISMS	2,26E-03	[MG.KGWWT-1]	O
SECONDARY POISONING			
TOXICOLOGICAL DATA USED FOR EXTRAPOLATION TO PNEC ORAL	33,3	[MG.KG-1]	O
ASSESSMENT FACTOR APPLIED IN EXTRAPOLATION TO PNEC ORAL	90	[-]	S
PNEC FOR SECONDARY POISONING OF BIRDS AND MAMMALS	0,37	[MG.KG-1]	O
STP			
TOXICOLOGICAL DATA USED FOR EXTRAPOLATION TO PNEC MICRO	100	[MG.L-1]	S
ASSESSMENT FACTOR APPLIED IN EXTRAPOLATION TO PNEC MICRO	10	[-]	S
PNEC FOR MICRO-ORGANISMS IN A STP	10	[MG.L-1]	O
RISK CHARACTERIZATION			
ENVIRONMENTAL EXPOSURE			
LOCAL			
RISK CHARACTERIZATION OF [1 ""] [INDUSTRIAL USE]			
WATER			
RCR FOR THE LOCAL FRESH-WATER COMPARTMENT	2,57E-07	[-]	O
SEDIMENT			
RCR FOR THE LOCAL FRESH-WATER SEDIMENT COMPARTMENT	2,94E-07	[-]	O
SOIL			
RCR FOR THE LOCAL SOIL COMPARTMENT	4,57E-04	[-]	O
STP			
RCR FOR THE SEWAGE TREATMENT PLANT	0	[-]	O
PREDATORS			
RCR FOR FISH-EATING BIRDS AND MAMMALS (FRESH-WATER)	2,29E-10	[-]	O
RCR FOR WORM-EATING BIRDS AND MAMMALS	2,21E-05	[-]	O
RISK CHARACTERIZATION OF [2 ""] [INDUSTRIAL USE]			
WATER			
RCR FOR THE LOCAL FRESH-WATER COMPARTMENT	0,181	[-]	O
SEDIMENT			
RCR FOR THE LOCAL FRESH-WATER SEDIMENT COMPARTMENT	0.206	[-]	O
SOIL			
RCR FOR THE LOCAL SOIL COMPARTMENT	3,13E-02	[-]	O
STP			
RCR FOR THE SEWAGE TREATMENT PLANT	5,46E-07	[-]	O
PREDATORS			
RCR FOR FISH-EATING BIRDS AND MAMMALS (FRESH-WATER)	1,77E-05	[-]	O
RCR FOR WORM-EATING BIRDS AND MAMMALS	5,05E-04	[-]	O
RISK CHARACTERIZATION OF [3 ""] [INDUSTRIAL USE]			
WATER			
RCR FOR THE LOCAL FRESH-WATER COMPARTMENT	2,57E-07	[-]	O
SEDIMENT			
RCR FOR THE LOCAL FRESH-WATER SEDIMENT COMPARTMENT	2,94E-07	[-]	O
SOIL			

RCR FOR THE LOCAL SOIL COMPARTMENT	9,78E-06	[-]	O
STP			
RCR FOR THE SEWAGE TREATMENT PLANT	0	[-]	O
PREDATORS			
RCR FOR FISH-EATING BIRDS AND MAMMALS (FRESH-WATER)	2,29E-10	[-]	O
RCR FOR WORM-EATING BIRDS AND MAMMALS	5,19E-07	[-]	O
REGIONAL			
WATER			
RCR FOR THE REGIONAL FRESH-WATER COMPARTMENT	2,57E-07	[-]	O
SEDIMENT			
RCR FOR THE REGIONAL FRESH-WATER SEDIMENT COMPARTMENT	4,73E-07	[-]	O
SOIL			
RCR FOR THE REGIONAL SOIL COMPARTMENT	4.95E-07	[-]	O

APPENDIX C

Endosulfan application data

Country	Crop	Conc.	AR	No. Apl
		[w/w]	[kg ai/ha]	[-]
Belgium	Fruits	0.35	0.35-1.75	-
	Berries	0.35		-
	Strawberry	0.35	0.525	-
	Mushrooms	0.35	14	-
	Potato	0.35	0.175-0.525	-
	Rape	0.35	0.6-0.7	-
Finland	Currant, Black	0.35	0.375-1.5	1-2
	Strawberry	0.35	0.75-1.5	1
Greece	Apple	0.35	0.074-0.098	1
	Pear	0.35	0.074-0.098	1
	Cherry	0.35	0.074-0.098	1
	Grapes	0.35	0.074-0.098	1
	Strawberry	0.35	0.074-0.098	1-2
	Olives	0.35	0.074-0.098	1-2
	Cucumber	0.35	0.074-0.098	1
	Melon	0.35	0.074-0.098	1-3
	Squash, summer	0.35	0.074-0.098	1-3
	Watermelon	0.35	0.074-0.098	1-3
	Egg plant	0.35	0.074-0.098	1-3
	Peppers	0.35	0.074-0.098	1-3
	Tomato	0.35	0.074-0.098	1-3
	Potato	0.35	0.074-0.098	1-3
	Cotton	0.35	0.074-0.098	1-2
	Alfalfa (seed)	0.35	0.074-0.098	1
	Clover (seed)	0.35	0.074-0.098	1
Ireland	Apple & Pear	0.50	0.625-0.85	-
	Currant, Black, White & Red	0.50	0.625-0.85	-
	Brassicas	0.50	0.625-0.85	-
	Beans	0.50	0.625-0.85	-
	Cucumber	0.50	0.625-0.85	-
	Tomato & Pepper	0.50	0.625-0.85	-
	Carrot	0.50	0.625-0.85	-
	Potato	0.50	0.625-0.85	-
	Sugar Beet	0.50	0.625-0.85	-
	Celery	0.50	0.625-0.85	-
	Rape	0.50	0.625-0.85	-
Italy	Citrus fruits	0.33	1	1
	Peach	0.33	0.75	1
	Grapes	0.33	0.5	1-2
	Vegetables	0.33	0.5	1-2
	Tomato	0.33	0.5	1-2
	Potato	0.33	0.5	1-2
	Sugar Beet	0.33	0.5	1-2
	Tree nut	0.33	0.5	1-2

Endosulfan application data, continued

Country	Crop	Conc.	AR	No. Apl
		[w/w]	[kg ai/ha]	[-]
Portugal	Apple & Pear	0.35	1.2-2.45	-
	Brassicas	0.35	1.2-2.45	1-3
	Cabbage	0.35	1.2-2.45	1-3
	Tomato	0.35	1.2-2.45	-
	Maize	0.35	1.2-2.45	-
	Sugar Cane	0.35	1.2-2.45	-
Spain	Citrus fruits	0.35	2.1-6.3	1-3
	Stone fruits	0.30	0.675-1.35	-
	Grapes	0.35	0.32-0.63	1-3
	Olives	0.35	0.53-1.58	-
	Brassicas	0.35	0.53-1.58	-
	Cucurbite	0.35	0.53-1.58	-
	Egg plant	0.35	0.53-1.58	-
	Peppers	0.35	0.53-1.58	-
	Tomato	0.35	0.53-1.58	-
	Potato	0.35	0.53-1.58	-
	Asparague	0.35	0.53-1.58	-
	Hazelnuts	0.35	0.53-1.58	1-3
	Cotton	0.35	0.53-1.58	1-3
Sweden	Currants, Black	0.35	0.35-0.7	1
	Strawberry	0.35	0.35-1.05	1-2
UK	Blackberries	0.20	0.5	3
	Currant, Black	0.20	0.6	3
	Currant, Black	0.20	0.9	3
	Strawberry	0.20	0.5	1

Conc.: concentration, weight fraction

AR: application rate in kg active ingredient (a.i.) per ha

No. Apl: number of applications during growing season

European Commission

EUR [ECB: click here to insert EUR No.] - European Union Risk Assessment Report [ECB: click here to insert SUBSTANCE NAME, and volume no.]

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Environment and quality of life series

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The report provides the comprehensive risk assessment of the substance hexachlorocyclopentadiene (HCCP). It has been prepared by the Netherlands in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

Part I - Environment

This part of the evaluation considers the emissions and the resulting exposure to the environment in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined.

The environmental risk assessment concludes that there is no concern for any compartment arising from the use of the substance.

Part II – Human Health

This part of the evaluation considers the emissions and the resulting exposure to human populations in all life cycle steps. The scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

There is concern for systemic effects after repeated exposure to hexachlorocyclopentadiene (HCCP) for workers using HCCP in the production of pesticides and flame retardants, as well as in occupational scenarios using products containing residual HCCP, or with unintentional formation/occurrence of HCCP. For the two first scenarios, there is also concern for local effects in the respiratory systems. There is no occupational concern for the endpoints acute toxicity, irritation, sensitisation, mutagenicity, carcinogenicity, and reproductive toxicity.

There is no concern for any endpoints for consumers and humans exposed via the environment.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commission's committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.