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INTEGRATED CRITERIA DOCUMENT CHLOROBENZENES

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Mailing list Integrated Criteria Document Chlorobenzenes

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CONTENTS

SUMMARY

This document on the subject of chlorobenzenes contains data concerning sources and distribution, the risks based on a comparison of exposure levels and toxic concentrations, and also technical possibilities of reducing these risks.

The chlorobenzenes are a group comprising 12 compounds, which are characterized by a basic structure consisting of a benzene ring on which from one to all six hydrogen atoms have been replaced by chlorine atoms. Chlorobenzenes do not occur naturally: they are produced by man, usually by chlorination of benzene, but can possibly also be formed when different streams of waste water are combined and/or by degradation of chlorinated aromatics. There are standards and guidelines in the Netherlands for soil and groundwater, and for surface water and sediments.
Chlorobenzenes are not produced commercially in the Netherlands. However, one industrial process generates hexachlorobenzene as a by-product (430 tonnes per year), which is exported as waste. The annual consumption of chlorobenzenes is approximately 1800 tonnes, including about 1100 tonnes of monochlorobenzene as a solvent. The chlorobenzene input to the environment in the Netherlands has generally decreased during the past few years. In 1987, the total chlorobenzene emission into soil, water and air was 2, 7.5 and 370 tonnes per year, respectively. In addition, 740 tonnes of chlorobenzenes are generated annually as waste. 1,4-Dichlorobenzene is the most important congener both quantitatively and qualitatively. Diffuse atmospheric emission is the major pathway for entry of this compound into the environment (260 tonnes per year), mainly from the use of air fresheners, including urinal tablets. A summary of the fluxes in the environment is given in figure A.

The rate at which chlorobenzenes are degraded in the environment varies from a few days to several years, depending on the degree of chlorination, the matrix and environmental conditions.

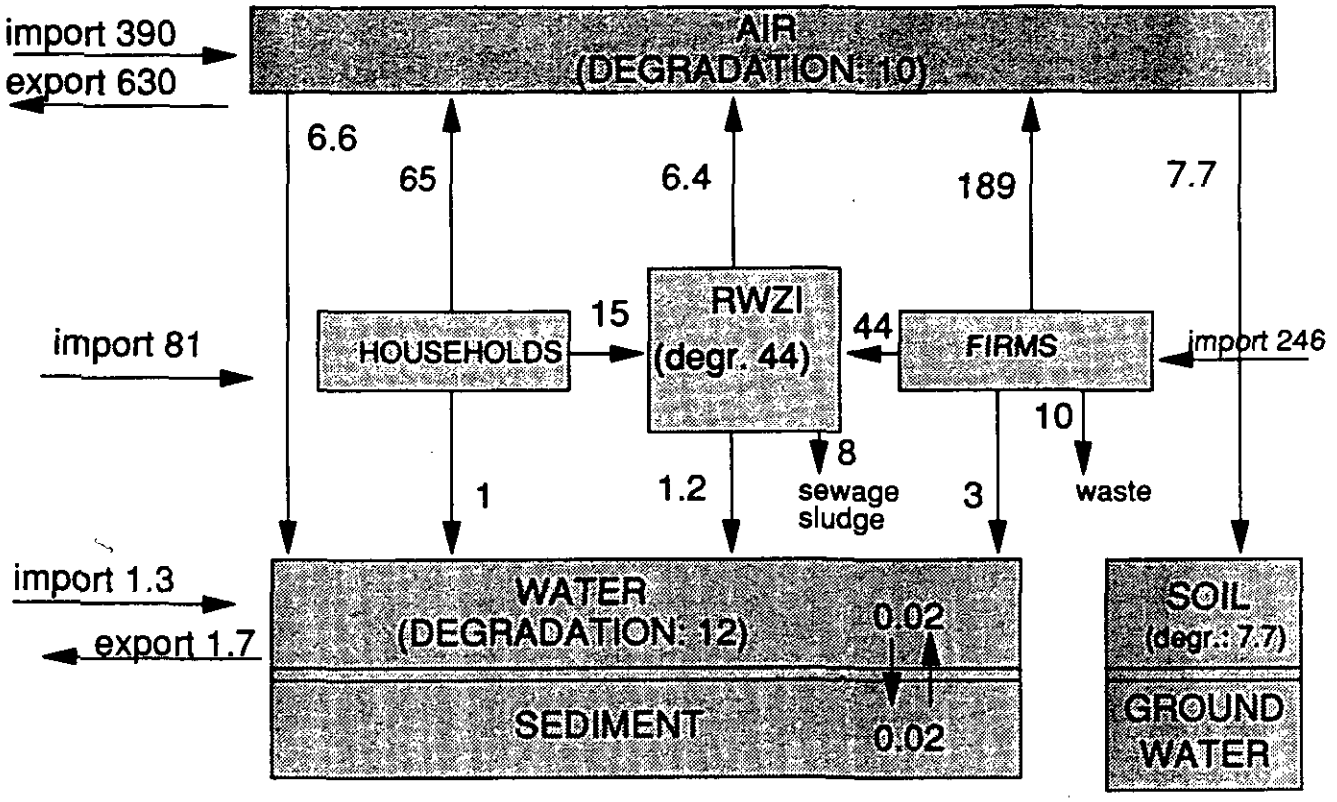

Figure A. Schematic summary of the 1,4-dichlorobenzene emissions in the Netherlands, the contributions from abroad, and the flows in the Dutch environment (in tonnes, base year 1987)

Data on the occurrence of chlorobenzenes in the environment are not complete. There are usually also insufficient toxicological data available for deriving maximum permissible concentrations. Although for this reason a definitive statement cannot be made about the risks of chlorobenzenes, there are sufficient indications for supposing that the risks associated with the current exposure levels are limited.

* The toxicologically maximum acceptable oral dose for man is (as far as is known) at least a factor of 100 higher than the actual exposure level. It is assumed that this is also true of those chlorobenzenes for which insufficient toxicological data are available for underpinning a recommended level, provided these chlorobenzenes are not genotoxic carcinogens.

  With regard to inhalation exposure, the toxicological data are insufficient for deriving recommended levels. The no-effect levels, as determined experimentally in animals for the lower chlorinated benzenes (100-2000 $mg.m^{-3}$), are however more than a million times higher than the average exposure concentration in the ambient air. For those chlorobenzenes for which no effect data are available, too, the risk

average exposure concentration in the ambient air. For those chlorobenzenes for which no effect data are available, too, the risk appears to be limited in view of the low source strengths. 1,4-Dichlorobenzene seems to entail the greatest risk. This congener is present at the highest concentration in air and is, albeit with limited evidence, considered to be a carcinogen with a threshold. However, indicative estimates show that this risk is also limited. Taking into account the autonomous developments, in which the 1,4-dichlorobenzene emission will fall further (about 350 tonnes in 1985, about 260 tonnes in 1987, about 100 tonnes in 1988, 0-80 tonnes in the 1990s) because of reduced use, the risk of 1,4-dichlorobenzene is negligible.

* Methods for deriving toxicological recommended levels for ecosystems are currently under discussion. The data for water are insufficient to derive a maximum acceptable risk level. In order to give an indication, a modification of the EPA method was employed, in which values were derived on the basis of chronic experimental data and chronic quantitative structure-activity relationships. If 1% of these indicative maximum acceptable risk levels were used as a basis for establishing desirable levels, then the concentrations in the Dutch surface waters are usually below these desirable levels.

  Values for sediment were derived on the basis of the indicative maximum acceptable risk levels proposed for water, using partition coefficients applying for sediment. Data on concentrations in sediments are available mostly for hexachlorobenzene. On a national scale, they are usually at least a factor of 1000 lower than the indicative maximum acceptable risk levels. Based on the properties of the chlorobenzenes (HCB is comparatively strongly accumulative), it is assumed that the risks from exposure to the other congeners are also limited. It should be noted that the current proposal for the hexachlorobenzene concentration (M list) in sediments (0.004 $mg.kg^{-1}$) is considerably lower than the recommended level derived in this report (6 $mg.kg^{-1}$).

  For soil, an indicative maximum acceptable risk level has been calculated for a number of di- and trichlorobenzenes employing the modified EPA method. Indicative values for the other congeners were derived by the use of equilibrium partition coefficients. Data on

concentrations in soil are available only for hexachlorobenzene and, as in the case of sediment, it is assumed that the risks are limited. Calculations indicate that the occurrence of biomagnification in food chains is unlikely.

In view of the autonomous developments, the exposure levels, and thereby the risks, of chlorobenzenes will decrease further in the future. Based on the risks estimated in this report, there appears to be no need for taking additional measures to reduce the emissions still further.

INTRODUCTION

Environmental policy at government level is first of all aimed at attaining and maintaining an environmental quality which ensures the general health and wellbeing of man and the preservation of animals, plants and goods, as well as specific uses of the substances in question (Indicative Multi-year Programme - Environmental Management 1986-1990). However, with insufficient knowledge it is impossible for the time being to describe fully the general environmental quality desired. Attention is therefore being concentrated on factors which are believed to entail considerable risks, such as environmentally harmful substances. A selection has been made of the many substances of relevance, because of emission or use, and a priority list compiled. So-called integrated criteria documents are drawn up for most of these priority substances.

Integrated criteria documents contain, per substance or substance group, data on the sources and the distribution pattern (soil, water, air, biota), the risks of actual exposure concentrations for man, (parts of) ecosystems and materials, and the technical possibilities and financial consequences for the industries concerned of reducing these risks. This information serves as the scientific basis for formulating the effect-oriented environmental policy. This policy is aimed at attaining as large a risk reduction as possible, the desirable level being the ultimate goal. This level is the concentration in the environment at which no adverse effects (i.e. effects the risk of which are considered to be negligible) occur for man, plants, animals and materials. If the desirable level cannot be reached within a reasonable period of time, a limit value is established for a limited period, with the risks lying between the maximum permissible and the desirable concentrations. In addition to the possible risk reduction, economic and social factors are also determinants in setting this limit value. This document is confined to the provision of information necessary for the establishment of the above-mentioned environmental quality criteria in terms of policy; the information supplied may also result in a general task-setting for the emission reductions per source type. The sections of this document do not, therefore, contain a policy opinion.

The National Institute of Public Health and Environmental Protection (RIVM) is responsible for drawing up integrated criteria documents. Haskoning, Royal Engineering and Architect's firm, participated in the realization of this report, while the Institute for Environmental Issues (IvM) also made a contribution. Government, business and industry, and representatives from scientific groups were involved in the preparation of this document. For example, the document has been checked in its entirety by a Review Committee of the RIVM, while an Advisory Board composed of staff from the Ministry of Housing, Physical Planning and the Environment (VROM), the Department of Inland Waterways/National Institute for Wastewater Research (DBW/RIZA) and the Ministry of Agriculture, Nature and Fisheries (LNV) gave guidance in its compilation. Business and industry supplied important, partly confidential, information through the ad hoc Working Group on Integrated Criteria Documents of the Office of Environment and Physical Planning of the Council of Dutch Employers' Unions, VNO and NCW. In case of differences of opinion, an addendum drawn up by the ad hoc Working Group may be added to the document. This possibility also exists for environmental groups through the Nature and Environment Foundation (Stichting Natuur en Milieu). At a later stage, the Health Council will publish a brief report on the document, including any addenda.

This document deals with chlorobenzenes, a group comprising 12 compounds, which are characterized by a basic structure consisting of a benzene ring on which from one to all six hydrogen atoms have been replaced by chlorine atoms. Chlorobenzenes are produced by man, usually by chlorination of benzene, but can possibly also be formed when different streams of wastewater are combined and/or by degradation of chlorinated aromatics. In principle, all the chlorobenzenes are evaluated. In accordance with the commission, emphasis has been laid especially on the diffuse sources, ecotoxicity and emission-control measures. In compliance with the wishes of the commissioning body, the sections concerning effects (in particular human toxicity) will be based as much as possible on existing recent reviews; the original literature is only consulted when the review papers contain inconsistent data or conclusions, and when specific data are used for deriving the toxicological recommended levels.

1. PROPERTIES AND EXISTING STANDARDS

1.1. PROPERTIES

1.1.1. Nomenclature, molecular structure and registration numbers

The names and molecular formulas of the twelve chlorobenzenes (congeners) are summarized in table 1.1.

Table 1.1. Nomenclature, molecular weight, molecular formula and Chemical Abstracts Service (CAS) registration number (NIOSH, 1983) of the chlorobenzenes

Name of the compound	*Abbreviation*	*Molecular weight*	*Molecular formula*	*CAS*
monochlorobenzene	*MCB*	*112.56*	C_6H_5Cl	*108-90-7*
1,2-dichlorobenzene	*1,2-DCB*	*147.01*	$C_6H_4Cl_2$	*95-50-1*
1,3-dichlorobenzene	*1.3-DCB*	*147.01*	$C_6H_4Cl_2$	*541-73-1*
1,4-dichlorobenzene	*1,4-DCB*	*147.01*	$C_6H_4Cl_2$	*106-46-7*
1,2,3-trichlorobenzene	*1,2,3-TCB*	*181.41*	$C_6H_3Cl_3$	*87-61-6*
1,2,4-trichlorobenzene	*1,2,4-TCB*	*181.41*	$C_6H_3Cl_3$	*120-82-1*
1,3,5-trichlorobenzene	*1,3,5-TCB*	*181.41*	$C_6H_3Cl_3$	*107-70-3*
1,2,3,4-tetrachlorobenzene	*1,2,3,4-TeCB*	*215.86*	$C_6H_2Cl_4$	*634-66-2*
1,2,3,5-tetrachlorobenzene	*1,2,3,5-TeCB*	*215.86*	$C_6H_2Cl_4$	*634-90-2*
1,2,4,5-tetrachlorobenzene	*1,2,4,5-TeCB*	*215.86*	$C_4H_2Cl_4$	*95-94-2*
pentachlorobenzene	*PeCB*	*249.35*	C_6HCl_5	*608-93-5*
hexachlorobenzene	*HCB*	*284.80*	C_6Cl_6	*118-74-1*

1.1.2. Physicochemical properties

A few environment-relevant basic data are listed in table 1.2.

Table 1.2. Physicochemical and organoleptic properties of chlorobenzenes (Mackay and Shiu, 1981; Verschueren, 1983; Kamlet et al., 1988)

Compound	Melting point (°C)	Boiling point (°C)	Density (air=1)	Vapour pressure (25 °C) Pa	Solub. (20 °C) mg/l	log Kow	Recognition threshold water µg/l	Recognition threshold air $mg.m^{-3}$
MCB	-45	132	3.9	1580	500	2.8	100	1-10
1,2-DCB	-18	180	5.1	196	144	3.3	10	305
1,3-DCB	-25	173	5.1	307	125	3.4	20	
1,4-DCB	53	174	5.1	90	83	3.5	30	90-180
1,2,3-TCB	53	218	6.3	28	17	3.8	10	
1,2,4-TCB	17	213	6.3	61	30	3.9	5	
1,3,5-TCB	63	208	6.3	28	25	4.0	50	
1,2,3,4-TeCB	48	254		5	4.3	4.3	20	
1,2,3,5-TeCB	55	240		10	3.5	4.3	400	
1,2,4,5-TeCB	139	244		0.7	0.6	4.4	130	
PeCB	86	277		2.2	0.56	4.8	60	
HCB	230	322	9.8	0.0015	0.005	5.4	3000	

* The detection threshold (the concentration of a substance in air which produces a positive response in 50% of the test panel members) is a factor of 5-10 lower; however, 1,4-DCB already gives "a pleasant fresh odour" at as low a concentration as 1 $mg.m^{-3}$

1.2 STANDARDS AND GUIDELINES

1.2.1. Soil and groundwater

A testing framework for the assessment of the concentration levels in soil has been given in a draft of the Soil Cleanup Guide (VROM, 1988) (table 1.3.) The guidelines mentioned in this guide should not be regarded as standards but as an assessment framework.

Table 1.3. Testing framework for the assessment of the concentration levels of chlorobenzenes in soil (VROM, 1988)

Compound	Soil ($mg.kg^{-1}$ d.w.)			Groundwater ($\mu g.l^{-1}$)		
	A	B	C	A	B	C
Chlorobenzenes (individual)	*	1	10	0.01(d)	0.5	2
Chlorobenzenes (total)	-	2	20	-	1	5

A = reference value
B = testing value for the purpose of further investigation
C = testing value for the purpose of soil-cleanup studies
* = dichlorobenzene, trichlorobenzene, tetrachlorobenzene and hexachlorobenzene: 0.01 $mg.kg^{-1}$ dry weight
d = the reference value for a good soil quality lies below the detection limit of commonly used methods. The figure reported gives an indication of this detection limit

The reference value given in the Environmental Programme - Progress Report 1988-1991 (MPV-88,1987) for di-, tri-, tetra- and pentachlorobenzene is 10 $\mu g.kg^{-1}$ for each compound. This value applies to a soil with an organic-matter content of 10%. At this or lower concentrations the soil is considered to be multifunctional, that is, these compounds are not expected to cause adverse effects.
To protect groundwater against contamination, the EEC (1980) has issued a directive prohibiting direct or indirect discharge of halogenated organic compounds and substances from which such compounds may be formed in water.

1.2.2. Surface water and sediments

The Third Water Management Memorandum (1989) gives the general environmental quality (quality objective 2000) for water and sediments, and the testing value and "signal" value for sediments. For the measurement and testing of the general environmental quality, a distinction is made between substances on the M list and the I list (table 1.4.). The M list contains the most relevant problem substances, whose concentrations must be regularly measured.

Table 1.4. Standards for the general environmental quality of water (total concentration in µg/l) and sediments (converted to the standard soil containing 10% organic matter and 25% clay (diameter < 2 µm); mg.kg^{-1})

Compound	*M list*		*I list*		*Provisional testing value sediment*	*Provisional "signal" value sediment*
	water	*sediment*	*water*	*sediment*		
DCBs			*2*			
TCBs			*0.4*	*0.3*		
TeCBs			*0.2*	*0.3*		
PCB				*0.3*	*0.3*	*0.5*
HCB		*0.004*			*0.02*	

The standards for surface water and sediments in the Third Water Management Memorandum will be replaced in the short term (see section 1.2.1).

The Quality Objectives and Surface Water Measurements Decree (Staatsblad, 606) stipulates that the maximum permissible concentration of extractable organically bound chlorine in surface water intended for the production of drinking water is 10 µg Cl.l^{-1}. According to this Decree, the standard is 0.05 ug.l^{-1} for hexachlorobenzene and 0.1 µg.l^{-1} for the summed concentrations of ten specified organochlorine pesticides. To bring the standards of the Quality Objectives and Surface Water Measurements Decree and those of the Water Board Decree (Waterleidingbesluit, 1984) into harmony, a proposal has been published in the Gazette (Staatscourant, 143, 1989) to extend the ten above-mentioned pesticides to include all pesticides. In accordance with the standards for drinking water in the Water Board Decree, the standard for the other pesticides in surface water intended for the production of drinking water will be set at 0.1 µg.l^{-1} for each individual compound and at 0.5 µg.l^{-1} for the summed concentrations of the pesticides.

With regard to shellfish water, shellfish should not be characterized by an unnatural taste, and the concentration of halogenated organic compounds in the shellfish water or in the soft tissue of shellfish should not be so high that shellfish and their larvae are adversely affected (Staatsblad 606, 1983; derived from the EEC Directive, 1975).

The Environmental Programme 1989-1992 (MPV-89, 1988) has recently given the initial impetus towards recommended standards for sediments, with the assumption that the general environmental quality of sediments and the reference value for soil quality (table 1.3.) indicate in principle an identical protection level. For the general environmental quality of sediments, the concentration of penta- and hexachlorobenzene should not exceed 2.5 $\mu g.kg^{-1}$ and that of the extractable halogenated organic compounds 5,500 $\mu g.kg^{-1}$. The provisional C value for sediments, the value above which investigation into the need for cleanup is urgent, has been set at 500 $\mu g.kg^{-1}$ for penta- and hexachlorobenzene and at 20,000 $\mu g.kg^{-1}$ for extractable halogenated organic compounds.

European Community

For the required quality of shellfish water, the limit value for halogenated organics is the concentration of each compound in the soft tissue of shellfish having no adverse effects on shellfish and their larvae. As a guideline, the concentration of each compound in the soft tissue of shellfish should be so low that it contributes to a good quality of shellfish products (EEC, 1979).

Canada

The standards for chlorobenzenes in surface water in Canada are presented in table 1.5.

Table 1.5. Standards for chlorobenzenes ($\mu g.l^{-1}$) in surface water in Canada

Compound	*Concentration*	*Compound*	*Concentration*
MCB	*15*	*1,3,5-TCB*	*0.65*
1,2-DCB	*2.5*	*1,2,3,4-TeCB*	*0.10*
1,3-DCB	*2.5*	*1,2,3,5-TeCB*	*0.10*
1,4-DCB	*4*	*1,2,4,5-TeCB*	*0.15*
1,2,3-TCB	*0.9*	*PeCB*	*0.030*
1,2,4-TCB	*0.5*	*HCB*	*0.0065*

1.2.3. Air

Tables 1.6 and 1.7 list the quality criteria in the workplace and for ambient air, respectively.

Table 1.6. Air quality in the workplace [MAC values, time-weighted average (TWA) for 8 hours a day, 40 hours per week] in mg.m^{-3}

Country	MAC value	Comments	Reference
The Netherlands	350	MCB	National MAC list (1989)
	300	1,2-DCB	
	450	1,4-DCB	
	40	1,2,4-TCB	
	150	1,4-DCB; proposal	WvD (1988)
	0.03	HCB; proposal	WvD (1989)
Western Germany	230	MCB	TNO (1977)
	5	MCB; 30 min; basic value	
	15	MCB; 30 min; permissible level	
	450	1,4-DCB	
Eastern Germany	50	MCB	TNO (1977)
	150	1,2-DCB	
	200	1,4-DCB	
US	350	MCB	TNO (1977)
	300	1,2-DCB; ceiling value	
	350	1,4-DCB	
USSR	50	MCB	TNO (1977)
	0.1	MCB; 24 hr; basic value	
	0.1	MCB; 20 min; permissible level	
	20	1,2-DCB	
	20	1,4-DCB	
Czechoslovakia	200	MCB	TNO (1977)

Table 1.7. Ambient air standards (M.I.C. values; mg.m^{-3}; IDC, 1985)

Country	Standard	Comments
Western Germany	5	average value; may be exceeded once in any 4 h 30 min
	15	"maximum" value for a 30-minute period
USSR	0.1	daily average
	0.1	"maximum" value; maximum measuring time, 20 minutes

In Western Germany (TA-Luft, 1986), the maximum emission concentration for monochlorobenzene and 1,4-dichlorobenzene is 100 $mg.m^{-3}$, at an emission rate exceeding 2 kg per hour, and that for 1,4-dichlorobenzene is 20 $mg.m^{-3}$ when the emission rate is greater than 0.1 kg per hour.

1.2.4. Food and drinking water

Standards for chlorobenzenes in foodstuffs have not been established in the Netherlands. The Water Board Decree (Waterleidingbesluit, 1984) stipulates that the concentration of individual pesticides in drinking water (including hexachlorobenzene) be no more than 0.1 $\mu g.l^{-1}$ and that of the summed concentrations of the pesticides and their degradation products no more than 0.5 $\mu g.l^{-1}$.

In accordance with an EEC directive, the maximum permissible concentration of halogenated hydrocarbons in drinking water is 1 $\mu g.l^{-1}$ for each compound.

The WHO (1984) uses the following guideline levels:

- monochlorobenzene: an Acceptable Daily Intake (ADI) of 1.5-15 ug per kg body weight per day and for drinking water, based on the "odour threshold value", a guideline of 3 $\mu g.l^{-1}$ and a limit value of 5-50 $\mu g.l^{-1}$;
- 1,2-dichlorobenzene: an ADI of 1.4-14 μg per kg body weight per day and for drinking water, based on the odour threshold value, a guideline of 0.3 $\mu g.l^{-1}$ and a limit value of 5-50 $\mu g.l^{-1}$;
- 1,4-dichlorobenzene: an ADI of 1.4-14 ug per kg body weight per day, and a guideline of 0.1 $\mu g.l^{-1}$ and a limit value of 5-50 $\mu g.l^{-1}$ for drinking water;
- hexachlorobenzene: a guideline of 0.01 $\mu g.l^{-1}$ in drinking water. The ADI for pentachlorobenzene is 1.17 mg per kg body weight. There is a difference of opinion over the ADI for hexachlorobenzene. The IARC uses an ADI of 0.6 μg per kg body weight, and the WHO withdrew this ADI in 1978 and recommends that exposure be limited to the lowest feasible level.

1.2.5. Miscellaneous

The Chemical Waste Act defines waste as chemical waste when its concentration of halogenated organic compounds exceeds 5 $g.kg^{-1}$. According to the Pesticides Act, a number of highly chlorinated pesticides should contain no more than 0.1% hexachlorobenzene, and according to the Commodity Board Regulation, pig feed no more than 20 $\mu g.kg^{-1}$ and other animal feeds no more than 30 $\mu g.kg^{-1}$.
According to the Residues Order, the maximum permissible concentration of hexachlorobenzene in milk is 8, in meat and eggs 200, in potates 20 and in vegetables 50 $\mu g.kg^{-1}$ (Contaminant Booklet, 1987).

2. PRODUCTION, APPLICATIONS, SOURCES AND EMISSIONS

This chapter summarizes the production, applications, sources and emissions of all 12 chlorobenzenes. A detailed description of the problems outlined in this chapter has been given in the interim report drawn up by Haskoning (1989).

2.1. PRODUCTION AND APPLICATIONS

2.1.1. Production

Chlorobenzenes are not produced in the Netherlands (telephonic business information). HCB is liberated as a by-product in the waste stream of one industrial process. Processes for the manufacture of chlorobenzenes are described in Haskoning (1989).
Table 2.1. summarizes the trade volume of chlorobenzenes in the Netherlands. The consumption in this table has been calculated from import and export data and production figures of the industries concerned.

2.1.2. Applications

The current uses of chlorobenzenes in the Netherlands are listed in table 2.2.

Table 2.1. Trade volume of chlorobenzenes in the Netherlands (tonnes per year, 1987)

Compound	Imports	Exports	Production	Consumption
MCB	ca 1600	ca 600	0	1000
1,2-DCB	-	-	0	30
1,3-DCB	-	-	0	332
1,4-DCB	354	28	0	326
1,2,3-TCB	-	-	0	5
1,2,4-TCB	-	-	0	160
1,3,5-TCB	-	-	0	5
1,2,3,4-TeCB	-	-	0	0
1,2,3,5-TeCB	-	-	0	0
1,2,4,5-TeCB	-	-	0	0
PeCB	-	-	0	0
HCB	-	-	430*	0

* is liberated as a by-product in the waste stream of one industrial process

\- import and export data are not known

Table 2.2. Summary of the consumption (tonnes) of chlorobenzenes in the Netherlands (1987)

Compound	Application	Consumption	Industrial sector
MCB	raw material for manufacture of organotin compounds	ca 350	pesticides industry
	raw material for manufacture of tetradifon	262	pesticides industry
	solvent for manufacture of dichlobenil	42	pesticides industry
	raw material for manufacture of specialities	100	pharmaceutical industry
	solvent for manufacture of isocyanates	ca 160	other chemical industry
	miscellaneous	ca 90	
		total ca 1000	
1,2-DCB	solvent for manufacture of specialities	30	pharmaceutical industry
		total 30	
1,3-DCB	raw material for manufacture of chlorfenvinfos	332	pesticides industry
		total 332	
1,4-DCB	toilet blocks, urinal tablets, mothballs	326	catering ind. households
		total 326	
1,2,3-TCB		total ca 5	
1,2,4-TCB	raw material for manufacture of tetradifon	159	pesticides industry
	dye carrier	0.5	textile ind.
		total 160	
1,3,5-TCB		total ca 5	
TeCB		total 0	
PeCB		total 0	
HCB		total 0	

2.2 SOURCES AND EMISSIONS

Possible sources of chlorobenzenes have been selected on the basis of their uses in the Netherlands and a DWB/RIZA study on, among other things, the occurrence of mono- and hexachlorobenzene in industrial waste waters (Van Starkenburg and Van Luin, 1985).

It was found that a number of industrial sectors do not use chlorobenzenes as raw materials and that chlorobenzene emissions do not occur here or are

negligible. They are the paint and printing ink industries, metal industry, adhesives and glues industry, cooling water, animal feeds industry, rubber industry, hospitals, and fats, margarine and dairy industries. These sectors are not considered in this study (for this, see Haskoning, 1989). The other selected sources are discussed in the following sections.

2.2.1. Pesticides industry

Chlorobenzenes are used in the pesticides industry in the Netherlands as raw materials for syntheses and as solvents (tel. bus. inf.; De Bruin, 1986).

Monochlorobenzene is used as a raw material in the manufacture of organotin compounds (fentin). The annual consumption of MCB for this application has been estimated at 350 tonnes (tel. bus. inf.). The amount of MCB released to surface water is expected to be negligible. The wastewater-discharge regulations of the company concerned do not mention chlorobenzenes. The waste water is periodically checked by the Department of Public Works. However, analyses for chlorobenzenes are not performed, but the sum parameter EOCl (extractable organic chlorine) is measured. Atmospheric releases of MCB are estimated at about 50 kg per year (tel. bus. inf.).

In 1987, 262 tonnes of MCB and 159 tonnes of 1,2,4-TCB were used in the production of the pesticide tetradifon (tel. bus. inf.).

Approximately 12 tonnes of MCB per year are emitted into the atmosphere during the manufacturing operation. There is no measurable emission of 1,2,4-TCB to the atmosphere (tel. bus. inf.). Less than 3 kg of chlorobenzenes are released to surface waters per year. The production of tetradifon generates liquid waste, containing 130 tonnes of MCB and 57 tonnes of DCB. This waste is disposed of as chemical waste and incinerated at AVR Chemie (incinerating facility for chemical waste).

MCB is used as a solvent in the manufacture of the herbicide dichlobenil (dichlorobenzonitrile). Consumption in 1987 was estimated at 42 tonnes (tel. bus. inf.). The production of the pesticide chlorfenvinfos (Birlane) in the Netherlands consumed 332 tonnes of 1,3-DCB in 1987 (tel. bus. inf.).

The Department of Public Works and the company concerned have carried out (separately) an investigation into chlorine compounds in the waste water at

the location where dichlobenil and chlorfenvinfos are manufactured. The estimated chlorobenzene emissions were:

- DCB: all three isomers have been detected, a total of about 100 kg per year;
- TCB: about 110 kg of 1,2,4-TCB and about 30 kg of 1,2,3-TCB per year;
- TeCB, about 25 kg per year.

The other chlorobenzenes were not detected or their emissions were less than 10 kg per year. Chlorobenzene emissions to air are estimated to be 10 kg MCB and 50 kg 1,3-DCB per year at most. Table 2.3. summarizes the chlorobenzene wastes and emissions from the pesticides industry.

Table 2.3. Chlorobenzene wastes and emissions from the pesticides industry

Pesticide	*Chloro-benzene*	*Consumption*	*Emission*			*Waste*
			soil	*water*	*air*	
Organotin	*MCB*	*350*			*0.05*	
Tetradifon	*MCB*	*262*			*12*	*130*
	1,2,4-TCB	*159*			*0*	
	DCB	*0*				*57*
	sum of chloro-benzenes			*<0.003*		
Dichlo-benil	*MCB*	*42*		*0**	*0.01**	
Chlorfen-vinfos	*1,3-DCB*	*332*		*0.1**	*0.05*,***	
	1,2,4-TCB	*0*		*0.11**		
	1,2,3-TCB	*0*		*0.03**		
	TeCB	*0*		*0.025**		

* *Emission at the location where dichlobenil and chlorfenvinfos are among the compounds produced*
** *sum of dichlorobenzenes*

2.2.2. Pharmaceutical industry

In the pharmaceutical industry, one company used in 1989 about 100 tonnes of MCB as a raw material in the manufacture of specialities. Of this amount, approximately 60 tonnes were converted into products, about 30 tonnes were disposed of as chemical waste, while about 9.5 tonnes were released into the atmosphere and about 0.5 tonne to water. In 1989 the same

firm used 30 tonnes of 1,2-DCB as a solvent, of which approximately 25 tonnes were disposed of as chemical waste, about 4.75 tonnes were emitted to the atmosphere and about 0.25 tonne to water.

An investigation was conducted in 1986 into the quality of the waste water from the pharmaceutical industry as part of the research project "Operationalization of the concepts of best feasible and best available techniques" (VROM and DBW/RIZA, 1986). The study registered emissions into surface water, and covered five large manufacturing and two drug-formulating plants. From this study it was estimated that one of the five plants discharged annually 2 tonnes of 1,3-DCB into surface water. At another plant, MCB was detected in the waste water. After in-plant treatment of the waste water, MCB emission into surface water was no longer registered. The source of the 1,3-DCB detected is as yet not clear (tel. bus. inf.). One possible explanation could be that 1,3-DCB results from degradation of chlorinated aromatics or is formed from chloro- and benzene-containing compounds.

The sludge from a sewage treatment facility at a pharmaceutical company was shown to contain 1,3,5-TCB and MCB. The company generates about 600 kg 1,3,5-TCB and about 100 kg MCB per year. Chlorobenzenes are not used, but chlorination processes are carried out. It is assumed that chlorobenzenes are formed as by-products during manufacturing.

An indication of the emissions to air and surface water can be obtained from the amounts of MCB and 1,3,5-TCB in the sludge, using the TIMAS model (Ros and Van de Poel, 1989) (table 2.4.).

Table 2.4. Calculated water and air emissions from a sewage treatment facility at a pharmaceutical company with known annual sludge load

	Sludge	*Emission*	
		water	*air*
MCB	*100 kg*	*50 kg*	*1300 kg*
1,3,5-TCB	*600 kg*	*30 kg*	*400 kg*

2.2.3. Other chemical industry

MCB is used as a solvent for the manufacture of isocyanates (tel. bus. inf.). The consumption of MCB for this application was 160 tonnes in 1987 (tel. bus. inf.). On the basis of measurements by the Department of Public Works made between 1986 and 1988, it can be calculated that annually about 50 kg MCB are discharged into surface water (tel. inf. Dept. of Public Works).

MCB is emitted into air at several points during the manufacturing operation. The total air emission of MCB is about 80 tonnes per year. A preliminary investigation showed that the scrubbers account for 50% of the current atmospheric emission (tel. bus. inf.).

Approximately 50 tonnes of MCB are disposed of as chemical waste, while about 30 tonnes are recovered. The isocyanate produced contains about 10 to 50 mg MCB per kg of isocyanate as an impurity. The total amount of MCB present in isocyanate is less than 100 kg per year.

MCB is liberated during the production of plastics from isocyanates, in which it is present as an impurity. The isocyanate is imported from Portugal. Chlorobenzenes are not used in the manufacture of plastics. The amount of MCB emitted into surface water is about 10 kg per year (tel. bus. inf.).

The manufacture of tetrachloromethane (carbon tetrachloride) and tetrachloroethylene generates annually 600 tonnes of chlorine-containing waste (tel. bus. inf.). Chlorobenzenes are not used in this process. Carbon tetrachloride and tetrachloroethylene are coproduced in one manufacturing process. The chlorine-containing waste contains about 70% (430 tonnes) hexachlorobenzene, about 25% hexachlorobutadiene and about 5% hexachloroethane. All the waste is collected, distilled, crystallized and stored in solid form in steel drums and transported to a purpose-built dump in a salt mine in western Germany. Crystallization occurs under cooling with water. The waste water is piped to a treatment plant where it is passed through an activated carbon bed. The final effluent is discharged into surface water. The annual emission of HCB into surface water is about 3 kg and that into air about 75 kg (tel. bus. inf.). The manufacture of tetrachloromethane and tetrachloroethylene was discontinued in the spring of 1990 (tel. bus. inf.).

In 1984/1985 DBW/RIZA analyzed the waste water from six chemical plants for the presence of chlorohydrocarbons. The findings have not been published because of confidentialty (tel. inf. DBW/RIZA). The investigation revealed that the waste water contained chlorobenzenes among other substances, whereas these compounds had not been used as a solvent or raw material in the manufacturing process. In addition, it was found in several cases that the concentration of chlorobenzenes in the effluent was higher than in the influent. The total annual inputs to water of 16 chlorohydrocarbons, including chlorobenzenes, from the production processes at the plants investigated ranged between 1 and 300 kg. The unexpected presence of chlorobenzenes in industrial waste water is probably due to the formation of chlorobenzenes during manufacturing, or the degradation of chlorinated aromatics.

2.2.4. Textile industry

1,2,4-Trichlorobenzene is used in the textile industry as a carrier for applying dyes to polyester fabric. Carriers are employed for obtaining satisfactory bonding between the disperse dyes and polyester fibres. The function of the carrier is to effect a shift from the crystalline to a more amorphous fibre structure so that the dye penetrates the fibre more deeply and diffuses more evenly. Carriers are now only used in the dyeing of wool-polyester blends. Other blends are dyed by, for example, the High Temperature (HT) process which does not require carriers. As a result, the demand for trichlorobenzenes in the Netherlands has declined sharply in the past few years (VROM, 1987; tel. bus. inf.). The manufacturer has often already added the carrier to the dye (as a so-called levelling agent).
The current consumption of 1,2,4-TCB in the textile industry is estimated at about 500 kg per year at most (tel. bus. inf.). The use of trichlorobenzene leads to emissions chiefly into air and to a smaller extent into water. An estimated 70% of the carriers evaporates during textile drying while about 30% remains behind in the dye bath. The maximum atmospheric emission of 1,2,4-TCB is 350 kg per year. Assuming 100% discharge of the dye bath to the sewer and a treatment efficiency of 90% (as for other chlorobenzenes; CUWVO, 1986) in sewage treatment facilities, then the annual emission to surface water is 15 kg. Possibly this emission

is smaller since several textile-dyeing plants treat the waste water before discharging it to the sewer.

2.2.5. Wood-preserving industry

Chlorobenzenes are not used in the wood-preserving industry in the Netherlands (tel. bus. inf.; VROM, 1986a). A study by Van Starkenburg and Van Luin (1985) found MCB in the waste water from one of the two inpregnating plants investigated. An annual load of 1.8 tonnes was calculated, based on the measured concentration and the average flow rate. HCB was not detected in the waste water from these two plants. The presence of MCB in the waste water cannot be explained by the use of preservatives. The study also found pentachlorophenol in the waste water, the annual loads being 6.6 g and 10 g, respectively.

2.2.6. Laundries

Chlorobenzenes are not used in laundries in the Netherlands (VROM, 1986b). The study by Van Starkenburg and Van Luin (1985) found MCB concentrations ranging from 2.6 to 27 mg per litre in the waste water from the laundry investigated. This laundry carried out both dry- and wet-cleaning operations. The amounts of MCB found could possibly have come from the industrial clothing handed in for cleaning. It was calculated from the measured concentrations that the establishment investigated discharged annually about 1 tonne of MCB to water. However, this calculated value as such cannot be extrapolated to the roughly 850 laundries in the Netherlands (tel. inf. DBW/RIZA).
The source of the MCB in the waste water is still unknown. In dry-cleaning establishments, the cleansing of fabrics is done with organic solvents, in particular perchloroethylene. After completion of the process, the laundry recovers the solvent by distillation. The residue is collected and treated as chemical waste. Theoretically therefore, there are no emissions to water. By contrast, wet-cleaning establishments emit chiefly into water. The occurrence of chlorobenzenes in the waste water may be due to their presence in the material to be cleaned.

2.2.7. Diffuse sources

- Disinfectants

1,4-Dichlorobenzene is the only chlorobenzene used in disinfectant products, namely, air fresheners, toilet blocks, urinal tablets and mothballs. Its use in air fresheners has fallen to zero in the 1980s. There has also been a sharp decline in the use of 1,4-DCB in mothballs. The consumption of 1,4-DCB for this purpose was only a few per cent of the total amount.

Information provided by the industrial sector and producers regarding the consumption of 1,4-DCB agrees with the imported quantities registered by the Central Statistical Bureau (CBS). The consumption of 1,4-DCB in the Netherlands in 1987 is estimated at 326 tonnes.

The use of 1,4-DCB as a disinfectant has declined sharply in the last few years. Suppliers and consumers of 1,4-DCB assume that 1,4-DCB consumption in 1989 was approximately 100 tonnes (tel. bus. inf.). Based on information from processors of 1,4-DCB, it can be estimated that about 75% of the 1,4-DCB is used by hotels, restaurants, etc. and about 25% by private households. Hotels, restaurants, public lavatories and the like discard annually an estimated 10 tonnes of 1,4-DCB from toilet blocks and urinal tablets with industrial waste (tel. bus. inf.). This corresponds to about 4% of the total consumption.

Toilet blocks contain about 10-20% 1,4-DCB as well as cleansing agents. Urinal tablets and mothballs are essentially 100% 1,4-DCB (Van Dongen et al., 1988; tel. bus. inf.). The 1,4-DCB-free toilet blocks and urinal tablets consist of cleansing agents to which a perfume has been added (tel. bus. inf.).

In a study of diffuse sources (CUWVO, 1986), the emissions of chlorobenzenes by residents were measured (see 2.2.7., Households/companies). Based on these data and the behaviour of 1,4-DCB in a sewage treatment plant (STP) (chapter 3), 1,4-DCB emissions and amounts in wastes can be calculated (figure 2.1.).

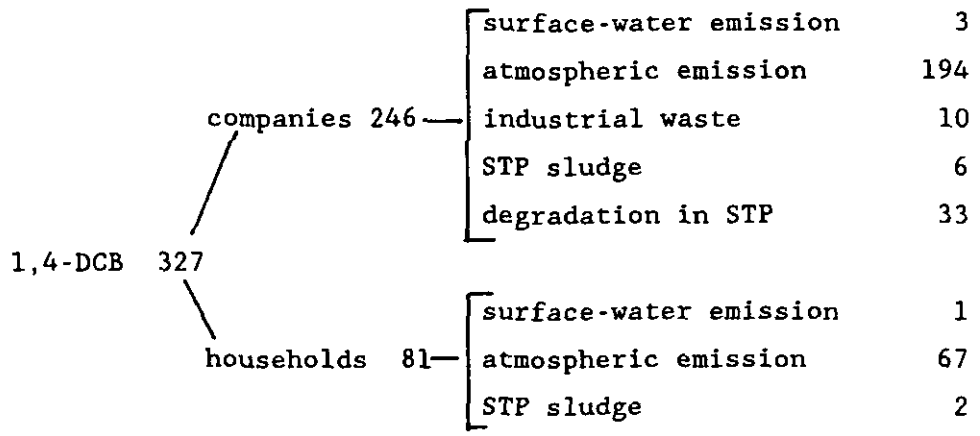

Figure 2.1. 1,4-DCB in wastes and emissions from toilet blocks and urinal tablets (tonnes per year, 1987)

- Volatile chlorinated hydrocarbons

HCB is an unwanted by-product in the manufacture of tetrachloromethane and tetrachloroethylene (see 2.2.3.). It does not seem impossible that the products may be contaminated with chlorobenzenes. Information provided by the manufacturers and wholesalers of volatile chlorinated hydrocarbons suggests that it is unlikely, but cannot be entirely ruled out, that chlorobenzenes are present as impurities in these products. According to the product specifications, they contain less than 10 ppm (parts per million) of other chlorine compounds, mostly other volatile chlorinated compounds. The fraction of high-boiling compounds is 10 ppm at most (tel. bus. inf.).

A study by Bremmer et al. (1988) shows that the discharge of volatile chlorinated hydrocarbons into water is estimated at 1500-2000 tonnes per year. This means that the total emission of chlorobenzenes from volatile chlorinated hydrocarbons into water does not exceed 20 kg per year.

- Degradation and conversion

Degradation and conversion of certain pesticides can in theory result in the formation of chlorobenzenes. Approximately 600 tonnes of chlorobenzene derivatives are used annually in the Netherlands as pesticides in

agriculture and horticulture (Bremmer et al., 1988). Based on these data it can be estimated that the diffuse emission of chlorobenzenes from the use of pesticides is at most 2 tonnes per year.
Assuming 2.5% leaching and runoff, the diffuse emission into surface water does not exceed 50 kg per year.
The formation of chlorobenzenes from other compounds at room temperature is unlikely. For example, electrophilic substitution of one or more H atoms of benzene by chlorine will not occur in waste water.

- Households and companies

The possibility exists that chlorobenzene residues are present in certain products (e.g., plastics, textile, volatile chlorinated hydrocarbons). If such is the case, then households and companies are sources of diffuse chlorobenzene emissions. The chlorobenzenes which are released by degradation/conversion and possibly from products are included under this diffuse source category.
Households: The emission factors per resident are derived from the studies by the STORA (1985) and Van Luin (1984). The dwelling-related emissions per resident are presented in table 2.5. These values do not much differ from those found recently by Teurlinckx (1989). The concentrations of 1,2,4-TCB and 1,3,5-TCB were below the detection limit, so that their loads cannot be calculated. As regards 1,3-DCB, TeCBs and PCB, it can be stated that emissions via domestic waste water from direct use in households are probably negligible.

Table 2.5. Emissions of chlorobenzenes via domestic waste water in the Netherlands in 1987, in tonnes (extrapolation from CUWVO, 1986)*

	MCB	*1,2-DCB*	*1,4-DCB*	*1,2,3-TCB*	*HCB*
Total emission	*0.125*	*0.600*	*15.660*	*0.030*	*0.0045*
- of which direct to surface water	*0.006*	*0.030*	*0.783*	*0.002*	*0.0002*
- of which to STP	*0.119*	*0.570*	*14.877*	*0.029*	*0.0043*
- of which to surface water	*0.024*	*0.057*	*0.298*	*0.003*	*0.0002*
Total input to surface water	*0.030*	*0.087*	*1.081*	*0.005*	*0.0004*

** Assuming 15 million residents and 95% connections to STP (TNO, 1989)*

Companies: It can be assumed from the data of Van Starkenburg and Van Luin (1985) concerning the industrial sectors not considered here, and data on the number of companies per sector, that the total diffuse chlorobenzene emission from industrial plants is of the same order of magnitude as that from households.

2.2.8. Transboundary emissions

As regards the Rhine and Meuse rivers, only data on the presence of di-, tri-, tetra- and hexachlorobenzene are available (Dept. of Public Works, 1980-1988). Since the diffuse emissions of mono-, tri- and pentachlorobenzene (PCB is not produced commercially) by companies and households are very small, it seems reasonable to state that transboundary emissions of these compounds are negligible. The importation of chlorobenzenes via cross-border rivulets has been disregarded, because of the relatively low flow rate compared with that of the Rhine and Meuse (< 1%). The transboundary emissions of chlorobenzenes are presented in table 2.6.

Table 2.6. Estimates of the transboundary emissions of chlorobenzenes via surface water in 1987 (tonnes)

Compound	*Emission*
1,2-DCB	*2*
1,3-DCB	*2*
1,4-DCB	*2*
TCBs	*3*
TeCBs	*0.1*
HCB	*0.2*

2.2.9. Urban waste

Approximately 5.7 million tonnes of domestic waste are produced annually in the Netherlands. It is presented as bagged refuse (4.3 million tonnes), as glass deposited in bottle banks (0.2 million tonnes), as old paper

collected by clubs and schools (0.5 million tonnes) and as bulky domestic waste (0.7 million tonnes). In addition, municipalities and private collectors collect 1.8 million tonnes of waste from small enterprises (shops, offices, etc.) and the services sector. The total volume of collected waste is disposed of in various ways, namely, dumping, incineration and reuse/recycling (Cornelissen, 1987).
In a study on the presence of chlorinated aromatics in bagged refuse (Janssens et al., 1988) the waste was separated into a number of fractions. The concentration of hexachlorobenzene, among other substances, was determined in fractions which were expected to contain possibly chlorobenzenes. The number of random samples was limited. If it is assumed that urban waste has the same HCB content as bagged refuge, then it can be derived from these data that the annual supply of hexachlorobenzene is about 1.5 mg per tonne of urban waste. Based on this figure it can be calculated that 11.3 kg HCB are annually disposed of via urban waste. It was reported in section 2.2.7. that an estimated 10 tonnes of 1,4-DCB from toilet blocks and urinal tablets are removed with industrial waste each year.
Sein (1989) has determined atmospheric emissions of HCB at three incinerating plants. It was calculated from this study that incinerators emitted a total of about 10 kg HCB per year into the atmosphere. It was also calculated that 50 kg per year were carried away in fly ash from incinerators. It can be concluded that the emission of HCB, and probably also of other chlorobenzenes, from the incineration of urban waste is very small.

2.2.10. Sewage sludge

DBW/RIZA has conducted an investigation into the presence of hexachlorobenzene in sewage sludge at 6 sewage treatment plants. The results of this study and a supplementary literature search show that the average HCB concentration in sewage sludge is 0.01-0.1 $mg.kg^{-1}$. Of the total amount of sewage sludge in the Netherlands (about 0.6 Mtonne dry weight), 60% eventually ends up diffusively on the soil via reuse, and about 40% is dumped under controlled conditions (CBS, 1988). Assuming an

average concentration of 0.01-0.1 $mg.kg^{-1}$ HCB in sewage sludge, this amounts to an annual diffuse input to soil of less than 20 kg. It was reported in section 2.2.7. that the estimated total amount of HCB in STP sludge is about 8 tonnes.

2.3. Summary and conclusions

Chlorobenzenes are not produced commercially in the Netherlands; one industrial process generates HCB as a by-product. The use of chlorobenzenes, with the exception of 1,4-DCB, is limited to the pesticides industry (MCB, 1,3-DCB and 1,2,4-TCB), the pharmaceutical industry (MCB, 1,2-DCB) and, to a smaller extent, the textile industry (1,2,4-TCB). 1,4-DCB is used in toilet blocks, urinal tablets and mothballs in the catering industry and in households.

A summary of the consumption of chlorobenzenes and their emissions into soil, water, air and waste (disposal route) is given in table 2.7.
Quantitatively, air emissions are the most important, totalling about 370 tonnes per year. The largest contributors to this are the 1,4-DCB emission of 261 tonnes per year from the use of toilet blocks and urinal tablets and the 80 tonnes of MCB per year liberated during the manufacture of isocyanate.
The emission of chlorobenzenes into surface water is about 7 tonnes per year, of which more than half results from the use of 1,4-DCB in toilet blocks and urinal tablets.
The diffuse emission of chlorobenzenes into soil is about 2 tonnes per year, due to degradation of pesticides.

Table 2.7. Summary of consumption and emissions of chlorobenzenes (tonnes per year; 1987). This does not include atmospheric deposition

Compound	Source	Number of sources	Consumption	Emission* soil	water	air	Waste*	Disposal route
MCB	-pesticides industry	4	654			12.1	130	inciner. AVR
	-pharmaceutical industry	1	100		0.55	10.8	30	chem. waste
	-other chemical industry	1	250		0.05	80	50	chem. waste
1,2-DCB	-pharmaceutical industry	1	30		0.25	4.75	25	chem. waste
	-households	>1000			0.087			
	-companies	>1000			0.087			
1,3-DCB	-pesticides industry	1	332		0.1**	0.05	57**	inciner. AVR
	-pharmaceutical industry	1			2			
1,4-DCB	-households	>1000			1	67	2	sludge
	-companies	>1000			3	194	6	sludge
	-households/ companies		326				10	dumping
1,2,3-TCB	-(see table 2.2.)		5					
1,3,5-TCB	-(see table 2.2.)		5					
	-pharmaceutical industry				0.03	0.4		
1,2,4-TCB	-pesticides industry		159		0.11			
	-textile ind.		0.5			0.35		
HCB	-other chem.ind.	1				0.075	430	export
Chloro-benzenes	-agriculture/ horticulture	>1000		2				

* quantities less than 50 kg per year are not given

** sum of chlorobenzenes

Chlorobenzenes were detected in the waste water from a number of industries, due to the formation of chlorobenzenes during the manufacturing operation or by the degradation of chlorinated aromats.

3. DISTRIBUTION AND CONVERSION

3.1. FORMS OF OCCURRENCE

Chlorobenzenes are moderately to sparingly soluble in water and behave as lipophilic compounds. The lipophilicity, expressed in log K_{ow}, increases with an increasing number of chlorine atoms on the benzene ring, from nearly 3 for MCB to more than 5 for the slightly soluble HCB (see table 1.2.). In the water phase the latter compound exhibits an affinity for biota and suspended matter/sediment, which is also several orders of magnitude greater than that of the lower chlorinated benzenes.

In river water of the Rhine-Meuse estuary, the fractions of dissolved PeCB and HCB are usually greater than the fractions transported in particulate form. However, the reverse was the case in the mixing zone of this estuary (Duinker and Hillebrand, 1979). The concentration in the sediment is heavily dependent on the particle size: the level in the fine particles was over two orders of magnitude greater than that in the coarse particles. Duinker et al. (1982) calculated on the basis of measurement data in the Elbe estuary that approximately 45% of PeCB and nearly 80% of HCB were adsorbed onto the suspended material.

The vapour pressure of chlorobenzenes decreases as the number of chlorine atoms increases, from about 1500 Pa for MCB (Mackay and Shiu, 1981) to a value for HCB which is estimated to be 3 to 5 orders of magnitude lower. Since the solubility of chlorobenzenes also sharply decreases with increasing number of chlorine substituents, the Henry's law constant (H, calculated from the vapour pressure/solubility quotient) is not appreciably influenced by the number of chlorine atoms. The Henry's law constant for the chlorobenzenes, with the exception of HCB, lies within the range of 100 to 1000 $Pa.m^3.mol^{-1}$ (Mackay and Shiu, 1981).

The air-water partition coefficient, calculated as H/RT ($= C_{air}/C_{water}$), for the various chlorobenzenes is presented in table 3.1. It shows that the partition coefficient for nearly all chlorobenzenes with 1 to 4 Cl atoms lies between 0.05 and 0.15. However, 1,2,3,5-TeCB and PeCB are more volatile (0.3 and 0.4, respectively) and the volatility of HCB is considerably lower (0.034). The Henry's law constant for HCB given by Mackay and Shiu (1981) is more than one order of magnitude lower than has

been calculated in table 3.1. (5 $Pa.m^3.mol^{-1}$). The partition coefficient would then also be lower (0.002).

Table 3.1. Henry's law constants (H) and partition coefficients (H/RT) for chlorobenzenes

Compound	*Henry's law constant ($Pa.m^3.mol^{-1}$)*	*Partition coefficient (dimensionless)*
MCB	*356.1*	*0.146*
1,2-DCB	*200.0*	*0.082*
1,3-DCB	*361.2*	*0.148*
1,4-DCB	*161.1*	*0.066*
1,2,3-TCB	*306.0*	*0.126*
1,2,4-TCB	*367.3*	*0.151*
1,3,5-TCB	*202.9*	*0.083*
1,2,3,4-TeCB	*261.1*	*0.107*
1,2,3,5-TeCB	*604.9*	*0.248*
1,2,4,5-TeCB	*261.1*	*0.107*
PeCB	*977.7*	*0.401*
HCB	*82.6*	*0.034*
	*(5.0)**	*(0.002)**

* *see text*

Chlorobenzenes are generally present in the atmosphere in the gaseous state. As a rule of thumb, at least 80% of a compound with a vapour pressure above 10^{-4} Pa exists in the gaseous phase (Wittlinger and Ballschmiter, 1987). Analysis of aerosol samples could barely detect chlorobenzenes, if at all (Atlas and Giam, 1988).

3.2. BEHAVIOUR IN SOIL

The behaviour of chlorobenzenes in soil is determined by the interaction of the following processes: leaching (transport), sorption and desorption, volatilization, chemical and biological conversion, and bound-residue formation.

3.2.1. Dispersion

Volatilization of chlorobenzenes from the soil is slow unless they are present near the surface (De Greef et al., 1986). Beall (1976) found a 55% loss of HCB through evaporation from the surface 2 cm of soil within 2 weeks, with no loss from the 2-4 cm depth over a 19-month period. Kilzer et al. (1979) and Wilson et al. (1981) reported that the volatilization rates from soils are generally one order of magnitude lower than from water. In column experiments, 2-6% of the applied 1,4-DCB was observed to volatilize from unsaturated soil profiles (Lagas et al., 1986) and Wilson et al. (1981) found in column experiments that 27-54% of the HCB applied to the soil surface had volatilized. Percentages of 14 and 21% were determined for MCB and 1,4-DCB, respectively, by Piwoni et al. (1986), while volatilization of 1,2,4-TCB was calculated to be 89%. Marinucci and Bartha (1979) found that 2-40% of 1,2,3-TCB and 1,2,4-TCB volatilized from the soil in a batch experiment, with volatilization decreasing with increasing soil organic matter content. Scheunert and Korte (1986) reported volatilization percentages of 3.5 for HCB, 8.4 for PeCB and 23% for 1,2,4-TCB in soil-plant laboratory test systems.

Sorption in the soil-water system is described by the soil-water partition coefficient K_{sw}. The magnitude of K_{sw} depends on the properties of the compound (section 3.1.) and the organic carbon content of the soil. If the soil organic carbon content is less than 0.1%, then sorption is weak and greatly dependent on the specific surface area of the soil. The sorption of chlorobenzene molecules is seen as a form of hydrophobic sorption (Engfield and Bengtsson, 1988; Matthess, 1989; Schwarzenbach and Westall, 1985):

$$K_{sw} = foc \cdot a \cdot K_{ow}^{\,b} \quad \text{.....Ia}$$

or:

$$\log K_{sw} = \log foc + A + b.\log K_{ow} \quad \text{.....Ib}$$

where:

foc = the organic-carbon fraction

a,b,A = constants (A = log a)

K_{ow} = the octanol-water partition coefficient

In a study with MCB, 1,4-DCB, 1,2,4-TCB, 1,2,3-TCB, 1,2,4,5-TeCB and 1,2,3,4-TeCB, Schwarzenbach and Westall (1981) found a value of 0.49 for A and 0.72 for b. The equation Ib is presented in figure 3.1. for four chlorobenzenes in different sediments and soil materials.
The mobility of chlorobenzenes in soil is expressed as a retardation of their transport velocity relative to the pore-water velocity:

$v_w = R.v_c$ II

where:

v_w, v_c = the transport velocity of water and compound, respectively

R = the retardation factor

with $R = 1 + K_{sw}\, p / \theta$

where:

p = the soil bulk density

θ = the volumetric soil water content

The retardation factor for all chlorobenzenes can be calculated using the equations Ia,b and II. For a soil with an organic-carbon content of 1% (about 1.7% organic matter), the retardation factor ranges from about 10 for MCB to 1000 for HCB.

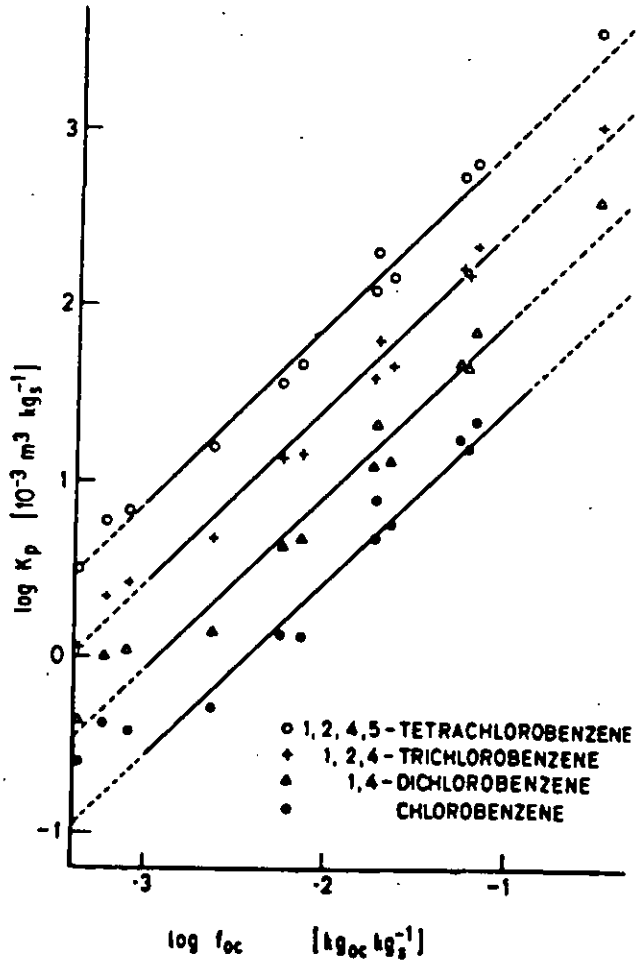

Figure 3.1. Soil-water partition coefficient (K_{sw}) as a function of the organic-carbon content of the soil (Schwarzenbach and Westall, 1981)

3.2.2. Conversion

- Abiotic conversion

No data on the chemical degradation of chlorobenzenes are known. It is assumed that this process does not make a significant contribution to their removal from the soil. The sterile experiments which have been carried out did not find any conversion (Isensee et al., 1976; Marinucci and Bartha, 1979; Wilson et al., 1983). This also applies to photolysis of chlorobenzenes.

- Biotic conversion

Biological conversion of chlorobenzenes in soil has been investigated in the top soil mainly for higher chlorinated benzenes, and in groundwater chiefly for lower chlorinated benzenes. Biotransformation has been demonstrated for nearly all chlorobenzene congeners. In general, the lower

chlorinated benzenes (mono- , di- and tri-) are biotransformed especially under aerobic conditions and the higher chlorinated benzenes, from dichlorobenzene onwards, can be anaerobically converted.
Mineralization and/or utilization of chlorobenzenes as a source of carbon and energy has generally been described for pure cultures of microorganisms, and only for the aerobic metabolism of MCB (Reineke and Knackmuss, 1984; Oldenhuis et al., 1989), the DCBs (1,2-DCB: Haigler et al., 1988; 1,3-DCB: De Bont et al., 1986; 1,4-DCB: Schraa et al., 1986; Spain and Nishino, 1987; Schwarzenbach et al., 1983), and 1,2,3-TCB and 1,2,4-TCB (Oldenhuis et al., 1989; Marinucci and Bartha, 1979; Van der Meer et al., 1987). Springer and Rast (1988) reported the oxidation of 1,2,4,5-TeCB by an isolate.

Anaerobic biotransformations in soil or groundwater have not been described. Anaerobic dechlorination of HCB (Tiedje et., 1987; Fathepure et al., 1988), the three TCB isomers (to DCBs) and the subsequent reaction of the DCB isomers to MCB (Bosma et al., 1988) have been reported in anaerobic sewage sludge or sediment. Barber (1988) has described persistence of 1,4-DCB in anaerobic groundwater over a period of at least 20 years. Dispersion of such less hydrophobic chlorobenzenes is then very likely.
Transformation of the tri- and higher chlorinated benzenes in aerobic soils is generally very slow. Little attention has been paid here to the transformation kinetics. Half-lives of 1 to 6 years have been reported for HCB (Beck and Hansen, 1974; Freitag et al., 1974), but there are also studies in which transformation of HCB was not observed (Isensee et al., 1976; Kloskowski et al., 1981). Beck and Hansen (1974) give a half-life of 0.5-1 year for PeCB. For TCBs, data are available for the 1,2,4-isomer: 3 years (Marinucci and Bartha, 1979), 120 days (Haider et al., 1974) and 11-87 days (Kincannon and Sin Lin, 1986), and for the 1,2,3-isomer: 9 years (Marinucci and Bartha, 1979). For a mixture of 1,2-DCB and 1,4-DCB, Haider et al. ((1974) found a half-life of 2 years, but Kincannon and Sin Lin (1974) 7-18 days, and the results of Wilson et al., (1981) also point to short half-lives.
Biotransformation of the lower chlorinated benzenes has been studied chiefly in river-bank and wastewater infiltration systems. In general, MCB, the DCBs and 1,2,4-TCB have been shown to disappear from the system,

presumably by degradation. The degradation rate was found to vary widely depending on the conditions, with half-lives ranging from hours to years. Possible explanations for this are the availability of oxygen, primary carbon sources and nutrients (Barber et al., 1988; Bouwer and McCarthy, 1983). In column experiments simulating rapid infiltration systems, high removal percentages were observed under aerobic conditions after relatively short soil percolation periods (Hutchins et al., 1983, 1984; Wilson et al., 1981; Bouwer et al., 1981; Piwoni et al., 1986). This rapid removal was not always observed in an actual field situation (Bouwer et al., 1984). Bosma et al. (1988) reported rapid biodegradation of MCB as well as 1,2-DCB and 1.4-DCB under aerobic conditions during dune infiltration of surface water. Results from bank infiltration of river water also indicate rapid biotransformation of 1,4-DCB under aerobic conditions (half-lives of from days to weeks), but that no transformation occurred under denitrification conditions (Schwarzenbach et al., 1983). These findings were confirmed by Kuhn et al. (1985) in laboratory column studies, in which they found a half-life ranging from hours to days.

MCB, the DCBs and 1,2,4-TCB were aerobically degraded after long adaptation periods of the microorganisms (10-500 days) in both batch systems and column experiments, with half-lives varying from hours to days in the presence of acetate as the primary substrate (Bouwer and McCarthy, 1981, 1982), but none of these compounds was biotransformed under anoxic (methanogenic - Rittman et al., 1980, or denitrifying - Bouwer and McCarthy, 1983) conditions. The pathway of aerobic removal of MCB, 1,3-DCB and 1,4-DCB was shown to be mineralization.

As regards biotransformation in groundwater, Wilson et al. (1983, 1986) reported widely varying half-lives for MCB in different aquifer materials, ranging from 0.1 to 2 years. Roberts et al. (1980) could not demonstrate conversion of MCB in aquifer material. Swindoll et al. (1988) found slow aerobic biotransformation of MCB and TCBs in groundwater.

In summary, aerobic biotransformation of chlorobenzenes with up to three chlorine atoms has been demonstrated to occur in soil and groundwater (at a rate decreasing with increasing number of chlorine substituents). There was no evidence of conversion of the tri- or lower chlorinated benzenes in soil and groundwater under anoxic conditions, and the behaviour of higher chlorinated benzenes has not been investigated. In sediments, however,

higher chlorinated benzenes from di- to hexachlorobenzene can be biotransformed under anaerobic conditions. The aerobic biotransformation rates in soils vary widely and appear to depend chiefly upon parameters not yet extensively studied, such as primary substrates and nutrients. Very high biodegradation rates can be attained after a long adaptation phase.

There are two pathways for the aerobic conversion of the chlorobenzenes: formation of catechols with two hydroxyl groups (mediated by a dioxygenase), and formation of phenols (by a monooxygenase). The major transformation pathway under anaerobic conditions is reductive dechlorination resulting in the formation of lower chlorinated benzenes, with monochlorobenzene as the end-product.

Data are not available for either the relationship between biotransformation and soil temperature and pH, or for the influence of the soil type. Although a high degree of mineralization has been found in pure and enrichment cultures for the various chlorobenzenes (up to 48% for HCB - Haider et al., 1974; and up to 43% for DCBs - Spain and Nishino, 1987; Haider et al., 1974; Haigler et al., 1988), it was markedly lower in soil. Maximum values of 27% for MCB, 6% for DCBs and 33% for TCBs have been reported in soil incubation experiments (Haider et al., 1974). Bouwer and McCarthy (1981) found percentages of 48, 34 and 63% for MCB, 1,3-DCB and 1,4-DCB, respectively, in column studies.

Data on bound-residue formation (portion of the compound that cannot be released from the soil by exhaustive organic solvent extraction) are limited. Scheunert and Korte (1986) found in a 1-week soil-plant test that the formation of bound residues increased as the number of chlorine substituents decreased: 0.7% for HCB, 1.1% for PeCB and 3.5% for 1,2,4-TCB. Similar percentages were also found after a longer incubation period (Scheunert et al., 1985). However, these percentages are relatively low compared with, for example, chlorophenols.

3.3. BEHAVIOUR IN SURFACE WATER

3.3.1. Dispersion

Volatilization is a major mechanism for removal of chlorobenzenes from the water phase. This is true especially for artificial aquatic systems such as a sewage treatment plant (STP). Using the Simpletreat model, the fate of 1,4-DCB in a STP was calculated (Struijs, 1989), with no degradation, with biodegradation and with rapid biodegradation occurring (table 3.2.). The results are in good agreement with observations in laboratory-scale tests (Topping, 1987).

Table 3.2. Removal percentages (%) of 1,4-dichlorobenzene from waste water in a STP

Degree of loading	*Degradation*	*Surface water*	*Sludge*	*Air*
Overload, low temperature	*0*	*18*	*15*	*67*
Normal load	*57*	*6*	*13*	*24*
Low load	*75*	*2*	*13*	*10*

Under natural conditions, transfer of chlorobenzenes to the atmosphere is usually rapid, depending on the water depth, compared with other processes which determine their fate in water. In a 1-year study, Schwarzenbach et al. (1979) estimated an average annual mass transfer coefficient (k) of 1 cm per hour for 1,4-DCB in Lake Zurich. This implies that in a body of surface water with a depth relevant to the Netherlands (1-4 m), a half-life of several days can be calculated. Table 3.3. summarizes k values and half-lives for the chlorobenzenes at 20 ^{0} C, calculated using the Henry's law constant (see table 3.1.) according to the model of Liss and Slater (1974). The experimentally determined half-life is about 2 days for the DCBs (Canton et al., 1985) and 10 hours for HCB in 10 cm-deep water and at a wind speed of 1.7 m.s^{-1} (Sugiura et al., 1984). On the basis of model experiments, Hellmann (1987) calculated that of HCB, if discharged into the River Rhine at Basel, 21% must have evaporated after 6 days (Lobith).
The change in concentrations of di- and trichlorobenzenes at various locations off the Dutch coast in the period 1983-1984 (Van der Meent et

al., 1985) suggests a significant role of seawater-air exchange as compared with mixing of sea- and river water.

Table 3.3. Mass tranfer coefficients (cm per hour) and volatilization half-lives (in hours) at different water depths

Compound	*k*	*Water depth*		
		0.1 m	*1 m*	*4 m*
MCB	*2.04*	*3.4*	*34*	*140*
1,2-DCB	*1.74*	*4.0*	*40*	*160*
1,3-DCB	*1.78*	*3.9*	*39*	*160*
1,4-DCB	*1.72*	*4.0*	*40*	*160*
1,2,3-TCB	*1.60*	*4.3*	*43*	*170*
1,2,4-TCB	*1.61*	*4.3*	*43*	*170*
1,3,5-TCB	*1.57*	*4.4*	*44*	*180*
1,2,3,4-TeCB	*1.46*	*4.8*	*48*	*190*
1,2,3,5-TeCB	*1.49*	*4.7*	*47*	*190*
1,2,4,5-TeCB	*1.46*	*4.8*	*48*	*190*
PeCB	*1.39*	*5.0*	*50*	*200*
HCB	*1.17*	*5.9*	*59*	*240*

Duinker and Hillebrand (1979) found that penta- and hexachlorobenzene behaved conservatively in the mixing zone, their concentrations decreasing linearly with increasing salinity. Exchange of these compounds between the dissolved and suspended phases could not be demonstrated. The measured concentrations in sediments of fresh water and the estuarine mixing zones are probably due to the supply of material adsorbed onto suspended particles, a proportion of which deposits. Duinker and Hillebrand (1979) explained the values reported by them by (a) mixing of fluvial and marine particles, (b) sedimentation, starting in the freshwater basin and extending into the mixing zone, and (c) resuspension.

Adsorption onto suspended particles and transport to the sediment will play a greater part in fresh water as the degree of chlorination increases. Wegman and Hofstee (1982) found the ratio between the HCB concentrations in sediment and in water to be 1300 in the Boven Merwede River and 1200.kg^{-1} dry wt in Lake Ketel. This experimentally determined partition coefficient is roughly a factor of 5 lower than would be expected on the basis of the K_{ow} of HCB and the organic-carbon content of the sediment when this is estimated at 5%. Sugiura et al. (1984) reported a partition coefficient of 2627 in an experimental pond (the organic-carbon content of the sediment was not stated).

3.3.2. Abiotic conversion

Hydrolysis of chlorobenzenes is unlikely to occur under environmental conditions; accordingly, quantitative data on hydrolysis rates were not found in the literature.

The rate constant for the reaction of MCB with photochemically produced hydroxyl radicals was found to be 4×10^{9} $mol^{-1}.s^{-1}$ (Farhataziz and Ross, 1977; Mansour et al., 1985). Mansour et al. (1985) furthermore measured a reaction rate constant for 1,2-DCB of 3×10^{9} $mol^{-1}.s^{-1}$, while the rate of the reaction with photochemically produced peroxyl radicals was about 10 times slower for both chlorobenzenes.
Anbar and Neta (1967) reported the following rate constants for the reaction with photochemically produced hydrated electrons in aqueous solution ($e^{-}aq$):

- MCB : 5.0×10^{8} $mol^{-1}.s^{-1}$
- 1,2-DCB: 4.7×10^{9} $mol^{-1}.s^{-1}$
- 1,3-DCB: 5.2×10^{9} $mol^{-1}.s^{-1}$
- 1,4-DCB: 5.0×10^{9} $mol^{-1}.s^{-1}$

Using a $[OH^{\cdot}]$ of 10^{-16} $mol.l^{-1}$ (Mansour et al., 1985), an $[e^{-}_{aq}]$ of $1.1 \times 10^{(-17)}$ $mol.l^{-1}$ per mg dissolved organic carbon (DOC) per litre surface water (Breugem et al., 1985), and an average DOC concentration in Dutch water bodies of 4 $mg.l^{-1}$, half-lives of approximately 300 days for both processes can be calculated for the Netherlands. The reaction rates of the higher chlorinated benzenes are expected to be of the same order of magnitude. The above-mentioned processes will therefore be of minor importance in the removal of chlorobenzenes from the aquatic environment.

Quantitative data on oxidation by photochemically generated singlet oxygen were not found in the literature. Scully and Hoigne (1987), however, have made it reasonable to suppose that for chlorobenzenes, the rate of this process too will be negligible.
Direct phototransformations have been extensively studied by Boule et al. (1985, 1987), Crosby and Hamadmad (1971), Dime (1981), Sugiura et al. (1984) and Tissot et al. (1984). For the lower chlorinated benzenes in particular, photohydrolysis was found to be the main photochemical loss

process. For example, MCB was quantitatively converted to phenol, while irradiation of the various di- and trichlorobenzenes resulted in the formation of mono- and dichlorophenol, respectively. In the latter case, however, a substituent effect is clearly involved. In addition to the type and position of the substituents, the photolysis rate was also found to be strongly influenced by conjugation effects: electron-donating groups accelerate photolysis whereas electron-withdrawing groups retard it. Accordingly, going from MCB to the various TCB isomers, the quantum yield decreases sharply. In the case of the higher chlorinated benzenes, the deactivating effect of the large number of electron-seeking Cl atoms on photohydrolysis is so great that the photochemically induced dechlorination (reduction) of the aromatic ring becomes dominant: irradiation of TeCB yields a mixture of TCB and trichlorophenol (TCP) while irradiation of PeCB and HCB results in the formation of TeCB and PeCB, respectively. The quantum yields gradually increase going from TeCB to HCB.

Rates of phototransformation under environmental conditions can be estimated from the following data. Crossland and Wolff (1985) found a rate constant of 0.15-0.34.day^{-1} for PCP in a 1 metre-deep pond with a water composition similar to that of Dutch surface waters. In addition, Boule et al. (1985) measured the following quantum yields for MCB, 1,2-DCB, 1,3-DCB, 1,4-DCB, 1,2,4-TCB, 1,3,5-TCB and PCP: 0.1, 0.02, 0.06, 0.01, 0.002, 0.006 and 0.015 respectively. The data published by Sugiura et al. (1984) on photolysis rates of HCB and PCP show that HCB was converted 450 times more slowly than PCP, which is a consequence of the poor spectral overlap between the solar spectrum and the UV absorption spectrum of HCB. By combining the measured quantum yields of various chlorobenzenes and PCP with the field data of Crossland and Wolff (1985), the direct phototransformation rates in Dutch surface waters can be calculated, after correction for the average water depth. Moreover, the photolysis rates of the tetrachlorobenzene isomers and pentachlorobenzene can be estimated by interpolation. The estimated half-lives are 2-5 days for MCB, 12-28 days for 1,2-DCB and 1,4-DCB, 3-7 days for 1,3-DCB, 50-110 days for TCBs, and more than 150 days for TeCBs, PeCB and HCB.

3.3.3. Biodegradation

Few reports have appeared on the biological degradation of chlorobenzenes under anoxic and aerobic conditions. In general, it can be stated that chlorobenzenes are less readily degraded by aerobic microorganisms than are chlorophenols. As with the chlorophenols, resistance to aerobic degradation increases as the number of chlorine atoms on the aromatic ring increases. Microbial degradation of chlorobenzenes under aerobic conditions has only been demonstrated for MCB (Bartholomew and Pfaender, 1983), 1,2-DCB (Haigler et al., 1988), 1,3-DCB (De Bont et al., 1986) 1,4-DCB (Spain and Nishino, 1987; Schraa et al., 1986) and 1,2,4-TCB (Bartholomew and Pfaender, 1983; Van der Meer et al., 1987). 1,4-DCB readily degraded in an OECD(1981)/EEC(1984) screening test (Topping, 1987; Canton et al., 1985) and in a laboratory-scale sewage treatment plant (Topping, 1987). The other dichlorobenzenes were not biodegradable in the screening test (Canton et al., 1985), which can be explained by the long enzyme induction times as observed by Haigler et al. (1988).
It is believed that the initial step in the degradation of chlorobenzenes is conversion to the corresponding catechol catalyzed by dioxygenase enzymes, thereby making ring cleavage possible, followed by mineralization. This requires that there are not two adjacent chlorine substituents on the ring. Consequently, hexa-, penta-, 1,2,3,5-tetra-, 1,2,4,5-tetra-, and 1,3,5-trichlorobenzene probably cannot be aerobically degraded.

The "reductive dechlorination" mediated by specific bacteria can occur under anaerobic conditions. This process is very important because a chlorine atom is replaced by a hydrogen atom, the dechlorinated product being more susceptible to further aerobic microbial attack. Unlike aerobic biodegradation, reductive dehalogenation on the aromatic ring proceeds more readily as the degree of chlorination increases. Fathepure et al. (1988) found complete biotransformation of HCB in anaerobic sewage sludge within 3 weeks. HCB was dechlorinated via two routes, both involving the sequential removal of chlorine from the aromatic ring. The major route was HCB -> PeCB -> 1,2,3,5-TeCB -> 1,3,5-TCB, which remained unchanged. The minor route was HCB -> PeCB -> 1,2,4,5-TeCB -> 1,2,4-TCB, which was further dechlorinated to DCBs.

In another study, the reductive dechlorination of all TCBs to MCB was demonstrated in columns filled with anaerobic sediment collected from the Rhine River at Wageningen (Bosma et al., 1988). The reaction started only after a long microbial adaptation period, which varied from 3 months for 1,2,3-TCB to 6 months for 1,3,5-TCB. After more than one year, all TCBs were rapidly converted to MCB by the microorganisms in this sediment. In addition, it was found that dechlorination of DCBs occurred only when TCBs were no longer present, which is also an indication of the preference of these microorganisms for higher chlorinated benzenes.
There is also indirect evidence that the higher chlorinated benzenes in particular are susceptible to reductive dechlorination. Oliver and Nicol (1982) found in sediment cores from the Great Lakes in Canada and the US that the ratio of 1,4-DCB to HCB increased dramatically with increasing age of the sediment, from about 0.4 in the top layer (0-1 cm, dating from the period 1976-1980) to about 20 in the deeper layer (6-7 cm, 1932-1941). A possible explanation for this is that the relatively higher concentrations of the lower chlorinated benzenes in the older layers are the result of reductive dechlorination of highly chlorinated benzenes (Bailey, 1983). A striking feature is that the measured concentrations of the DCBs in Lake Ketel sediment were not only markedly higher than the concentration of the much more hydrophobic HCB (Beurskens, 1989), but that they bore no relationship to the levels in the overlying water (see 4.4.): if the partition coefficient of 1,4-DCB is estimated using the K_{ow} and the organic-carbon fraction of the Lake Ketel sediment, then the concentration in the sediment proves to be a factor of 45 too high. There are two possible explanations for this discrepancy, one being the reductive removal of Cl from higher chlorinated benzenes which initially partitioned to the sediment, and the other the observed decrease in the DCB input to surface water (see section 4.4.1.; see also 3.2.).

In summary, the following picture emerges from combining the volatilization and transformation rates of chlorobenzenes in the aquatic environment:
- biotic transformations are generally of minor importance;
- for the lower chlorinated benzenes (mono-, di and tri-), the removal rate is determined equally by volatilization and phototransformation;

- volatilization is the predominant process for removal of the higher chlorinated benzenes from the water phase;
- in anerobic sediment, only biotic processes play a role. If these processes occur, then this will lead to an increase in the lower chlorinated benzenes which, because of their limited hydrophobicity, may leach to the groundwater.

Figure 3.2. shows the overall half-life for removal of the chlorobenzenes from the water phase as a function of the number of chlorine atoms on the ring.

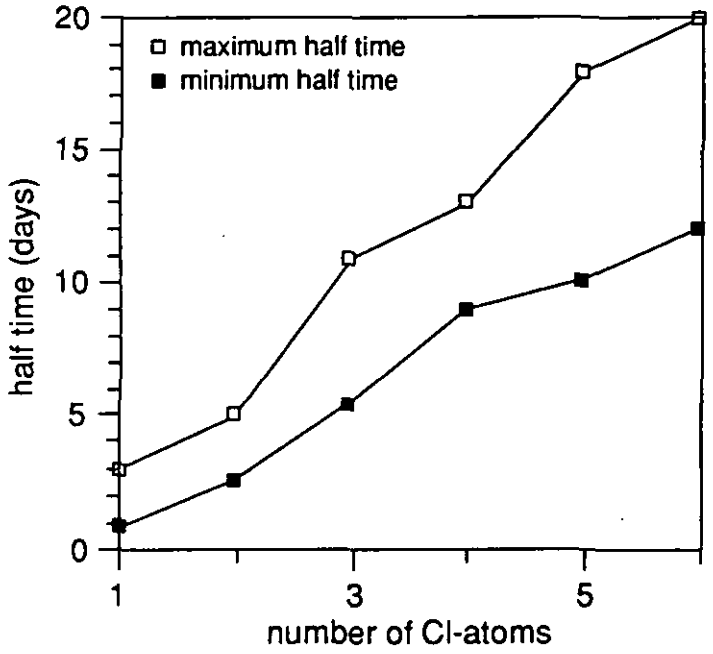

Figure 3.2. Overall half-lives for the removal of chlorobenzenes from the water phase as a function of the number of chlorine atoms

3.4. BEHAVIOUR IN AIR

3.4.1. Deposition

Chlorobenzenes are removed from the atmosphere by both dry (d) and wet (w) deposition. The deposition velocity depends on the (chemical) properties of the depositing substance and the type of surface (vegetation, soil, water), as well as on the meteorological conditions (atmospheric stability).
The dry deposition flux can be estimated from the product of the deposition velocity and the airborne concentration. Data on the deposition velocities

of chlorobenzenes are not available. Deposition velocities of gaseous organic compounds are generally very low. It is believed that the deposition process is determined by the conversion and transport of a substance in soil and water (Tucker and Preston, 1984). Assuming a deposition velocity v_d of 10^{-2}-10^{-3} $cm.s^{-1}$ (this is of the same order of magnitude as the deposition velocity of acetone; Judeikis, 1982) and setting the mixing height at 800 m, then the removal rate $k_d = v_d/H = 5x10^{-2}$-$5x10^{-3}$ % per hour. It is estmated that the atmospheric residence time due to dry deposition varies from nearly 3 months to more than 2 years.

In wet removal, a distinction can be made between:

- washout (below-cloud scavenging), a process occurring below the cloud and in which gaseous or particulate pollutants are scavenged in falling raindrops;
- rainout (in-cloud scavenging), a process occurring in the clouds and in which substances are scavenged in cloud droplets and subsequently removed via the precipitation.

Washout is important for aerosols larger than 1 μm in diameter and for readily soluble gases. In the case of less readily soluble gases, such as the chlorobenzenes, the cloud droplets will already be virtually saturated with these compounds so that below the cloud little more material can be taken up in the falling drops. Therefore, rainout will be the principal removal process for chlorobenzenes.

The annual input to the soil due to wet deposition can be estimated from the concentration in precipitation and the rain intensity. A typical removal constant k_w for wet deposition can be estimated using the scavenging ratio W (defined as the ratio of precipitation concentration to air concentration; see table 3.4.) and the average rain intensity R:

$$k_w = WR / H$$

where h is the mixing layer height. In the determination of k_w, the annual rainfall was taken to be 750 mm and the average mixing layer height 800 m. The estimated atmospheric residence time due to wet deposition varies from 7 months to more than 20 years.

Table 3.4. Scavenging ratio and average removal rate for a few chlorobenzenes

Compound	*W*	k_w *(% per hour)*	*Reference*
MCB	*6.2*	7×10^{-5}	*Eisenreich et al. (1981)*
1,2-DCB	*46±13*	5×10^{-4}	*Ligocki et al. (1985)*
1,4-DCB	*39±10*	4×10^{-4}	*Ligocki et al. (1985)*
1,2,4-TCB	*66±51*	7×10^{-4}	*Ligocki et al. (1985)*
HCB	1.5×10^{3}	2×10^{-2}	*Eisenreich et al. (1981)*

Although the dry deposition velocity is low, it represents the main input to soil and surface water. The ratio of the wet to the dry deposition flux is given by:

$$Fw/Fd = AW / v_d \Delta t$$

where A is the annual precipitation (750 mm) and $\Delta t = 3.15 \times 10^{7}$ s. On the assumption that $v_d = 10^{-2}$ cm.s^{-1}, the dry deposition flux is greater than the wet flux so long as W is less than about 4000.

3.4.2. Conversion

The atmospheric sinks for chlorobenzenes are reaction with OH radicals and photolysis.

Reaction with OH·

In the reaction with an electrophilic agent such as OH·, Cl substituents tend to reduce the reactivity of the aromatic ring. The reaction of the OH radical with chlorobenzenes is much slower than with benzene (rate constant, 1.0×10^{-12} cm^{3}.s^{-1}; Rinke and Zetzsch, 1984). The reaction with the OH radical is initiated by addition of OH to the aromatic ring; however, subsequent reaction products have not been identified.

Rate constants for the OH reaction (k_{OH}) have been determined experimentally for only a few chlorobenzenes. It is known however that a good correlation exists between the k_{OH} and the ionization potential I_p

(Gusten et al., 1984). An estimate of the k_{OH} has been obtained by applying the regression equation:

$$\log k_{OH} (cm^3.s^{-1}) = 2 - 3/2\ I_p\ (eV)$$

The ionization potentials have been determined with the help of semi-empirical orbital calculations, using the MNDO approach (Dewar and Thiel, 1977; Dewar and Rzepa, 1983). Compared with the available measurements, the calculated I_p's show an overestimation. This leads to an underestimation of kOH when applying the empirical relationship between k_{OH} and I_p; see the measured values for dichlorobenzenes (table 3.5.).

A second empirical estimation method, based on structural characteristics (Zetzsch, 1983), leads to estimates of k_{OH} which are 4-8 times higher. Uncertainties in k_{OH} and thereby in the atmospheric residence time are large, because reaction with OH. is the main process for removal of chlorobenzenes from the atmosphere.

Assuming an average OH radical concentration of $10^6.cm^{-3}$, the pseudo first-order transformation rate $kc = k_{OH}[OH] = 5x10^{-3}$ -0.6% per hour, corresponding to a residence time of 1 week to 2 years.

Table 3.5. The ionization potentials I_p (eV) and the associated rate constants kOH ($cm^3.s^{-1}$)

Compound	I_p calc. (a)	I_p avg.	k_{OH} ($x10^{13}$) calc.	k_{OH} ($x10^{13}$) avg.
MCB	9.62	9.07 (b)		6.7-9.4 (f)
1,2-DCB	9.85	9.07 (b)	1.7	4.2 (c)
1,3-DCB	9.89	9.12 (b)	1.5	7.2 (c)
1,4-DCB	9.82	8.95 (b)	1.9	3.2 (c)
1,2,3-TCB	10.11		0.68	
1,2,4-TCB	10.04	9.04 (b)	0.87	5 (d)
1,3,5-TCB	10.20		0.50	
1,2,3,4-TeCB	10.22		0.47	
1,2,3,5-TeCB	10.26		0.41	
1,2,4,5-TeCB	10.21		0.48	
PeCB	10.39		0.26	
HCB	10.56	9.19 (e)	0.15	

(a) De Leeuw (1989)
(b) Rosenstock et al. (1977)
(c) Wahner and Zetzsch (1983)
(d) Rinke and Zetzsch (1984)
(e) Gusten et al. (1984)
(f) Atkinson (1985)

Photolysis

In addition to the reaction with OH radicals, chlorobenzenes undergo photolysis (Bunce et al., 1988). This process is initiated by cleavage of a C-Cl bond, followed by reaction of the radical formed with oxygen to give phenolic products. Since the chlorobenzenes absorb weakly at wavelengths above 300 nm, solar degradation is of minor importance. Of the chlorobenzenes studied by Bunce et al. (1988) (MCB, 1,2-DCB, 1,3-DCB, 1,2,4-TCB and 1,3,5-TCB), only the vapour-phase absorption spectrum of 1,2,4-TCB shows some overlap with the solar spectrum. The estimated maximum photolysis rate for 1,2,4-TCB (high summer: clear sky, midday) was only 0.03% per hour (Bunce et al., 1988); the photolysis rates for the other chlorobenzenes are even lower. Under optimal conditions, the minimum residence time of 1,2,4-TCB due to photolysis is approximately 4 months. Laboratory experiments showed that 2,5-dichloro-6-nitrophenol was the main product when 1,4-DCB was exposed to ultraviolet rays in the presence of very high nitrogen oxide concentrations (about 1000 ppm) (Nojima and Kanno, 1980). It is not clear whether this reaction also occurs under atmospheric conditions.

Although the fate and the atmospheric reaction of chlorobenzenes is still insufficiently known, HCl will be formed in the atmosphere during the degradation of chlorobenzenes. This HCl will have an acidifying effect after its deposition, but the contribution to the total acid deposition is small. The Cl emission in the form of chlorobenzenes in the Netherlands is about 180 tonnes of chlorine per year; this is about 1% of the estimated HCl emission (Lightowlers and Cape, 1988).

The atmospheric residence time is given by:

$\sigma = 1 / (k_d + k_w + k_c + k_{h\lambda})$

Based on the above data, a residence time ranging between about 6 days and 1 year is estimated for chlorobenzenes. Transport from the troposphere to the stratosphere occurs over a time-scale of 2-3 months. There may be some slight transport of the least reactive chlorobenzenes to the stratosphere, where rapid photochemical degradation will occur as a result of the intense UV radiation at this height. However, the contribution to the stratospheric Cl concentration will be small compared to the contribution from other

chlorine-containing compounds (in particular CFCs). Therefore, chlorobenzenes will not play a significant role in the chemical processes governing the formation and destruction of the stratospheric ozone layer.

3.5. BEHAVIOUR IN BIOTA

The data reported in this section have been taken from a background report (Appendix) on the effects of chlorobenzenes, drawn up for this integrated criteria document.

The bioaccumulation of chlorobenzenes in aquatic organisms increases with an increasing number of chlorine atoms on the benzene ring. Bioconcentration factors (BCF = concentration in the organism/concentration in water) ranging from 12 for MCB to more than 100,000 for HCB have been reported. Little is known about bioaccumulation in terrestrial organisms. In view of the lipophilic nature of the higher chlorobenzenes, biomagnification could constitute a hazard to both aquatic and terrestrial organisms. No data are known for aquatic organisms, and those for terrestrial organisms are too limited for a risk assessment to be made.

3.6 SUMMARY AND CONCLUSIONS

In the soil, only volatilization from the top layer plays an important role in the removal of chlorobenzenes from the soil. Chlorobenzenes adsorb strongly to soil. MCB moves through a soil containing 1% organic matter 10 times, and HCB 1000 times, more slowly than through water, so that they probably do not constitute a contamination hazard to deep groundwater. Aerobic biodegradation decreases and anaerobic biodegradation increases with increasing number of chlorine substituents. The biotic half-life of 1,4-DCB is a few weeks to months and that of HCB 1-6 years.

The rate of removal of the lower chlorinated benzenes from water is determined equally by volatilization and phototransformation. Volatilization is the principal removal process for the higher chlorinated benzenes. The overall half-life is a function of the number of chlorine

atoms in the molecule, and increases from an average of two days for MCB to 16 days for HCB.
Adsorption to suspended particles and partitioning to the sediment increase as the degree of chlorination increases.
The estimated half-lives for abiotic removal from water are a few days for the lower chlorinated benzenes and a few weeks for the higher chlorinated ones. Biotic degradation of chlorobenzenes is of minor importance in water. As in soil, aerobic biodegradation decreases and anaerobic biodegradation increases with increasing number of chlorine substituents. In the latter situation, the resulting lower chlorinated benzenes can be transported to deeper soil layers with the percolating water.

Chlorobenzenes usually occur in the atmosphere in the gaseous state. Four processes are important in the removal of chlorobenzenes from the atmosphere, namely, dry and wet deposition, reactions with OH radicals, and photolysis.
Dry deposition, with a residence time ranging from 3 months to more than 2 years, makes a greater contribution to elimination from the atmosphere than does wet deposition, for which the residence time lies between 7 months and 20 years.
Atmospheric conversion of chlorobenzenes occurs by reaction with OH radicals and photolysis. The residence time due to OH-radical reactions lies between 1 week and 2 years. Under optimum conditions (clear sky at midday in high summer), the minimum residence time due to photolysis is approximately 4 months.
The overall atmospheric residence time of chlorobenzenes ranges between 1 week and 1 year.
There may be some slight transport of the least reactive chlorobenzenes to the stratosphere. However, the contribution to the stratospheric Cl concentration will be small compared to that from other chlorine-containing compounds (particularly CFCs). Chlorobenzenes do not play an important part in the stratospheric chemistry.

4. CONCENTRATIONS, FLUXES AND EXPOSURE LEVELS

4.1. MEASUREMENT TECHNIQUES

A large number of analytical methods for determining chlorobenzenes have been described in the literature. Most methods have been designed for a select number of chlorobenzene congeners. These analytical methods are listed in table 4.1., comprising the techniques used for sample pretreatment, cleanup and analysis, with specification of the sample sizes and detection limits for the chlorobenzenes investigated. In addition, an estimate of the cost per analysis is given, based on the required analysis time, reagents and instrument capacity.

The most commonly used sample preparation method for the volatile chlorobenzenes (mono-tri) is the purge-and-trap technique. Strottmeister et al. (1988) introduced the micro-extraction method, which also made it possible to determine the less volatile chlorobenzenes (tetra-hexa) along with the volatile ones. The extractant employed is usually hexane (Wammes et al., 1986) or pentane (Strottmeister et al., 1988).

Analysis is generally by gas chromatography (GC) with flame ionization detection (FID; Yao and Zlatkis, 1987) or electron capture detection (ECD; Wammes et al., 1986). A GC with dual FID/ECD method has been described by Termonia and Alaerts (1985). Analysis using gas chromatography/mass spectrometry (GC/MS) is not often used, since this method is found to be laborious and requires special equipment (Fast et al., 1987; Cuiu et al., 1986). However, GC/MS is often used as a confirmation method.

4.1.1. Soil

Greve et al. (1989) decribed a method for analyzing HCB in soil. The soil was first extracted with acetone. After addition of water to the concentrated acetone extract, the resulting mixture was extracted with hexane. The extract was then analyzed without cleanup using GC with ECD and confirmation was carried out by GC/MS.

For the determination of volatile chlorobenzenes, Fast et al. (1987) extracted a suspension of soil and water with nitrogen. The extracted

chlorobenzenes were concentrated on a Tenax-packed column and analyzed using a GS/MS equipped with a desorption unit.

4.1.2. Water

The volatile chlorobenzenes are first concentrated (purge-and-trap) on a column packed with Tenax (Vandegrift, 1988) or graphite fluoride (Yao and Zlatkis, 1987), followed by desorption with helium in a special desorption device and transfer of the desorbed compounds onto the gas chromatograph. The breakthrough volumes for chlorobenzenes are greater on the graphite fluoride column than on the Tenax column (Yao and Zlatkis, 1987). Desorption from a graphite fluoride column is carried out at a higher temperature (300^{0}C) than from a Tenax column (180^{0}C).
The nonvolatile hexachlorobenzene can be isolated by extracting the water sample with hexane or pentane. The moderately volatile chlorobenzenes (tri-penta) can be isolated using the micro-extraction method (extract 1 litre of water with 1 ml of pentane) and analyzed without preconcentration by GC/FID (Strottmeister et al., 1988).

4.1.3. Air

For the analysis of chlorobenzenes in ambient air, the purge-and-trap technique is invariably employed. The adsorbant used is graphite fluoride, Florisil, Tenax or activated charcoal. Chang et al. (1985) used Florisil for trapping the chlorobenzenes, and they were extracted from the adsorbent by sequential Soxhlet extraction with pentane and methylene chloride. The extract was then separated on a 1.25% H_2O-deactivated Florisil column and the fractions analyzed by GC/FID. Fast et al. (1987) used activated charcoal and eluted the chlorobenzenes from the column with 1 ml of carbon disulphide. As with water samples, Yao and Zlatkis (1987) also used graphite fluoride for air samples. A similar method was employed by Termonia and Alaerts (1985), but with Tenax as the adsorbent.

Table 4.1. Analytical methods and detection limits for chlorobenzenes in soil, water and air, and the estimated cost per analysis (in guilders, 1988 price level)

Sample pretreatment	Cleanup/ desorption	Quantification method	Sample size	Congeners	Detection limit	Ref.	Cost est.
Soil							
purge and trap adsorbent: Tenax purge gas: nitrogen		GC/MS	2 g	MCB, DCB and TCB		1	500
extraction with acetone separation with hexane		GC/ECD	25 g	HCB	0.5 ug/kg	2	400
Water							
purge and trap adsorbent: graphite fluoride purge gas: helium	desorption with helium at 300 C	GC/FID	5 ml	MCB and DCB	0.1 mg/l MCB 0.5 mg/l DCB	3	150
purge and trap adsorbent: Tenax purge gas: helium (15 min)	desorption with helium at 180 C	GC/FID with cryotrap	50 ml	DCB	2 ug/l DCB	4	200
extraction with pentane		GC/FID	1 l	all CBs	0.3-0.5 ug/l	5	200
extraction with hexane	chromatography on acid/base column $AgNO_3/Al_2O_3$ column	GC/MS		DCB, TCB TeCB, PeCB and HCB		6	
extraction with hexane	5% Al_2O_3	GC/ECD	0.5 l	HCB	0.01 ug/l	7	300
Air							
purge and trap adsorbent: graphite fluoride	desorption with helium at 300 C	GC/FID	3 l	MCB		3	150
trapping on Florisil column desorption: pentane/methylene chloride	fractionation on 1.25% H_2O-deactivated Florisil	GC/FID		PeCB, HCB		8	350
purge and trap adsorbent: Tenax	desorption with hydrogen at 200 C	GC/FID/ECD		MCB, DCB and TCB		9	200
trapping on activated charcoal	desorption with carbon disulphide	GC/FID	1000 l	MCB, DCB and TCB	0.8 ug	1	200

1 Kliest and Van de Wiel (1987)
2 Greve et al. (1989)
3 Yao and Zlatkis (1987)
4 Vandegrift (1988)
5 Strottmeister et al. (1988
6 Cuiu et al. (1986)
7 Wammes et al. (1985)
8 Chang et al. (1985)
9 Termonia and Alaerts (1985)

4.2. BACKGROUND CONCENTRATIONS

Turkstra (1988) has postulated that all halogenated organic micropollutants are due only to human activities. Data on natural sources and background concentrations were not found in the literature.

4.3. OCCURRENCE IN SOIL AND GROUNDWATER

4.3.1. Occurrence in soil

Smelt (1976) reported the occurrence of HCB residues on plots which had been treated in the past with HCB-containing pesticide formulations. He found a median of 90 $\mu g.kg^{-1}$ soil for 22 field samples and of 160 $\mu g.kg^{-1}$ soil for 10 greenhouse soils. According to Smelt, nearly all these concentration levels are attributable to several soil treatments in the past with quintozene (pentachloronitrobenzene) formulations.
Edelman (1984) analyzed 96 soil samples from the top soil (0-10 cm) of 38 nature reserves for hexachlorobenzene (HCB). The concentrations in 74 of these samples were below the detection limit of 1 $\mu g.kg^{-1}$ soil, 20 samples had a level of 1-10 $\mu g.kg^{-1}$, 1 sample contained 40-50 $\mu g.kg^{-1}$ and 1 sample 70-80 $\mu g.kg^{-1}$. The last two samples were both from the Geer polder, which consists of a peaty clay soil. According to Edelman, the high HCB levels are possibly due to windblown pesticides.
A start has recently been made with the Soil Quality Monitoring Programme. Soil samples were taken at 40 locations in the Netherlands at two depths below ground level (0-10 cm and 10-30 cm). The locations represented 10 different combinations of land use/soil type, so that each combination was sampled at 4 locations. At each sampling location, four samples were taken from each depth. The samples were analyzed for HCB, with a detection limit of 0.5 $\mu g.kg^{-1}$. Table 4.2. presents the results after statistical processing (De Kwaadsteniet, 1989).

Table 4.2. 95% Confidence intervals for the average HCB concentration ($\mu g.kg^{-1}$) for 10 different combinations of land use/soil type at several depths (detection limit: 0.5 $\mu g.kg^{-1}$)

Land use/soil type	*Depth (below ground level)*	
	0-10 cm	*10-30 cm*
grassland/ordinary hydropodzol	*0.1-20*	*0.1-17*
grassland/thick earth soil	*0.2- 6*	*0.2-10*
grassland/clay earthy peat soil	*0.5- 4*	*0.3- 2*
farmland/calcareous loam - clay loam	*0.4- 2*	*0.3- 2*
farmland/ordinary hydropodzol	*0.2-34*	*0.2- 6*
farmland/thick earth soil	*0.8-29*	*0.2-12*
orchard/calcareous loam - clay loam	*< 0.5*	*< 0.5*
orchard/thick earth soil	*0.2- 6*	*0.2 -8*
forest/ordinary hydropodzol	*< 0.5*	*< 0.5*
forest/sandy hydrovague soil	*< 0.5*	*< 0.5*

4.3.2. Occurrence in groundwater

Unpublished studies by the Groundwater Quality Monitoring Network of the RIVM gave the following result (Peeters, 1989). In the autumn of 1986, 38 wells of the monitoring network were sampled at a depth of 10 m below ground level and the samples analyzed for mono-, di- and trichlorobenzenes. The detection limit was exceeded in three wells (table 4.3.).

Table 4.3. Measurements of chlorobenzenes in wells of the Groundwater Quality Monitoring Network of the RIVM, sampled in the autumn of 1986, where one or more chlorobenzenes exceeded the detection limit

Compound	*Concentration ($\mu g.l^{-1}$) at locations with positive observations*		
	Esch and Weel	*Hansweert*	*Sluiskil*
MCB	*< 0.5*	*< 0.5*	*< 0.5*
1,2-DCB	*0.3*	*0.3*	*0.2*
1,3-DCB	*0.3*	*< 0.1*	*< 0.1*
1,4-DCB	*0.3*	*< 0.1*	*< 0.1*
1,2,3-TCB	*< 0.1*	*< 0.1*	*< 0.1*
1,2,4-TCB	*0.1*	*< 0.1*	*< 0.1*
1,3,5-TCB	*< 0.1*	*< 0.1*	*< 0.1*

Sampling was repeated in the autumn of 1987, but this time in 114 wells of the monitoring network and at depths varying from 10 to 30 m below ground level. The detection limits for the TCBs were 50 percent lower and those for DCBs 5 times higher than in 1986. The concentrations of the chlorobenzenes studied were below the detection limit in all samples.
KIWA (Veenendaal et al., 1986) sampled the raw groundwater at all pumping stations in the Netherlands, including those infiltrated with surface water, and analyzed the samples for DCBs (period September 1983-June 1985). The histogram of figure 4.1. includes the observations in which DCB isomers were detected at concentrations equal to or higher than 0.1 ug/l (positive observations).

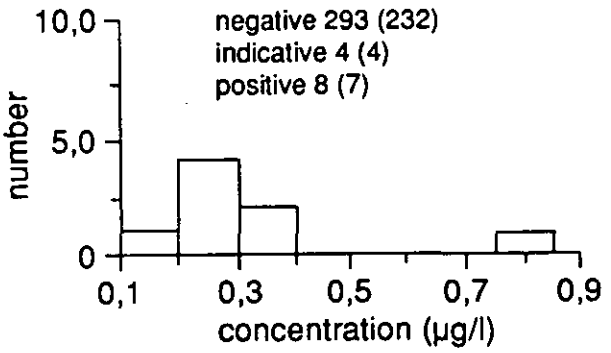

Figure 4.1. Histogram for dichlorobenzene isomers in groundwater (Veenendaal et al., 1986). Indicative observations are those with concentrations below 0.1 µg.l^{-1}. The number of pumping stations is given in parentheses

The positive observations by KIWA and the Groundwater Quality Monitoring Network invariably concern bank groundwater recharged by the infiltration of river water.

4.4 OCCURRENCE IN WATER AND SEDIMENTS

4.4.1. State water bodies

The concentrations of all chlorobenzenes except MCB are measured by the Department of Public Works at several locations (Rhine River: Lobith; Meuse River: Eysden; Western Scheldt River: Schaar van Ouden Doel; North Sea Canal: KM 2, Nieuwe Waterweg Canal: NM 37). The maximum and annual average concentrations of the various DCBs, TCBs and TeCBs, and of PeCB and HCB measured in the period 1980-1988 are presented in table 4.4.

Table 4.4. Summary of the occurrence of chlorobenzenes in Dutch surface waters, showing the maximum and annual average concentrations ($\mu g.l^{-1}$)

	Rhine		Meuse		Western Scheldt		North Sea Canal		Nieuwe Waterweg	
	max.	avg.	max.	avg.	max.	avg.	max.	avg.	max.	avg.
1,2-dichlorobenzene										
1986	0.20	0.05	1.10	0.11	0.20	0.08	<0.10	<0.01	0.30	0.08
1987	<0.10	<0.01	<0.10	<0.01	<0.10	<0.01	0.20	0.02	<0.10	<0.01
1988	0.60	0.12	<0.10	<0.01	<0.10	<0.01	<0.10	<0.01	<0.10	<0.01
1,3-dichlorobenzene										
1986	0.10	0.01	0.80	0.07	0.60	0.18	0.80	0.27	0.40	0.08
1987	<0.10	<0.01	<0.10	0.00	0.60	0.11	3.30	0.35	<0.10	<0.01
1988	0.30	0.06	0.01	<0.001	<0.10	<0.01	0.10	0.02	<0.10	<0.01
1,4-dichlorobenzene										
1986	0.10	0.03	0.20	0.03	0.10	0.03	0.10	0.03	0.40	0.08
1987	0.10	0.02	<0.10	<0.01	0.10	0.01	0.10	0.01	<0.10	<0.01
1988	0.60	0.12	0.10	0.02	0.10	0.02	<0.10	<0.01	<0.10	<0.01
1,2,3-, 1,2,4- and 1,3,5-trichlorobenzene										
1982	0.20	0.052							0.09	0.038
1983	0.10	0.060	0.06	0.008	0.40	0.119			0.09	0.035
1984	0.13	0.032								
1985	0.04	0.027	0.01	0.001	0.62	0.142			0.05	0.022
1986	0.04	0.021	0.02	0.006	0.13	0.036			0.04	0.015
1987	0.06	0.024	0.02	0.005	0.10	0.037			0.03	0.013
1988	0.03	0.018	0.01	0.002	0.09	0.044			0.01	0.003
1,2,3,4-, 1,2,3,5- and 1,2,4,5-tetrachlorobenzene										
1986	<0.01	<0.001	<0.01	<0.001	<0.01	<0.001			0.02	0.002
1987	0.01	0.001	<0.01	<0.001	<0.01	<0.001			<0.01	<0.001
1988	0.01	0.002	<0.01	<0.001	<0.01	<0.001			<0.01	<0.001
pentachlorobenzene										
1987	0.005	0.002	<0.001		<0.001		<0.001		0.001	0.001
1988	0.004	0.002	<0.001		<0.001		<0.001		0.001	0.001
hexachlorobenzene										
1982	0.04	0.010	0.05	0.004	0.01	0.001	0.01	0.002	<0.01	<0.001
1983	0.05	0.010	0.01	0.001	<0.001	<0.001	<0.001	<0.001	0.01	0.002
1984	0.03	0.007	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	0.003	0.002
1985	0.04	0.007	<0.001	<0.001	<0.001	0.001	<0.001	<0.0001	0.003	0.002
1986	0.01	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.0001	0.004	0.002
1987	0.02	0.002	0.01	<0.001	<0.001	<0.001	<0.001	<0.0001	0.005	0.001
1988	0.01	0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.0001	0.003	0.001

It should be noted that in the case of the TeCBs, the concentration of 1,2,4,5-TeCB was also measured as a separate parameter at all sampling points; the concentrations in all samples were below the detection limit (0.001 ug/l). Figure 4.2. shows the measured HCB concentrations in the period 1980-1988.

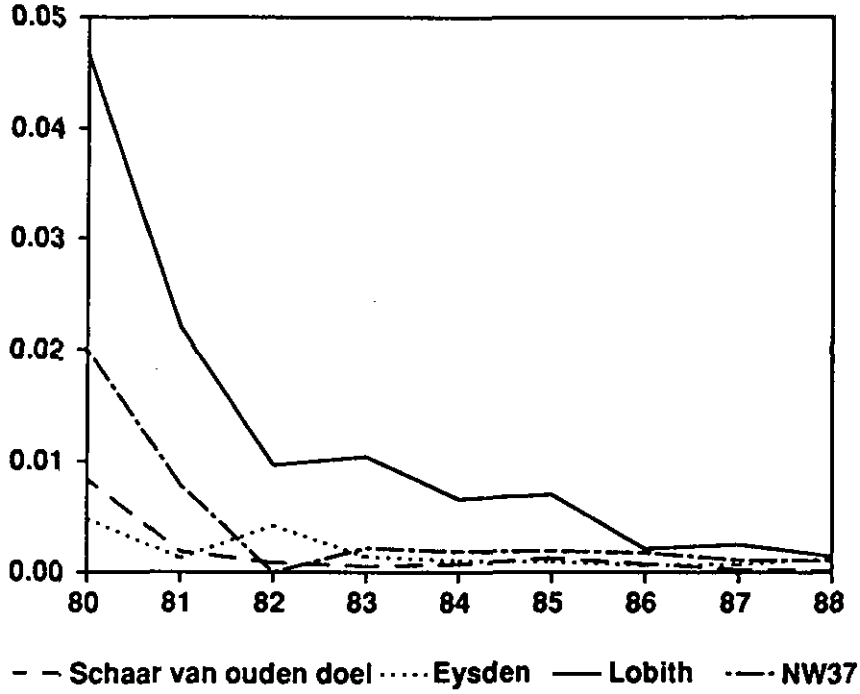

Figure 4.2. Annual average concentrations of hexachlorobenzene in Dutch State water bodies ($\mu g.l^{-1}$)

It is clear from the foregoing table and figure that the measured annual average concentrations have stabilized. The concentrations of the DCBs individually and those of the TCBs collectively appear to stabilize at a level of 0.02-0.03 $\mu g.l^{-1}$. The concentrations of the TeCBs collectively, PeCB and HCB are currently so low that they only sporadically exceed the detection limit (0.001 $\mu g.l^{-1}$). In addition, since the 1970s, the cooperating Rhine and Meuse Water Companies (RIWA, 1988) have occasionally measured chlorobenzene concentrations in the Meuse River (Keizersveer, Heusden), Lek River (Hagestein) and Lake IJssel (Andijk). Annual average MCB, DCB and TCB concentrations around the detection limit (0.1 $\mu g.l^{-1}$) were measured at each of these locations between 1983 and 1988. The average HCB concentrations were also below the detection limit (0.01 $\mu g.l^{-1}$, and as low as 0.0005 $\mu g.l^{-1}$ for the Hagestein location in 1988).

The concentrations of the various DCBs and TCBs in the Dutch coastal waters have been measured by Van de Meent et al. (1985), and it was found that the concentrations were in the 0.001 $\mu g.l^{-1}$ range, with values often equal to those of the blanks used, or lower than the detection limit. It can be concluded that:

- the concentrations gradually decrease in a northward direction;
- the concentrations decrease fairly rapidly in a seaward direction:
- the measured concentrations are the result of the mixing of relatively clean water originating from the Atlantic Ocean with polluted Rhine water on the one hand, and air-seawater exchange through volatilization and dry or wet deposition processes on the other.

4.4.2. Non-State water bodies

In 1986 DBW/RIZA determined HCB concentrations in non-State water bodies. The average measured concentration in 23 observations was 0.001 $\mu g.l^{-1}$, with a maximum of 0.01 $\mu g.l^{-1}$. Data on concentrations of the other chlorobenzenes in non-State water bodies were not found in the literature. In view of the very small emissions into surface water (see chapter 2), with the exception of the relatively volatile 1,4-DCB, it can be expected that the various chlorobenzenes will also be present at relatively low concentrations.

4.4.3. Sediments

Data on the occurrence of chlorobenzenes in sediment concern mostly HCB, the chlorobenzene congener which, based on its K_{ow}, may be expected to be present in sediments at the highest concentrations. Turkstra (1988) has drawn up a memorandum, which deals with the sediments issue. The median of the measured HCB concentrations in the Rhine, Meuse and Hollandse IJssel rivers was around 30 $\mu g.kg^{-1}$ d.w. High levels have been detected in Rotterdam: Chemie Harbour (560 $\mu g.kg^{-1}$ d.w.; 1981) and Geul Harbour (300 $\mu g.kg^{-1}$ d.w.; 1981), Delfzijl: Zeehaven Canal (3960 $\mu g.kg^{-1}$ d.w.; 1982), and in Lake Ketel (100 $\mu g.kg^{-1}$ d.w.; 1983). Lower concentrations were found in Lake IJssel and the lakes between former coast and empoldered land (< 10

$\mu g.kg^{-1}$ d.w.; 1983-1986). Furthermore, high PeCB levels were found in the Zeehaven Canal (personal communication, RIZA).

The Project Group for Cataloguing Sediments (Projectgroep Inventarisatie Onderwaterbodems, 1987) has made an inventory of the quality of the sediments in the province of North Brabant. The total number of measuring points was 106; the concentrations were below 10 $\mu g.kg^{-1}$ d.w. in 78 cases and below 1 $\mu g.kg^{-1}$ d.w. in 21. Actual values were determined in only 6 cases, and were found to range between 1 and 5 $\mu g.kg^{-1}$ d.w.

In summary, it can be stated that the HCB concentrations in the sediments of the large rivers are currently around 30 ug per kg dry weight. However, considerably higher levels may be found in local pollution situations. As regards the expected HCB concentrations in sediments, they will gradually adjust themselves to the stabilization of the HCB concentrations in Dutch surface waters at a level of 0.001 $\mu g.l^{-1}$ as reported in section 4.4.1. On the basis of relationships between the octanol-water and the organic carbon-water partition coefficients, it can be calculated that the HCB concentrations in the sediments will eventually reach a level of 4-5 ug per kg dry weight. This adjustment is a slow process, lasting about 10 to 15 years (Japenga et al., 1987).

4.5. OCCURRENCE IN AIR

4.5.1. Concentrations in indoor air

Occupational setting

Data on chlorobenzenes in the working environment in the Netherlands are only known for outdoor air.

Nonoccupational setting

The chlorobenzene concentrations in indoor air will generally be similar to those in outdoor air, unless products/materials which may release chlorobenzenes are present in the indoor environment. Table 4.5. lists a number of products/materials from which chlorobenzenes may be released (see chapter 2).

Table 4.5. Uses of chlorobenzenes (Arbeidsinspectie (Labour Inspectorate) 1986; De Bruin, 1986; Sax et al., 1981; Morita, 1977; Starkenburg and Van Luin, 1985; WHO, 1980)

Compound	Use
1,4-DCB	pesticide, also for household use in mothballs (decreasing), in air fresheners and toilet blocks
1,2,4-TCB	herbicide, insecticide (termites)
1,2,4,5-TeCB	impregnating agent to increase resistance to moisture, impregnating agent for electrical insulation and for reinforcing packaging material
PeCB	fungicide, flame retarder
HCB	additive in rubber products, fungicide in agriculture (grain storage), and wood preservation

An increase in concentration relative to outdoor air can be caused, for example, by evaporation of 1,4-DCB from air fresheners. There are virtually no data on concentrations which can result from this application especially in toilets. A measurement in the toilet of a house in Japan (Morita and Ohi, 1975) yielded a concentration of 315 $\mu g.m^{-3}$. Model calculations indicate that with an annual consumption of 10 toilet blocks containing 100% 1,4-DCB, annual average 1,4-DCB concentrations ranging from 100 to 1000 $\mu g.m^{-3}$ can be expected in the toilet and from 2 to 80 $\mu g.m^{-3}$ in the living room. Table 4.6. summarizes the results of a number of studies on the occurrence of 1,4-DCB in residential indoor air (Dongen et al., 1989).

Table 4.6. Measured concentrations of 1,4-dichlorobenzene ($\mu g.m^{-3}$) in homes (Dongen et al., 1989)

Country	Number of homes	Place/time	Conc.	Range	Percentiles p50	p90	p95	p98	Averaging time	Ref.
NL (Ede)	134	living room, winter	7.2	<0.6-140	1.8	14	25	50	1 week	1
(R'dam)	89	living room		<0.6-299					1 week	2
(Ede)	96	living room		<0.6-240					1 week	2
W.Germany	500	living room	22	<0.1-1270	4.7	17	33	110	2 weeks	3
USA	347	personal, at night			5	70	150		12 hours	4,5
Italy	15		62	<5 -230					4-7 days	6

1 Lebret et al. (1984, 1986)
2 Lebret et al. (1986)
3 Krause et al. (1987)
4 Hartwell and Pellizzari (1987)
5 Wallace and Pellizzari (1987)
6 Debartoli et al. (1987)

4.5.2. Concentrations in outdoor air

Occupational setting

During cleanup operations in the Volgermeer polder, the ambient air concentrations of TeCBs rose to over 0.1 $\mu g.m^{-3}$ (table 4.7; Heida, 1986).

Table 4.7. Ambient air concentrations of chlorobenzenes ($\mu g.m^{-3}$) during cleanup operations in the Volgermeer polder

Conditions	*1,2,4-TCB*	*1,2,3,4-TeCB*	*1,2,3/4,5-TeCB*	*PeCB*
Background conc.	*0.00004-0.0001*	*0.00002-0.0001*	*0.00001-0.0001*	*0.00002-0.00098*
During operations	*0.00014-0.033*	*0.00014-0.106*	*0.00017-0.081*	*0.00013-0.024*

Nonoccupational setting

National/regional

Data on outdoor air concentrations in the Netherlands are scarce. Measurements in the USA and Norway (Pacyna and Oehme, 1988) gave HCB background levels ranging from 0.0001 to 0.0006 $\mu g.m^{-3}$. Measurements made in 1982/1983 at five stations in the Netherlands showed similar HCB concentrations (see table 4.8.). DCB levels were found to be elevated in areas of concentrated industry and population, such as Vlaardingen. The occurrence of increased 1,2-DCB levels cannot be explained on the basis of the chlorobenzene emissions (see chapter 2). The air in Hamburg also had elevated 1,2-DCB and 1,3-DCB concentrations, of the same order of magnitude as 1,4-DCB, without an emission source being known.

Table 4.8. Concentrations ($\mu g.m^{-3}$) of a number of chlorobenzenes at 5 locations in the Netherlands (period October 1982-October 1983; Thijsse and Huygen, 1985)

Compound	*Witteveen*	*Rekken*	*Biest-Houtakker*	*Bilthoven*	*Vlaardingen*
1,2-DCB	*0.002*	*0.003*	*0.005*	*0.004*	*0.013*
1,3-DCB	*0.0011*	*0.003*	*0.002*	*0.003*	*0.009*
1,4-DCB	*0.016*	*0.017*	*0.028*	*0.036*	*0.110*
HCB	*0.0005*			*0.004*	*0.003*

Urban/local

In Hamburg 25 daily samples were taken at 12 locations in 1986/1987 (Bruckmann et al., 1988a) (table 4.9.). One striking feature was that at 1 location, where a pesticide-manufacturing plant had been in operation up to 3 years prior to sampling, greatly elevated chlorobenzene concentrations were still measured in the air (at a height of about 1.5 m).

Table 4.8. Concentrations of chlorobenzenes ($\mu g.m^{-3}$) in the ambient air of Hamburg (Bruckmann et al., 1988a)

Compound	City	Contaminated site
1,2-DCB	0.070	0.100
1,3-DCB	0.060	0.100
1,4-DCB	0.130	0.200
1,2,3-TCB	0.0013	0.046
1,2,4-TCB	0.0028	0.170
1,3,5-TCB	0.0002	0.009
1,2,3,4-TeCB	0.0006	0.028
1,2,(3/4),5-TeCB	0.0008	0.021
PeCB	0.0005	0.005
HCB	0.0006	0.0006

In the vicinity of point sources

Measurements of chlorobenzenes in the air around point sources are not known. Chlorobenzenes can be expected, for example, near sewage treatment plants (STPs) and waste incinerators. Model calculations have been performed for an industrial STP emitting annually about 1.3 tonnes of MCB and 1 tonne of 1,3,5-TCB (table 4.10.; Eerens, 1990). The annual average

concentration of MCB can be about 0.4 $\mu g.m^{-3}$ and the hourly values (99th percentile) can rise to about 5 $\mu g.m^{-3}$ at a distance of 500 metres from the source.

Table 4.10. Calculated concentrations of MCB and 1,3,5-TCB ($ng.m^{-3}$) near an industrial STP (Eerens, 1990)

Compound	Annual average concentration		99th Percentile (1-h values)	
	100 m	500 m	100 m	500 m
MCB	2.1 (1.1-3.0)	0.27 (0.1 -0.4)	27 (16-38)	3.8 (2.7-4.9)
1,3,5-TCB	1.4 (0.6-2.2)	0.19 (0.08-0.3)	20 (10-30)	2.7 (2 -3.5)

The ratio between the various chlorobenzenes originating from incinerators was found to be relatively constant. As can be seen from figure 4.1., the highly chlorinated benzenes are the main compounds formed (Ballschmiter et al., 1988). On the basis of measurements of HCB emissions at 3 waste incinerators in the Netherlands and the ratio between HCB and PeCB, it was estimated by means of model calculations (Jaarsveld and Onderdelinden, 1989) that the annual average concentration increase of the most commonly found chlorobenzene (PeCB) will be no more than $5x10^{-6}$ $\mu g.m^{-3}$. Depending on the meteorological situation, maximum hourly values can be a factor of 10 to 20 higher (10^{-4} $\mu g.m^{-3}$).

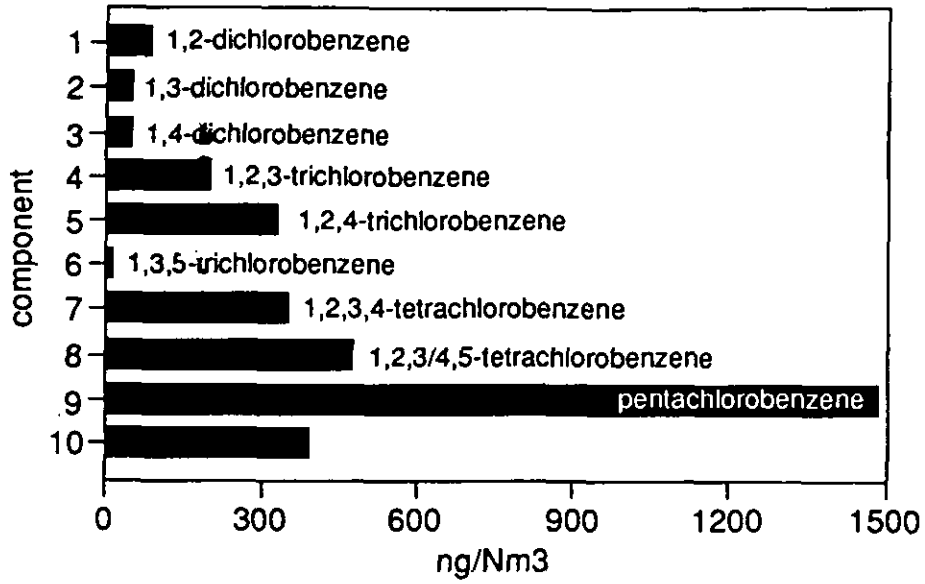

Figure 4.3. Chlorobenzene concentrations in flue gas from a waste incinerator

Rainwater/deposition

Data on concentrations in rainwater in the Netherlands are available for HCB only. The measured concentration is nearly always below the detection limit of 0.01 $\mu g.l^{-1}$. Foreign data (table 4.11.) show that the chlorobenzene level in rainwater rarely exceeds 0.1 $\mu g.l^{-1}$.

Table 4.11. Concentrations of chlorobenzenes in rainwater ($\mu g.l^{-1}$; Czuczwa et al., 1988; Bruckmann et al., 1988b; Ligocki et al., 1985)

Compound	Hamburg, 1987		Switzerland, 1985/86		US, Portland, 1984	
	avg.	max.	avg.	max.	avg.	max.
1,2-DCB	0.01	0.03	0.04	0.11	0.0003	0.0006
1,3-DCB	0.01	0.06				
1,4-DCB	0.01	0.03			0.0048	0.007
1,2,3-TCB	<0.002	0.005				
1,2,4-TCB	<0.002	0.003			0.0003	0.0005
1,3,5-TCB	<0.002	0.002				
1,2,3,4-TeCB	<0.002	0.003				
1,2,3/4,5-TeCB	<0.002	0.003				
PeCB	<0.002	<0.002				
HCB	<0.002	<0.002				

4.6 OCCURRENCE IN FOOD AND DRINKING WATER

4.6.1. Food

HCB is the only chlorobenzene which has been studied in foodstuffs. Two studies, conducted in 1976 and 1978 (Greve and Van Hulst, 1977, 1978), in which duplicate 24-hour diets were analyzed for HCB, found a median of 1 ug, and a maximum of 12 and 3 ug respectively, for the daily intake. In October 1984 and March 1985 the RIVM (1987) analyzed two series of duplicate 24-hour diets for HCB. The highest intake found was $\leq$ 1 ug per person per day.
Total diet studies were carried out by the CIVO-TNO in the periods 1976-1978 (De Vos et al., 1984) and 1984-1986 (De Vos et al., 1987). They determined the HCB levels in food groups which together make up the total daily diet of 18-year-old males. The intake for the two periods was 1 and 0.27 ug per person per day, respectively. The highest concentrations were measured in foods of animal origin. The observed intake is in agreement with recent foreign studies.
The RIVM and CIVO-TNO studies show that the HCB level has fallen in the last few years.

4.6.2. Drinking water

Two drinking-water suppliers have included chlorobenzenes in their measurement programme. These companies prepare drinking water from surface water, after dune filtration and/or storage in reservoirs (Duinwaterleiding 's Gravenhage, 1987; Gemeentewaterleidingen Amsterdam, 1988, 1989). Chlorobenzene concentrations in the drinking water did not exceed the detection limit. The detection limit is 0.1 $\mu g.l^{-1}$ for MCB (gas stripping/GC/MS) and 0.01 $\mu g.l^{-1}$ for the other chlorobenzenes (solvent-extraction/GC/MS). It is not known whether chlorobenzenes form as a result of disinfection of drinking water with chlorine.
Where soil is contaminated with chlorobenzenes, permeation into the drinking water via high-pressure and low-pressure polyethylene pipes (HPPE, LPPE) is quite conceivable. The experimentally measured permeability

coefficients for chlorobenzenes from soil water and "soil air" (dry soils) are higher than for a number of other substances for which these coefficients have been determined (Veenendaal et al., 1985). The calculated concentrations in drinking water are presented in table 4.12.

Table 4.12. Calculated concentrations ($\mu g.l^{-1}$) of monochlorobenzene in drinking water after permeation through high-pressure and low-pressure polyethylene pipes (HPPE, LPPE) at a concentration of 1 mg per litre in soil water, and after 8 hours and 2 days of stagnation in the pipes, respectively

	Permeation from soil water		*Permeation from soil air*	
	HPPE	*LPPE*	*HPPE*	*LPPE*
8 Hours	*4.5*	*5.3*	*13*	*21*
2 Days	*27*	*32*	*81*	*128*

4.7. FLUXES IN THE ENVIRONMENT

The fluxes in the Dutch environment have been calculated for 1,4-DCB because, on the one hand, the flows of this compound through the environment are relatively large (see table 2.7.) and, on the other, the daily exposure to this chemical approaches the toxicological recommended level. The Simplesal multicompartmental box model (Van de Meent, 1989) based on the fugacity model of Mackay et al. (1985) was used for calculating the fluxes. The fluxes are based on a schematized representation of the Dutch environment, in which the air over the Netherlands, the surface water and the soil (including groundwater) are regarded as one ideal mixed system. Of course, this oversimplifies the reality; the sole purpose of the calculations is to obtain an idea of the relative material flows in the Dutch environment. The model parameters with specific values for the Dutch situation are:

Total surface area	45,750 km^2 (88% land, 12% water)
Height of soil column	15 cm
Height of water column	2.5 m

Height of air column	800 m
Height of sediment solumn	3 cm
Organic-carbon content of sediment	5 %
Organc-carbon content of soil	2 %
Residence time in air	0.825 days
Residence time in water	50 days

The values reported in chapters 1-4 were used for the 1,4-DCB-specific parameters and the average 1,4-DCB concentrations in the various environmental compartments.

- Soil : an average degradation rate in soil of $0.023.day^{-1}$ was used (section 3.3.); it was furthermore assumed that there is no emission to soil.
- Water: it was assumed that the emission is 5.2 tonnes per year (section 2.2.), the 1,4-DCB concentration in the inflowing water is 20 $ng.l^{-1}$ (section 4.4.) and the annual average degradation rate is $0.2.day^{-1}$ (section 3.3.). The sedimentation rate used was 10 mm per year, while the resuspension rate was taken to be 9.8 mm per year.
- Air : it was assumed that the emission is 261 tonnes per year (section 2.2.), the 1,4-DCB concentration in the inflowing air is 24 $ng.m^{-3}$ (section 4.5.) and the atmospheric conversion rate is $0.02.day^{-1}$ (section 3.4.).

For the other parameters the reader is referred to Mackay et al. (1985). The calculated steady-state concentrations in the various environmental compartments are given in table 4.13. The compartmental and intercompartmental flows of 1,4-DCB are shown in table 4.14. and figure 4.4.

Table 4.13. Calculated steady-state concentrations of 1,4-dichlorobenzene in the environmental compartments

Soil	*0.1 $\mu g.kg_1^{-1}$*
Water	*6.9 $ng.l^{-1}$*
Sediment	*0.8 $\mu g.kg^{-1}$*
Suspended matter	*1,2 $\mu g.kg_3$*
Air	*39 $ng.m$*

Table 4.14. Compartmental and intercompartmental flows of 1,4-dichlorobenzene (in tonnes per year)

	Air	*Water*	*Soil*	*Sediment*
Imports	*389*	*1.7*		
Exports	*625*	*1.2*		
Accumulation			*0.04*	
Conversion	*12*	*11.3*	*7.7*	
Flux to soil	*7.7*			
Flux to water	*6.6*			*0.02*

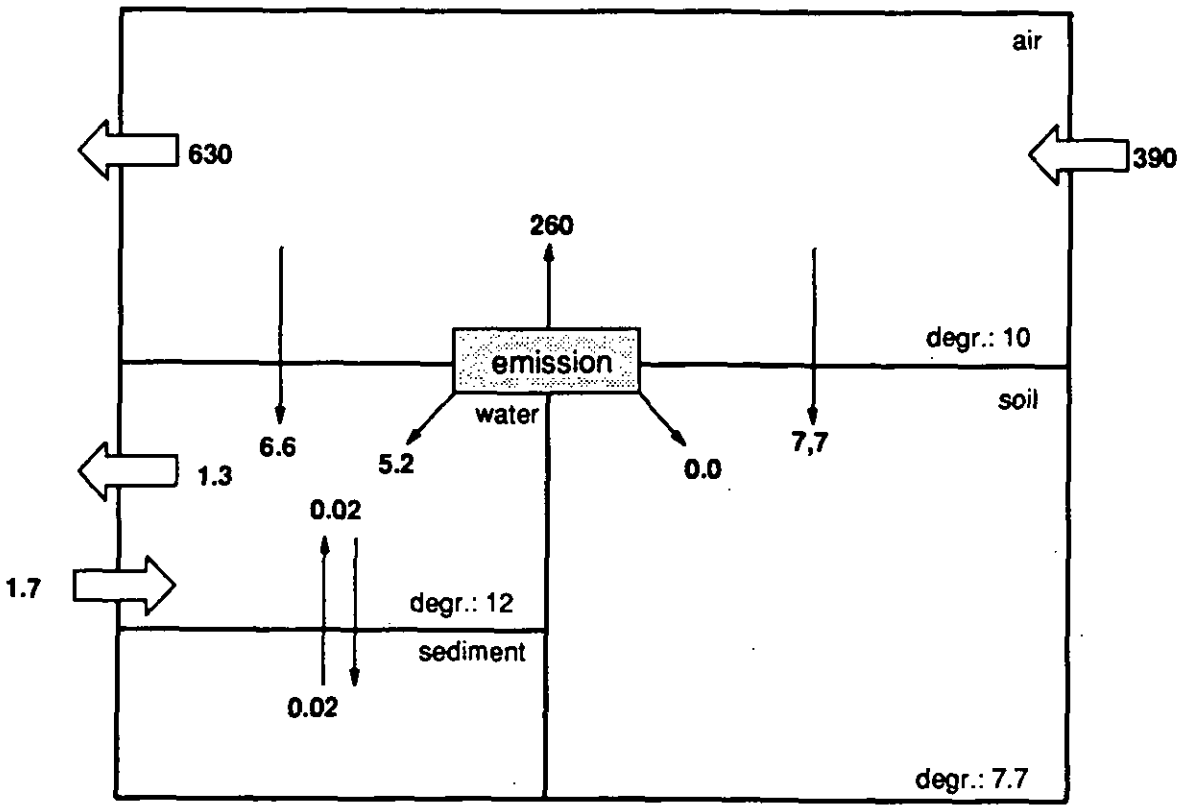

Figure 4.4. Fluxes of 1,4-dichlorobenzene in the Netherlands (rounded figures, in tonnes per year)

It can be deduced from the above data that the total emission is about 265 tonnes and the total imports about 390 tonnes per year, giving a total annual load of about 655 tonnes. The greater part of this is exported by way of the environment (96%), while the remainder is degraded in the Dutch environment. Accumulation is negligible. The calculated concentrations in the air, water phase and sediments agree fairly well with the most recent measured values. It should be noted that the compartment groundwater has not been included in the model employed. In view of the fact that 1,4-DCB has been detected in riverbank groundwater (see 4.3.2.), there is a flux to groundwater due to seepage (see 3.3.3.).

4.8. EXPOSURE LEVELS

On the basis of the concentrations in ambient air, food and drinking water, an estimate can be made of the daily intake of chlorobenzenes by man via these exposure routes. The volume of air inhaled is taken to be 12 m^3 per day, of which 9 m^3 is indoor and 3 m^3 outdoor air. If there are no sources of chlorobenzenes indoors, then the indoor air concentration is equated to the rural background level. Rough estimates of the levels to which the Dutch population is exposed are presented in table 4.15. Absorption, following both oral and inhalation exposure, is assumed to be complete. The principal route of exposure to HCB is ingestion, and exposure to the other chlorobenzenes presumably occurs mainly by inhalation.
In 1989 about 25 tonnes of 1,4-DCB were used in private households. Assuming an annual consumption of 0.25 kg per household and an average number of 2.5 persons per household, then some 250,000 persons were exposed to elevated 1,4-DCB concentrations. Of these, an estimated 50,000 to 100,000 persons were chronically exposed because they stayed indoors for longer periods of time (children, housewives, elderly people).

The exposure of organisms in ecosystems is complicated. In aquatic systems, the exposure level is determined primarily by the concentration in the water. The exposure level for terrestrial organisms varies widely, depending on living habits, physiology et cetera.

Table 4.15. Estimate of the annual average daily intake (ug) of chlorobenzenes via air, food and drinking water in the Netherlands. The figures in parentheses are estimated maximum annual averages

Compound	Food*	Air		Total intake
		Indoor	Outdoor	
MCB		0.0001	0.0001 (0.001)	0.0002 (0.001)
1,2-DCB		0.03	0.03 (0.2)	0.06 (0.23)
1,3-DCB		0.03	0.03 (0.2)	0.06 (0.23)
1,4-DCB		0.2	0.2 (0.4)	0.4 (0.6)
idem **		65 (1000)	0.2 (0.4)	65 (1000)
1,2,3-TCB		0.0006	0.0002 (0.004)	0.0008 (0.004)
1,2,4-TCB		0.0006	0.0002 (0.008)	0.0008 (0.009)
1,3,5-TCB		0.0006	0.0002 (0.001)	0.0008 (0.001)
1,2,3,4-TeCB		0.0005	0.0002 (0.002)	0.0007 (0.002)
1,2,3,5-TeCB		0.0005	0.0002 (0.002)	0.0007 (0.002)
1,2,4,5-TeCB		0.0005	0.0002 (0.002)	0.0007 (0.002)
PeCB		0.005	0.002	0.0025
HCB	0.27 (1)	0.03	0.01	0.31 (1.04)

* *Only data on HCB in foods are known. It is reasonable to suppose that the concentrations of the other chlorobenzenes will be lower than those of HCB. The relative contribution via drinking water has not been included. It is at most 0.2 µg per day for HCB and 0.02 µg per day for the other chlorobenzenes, assuming that the daily consumption of drinking water is 2 litres.*

** *Situation in which DCB-containing toilet air fresheners are used.*

4.9. SUMMARY AND CONCLUSIONS

The detection limits of available analytical methods are sufficiently low to permit the testing of the current pollution levels of chlorobenzenes against the standards currently in force. A summary of the average and maximum concentrations in the environmental compartments is given in table 4.16.

Table 4.16. Average (and maximum) of measured concentrations in the environmental compartments

Compound	Soil (µg/kg)	Groundwater (µg/l)	Surface water (µg/l)	Sediment (µg/kg)	Air (µg.m^{-3}) indoor	Air (µg.m^{-3}) outdoor
MCB		<0.5 (<0.5)				(0.4)***
1,2-DCB		<0.1 (0.3)	0.03 (0.6)		0.004	(0.013)
1,3-DCB		<0.1 (0.3)	0.02 (0.3)		0.002	(0.009)
1,4-DCB		<0.1 (0.3)	0.04 (0.6)	7.2(299)	0.024	(0.110)
1,2,3-TCB		<0.1 (<0.1)	0.02 (0.09)*			
1,2,4-TCB		<0.1 (0.1)	0.02 (0.09)*			(0.033)
1,3,5-TCB		<0.1 (<0.1)	0.02 (0.09)*			(0.3)***
1,2,3,4-TeCB			<0.002 (0.01)**			(0.016)
1,2,3,5-TeCB			<0.002 (0.01)**			
1,2,4,5-TeCB			(<0.001)			(<0.081)
PeCB			<0.001 (0.005)			(0.024)
HCB	<10 (<80)		<0.001 (0.01)	30 (3960)	0.0002	(0.0003)

* *sum of the trichlorobenzenes*
** *sum of the tetrachlorobenzenes*
*** *calculated maximum annual average concentration at a distance of 500 metres from an industrial STP*

In soil, only the presence of HCB has been investigated. The median concentration in soils treated in the past with HCB-containing pesticides ranged from 90 to 160 µg.kg^{-1}. The positive observations in groundwater concern in all cases bank groundwater, recharged by infiltration of river water.

In surface water, the highest concentrations were found in the River Rhine. The concentrations of the various di- and trichlorobenzenes in the Dutch coastal waters were in the 0.001 µg.l^{-1} range; they decreased gradually in a northward direction and fairly rapidly in a seaward direction.
In the sediments of the large rivers, high HCB concentrations were detected in local pollution situations (median, 30; maximum, about 4000 µg.kg^{-1} dry weight). It is expected that the concentrations in sediments will be in equilibrium with those in the overlying water in 10 to 15 years' time, reaching a level of 4 to 5 µg.kg^{-1} dry weight.

In indoor air, the chlorobenzene concentrations were the same as in outdoor air, except in cases where 1,4-dichlorobenzene evaporated from air fresheners in the toilet. In this situation, maximum values of 300 µg.m^{-3}

have been measured in living rooms and values of up to 1000 $\mu g.m^{-3}$ have been calculated in toilets.
The outdoor air levels of DCBs in areas of concentrated industry and population (Vlaardingen) were 4 times higher than the national average. TCB concentrations of up to more than 100 $ng.m^{-3}$ have been measured in work situations (cleanup of the Volgermeer polder).

For man, the principal route of exposure to HCB is ingestion, and exposure to the other chlorobenzenes occurs mainly by inhalation. Exposure to 1,4-DCB can be greatly increased through the use of 1,4-DCB-containing air fresheners (table 4.15.). The average daily intake of 1,4-DCB is 0.4 μg, and 65 μg when 1,4-DCB-containing air fresheners are used. An estimated 50,000 to 100,000 persons are affected.

The fluxes of the most important compound (1,4-DCB) in the environment are shown in figure 4.4. The total annual emission is 265 tonnes and the total imports are estimated at about 390 tonnes per year. Of the total amount, the major part (96%) is exported via water and air, and the remainder degraded in the Dutch environment. The calculated concentrations in air, water and sediment agree fairly well with the most recent measured values.

5. EFFECTS

This chapter is a summary of an extensive background report on the toxic effects of chlorobenzenes. This report (Hesse et al., 1991) contains the references of the literature reviewed and has been added as an Appendix to the Integrated Criteria Document.

5.1. HUMAN TOXICITY

5.1.1. Kinetics and metabolism

Monochlorobenzene

MCB is absorbed from the gastrointestinal tract and the lungs; quantitative data are not available. Absorption through the skin appears to be minimal. Shortly after inhalation exposure of rats to MCB, it was found in several tissues, with adipose tissue having the highest concentration. Tissue clearance was rapid. The main metabolites of MCB were 4-chlorophenol, 4-chlorocatechol and 4-chlorophenyl-mercapturic acid. The greater part of the metabolites was excreted in the urine and only a small proportion was present in the faeces. After inhalation exposure of rats to MCB, the percentage excreted in the exhaled breath increased with increasing exposure concentration.

Dichlorobenzene

Experimental studies indicate that DCBs are absorbed following exposure by various routes of entry into the body. After oral, inhalation or subcutaneous exposure to 1,4-DCB, the tissue distribution was found to be similar. The highest concentrations were measured in adipose tissue, followed by liver, kidneys and lungs. After inhalation exposure of rats to 1,4-DCB, a difference in the 1,4-DCB levels in the liver and kidneys was observed between males and females; female rats had significantly higher levels in the liver than males, while male rats had significantly higher levels in the kidneys than females. 1,2-DCB and 1,4-DCB are oxidized mainly to 3,4- and 2,5-dichlorophenol, respectively, which are subsequently conjugated. Within 24 hours after exposure to DCB, 50% to 90% of the administered dose is excreted in the urine in the form of metabolites. A

small percentage is eliminated with the faeces. A proportion of the DCB initially excreted in the bile is reabsorbed in the liver (enterohepatic circulation), and eventually excreted in the urine. In humans occupationally exposed to 1,4-DCB, a positive relationship was found between urinary excretion of 2,5-dichlorophenol and exposure to 1,4-DCB. No studies on 1,3-DCB were available.

Trichlorobenzene

TCBs are absorbed following oral, inhalation and dermal exposures. In rats treated with oral doses of 1,2,3-, 1,2,4- and 1,3,5-TCB, the highest concentrations were found in liver, kidneys, adipose tissue, bladder and gastrointestinal tract. Elevated levels in skin and muscle tissue have also been reported. The highest concentrations and longest retention times were generally measured after exposure to 1,3,5-TCB. TCBs are metabolized to trichlorophenols, which are conjugated with glutathione. After administration of 1,2,3-, 1,2,4- and 1,3,5-TCB, the main metabolites formed were 2,3,4-trichlorophenol, 2,4,5- and 2,3,5- trichlorophenol, and 2,3,5- and 2,4,6-trichlorophenol, respectively. Rats fed TCBs excreted about 70% in the urine and 15% in the faeces within 24 hours. A small proportion was exhaled. Excretion was slower in monkeys; after 24 hours, 40% of the administered dose appeared in the urine and less than 1% in the faeces. Unlike rats, this species does not use glutathione in metabolizing 1,2,4-TCB. TCBs also undergo enterohepatic circulation.

Tetrachlorobenzene

TeCBs are absorbed following oral administration. No data are available on absorption upon inhalation or dermal exposure. In rats and rabbits, oral administration of the various isomers produced the same tissue distribution patterns. TeCBs were detected in adipose tissue, skin, kidneys, liver and intestine, with 1,2,4,5-TeCB leading to the highest tissue concentrations. A teratogenicity study with rats showed that there was no or only very little accumulation of 1,2,3,4- and 1,2,3,5-TeCB in the mother or foetus, whereas 1,2,4,5-TeCB accumulated strongly in both mothers and foetuses.
In rats and rabbits, the TeCBs were converted mainly to chlorophenols; 1,2,3,4-TeCB was metabolized to 2,3,4,5- and 2,3,4,6- tetrachlorophenol, 1,2,3,5-TeCB to 2,3,4,6-tetrachlorophenol and, finally, 1,2,4,5-TeCB to

2,3,5,6-tetrachlorophenol. The principal metabolite in the urine of monkeys exposed to 1,2,3,4-TeCB was an N-acetyl-S-compound; 2,3,4,5-tetrachlorophenol was a minor metabolite. After oral administration of 1,2,3,4- and 1,2,3,5-TeCB to rats, approximately 50% of the dose was excreted in the urine and faeces within 48 hours. The excretion of 1,2,4,5-TeCB was much slower; only 8% was excreted after 48 hours.

Pentachlorobenzene

PeCB is absorbed following oral administration. A dose-related accumulation of PeCB in the body fat of rats was observed. Rabbits metabolized PeCB to pentachlorophenol and 2,3,4,5-tetrachlorophenol. No quantitative data on PeCB excretion are available.

Hexachlorobenzene

HCB is absorbed following oral exposure. No data are available on absorption following inhalation or dermal exposure. The extent of absorption depends on the vehicle in which the compound is administered; approximately 80% of HCB in an oil solution is absorbed, but only 20% of HCB in an aqueous solution. After oral administration of HCB to monkeys, the highest levels were found in adipose tissue, followed by bone marrow and adrenal cortex. Rats had also high levels in skin and muscle. It has been demonstrated in several species that HCB crosses the placenta and accumulates in the foetuses in a dose-related manner. The compound is metabolized comparatively slowly. More than 30 metabolites have been identified, the principal ones being pentachlorophenol, tetrachlorophenol, tetrachlorothioquinone and pentachlorothiophenol. Lower chlorinated benzenes and phenols have also been detected, as well as various conjugates. HCB metabolites are excreted mainly in the urine, while unmetabolized HCB is eliminated predominantly in the faeces (the percentage of unchanged HCB in urine and faeces was 4 and 80%, respectively.

Summary

The metabolic behaviour of the various chlorobenzenes changes gradually as the degree of chlorination increases. The chlorobenzenes become more lipophilic and the accumulation in adipose tissue and fatty organs greater as the number of chlorine atoms in the molecule increases. The

biotransformation and urinary excretion decrease with an increasing number of chlorine atoms. The difference in elimination half-lives between, for example, 1,4-DCB and HCB is estimated to be at least a factor of 10. The excretion of HCB, in particular, is slow and takes place mainly via the faeces. The tissues contain predominantly unchanged HCB.

5.1.2. Toxicity

- Experimental studies

The oral LD50s of MCB, DCBs, TCBs, TeCBs, PeCB and HCB are 400-2830, 500-3375, 750-2260, 1035-3000, 250-1370 and 1700-32,100 $mg.kg^{-1}$ body wt, respectively (EPA, 1984; Allen et al., 1984).

Monochlorobenzene

Oral administration of high doses of HCB caused a reduction in body weight gain and increased mortality, as well as hepato- and nephrotoxicity (elevated serum enzyme activities, increased liver and kidney weights, histopathological changes, and necrosis). At higher dose levels, suppression of bone marrow activity occurred in mice, and myeloid depletion of the thymus, spleen and bone marrow in mice and rats.

In a 13-week oral study with mice and rats, the above effects were observed at dosages of 125 $mg.kg^{-1}$ body wt or higher, as well as a disturbance of porphyrin metabolism (porphyria). The 60 $mg.kg^{-1}$ body wt dose caused a slight decrease in the weights of spleen and heart only in male mice and rats, respectively. In an oral subchronic study with dogs, a similar dose produced gastrointestinal disturbances and minimal histopathological changes; the no-effect dose was determined to be 27.3 $mg.kg^{-1}$ body wt. In an oral 2-year (carcinogenicity) study with rats and mice, an effect was reported only in male rats in the highest dose group (120 $mg.kg^{-1}$ body wt). A significant increase in neoplastic nodules was found in the livers of these rats. The no-effect dose was 60 $mg.kg^{-1}$ body wt. A number of unpublished studies with MCB had widely varying results; one study found effects after inhalation of 0.1 $mg.m^{-3}$ in air, whereas other studies noted no effects at concentrations of 750 and as high as 2,500 $mg.m^{-3}$. Since these studies are not available for evaluation, they are disregarded.

In a two-generation reproduction study with rats, inhalation of up to 450 ppm (2070 $mg.m^{-3}$) MCB in air had no adverse effects on reproduction or fertility. In a teratogenicity study with rats and rabbits, the highest concentration tested (590 ppm; 2715 $mg.m^{-3}$) did not result in any embryotoxic or teratogenic effects in the rabbits. In the rats, a slight delay in foetal skeletal growth was observed at 590 ppm (2170 $mg.m^{-3}$), an exposure level that is maternally toxic.

Dichlorobenzene

The effects of subchronic oral and inhalation exposures to DCBs were mostly the same as those caused by MCB; at high dose levels, there was mortality and a reduction in body weight (gain), hepato- and nephrotoxicity (elevated serum enzyme activities, increased liver and kidney weights, histopathological changes, and necrosis), and induction of porphyria. In addition, effects were observed on the thymus and spleen (depletion) in rats and on heart and muscle tissue in mice.

1,2-DCB

Treatment of rats with 188 mg 1,2-DCB.kg^{-1} body wt for about 6 months resulted in increased liver and kidney weights; the no-effect dose in this study was 19 $mg.kg^{-1}$ body wt. In oral 13-week studies, no-effect doses of 60 and 125 $mg.kg^{-1}$ body wt were derived for rats and mice, respectively. In an oral 2-year (carcinogenicity) study with rats and mice (0, 60 or 120 $mg.kg^{-1}$ body wt), the increase in regeneration of the renal tubular epithelium observed in male mice was significant only in the high dose group (control group, 17%; low dose group, 24%; high dose group, 35%). In a subchronic inhalation experiment with small numbers of rats, guinea pigs, rabbits and monkeys, no effects were found at a concentration of 93 ppm (560 $mg.m^{-3}$). In a teratogenicity study, inhalation of the highest dose tested, 400 ppm of 1,2-DCB (2400 $mg.m^{-3}$), caused no embryotoxic or teratogenic effects in rats and rabbits, but did have (slight) toxic effects in the dams.

1,4-DCB

Exposure of rats to 100 $mg.kg^{-1}$ body wt for 4 weeks had no adverse effects. In a 6-month study with rats, animals given 188 mg 1,4-DCB.kg^{-1} body wt

showed increased liver and kidney weights. A dose of 19 $mg.kg^{-1}$ body wt was without effect. In an oral 13-week study with rats and mice, no-effect doses of 150 and 388 $mg.kg^{-1}$ body wt, respectively, were reported.
In an oral 2-year (carcinogenicity) study with 1,4-DCB, the lowest doses tested (150 $mg.kg^{-1}$ body wt for male rats and 300 $mg.kg^{-1}$ body wt for female rats and male and female mice) produced toxic effects on the kidneys (nephropathy) and liver (hepatocellular degeneration). An inhalation experiment, in which small numbers of rats, mice, guinea pigs, rabbits and monkeys were exposed for 6-7 months to 1,4-DCB, resulted in a no-effect dose of 96 ppm (577 $mg.m^{-3}$).
An oral teratogenicity study with rats (250-1000 $mg.kg^{-1}$ body wt) provided no evidence of teratogenic activity; an embryotoxic effect was however observed at concentrations of 500 $mg.kg^{-1}$ body wt or higher (extra ribs). In an inhalation study with rabbits, the highest dose tested (800 ppm of 1,4-DCB; 4800 $mg.m^{-3}$) *caused no teratogenic or embryotoxic effects.*

Trichlorobenzene

Most data on the toxicity of TCBs concern 1,2,4-TCB, which is considered to be the most toxic isomer. Oral and inhalation exposures resulted in hepato- and nephrotoxicity (enzyme induction, increased organ weights, and transient histopathological changes) and porphyria.
In a briefly reported oral study in which monkeys were exposed to 1,2,4-TCB for 13 weeks, a no-effect dose for enzyme induction of 25 $mg.kg^{-1}$ body wt was established. In an oral 13-week study with rats, enzyme induction was observed even at the lowest concentration tested (10 $mg.kg^{-1}$ body wt). This effect had disappeared after a 30-day recovery period. Subacute inhalation of 30 ppm of 1,2,4-TCB (223 $mg.m^{-3}$) resulted in an increase in urinary porphyrin excretion in rats and a decrease in relative liver weight in rabbits. A no-effect dose of 100 $mg.m^{-3}$ for 1,3,5-TCB was determined in a 13-week inhalation experiment with rats. Rats, rabbits and monkeys exposed to an atmosphere containing 100 ppm of 1,2,4-DCB (740 $mg.m^{-3}$) showed changes in their lungs and kidneys after both 4 and 13 weeks, whereas these effects had disappeared at the termination of the study (26 weeks). Application of TCBs (ca 70% 1,2,4-TCB and 30% 1,2,3-TCB) to the skin of rabbits produced local effects in all dose groups (30-450 $mg.kg^{-1}$ body wt);

only at the highest dose level did a slight systemic effect occur (an increase in urinary coproporphyrin excretion.

In a multi-generation study in which rats received 1,2,4-TCB in their drinking water (25-400 $mg.l^{-1}$), no effects on reproduction were found. In a teratogenicity study with rats, the highest doses of TCBs (300 $mg.kg^{-1}$ body wt of 1,2,4-TCB and 600 $mg.kg^{-1}$ of 1,2,3- and 1,3,5-TCB) produced no embryotoxic or teratogenic effects. In another study, female rats were treated with 36, 120, 360 or 1200 mg 1,2,4-TCB.kg^{-1} body wt. There was mortality of dams at the two highest doses, and effects on the liver (enzyme induction and slight hepatocellular hypertrophy) at dosages of 120 $mg.kg^{-1}$ body wt and higher. Slight embryonic growth retardation was reported at 360 $mg.kg^{-1}$ body wt; the no-effect dose was 120 $mg.kg^{-1}$ body wt. There were no teratogenic effects.

Tetrachlorobenzene

Toxicity studies with TeCBs are limited and concern only oral exposure. A subacute study with TeCB reported effects on liver, kidneys, thyroid and lungs. In a 90-day study with rats, administration of TeCBs produced primarily hepato- and nephrotoxicity (increased organ weights and histopathological changes). At similar dosage levels, the effects of 1,2,4,5-TeCB were the most severe. No significant effect was reported at a concentration of 5 mg 1,2,4,5-TeCB.kg^{-1} of diet (0.34 or 0.40 $mg.kg^{-1}$ body wt for males and females, respectively).

In a teratogenicity study, rats were given TeCBs in doses of 50, 100 or 200 $mg.kg^{-1}$ bdy wt for each isomer. Administration of 1,2,4,5-TeCB was maternally toxic; nearly all animals in the highest dose group died before termination of the study, and effects such as, for example, enzyme induction were observed at the lower dose levels. The highest dose of 1,2,3,4- and 1,2,3,5-TeCB caused a decrease in the number of live foetuses per litter. No teratogenic effects were reported.

Pentachlorobenzene

Only one study with rats (subchronic toxicity combined with effects on reproduction) was available. Subchronic feeding of 25 $mg.kg^{-1}$ body wt or more resulted in effects on the liver and kidneys (increased organ weights and histopathological alterations), which were not observed in animals

treated with 12.5 mg.kg^{-1} body wt. Concentrations of up to 20 mg.kg^{-1} body wt had no adverse effects on reproductive performance (number and size of litters). Suckling young of females exposed to 12.5 mg.kg^{-1} body wt or more exhibited tremors 4-14 days after birth, as well as increased relative liver weights. The no-effect dose was 6.3 mg.kg^{-1} body wt.

Hexachlorobenzene

Oral administration of HCB resulted in a disturbance of porphyrin metabolism in female rats and rabbits, accompanied by increased porphyrin levels in the liver and urine. Subacute oral exposure to HCB affected the immune system of rats (increased humoral immune response) and mice (suppression of both the humoral and cell-mediated immune response). There was an increase in liver and kidney weights, as well as induction of liver enzymes. In an oral 14-day study with rats, the no-effect dose for enzyme induction was determined at 1 mg.kg^{-1} body wt. Treatment of male mice with 12.5 mg.kg^{-1} body wt affected their serum testosteron levels.

Subchronic studies have shown that female rats are more susceptible to the induction of porphyria by HCB than their male counterparts. This may be related to a possibly more rapid metabolism of HCB by female animals under the influence of oestrogens. The no-effect dose for porphyria in female rats was 2 mg.kg^{-1} body wt. Changes in the hepatic ultrastructure (using electron microscopy) were observed in rats given dosages of 0.25 mg.kg^{-1} body wt or more; the no-effect dose was 0.05 mg.kg^{-1} body wt. Oral administration of 0.033 mg.kg^{-1} body wt (the only dose tested) to a small number of monkeys for 18 months did not have any adverse effects. In chronic (carcinogenicity) studies (rat, mouse, hamster), toxic effects were reported at dose levels of 4 mg.kg^{-1} body wt and higher. A no-effect dose could not be derived from this study.

In studies in which rats were exposed both pre- and postnatally to HCB, even the lowest dose tested (0.2 mg.kg^{-1} body wt) produced effects on the immune system (enhanced humoral and cell-mediated immune responses). In an oral two-generation study with rats, the viability index was reduced at doses of 2 mg.kg^{-1} body wt or higher; this effect was not reported at 0.4 mg.kg^{-1} body wt. In a four-generation study with rats, reproductive effects were observed at concentrations of 8 mg.kg^{-1} body wt and higher; the no-effect dose was 1 mg.kg^{-1} body wt. In a teratogenicity study with rats

(exposed to 120 $mg.kg^{-1}$ body wt), there was no evidence of teratogenic activity; however, an embryotoxic effect did occur at 40 $mg.kg^{-1}$ body wt or more.

Summary

There is a clear similarity between the effects of the various chlorobenzenes. The target organs of chlorobenzene toxicity were the liver and kidneys. All chlorobenzenes produced increased organ weights, enzyme induction and histopathological changes. A number of chlorobenzenes caused necrosis. A disturbance of porphyrin metabolism was reported with all chlorobenzenes, but was the most evident after exposure to HCB. In addition, the lower chlorinated benzenes suppressed the activity of bone marrow, spleen and thymus. The induction of liver microsomal enzymes and the interference with normal porphyrin metabolism are the most sensitive parameters. Microsomal enzyme induction can already be observed after a relatively short exposure time, and the sensitivity of this parameter does not appear to increase after more prolonged exposure. The available studies indicate that the chlorobenzenes become more toxic as the degree of chlorination increases. The no-effect doses of MCB, 1,2-DCB, 1,4-DCB, TCBs, TeCBs, PeCB and HCB were 30, 60, 20, 20, 2, 6 and 0.05 $mg.kg^{-1}$ body wt, respectively. In the absence of any more definitive information, HCB seems to be the most toxic chlorobenzene.

- Human studies

Dichlorobenzene

Workmen exposed to 1,4-DCB concentrations ranging from 80 to 160 ppm (481-962 $mg.m^{-3}$) experienced painful eye and nose irritation. A number of case reports of DCB exposure (mostly 1,4-DCB) showed effects on the liver, blood, central nervous system, and respiratory system.

Hexachlorobenzene

An epidemic of HCB intoxication occurred during the years 1955 to 1959 in southeastern Turkey, where some of the wheat which had been treated with this fungicide, and which was intended for planting, was ground and used as flour for bread. The daily intake of HCB was estimated as having ranged

from 0.5 to 2.0 g per person over a period of several months to two years. Several thousand persons developed porphyria cutanea tarda (PCT). The clinical manifestations included skin lesions, weakness and porphyrinuria (increased urinary excretion of porphyrins). Young children, who were breast-fed, developed a condition known as "pink-sore", characterized by fever, diarrhoea and nausea, among other symptoms. The mortality rate among these children was 95%. Since then, the exposed population has been the subject of many studies. Twenty years after the incident, several signs and symptoms of HCB intoxication (cutaneous and neurological effects as well as skeletal abnormalities) were still evident in many of the individuals. A number of patients still showed abnormal porphyrin metabolism.
No toxic effects were reported in workers occupationally exposed to HCB concentrations ranging from <1 to 13 ppb in the workplace air.

5.1.3. Genotoxicity

Studies on the genotoxicity of chlorobenzenes are rather limited. As regards in vitro tests, all chlorobenzenes were negative in the Ames Salmonella typhimurium/mutagenicity assay. In addition, a number of chlorobenzenes (MCB, 1,4-DCB and TCBs) were tested in cultured mammalian cells for one or more of the following end-points: gene mutations, chromosome aberrations and sister chromatid exchanges. Of these tests, only one was questionable (1,4-DCB) or questionable/positive (MCB), while all the other tests were negative. Therefore, the in vitro tests do not provide clear indications of genotoxic activity of the chlorobenzenes.
With regard to in vivo testing, a few studies with negative results were available. The compounds tested were 1,4-DCB (mouse micronucleus test in peripheral blood; mouse dominant lethal test; chromosome aberrations in rat bone-marrow cells) and HCB (test with Drosophila melanogaster, and two dominant lethal tests with rats). In addition, one study, a mouse micronucleus test in bone marrow, found clear positive responses for all chlorobenzenes included in the test: MCB, 1,2-DCB, 1,3-DCB, 1,4-DCB, 1,2,3-TCB, 1,2,4-TCB and 1,3,5-TCB (Mohtashamipur et al., 1987). This test was conducted with compounds which were at least 98% pure, according to a generally accepted procedure (two intraperitoneal injections). Furthermore, a (positive) dose-response relationship was established for all compounds.

In view of the findings of this study and the fact that the compounds are chemically related, it cannot be ruled out that the other chlorobenzenes would also have been positive in this test system. It should be mentioned here that it is highly desirable that the data of Mohtashamipur et al. (1987) are verified. It is provisionally concluded that the data are too limited for considering the chlorobenzenes to be genotoxic.
Two studies reported an increased frequency of chromosomal aberrations in peripheral lymphocytes of humans exposed to 1,2-DCB and 1,2,4,5-TeCB, respectively. For several reasons (type of chromosomal aberration not specified, no individual data, simultaneous exposure to more than one compound), both studies are disregarded.

5.1.4. Carcinogenicity

As far as is known, only MCB, 1,2-DCB, 1,4-DCB and HCB have been tested in experimental animals for carcinogenicity, and no epidemiological studies are available.

Monochlorobenzene

F344/N rats (m/f) and B6C3F1 mice (f) were given 0, 60 or 120 mg.kg^{-1} body wt by stomach tube daily for 2 years. Male mice received doses of 0, 30 or 60 mg.kg^{-1} according to the same schedule. Only in male rats in the highest dose group was a significant increase in neoplastic liver nodules observed. Mice and female rats did not show an increased incidence of tumours. The incidence of pituitary tumours decreased in exposed rats. From these studies it is concluded that there is no evidence that MCB is carcinogenic in experimental animals.

1,2-Dichlorobenzene

The carcinogenicity of 1,2-DCB has been studied in F344/N rats and B6C3F1 mice; they were given 0, 60 or 120 mg.kg^{-1} body wt by stomach tube daily for 2 years. Based on the results of these experiments it is concluded that there is no evidence that 1,2-DCB is carcinogenic.

1,4-Dichlorobenzene

The carcinogenicity of 1,4-DCB has been studied in rats and mice. Male F344/N rats were given 0, 150 or 300 mg.kg^{-1} body wt by stomach tube daily for 2 years, while female rats and male and female B6C3F1 mice received doses of 0, 300 or 600 mg.kg^{-1}. A significant increase in the incidence of benign and malignant renal tumours was observed in male rats in the highest dose group. Male and and female mice showed a significantly increased incidence of benign and malignant liver tumours. However, recent studies indicate that the development of renal tumours is promoted by a chronic 1,4-DCB-induced nephropathy, in which a particular protein (alpha-2u globulin) plays an essential role. This protein is male rat-specific; humans do not synthesize it. Furthermore, the observed benign and malignant liver tumours occur naturally in the mouse strain used (B6C3F1). The spontaneous incidences varied from 16 to 60% in males and from 2 to 20% in females. From these data it is concluded that there is limited evidence for the carcinogenicity of 1,4-DCB in experimental animals.

Hexachlorobenzene

The carcinogenicity of HCB has been investigated in (sub-)chronic oral studies with rats, mice and hamsters. Administration of HCB (4 mg.kg^{-1} body wt or more) to male and female rats caused a significantly increased incidence of liver and kidney tumours. The development of these tumours was accompanied by manifest toxicity in the target organ (including increased organ weight, nodules, hyperplasia). In hamsters, the main target organ of oral exposure to HCB (4-16 mg.kg^{-1} body wt) was the liver: cirrhosis, hyperplasia of the bile ducts and hepatomas. The incidence of liver tumours was also significantly increased in mice after oral administration of 6-32 mg.kg^{-1} body wt for about 2 years. The HCB-induced tumours cannot be attributed to a specific mechanism as was the case with the development of renal tumours in 1,4-DCB-exposed male rats, because HCB induces tumours in more than one organ of both sexes of several animal species. It is clear, however, that the development of tumours is accompanied by toxicity in the target organs. Based on these studies it is concluded that there is sufficient evidence that HCB is carcinogenic in experimental animals.

5.2. ECOTOXICITY - AQUATIC ORGANISMS

5.2.1. Accumulation

Experimental studies (with mostly freshwater organisms) have shown that all chlorobenzenes bioaccumulate; whole-body bioconcentration factors (BCF = concentration in organism/concentration in water) of about 700 for MCB to nearly 80,000 for HCB have been reported. The magnitude of bioconcentration is determined especially by the lipophilicity of the chlorobenzenes (Kow = n-octanol/water partition coefficient), which increases as the degree of chlorination increases. Various quantitative structure-activity relationships (QSARs) have been developed to relate bioconcentration to either lipophilicity or water solubility (S; decreases with increasing number of chlorine atoms).

Chlorobenzenes also bioaccumulate in marine organisms, but to a lesser degree than in freshwater organisms. As regards bioaccumulation from sediment, a few studies (worms and midge larvae) indicate that uptake is correlated better with interstitial water concentrations than with total-sediment concentrations.

5.2.2. Toxicity

The L(E)C50 and NOE(L)C values reported in this section are based on tests which were adequately described and conducted in accordance with current guidelines for aquatic toxicity testing *(LC50 and EC50 values are lethal concentrations and effect concentrations, respectively, for 50% of the exposed organisms; NOEC and NOLC values are no-observed-effect concentrations and no-observed-lethal concentrations, respectively).*

- Freshwater organisms

For nearly all chlorobenzenes, toxicity data from short-term (single-species) tests (48/96-h L(E)C50 values) were available for algae, crustaceans and fish (see table 5.1.). The lowest L(E)C50 values were 660 $\mu g.l^{-1}$ for MCB (a short-term early life stage test with fish), 700 $\mu g.l^{-1}$ for DCBs, 350 $\mu g.l^{-1}$ for TCBs, 860 $\mu g.l^{-1}$ for TeCBs, 250 $\mu g.l^{-1}$ for PeCB and <30 $\mu g.l^{-1}$ for HCB. A number of studies reported L(E)C50s equal to or

exceeding the water solubility of the compounds. The relevance of these data, obtained using solvents, is debatable.

Data regarding chronic toxicity are rather limited (table 5.2.). For most chlorobenzenes, only *NOE(L)C* values for crustaceans (usually Daphnia magna) and fish (several species) were available. However, results from early life stage tests with fish, which are generally considered to be (very) sensitive, were available for all (groups of) isomers. The lowest NOE(L)C values were 320 $\mu g.l^{-1}$ for MCB, ($\geq$)122 $\mu g.l^{-1}$ for DCBs, 40 $\mu g.l^{-1}$ for TCBs, 10 $\mu g.l^{-1}$ for TeCBs, 10 $\mu g.l^{-1}$ for PeCB and 1.8 $\mu g.l^{-1}$ for HCB. It is apparent from these data that the toxicity increases as the degree of chlorination (and thereby the lipophilicity) increases. Table 5.2. lists a number of QSARs in which (short- and long-term) toxicity has been related to parameters such as Kow and water solubility.

- Marine organisms

Data on the toxicity of the chlorobenzenes to marine organisms are very limited, especially with regard to chronic toxicity. The lowest 48/96-h L(E)C50 values were 540 $\mu g.l^{-1}$ for 1,2,4-TCB, 3700 $\mu g.l^{-1}$ for 1,2,3,5-TeCB, 320 $\mu g.l^{-1}$ for 1,2,4,5-TeCB and 800 $\mu g.l^{-1}$ for PeCB. The only long-term study (using the fish Cyprinodon variegatus) resulted in an NOLC of 90 $\mu g.l^{-1}$ for 1,2,4,5-TeCB.

Table 5.1. Summary of available L(E)C50 and NOE(L)C values from short- and long-term tests with freshwater organisms (in $\mu g.l^{-1}$), respectively

Chlorobenzene	*Short-term tests L(E)C50 (n)*	*Long-term tests NOE(L)C (n)*
MCB	*660 - 50,000 (a,c,f)*	*320 - 8,500 (c,f)*
1,2-DCB	*740 - 20,000 (a,c,f)*	*185 - 505 (c)*
1,3-DCB	*1,200- 31,000 (a,c,f)*	*650 - 2,400 (c,f)*
1,4-DCB	*700 - 31,000 (a,c,f)*	*122 - 2,100 (a,c,f)*
1,2,3-TCB	*350 - 5,990 (a,c,f)*	*40 - 450 (a,c,f)*
1,2,4-TCB	*1,200- 6,300 (a,c,f)*	*100 - 500 (a,c,f)*
1,3,5-TCB	*9,070 (a)*	
1,2,3,4-TeCB	*1,100- 4,100 (a,f)*	*10 - 310 (a,c,f)*
1,2,3,5-TeCB	*860 - 9,700 (a,c,f)*	
1,2,4,5-TeCB	*	
PeCB	*250 - 300 (c,f)*	*10 - 110 (c,f)*
HCB	*	*1.8 (c)*

(n) = species for which an L(E)C50 or NOE(L)C value is available; where a = algae; c = crustaceans; f = fish

* = *toxicity values $\geq$ the water solubility*

Table 5.2. Summary of a number of quantitative structure-activity relationships (QSARs)

QSAR		*Reference*
Acute toxicity		
log 1/EC50= -0.587 log S + 2.419		*Wong et al. (1984)*
log 1/EC50= 0.985 log Kow - 2.626	*(r=0.985)*	
log EC50= -0.301 - 0.548 log S	*(r=0.989)*	*Bobra (1985)*
log EC50= 3.55 - 0.659 log Kow	*(r=0.981)*	
log 1/LC50= 0.845 log Kow - 4.63	*(r=0.980)*	*Konemann (1980)*
log LC50= 0.85 log Kow - 1.37	*(r=0.980)*	*Hoornstra (1988)*
log 1/LC50= 0.90 log Kow - 2.65	*(r=0.924)*	*Richter et al.(1983)*
log 1/EC50= 0.69 log Kow - 3.18	*(r=0.990)*	*De Wolf et al.(1988)*
log 1/LC50= 0.94 log Kow - 4.62	*(r=0.977)*	*Van Leeuwen et al. (1990)*
Chronic toxicity		
log 1/NOEC$_r$= 0.67 log Kow - 2.82	*(r=0.995)*	*De Wolf et al.(1988)*
log NOEC$_g$=-0.90 log Kow + 3.80	*(r=0.96)*	*Van Leeuwen et al. (1990)*

r = regression coefficient
NOEC = no-observed-effect concentration based on reproduction (r) or growth (g); NOEC and L(E)C50 values expressed in μmol.l^{-1}

5.3. ECOTOXICITY - TERRESTRIAL ORGANISMS

5.3.1. Accumulation

Data on the accumulation of chlorobenzenes by terrestrial organisms from soil are very limited. Studies in which earthworms (Lumbricus terrestris and Allolobophora longa) were chronically exposed to HCB and 1,2,3,4-TeCB have reported BCFs of 2 and 4, respectively. In a terrestrial laboratory microcosm, consisting of an artificial soil, various crops, numerous invertebrates and two voles, there was no indication of bioaccumulation.

5.3.2. Toxicity

- Invertebrates

A limited number of tests have been conducted to investigate the toxicity of chlorobenzenes to invertebrates. The 10-d LC50 of 1,4-DCB for earthworms

was reported as 390 $mg.kg^{-1}$ dry soil. The long-term toxicity of 1,2,3-TCB to the earthworms Eisenia andrei and Lumbricus rubellis was studied in four different soils: an artificial (OECD) soil, a peat soil, a humic sandy soil, and a moderately humic sandy soil. The 14-d LC50s in E. andrei ranged from 133 $mg.kg^{-1}$ dry soil (in the OECD soil) to 547 $mg.kg^{-1}$ (in the peat soil) and those in L. rubellis from 115 $mg.kg^{-1}$ (in the moderately humic sandy soil) to 563 $mg.kg^{-1}$ (in the peat soil). The LC50s of 1,2,4-TCB, determined for 4 different species of earthworm and using EEC artificial soil, ranged from 127 to 251 $mg.kg^{-1}$ dry soil.

- Vertebrates

A 14-d LD50 of 2400 $mg.kg^{-1}$ body wt was reported for 1,4-DCB in quails. Subacute exposure to doses of 50 $mg.kg^{-1}$ body wt or more caused porphyria in quails. Subchronic oral administration of HCB caused increased mortality, toxic effects on the liver (increased weight and enzyme induction) and porphyria, resulting in elevated liver porphyrin levels. The no-effect dose was 1 mg HCB.kg^{-1} of diet, equivalent to 0.1 $mg.kg^{-1}$ body wt. In oral reproduction studies with ferrets and mink, even the lowest dietary concentration tested (1 $mg.kg^{-1}$, equivalent to 0.04 $mg.kg^{-1}$ body wt), had adverse effects on reproduction (decreased litter size, increased percentage of stillbirths, etc.).

5.4. AGRICULTURAL CROPS AND LIVESTOCK

5.4.1. Agricultural crops

- Accumulation

Data on the accumulation of chlorobenzenes in agricultural crops are limited. In an outdoor experiment, BCFs of 1,2,4-TCB, PeCB and HCB in barley and cress were determined in a soil containing 2 mg of the compound per kg of dry weight (pH=6.4, OM=2.1%). The calculated BCFs (after 11 days) ranged from 2.1 for PeCB in cress to 36 for TCB in barley. Over the course of time (80 days for cress and 125 days for barley), the BCFs had fallen by a factor of 10, probably due to growth dilution. In another study with the same plants, the uptake of a group of organic compounds (including a number of chlorobenzenes) via the roots and leaves was investigated. A positive

correlation was found between the Kow and the root concentration factor (ratio of concentration in root to concentration in soil solution). The uptake of the compound by barley via the leaves was positively correlated with its volatility from the soil. These correlations were not demonstrated for cress.

- Toxicity

Data on the toxicity of chlorobenzenes to agricultural crops are restricted to one study with lettuce and one with cereals. The study with lettuce (Lactuca sativa) resulted in 2-w LC50 values, based on growth, of 248 $mg.kg^{-1}$ dry weight for MCB, 1-4 $mg.kg^{-1}$ for 1,2,3-TCB, 48 $mg.kg^{-1}$ for 1,2,4-TCB, 123 $mg.kg^{-1}$ for 1,3,5-TCB, 32 $mg.kg^{-1}$ for 1,2,3,4-TeCB, 1.3 $mg.kg^{-1}$ for 1,2,3,5-TeCB, 2 $mg.kg^{-1}$ for 1,2,4,5-TeCB and 56 $mg.kg^{-1}$ for PeCB. In addition, NOEC values (based on growth) were reported for a number of chlorobenzenes: 10 $mg.kg^{-1}$ for 1,4-DCB, 1 $mg.kg^{-1}$ for 1,2,3-TCB, 10 $mg.kg^{-1}$ for 1,2,4-TCB, 1,3,5-TCB, 1,2,3,4-TeCB and PeCB, and 100 $mg.kg^{-1}$ for HCB. The effect of 1,2,4,5-TeCB on the germination and seedling vigour of barley, oats and wheat was studied in a sandy soil, a sandy loam soil, a clayey loam soil and a clay soil (organic matter contents not reported). The crops were planted 1 to 125 days after 6 applications of the chemical, resulting in soil concentrations corresponding to 12-980 $mg.kg^{-1}$. The lowest concentration was already detrimental to crops planted one day after application, except in the clay soil. In this soil, adverse effects were seen at concentrations of 320 $mg.kg^{-1}$ and higher. The severity of the effects decreased as the time interval between application and planting increased.

5.4.2. Livestock

- Accumulation

Data on the accumulation of chlorobenzenes in livestock are limited to HCB. After subchronic exposure, the concentrations of HCB in adipose tissue of chickens and laying hens were 20-30 times that in the diet (0.125-12.5 $mg.kg^{-1}$ body wt). Sheep, lambs and piglets accumulated HCB in their body fat to concentrations about 10-fold higher than the dietary level. In one study with piglets, HCB concentrations in adipose tissue were reported to

be 300 times higher than in the dose administered. Since tissues of control animals also contained significant amounts of HCB, the authors supposed that as a result of (HCB) contamination, the dosages were (much) higher than intended.

- Toxicity

Most data on the toxicity of chlorobenzenes to livestock concern HCB. The only study involving other chlorobenzenes indicated that a single dose of 800 $mg.kg^{-1}$ body wt of MCB, 1,4-DCB and 1,2,4-TCB increased liver porphyrin levels in 1-day-old chicks. The toxicity of HCB has been studied in chickens, swine, lambs and sows. No adverse effects were observed in chickens at concentrations of up to 22.5 $mg.kg^{-1}$ body wt. In a 90-day study with swine, a dose of 4 $mg.kg^{-1}$ body wt produced effects on the liver, but these effects were not observed at 0.4 $mg.kg^{-1}$. The administration of 0.5 $mg.kg^{-1}$ body wt to pigs caused induction of liver enzymes. The no-effect dose was 0.05 $mg.kg^{-1}$ body wt. Pregnant sows receiving 0.025 $mg.kg^{-1}$ body wt in the diet were not adversely affected.

5.5. SUMMARY AND TOXICOLOGICAL RECOMMENDED LEVELS

5.5.1. Human toxicity

As a rule the establishment of a recommended level is considered to be sound only when a certain "minimum package" of toxicological data concerning genotoxicity, carcinogenicity, reproductive toxicity and/or teratogenicity, and (sub)chronic toxicity is available. Based on this premise, a toxicological recommended level for oral exposure can be derived only for MCB, 1,2-DCB, 1,4-DCB and HCB. It would not be possible in principle to derive a toxicological recommended level for the other chlorobenzenes, that is, 1,3-DCB, 1,2,3-TCB, 1,2,4-TCB, 1,3,5-TCB, 1,2,3,4-TeCB, 1,2,3,5-TeCB, 1,2,4,5-TeCB and PeCB. However, since it concerns a group of related compounds exhibiting similar, or at least predictable, behaviour as regards metabolism, toxicity and genotoxicity, it was decided to establish for these chlorobenzenes an indicative toxicological recommended level for oral exposure.

The data regarding inhalation exposure are for all chlorobenzenes insufficient for deriving an (indicative) toxicological recommended level.
The metabolic behaviour of the various chlorobenzenes changes gradually as the degree of chlorination increases. With an increase in the number of chlorine atoms in the molecule, the chlorobenzenes become more lipophilic and the accumulation in adipose tissue and fatty organs increases. The biotransformation of the chlorobenzenes and their elimination via urine decrease with an increasing number of chlorine atoms; the difference in elimination half-life between, for example, 1,4-DCB and HCB has been estimated to be at least a factor of 10. The excretion of HCB in particular is slow, and occurs mainly via the faeces. The tissues contain chiefly unchanged HCB.
The toxicity of the chlorobenzenes, when administered repeatedly, also increases with the degree of chlorination, which may be partly explained by decreased elimination and increased accumulation.
The induction of liver microsomal enzymes and the interference with normal porphyrin metabolism are sensitive toxicological parameters for all chlorobenzenes. Microsomal enzyme induction is already observable after a relatively short exposure period, and the sensitivity of this parameter does not seem to increase after more prolonged exposure. Directed research into liver microsomal enzyme induction by the chlorobenzenes has been carried out many times in subchronic experiments, but much less frequently in chronic experiments, which are aimed especially at carcinogenic properties. Regarding toxicity therefore, this evaluation has as much as possible been based on the data on enzyme induction.
As already mentioned, there is a suspicion that the chlorobenzenes might have genotoxic properties. However, this is based on only one study in which MCB, DCBs and TCBs were tested for their potency to induce micronuclei in the bone marrow of mice. In other test systems, the chlorobenzenes showed no or only very little activity. Therefore, the evidence for genoticity of this group of compounds is weak.
Carcinogenicity studies with a number of chlorobenzenes have shown that the development of tumours was usually accompanied by toxicity in the target organ. Another striking observation is that for the most toxic chlorobenzene, HCB, the signs of carcinogenicity were the most pronounced. In studies in which 3 species were exposed to HCB, hepatotoxicity was also

accompanied by the development of tumours. Based on the limited evidence of genotoxicity and the correlation between toxicity and carcinogenicity, it seems justified to assume provisionally the existence of a threshold in establishing an (indicative) recommended level.

- Oral exposure

Monochlorobenzene

In studies in animals, there was no evidence of carcinogenicity of MCB. There is limited evidence of genotoxicity. Oral teratogenicity or reproduction studies have not been conducted.

A 2-year (carcinogenicity) study resulted in a no-effect dose of 60 $mg.kg^{-1}$ bodywt. In subchronic experiments, similar dosages did produce a slight effect in rats, mice and dogs (slight increase in heart and spleen weights); the no-effect dose was (about) 30 $mg.kg^{-1}$ body wt. Applying a safety factor of 100 (for extrapolation of animal data to man), a maximum acceptable intake of 0.3 $mg.kg^{-1}$ body wt is calculated for man for lifelong exposure.

1,2-Dichlorobenzene

In experiments in animals, there was no evidence of carcinogenicity of 1,2-DCB. There is limited evidence of genotoxicity. Oral teratogenicity or reproduction studies have not been conducted.

In a chronic (carcinogenicity) study, only the highest dose produced a significant effect (increased regeneration of the renal tubular epithelium).

A dose of 60 $mg.kg^{-1}$ body wt was without effect. Applying a safety factor of 100, the maximum daily intake for man is 0.6 $mg.kg^{-1}$ body wt for lifelong exposure.

1,4-Dichlorobenzene

Experiments in animals provided limited evidence of carcinogenicity of 1,4-dichlorobenzene. Based on the limited evidence of genotoxicity and the correlation between toxicity and carcinogenicity, it seems justified to assume provisionally the existence of a threshold in establishing a

recommended level. No evidence of teratogenicity was found, and doses of 500 mg.kg^{-1} body wt or more produced an embryotoxic effect.
In a chronic (carcinogenicity) study, the lowest dose tested (150 mg.kg^{-1} bodywt) caused effects on the kidneys and liver of rats. In another experiment in which rats were given 1,4-DCB for about 6 months, the lowest dose tested (19 mg.kg^{-1} body wt) was without effect. The second lowest dose (188 mg.kg^{-1} body wt) produced increased liver and kidney weights. Since this was the only effect observed at a dose level which is tenfold higher than the no-effect dose, a safety factor of 100 is considered adequate. Based on 19 mg.kg^{-1}, a maximum acceptable daily intake of 0.2 mg.kg^{-1} body wt was calculated for man for lifelong exposure.

Hexachlorobenzene

In experiments in animals, there was sufficient evidence of the carcinogenicity of HCB. There is limited evidence of genotoxicity, but it is assumed provisionally that a threshold exists. There was no evidence of teratogenic or reproductive effects. Doses of 40 mg.kg^{-1} body wt and higher produced embryotoxicity.
An oral subchronic study resulted in a no-effect dose of 2 mg.kg^{-1} body wt for the induction of porphyria (in female rats) and liver enzymes. In a study in which rats were exposed pre- and postnatally to HCB, the lowest dose tested (0.2 mg.kg^{-1} body wt) produced effects on the immune system. A no-effect dose of 0.05 mg.kg^{-1} body wt was determined in rats for changes in the hepatic ultrastructure. A similar dosage fed to a small group of monkeys did also not elicit an adverse response. A no-effect dose could not be derived from the available chronic studies.
Because the parameters described above are toxicologically sensitive, a safety factor of 100 is considered to be adequate despite the fact that the no-effect dose is derived from subchronic studies. This establishes a *maximum daily intake for man of* 0.5 mg.kg^{-1} body wt *for lifelong exposure.*

Other chlorobenzenes

For the other chlorobenzenes, only an indicative recommended level can be established on the basis of the available information. It is assumed provisionally that application of the threshold concept is justified and

that the recommended level should be based as far as possible on microsomal enzyme induction.

Trichlorobenzenes

In a 13-week study with rats, enzyme induction was found at the lowest dose tested (10 $mg.kg^{-1}$ body wt), but this effect had disappeared after a 30-day recovery period. A study with monbkeys (exposed for 13 weeks) resulted in a no-effect dose of 25 $mg.kg^{-1}$ body wt. There was no evidence of teratogenic or reproductive effects. Embryotoxicity, accompanied by maternal toxicity, occurred at a dosage of 360 $mg.kg^{-1}$ body wt or higher. In establishing the indicative recommended level, a safety factor of 500 is applied because a dose of as little as 10 $mg.kg^{-1}$ body wt was capable of inducing enzymes. This results in an indicative recommended level of 0.02 $mg.kg^{-1}$ body wt.

Tetrachlorobenzenes

With respect to toxicity (enzyme induction), one subchronic study with rats was available, in which 1,2,4,5-TeCB was found to be the most toxic isomer. The no-effect dose for 1,2,4,5-TeCB in this study was 5 $mg.kg^{-1}$ of diet (equivalent to 0.34 and 0.40 $mg.kg^{-1}$ body wt for males and females, respectively). There was no evidence of teratogenicity. An embryotoxic effect was produced by 200 $mg.kg^{-1}$ body wt of 1,2,3,4-TeCB and 1,2,3,5-TeCB. Administration of a similar dose of 1,2,4,5-TeCB resulted in the death of nearly all the dams.

Using the no-effect dose of 0.4 $mg.kg^{-1}$ body wt and applying a safety factor of 100, an indicative recommended value of 0.004 $mg.kg^{-1}$ body wt is obtained.

Pentachlorobenzene

One combined subchronic and reproductive toxicity study with rats was available, resulting in a no-effect dose of 12.5 $mg.kg^{-1}$ body wt. However, suckling young of females in this dose group showed tremors, as well as increased relative liver weights. The no-effect dose was 6.3 $mg.kg^{-1}$ body wt. No indicative recommended level is established for pentachlorobenzene because of the absence of data on enzyme induction.

5.5.2. Ecotoxicity - aquatic environment

A number of extrapolation methods, currently under discussion, are used for deriving toxicological recommended levels on the basis of single-species laboratory tests. The RIVM/DGM will take a position shortly on the extrapolation method to be used and the derivation of recommended levels. What is certain is that a distinction will be made between a preliminary hazard assessment and a refined hazard assessment method. The first method is used when fewer than 4 NOECs from long-term studies with different taxonomic groups are available, and the second when at least 4 NOECS are available.

For all chlorobenzenes the data from long-term studies were so limited that only the first extrapolation method could be applied. The reader is referred to Appendix A of this document for a description of this method. The results obtained with this method are presented in table 5.3. In principle, the lowest experimentally determined NOEC or L(E)C50 value was used. However, when several values for the same parameter were available for the same test species, the geometric mean of these values was used. Data from short-term toxicity tests were not included in the derivation of indicative maximum acceptable risk levels (MARs) for those chlorobenzenes of which 3 NOECs from long-term studies with algae, crustaceans and fish were available (1,4-DCB, 1,2,3-TCB, 1,2,4-TCB and HCB).

The (limited) experimental data show that the toxicity of the chlorobenzenes increases as the degree of chlorination increases. This is confirmed by values calculated with the use of QSARs. For example, using the chronic QSAR for crustaceans of De Wolf et al. (1988) (log 1/NOEC = 0.67 log K_{ow} - 2.82), the following chronic NOECs were calculated: 930 $\mu g.l^{-1}$ for MCB, 540 $\mu g.l^{-1}$ for DCBs, 300 $\mu g.l^{-1}$ for TCBs, 170 $\mu g.l^{-1}$ for TeCBs, 90 $\mu g.l^{-1}$ for PeCB and 45 $\mu g.l^{-1}$ for HCB. A difference in toxicity between isomers with the same number of chlorine atoms cannot be demonstrated on the basis of the experimental data, so that one value is derived for each group of isomers. The establishment of the indicative MARs of for the various groups of isomers has been based in principle on that compound for which the most experimental values were available. In addition, the theoretical difference in toxicity, as is apparent from QSAR

values, has had an influence on the difference in MARs of the isomer groups.

This has resulted in indicative maximum acceptable risk levels of 30, 20, 10, 5, 2.5 and 0.2 $\mu g.l^{-1}$ for MCB, DCBs, TCBs, TeCBs and HCB respectively (see table 5.2.).
The limited toxicity data for marine organisms are in the same range as those for freshwater organisms. Therefore, the (indicative) maximum acceptable risk levels for sea water are equated to those for fresh water.

Table 5.3. Calculated concentrations ($\mu g.l^{-1}$) for the chlorobenzenes in fresh water, according to the preliminary hazard assessment (PHA) method ("modified" EPA method, OECD Workshop, 1990)

Compound	input (a)		result (ug/l)		
	lowest NOEC I (n)	lowest L(E)C50 II (n)	EPA modification I (b)	II (c)	indicative "MAR"
MCB	320 (2)	660 (3)	32	6.6	30
1,2-DCB	340 (1*)	1230 (3)	34	12	20
1,3-DCB	680 (2)	3270 (3)	68	33	20
1,4-DCB	304 (3)		30		20
1,2,3-TCB	40 (3)		4		10
1,2,4-TCB	190 (3)		19		10
1,3,5-TCB	260 (**)	490 (1**)	26	4.9	10
1,2,3,4-TeCB	25 (2)	340 (2*)	2.5	3.4	5
1,2,3,5-TeCB	180 (**)	1580 (3)	18	15.8	5
1,2,4,5-TeCB	150 (**)	(d)	15		5
PeCB	35 (2)	250 (3)	3.5	2.5	2.5
HCB	1.8 (3)		0.18		0.2

"MAR": maximum acceptable risk level

(n) The number of taxonomic groups for which NOE(L)C or L(E)C50 values are available. The figures indicate the number of experimental values, (*) the number of values estimated on the basis of QSARs. Four QSARs were used: log 1/EC50 = 0.69 log Kow - 3.18 and log 1/NOEC = 0.67 log Kow - 2.82 for crustaceans (De Wolf et al., 1988), and 1/LC50 = 0.94 Kow - 4.62 and log 1/NOEC = 1.06 Kow - 4.57 for fish (Van Leeuwen et al., 1990).

(a) In principle, the lowest NOE(L)C or L(E)C50 values were used. However, when several values for the same parameter were available for the same test species, the geometric mean of these values was used.

(b) an extrapolation factor of 10 has been applied.

(c) an extrapolation factor of 100 has been applied when there is at least 1 reliable L(E)C50 value available for algae, crustaceans and fish; a factor of 1000 has been applied in the other cases.

(d) Toxicity values for 1,2,4,5-TeCB are approximately equal to or exceed the water solubility limit (560 $\mu g.l^{-1}$).

5.5.3. Ecotoxicity - terrestrial environment

With regard to terrestrial organisms, the data are so limited that only the preliminary hazard assessment method can be employed in the derivation of the toxicological recommended level for soil (see appendix A). The results from this extrapolation method are presented in table 5.4. The NOECs and EC50s reported in this table are the values obtained after conversion of the experimental values in the test soil to a standard soil with a 10% organic matter content.

Application of this extrapolation method results in indicative MARs ranging from 0.005 to 0.4 $mg.kg^{-1}$ for 1,4-DCB, TCBs, TeCBs and PeCB, and a MAR of 50 $mg.kg^{-1}$ for HCB. The available data do not show that the toxicity tends to increase with an increasing degree of chlorination. One possible explanation for this is the different mode of administration (readily soluble compounds in aqueous solution, poorly soluble compounds usually as a solid) and thereby the bioavailability. For this reason a range of 0.01 to 1 $mg.kg^{-1}$ dry weight is given as indicative of a maximum acceptable risk level for individual chlorobenzenes in a standard soil containing 10% organic matter. It should be noted that plants appear to be relatively sensitive to some chlorobenzenes, for example, 1,2,3-TCB and 1,2,3,5-TeCB.

Table 5.4. Calculated concentrations for the chlorobenzenes in soil, according to the preliminary hazard assessment (PHA) method ("modified" EPA method, OECD Workshop, 1990) (in mg.kg^{-1} dry weight)

Compound	input (a)		result (mg/kg)		
	lowest NOE(L)C I (n)	lowest L(E)C50 II (n)	EPA modification I (b)	EPA modification II (c)	indicative "MAR"
MCB					
1,2-DCB					
1,3-DCB					
1,4-DCB	50 (1)	390 (1)	5	0.4	0.4
1,2,3-TCB	5 (1)	5 (1)	0.5	0.005	0.005
1,2,4-TCB	50 (1)	127 (2)	5	0.1	0.1
1,3,5-TCB	50 (1)	615 (1)	5	0.6	0.6
1,2,3,4-TeCB	50 (1)	160 (1)	5	0.2	0.2
1,2,3,5-TeCB		7 (1)		0.007	0.007
1,2,4,5-TeCB		10 (1)		0.01	0.01
PeCB	50 (1)	280 (1)	5	0.3	0.3
HCB	500 (1)		(50)		

(n) the number of taxonomic groups for which NOE(L)C or L(E)C50 values are available.

(a) the experimental values (V) have been converted to estimated values in a "standard soil" (% OM-s = 10%) on the basis of the organic matter content of the test soil (% OM-t) using the formula:
Vstandard soil = Vexperiment x 10 / % OM-t.
In the test with plants, the OM content of the test soil was 1.4%; an OM content of 2% has been used in the conversion to the standard soil.

(b) An extrapolation factor of 10 has been applied to the NOE(L)C value.

(c) An extrapolation factor of 10 has been applied.

6. EMISSION-CONTROL MEASURES

This chapter deals with measures to reduce the emissions of chlorobenzenes into soil, water, air and waste. A distinction will be made between autonomous developments, developments already in progress, policy-controlled or otherwise, and additional measures. In the discussion of emission-control measures, the emphasis will be on the principal emission sources of chlorobenzenes identified in chapter 2 and in the same order.
The emission reduction issue is described in detail in Haskoning (1989).

6.1. APPLICATIONS OF CHLOROBENZENES

6.1.1. Pesticides industry

- Autonomous developments

It is expected that the consumption of chlorobenzenes in the pesticides industry will possibly grow slightly. Most of this growth will result from increased use of MCB. However, predictions of the future consumption of chlorobenzenes depend on possible national and international agreements on the approval and registration of pesticides produced in the Netherlands. At present, there are no indications that changes in the procedure may be expected in the short term (tel. inf. VROM).
The current emission of chlorobenzenes into surface waters amounts to 0.3 tonne per year. The concentration of the chlorobenzenes in the discharged water lies around the ng or ug per litre level. During the past few years, all companies concerned have constructed new/improved wastewater treatment plants, or will do so in the near future.
Licensing authorities have established tighter limitations on, among other things, emissions to surface water as part of the granting of a revised VWO permit (Pollution of Surface Water Act). The wastewater-discharge guidelines do not name chlorobenzenes specifically in all cases. As a result of improved wastewater treatment facilities and increasing recycling of chlorobenzenes as solvents, it may be assumed that the chlorobenzene concentrations in waste water will fall.
The emission of chlorobenzenes into air is over 12 tonnes annually and consists mostly of MCB liberated during the manufacture of tetradifon. One

of the conditions of the revised Nuisance Act permit sets a maximum of 3 kg per hour on the emission of MCB to air as of January 1991. With a planned production time of 2,000 hours per year, this amounts to an annual emission of 6 tonnes. The principal sources of the other chlorobenzene emissions are the transfer by pump of liquids and the filling of tanks and drums. These emissions are difficult to avoid. "Good housekeeping" can further reduce these emissions.

6.1.2. Other chemical industry

- Autonomous developments

The production of tetrachloromethane (carbon tetrachloride) and tetrachloroethylene was discontinued in the spring of 1990. The manufacturing process generates annually about 600 tonnes of chlorine-containing waste with a HCB content of about 430 tonnes. The discontinuation of the production of these chemicals eliminates the annual emission of 75 kg HCB into air and of 3 kg HCB into surface water.

Approximately 50 kg MCB are emitted into (salt) surface water during the manufacture of isocyanates (tel. bus. inf.). The revised WVO permit requires that the EOX (extractable organic halogen) concentration is 1 $mg.l^{-1}$ at most. The total atmospheric emission of MCB is currently about 80 tonnes per year. The company concerned has announced that, following assessment of the magnitude of the emission, measures will be taken to reduce the emission into air. At present, stages of the manufacturing process are being examined to determine where the emissions occur and their magnitude. Inspection authorities will be approached shortly to discuss the measures and the time required for their implementation.

6.1.3. Textile industry

- Additional measures

Additional measures for reducing emissions of 1,2,4-TCB can be divided into substitutes, process measures and treatment techniques.

The dyeing of wool-polyester blends is not possible without the use of carriers. The temperature during the dyeing of wool-polyester blends should not exceed 120 oC because otherwise the wool fibres become irreparably

damaged. However, the concentration of carriers can be reduced when the temperature increases, from 2-8 $g.l^{-1}$ at 100 ^{0}C, 2-5 $g.l^{-1}$ at 106-108 ^{0}C, to 1 $g.l^{-1}$ at 120 ^{0}C. On the other hand, to protect the wool at a temperature of 120 ^{0}C, a heterocyclic methylol compound (based on formaldehyde) must be added (Tebodin, 1987; CUWV), 1989), but this is not (or no longer) practiced in the Netherlands. The use of carriers is not essential in the dyeing of polyester-cotton blends (Tebodin, 1987; CUWVO, 1989). One process measure which can reduce 1,2,4-TCB emissions is the recovery of residues from the dyebaths and their disposal as chemical waste (Tebodin, 1987; CUWVO, 1989).

The waste water from the textile-dyeing industry, after pretreatment if necessary, is discharged into the sewer. 1,2,4-TCB emissions can be reduced by treating the waste water before discharging it into the sewer. In addition to curtailing the use of carriers, 1,2,4-TCB can be replaced by nonhalogenated carriers, such as ortho-phenylphenol and biphenyl, for dyeing wool-polyester blends.

It is not very particularly useful to propose specific treatment techniques for 1,2,4-TCB only. The wastewater situation in the textile-refining industry and the carpet industry has been the subject of discussion during the past few years. Additional measures to reduce environmentally objectionable substances had been expected in mid-1989. In view of the nature of the compounds and the quantities consumed annually (about 0.5 tonne of 1,2,4-TCB against more than 200 tonnes of dyes), the measures will be directed primarily at dyes, fungicides and heavy metals and, to a lesser extent, carriers such as 1,2,4-TCB.

6.1.4. Disinfectants

- Autonomous developments

The use of air fresheners, toilet blocks, urinal tablets and mothballs has declined from about 350 tonnes to about 100 tonnes per year in the period 1985-1988. Most companies in the Netherlands no longer use 1,4-DCB in the above-mentioned products (tel. bus. inf.). 1,4-DCB is now only used in air fresheners (blocks), toilet blocks and urinal tablets. According to the few companies still incorporating 1,4-DCB in these products and one manufacturer of 1,4-DCB, consumption will stabilize at about 80 tonnes per

year in the 1990s (tel. bus. inf.). The other 1,4-DCB producer states that consumption in the Netherlands will possibly have fallen to zero by 1993 (tel. bus. inf.).

- Additional measures

No concrete policy plans exist regarding the use of 1,4-DCB in air fresheners, et cetera (tel. inf. VROM). It is also expected that a few companies will continue to use 1,4-DCB as long as this is not prohibited. It is advisable to come to an agreement about measures on an international level, making it possible to discontinue the importation of 1,4-DCB-containing products. These products are imported mainly from Japan and Switzerland.
Substitutes for 1,4-DCB are available, namely, cleansing agents to which a perfume has been added.

6.1.5. Other industrial sectors

- Autonomous developments

Chlorobenzenes are not (or no longer) used in the other industrial sectors, so that additional policy measures are not necesssary. Nevertheless, chlorobenzenes have been detected in the waste water from a few industries. It is advisable to conduct further investigations into the origin of chlorobenzenes in these waste waters.

6.1.6. Diffuse emissions

Detectable levels of MCB, 1,2-DCB, 1,4-DCB, 1,2,3-TCB, TeCB and HCB have been found in domestic waste water, while chlorobenzenes were also present in the waste water from several industries. Neither investigation could provide an unequivocal explanation for the presence of chlorobenzenes in this waste water, because not in all cases were chlorobenzenes used directly. One exception is 1,4-DCB, which is used directly in toilet blocks and urinal tablets. Note that the contribution to the diffuse input to water and soil due to atmospheric deposition is relatively significant (see figure 4.4.), and that the emissions of the chlorobenzenes concerned are

all (with the exception of 1,4-DCB) less than 100 kg per year. Therefore, additional measures do not appear to be urgent.

6.1.7. Urban waste

The policy of the Ministry of VROM for household refuse (representing about 70% of the urban waste) for the year 2000 provides that half the waste will be incinerated and the other half recycled/reused, so that the dumping of household waste would then come to an end (VROM, 1988). Approximately 50% of the residential waste was dumped in 1986. To realize these policy intentions, the following measures have been proposed (VROM, 1988):

- a ban on marketing certain products;
- the separate presentation and collection of waste components;
- a change in the acceptation policy of waste-treatment facilities;
- an increase in waste-treatment charges;
- the incineration of unrecyclable domestic waste.

Based on an estimated volume of 6 million tonnes of household refuse in the year 2000, an estimate can be made of the emissions of chlorobenzenes resulting from the processing of urban waste. It is tentatively assumed that the chlorobenzene content of urban waste remains constant in the period 1987-2000. The maximum amount of chlorobenzenes disposed of via urban waste is then 12 kg, of which half is incinerated and the other half recycled/reused. With a combustion efficiency of at least 98%, this results in a maximum emission into air of 0.24 kg and a maximum input to fly ash of 0.24 kg (objective, 100% reuse in 2000). These emissions are negligible.

According to the task set by the Ministry of VROM, the recycling and reuse of domestic waste will increase to 50% of the total volume by the year 2000 against 15% in 1986 (VROM, 1988). The urban waste fractions suitable for increasing recycling (mainly vegetable, fruit and garden waste) usually contain less chlorobenzenes than the fractions which are incinerated (Bremmer et al., 1987, 1988; Cornelissen, 1987; Janssens et al., 1988).

Since the concentrations of chlorobenzenes in domestic waste are already very low, it may be expected that chlorobenzenes will not be present in reused domestic waste.

6.1.8. Sewage sludge

The policy aims regarding sewage sludge (VROM, 1988) should result in a decrease in dumping and use as a fertilizer and an increase in incineration of sewage sludge, and a reduced volume of sewage sludge in the year 2000 (about 0.6 million tonnes dry weight in 1986).
It was reported in chapter 2 that the total volume of sewage sludge contains less than 100 kg chlorobenzenes. When the policy aims are achieved, both the diffuse input to soil and emissions to air resulting from the incineration of sewage sludge will be negligible by the year 2000.

6.2. SUMMARY AND CONCLUSIONS

Developments already in progress, policy-controlled or otherwise, have resulted in a decline in the use of chlorobenzenes. The principal sources of the current chlorobenzene emissions are the use of 1,4-DCB in air fresheners (blocks), toilet blocks and urinal tablets, and the use of MCB as a solvent. It is expected that the consumption of 1,4-DCB will decline in the near future and possibly have fallen to zero by 1992.
The emission of MCB into air by the other chemical industry has only recently been recognized. A screening of the manufacturing process is currently taking place in order to map the emissions. Based on the findings, measures will be taken to reduce the emission of MCB.
The current emissions of chlorobenzenes and the anticipated emissions in the year 2000 with autonomous developments and with additional emission-control measures are presented in table 6.1. The atmospheric deposition of chlorobenzenes is expected to decrease, especially in view of the relatively sharp fall in the emissions to the ambient air.

Table 6.1. Current emissions of chlorobenzenes and estimates of the anticipated emissions with autonomous developments and with additional emission-control measures (in tonnes per year). The atmospheric emission has not been included

	Current emissions (1987)	*Emissions with autonomous developments (2000)*	*Emissions with additional emission-control measures (2000)*
Soil	*2*	*1.5*	*1*
Water	*7.5*	*4*	*3*
Air	*370*	*110*	*40*

7. EVALUATION

7.1. EXCEEDING OF THE CURRENT STANDARDS AND GUIDELINES

7.1.1. Soil and groundwater

Data on chlorobenzene concentrations in Dutch soils are available only for HCB. Comparison of the testing level (chapter 1, table 1.3.) with these data (chapter 4, section 4.3.1.) indicates that the reference value is usually not exceeded in nature reserves. This is obvious because the reference values have been derived from the concentrations in relatively unpolluted areas in the Netherlands. The Soil Quality Monitoring Network found that the reference value is not exceeded in the greater part of the soil in the Netherlands. Only in soils which had been treated in the past with HCB-containing pesticide formulations are the levels well above the reference value but stay, on average, below the testing value (B) for the purpose of further investigation.
With regard to groundwater, the reference value (0.01 $\mu g.l^{-1}$) lies below the detection limit of commonly used methods. The concentrations in (riverbank) groundwater are usually below 0.1 $\mu g.l^{-1}$ and thereby below the testing value (B) for the purpose of further investigation.

7.1.2. Surface water and sediments

Provisional standards have been established for all chlorobenzenes with the exception of MCB (chapter 1, table 1.4.), while measurement data in surface waters are available for all compounds except MCB and PeCB. The provisional standards are not exceeded in the Dutch fresh and salt surface waters, with the exception of those for HCB in the Rhine River and a few smaller non-State water bodies.
With regard to sediments, only data on HCB are available. The HCB concentration in the State water bodies exceeds the current standard by roughly a factor of 7 to 8. The standard is usually not exceeded in sediments in the province of North Brabant. HCB levels can be elevated locally, due to point-source discharges, and the provisional "signal" value may even be exceeded (Rotterdam-Chemie Harbour; Delfzijl-Zeehaven Canal).

7.1.3. Air

Standards or guidelines have not been established in the Netherlands for the general environmental quality of the compartment air.

7.2. RISKS AND RISK GROUPS

7.2.1. Risks to man

- Oral exposure

For a number of chlorobenzenes (MCB, 1,2-DCB, 1,4-DCB and HCB), the available data are sufficient to derive a scientifically underpinned recommended level. On the basis of long-term studies it was concluded that there is no evidence that MCB and 1,2-DCB are carcinogenic in experimental animals. There was limited and sufficient evidence of carcinogenicity of 1,4-DCB and HCB, respectively. In both cases the development of tumours was accompanied by the occurrence of toxicity in the target organs (liver and kidneys). With regard to genotoxicity, it was concluded that the data are too limited for considering the chlorobenzenes to be genotoxic. For this reason and because of the correlation between toxicity and carcinogenicity, the existence of a threshold was provisionally assumed for these chlorobenzenes. An indicative recommended level was derived for the other chlorobenzenes. Table 7.1. compares the proposed maximum acceptable daily intakes for man with the exposure levels in the Netherlands through food and drinking water.

Table 7.1. Comparison of the proposed toxicologically maximum acceptable oral doses with the actual total exposure levels in the Netherlands (in μg.day^{-1}, assuming a body weight of 60 kg). Indicative maximum acceptable oral doses are given in parentheses

Name of compound	*Acceptable oral dose*	*Actual oral dose*
MCB	*18,000*	*< 1*
1,2-DCB	*36,000*	*< 1*
1,3-DCB	*(12,000)*	*< 1*
1,4-DCB	*12,000*	*< 1*
TCBs	*(1,200)*	*< 1*
TeCBs	*(3,000)*	*< 1*
PeCB	*>30*	*< 1*
HCB	*30*	*0.3 (max. 1)*

In view of the large differences between the maximum acceptable dose and the average and maximum exposure level, the risks to man of the chlorobenzenes mentioned can be regarded as nil. Given the fact that

- the concentration of the other individual chlorobenzenes in drinking water is below the limit of detection (estimated maximum dose is 0.02 ug per day, assuming that the consumption of drinking water is 2 litres per person per day),
- HCB is very likely present in food at the highest concentrations due to the relatively strong accumulative nature of this congener, and
- HCB is very probably the most toxic chlorobenzene, it can be supposed that the risks to man of the chlorobenzenes for which insufficient data are available for deriving a recommended level are no greater than those from exposure to HCB, provided these chlorobenzenes are not genotoxic carcinogens.

- Inhalation exposure

Because of insufficient data it was not possible to derive recommended levels for exposure by inhalation. However, levels have been observed for a number of chlorobenzenes below which no toxic effects occurred, ranging from 100 mg/m3 for the TCBs, 500-600 mg/m3 for the DCBs, to 2000 mg/m3 for MCB. The margin between these experimentally determined no-effect levels

and actual maximum exposure concentrations (see table 4.16.) is greater than 10(6) for all compounds. This margin seems to be sufficiently large for regarding the risks from the current exposure levels of the chlorobenzenes mentioned as very limited.

Although no effect data are available for the other chlorobenzenes, it is reasonable to suppose, on the basis of the emission data (table 2.7.) and the data on the airborne concentrations (tables 4.8 to 4.10 inclusive), that the risks to man of these compounds are also limited. A possible exception is 1,4-DCB, which is considered to be a nongenotoxic carcinogen (albeit with limited evidence) and can be present at relatively high concentrations in indoor and outdoor air. One risk group are individuals who are exposed to elevated 1,4-DCB concentrations resulting from the use of this compound as a disinfectant, particularly those who stay indoors for relatively long periods of time, such as babies, toddlers, housewives and elderly people (an estimated 50,000 to 100,000 persons). In homes where DCB-containing air fresheners and toilet blocks are used, the average total intake is estimated at 65 ug per person per day (based on a respiration volume of 12 m3 per day and a ratio of indoor to outdoor air of 9:3, assuming complete absorption). This exposure level is more than 185 times lower than the maximum acceptable level determined from the only reliable oral study, assuming complete absorption following oral exposure. It should be noted that the consumption of 1,4-DCB has declined considerably during the past few years (from about 350 tonnes in 1985 to about 100 tonnes in 1988) and is expected to fall further to 0-80 tonnes per year in the 1990s as a result of autonomous developments (see section 6.1.4.). Based on these considerations, the risk of 1,4-DCB to man appears to be negligible, certainly in the near future.

- Organoleptic effects

Chlorobenzenes are known for their organoleptic properties. The odour thresholds are so low (see table 1.2.) that for a number of chlorobenzenes they are below the chemical-analytical detection limit. For example, the concentrations in drinking water (see section 4.6.2.) lie below the chemical-analytical limit of detection, but it is possible that the odour threshold for DCBs and TCBs is exceeded. The extent to which it is exceeded

in these situations will be so small that the odour nuisance is limited. This raises the question of whether chlorobenzenes actually do cause nuisance: the compounds give off a pleasant fresh odour and are employed for this reason.

7.2.2. Risks to ecosystems

- Aquatic environment

In accordance with the latest insights, the available data are insufficient to establish a scientifically-based recommended level, but it is possible to give indicative recommended levels. In table 7.2. these indicative values are compared with the concentrations of chlorobenzenes in water. There is a wide margin between the indicative maximum acceptable risk levels and the exposure concentrations by way of the water phase. If 1% of the maximum acceptable risk level (in accordance with the policy memorandum "Premises for Risk Assessment") were to be used as the basis for establishing a desirable level, then the concentrations in the Dutch surface waters usually do not exceed the desirable level.

In view of the strong exchange of chlorobenzenes between aquatic organisms and the water phase, biomagnification will very probably not occur.

If it is desirable to have recommended levels for sediment, the use of equilibrium partition coefficients seems, given the lack of adequate sediment toxicity data, to be the most appropriate approach (Van de Meent et al., 1990). Table 7.3. presents recommended levels for sediment based on a relationship between the equilibrium partition coefficient (Kp) and the octanol-water partition coefficient (K_{ow}) derived for substituted benzenes ($\log Kp = 0.73 \log K_{ow} - 1,47$, Schwarzenbach and Westall, 1985).

Table 7.2. Comparison of the indicative maximum acceptable risk levels MAR) for aquatic organisms and the concentrations in surface water

Compound	Indicative MAR (µg/l)	Concentrations in surface water µg/l average	maximum
MCB	30	< 0.01 *	?
1,2-DCB	20	0.03	0.6
1,3-DCB	20	0.02	0.3
1,4-DCB	20	0.04	0.6
1,2,3-TCB	10	0.02 **	0.09 **
1,2,4-TCB	10	0.02 **	0.09 **
1,3,5-TCB	10	0.02 **	0.09 **
1,2,3,4-TeCB	5	< 0.002 ***	0.01 ***
1,2,3,5-TeCB	5	< 0.002 ***	0.01 ***
1,2,4,5-TeCB	5	< 0.001	< 0.001
PeCB	2.5	< 0.001 *	< 0.001 *
HCB	0.2	< 0.001	0.01

* estimate based on emission data
** sum of TCBs
*** sum of TeCBs

Table 7.3. Recommended levels for chlorobenzene concentrations in sediment derived from the recommended levels for surface water (MAR) using equilibrium partition coefficients

Compound	MAR-water (µg/l)	log Kp	Partition coeff. (l/kg)	MAR-sediment (indicative,mg/kg)
MCB	30	2.3	200	6
1,2-DCB	20	2.7	500	10
1,3-DCB	20	2.8	630	13
1,4-DCB	20	2.9	800	16
1,2,3-TCB	10	3.1	1300	13
1,2,4-TCB	10	3.2	1600	16
1,3,5-TCB	10	3.25	1800	18
1,2,3,4-TeCB	5	3.5	3200	16
1,2,3,5-TeCB	5	3.5	3200	16
1,2,4,5-TeCB	5	3.5	3200	16
PeCB	2.5	3.8	6300	16
HCB	0.2	4.5	32000	6

Data on chlorobenzenes in sediments concern mostly HCB.

The concentrations in the sediments are at least a factor of about 1000 lower than the indicative maximum acceptable risk levels. The chlorobenzene

concentrations in heavily polluted sediments in harbour areas are well below the indicative maximum acceptable risk levels.

- Terrestrial environment

The indicative maximum acceptable risk levels for soil as determined from soil toxicity data are in the 0.01-1 $mg.kg^{-1}$ range. The indicative maximum acceptable risk levels derived for sediments are consistently higher than those derived for soil, namely, 6-18 $mg.kg^{-1}$. One of the causes of this is that the partition coefficients used apply to sediment and not to soil; the partition coefficients for soil are generally lower than those derived for sediments, due to a lower carbon content of the soil.
Data on chlorobenzene concentrations in soil are available only for HCB. Considering the K_{ow} (table 2.1.) and the chlorobenzene load in the soil (table 2.7.), it is assumed that in the Netherlands the concentrations of chlorobenzenes other than HCB are generally much lower than 0.01 $mg.kg^{-1}$.

The concentrations in groundwater (table 4.16.) are well below the maximum permissible concentrations proposed for surface water. Based on these estimates it is assumed that the risks associated with the presence of chlorobenzenes in soil and groundwater are limited in the Netherlands.

As regards the risks of biomagnification, only HCB is possibly important. However, hardly any bioaccumulation occurs in plants. Bioaccumulation is also limited in herbivores; for HCB, the bioconcentration factor in fat is 10-30 and considerably lower in other tissue (muscle). Nevertheless, carnivores such as otters and cormorants could possibly constitute a risk group, because they are specialistic fish-eaters.
Assuming a bioconcentration factor of 12,500 for HCB in a fish with 5% body fat, based on the K_{ow} (set at 5.4 in chapter 1), then the fish could contain over 0.01 $mg.kg^{-1}$ at the average concentration of 0.001 $\mu g.l^{-1}$ found in Dutch surface water. Although no toxicity data are available for otters and cormorants, it can be assumed that there is little difference in the toxicity of HCB to quails and cormorants, and that the toxicity to otters differs little from that to other mustelids such as ferrets and mink. Data are available for these animals: unacceptable effects occurred even at the lowest concentrations tested (5 and 1 mg HCB.kg^{-1} of feed,

respectively) (see 5.3.). Although biomagnification effects cannot be ruled out, the calculated margin of 100-500 seems sufficiently large for considering the risks to be limited.

7.3. ENVIRONMENTAL QUALITY OBJECTIVES

For all environmental compartments, the available data are insufficient for giving a recommended level a sound underpinning. For this reason the values reported in table 7.4. can only be regarded as indicative. Note that, in accordance with the policy memorandum "Premises for Risk Assessment", the desirable levels are a factor of 100 lower than the maximum permissible levels.

Table 7.4. Indicative maximum permissible concentrations of chlorobenzenes in the environment

Compound	*Soil (mg/kg)*	*Sediment*	*Surface water/Groundwater (µg/l)*	*Air ($mg.m^{-3}$)*
MCB	*0.01-1*	*5-20*	*30*	-
1,2-DCB	*0.01-1*	*5-20*	*20*	-
1,3-DCB	*0.01-1*	*5-20*	*20*	-
1,4-DCB	*0.01-1*	*5-20*	*20*	-
1,23-TCB	*0.01-1*	*5-20*	*10*	-
1,2,4-TCB	*0.01-1*	*5-20*	*10*	-
1,3,5-TCB	*0.01-1*	*5-20*	*10*	-
1,2,3,4-TeCB	*0.01-1*	*5-20*	*5*	-
1,2,3,5-TeCB	*0.01-1*	*5-20*	*5*	-
1,2,4,5-TeCB	*0.01-1*	*5-20*	*5*	-
PeCB	*0.01-1*	*5-20*	*2.5*	-
HCB	*0.01-1*	*5-20*	*0.2*	-

7.4. MEASURING STRATEGIES

With regard to soil and groundwater, a general measuring strategy is considered to be of limited use.

Regarding surface water, the data on hand indicate that the measuring activities in State water bodies can be slowed down. Research could concentrate on monitoring the emissions of chlorobenzenes by the pesticides

industry and on analyzing the receiving water on the spot. Measuring activities for sediment are not necessary.
With regard to air, measuring efforts on a national scale are also not necessary. It is important, however, to follow the expected development in the use and emissions of MCB (pesticides industry) and 1,4-DCB (disinfectants).

7.5. FEASIBILITY OF THE ENVIRONMENTAL QUALITY CRITERIA

Based on the data on the concentration levels in the Dutch environment, it is assumed that, in general, these concentrations do not exceed the desirable levels (defined as 1% of the maximum acceptable concentration). Autonomous developments will ensure that the concentrations in the environment will fall still further. Possibly the MCB concentration is an exception, but the increase will very likely not lead to alarming situations.

7.6. CONCLUSIONS AND RECOMMENDATIONS

Although not all data are available for an adequate risk assessment, the conclusion seems justified that the risks associated with the current chlorobenzene concentrations and those expected in the future are generally limited. The current exposure levels for both man and aquatic and terrestrial organisms are (as far as is known) well below the toxicological acceptable limits, and desirable levels derived from them (set at 1% of the maximum permissible level in accordance with the policy memorandum "Premises for Risk Assessment", VROM, 1989) are in most situations not exceeded.
In view of the autonomous developments (including a decrease in the incineration of PVC-containing waste in the context of the dioxins problem), the exposure concentrations, and thereby the risks, of chlorobenzenes will decrease further in the near future. This appears to obviate the necessity of taking additional measures to reduce to emissions of chlorobenzenes still further. Further research in support of policy measures is not necessary. From a scientific point of view, however, it is desirable to study the formation of chlorobenzenes in waste water.

APPENDIX A: Derivation of maximum acceptable risk levels for ecosystems

Depending on the nature and amount of information obtained from laboratory experiments, either a preliminary hazard assessment or a refined hazard assessment method is used. Given the available information on the ecotoxicity of chlorobenzenes, this appendix is confined to the preliminary hazard assessment.

PRELIMINARY HAZARD ASSESSMENT

This method is used when insufficient information is available for deriving a maximum acceptable risk level. This is the case when the data set comprises fewer than 4 chronic NOEC values from tests with different species (differing in function, bodily structure, route of exposure, etc.), so that some allowance is made for the diversity of species or taxonomic groups in ecosystems. As effect parameters, only parameters which have a direct influence on the species at population level are in principle considered. They are primarily death, growth and reproduction and, secondarily, histopathological effects on reproductive organs, eggshell thickness, et cetera. The results of the Minitox (effects on the energy balance) are also judged to be ecologically relevant and should be included in the evaluation.

The method has been derived from the method of the EPA (1984) and its modification as proposed by Van de Meent et al. (1990), and is in accordance with what has been agreed at the OECD workshop in December 1990. The result obtained is a provisional ecotoxicological recommended level, from which an indicative maximum acceptable risk level can be derived.
The method assumes for all compounds that there is a constant difference (a factor of 10) between acute and chronic toxicity, and between laboratory single-species toxicity and ecosystem toxicity. The relevant toxicity datum is divided by a factor, the magnitude of which decreases the more information is available. With respect to the data processing, the following rules are applied:

- the toxicity data are evaluated for representativeness as regards abiotic factors: only those toxicity data are used which have been obtained in

tests conducted under abiotic conditions prevailing in the Netherlands (e.g. pH, hardness, and so on).

- If toxicity data for the same test species are available for the same effect parameter, these data are weighed by calculating a geometric mean.
- If toxicity data for the same test species are available for different effect parameters, only the lowest value is used.
- If toxicity data for different test species from a taxonomic group are available, only the lowest value is used.
- If a reliable compound-specific ratio between an acute L(E)C50 and a chronic NOEC for the same species is available, then, in the absence of sufficient chronic values, this ratio may be used for deriving a chronic NOEC for a species for which only an acute L(E)C50 is available. This derivation procedure may only be employed within a taxonomic group (e.g., within the groups of algae, crustaceans or fish). In the case of several ratios being available, the geometric mean of these ratios is used.
- If the information required is only partly available (e.g., fewer than 3 chronic NOEC values for the obligatory taxonomic group), then, after applying the appropriate application factors, the lowest value obtained is considered to be the indicative maximum acceptable risk level.

The data specific to the various environmental compartments are given below. It should be noted that within the framework of integral standard-setting, equilibrium is assumed in respect of the distribution of a substance over the environmental compartments, and that therefore coordination takes place on the basis of the environmental compartment running the greatest risk.

WATER

Available information	Application factor
Lowest acute L(E)C50 or QSAR estimate of acute toxicity	1000
Lowest L(E)C50 or QSAR for at least 3 groups (algae, daphnia and fish)	100
Lowest NOEC or QSAR for at least 3 groups (algae, daphnia and fish)	10

SEDIMENT

Toxicity data for sediment are often not available. The indicative maximum acceptable risk level is based on (a) the value derived from that determined for surface water employing the equilibrium partition method (EPA, 1989), and (b) the value derived for soil on the basis of soil toxicity data. The lowest value is used as the recommended level.

SOIL

For sediment and soil, the same indicative maximum acceptable risk level could be chosen as the starting-point. However, if soil toxicity data are available, these are used as the basis. The toxicity data are first converted to those applying to the standard soil (10% organic matter; 25% clay). Next, a method is employed analogous to that proposed for surface water:

Available information	Application factor
Lowest acute L(E)C50 or QSAR estimate of acute toxicity	1000
Lowest L(E)C50 or QSAR for at least 3 groups (microbe-mediated processes, earthworms, arthropods and plants)	100
Lowest NOEC or QSAR for at least 3 groups (microbe-mediated processes, earthworms, arthropods and plants)	10

GROUNDWATER

Toxicity data for groundwater are often not available. Therefore, the indicative maximum acceptable risk level is (a) equated to that for surface water, and (b) derived from that determined for soil using the equilibrium partition method (EPA, 1989). The lowest value is used as the recommended level.

AIR

With regard to the air compartment, data on animal species other than mammals (birds, insects) are usually not available. Since for man the aim is to protect each individual, it is assumed that the maximum risk levels derived for man (either from animal experimental or epidemiological data)

are in most cases sufficiently restrictive to protect the ecosystem. If indications point to a high degree of sensitivity of plants to a given compound, then an indicative maximum acceptable risk level is derived for plants, analogous to the method described above. The lowest value is used as the risk level.

FOOD

Biomagnification may be very important for birds and mammals, especially in the case of substances which tend to bioaccumulate in tissues. In deriving an indicative maximum acceptable risk level, no distinction is initially made between birds and mammals, but an indicative maximum acceptable risk level is derived for the group as a whole in accordance with the table below.

Available information	Application factor
Lowest LC50 or QSAR estimate of acute toxicity	1000
Lowest L(E)C50 or QSAR for at least 3 different species (mammals and/or birds)	100
Lowest NOEC or QSAR for at least 3 different species (mammals and/or birds) *	10

* subacute (exposure < 1 months) data can be extrapolated to chronic data by applying an extra factor of 10

On the basis of the bioconcentration factor (BCF) in foods (e.g. fish), determined as the geometric mean in the case of a number of reliable data, it is established whether the indicative maximum acceptable risk levels should be lowered in order to provide adequate protection to birds and mammals. If measurement data concerning bioconcentration are not available, it is derived using the equation: $BCF = 0.05\ K_{ow}$.

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NATIONAL INSTITUTE OF PUBLIC HEALTH AND ENVIRONMENTAL PROTECTION

BILTHOVEN

THE NETHERLANDS

APPENDIX to Report no. 710401015
INTEGRATED CRITERIA DOCUMENT CHLOROBENZENES
EFFECTS

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CONTENTS

5 RISK ASSESSMENT

INTRODUCTION

Data in the present Appendix are underlying those in the chapter on "effects" (chapter 5) of the "Integrated Criteria Document Chlorobenzenes" (Slooff et al., 1991). The Criteria Document, prepared by the National Institute of Public Health and Environmental Protection in The Netherlands, comprises a systematical survey and a critical evaluation of the most important data on chlorobenzenes, as much as possible with regard to the specific situation in The Netherlands. The information in the Criteria Document will serve as a scientific basis for an "effect oriented policy" in The Netherlands, especially with regard to the general population and aquatic and terrestrial ecosystems.
The Criteria Document, including the present Appendix, has been written on behalf of the Ministry for Housing, Physical Planning and Environment, Directorate Substances and Risk-management.

The data which are considered to be necessary for a risk assessment for the general population, are described in chapter 1. Data on the impact of chlorobenzenes on aquatic and terrestrial organisms are described in chapter 2 and chapter 3, respectively. In chapter 4 data on agricultural crops and livestock are described. Chapter 5 contains the risk assessment for man and the environment.

1. HUMAN TOXICITY

1.1 KINETICS AND METABOLISM

1.1.1 Animal studies

Monochlorobenzene

Oral exposure

After oral administration of MCB (34 mg.kg^{-1} bw) to rats the urinary concentrations of 4-chlorophenyl-mercapturic acid (MA) and 4-chlorocatechol were reported to be about 13% and 5% of the administered dose, respectively (Ogata and Shimada, 1983). Following oral administration of approximately 4 g ^{14}C-labelled MCB to two rabbits the majority of metabolites was found in the urine and only small amounts were present in the faeces or in the tissues. The overall recovery was low (about 20%), which was probably due to loss by exhalation. The urinary metabolites were ethereal sulphates (33.9% of the dose administered), glucuronides (33.6%), mercapturic acids (23.8%), diphenols (4.2%), monophenols (2.8%) and 3,4-dihydro-3,4-dihydroxychlorobenzene (0.6%) (Smith et al., 1972). Following a single oral dose of 150 mg.kg^{-1} bw of MCB to rabbits the urine contained glucuronide (25%), ethereal sulphates (27%) and mercapturic acid (20%) (Spencer and Williams, 1950, Smith et al., 1950). Although absolute quantities and ratios may differ among species, the principal metabolites of MCB are 4-chlorophenol, 4-chlorocatechol and MA (Ware, 1988). Absorption from the gastro-intestinal tract increases in the presence of fats and oils (Deichman, 1981).

Inhalatory exposure

After male rats were exposed to 100, 400 or 700 ppm (470, 1,880 or 3,290 mg.m^{-3}) of ^{14}C-labelled MCB vapor for 1 or 5 days MCB was found in all examined tissues (blood, fat, kidneys, lungs and liver). The concentrations increased in proportion to exposure concentrations, except for adipose tissues, which increased more than 30-fold between 100 and 700 ppm. Data from rats killed 16 and 48 hrs after dosing demonstrated rapid

tissue clearance. With increasing exposure concentrations the percentage excreted in the urine decreased (from 95% to 56%) and the percentage exhaled (unchanged) increased (from 5% to 44%). The total amount excreted increased more than proportionately at 700 ppm. A dose-dependent decrease in the relative abundance of the metabolite mercapturic acid was observed. After multiple exposures the tissues contained higher amounts and more was excreted in the urine. The urinary metabolite pattern was similar (Sullivan et al., 1983).

Other routes of exposure

After a intraperitoneal injection of MCB (56, 113 and 225 $mg.kg^{-1}$ bw) to rats, the amounts of MA and 4-chlorocatechol excreted in the urine were about 25% and 5% of the initial dose, respectively (Ogata and Shimada, 1983). In a study in which rats were given one intraperitoneal injection of 225 $mg.kg^{-1}$ bw, the urinary excretion of MA and chlorophenols (including 4-chlorophenol) was reported to be about 20% and 10% of the dose, respectively (Yoshida and Hara, 1985). Male rats received intraperitoneal doses varying between 2 and 14.7 $mmol.kg^{-1}$ bw (245-1660 $mg.kg^{-1}$ bw). The plasma and liver concentrations measured 24 hours after treatment increased dose related. The fraction of the dose excreted decreased with increasing dose; at the lowest dose about 60% was excreted, whereas at the highest dose only about 20% was excreted within 24 hours (Dalich and Larson, 1985). Absorption through the skin of dermally treated rabbits appeared to be minimal or negligible (Deichman, 1981)

Dichlorobenzene (1,2-, 1,3- and 1,4-)

Oral exposure

Three hours after rats were given a single oral dose (200 or 800 $mg.kg^{-1}$ bw) blood, adipose tissue, kidney, liver, lung, heart and brain contained measurable levels of 1,4-DCB. After 48 hours levels in adipose tissue was still high, whereas at that time 1,4-DCB had completely disappeared from the other tisues. Two metabolites (2,5-dichlorophenyl methyl sulfoxide and 2,5-dichlorophenyl methyl sulfone) emerged in the blood, and were found for many hours even after 1,4-DCB had almost disappeared from the blood. Within 24 hours about 45% and 6% of the administered dose appeared in the urine

and faeces, respectively. The excretion of the two metabolites into the urine was much less than that of 2,5-dichlorophenol. After 96 hours the amounts excreted in urine and faeces were 48.3% and 6.5%, respectively (Kimura et al., 1979). After female rats were given oral of 250 $mg.kg^{-1}$ bw per day during 10 days highest concentrations were found in fat, liver, kidneys and lungs. The concentrations declined rapidly in plasma and tissues after 5 days. 97.1% of the administered dose was excreted in the urine, 1.0% was expired and 2.0% excreted in the faeces. The urine contained two main metabolites, namely a sulphate and a glucuronide of 2,5-dichlorophenol (about 50% and 33% of the excreted dose, respectively) and two minor compounds: dihydroxydichloro-benzene and a mercapturic acid of 1,4-DCB. The major compound in bile was found to be the glucuronide of 2,5-dichlorophenol (about 36%). Experiments with rats with cannulated bile ducts indicate that considerable enterohepatic circulation occurs in intact animals and that much of the material eliminated in the bile was reabsorbed to be excreted in the urine (Hawkins et al., 1980).

The metabolism of 1,2-DCB and 1,4-DCB was studied in rabbits receiving a single dose of 500 $mg.kg^{-1}$ bw by gavage. 1,2-DCB was mainly oxidized to 3,4-dichlorophenol (about 30% of the dose administered), which is conjugated with glucuronic and sulphuric acids. Conjugates of 2,3-dichlorocatechol and 3,4-dichloro-catechol were (excreted as) minor metabolites as well as 3,4-dichlorophenyl-mercapturic acid. The main excretion products were glucuronide (48% of the administered dose), ethereal sulphate (21%), mercapturic acid (5%), 3,4-dichlorophenol (30%) and 2,3-dichlorophenol (9%). 1,4-DCB was mainly oxidized to 2,5 dichlorophenol, which is conjugated. 2,5 Dichloroquinon occurred (about 6% of the dose), but no mercapturic acid or dichlorocatechol was found. The major excretion products were glucuronide (36%), ethereal sulphate (27%) and 2,5-dichlorophenol (35%) (Azouz et al., 1955).

Inhalatory exposure

Female rats were exposed to about 1,000 ppm ^{14}C-labelled 1,4-DCB for 3 hrs/day during 2,4,6,8 or 10 days. The distribution was similar to that after oral administration; highest levels occcurred in fat, kidneys, liver and lungs. Of the total amount of ^{14}C excreted during 5 days 97.4% appeared in the urine, 2.5% in the faeces and 0.2% was expired. The pattern of

metabolites in the urine and in the bile was also similar (Hawkins et al., 1980). The organ distribution of 1,4-DCB was compared in male and female rats after inhalatory exposure to 500 ppm for 25 hours. Though no differences in serum levels were observed between male and female rats, the 1,4-DCB levels in the livers of females were significantly higher than those in males, whereas significantly higher levels were found in the kidney of males than of females (Umemura et al., 1990).

Other routes of exposure

After repeated subcutaneous doses of ^{14}C-MCB (250 mg.kg^{-1} per day) given to rats of distribution and excretion (metabolite) pattern was found to be very similar to that after oral or inhalatory exposure. The amount excreted in the urine was somewhat smaller (90.5%) and the amount expired greater (6.4%). After subcutaneous doses tissue concentrations declined more slowly (Hawkins et al., 1980).

Trichlorobenzene (1,2,3-, 1,2,4- and 1,3,5-)

Oral exposure

After rats were given single doses of ^{14}C-labelled 1,2,3-, 1,2,4- or 1,3,5-TCB (10 mg.kg^{-1} bw) by gavage radioactivity appeared in the blood and tissues within 30 min, indicating a rapid absorption of all three isomers. Highest radioactivity was found in liver, kidney, fat, bladder and gastrointestinal tract. Radioactivity was also relative high in adrenal tissue (for 1,2,4- and 1,3,5-) and in the epidymis (for 1,2,3-). The concentrations were generally higher after dosing with 1,3,5-TCB than after dosing with the other isomers. After 7 days tissue concentrations of 1,2,3- and 1,2,4-TCB declined to very low or background levels. In the case of 1,3,5-TCB significant levels of radioactivity were still measured in the tissues after 56 days. Excretion data were given of 1,2,3- and 1,3,5-TCB; within 24 hours 92% and 83% of the administered dose of 1,2,3- and 1,3,5-TCB, respectively, was excreted. After 48 hours an additional 4% of both compounds was excreted (Chu et al., 1987). In male rats given a single oral dose of ^{14}C-labelled 1,2,4-TCB (50 mg.kg^{-1} bw) the highest levels of the label were found in the adipose tissue and to a lesser content in skin, muscle and intestine. Other organs did not show significant increased

levels. After 3 and 7 days the adipose tissue showed only slightly higher levels than the other organs. The excretion into the urine and the faeces was about 66% and 17% of the given dose, respectively, after 7 days. The urine contained a mixture of conjugated forms (about 90%) and free (unconjuated) forms (10%). The amount of unchanged 1,2,4-TCB and halogenated derivatives (1,2-, 1,3- and 1,4-DCB's) in the breath amounted to about 2.1% of the given dose. Comparing the biliary excretion of two rats (45%) with the faecal excretion (20%), an enterohepatic circulation of TCB and its metabolites is indicated. (Tanaka et al., 1986).

Following a single oral administration 10 $mg.kg^{-1}$ bw of ^{14}C-labelled 1,2,4-TCB to 16 rats and 2 rhesus monkeys urine was collected and metabolites determined. By 24 hours rats excreted 84% of the administered dose in the urine and monkeys 40%. The amounts in the faeces were 11% for rats and less that 1% for monkeys. Based on the urinary metabolite pattern there appeared to be a species difference between rat and monkey in the metabolism of 1,2,4-TCB. The initial formation of arene oxides is identical in both species. In rats the next step is conjugation with glutathion, whereas in monkeys hydrolysis of arene oxides occurs. The resulting dihydrodiol is excreted as a glucuronide. The slower excretion of 1,2,4-TCB by monkeys compared to rats could be (partly) explained by this (Lingg et al., 1982).

After oral administration of the major (urinary) metabolites of 1,2,3-TCB in the rabbit were found to be 2,3,4-trichlorophenol, 2,3,6- and 3,4,5-trichlorophenol were minor metabolites. The major metabolites of 1,2,4-TCB were 2,4,5- and 2,3,5-trichlorophenol. Three metabolites of 1,3,5-TCB were found; 2,3,5- and 2,4,6-trichlorophenol and a third metabolite, which was probably a dichlorobenzene (Kohli et al., 1976).

Following a single oral dose of 500 $mg.kg^{-1}$ bw of 1,3,5-TCB two rabbits expired in 9 days about 10% of the dose unchanged and about 1% as MCB. In the urine from the first 3 days 2,4,6-trichlorophenol was predominant, whereas from days 4 to 9 the monochlorophenols became more important. The main bulk was found unchanged in the tissues and gut contents 8-9 days after dosing (Parke and Williams, 1960).

Other routes of exposure

After intravenous administration of 1,2,4-TCB to 16 rats and 2 rhesus monkeys the urine was collected at 24 hours and metabolites were determined. The monkey and the rats had excreted 22% and 78% of the administered dose in the urine, respectively. Rats excreted 7% in the faeces, this amount was not determined by the two monkeys. For further information on metabolite patterns and the apparent difference in metabolism between rats and monkeys, see "oral exposure" (Lingg et al., 1982).

Placental transfer

In a toxicokinetic study incorporated into a teratogenicity study it was found that none of the three TCB isomers accumulates in the fetus of rats (given oral doses up to 300 $mg.kg^{-1}$ bw of 1,2,4-TCB and doses up to 600 $mg.kg^{-1}$ bw of 1,2,3- and 1,3,5-TCB by gavage on days 6 through days 15 of gestation) (Black et al., 1988).

Tetrachlorobenzenes (1,2,3,4-, 1,2,3,5- and 1,2,4,5-)

Oral exposure

Male rats were given oral doses of 10 $mg.kg^{-1}$ bw of ^{14}C-labelled 1,2,3,4-, 1,2,3,5- and 1,2,4,5-TeCB. In the case of 1,2,3,4-TeCB after 48 hours 51% of the administered dose was excreted (15% and 36% in urine and faeces, respectively). 1,2,3,5-TeCB was excreted for 25% and 21% into the urine and the faeces, respectively. The excretion of 1,2,4,5-TeCB was much slower. After 48 hours only 8% of the dose given was excreted (6% and 2% in urine and faeces, respectively). With regard to 1,2,3,4-TeCB the urinary metabolites were 2,3,4,5-tetrachloropenol (the major one) and 2,3,4,6-tetrachlorophenol (the minor one). The major metabolite of 1,2,3,5-TeCB was 2,3,4,6-tetrachlorophenol (49% of the excreted material) and that of 1,2,4,5-TeCB was 2,3,5,6-tetrachlorophenol (61%) (Chu et al., 1984).

After single oral doses of 1,2,3,4-, 1,2,3,5- and 1,2,4,5-TeCB the urinary metabolites of rabbits were determined. The metabolites that were formed after administration of 1,2,3,4-TeCB were 2,3,4,5- and 2,3,4,6-tetrachlorophenol. The same metabolites appeared in the urine after the rabbits were given 1,2,3,5-TeCB and in addition 2,3,5,6-tetrachlorophenol

and a more polar product (which was not further determined) were formed. After dosing 1,2,4,5-TeCB only one metabolite was formed, namely 2,3,5,6-tetrachlorophenol (Kohli et al., 1976).
In the urine of squirrel monkeys, repeatedly exposed to ^{14}C-labelled 1,2,3,4-TeCB at a dose of 100 $mg.kg^{-1}$ bw in corn oil by gavage, N-acetyl-s-(2,3,4,5-tetrachlorophenyl) cysteine was found to be the major metabolite. A minor metabolite was identified as 2,3,4,5-tetrachlorophenol. This is in contrast with the data on rabbits and rats, in which the tetrachlorophenols are major metabolites (Schwartz et al., 1985).

Placental transfer
In a teratogenicity study on rats the amounts of the three TeCB-isomers were determined in maternal and fetal tissues after oral exposure. In the maternal tissues the levels of 1,2,3,4- and 1,2,3,5-TeCB were somewhat and those of 1,2,4,5-TeCB strongly (about 100-fold more than the two other isomers) increased. Perirenal fat contained in all cases the highest levels. In fetal tissues treatment with 1,2,3,4- and 1,2,3,5-TeCB had not resulted in higher levels, whereas treatment with 1,2,4,5-TeCB did increase those levels significantly (Kacew et al., 1984).

Pentachlorobenzene

Oral exposure
In male and female rats fed PeCB at dietary concentrations of 0, 125, 250, 500 or 1,000 $mg.kg^{-1}$ for 100 or 180 days, respectively, a dose dependent accumulation of PeCB in adipose tissue was found. The concentration in the tissue was about 2 times the dietary concentration (Linder et al., 1980).
After a single oral dose of PeCB two metabolites were detected in the urine of rabbits, which were pentachlorophenol and 2,3,4,5-tetrachlorophenol (Kohli et al., 1976).

Hexachlorobenzene

Oral exposure

In female rats orally treated with ^{14}C-labelled HCB it appeared that the extent of intestinal absorption depends on the form of application. When given as a solution in oil about 80% was absorbed, regardless of the dose administered (16, 120 or 970 mg.kg^{-1} bw). When given as an aqueous suspension about 20% was absorbed of the lowest dose and about 6% of the higher doses (Koss and Koransky, 1975). Following oral administration of HCB to rats highest concentrations were reported in fat, muscle and skin tissues. Other tissues (e.g. kidneys, lungs, heart, spleen and blood) generally contained lower amounts (EPA, 1984).

After rats were treated with a single oral dose of 12 or 30 mg.kg^{-1} bw of HCB in cottonseed oil about 22% was excreted unchanged in the faeces (Albro and Thomas, 1974). HCB is metabolized slowly into other chlorinated bezenes, chlorinated phenols and other minor metabolites and forms of glucuronide and glutathion conjugates. The tissues were found to contain mainly unchanged HCB together with only small amounts of metabolites. Metabolites were mainly excreted in the urine, the faeces contained only small amounts of metabolites. The excretion of HCB from treated animnals is slow and occurs mainly through the faeces. It is characterized by an initial rapid phase followed by a slow phase (EPA, 1984). The metabolism of HCB was reviewed extensively by Renner (1981), Renner et al. (1985) and Renner (1988).

After female rhesus monkeys (5) were given oral doses of 8-128 mg.kg^{-1} bw a day during 60 days, highest HCB contents were found in tissues containing high lipid amounts: body fat, bone marrow and the adrenal cortex. Adrenal medulla, liver, brain, and kidney contained smaller amounts. In one very thin monkey, with almost no adipose tissue higher HCB amounts were found in non-fat tissues and serum than in adipose tissue. This animal also had high brain levels and showed severe neurological damage. The authors noted that based on these data physically thin persons may be more susceptible to HCB poisoning (Knauf and Hobson, 1979). Male and female rhesus monkeys were given daily doses of 110 μg ^{14}C-labelled HCB (about 33 μg.kg^{-1} bw) for 18 months. At the end of the exposure period about 6% of the administered dose was excreted in the urine and about 50% in the faeces of both sexes. The

main urinary metabolite was pentachlorophenol (more than 50% of the excreted amount). Other metabolites were pentachlorobenzene, tetrachlorobenzenes and unchanged HCB. Faecal excretion consisted of 99% of HCB (Rozman et al., 1978).

Other routes of exposure

After rats were given single intraperitoneal doses of ^{14}C-labelled HCB (4 mg.kg^{-1} bw) radioactivity was highest in fat and in the skin. Liver, brain, kidney, blood and muscle contained amounts about 50-fold lower than fat (Koss and Koransky, 1975). After rats were given 2 or 3 intraperitoneal doses of ^{14}C-labelled HCB (total dose 260 or 390 mg.kg^{-1} bw) the major urinary metabolites were pentachlorophenol, tetrachlorohydroquinone and pentachlorothiophenol, together accounting for more than 90% of the radioactivity. A minor metabolite was tetrachlorothiophenol. The faeces contained pentachlorophenol and pentachlorothiophenol. After 4 weeks the 2/3 of the administered dose was retained in the body and about 1/3 was excreted (for 50% unchanged HCB) (Koss et al., 1976).
After rats were given a single intraperitoneal dose of 4 mg.kg^{-1} bw of ^{14}C-labelled HCB (in oil solution) within 2 weeks 34% of the administered dose was excreted in the urine and 5% in the faeces. The percentage unchanged HCB in the urine and faeces were 4% and 80% of the excreted amounts, respectively (Koss and Koransky, 1975).

Placental transfer

Placental transfer of HCB has been demonstrated in rats, mice, hamsters, monkeys and guinea pigs. After pregnant rats were administered orally doses of 5 to 120 mg.kg^{-1} bw of HCB during days 6-16 of pregnancy, HCB residues were determined in maternal and fetal livers, fetal brain and whole fetus. The compound crossed the placenta and accumulated in the fetus in a dose-dependent way. The maternal liver contained the highest amounts of HCB (up to 86 mg.kg^{-1}), followed by the fetal liver (up to 36 mg.kg^{-1}), whole fetus and fetal brain (18 mg.kg^{-1}) (Villeneuve and Hierlihy, 1975). The tissue distribution of HCB was studied in pregnant hamsters and guinea pigs given 0, 1.0, 10.0 or 50.0 mg.kg^{-1} bw (in corn oil) a day by gavage from day 5 to 10 of gestation for hamsters and from day 14 to 19 for guinea pigs. Samples of fat, thymus, skin, liver, lung, brain, spleen, urinary bladder, muscle,

plasma and blood were analyzed as well as fetuses placentas and yolk sacs. In maternal hamsters fat had the highest accumulation of HCB (up to 2,260 $mg.kg^{-1}$ wet weight at the highest dose) and followed by thymus and the skin. For all organs, including fetus and placenta, there was a dose-response relationship. The concentrations in the fetus (up to 13 $mg.kg^{-1}$ wet weight at the highest dose) were lower than in the placenta. Most tissues of the guinea pig also showed a dose-dependent increase in levels, with highest amounts in fat (1,460 $mg.kg^{-1}$), thymus, skin and liver. The fetus contained also less HCB (4 $mg.kg^{-1}$) than the placenta (Courtney et al., 1985).
The tissue distribution of HCB administered orally to pregnant and nonpregnant mice was found to be similar. Highest concentrations were found in fat, thymus, skin and urinary bladder (Courtney et al., 1976).
The transfer of HCB to nursing infant rhesus monkeys from lactating mothers receiving 64 $mg.kg^{-1}$ bw a day for 60 days was studied. The study included three mother-infant pairs. Milk levels were about 12 times higher than the maternal serum levels. Serum levels were higher in the infants than in their mothers. In the fetus fat, bone marrow, lymph nodes and adrenals contained highest HCB levels (Bailey et al., 1980).

1.1.2 Human studies

Monochlorobenzene

Oral exposure
MCB was administered orally to a male volunteer three times at a dosage of 0.3 $mmol.kg^{-1}$ bw (34 $mg.kg^{-1}$ bw) and the excretion of two metabolites (MA and 4-chlorocatechol) was determined. It appeared that 4-chlorocatechol was the main metabolite (Ogata and Shimada, 1983).

Inhalatory exposure
In the urine of 11 workers exposed to about 3.15 ppm MCB (TWA-value) 4-chlorocatechol, 2-chlorophenol, 3-chlorophenol, 4-chlorophenol and MA accounted for 76.9%, 3.2%, 7.1%, 12.4% and 0.4%, respectively, of the total amount excreted (Yoshida et al., 1986). 4-Chlorocatechol also appeared to be the main metabolite in the urine from two men inhalatory exposed to MCB (0.84 ppm x 415 min or 0.5 ppm x 228 min) (Ogata and Shimada, 1983).

1,4-Dichlorobenzene

Inhalatory exposure

The urinary excretion of 2,5-dichlorophenol, a metabolite of 1,4-DCB, was studied among workers exposed to 1,4-DCB in various industrial plants. A roughly lineair relationship was observed between the urinary excretion of 2,5-dichlorophenol at the end of the work shift and exposure to 1,4-DCB. It was concluded that 2,5-dichlorophenol could be used as index of exposure to 1,4-DCB (Pagnotto and Walkley, 1965). In another study the relationship between occupational exposure to 1,4-DCB and urinary excretion of the unchanged compund in the urine of 4 workers was studied. A significant relationship was found between the difference of 1,4-DCB urinary concentration at the beginning and end of a working day and the 1,4-DCB environmental concentration (Ghittori et al., 1985).

Summary and conclusions "kinetics and metabolism"

MCB is absorbed after oral and inhalatory exposure. Absorption after dermal treatment of rabbits seemed minimal or negligible. Shortly after oral treatment of rats MCB was found in all tissues examined, with fat tissue containing highest amounts. A rapid tissue clearance was observed. The principal metabolites of MCB were found to be 4-chlorophenol, 4-chlorocatechol and 4-chlorophenyl-mercapturic acid. The majority of the metabolites were excreted in the urine and only small amounts were present in the faeces. After inhalatory exposure the percentage of MCB exhaled by rats increased with increasing exposure concentrations.

Experimental studies indicate that DCB's are absorbed after different routes of uptake. After oral, inhalatory or subcutaneous exposure tissue distribution appeared to be similar. Highest levels occurred in fat, liver, kidneys and lungs. After inhalatory exposure to 1,4-DCB a difference in organ distribution was observed between male and female rats; females had significant higher levels of 1,4-DCB in their livers, whereas the kidneys of the males contained significant higher levels compared to those of the female rats. 1,2-DCB and 1,4-DCB were mainly oxidized to 3,4- and 2,5-dichlorophenol, respectively, which were further conjugated. Within 24

hours after exposure 50% to 90% of the administered dose was excreted in the urine as metabolite. A small amount was excreted in the faeces. DCB's were reabsorbed via the enterohepatic circulation.

TCB's are absorbed after oral, inhalatory and dermal exposure. In rats orally treated highest amounts were found in liver, kidneys, fat tissue, bladder and gastro-intestinal tract. Increased contents were also reported for skin and muscle tissues. Tissue levels were generally highest after treatment with 1,3,5,-TCB. TCB's were metabolized to trichlorophenols, which were further conjugated with glutathion. In contrast to rats, monkeys did not use glutathion in their metabolism of TCB's. Rats excreted within 24 hours after an oral dose about 70% in the urine and about 15% in the faeces. By monkeys the excretion occurred slower; after 24 hours 40% was excreted in the urine and less than 1% in the faeces. TCB's were also reabsorbed in via the enterohepatic cyclus.

TeCB's are absorbed after oral exposure. No data are available on absorption after inhalatory or dermal exposure. In rats the tissue distribution patterns were similar after dosing the different isomers. TeCB's occurred in fat tissue, skin, kidneys, liver and guts and 1,2,4,5-TeCB resulted in the highest concentrations. From a teratogenicity study it appeared that 1,2,3,4- and 1,2,3,5-TeCB did (hardly) not accumulate in maternal rats or in fetusses. In contrast, 1,2,4,5-TeCB did accumulate in both maternal animals and fetusses. Rats and rabbits mainly metabolized TeCB's to chlorophenols, which were conjugated. In the urine of monkeys a N-acetyl-S-compound appeared to be the major metabolite. After oral treatment rats excreted within 48 hours 50% of the dose into the urine and the faeces. The excretion of 1,2,4,5-TeCB was slower; within 48 hours only 8% was excreted.

PeCB is absorbed after oral exposure. A dose-dependent accumulation in fat occured in rats. In rabbits PeCB was metabolized to pentachlorophenol and 2,3,4,5-tetrachlorophenol. No further data were available.

HCB is absorbed after oral exposure. No data regarding absorption after inhalatory or dermal exposure were available. HCB administered in an oil solution was absorbed for about 80% and HCB in an aqueous solution for about 20%. Monkeys concentrated HCB in fat tissue, bone marrow and adrenals. Rats also had high amounts in skin- and muscle tissues. HCB has been demonstrated to transfer the placenta in various species and to

accumulate dose-related in the fetusses. The compound was metabolized slowly, the principal metabolites were pentachlorophenol, tetrachlorophenol, tetrachlorothioquinone and pentachlorothiophenol. Lower chlorinated chlorobenzenes and chlorophenols wee also formed as well as different conjugates. The majority of the metabolites were excreted in the urine, whereas unchanged HCB was mainly excreted in the faeces.

The metabolic behaviour of the chlorobenzenes changes gradually with an increasing degree of chlorination. With an increasing number of chloroatoms the substances become more lipofile and accumulate to a greater extent in fat tissue and "fat-rich" organs. The biotransformation and the elimination via the urine decrease with an increasing number af chloroatoms; the difference in elimination halflife times between for example 1,4-DCB and HCB is estimated to be at least a factor of 10. Especially HCB is biotransformed very slowly and its excretion is mainly via the faeces. The tissues contain predominantly unchanged HCB.

1.2 TOXICITY

1.2.1 animal studies

Monochlorobenzene

Acute toxicity

Data on the acute toxicity of MCB are given in table 1.1. After acute exposure effects were described on the liver, kidney, lungs and central nervous system (narcotic signs and depression) (EPA, 1984).

Subacute toxicity

Oral exposure

Exposure of male and female rats to 0, 125, 250, 500, 1,000 or 2,000 $mg.kg^{-1}$ bw of MCB in corn oil by gavage for 14 days resulted in death at the two highest doses. In the groups receiving up to 500 $mg.kg^{-1}$ no adverse effects were observed (NTP, 1985a). An effect on the porphyrin metabolism was observed in rats receiving 1,140 $mg.kg^{-1}$ bw for 5 days. This effect was, however, much less than the effect caused by more highly chlorinated congeners (Rimington and Ziegler, 1963). Exposure of male and female mice to 0, 30, 60, 125, 250 or 500 $mg.kg^{-1}$ MCB in corn oil by gavage for 14 days did not result in toxicity or mortality (NTP, 1985a).

Subchronic toxicity

Oral exposure

Male and female rats and mice were exposed to 0, 60, 125, 250, 500 or 750 $mg.kg^{-1}$ bw of MCB (in corn oil) by gavage, 5 days a week for 13 weeks. The two highest doses decreased survival and final mean body weight of both species. An increase in urinary uroporphyrin (rats) and coproporphyrin excretion (rats, mice) was observed at these levels. At $\geq$125 $mg.kg^{-1}$ bw toxicity was observed in several tissues; increased liver- and kidney-weights, a dose-dependent hepatocellular necrosis, nephropathy and depletion of bone marrow, spleen and thymus in both species. Only male

animals showed an effect at 60 $mg.kg^{-1}$ bw; splenic and heart weights were slightly decreased in male rats and male mice, respectively (NTP, 1985a). In a feeding study rats received 12.5, 50, 100 or 250 $mg.kg^{-1}$ bw of MCB a day for 93-99 days. The highest dose resulted in retarded growth and liver and kidney weights were increased at 100 and 250 $mg.kg^{-1}$ bw. No effects were reported for the lowest doses (Monsanto, 1967, cited by Knapp et al., 1971 [abstract] and EPA, 1984). In a study conducted by Flury and Zernik rats were exposed to 14, 144 or 288 $mg.kg^{-1}$ bw for 5 days a week during 192 days. The two highest doses resulted in effects on the liver and kidneys. The no-effect-level was 14 $mg.kg^{-1}$ bw (Flury and Zernik, 1931, cited by Deichmann, 1981).

MCB was administered to dogs at doses of 27.3, 54.5 or 272.5 $mg.kg^{-1}$ bw a day on 5 days a week for 93 days by means of a capsule. Exposure to the highest dose resulted in increased mortality and effects on the liver, kidneys, gastro-intestinal mucosa and haematopoietic tissue and in changes in several blood parameters. Dogs in the mid dose group showed diarrhea, vomiting and minimal histologic changes. The no-effect-level was 27.3 $mg.kg^{-1}$ bw (Monsanto, 1967, cited by Knapp et al., 1971 [abstract] and EPA, 1984).

Inhalatory exposure

The EPA reported a number of subchronic inhalation studies (dog, rat, rabbit) with (no-) effect-levels varying widely. One east-european study (Khanin, 1977, unpublished) reported hepatic and renal effects at a dose as low as 0.1 $mg.m^{-3}$ (rat), whereas other studies resulted in no-effect-levels of 750 $mg.m^{-3}$ (dog) or 2,000 $mg.m^{-3}$ (rat) (Monsanto Company, 1978, unpublished). In a study reported by Dilley (1977, unpublished) a concentration of about 345 $mg.m^{-3}$ was considered to be a marginal effect level in rats; a decreased SGOT occurred after 24 weeks of exposure, but exposure to about 100 $mg.m^{-3}$ resulted in neurotoxic effects in other studies (EPA, 1984).

Chronic toxicity

Oral exposure

Groups of 50 male and 50 female rats and groups of 50 female mice were administered MCB in corn oil by gavage, 5 days a week for 103 weeks, at doses of 0 (vehicle control), 60 or 120 $mg.kg^{-1}$ bw (carcino-genicity study). A group of 50 male mice received doses of 0, 30 and 60 $mg.kg^{-1}$ on the same schedule. Untreated controls consisted of 50 male and 50 female rats and mice. In male rats a significant increase in liver noduli was observed only in the highest dose group. No compound-related clinical signs of toxicity were observed at any time during the studies in male or female rats or female mice. A minimal to mild hepatocellular necrosis was observed in some of the treated animals as well as in some of the controls. The evidence for mild MCB-induced hepatocellular necrosis was considered equivocal (NTP, 1985a).

Reproduction and teratogenicity

Inhalatory exposure

In a two-generation reproduction study rats were exposed to 0, 50, 150 or 450 ppm of MCB (0, 230, 690 and 2070 $mg.m^{-3}$) for 10 weeks prior to mating, during mating, gestation and lactation. All F2 pups were observed through weaning at which time they were killed. Exposures up to 450 ppm did not have any adverse effects on reproductive performance or fertility of male or female rats. Effects on the liver and kidneys were observed in F1 and F0 male rats. In F0 and F1 males from the highest dose groups effects on the testicular germinal epithelium were seen. The relationship of these testicular changes to exposure to MCB is unclear according to the authors, because there was no increase in intensity and/or incidence among F1 males that had longer exposure (Nair et al., 1987). The embryotoxic and teratogenic potential of inhaled MCB was evaluated in rats and rabbits exposed to 0, 75, 210 or 590 ppm of MCB (0, 345, 966, 2714 $mg.m^{-3}$) via inhalation for 6 hr/day during days 6 through 15 (rats) or days 6 through 18 (rabbits) of gestation. Inhalation of 590 ppm caused elevated liver weights in both species and decreased body weight gain and feed consumption in rats. Fetal effects were limited to a sligh delay in skeletal

development which only occurred in rats exposed to 590 ppm, a maternally toxic concentration. No further embryotoxic or teratogenic effects were observed (John et al., 1984).

Dichlorobenzene (1,2-, 1,3- and 1,4-)

Acute toxicity

Data on the acute toxicity of DCB are given in table 1.1. Acute effects of 1,2-DCB and 1,4-DCB included central nervous system depression and liver and kidney damage. Acute inhalation also caused eye and nose irritation.

Subacute toxicity

Oral exposure

Groups of 5 male and female rats were given 0, 60, 125, 250, 500 or 1,000 $mg.kg^{-1}$ bw of 1,2-DCB in corn oil for 14 days. At the highest dose all animals died, but no increased mortality was seen up to 500 $mg.kg^{-1}$ bw. A dose related decrease in body weight (gain) occurred at 125 and 500 $mg.kg^{-1}$ bw in both sexes (depression up to 10%) (NTP, 1985b). Oral administration of 455 $mg.kg^{-1}$ bw 1,2-DCB for 15 days or 770 $mg.kg^{-1}$ bw 1,4-DCB for 5 days caused the induction of hepatic porphyria in rats (Rimington and Ziegler, 1963). Two studies were conducted with 1,2-DCB in mice. In the first study (exposure between 250 and 4,000 $mg.kg^{-1}$ bw) nearly all animals died, whereas in the second one (exposure between 30 and 500 $mg.kg^{-1}$ bw) no increased mortality occurred. The reason for the discrepancy between survival in the first versus the second study is not known. Results from a 13-week study (see subchronic exposure) were, however, more consistent with the second study than with the first one (NTP, 1985b).

Daily exposure of rats to 800 $mg.kg^{-1}$ bw of 1,3-DCB for 9 days caused hepatic porphyria (Poland et al., 1981, evaluated by the EPA).

Groups of 5 male and female rats were exposed to 60, 125, 250, 500 or 1,000 $mg.kg^{-1}$ bw of 1,4-DCB in corn oil by gavage for 14 days. No toxic effects were seen. In a 14-day study performed at higher doses increased mortality occurred at $\geq$1,000 (in females) and a decrease in body weight (gain) was observed at 500 $mg.kg^{-1}$ bw (in males) (NTP, 1987). Rats administered 20-40

mg.kg^{-1} bw 1,4-DCB for 14 days showed an increased activity of several metabolic enzymes (glucuronyltransferase and O-ethyl O-p-nitrophenylphosphonothioate). The no-effect-level was 10 mg.kg^{-1} bw (Carlson and Tardiff, 1976). Exposure of rats (two per group) to 10, 100 or 500 mg.kg^{-1} bw of 1,4-DCB by gavage 5 days a week for 4 weeks resulted in liver- and kidney toxicity at the highest dose. No toxic effects occurred in the lower dose groups (Hollingsworth et al., 1956).
Two 14-day studies with 1,4-DCB were conducted with mice. In the first study in which 5 male and female mice were exposed to 1,4-DCB between 250 and 4,000 mg.kg^{-1} bw a scattered pattern of deaths in all dose groups occurred. In a second study performed at lower doses (60-1,000 mg.kg^{-1} bw) no compound-related deaths occurred nor decreased body weight (gain) (NTP, 1987).

Subchronic toxicity

Oral exposure
Groups of 10 male and female rats and mice were administered 1,2-DCB at doses of 0, 30, 60, 125, 250 or 500 mg.kg^{-1} bw in corn oil for 5 days a week during 13 weeks. In rats the highest dose caused increased mortality among females. Microscopically effects were found on the liver (≥125 mg.kg^{-1} bw), thymus and kidney (500 mg.kg^{-1} bw). Minimal increases in serum cholesterol levels in males (at 30 and ≥125 mg.kg^{-1} bw), in serum glucose levels (at 30 and ≥125 mg.kg^{-1} bw) and serum total protein levels (at all doses) in females. At the lower doses (30 and 60 mg.kg^{-1} bw) these parameters were not consistent and/or dose-related increased. Therefore these minimal changes were considered to be not biologically significant. The no-effect-level for rats was 60 mg.kg^{-1} bw. In mice there was also an increased mortality in the highest dose group. This dose also caused (microscopically observed) effects on the liver, thymus, muscle, spleen and heart. Only the liver showed lesions at 250 mg.kg^{-1} bw. For mice the no-effect-level was 125 mg.kg^{-1} bw (NTP, 1985b). Exposure of rats to 19, 188 or 376 mg.kg^{-1} bw of 1,2-DCB (in olive oil) by gavage 5 days a week for a total of 138 doses in 192 days, resulted in slight liver- and kidney toxicity at the highest dose. The mid dose caused slight increased liver and kidney weights, whereas the lowest dose was without effects (Hollingsworth et al.,

1958). In mice, exposed to 0, 30, 60, 125, 250 or 500 mg.kg^{-1} bw in corn oil by gavage during 13 weeks, the highest dose caused increased mortality. These dose also caused toxic effects on several organs liver, kidney, thymus, spleen, heart and muscle). At 250 mg.kg^{-1} bw the only compound-related effects was liver lesions and no effect were found at 125 mg.kg^{-1} bw. The minor hematological changes occurring at the two lower doses (increase in white blood cell counts, increase in relative number of lymphocytes) and the increased relative splenic weights in females were considered to be not biologically significant. The no-effect-level appeared to be 125 mg.kg^{-1} bw (NTP, 1985b). In one study oral exposure of rats to doses varying between 0.01 and 0.1 mg.kg^{-1} bw for 5 months resulted in effects on the hematopoietic system. Because this study was not available for evaluation, it is left out of consideration (Varshavskaya, 1967, cited in EPA, 1984).

In two 13-week studies rats were exposed to 1,4-DCB at doses between 37.5 and 1,500 mg.kg^{-1} bw in corn oil by gavage. Increased mortality occurred at 900 mg.kg^{-1} bw. Male rats were more sensitive to 1,4-DCB than female rats, and the kidneys seemed to be the most sensitive organ. Renal tubular regeneration was observed in male rats receiving ≥300 mg.kg^{-1} bw as well as a decrease in body weight (gain) and changes in several blood parameters. The no-effect-level for rats appeared to be 150 mg.kg^{-1} bw (NTP, 1987). Exposure of female rats to 19, 188 or 376 mg.kg^{-1} bw of 1,4-DCB (in olive oil) by gavage for a total of 138 doses in 192 days, resulted in increased liver and kidney weights, focal necrosis and slight cirrhosis of the liver at the highest dose. Liver and kidney weights were increased at 188 mg.kg^{-1} bw, whereas no effects were seen at the lowest dose. Rabbits exposed to 1,000 mg.kg^{-1} bw (92 doses in 219 days) or 500 mg.kg^{-1} bw (263 doses in 367 days) of 1,4-DCB (in olive oil) by gavage showed weight loss, tremors, weakness and liver toxicity (Hollingsworth et al., 1956).

Mice were exposed to 1,4-DCB at doses between 84 and 1,800 mg.kg^{-1} bw in corn oil by gavage for 13 weeks. Increased mortality occurred at 1,500 mg.kg^{-1} bw and the liver seemed to be the most sensitive organ. A doses ≥ 600 mg.kg^{-1} bw a dose-related hepatocellular degeneration occured in both males and females as well as a decrease in body weight (gain) and changes in blood and clinical parameters. In this study the no-effect-level for mice was 338 mg.kg^{-1} bw (NTP, 1987).

Inhalatory exposure

Exposure of 20 rats, 8 guinea pigs, 2 rabbits and 2 female monkeys to 1,2-DCB at a concentration of 93 ppm (560 $mg.m^{-3}$; 7 hrs/day, 5 d/wk for up to 7 months) did not result in adverse effects. Exposure of male and female rats and guinea pigs and female mice to 49 ppm (290 $mg.m^{-3}$; 7 hrs/day, 5 days a week for 6.5 months) did also not result in adverse effects (Hollingsworth et al., 1958).

In similar studies inhalation of 798 ppm of 1,4-DCB (4790 $mg.m^{-3}$; 8 hrs/day 5 d/wk with a total of 20-69 exposures) caused increased mortality among rats, rabbits and guinea pigs. The symptoms included marked tremors, weakness, loss of weight, eye irritation and unconsciousness as well as histopathological changes in liver, kidney and lungs. At dose of $\geq$173 ppm (1038 $mg.m^{-3}$; 7 hrs/day, 5 days a week for 16 days) several slight effects were seen in rats (on liver, kidneys and lungs), in guinea pigs (on the spleen and lungs) and in rabbits (lungs). Inhalation of 96 ppm (576 $mg.m^{-3}$; 7 hrs/day, 5 d/wk during 6-7 months) was without effects (Hollingsworth et al., 1956). Subchronic exposure of male and female rats and female mice to 75 or 500 ppm of 1,4-DCB (450 or 3000 $mg.m^{-3}$; 5 hrs/d on 5 d/wk) did not cause toxicity, except for male rats in the highest dose group. Male rats showed increased liver-and kidney weights and slightly elevated urinary coproporphyrin excretion (unpublished data from Riley et al., 1980, summarized by Loeser and Litchfield, 1983).

Chronic toxicity

Oral exposure

Groups of 50 male and 50 female rats and mice were administered 1,2-DCB in corn oil by gavage at doses of 0 (vehicle control), 60 or 120 $mg.kg^{-1}$ bw, 5 days a week during 103 weeks. Untreated controls consisted of 50 male and 50 female rats and mice. An increase in tubular regeneration in the kidneys of male mice was only significant in the highest dose group (control 17%, low dose 24% and high dose 35%). No other nonneoplastic changes were observed. Data considering carcinogenicity are described in 1.4 (NTP, 1985b).

In a two year (carcinogenicity-) study groups of 50 male rats were given 1,4-DCB by gavage at doses of 0, 150 or 300 $mg.kg^{-1}$ bw and female rats and

male and female mice were given 0, 300 or 600 mg.kg^{-1} bw for 5 days a week during 103 weeks. In rats the incidence of nephropathy was observed in both sexes. An increased incidence of parathyroid hyperplasia occurred in males. In mice the incidences of liver lesions increased (both sexes). Effects were further seen on the kidney (nephropathy) and the haematopoietic system (lymphoid hyperplasia). Data considering the carcinogenicity are described in 1.4 (NTP, 1987).

Reproduction and teratogenicity

Oral exposure

Groups of pregnant rats were treated with 0, 250, 500, 750 or 1,000 mg.kg^{-1} bw of 1,4-DCB a day during days 6 through 15 of gestation by gavage. The incidence of most common malformations in fetuses was not increased. A significant increase in the number of skeletal variations was observed at 750 mg.kg^{-1} bw or more and a dose-related increase in the frequency of an extra rib was seen at 500 mg.kg^{-1} bw or more. At doses of 500 mg.kg^{-1} bw or more signs of maternal toxicity were seen, resulting in a reduction in food consumption and weight gain. The authors stated that the embryotoxicity could be a consequence of maternal suffering rather than of a direct effect of the chemical itself and concluded that 1,4-DCB was not teratogenic in the rat (Giavani et al., 1986).

Inhalatory expoure

Rats and rabbits were inhalatory exposed to 0, 100, 300 or 400 ppm 1,2-DCB (0, 600, 1800 or 2400 mg.m^{-3}) and rabbits to 0, 100, 300 or 800 ppm 1,4-DCB (0, 600, 1800 or 4800 mg.m^{-3}) for 6 hours a day on day 6 through 15 (rats) or 6 through 18 (rabbits) of gestation. Rats showed maternal toxicity was observed at all doses of 1,2-DCB and liver weight was significantly increased at 400 ppm. No teratogenic or embryotoxic effects were seen. In rabbits slight maternal toxicity (decreased body weight) occurred in the highest dose groups (400 ppm of 1,2-DCB and 800 ppm of 1,4-DCB). In rabbits there were also no teratogenic or fetotoxic effects (Hayes et al., 1985). Unpublished data indicate that 1,4-DCB did not cause embryotoxic, fetotoxic or teratogenic effects in rats at doses up to 500

ppm (3000 $mg.m^{-3}$) (Hodge et al., 1977, reported by Loeser and Litchfield, 1983).

Trichlorobenzenes (1,2,3-, 1,2,4- and 1,3,5-)

Acute toxicity

Oral LD50-values for TCB are given in table 1.1. After acute inhalatory exposure effects were seen on the liver, kidney and ganglion cells at all levels of the brain and the mucous membrane as well as irritation of the lungs and functional changes in the respiratory system (EPA, 1984).

Subacute toxicity

Oral exposure

The content of Cyt P-450 and activities of several enzymes were increased by oral administration of 250 $mg.kg^{-1}$ bw 1,3,5-TCB once daily for 3 days in rats (Ariyoshi et al., 1975). Oral exposure of rats to 10-40 $mg.kg^{-1}$ bw of 1,2,4-TCB for 14 days resulted in significant increased microsomal functions and enzymes (including Cyt P-450). The activity of glucuronyl-transferase decreased (Carlson and Tardiff, 1976). Induction of hepatic enzymes in rats was found for at least 16 days after administration of 1,2,4-TCB at a level of 180 $mg.kg^{-1}$ bw a day during 7 days (Smith and Carlson, 1980). In rats given 0.1 $mmol.kg^{-1}$ of 1,2,4-TCB by gavage daily during 14 days the serum arylesterase activity decreased and the liver arylesterase increased (Carlson, 1980). Exposure to 1,2,3-TCB (785 $mg.kg^{-1}$ bw) for 7 days and 1,2,4-TCB (730 $mg.kg^{-1}$ bw) for 15 days caused induction of hepatic porphyria in rats (Rimington and Ziegler, 1963). Rhesus monkeys were given daily oral doses of 1, 5, 25, 90, 125 or 174 $mg.kg^{-1}$ bw of 1,2,4-TCB for 90 days. Effects were observed at doses of $\geq$90 $mg.kg^{-1}$ bw. Additional data on this study have not been reported (Smith et al., 1978, abstract).

Inhalatory exposure

Groups of 20 rats, 4 rabbits and 2 dogs were exposed to 1,2,4-TCB (7 hr/day, 5 d/week for 6 weeks) at concentrations of 0, 30 or 100 ppm (0,

223, 742 $mg.m^{-3}$). In rats liver weight (both absolute and relative) and kidney weight (relative) increased at 100 ppm. In rabbits relative liver weight decreased at 30 and 100 ppm. Urinary excretion of porphyrins increased (reversible) in rats at 30 and 100 ppm (Kociba et al., 1981).

Other routes of exposure

Groups of 5 male and female rabbits were dermally exposed to undiluted TCB (about 70% 1,2,4-TCB and 30% 1,2,3-TCB) at concentrations of 0, 30, 150 or 450 $mg.kg^{-1}$ bw for 5 days a week during 4 weeks. Topical effects were seen in all treated rabbits. A slight increase in urinary coproporphyrin levels was observed at 450 $mg.kg^{-1}$ bw, but this was considered to be only a slight or questionable effect of treatment. Therefore it was concluded that systemic effects are unlikely to occur under conditions were there is no topical effect (Rao et al., 1982).

After immature female rats were given ip injections of 1,2,4-TCB (0, 250 or 500 $mg.kg^{-1}$ bw) on 3 consecutive days. Liver and adrenal weights were found to be increased, whereas body weight and uterus weight decreased (Robinson et al., 1981).

Subchronic toxicity

Oral exposure

Rats were given 1,2,4-TCB at daily oral doses of 0, 50, 100 or 200 $mg.kg^{-1}$ bw for (30, 60, 90 or) 120 days. After 120 days a significant increase in liver porphyrin was observed for all doses. A transient increase in liver weight occurred (Carlson, 1977). In an oral 90-day study rats were exposed to 1,2,4-TCB at doses of 0, 10, 20 or 40 $mg.kg^{-1}$ bw a day. The relative liver weights increased in the highest dose group. Enzyme activities (cyt P-450, cytochrome c reductase etc.) increased at all doses. After 30-day recovery period the effects on the enzyminduction were restricted to the two highest doses (Carlson and Tardiff, 1976).

Inhalatory exposure

Groups of 20 male and female rats were exposed to vapors of 1,3,5-TCB at concentrations of 0, 10, 100 or 1,000 $mg.m^{-3}$ for 6 hours a day, 5 days a week during 13 weeks. No changes were observed in several organs or in

blood or clinical parameters. The only effect that seemed treatment-related was found in the highest dose group; 3 males developed squamous metaplasia and hyperplasia in the respiratory epithelium of the nasal passages (due to local irritation or stress, according to the authors) (Sasmore et al., 1983). Groups of rats, rabbits and monkeys were exposed to vapors of 1,2,4-TCB at levels of about 0, 25, 50 and 100 ppm (0, 186, 370 and 742 $mg.m^{-3}$). The only compound related effects observed in these studies were transient changes in liver and kidney of rats (hypertrophy of hepatocytes, granulae in the liver, biliary hyperplasia and kidney hyaline degeneration) sacrified after 4 and 13 weeks. After 26 weeks of exposure these effects were not observed (Coate et al., 1977).

Reproduction and teratogenicity

Oral exposure

In a multi-generation study rats were exposed to 1,2,4-TCB at levels of 0, 25, 100 or 400 ppm in the drinkingwater. The study covered the period beginning with the birth of the F0 generation and continued through weaning of the F2 generation. No treatment related effects on fertility, growth, viability, locomotor activity or blood parameters were found. At the 400 ppm dose level adrenal gland enlargement was observed in both sexes of the F1 and the F2 generation at 95 days of age (Robinson et al., 1981). Female rats received 1,2,4-TCB at doses of 75, 150 or 300 $mg.kg^{-1}$ bw or doses of 150, 300 or 600 $mg.kg^{-1}$ bw of 1,2,3- or 1,3,5-TCB in corn oil by gavage on days 6 through day 15 of gestation. None of the TCB isomers produced any teratogenic of fetotoxic effects. With respect to maternal toxicity 1,2,4-TCB appeared to be the most toxic (effects at 150 $mg.kg^{-1}$ bw) and 1,2,3-TCB the least toxic (effects at 600 $mg.kg^{-1}$ bw) (Black et al., 1988). In another study female rats were given 1,2,4-TCB at doses of 0, 36, 120, 360 and 1,200 $mg.kg^{-1}$ bw by gavage on days 9 through day 13 of gestation. In the two highest dose groups maternal deaths occurred (6/6 and 2/9 rats, respectively). At 120 $mg.kg^{-1}$ bw and 360 $mg.kg^{-1}$ bw hepatic enzyme induction in maternal rats occurred. A retarded embryonic growth was obvious at 360 $mg.kg^{-1}$ bw. No teratogenic effects were observed (Kitchin and Ebron, 1983).

Tetrachlorobenzenes (1,2,3,4-, 1,2,3,5- and 1,2,4,5-)

Acute toxicity

Oral LD50-values for TeCB's are shown in table 1.1.

Subacute toxicity

Oral exposure

Rats were given daily oral doses of 660 $mg.kg^{-1}$ bw of 1,2,3,4-TeCB (in liquid paraffin) or 905 $mg.kg^{-1}$ bw of 1,2,4,5-TeCB (in 1% cellofas) during 5 or 10 days, respectively. The urinary excretion of porphyrines and porphyrin precursors was elevated by 1,2,3,4-TeCB, but not by 1,2,4,5-TeCB. The absence of this effect could have been due to poor absorption. Rats treated with both substances showed loss of weight and appetite. Nonnecrotic liver cell degeneration was also observed (Rimington and Ziegler, 1963).

Subchronic toxicity

Oral exposure

In a 90-day study rats were fed diets containing 1,2,3,4-, 1,2,3,5- or 1,2,4,5-TeCB at levels of 0, 0.5, 5.0, 50 or 500 $mg.kg^{-1}$ for 90 days. Based on body weight gain and food consumption it was estimated that the amounts ingested ranged from 0.034-34 $mg.kg^{-1}$ bw for males and from 0.042-41 $mg.kg^{-1}$ bw for females. Morphological changes in the liver and kidneys occurred in all dose groups, including the control group. No statistical test was done, but the lesions were more frequent and more severe in the animals fed 1,2,4,5-TeCB. A significant increase in liver and kidney weights as well as haematological changes were seen at the highest dose of 1,2,4,5-TeCB. The hepatic microsomal aniline hydroxylase and aminopyrine demethylase activities were increased by 1,2,4,5-TeCB at 50 and 500 $mg.kg^{-1}$ diet. No statistical significant effects were reported at a concentration of 5 $mg.kg^{-1}$ diet (corresponding to 0.34 or 0.40 $mg.kg^{-1}$ bw for males and females, respectively) (Chu et al., 1984).

Exposure of rats and rabbits to 1,2,4,5-TeCB for 8 months caused effects at doses of 0.005 and 0.05 mg.kg^{-1} bw, respectively. Because this study was not available for evaluation, it is left out of consideration (Fomenko, 1965, cited in EPA, 1984).

Chronic toxicity

Oral exposure
The 2-year study conducted by Braun et al. (1978) was considered to be inadequate and will be left out of consideration.

Reproduction and teratogenicity

Oral exposure
In a teratogenicity study all three TeCB-isomers were administered daily at doses of 50, 100 or 200 mg.kg^{-1} bw to female rats by gavage on day 6 through day 15 of gestation. Increased mortality was limited to the highest dose of 1,2,4,5-TeCB; 9 out of 10 dams died. An increase of serum cholesterol level and aniline hydroxylase activity was observed in the 50 and 100 mg.kg^{-1} bw groups of 1,2,4,5-TeCB. At the highest doses of 1,2,3,4- and 1,2,3,5-TeCB a decrease in the mean number of live fetuses per litter occurred. No teratogenic effects were seen (Kacew et al., 1984 and Ruddick et al., 1981, abstract).

Pentachlorobenzene

Acute toxicity

Oral LD50-values for PeCB are given in table 1.1. After acute oral exposure rats and mice showed tremors, weakness and labored breathing. To determine a dermal LD50 one concentration (2,500 mg.kg^{-1} bw) was tested on rats, but no toxic effect (or mortality) were seen at this dose (Linder et al., 1980).

Subacute toxicity

The content of Cyt P-450 and activities of two hepatic enzymes (aminopyrine demthylase and aniline hydroxylase) were increased by oral administration of 250 $mg.kg^{-1}$ bw PeCB once daily for 3 days in rats (Ariyoshi et al., 1975).

Subchronic toxicity

Oral exposure

In a study conducted by Linder et al. the effects of subchronic exposure of PeCB in rats was studied as a part of an investigation of the effects on reproduction. Weanling male rats were given dietary levels of 0, 125 or 1,000 $mg.kg^{-1}$ for 100 days and weanling female rats were given 0, 125, 250, 500 or 1,000 $mg.kg^{-1}$ for 180 days. Based on food consumption the daily dosages were estimated to be highest in the 1,000 $mg.kg^{-1}$ bw female group, namely 134 (in the first week) to 55 $mg.kg^{-1}$ bw after 6 months. After 67 days of treatment, both males and females were pair-bred with untreated partners. The pregnant rats were allowed to whelp and their litters were observed through weaning (see *reproduction and teratogenicity)*. No mortality nor clinical signs were obvious in the adult rats. At necropsy effects were found on the liver (at 500 and 1,000 $mg.kg^{-1}$ bw), the kidney and adrenals (at 1,000 $mg.kg^{-1}$ bw. No evidence of porphyria was observed (comparison to HCB). A dietary level of 250 $mg.kg^{-1}$ appeared to be the no-effect-level (Linder et al., 1980).

Reproduction and teratogenicity

Groups of rats were given PeCB at dietary levels of 0, 125, 250, 500 or 1000 $mg.kg^{-1}$. Both males and females were treated for 67 days before mating with untreated males or females. Pregnant females continued to receive treated diets for a total of 180 days. Treatment of males had no effect on the reproduction or survival of the pups. Significant mortality occurred in the pups of females fed 1,000 $mg.kg^{-1}$. Tremors developed 4-14 days after birth in suckling pups of mothers fed 250 $mg.kg^{-1}$ or more. By the time of weaning tremors were no longer evident. An increased relative liver weight

occurred in pups of females fed 250 $mg.kg^{-1}$ diet or more. The no-effect-level appeared to be 125 $mg.kg^{-1}$ diet (corresponding to 6.3 $mg.kg^{-1}$bw) (Linder et al., 1980). Female rats were administered PeCB at level of 0, 50, 100 or 200 $mg.kg^{-1}$ bw daily on days 6 through 15 of gestation. The number of live fetuses was not affected. The mean fetal weight was decreased in the highest dose group. The incidences of uni- and bilateral extra ribs were 4/127, 28/129, 21/122 and 63/100, respectively for the dose groups. The highest dose level also caused sternal effects (Khera and Villeneuve, 1975 and Villeneuve and Khera, 1975). In another study no embryotoxic (development or survival) or teratogenic effects were observed in mice treated with 50 or 100 $mg.kg^{-1}$ bw on days 6-15 of gestation) (Courtney et al., 1977, cited in EPA, 1984).

Hexachlorobenzene

Data concerning the toxicity of HCB to livestock have been summarized in chapter 4: Agricultural crops and livestock.

Acute toxicity

LD50-values of HCB are shown in table 1.1.

Subacute toxicity

Oral exposure

HCB has been reported to induce the activity of hepatic microsomal enzymes in mice and rats. Subacute oral exposure to HCB resulted in increased cytochrome P-450 and cytochrome b5 contents and in increased activities of aminopyrine demethylase, ϕ-aminolevulinic acid (Ariyoshi et al., 1975), aryl hydrocarbon hydroxylase and aminopyrine-N-demethylase (Cantoni et al., 1987), cytochrome c reductase (Carlson, 1978), EPN (O-ethyl-o-p-nitrophenyl phenylphosphono-thioate) detoxification and azoreductase (Carlson and Tardiff, 1976), acetanilide hydroxylase and acetanilide esterase (Carlson et al., 1979), serum and liver arylesterase, procaine esterase (Carlson et al., 1980), aniline hydroxylase, 4-nitroanisole O-demethylase, biphenyl 2- and 4-hydroxylase (Turner and Green, 1974). In a

14-day study a dietary concentration of 20 mg.kg^{-1}HCB (1 mg.kg^{-1}bw) was reported to be the highest no-effect-level for enzyme induction in rats (Tonkelaar, den, and Van Esch, 1974).

The immunotoxic potential of HCB has been investigated in weaned rats and in rats with combined pre- and postnatal exposure (for these studies see reproduction and teratogenicity). In the study with weaned rats given dietary doses of 500, 1,000 or 2,000 mg.kg^{-1} (50, 100 or 200 mg.kg^{-1} bw) for three weeks no effects were found on the phagocytizing and killing capacity of macrophages, and on parameters of the cell-mediated immunity. With respect to humoral immunity both the primary and secondary IgM and IgG responses to tetanus toxoid were significantly increased, but no difference was found in the IgM response to *Escherichia coli* LPS. Regarding cell-mediated immunity, no significant effects were found on mortality to a *Listeria monocytogenes* infection, on rejection of skin transplants and on delayed type hypersensitivity to tuberculin. No effect was found on the response of the thymus and spleen cells to several mitogens. At the intermediate and high level rats had increased spleen weights and thymus weights were decreased at the highest level (Vos et al., 1979). In contrast, experiments conducted by Loose et al. (1978a, 1978b) showed that HCB suppresses the humoral and cell-mediated immune response in mice. In this study mice received 167 mg.kg^{-1} HCB through their diet (25 mg.kg^{-1} bw) for 3 or 6 weeks. The susceptibility to malaria *(Plasmodium berghei)* infection and to bacterial endotoxins appeared to be enhanced by treatment (Loose et al., 1978a). In addition the antibody synthesis to the antigen sheep RBC was significantly depressed. All immunoglobulin concentrations, but mainly IgA, were found to be decreased (Loose et al., 1978b).

In female beagle dogs orally treated with doses varying between 50 or 150 mg.kg^{-1} bw a day for 21 days effects included enlarged livers (with histopathological changes) and physiological changes in the central nervous system (Sundlof et al., 1981).

Incresed porphyrin levels in the liver and urine have been reported for rats and rabbits. Exposure of female rats to 50 mg.kg^{-1} bw every other day during 15 weeks resulted in increased relative weights of liver, spleen, kidneys and adrenal glands. Contents of porphyrins in the liver and the urine increased. After treatment the rats were held for additional 38 weeks, in which no HCB was administered. At the end of this period organ

weights and urinary porphyrin levels returned to normal, whereas liver porphyrin levels were higher than after 15 weeks of treatment. The authors could not explain this porphyria of the liver even after treatment had stopped for longer time (Koss et al., 1978). Exposure of female rats to 100 $mg.kg^{-1}$ bw every other day for 6 weeks resulted in increased liver uroporphyrin and decreased coproporphyrin levels. These changes were due to a gradually decreased activity of uroporphyrinogen decarboxylase activity (UDA) during treatment untill it was nearly completely inhibited. After the treatment had stopped the rats were held for another 18 months. The activity of UDA continued to be inhibited for a while before it returned to normal (Koss et al., 1983). Exposure of male mice to dietary concentrations of 2.5, 25 or 250 $mg.kg^{-1}$ HCB (0.125, 1.25, 12.5 $mg.kg^{-1}$ bw) for 21 days resulted in significant lower testosteron levels in blood at the highest dose group. Mice in this dose group also had significantly increased liver and decreased prostate and seminal vesicle weights. Increased hepatic enzym activities occurred. In this study the no-effect-level was 25 $mg.kg^{-1}$ diet (1.25 $mg.kg^{-1}$ bw) (Elissalde and Clark, 1979).

Four animal species (rabbit, guinea pig, mice and rats) were given dietary concentrations of 0.5% HCB for 6 weeks. In rabbits the porphyrin metabolism was disturbed at this dose (150 $mg.kg^{-1}$ bw). In rats (250 $mg.kg^{-1}$ bw) HCB also affected the porphyrin metabolism but to a lesser content than in rabbits In guinea pigs and mice (200 and 750 $mg.kg^{-1}$ bw, respectively) severe neurological symptoms developed (Matteis, de, et al., 1961). Five female monkeys were given daily doses varying between 8 and 128 $mg.kg^{-1}$ bw by gavage during 60 days. Dose-related effects were seen on the thymus, liver, kidney and ovaries (Iatropoulos et al., 1976).

Inhalatory exposure

A study with rats demonstrated that exposure to aerosols containing approximately 35 $mg.m^{-3}$ of HCB resulted in slight changes in humoral and pulmonary cellular defenses. The slight alteration in macrophage function coupled with changes in lymphocyte responses could indicate possible immune modulation after inhalatory exposure (Sherwood et al., 1989).

Subchronic toxicity

Oral exposure

A siginicant increase in liver gamma-glutamyl transferase was observed in rats given daily doses of 997 mg.kg^{-1} bw for 60 or 90 days. The enzyme activity increased also, although less marked, in serum and in the small testine (Adjarov et al., 1982).

In most subchronic studies effects on the porphyrin metabolism were reported. In female rats given orally doses of 0, 50, 100 or 200 mg.kg^{-1} bw during 30-120 days liver and urine porphyrin levels were elevated at all doses. All rats showed increased liver weights. The responses were dose- and time-dependent (Carlson, 1977). Rats given dietary concentrations of 0.2% HCB (100 mg.kg^{-1} bw) for 45-100 days showed increased liver weights and increased cytochrome P-450 and cytochrome b5 levels. After 15 days HCB feeding porphyria was observed (Stonard, 1974). Of a total of 33 rats which were fed 100 mg.kg^{-1} bw during 50 days, 13 died in the first 4 weeks. In the remaining rats a significant increase in urinary excretion of porphyrins and porphyrin precursors was noted as well as hepatomegaly and liver cell degeneration (Ockner and Schmid, 1961). Microsomal enzyme induction and an increased urinary excretion of porphyrins and porphyrinprecursors were found in rats treated with a diet containing 0.2% HCB (100 mg.kg^{-1} bw) for 100 days (Lissner et al., 1975). The livers of rats fed a diet containing 0.2% HCB (100 mg.kg^{-1} bw) for 9 weeks were studied with an light and electron microscopy. A marked enlargement of the hepatocytes was observed (Medline et al., 1973). Female rats which were fed dietary concentrations of 200 mg.kg^{-1} of HCB (10 mg.kg^{-1} bw) for 15 weeks developed a massive porphyria (due to depression of uroporphyrinogen). In males no effects were seen, which indicates that female rats are much more sensitive to porphyrinogenic effects of HCB than are males. In another study rats were given the same concentration of HCB for 90 weeks. Kidney weights were increased and a mild to severe nephrosis, especially in males, was seen. Liver UDA was significant lower than in controls and the kidney porphyrin concentration appeared to be raised (Smith et al., 1985). In a study in which male and female rats were given 14 mg.kg^{-1} bw every other day during 103 days it appeared that female rats are more susceptible to the induction

of porphyria than are males. This might be associated with a faster metabolism of HCB, perhaps under influence of oestrogen levels (Rizzardini and Smith, 1982). In the livers of female rats fed 0.01% HCB (5 $mg.kg^{-1}$ bw) for 98 days porphyria developed (Smith et al., 1980). Rats were fed daily doses of 0, 0.5, 2, 8, 32 $mg.kg^{-1}$ bw of HCB during 15 weeks. The two highest doses caused adverse effects; increased mortality (females), increased organ weights and an increased activity of liver enzymes. Only females developed porphyria at these doses. The results indicated that female rats are more sensitive to HCB than male rats. The no-effect-level appeared to be 2.0 $mg.kg^{-1}$ bw (Kuiper-Goodman et al., 1977). Female rats were given 0, 0.5, 2, 8 or 32 $mg.kg^{-1}$ bw by gavage twice a week during 29 weeks. An increased liver weight occurred in the 32 $mg.kg^{-1}$ bw group. A dose-dependent response between the HCB concentration and the morfological alterations in the liver was observed. A marked enlargement of hepatocytes and porphyria ($\geq$8 $mg.kg^{-1}$ bw) occurred. The enlargement of hepatocytes was moderate in the 2 $mg.kg^{-1}$ bw group and did not occur at the lowest dose. The no-effect-level was 0.5 $mg.kg^{-1}$ bw (Böger et al., 1979). Groups of 5 male and female beagle dogs were administered 0, 1, 10, 100 or 1000 mg per dog (0.1, 1.3, 12.5 or 125 $mg.kg^{-1}$ bw) daily by means of a capsule for one year. Mortality, body weight loss and several gastrointestinal effects occurred at highest and next highest dose. Hyperplastic gastric lymphoid nodules were observed in all dose groups, including the controls, but in treated animals the lesions were more severe. The lack of evidence for pophyria suggested that dogs are insensitive to this effect of HCB (Gralla et al., 1977). Rats were exposed to diets containing 1, 5, 10 or 25 $mg.kg^{-1}$ HCB for 3, 6 or 12 months. Gross changes were not observed, but with an electron microscope hepatic ultrastructural changes were observed at dietary doses of 5 $mg.kg^{-1}$ diet (0.25 $mg.kg^{-1}$ bw) and more. The no-effect-level was 1 $mg.kg^{-1}$ diet (0.05 $mg.kg^{-1}$ bw) (Mollenhauer et al., 1975, 1976).

In 3 male and 3 female rhesus monkeys orally exposed to 110 μg HCB (about 33 $\mu g.kg^{-1}$ bw) for 18 months (only one dose tested) no adverse effect were observed (Rozman et al., 1978).

Reproduction and teratogenicity

Oral exposure

In a two-generation study rats were exposed to 0, 0.32, 1.6, 8 or 40 $mg.kg^{-1}$ HCB in the diet (0, 0.016, 0.08, 0.4 or 2 $mg.kg^{-1}$ bw). Fertility, gestation and lactation indices were not affected by treatment. The viability index was significantly lower in the highest dose group. F_0 males from the 8- and 40 $mg.kg^{-1}$-groups had increased liver and heart weights. At necropsy the F1 generation showed tumours (see carcinogenicity) (Arnold et al, 1985).

In a teratogenicity study female rats were given single oral doses of 1, 10, 20, 40, 60, 80 or 120 $mg.kg^{-1}$ bw during different periods (days 6-21, 6-16, 6-9 or 10-13) of gestation. Concentrations of 80 $mg.kg^{-1}$ bw or more caused maternal toxicity and a reduction in fetal weight. A dose-related increase in uni- and bilateral 14th rib was found in the groups treated during days 6-21, 6-16 and 10-13 of gestation. Sternal effects were observed in the experiment in which animals wer treated from days 6 to 21 (Khera, 1974). Female rats were fed dietary concentraions of 0, 60, 80, 100, 120 or 140 $mg.kg^{-1}$ of HCB (0, 3, 4, 5, 6 or 7 $mg.kg^{-1}$ bw) and allowed to raise to two litters (F1a and F1b). No toxic signs were observed in the maternal rats. The F1a and F1b rats had normal birth weights, but after 4 days suckling these were significantly lower than the control rats. A dose-related increase in mortality was seen in the pups. The LD50 for day 21 cumulative mortality from birth was determined to be 100 $mg.kg^{-1}$ (5 $mg.kg^{-1}$ bw) (Kitchin et al., 1982). Exposure of female rats to a diet containing 80 $mg.kg^{-1}$ of HCB (4 $mg.kg^{-1}$ bw) for 100 days (two weeks before mating to 35-36 days after weaning) did not result in effects on gestation indices or noenatal survival. About half of the dams had elevated liver porphyrin levels, suggesting a heterogenicity of response to the porphyrinogenic activity of HCB (Mendoza et al., 1979). The effects of HCB on body weight of preweanling rats after reciprocal transfer between treated and control maternal rats was examined. It was demonstrated that the transmission of HCB through milk had greater effects on body weights of rat pups than the placental transfer (Mendoza et al., 1978).

The immunotoxic potential of HCB has been investigated in rats with combined pre- and postnatal exposure to dietary levels of 50 or 150 $mg.kg^{-1}$. Body weights were not affected and only the highest dose group showed increased adrenal and liver weights. The cell mediated immunity (resistance to *Listeria monocytogenes* and *Trichinella spiralis* , allograft rejection and responsivity of thymus and spleen cells to T-cell mitogens) appeared to be slightly suppressed and the humoral immunity (antibody response to tetanus toxoid, to *T. spiralis*, to LPS and responsivity to B-cell mitogens) appeared to be strongly enhanced at levels of 50 $mg.kg^{-1}$ diet (2.5 $mg.kg^{-1}$ bw) (Vos et al., 1979). In a similar study with combined pre- and postnatal exposure rats were given diets containing 0, 4, 20 or 100 $mg.kg^{-1}$ (0.2, 1 or 5 $mg.kg^{-1}$ bw). From the results it was concluded that dietary levels as low as 4 $mg.kg^{-1}$ enhanced the humoral nd cell-madiated immunity and caused intra-alveolar macrophage accumulation. The developing immune system of the rat seems to be very sensitive to HCB exposure (Vos et al., 1983). HCB was administered to hamsters and guinea pigs at doses of 0, 1.0, 10.0 or 50.0 $mg.kg^{-1}$ bw by gavage on days 5 through 10 of gestation for the hamster and on days 14 through 19 for the guinea pig. At the highest dose liver weights were significantly increased in hamsters. No differences in number of live fetuses or in weights of fetuses and placenta were found. In guinea pigs a loss of weight was seen at doses of 10.0 $mg.kg^{-1}$ bw or more. No effect on liver weight was seen nor effects on the fetus (Courtney et al., 1985).

Mice received orally doses of 100 $mg.kg^{-1}$ bw HCB on days 7 through 16 of gestation. A significant increased incidence of abnormal fetuses per litter occurred. Maternal liver-to-body weights were found to be increased (Courtney et al., 1976).

HCB was orally administered to lactating monkeys for 60 days at 64 $mg.kg^{-1}$ bw a day. Three infant-mother pairs were used. Milk concentration ranged from 7.5 to 186 ppm milk. Two of three infants died as a result of exposure, whereas the mothers remained healthy (Bailey et al., 1980).

In a four generation reproduction study rats were exposed to dietary concentrations of 0, 10, 20, 40, 80, 160, 320 or 640 $mg.kg^{-1}$ (0, 0.5, 1, 2, 4, 8, 16, 32 $mg.kg^{-1}$ bw). The two highest concentrations were toxic to the F0 generation. Decreases were seen in fertility index ($\geq$320 $mg.kg^{-1}$) and viability and lactation indices ($\geq$160 $mg.kg^{-1}$). The average litter size was

decreased by 160 $mg.kg^{-1}$. Birth weights body weights of 5-d old pups were decreased by dietary levels of 80 $mg.kg^{-1}$. At dietary concentrations of 40 $mg.kg^{-1}$ liver weights were increased as well as the aniline hydroxylase activity. No effects were seen at the two lowest doses (Grant et al., 1977).

1.2.2 Human studies

Monochlorobenzene

No epidemiological studies regarding the effects of exposure to MCB are available. In a few case studies headaches, irritation of the respiratory tract and neurotoxic effects were reported (EPA, 1984).

Dichlorobenzenes

A number of case studies have been reported involving both long-term occupational exposure and (accidental) acute exposure to dichlorobezene. Of these cases 17 have involved exposure primarily through inhalation, 3 through ingestion and 3 most likely through dermal contact. Most cases involved 1,4-DCB. Although the exposures were not well defined and often involved other substances, the data suggest a common action on bone marrow and other organs of the blood-forming system (EPA, 1984).
From an industrial hygiene survey in a plant in which 1,4-DCB was handled it was reported that a faint odour was noted at doses of 15 to 30 ppm (90 to 180 $mg.m^{-3}$), and that the odor became strong at 30-60 ppm (180-360 $mg.m^{-3}$). Painfull irritation of the eyes and nose was reported at 80-160 ppm (480-960 $mg.m^{-3}$). At concentrations of >160 ppm (>960 $mg.m^{-3}$) the air could not be tolerated by persons who were not acclimated. The eyes of employees, exposed to concentrations up to about 550 ppm, showed no signs of cataract. No skin irritation was observed until solid particles were held on the skin for a very long period (Hollingsworth et al., 1956).

Hexachlorobenzene

One of the most notable human exposures to HCB occurred in Southeastern Turkey from 1955-1959. More than 4,000 people were exposed through ingestion of seed grain that had been treated with HCB and was at first intended for agricultural use. The doses ingested were estimated to have been 0.5-2.0 g per day for several months to two years. It was estimated that over 3,000, mostly children in the age of 6 to 16, developed porphyria cutanea tarda (PCT). The mortality rate was 3% to 10% annually.
The PCT-patients developed bullea on sun-exposed areas, hyperpigmentation, hypertrichosis, weakness and porphyrinuria. Children under the age of 4, which were breast fed, generally did not develop PCT but a condition called 'pink-sore' (pembe yara), with a mortality rate of 95%. The children had fever, diarrhea, vomiting, anorexia, convulsions and atrophy of muscles and cutaneous lesions (Cam and Nigogosyan, 1963).
The exposed population has been the subject of several studies since. In one study the clinical features of PCT 20 years after onset were described. The clinical symptoms of PCT were still obvious, consisting of dermatological, skeletal and (in some of the people) neurological symptoms as well as hepatic cirrhosis. From urine and faeces analyses it appeared that a minor part of the group was still porphyric. Exposition to other porphyric agents might have taken place, but this was not further studied (Cripps et al., 1980). In a group of 181 patients (examined 25 years afterwards) many had an abnormal porphyrin metabolism and further similar symptoms as described in the foregoing study (Peters et al., 1982). In another group of 204 patients it was also clear that the symptoms persisted (Cripps et al., 1984).

A group of workers employed in chlorinated solvents manufacture and (among others) exposed to HCB were followed for 1-4 years. Airborn concentrations ranged between <1 and 13 ppb, as time-weighted averages. Blood levels of HCB ranged between 160 and 320 ppb. Evaluation of urinary porphyrins and several other laboratory tests did not reveil any evidence of porphyria cutanea tarda or other adverse health effects. HCB levels correlated more significantly with the years worked than with environmental levels (Currier et al., 1980).

A population exposed to HCB through transportation and disposal of "hex" wastes (a mixture of HCB, hexachlorobutadiene and other chlorinated hydrocarbons) was examined for plasma HCB levels and toxic signs. The average HCB plasma level was significantly higher in exposed persons (2.4 ppb) than in control persons (0.5 ppb). There was no evidence of (cutaneous) porphyria. The exposed group had significantly higher lactate dehydrogenase (LDH) levels than the controls (Burns and Miller, 1975).
Among a group of 20 vegetable spraymen exposed to HCB-contaminated dimethyl-1,2,3,5,6-tetrachloroterephtalate HCB residues in blood were found. The mean blood level was 40 ppb, with a range of <1 to 310 ppb. There was no relationship between HCB residues and years of employment, uroporphyrin levels, coproporphyrin levels or serum enzymes (serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase and LDH) (Burns et al., 1974).

Summary and conclusions "toxicity"

- Experimental studies

There is a clear similarity in the effects of the different chlorobenzenes. The liver and kidneys were target organs of all chlorobenzenes; exposure resulted in increased organ weights, enzyme induction and histopathological changes. In some cases necrosis occurred. All chlorobenzenes disturbed the porphyrine metabolism, but this effect was the most evident by HCB. In addition, the lower chlorinated chlorobenzenes suppressed the activities of bone marrow, spleen and thymus. The microsomal enzyme induction and the interference with the normal porphyrin metabolism were the most sensitive parameters. Microsomal enzyme induction already occurs after short exposure periods and its sensitivity dose not seem to increase after longer exposure periods. The available studies indicate that the toxicity of the chlorobenzenes increases with an increasing degree of chlorination. Most studies concerned oral exposure.
MCB - In a chronic oral (carcinogenicity-) study with mice and rats only in the highest dose group of male rats (120 $mg.kg^{-1}$ bw) an effects was seen. In the livers of these animals a significant increase in neoplastic noduli was found. The dose-without-effct was 60 $mg.kg^{-1}$ bw. In subchronic oral

studies (dogs, rats, mice) similar doses resulted in slight effects; a dose of about 30 $mg.kg^{-1}$ bw was without effect. Inhalatory expsoure up to 450 ppm (2070 $mg.m^{-3}$) caused no adverse effects on reproduction or fertility of rats. Inhalation up to 590 ppm (2715 $mg.m^{-3}$) did not result in teratogenic effects in rabbits, but this dose caused a slight delay in skeletal development in rats accompanied by maternal toxicity.

1,2-DCB - Exposure of rats to 188 $mg.kg^{-1}$ bw of 1,2-DCB for about half a year caused increased liver- and kidney weights; this was not reported at 19 $mg.kg^{-3}$ bw. In an oral (carcinogenicity-) study with rats and mice an increase in tubular regeneration in the kidneys of male mice was only significant in the highest dose group (120 $mg.kg^{-1}$ bw); no effects were reported at 60 $mg.kg^{-1}$ bw. In a subchronic inhalation experiment with rats, rabbits and monkeys (small numbers) no effects were found at 93 ppm (560 $mg.m^{-3}$). In a teratogenicity study the highest dose (400 ppm; 2400 $mg.m^{-3}$) caused slight maternal toxicity in rats and rabbits, but no embryotoxic or teratogenic effects.

1,4-DCB - Rats exposed to 1,4-DCB (188 $mg.kg^{-1}$ bw) for about half a year showed increased liver- and kidney weights; no effects occurred at 19 $mg.kg^{-1}$ bw. In a chronic oral (carcinogenicity-) study the lowest tested doses (150 $mg.kg^{-1}$ bw for male mice and 300 $mg.kg^{-1}$ bw for female mice and male and female rats) resulted in several effects in the liver (hepatocellular degeneration) and the kidneys (nephropathy). An inhalation experiment in which rats, mice, guinea pigs, rabbits and monkeys (small numbers) were exposed for 6-7 months resulted in a dose-without-effect of 96 ppm (577 $mg.m^{-3}$). Oral exposure of rats (250-1000 $mg.kg^{-1}$ bw) provided no evidence of teratogenicity; an embryotoxic effect occurred at 500 $mg.kg^{-1}$ bw (extra ribs). Inhalation up to 800 ppm (4800 $mg.m^{-3}$) caused no teratogenic or embryotoxic effects in rabbits.

- TCB's - Most data concern 1,2,4-TCB, which is considered to be the most toxic isomer. In an oral 13-week study the lowest concentration (10 $mg.kg^{-1}$ bw) caused enzyminduction; after a 30-day "recovey" period this effect had disappeared. A 13-week inhalation experiment with rats (1,3,5-TCB) resulted in a dose-without-effect of 100 $mg.m^{-3}$. Inhalation of 100 ppm of 1,2,4-TCB (740 $mg.m^{-3}$) during 26 weeks did not cause lasting effects in several species. In rabbits dermally treated with TCB's (circa 70% 1,2,4-TCB and 30% 1,2,3-TCB) topical effects occurred in all dose groups (30-450

mg.kg^{-1} bw), only the highest dose caused slight sytemic effect (increased extrection of coproporphyrins in the urine). In a more-generation reproduction study with rats, exposed through drinking water (1,2,4-TCB; 25-400 mg.l^{-1}) no effects on reproduction were found. A teratogenicity study with rats also did not result in any effects at doses up to 300 mg.kg^{-1} bw (1,2,4-TCB) or 600 mg.kg^{-1} bw (1,2,3- and 1,3,5-TCB). In another study with rats a dose of 360 mg.kg^{-1} bw caused retarded embryonic growth accompanied with maternal toxicity; this was not reported at 120 mg.kg^{-1} bw.

- TeCB's - Toxicity studies with TeCB are limited and only concern oral exposure. In a 90-day diet study with rats exposure to TeCB's caused liver- and kidney toxicity. 1,2,4,5-TeCB was the most toxic isomer; the dose-without-effect was 5 mg.kg^{-1} diet, which corresponded to 0.34 or 0.4 mg.kg^{-1} bw for males and females, respectively. In a teratogenicity study with rats the highest doses of 1,2,3,4- and 1,2,3,5-TeCB (200 mg.kg^{-1} bw) caused a decrease in the number of live fetuses per litter. This dose was lethal to nearly all females in the 1,2,4,5-TeCB-group. No teratogenic effects were found.

- PeCB - Only one study (subchronic toxicity combined with reproduction toxicity) with PeCB was available. Oral exposure to 25 mg.kg^{-1} bw caused liver- and kidney toxicity in rats; the dose-without-effect was 12.5 mg.kg^{-1} bw. Suckling pups from mothers fed this dose developed tremors 4-14 days after birth; at a (maternal) dose of 6.3 mg.kg^{-1} bw this effect did not occur.

- HCB - For female rats, which are more sensitive to the induction of porphyria than males, a dose-without-effect of 2 mg.kg^{-1} bw was established. In a study with combined pre- and postnatal exposure the lowest dose tested (0.2 mg.kg^{-1} bw) still resulted in effects on the immune system of rats. For changes in liver cells of rats a dose-without-effect of 0.05 mg.kg^{-1} bw was established. A similar dose did also not result in effects in a small number of monkeys. No "chronic" dose-without-effect was available. In an oral two-generation study the viability index was lower at $\geq$2 mg.kg^{-1} bw, this was not reported at 0.4 mg.kg^{-1} bw. Effects on the reproduction were reported at doses of 8 mg.kg^{-1} bw and higher. No teratogenic effects were found in rats (doses up to 120 mg.kg^{-1} bw), but an embryotoxic effects occurred at 40 mg.kg^{-1} bw.

- Human studies

Human studies were only available for HCB. One of the most notable human exposures to HCB occurred in the Southeastern of Turkey from 1955 to 1959. More than 4,000 people were exposed through the ingestion of seed grain that had been treated with HCB and was at first intended for agricultural use. The estimated ingested doses varied from 0.5 to 2.0 g a day durong several months to two years. Over 3,000 people, mostly children, developed porphyria cutanea tarda (PCT), which was characterized by bullea on sun-exposed areas, hyperpygmentation, hypertrichosis, weakness and poprphyrinuria. Children under the age of 4 (which were breast-fed) generally developed clinical picture named 'pink-sore' (pembe yara), with a mortality rate of 95%. The children had fever, diarrhea, vomiting, anorexia, convulsions and atrophy of muscles and cutaneous lesions.

The exposed population has been the subject of several studies since. In many patients the clinical features of PCT (consisting of dermatological, skeletal and sometimes also neurological symptoms as well as liver cirrhosis and porphyria) were still obvious, 20 years after onset.

In workers among others exposed to HCB, no evidence of pophyria (or other HCB-induced effects) were found, although HCB levels in blood were in one study higher than those of controls.

Table 1.1 Acute toxicity of chlorobenzenes (mg/kg bw)

Chlorobenzene	route	species	parameter		reference
MCB	oral	rat	LD50	400-2,144	EPA '84, Allen et al.'79
	oral	rabbit	LD50	2,830	EPA '84
	i.p.	rat	LD50	7,400	EPA '84
	i.p.	guinea pig	LD50	4,100	EPA '84
	i.p.	mouse	LD50	1,355	Mohtashamipur et al. '87
	inh.	rat	LC50	2,965	EPA '84
	inh.	mouse	LC50	1,886	EPA '84
	dermal	rabbit	LD50	>10,000	EPA '84
1,2-DCB	oral	rat	LD50	2,138	EPA '84
	oral	rabbit	LD50	1,875	EPA '84
	oral	mouse	LD50	2,000	EPA '84
	oral	guinea pig	LD50	3,375	EPA '84
	oral	rat	LD50	500	Allen et al.'79
	i.p.	mouse	LD50	1,228	Mohtashamipur et al. '87
1,3-DCB	i.p.	mouse	LD50	1,062	Mohtashamipur et al. '87
1,4-DCB	oral	rat	LD50	500	EPA '84
	oral	rabbit	LD50	2,812	EPA '84
	s.c.	mouse	LD50	5,145	EPA '84
	i.p.	mouse	LD50	2,000	Mohtashamipur et al. '87
1,2,3-TCB	i.p.	mouse	LD50	1,390	Mohtashamipur et al. '87
1,2,4-TCB	oral	rat	LD50	756	EPA '84
	oral	mouse	LD50	766	EPA '84
	i.p.	mouse	LD50	1,223	Mohtashamipur et al. '87
1,3,5-TCB	i.p.	mouse	LD50	2,260	Mohtashamipur et al. '87
1,2,4,5-TeCB	oral	rat, rabbit	LD50	1,500	EPA '84
	oral	mouse	LD50	1,035	EPA '84
TeCB-isomers	oral	rat	LD50	1,200-3,000	EPA '84
PeCB	oral	rat	LD50	250	Allen et al. '79
	oral	rat	LD50	940-1,125	EPA '84
	oral	mouse	LD50	1,175-1,370	EPA '84
HCB	oral	rat	LD50	32,100	Allen et al. '79
	oral	rat	LD50	3,500-10,000	EPA '84
	oral	rabbit	LD50	2,600	EPA '84
	oral	cat	LD50	1,700	EPA '84
	oral	mouse	LD50	4,000	EPA '84

i.p. = intraperitoneal; inh. = inhalatory; s.c. = subcutaneous; LD50 = lethal dose for 50% of the exposed animals

1.3 GENOTOXICITY

- Experimental systems

The results from *in vitro* and *in vivo* genotoxicity tests with chlorobenzenes are summarized in table 1.2 and 1.3, respectively.

- *in vitro*

MCB was negative in the the *Salmonella typhimurium* gene mutation test (=Ames test), either with or without metabolic activation. The results of a mouse lymphoma (L5178Y) assay was equivocal when tested without activation, whereas with activation it was positive. In this positive test no dose-response relationship existed. MCB did not increase the frequency of chromosome aberrations in chinese hamster ovary cells. 1,2-DCB and 1,3-DCB were only tested in the Ames test; negative results were obtained. 1,4-DCB was negative in the Ames test. The results of a mouse lymphoma test were considered to be equivocal, both with and without activation (according to the NTP the test with activation was positive). In chinese hamster ovary cells 1,4-DCB did not increase the frequency of SCE's or chromosomal aberrations (NTP, 1987). 1,2,3-TCB, 1,2,4-TCB and 1,3,5-TCB were not mutagenic in the Ames test and did not incraese the frequency of chromosome aberrations in chinese hamster ovary cells. 1,2,3,4-TeCB, 1,2,3,5-TeCB, 1,2,4,5-TeCB, PeCB and HCB were only tested in the Ames test; the results were all negative.
Prasad (1970) conducted fungal mutation tests with MCB, 1,2-, 1,3- and 1,4-DCB. Besides the fact that this test is not a current test system, the "positive" results were considered equivocal. Therefore these results will not be taken into account.

- *in vivo*

In one mouse micronucleus test in bone marrow clear positive results were obtained for all chlorobenzenes that were included in the test: MCB, 1,2-DCB, 1,3-DCB, 1,4-DCB, 1,2,3-TCB, 1,2,4-TCB and 1,3,5-TCB. The test was conducted according to a commonly accepted procedure (two intraperintoneal injections). The purity of the test substances was at least 98%. Beside that, for all chlorobenzenes positive dose-response relationships were

found (Mohtashamipur et al., 1987). 1,4-DCB did not show an increased number of micronucleated cells among erythrocytes from peripheral blood (NTP, 1987). In a dominant lethal test 1,4-DCB was found to be negative at any maturation stage of the 8 week spermatogenic cycle in mice exposed up to 450 ppm (4610 $mg.m^{-3}$) (unpublished results from Anderson and Hodge (1976), evaluated by Loeser and Litchfield, 1983). In bone-marrow cells of rats exposed to levels up to 680 ppm (6965 $mg.m^{-3}$) no increase in the number of observable chromosomal aberrations could be detected (unpublished results from Anderson and Richardson (1976), evaluated by Loeser and Litchfield, 1983). 1,2,4,5-TeCB did not cause an increased frequency of sex-linked mutations in *Drosophila melanogaster*. Two dominant lethal tests with HCB in rats gave negative results.

- Human studies

In peripheral lymphocytes of a group of 8 males and 18 females accidentally exposed to vapors of 1,2-DCB (no quantitative data) during 4 working days a significant increase in chromosomal aberrations (9%) was found compared with a control group (2%). The chromosomal aberrations were divided into two groups: single or double breaks. No further specification of type of chromosomal aberration was given. A decrease (4%) in number of chromosomal aberrations in the exposed groups was found 6 months after exposure, which indicated an reversible effect. Although the concentration of the vapor was not determined, the symptoms of most exposed persons were consistent with those usually observed at concentrations above 100 ppm. Because of the fact that no types of chromosome aberrations were specified and the large variation in percentage of cells with chromosome aberrations (0-22%) the results are difficult to interpret and therefore the study will be left out of consideration (Zapata-Gayon et al., 1982).
In peripheral lymphocytes of workers exposed to 1,2,4,5-TeCB in producing organophosphate insecticides a significant increase in the frequency of chromosome aberrations was found compared to a control group (consisting of "normal" healthy persons). The concentration to which these workers were exposed was not determined. Although the authors considered chromosomal mutagenicity of 1,2,4,5-TeCB proven, this study is left out of

consideration in the present evaluation because the workers had been simultaneously exposed to other substances (Kiraly et al., 1979).

- Additional data

Various types of mitotic and chromosomal anomalies were observed in root tips of several plant species treated with 1,4-DCB (Carey and McDonough, 1943, Sharma and Bhattacharyya, 1956, Srivastava, 1966, Sarbhoy, 1980).
In several *in vivo* and *in vitro* tests it was demonstrated that MCB binds covalently to DNA and other macromolecules. About one day after an intraperitoneal injection into rats and mice, MCB was found to be covalently bound to DNA of the liver, kidneys and lung. The binding of MCB with DNA was found in vitro to be mediated by liver microsomes. The involvement of Cyt P-450 was indicated (Prodi et al., 1986, Grilli et al., 1985).
24 Hours after i.p. injections into mice and rats 1,2-DCB was covalently bound to DNA, RNA and proteins of the liver, kidney, lung and stomach (Colacci et al., 1990).

Summary and conclusions "genotoxicity"

Data on genotoxicity are rather limited. With regard to *in vitro* tests it appeared that all chlorobenzenes were negative in the *Salmonella typhimurium* gene mutation test (=Ames test). A number of chlorobenzenes (MCB, 1,4-DCB and TCB's) were tested in mammalian cells for one or more of the following end points: gene mutations, chromosome aberrations and "sister chromatid exchanges". From these tests only one was equivocal (1,4-DCB) or equivocal/positive (MCB), while all other tests were negative. Therefore, it is concluded that the *in vitro* studies show no clear indications for genotoxic activities of chlorobenzenes.
With regard to *in vivo* genotoxicity a few studies with negative results were available; this concerned 1,4-DCB (mous micronucleus test in peripheral blood, mous dominant lethal test, chromosome aberrations in rat bone marrow cells) and HCB (test with *Drosophila melanogaster*, and two dominant lethal tests with rats). However, in one mous micronucleus test in bone marrow, clear positive results were obtained for all chlorobenzenes that were included in the test: MCB, 1,2-DCB, 1,3-DCB, 1,2,3-TCB, 1,2,4-TCB

and 1,3,5-TCB). The test was conducted according to a commonly accepted procedure (two intraperintoneal injections) with substances that a purity of at least 98%. Beside that for all chlorobenzenes a positive dose-response relationship was found. As a result of this test and the chemical affinity of the substances it can not be excluded that the other chlorobenzenes would also have been positive in this test. It must be noted that the results of this test need to be verified. As yet, it is concluded that the data are too limited to consider the chlorobenzenes as genotoxic. Two studies reported an increased frequency of chromosomal aberrations in peripheral lymphocytes of humans exposed to 1,2-DCB or 1,2,4,5-TeCB. For several reasons (type of chromosomal aberrations not specified, no individual data, mixed exposure) these studies will be left out of consideration.

Table 1.2 Genotoxicity of chlorobenzenes in vitro

Species or test system	Endpoint	Dose	Purity test-subst.	Test results without act.	Test results with act.	Reference
MCB						
S. typh. TA98, 100, 1537, 1538	gene mut.	0-333 µg/plate$_t$	"pure"	-	-	NTP, 1985a
S. typh. TA98, 1537, 1538	gene mut.	-	-	-	-	Lawlor et al. '79 abstract
S. typh. TA98, 100, 1535, 1537	gene mut.	0-333 µg/plate	-	-	-	[1] Haworth et al. '83
S. typh. TA98, 100, 1535, TA1537, 1538.	gene mut.	0-1.28 µl/plate	98	-	-	[1] Shimizu et al. '83
Mouse lymphoma cells (L5178Y)	gene mut.	0-200 µg/µl		±	+	[5] McGregor et al. '88
CHO cells	chrom. ab.	0-400 µg/ml	-	-	-	[1] Sofuni et al. '85
1,2-DCB						
S. typh. TA98, 1537, 1538	gene mut.	-	-	-	-	Lawlor et al. '79 abstract
S. typh. TA98, 100, 1535, 1537	gene mut.	0-100 µg/plate$_t$	-	-	-	[1] Haworth et al. '83
S. typh. TA98, 100, 1535, 1537	gene mut.	0-333 µg/plate$_t$	-	-	-	NTP '85b
S. typh. 8 strains	gene mut.	1-5 µl/plate	≥90	-		[3] Andersen et al. '72
S. typh. TA98, 100, 1535, TA1537, 1538.	gene mut.	0-1.28 µl/plate	98	-	-	[1] Shimizu et al. '83
1,3-DCB						
S. typh. TA98, 100, 1535, 1537	gene mut.	0-100 µg/plate	-	-	-	[1] Haworth et al. '83
S. typh. TA98, 100, 1535, TA1537, 1538.	gene mut.	0-1.28 µl/plate	98	-	-	[1] Shimizu et al. '83
1,4-DCB						
S. typh. TA98, 1537, 1538	gene mut.	-	-	-	-	Lawlor et al. '79 abstract
S. typh. TA98, 100, 1535, 1537	gene mut.	0-100 µg/plate	-	-	-	[1] Haworth et al. '83
S. typh. TA98, 100, 1535, TA1537, 1538.	gene mut.	0-13105 µl/plate	99	-	-	[1] Shimizu et al. '83
S. typh. TA98, 100, 1535, 1537	gene mut.	0-100 µg/plate	-	-	-	NTP '87
mouse lymphoma cells (L5178Y)	gene mut.	0-100 µg/µl		±	±	[6] McGregor et al. '88
mouse lymphoma cells (L5178Y)	gene mut.	0-100 µg/µl	-	-	-	NTP '87
CHO cells	SCE's	0-150 µg/µl	-	-	-	NTP '87
CHO cells	chrom. ab.	0-150 µg/µl	-	-	-	NTP '87
CHO cells	chrom. ab.	0-200 µg/ml	-	-	-	[1] Sofuni et al. '85
1,2,3-TCB						
S. typh. TA98, 100, 1535, 1537	gene mut.	0-100 µg/plate$_t$	-	-	-	[1] Haworth et al. '83
CHO cells	chrom. ab.	0-63 µg/ml	-	-		[1] Sofuni et al. '85
1,2,4-TCB						
S. typh. TA98, 1537, 1538	gene mut.	-	-	-	-	Lawlor et al. '79 abstract
S. typh. TA98, 100, 1535, 1537	gene mut.	0-100 µg/plate$_t$	-	-	-	[1] Haworth et al. '83
S. typh. TA98, 100, 1535, 1537	gene mut.	0-1599 µg/plate$_t$	-	-	-	[7] Schoeny et al. '79
CHO cells	chrom. ab.	0-125 µg/ml$_t$	-	-		[1] Sofuni et al. '85

Table 1.2 continued

Species or test system	Endpoint	Dose	Purity test-subst.	Test results without act.	Test results with act.	Reference
1,3,5-TCB						
S. typh. TA98, 100, 1535, 1537	gene mut.	0-100 µg/plate$_t$	-	-	-	[1] Haworth et al. '83
CHO cells	chrom. ab.	0-125 µg/ml$_t$	-	-		[1] Sofuni et al. '85
TCB (isomer not given)						
S. typh. 8 strains	gene mut.	1-5 µl/plate	-	-		[3] Andersen et al. '72
1,2,3,4-TeCB						
S. typh. TA98, 100, 1535, 1537	gene mut.	0-33 µg/plate$_t$	-	-	-	[1] Haworth et al. '83
1,2,3,5-TeCB						
S. typh. TA98, 1537, 1538	gene mut.	-	-	-	-	Lawlor et al. '79 abstract
S. typh. TA98, 100, 1535, 1537	gene mut.	0-20 µg/plate$_t$	-	-	-	[1] Haworth et al. '83
1,2,4,5-TeCB						
S. typh. TA98, 1537, 1538	gene mut.	-	-	-	-	Lawlor et al. '79 abstract
S. typh. TA98, 100, 1535, 1537	gene mut.	0-1000 µg/plate$_t$	-	-	-	[2] Haworth et al. '83
PeCB						
S. typh. TA98, 1537, 1538	gene mut.	-	-	-	-	Lawlor et al. '79 abstract
S. typh. TA98, 100, 1535, 1537	gene mut.	0-1000 µg/plate$_s$	-	-	-	[1] Haworth et al. '83
HCB						
S. typh. TA98, 100, 1535, 1537	gene mut.	0-1000 µg/plate$_s$	-	-	-	[1] Haworth et al. '83

abn. mit. = abnormalities in behaviour of chromosomes during mitosis
act. = metabolic activation
chrom. ab. = chromosome aberraitons
gen. mut. = gene mutation
S. typh. = Salmonella typhimurium
t/s = highest concentraion is limited by toxicity to the bacteria or to solubility.

[1] Test compound solved in dimethyl sulfoxide
[2] Test compound solved in acetone
[3] Presence of metabolic activation not stated
[5] The overall (NTP-) conclusions of the tests conducted with or without activation ("positive" and "inconclusive", respectively) were confirmed by RIVM-experts (from the Laboratory of mutagenesis and carcinogenesis).
[6] The overall (NTP-) conclusion of the tests conducted without activation ("inconclusive") was confirmed by RIVM-experts. The overall (NTP-) conclusion of the tests with activation ("positive") has not been confirmed; the results were considerd to be "inconclusive" by RIVM-experts.
[7] Concentrations ranging from 102-1.4 x 10^3 µg/plate were tested, but the toxic dose was determined as 1599 µg/plate. 1,2,4-TCB was negative for mutagenicity in the presence of S9-mix prepared from uninduced rats or from rats induced by Arcolor 1254 or 1,2,4-TCB. The mutagenicity of 2-aminoanthracene appeared to be affected by 1,2,4-TCB-induced S9-mix.

Table 1.3 Genotoxicity of chlorobenzenes in vivo

Species or test system	Exposure	Result	Purity test-substance		Reference
MCB					
mouse micronucleus	2 intraperintoneal injections of 113-450 mg/kg bw	positive	≥98%		Mohtashamipur et al. '87
1,2-DCB					
mouse micronucleus	2 intraperitoneal injections of 94-375 mg/kg bw	positive	≥98%		Mohtashamipur et al. '87
1,3-DCB					
mouse micronucleus	2 intraperitoneal injections of 88-350 mg/kg bw	positive	≥98%		Mohtashamipur et al. '87
1,4-DCB					
mouse micronucleus	0-1,800 mg/kg bw by gavage 5 days a week for 13 weeks	negative	>99%	[2]	NTP '87
mouse micronucleus	2 intraperitoneal injections of 178-710 mg/kg bw	positive	≥98%		Mohtashamipur et al. '87
mouse dominant lethal	inhalatory exposure to 75, 225 or 450 ppm, 6 hrs/day for 5 days	negative	--	[3]	unpublished data from Anderson and Hodge '76
chromosome aberrations in rat bone marrow cells	single or multiple exposure to 75-680 ppm	negative	--	[3]	unpublished data from Anderson and Richardson '76
1,2,3-TCB					
mouse micronucleus	2 intraperitoneal injections of 125-500 mg/kg bw	positive	≥98%		Mohtashamipur et al. '87
1,2,4-TCB					
mouse micronucleus	2 intraperitoneal injections of 105-420 mg/kg bw	positive	≥98%		Mohtashamipur et al. '87
1,3,5-TCB					
mouse micronucleus	2 intraperitoneal injections of 213-850 mg/kg bw	positive	≥98%		Mohtashamipur et al. '87
1,2,4,5-TeCB					
Drosophila melanogaster	3,5 mM in medium	no increased frequency of sex-linked recessive lethal mutations	--	[1]	Parádi and Lovenyák '81
MCB rat dominant lethal	0-221 mg/kg bw by gavage for 5 consecutive days	negative	--		Simon et al. '79
rat dominant lethal	0-60 mg/kg bw by gavage for 10 consecutive days	negative	--		Khera '74

[1] The BASC technique was used for measuring X-linked recessive lethals.
[2] Peripheral erythrocytes were used.
[3] Evaluated by Loeser and Litchfield (1983).

1.4 CARCINOGENICITY

Monochlorobenzene

Groups of 50 male and 50 female F344/N rats and groups of 50 female B6C3F1 mice were administered chlorobenzene in corn oil by gavage, 5 days a week for 103 weeks, at doses of 0 (vehicle control), 60 or 120 $mg.kg^{-1}$ bw. A group of 50 male mice received doses of 0, 30 and 60 $mg.kg^{-1}$ on the same schedule. Untreated controls consisted of 50 male and 50 female rats and mice. A significant increase of the incidence of neoplastic noduli of the liver at the high dose was observed in male rats. The incidences were 4/50 in untreated controls, 4/50 in vehicle controls, 4/49 in the low dose group and 8/49 in the high dose group. Hepatocellular carcinomas occurred in two male rats in the vehicle control group. No increased incidence in liver adenomas or carcinomas was observed in female rats or in male or female mice. A significant decrease of pituitary adenomas or carcinomas was observed in male and female rats in the higher dose group compared to the vehicle controls. A significant decrease in endometrial stromal polyps in the low dose female rat group. The reasons for a decrease in these tumours are unknown, as stated by the NTP. On the basis of these studies it is concluded that there is no evidence for carcinogenicity of MCB in experimental animals (NTP, 1985a, Kluwe et al., 1985).

1,2-Dichlorobenzene

Groups of 50 male and 50 female F344/N rats and B6C3F1 mice were administered 1,2-DCB in corn oil by gavage at doses of 0 (vehicle control), 60 or 120 $mg.kg^{-1}$, 5 days a week during 103 weeks. Untreated controls consisted of 50 male and 50 female rats and mice. A dose-related increase in the incidence of malignant histiocytic lymphomas was observed in male and female mice. The incidences of all types of malignant lymphoma, which is considered to be a more appropriate comparison, were not significantly increased. Therefore, the NTP discounted the increase in malignant histiocytes, and concluded that, under the conditions of the present study, there was no evidence of carcinogenicity of 1,2-DCB in experimental animals (NTP, 1985b).

1,4-Dichlorobenzene

Groups of 50 male F344/N rats were given 1,4-DCB by gavage at doses of 0, 150 or 300 mg.kg^{-1} bw and female rats and male and female B6C3F1 mice were given 0, 300 or 600 mg.kg^{-1} bw for 5 days a week during 103 weeks. In male rats the incidences increased of renal tubular cell adenocarcinoma (1/50, 3/50 and 7/50), tubular cell adenoma and adenocarcinoma (combined; 1/50, 3/50 and 8/50) (both only significant in the high dose group) and pelvic epithelial cell hyperplasia (significant in low and high dose groups). In males the incidence of pelvis epithelial cell hyperplasia was significantly increased. No renal tumours were found in female rats. In mice the incidences increased of hepatocellular adenomas (5/50, 13/49 and 16/60 in males and 10/50, 6/48 and 21/50 in females) and hepatocellular carcinomas (14/50, 11/49, 32/50 in males and 5/50, 5/48, 19/50 in females), both significant in the higher dose groups. In the higher dose groups the incidence of hepatoblastoma and several types of pheochromocytoma were increased in male mice. On the basis of these data the NTP concluded that there is clear evidence of carcinogenicity of 1,4-DCB in male rats and male and female mice, but not in female rats (NTP, 1987).

However, some critical observations must be added to this conclusion. Recent studies indicate that the development of renal tumours in male F344 rats is based on a very specific mechanism. 1,4-DCB seems to bind reversible to the male rat-specific protein alpha(2u)-globulin. This complex is resistant to proteolytic hydrolysis, leading to accumulation in renal lysosomes and subsequent cytotoxicity and cell death. This results in increased cell proliferation that persists (providing exposure continues) which is thought to promote initiated cells to form preneoplastic and renal neoplasia in male rats. This syndrome is highly species and sex specific; humans do not synthesize alpha(2u)-globulin (Swenberg et al., 1989, Charbonneau et al., 1989). In mice hepatocellular adenomas and carcinomes were found. Since these tumours are common neoplasm in mice of this strain (spontaneous incidence from 16% up to 60% in males and from 2% to 20% in females) (Seiler et al., 1991), the relevance of these tumours is considered equivocal. On the basis of these data it is concluded that there is limited evidence of carcinogenicity of 1,4-DCB in experimental animals.

Hexachlorobenzene

In a group of 7 female Agus rats fed dietary concentrations of 100 $mg.kg^{-1}$ HCB (6-8 $mg.kg^{-1}$ bw) for 90 weeks all animals developed liver-cell tumours. The livers of the treated rats was twice the size of that of the controls. The onset of porphyria (in the urine) was seen but no other effects (Smith and Cabral, 1980). In another 90-week study in which F344/N rats were given dietary concentrations of 200 $mg.kg^{-1}$ HCB (10 $mg.kg^{-1}$ bw) all surviving females (10) had either neoplastic noduli or hepatocellular carcinoma. Only 2 out of 12 surviving males seemed to have "liver tumours", but histological examination of portions of the liver showed no noduli or carcinomas. Male livers showed hypertrophy, fatty degeneration and bile duct hyperplasia (Smith et al., 1985). Exposure of Sprague-Dawley rats to 0, 75 or 150 $mg.kg^{-1}$ HCB in the diet (0, 4 or 8 $mg.kg^{-1}$ bw) for 2 years resulted in increased incidences of renal cell adenoma (7/54, 7/56 and 15/54 in females and 7/54, 41/52 and 42/56 in males), renal cell carcinoma in females (1/52, 2/56 and 2/54), hepatic lesions, hepatocarcinoma (0/54, 3/52 and 4/56 in males and 0/52, 36/56 and 48/55 in females) and bile duct adenoma or carcinoma (0/54, 2/52 and 2/56 in males and 1/52, 19/56 and 29/55 in females) (Lambrecht et al., 1983a, 1983b, abstracts).
Syrian golden hamsters and Sprague-Dawley rats of both sexes were given 0, 200 or 400 $mg.kg^{-1}$ HCB in the diet for 90 days. In the hamster-experiment the liver was the most severily involved organ; (pre-) cirrhotic lesions, bile-duct hyperplasia and hepatomas (2/28 and 2/22 in the 200 and 400 $mg.kg^{-1}$ bw groups, respectively) were found (Lambrecht et al., 1982a, abstract). Rats showed besides liver neoplasms and lymphatic leukemias a veriety of renal lesions as well as renal adenomas (males and females) and carcinomas (only females) (Lambrecht et al., 1982b, abstract). Exposure of Syrian golden hamsters to dietary concentrations of 0, 50, 100 or 200 $mg.kg^{-1}$ HCB (0, 4, 8 or 16 $mg.kg^{-1}$ bw) for lifespan resulted in increased mortality and a decline in body weight at the highest dose. A dose-related increase in hepatomas (0/39, 14/30, 17/30 and 51/60 for females and 0/40, 14/30, 26/30 and 49/57 for males) and liver haemangio-endotheliomas (0/39, 0/30, 2/30 and 7/60 for females and 0/40, 1/30, 6/30 and 20/57 for males) was observed. In the mid and highest dose group some hamsters also developed thyroid adenomas or spleen haemangioendotheliomas (Cabral et al.,

1977). Exposure of male and female Swiss mice to dietary concentrations of 0, 50, 100 or 200 mg.kg^{-1} for 101-120 weeks resulted in increased mortality at the highest dose. The incidence of liver cell tumours was increased in the 100 and 200 mg.kg^{-1} dose group but not in the 50 mg.kg^{-1} dose groups. The incidences were 3/30 females and 3/29 males in the 100 mg.kg^{-1} group and 14/41 females and 7/44 males in the 200 mg.kg^{-1} group. With regard to lymphomas and lung adenomas the incidences in the control group were found to be higher (!) than in the treated groups. In a seperate experiment groups of 30 male and female mice were fed dietary doses of 300 mg.kg^{-1} HCB (36 mg.kg^{-1} bw) for 15 weeks. After 120 weeks, when the experiment was terminated, an increase in mortality was seen in males. Two treated mice developed liver cell tumours (1 male and 1 female) compared to none of the controls (Cabral et al., 1979). On the basis of these studies it is concluded that there is sufficient evidence of carcinogenicity of HCB in experimental animals.

Additional data

In a two generation feeding study rats were given 0, 0.32, 1.6, 8.0 or 32 mg.kg^{-1} HCB in the diet. At necropsy it appeared that the F1 generation had pituitary and subcutaneous tumours (Arnold et al., 1985).

In a feeding study male ICR mice were exposed to HCB and polychlorinated terphenyl (PCT) singly and in combination for 24 weeks. Administration of HCB in concentrations of 10 or 50 mg.kg^{-1} HCB did not increase tumor incidences. However, when administered in combination with PCT, it seemed to enhance the induction of liver tumours by PCT (Shirai et al., 1978).

Summary and conclusions "carcinogenicity"

Data on carcinogenicity are limited; only MCB, 1,2-DCB, 1,4-DCB and HCB were tested in experimental animals. There are no epidemiological studies. After MCB was orally administered to rats and mice (60 and 120 mg.kg^{-1} bw) for 2 years in male rats a significant increase in the incidence of neoplastic noduli of the liver was found. No increased incidences of tumours were observed in female rats or male and female mice. On the basis

of these studies it is concluded that there is no evidence of carcinogenicity of MCB in experimental animals.

Similar studies were carried out with 1,2-DCB (60 or 120 $mg.kg^{-1}$ bw) and 1,4-DCB (150, 300 or 600 $mg.kg^{-1}$ bw) in mice and rats. In the study with 1,2-DCB a dose-related increase in malignant histiocytic lymphoma was observed in mice. The incidence of all types of malignant lymphomas, which was considered to be more relevant, was not increased. Therefore it was concluded that there was no evidence for carcingenicity of 1,2-DCB in experimental animals. The "International Agency for Research on Cancer" (IARC) concluded that there was inadequate evidence of carcinogenicity of 1,2-DCB to animals (IARC, 1987b).

The carcinogenicity of 1,4-DCB was tested in mice and rats. Male rats were exposed to 0, 150 or 300 $mg.kg^{-1}$ bw of 1,4-DCB by gavage for 2 years, and female rats and male and female mice received doses of 0, 300 or 600 $mg.kg^{-1}$ bw. Male rats from the highest dose group had significantly increased incidences of renal carcinoma and adenoma. In male and female mice increased incidences were found of liver adenomas and carcinomas as well as of some types of pheochromocytoma. However, recent studies indicate that renal tumours in male rats develop as a result of alpha (2u)-globulin nephropathy. This protein is male rat specific and therefore the whole development of renal tumours is highly species and sex specific. Humans do not synthesize this protein. With respect to the hepatocellular tumours in mice it is emphasized that these types of neoplasm are common in this strain of mice (spontaneous incidence from 16% to 60% in males and from 2% to 20% in females). On the basis of these data it is concluded that there is limited evidence of carcinogenicity of 1,4-DCB in experimental animals.

The carcinogenicity of HCB was tested in (sub-)chronic oral studies with rats, mice and hamsters. Exposure of rats to HCB ($\geq$4 $mg.kg^{-1}$ bw) resulted in increased incidences of hepatocellular carcinoma, renal cell adenoma and carcinoma and bile duct adenoma and carcinoma. The development of these tumours was clearly accompanied by the occurence of toxicity in the target organs (increased organ weights, noduli and hyperplasia). In hamsters (exposed to 4-16 $mg.kg^{-1}$ bw), HCB mainly affected the liver; liver cirrhosis, hyperplasia of the bile duct and hepatomas. Mice exposed to 6-32 $mg.kg^{-1}$ bw during 2 years, showed an increased incidence of liver tumours. These HCB-induced tumours could not be explaned by a specific mechanism, as

was the case with renal tumours in male rats exposed to 1,4-DCB, because HCB induced tumours in several organs of both males and females of several species. The development of tumours was clearly accompanied by toxicity in the target organs. On the basis of these studies it is concluded that there is sufficient evidence of carcinogenicity of HCB in experimental animals.

2 ECOTOXICITY I - AQUATIC ORGANISMS

2.1 ACCUMULATION

Bioaccumulation of the chlorobenzenes is determined by aqueous solubility (S), lipid solubility as indicated by the n-octanol/water partition coefficient (Kow) and by the number of chlorine atomes. Most experimental data on bioaccumulation concerned freshwater fish; table 2.1 gives an overview of reported "whole-body" or "lipid" bioconcentration factors (BCF's) for these organisms *[The BCF is the concentration in organisms divided by the concentration in water]*. From the data it can be concluded that all chlorobenzenes bioconcentrate in freshwater fish, with the tendency to increase with degree of chlorination (Neely et al., 1974, Könemann and Van Leeuwen, 1980, Kenaga, 1980, Mackay, 1982, Oliver and Niimi, 1983, Hoornstra, 1988, Van der Naald and Bruggeman, 1988). From a study conducted by Giam et al. (1980) it appeared that HCB also accumulates in marine fish *(Fundulus similis)* , but to a lesser extent than freshwater fish; a BCF of 375 was determined. In a bioconcentration study the marine bivalve *Mytilus edulis* was exposed to PeCB for 21 days. Steady state was not completely reached, but at the end of this period the BCF was about 3,900 (Renberg et al., 1985).

The bioconcentration of a mixture of several chlorobenzenes (1,2-DCB, 1,3-DCB, 1,4-DCB, 1,3,5-TCB, 1,2,4-DCB, 1,2,3-TCB, 1,2,4,5-TeCB, 1,2,3,4-TeCB, PeCB and HCB and the chlorinated hydrocarbons hexachlorobutadiene and hexachloroethane) in rainbow trout were determined in a laboratory study. Exposure levels were either 'low' (ranging from 47 $ng.l^{-1}$ for 1,2-DCB to 0.32 $ng.l^{-1}$ for hexachlorobutadiene) or 'high' (ranging from 930 to 3.4 $ng.l^{-1}$ for the same substances). There was a high correlation between BCF's and Kow, except for HCB. Whole-body BCF's (high exposure group) were 560 for 1,2-DCB, 740 for 1,3-DCB, 720 for 1,4-DCB, 4,100 for 1,3,5-TCB, 3,200 for 1,2,4-TCB, 2,600 for 1,2,3-TCB, 13,000 for 1,2,4,5-TeCB, 12,000 for 1,2,3,4-TeCB and 20,000 for PeCB and HCB. BCF's in the 'low' exposure group were about a factor two lower. "Lipid "-BCF's were found by multiplying whole-body BCF's by 12 (Oliver and Niimi, 1983).

Larval stages of the midge *Chironomus decorus* were exposed to sediment-bound chlorobenzenes (MCB, 1,2-DCB, 1,2,4-TCB or HCB) in a flowthrough exposure system. Larvae were exposed to high- and low-organic content sediments. Experiments were carried out with water that contained no test chemical (nonequilibrium flow) or a concentration that was in equilibrium with that in the sediment. It appeared that the accumulation was mediated by the uptake of compounds from the interstitial water. BCF's calculated on the basis of interstitial water were comparable in all experiments (about 5 for MCB, 30 for 1,2-DCB, 200 for 1,2,4-TCB and 800 for HCB). Interstitial water BCF's highly correlated with Kow-values. BCF's calculated on the basis of sediment were <1 in all experiments. BCF's based on the concentration in overlying water under equilibrium exposure conditions correlated also strongly with Kow-values (Knezovich and Harrison, 1988).
The uptake of sediment-bound HCB by the deposit feeding clam *Macoma nasuta* was determined using a clam ventilation chamber (mass balance study). 10 possible uptake routes were studied. It appeared that uptake of HCB by the gut from ingested solids was the single most important route (accounting for 63% to 84% of HCB residues) (Boese et al., 1990). In an experiment with the deposit-feeding marine bivalve *Abra nitida* it was found that the bioaccumulation of HCB in a water-sediment system increased in the presence of suspended solids (Ekelund et al., 1987). The fish *Pimephales promelas* , the worm *Lumbriculus variegatus* and the amphidods *Hyalella azteca* and *Gammarus lacustris* were exposed to HCB in water with or without a bed of HCB-spiked sediment for about 28 days. The waterborn HCB concentration was similar in both tests. BCF's were significantly higher in aquaria without sediment in the *L. variegatus* test (25,000 versus 6,700) and in one of the two tests with *P. promelas* (94,000 versus 50,000). The BCF's for *H. azteca* and *G. lacustris* were similar in both test systems; about 23,000 and 42,000, respectively. In the other test with *P. promelas* the BCF was about 90,000. The sediment appeared to be a more efficient sink for HCB than the organisms (Schuytema et al., 1990).
The uptake and bioconcentration of 37 chemicals (including 1,2-, 1,3- and 1,4-DCB, 1,2,3-, 1,2,4- and 1,3,5-TCB, 1,2,3,4- and 1,2,4,5-TeCB, PeCB and HCB) from Lake Ontario sediments by worms has been studied in laboratory aquaria. A sediment sample (OM=4.6%) was collected from the lake and prepared for the experiment by adding the chemicals slowly over a period of

several days. After a few days the "contaminated" sediment was placed in aquaria and allowed to settle. The tanks were filled with filtered water from Lake Ontario. Then worms, mainly *Tubifex tubifex* and *Limnodrilus hoffmeisteri*, were added to the tanks and exposed for 79 days. BCF's (concentration in worm dry weight/concentration in sediment) were <1 for all chlorobenzenes except for PeCB and HCB, which were 1.9 and 3.1, respectively. BCF's expressed as the concentration in worms dry weight/ the concentration in interstitial water for PeCB and HCB were 19,000 and 24,000, respectively, very similar to those obtained with fish (Oliver, 1987).

In a model ecosystem five aquatic species were exposed to HCB to study bioaccumulation rates. HCB-treated soils (0.1, 1 or 10 $mg.kg^{-1}$) were placed in tanks which were then filled with water. After one day daphnids *(Daphnia magna)*, snails *(Helisoma* sp.), a few strains of alga *(Oedogonium cardiacum)* and water containing diatoms, rotifers etc. were added. At day 30 some daphnids were taken out and two mosquito fish *(Gambusia affinis)* were added. Three days later all organisms were harvested and two catfish *(Ictalurus punctatus)* were added and exposed for 8 days. Mean whole-body BCF's were 740, 1500, 910, 1600 and 10,610 for algae, snails, daphnids, mosquito fish and catfish, respectively. In a similar experiment soil was used that had been treated with HCB a year before. The water concentration was higher and tissue concentrations lower, resulting in much lower BCF's; 570, 75, 120 and 400 for algae, snails, daphnids and fish, respectively (Isensee et al., 1976).

Quantitative structure activity relationships (QSAR's)

Many QSAR's have been established to relate the BCF's of (groups of chemicals including) chlorobenzenes to either the aqueous solubility (S) or the n-octanol/water partition coefficients (Kow). Könemann and Van Leeuwen (1980), for example, studied the accumulation and elimination of 6 chlorobenzenes in the fish *Poecilia reticulata* . BCF's on the basis of fat weight were calculated and related to Kow. Lineair regression resulted in a good correlation when HCB was excluded from the calulations: log BCF= 0.980 log Kow - 0.063 (r=0.991). For compounds with Kow-values of about 6 (like HCB) a decrease in bioaccumulation is expected, caused by a sharp decrease

in magnitude of uptake rate constant beyond the optimum value (Könemann and Van Leeuwen, 1980). Other QSAR's based on fish data were, among others, calculated by Veith et al. (1979), Van der Naald and Bruggeman (1988) and Neely et al. (1974).

2.2 TOXICITY

INTRODUCTION

All tests were evaluated on the basis of the primary literature source and were conducted according to current guidelines for aquatic toxicity testing. MCB, DCB's and TCB's are highly volatile compounds. Therefore, tests with these compounds were only taken into account when a) a closed or continuous flow system was used, or b) toxicant concentrations were analyzed during the test or when c) both criteria were fulfilled. The following studies were thus left out of consideration: Abernethy et al. (1986), Bringmann and Kühn (1980), Dawson et al. (1977), Huthchinson et al. (1980), LeBlanc (1980), Millington et al. (1988) and Pickering and Henderson (1966) for freshwater organisms and Abernethy et al. (1986), Curtis et al. (1979), Dawson et al. (1977) and Heitmuller et al. (1981) for marine organisms.

Freshwater organisms short-term

Short-term toxicity tests with freshwater organisms resulting in reliable L(E)C50-values are summarized in table 2.3.

Additional information

After an acute intraperitoneal injection of 1,103 $mg.kg^{-1}$ bw of MCB to *Salmo gairdneri* behavioural changes were observed as well as hepatotoxicity (Dalich et al., 1982). HCB was not acutely toxic to freshwater organisms at concentrations up to or exceeding the water solubility of the compound, appearing from tests with *Procambarus clarki* (Laska et al., 1978), the alga *Selenastrum capricornutum* , the water flea *Daphnia magna* and the fish *Salmo gairdneri* and *Brachydanio rerio* (Calamari et al., 1982). In

addition, exposure of the fish *Micropterus salmoides* up to 10 $mg.l^{-1}$ of HCB for 15 days caused no toxic effects neither did intraperitoneal injections of HCB (125 $mg.kg^{-1}$) dissolved in peanut oil given to the fish *Fundulus grandis* or *P. clarki* (Laska et al., 1978).

Freshwater organisms long-term

Data on long-term toxicity tests with freshwater organisms resulting in NOL(E)C- and L(E)C50-vales are summarized in table 2.4 and 2.5, respectively.

Additional information

The survival of two gram negative bacteria *Serratia liquefaciens* and *Pseudomonas aeruginosa* was affected at 300 and 800 $\mu g.ml^{-1}$ of HCB (in a benzene-ethanol solution), respectively (Hamdy, 1988). Incubation of the alga *Chlorella pyrenoidosa* over a period of 46 h with HCB (0,001, 0,01, 0,1, 1 and 10 $mg.l^{-1}$ in nutrient solution which contained acetone) led to a decrease of all growth parameters studied (chlorophyll content, total nitrogen etc.) in a dose-dependent way. After an incubation period of three months only the highest concentration (10 $mg.l^{-1}$) had a slight negative effect on algal growth measured as chlorophyl content, while 0.1 and 1 $mg.l^{-1}$ had a significant stimulating effect (Geike and Parasher, 1976a). Incubation of the alga *Tetrahymena pyriformis* with HCB (0.001-0.5 $mg.l^{-1}$) for 10 days decreased growth measured as dry weight, carbohydrates and total nitrogen (Geike and Parasher, 1976b). Exposure to a concentration of 5 $\mu g.l^{-1}$ for 2 to 68 days under continuous flow conditions did not cause toxic effects in the cladoceran *Daphnia magna*, the amphipods *Hyalella azteca* and *Gammarus lacustris*, the worm *Lumbricus variegatus* and the fish *Pimephales promelas* (Nebeker et al., 1989). Long-term exposure (period not exactly given) to HCB at concentrations up to and exceeding its water solubility did also not cause toxicity in the crustacean *Procambarus clarki*, or in the fish *Poecilia latipinna*, *Fundulus grandis* and *Micropterus salmoides* (Laska et al., 1978).

The effect of 1,2,4-TCB on freshwater plankton was studied in an outdoor-model-ecosystem. A natural pond, rich in *Daphnia* and phytoplankton species, was divided into compartments. The investigation period covered two weeks and three weeks post-application phases. The mean initial (measured) concentration of 1,2,4-TCB was 215 $\mu g.l^{-1}$ decreasing to less than 40-80 $\mu g.l^{-1}$ within 20 days. With regard to phytoplankton no effects on diversity or abundance were observed. In contrast, 1,2,4-TCB was toxic to the daphnid-population. The mean number of daphnids from the treated compartments was less than 10% of the controls during post-application period. A regeneration phase seemed to begin at day 21, when the concentration was 50-100 $\mu g.l^{-1}$ (Lay et al., 1985).

Marine organisms short- and longterm

Short- and long-term toxicity tests with marine organisms resulting in L(E)C50- or NOL(E)C-values are summarized in table 2.6.

Additional information - short-term toxicity

The effects of exposure to 1,4-DCB and TCB (isomer not given) on the embryonic development and survival/development of larvae of the clam *Mercenaria mercenaria* and the oyster *Crassostrea virginica* were studied. The test compounds (in acetone solution) were renewed every second day. The tests with TCB resulted in 48-h EC50-values (based on development of eggs) of 3.1 $mg.l^{-1}$ and >10 $mg.l^{-1}$ for *C. virginica* and *M. mercenaria* . The 12-d LC50-value (larvae survival) for TCB was reported to be >10 $mg.l^{-1}$ for *M. mercenaria*. The tests with 1,2-DCB resulted in an 48-h LC50-value of >100 $mg.l^{-1}$ and a 12-d LC50-value of >100 $mg.l^{-1}$ for *M. mercenaria* (Davis and Hidu, 1969). The toxicity of HCB in seawater and sandy sediment (97% sand, 0.28% organic carbon) to the shrimp *Crangon septemspinosa* was determined in 96-h static tests. In both tests no mortality was found at the highest concentrations tested: 7.2 $\mu g.l^{-1}$ in the water-test and 300 $mg.kg^{-1}$ in the sediment-water test (McLeese and Metcalf, 1980).

Additional information - long-term toxicity

Exposure of marine phytoplankton (mixed laboratory cultutes of a diatom *Thalassiosira pseudonana* and a green alga *Dunaliella tertiolecta)* to 50 or

100 $\mu g.l^{-1}$ of HCB (dissolved in acetone) for 3 days did not result in effects on algal growth or size of progeny (Biggs et al., 1979). Exposure of the alga *Skeletonema costatum* to MCB in a closed static system for 5-days resulted in a NOEC-value of 100 $mg.l^{-1}$ (nominal), based on total cell count or total cell volume (Cowgill et al. 1989).
The toxicity of sediment-bound 1,2,4-TCB to the shrimp *Palaemonetes pugio* and the amphioxus *Branchiostoma caribaeum* was investigated. Sediments contaminated with 10,000 $\mu g.kg^{-1}$ were not lethal to *P. pugio* in both a static and a flow-through test. Exposure to 10,000 or 240,000 $\mu g.kg^{-1}$ of 1,2,4-TCB in sediment caused 0% and 100% mortality, respectively, to *B. caribaeum*. The 10-d LC50 was determined at 200,000 $\mu g.kg^{-1}$. It must be noted that 240,000 $\mu g.kg^{-1}$ TCB in sediment would yield a concentration of 13,000 $\mu g.l^{-1}$ in the overlying water, exceeding the lethal concentration for this organism (10,000 $\mu g.l^{-1}$) (Clark et al., 1987).

Quantitative structure activity relationships (QSAR's)

The toxicity of chlorobenzenes, especially the acute toxicity, correlates strongly with both the Kow and the aqueous solubility (S) of the substances. QSAR's have been developed using toxicity data derived from experiments with algae (Wong et al., 1984), daphnids (Bobra et al., 1985) and fish (Könemann, 1980, 1981, Veith et al., 1983, Neely, 1984) (see table 2.2). A high quality QSAR might indicate that the wotrking mechanism of the group of chemicals is similar. The lethal effect of the chlorobenzenes is probably caused by membrane perturbation and this seems to be a minimum effect: a hydrophobic substance is (within error) at least as toxic as is calculated from its QSAR, unless it is strongly metabolized (Könemann, 1981).
A QSAR-analysis was performed on substituted benzenes for which toxicity values have been obtained over 96-h in the fathead minnow *Pimephales promelas*. The additive toxicity of several substituent groups was determined. A decreasing contribution to toxicity was found to be Cl>Br>NO2>CH3>OCH3>NH2>OH. With regard to the chlorobenzenes as a seperate group it was found that the toxicity increases with the number of chlorine atoms and that the position of the chlorine atom on the benzene ring does not have a significant influence on the toxicity (Hall et al., 1984).

Summary and conclusions "Aquatic organisms"

Accumulation

Most experimental data of bioaccumulation concern freshwater organisms (mainly fish); "whole body" BCF's *[the concentration in organisms divided by the concentration in water]* ranged from 12-450, 66-740, 700-4100, 2400-13000, 3400-20000 and 7880-75000 for MCB DCB's, TCB's, TeCB's, PeCB and HCB, respectively. It appeared that all chlorobenzenes bioaccumulate, with the tendency increasing with the number of chlorine atoms. Bioaccumulation is mainly determined by lipid solubility as indicated by the n-octanol/water partition coefficient (Kow), which increases with the degree of chlorination. Many quantitative structure activity relationships (QSAR's) have been established to relate the BCF's of chlorobenzenes to either the water solubility or the lipid solubility.

Chlorobenzenes also accumulate in marine organisms (limited data), but to a lesser extent than freshwater organisms. A number of studies (worms and larvae of midges) indicate that the uptake of sediment-bound chlorobenzenes was mediated by uptake from interstitial water.

Toxicity to freshwater organisms

For most chlorobenzenes acute toxicity data (48 h L(E)C50-values) were available for algae, crustaceans and fish. The lowest L(E)50-values from "single species" tests were 660 $\mu g.l^{-1}$ for MCB (a short-term "early life stage" test with fish), 700 $\mu g.l^{-1}$ for DCB's, 350 $\mu g.l^{-1}$ for TCB's, 860 $\mu g.l^{-1}$ for TeCB's, 250 $\mu g.l^{-1}$ for PeCB and <30 $\mu g.l^{-1}$ for HCB. In some studies with higher chlorinated chlorobenzenes (1,2,3,5-and 1,2,4,5-TeCB, PeCB and HCB) L(E)C50-values were reported at concentrations up to or exceeding the water solubility. The relevance of these values, which were obtained using solvents, is debatable.

With respect to chronic toxicity data are rather limited. In most cases NOE(L)C-values were only available for crustaceans (mainly *Daphnia magna)* and fish (various species). Data on the toxicity of chlorobenzenes to developmental stages (embryo, larval, juvenile) of fish were reported for all (groups of) isomers. The lowest NOE(L)C-values were 320 $\mu g.l^{-1}$ for MCB, (≥)122 $\mu g.l^{-1}$ for DCB's, 40 $\mu g.l^{-1}$ for TCB's, 10 $\mu g.l^{-1}$ for TeCB's, 10 $\mu g.l^{-1}$ for PeCB and 1.8 $\mu g.l^{-1}$ for HCB. These NOEC-values show an

increasing toxicity with an increase in degree of chlorination. Toxicity is also (similar to bioconcentration) mainly determined by lipid solubility (Kow). QSAR's have been established to relate the, especially acute, toxicity of chlorobenzenes to either the water solubility or the lipid solubility (see table 2.2).

Toxicity to marine organisms

Data on the toxicity of chlorobenzenes to marine organisms are very limited, especially with regard to chronic toxicity. The lowest 48/96 h L(E)C50-values were 540 $\mu g.l^{-1}$ for 1,2,4-TCB, 3700 $\mu g.l^{-1}$ for 1,2,3,5-TeCB, 330 $\mu g.l^{-1}$ for 1,2,4,5-TeCB and 800 $\mu g.l^{-1}$ for PeCB. Only one long-term study (fish) was available, which resulted in a NOLC of 90 $\mu g.l^{-1}$.

Table 2.1 Overview of "whole-body" or "lipid" BCF's for freshwater organisms

Chlorobenzene	Species	BCF (2)	Reference(s)
HCB	fish	12-450	Kenaga '80; EPA, '84
1,2-DCB	fish	89-560	Barrows et al. '80; Oliver & Niimi '83
1,3-DCB	fish	66-740	Barrows et al. '80; Carlson & Kosian '87; Oliver & Niimi '83
1,4-DCB	fish	15-720	Barrows et al. '80; Neely et al. '74 Calamari et al. '82; Kenaga '80; Carlson & Kosian '87; EPA '84; Oliver & Niimi '83
	fish	1,800 *	Könemann '80
1,2,3-TCB	fish	700-2,600	Könemann & van Leeuwen '80
	fish	13,000 *	Könemann '80
1,2,4-TCB	fish	182-3,200	Barrows et al.'80; Veith et al. '79; EPA '84; Oliver & Niimi '83
1,3,5-TCB	fish	760-4,100	Könemann & van Leeuwen '80; Oliver & Niimi '83
	fish	14,000 *	Könemann '80
1,2,3,4-TeCB	fish	2,400-12,000	Carlson & Kosian '87; EPA '84; Oliver & Niimi '83
1,2,3,5-TeCB	fish	1,800-3,900	Barrows et al. '80; Konemann & van Leeuwen '80
	fish	72,000 *	Könemann '80
1,2,4,5-TeCB	fish	4,000-13,000	Kenaga '80; EPA '84; Oliver & Niimi '83
PeCB	fish	3,400-20,000	Barrows et al. '80; Kenaga '80; Renberg et al. '85; Carlson & Kosian '87 Könemann & van Leeuwen '80; Oliver & Niimi '83
	fish	260,000 *	Könemann '80
HCB	fish	7,880-22,000	Neely et al. '74; Kenaga '80; Veith et al. '79; Carlson & Kosian '87; Nebeker et al. '89; Oliver & Niimi '83
	crus.	13,200-75,000	Nebeker et al. '89
		354,000-6000,000 *	
	fish	177,000-306,000 *	Nebeker et al. '89; Könemann '80

* = "lipid"-BCF

(2) Whole body BCF, under flow-through conditions.

Table 2.2 Overview of a selected number of quantitative structure activity relationships
Toxicity - physical/chemical fators

Species or test-system	(group) of chemicals	QSAR	Reference
Acute toxicity			
Ankistrodesmus falcatus	benzene and 12 chlorobenzenes	log 1/EC50= -0.587 log S + 2.419 log 1/EC50= 0.985 log Kow- 2.626 (r=0.985)	* Wong et al. '84
Daphnia magna	6 chlorobenzenes	log EC50= -0.301-0.548 log S (r=0.989) log EC50= 3.55- 0.659 log Kow (r=0.981)	Bobra et al. '85
Poecilia reticulata 2-3 months old	benzene and 12 chlorobenzenes	log 1/LC50= 0.845 log Kow-4.63 (r=0.980)	** Könemann '80
idem	benzene and 12 chlorobenzenes	log LC50= 0.85 log K_{ow} -1.37 (r=0.980)	Hoornstra '88
Daphnia magna	chlorobenzenes	log 1/LC50= 0.90 log Kow -2.65 (r=0.924)	Richter et al. '83
Chronic toxicity			
Daphnia magna	4 chlorobenzenes and 4-chlorotoluene	log 1/$NOEC_r$ = 0.67 log Kow - 2.82 (r=0.995)	De Wolf et al. '88
Branchydanio rerio Pimephales promelas	4 chlorobenzenes and 4-chlorotoluene	log 1/NOEC = 0.67 log Kow - 2.82 (r=0.995)	Van Leeuwen et al. '90

r = regression coefficient
$NOEC_r$ = no-effect-concentration based on reproduction (in µmol/l)
$NOEC_g$ = no-effect-concentration based on growth (in µmol/l)

* HCB was left out of these equations because if its low toxicity.
** The validity of this QSAR ends at log Kow= ±6. This can be caused by the very slight solubility of very hydrophobic substances and by possible theoretical deviation from linearity of the QSAR at log Kow >6 (Könemann, 1980).

Table 2.3 Freshwater organisms - short-term toxicity tests with chlorobenzenes: L(E)C50-values

Organism	A	Test-type	Test sub. purity	Test-water.	pH	Hardness mg $CaCO_3$/l	Exp.-time	Crite-rion	Result µg/l		Reference
Monochlorobenzene											
Algae											
Selenastrum capricornutum	+	c-S	ag	s.w.	-	--	3-h	EC50	33,000	[1]	Calamari et al. '83
Ankistrodesmus falcatus	-	c-S	--	n.m.	8	--	4-h	$EC50_g$	49,980		Wong et al. '84
Crustaceans											
Daphnia magna	+	c-S	ag	s.w.	-	--	24-h	$EC50_i$	4,300	[1]	Calamari et al. '83
Daphnia magna	-	c-S	--	lake	8.0	160	48-h	$LC50^i$	13,000		Cowgill et al. '85
Daphnia magna	-	c-S	≥97%	s.w.	-	--	48-h	$EC50_i$	5,810		Abernethy et al. '86
Ceriodaphnia dubia/affinis	-	c-S	--	lake	8.0	90	48-h	$LC50^i$	7,900		Cowgill et al. '85
Fish											
Branchydanio rerio	+	c-S	ag	s.w.	7.4	320	48-h	LC50	10,500	[1]	Calamari et al. '83
Salmo gairdneri	+	c-S	ag	s.w.	7.4	320	48-h	LC50	4,100	[1]	Calamari et al. '83
Lepomis macrochirus	-	c-S	≥80%	r.w.	6.7-7.8	32-48	96-h	LC50	16,000	[4]	Buccafusco et al. '81
Pimephales promelas (fry)	-	c-S	rg	s.w.	7.6-8.3	96-125	96-h	LC50	22,300		Mayes et al. '83
Carassius auratus egg <1-d old --> hatching	+	c-CF	--	r.w.	7.3-8.1	200	3.5-d	LC50	4,080	α	Birge et al. '79
Micropterus salmoides egg <1-d old --> hatching	+	c-CF	--	r.w.	7.3-8.1	50	3.5-d	LC50	660	α	Birge et al. '79
1,2 - dichlorobenzene											
Algae											
Selenastrum capricornutum	+	c-S	ag	s.w.	-	--	3-h	EC50	2,200	[1]	Calamari et al. '83
Scenedesmus pannonicus	+	c-S	99.9	s.w.	-	--	24-h	EC50	17,000	α	Canton et al. '85
Ankistrodesmus falcatus	-	c-S	--	n.m.	8	--	4-h	$EC50_g$	20,000		Wong et al. '84
Crustaceans											
Daphnia magna	+	c-S	ag	s.w.	-	--	24-h	$EC50_i$	780	[1]	Calamari et al. '83
Daphnia magna	-	c-S	≥97%	s.w.	-	--	48-h	$EC50_i$	2,350		Abernethy et al. '86
Daphnia magna	+	c-S	99.9	s.w.	-	--	48-h	$EC50_i$	740	α	Canton et al. '85
								$LC50^i$	2,200	α	Canton et al. '85
Daphnia magna	-	c-S	--	tap	7.6-7.7	16	24-h	EC50	1,700		Kühn et al. '89
Fish											
Salmo gairdneri	+	c-S	ag	s.w.	7.4	320	48-h	LC50	10,000	[1]	Calamari et al. '83
Branchydanio rerio	+	c-S	ag	s.w.	7.4	320	48-h	LC50	6,800	[1]	Calamari et al. '83
Lepomis macrochirus	-	c-S	≥80%	r.w.	6.7-7.8	32-48	96-h	LC50	5,600	[4]	Buccafusco et al. '81
1,3 - dichlorobenzene											
Algae											
Scenedesmus pannonicus	+	c-S	99.4	s.w.	-	--	24-h	EC50	31,000	α	Canton et al. '85
Ankistrodesmus falcatus	-	c-S	--	n.m.	8	--	4-h	$EC50_g$	22,930		Wong et al. '84

Table 2.3 Freshwater organisms - short-term toxicity tests with chlorobenzenes: L(E)C50-values (continued)

Organism	A	Test-type	Test sub. purity	Test-water.	pH	Hardness mg $CaCO_3$/l	Exp.-time	Crite-rion	Result µg/l		Reference
Crustaceans											
Daphnia magna	+	S	98%	lake	7.1-7.7	45	48-h	LC50	7,400	α	Richter et al. '83
								$EC50_i$	4,200	α	Richter et al. '83
Daphnia magna	+	c-S	99.4%	s.w.	-	--	48-h	$EC50_i$	1,200	α	Canton et al. '85
							48-h	$LC50^i$	6,800	α	Canton et al. '85
Daphnia magna	-	c-S	--	tap	7.6-7.7	16	24-h	EC50	7,000		Kühn et al. '89
Fish											
Pimephales promelas (30-d old)	+	CF	98%	lake	7.3-7.6	45	96-h	LC50	7,800	α	Carlson & Kosian '87
Pimephales promelas	+	CF	--	lake	7.5	42-46	96-h	LC50	7,800		Veith et al. '83
Lepomis macrochirus	-	c-S	≥80%	r.w.	6.7-7.8	32-48	96-h	LC50	5,000	[4]	Buccafusco et al. '81
1,4 - dichlorobenzene											
Algae											
Selenastrum capricornutum	+	c-S	ag	s.w.	-	--	3-h	$EC50_g$	5,200	[1]	Calamari et al. '82
											Calamari et al. '83
Scenedesmus pannonicus	+	c-S	99.7	s.w.	-	--	24-h	EC50	31,000	α	Canton et al. '85
Ankistrodesmus falcatus	-	c-S	--	n.m.	8	--	4-h	$EC50_g$	20,000		Wong et al. '84
Crustaceans											
Daphnia magna	+	c-S	ag	s.w.	-	--	24-h	$EC50_i$	1,600	[1]	Calamari et al. '82
											Calamari et al. '83
Daphnia magna	+	c-S	99.4%	s.w.	-	--	48-h	$EC50_i$	700	α	Canton et al. '85
							48-h	$LC50^i$	2,200	α	Canton et al. '85
Daphnia magna	-	c-S	--	tap	7.6-7.7	16	24-h	EC50	3,200		Kühn et al. '89
Fish											
Salmo gairdneri	+	c-S	ag	s.w.	7.4	320	48-h	LC50	1,180	[1]	Calamari et al. '83
Branchydanio rerio	+	c-S	ag	s.w.	7.4	320	48-h	LC50	4,250	[1]	Calamari et al. '83
Pimephales promelas (30-d old)	+	CF	97%	lake	7.3-7.6	45	96-h	LC50	4,200	α	Carlson & Kosian '87
Pimephales promelas	+	S	--	r.s.w.	7.2-7.9	40-48	96-h	LC50	2,400	α	Curtis et al. '79
										[5]	Curtis & Ward '81
Pimephales promelas	+	CF	--	lake	7.5	42-46	96-h	LC50	4,000		Veith et al. '83
Pimephales promelas (fry)	-	c-S	rg	s.w.	7.6-8.3	96-125	96-h	LC50	3,600		Mayes et al. '83
Lepomis macrochirus	-	c-S	≥80%	r.w.	6.7-7.8	32-48	96-h	LC50	4,300	[4]	Buccafusco et al. '81
1,2,3 - trichlorobenzene											
Algae											
Selenastrum capricornutum	+	c-S	ag	s.w.	-	--	3-h	EC50	2,200	[1]	Calamari et al. '83
Ankistrodesmus falcatus	-	c-S	--	n.m.	8	--	4-h	$EC50_g$	5,990		Wong et al. '84

Table 2.3 Freshwater organisms - short-term toxicity tests with chlorobenzenes: L(E)C50-values (continued)

Organism	A	Test-type	Test sub. purity	Test-water.	pH	Hardness mg $CaCO_3$/l	Exp.-time	Crite-rion	Result µg/l		Reference
Crustaceans											
Daphnia magna	+	c-S	ag	s.w.	-	--	24-h	$EC50_i$	350	[1]	Calamari et al. '83
Daphnia magna	-	c-S	>97%	s.w.	6-7	--	48-h	$EC50_i$	2,720		Bobra et al. '83
Daphnia magna	-	c-S	≥97%	s.w.	-	--	48-h	$EC50_i$	1,450		Abernethy et al. '86
Fish											
Salmo gairdneri	+	c-S	ag	s.w.	7.4	320	48-h	LC50	710	[1]	Calamari et al. '83
Branchydanio rerio	+	c-S	ag	s.w.	7.4	320	48-h	LC50	3,100	[1]	Calamari et al. '83
1,2,4 - trichlorobenzene											
Algae											
Selenastrum capricornutum	+	c-S	ag	s.w.	-	--	3-h	EC50	3,900	[1]	Calamari et al. '83
Ankistrodesmus falcatus	-	c-S	--	n.m.	8	--	4-h	$EC50_g$	5,990		Wong et al. '84
Crustaceans											
Daphnia magna	+	c-S	ag	s.w.	-	--	24-h	$EC50_i$	1,200	[1]	Calamari et al. '83
Daphnia magna	+	S	--	lake	7.1-7.7	45	48-h	$LC50^i$	2,100	α	Richter et al. '83
Fish											
Pimephales promelas (30-d old)	+	CF	--	lake	7.3-7.6	45	96-h	LC50	2,800	α	Carlson & Kosian '87
Pimephales promelas	+	CF	--	lake	7.5	42-46	96-h	LC50	2,900		Veith et al. '83
Salmo gairdneri	+	c-S	ag	s.w.	7.4	320	48-h	LC50	1,950	[1]	Calamari et al. '83
Branchydanio rerio	+	c-S	ag	s.w.	7.4	320	48-h	LC50	6,300	[1]	Calamari et al. '83
Lepomis macrochirus	-	c-S	≥80%	r.w.	6.7-7.8	32-48	96-h	LC50	3,400	[4]	Buccafusco et al. '81
1,3,5-trichlorobenzene											
Algae											
Ankistrodesmus falcatus	-	c-S	--	n.m.	8	--	4-h	$EC50_g$	9,070		Wong et al. '84
1,2,3,4 - tetrachlorobenzene											
Algae											
Ankistrodesmus falcatus	-	c-S	--	n.m.	8	--	4-h	$EC50_g$	4,100		Wong et al. '84
Fish											
Pimephales promelas (30-d old)	+	CF	99%	lake	7.3-7.6	45	96-h	LC50	1,100	α	Carlson & Kosian '87
Pimephales promelas	+	CF	--	lake	7.5	42-46	96-h	LC50	1,100		Veith et al. '83
1,2,3,5 - tetrachlorobenzene											
Algae											
Chlamydomonas angulosa	-	S	--	n.m.	6.5	--	3-h	EC50	1,580		Hutchinson et al. '80

Table 2.3 Freshwater organisms - short-term toxicity tests with chlorobenzenes: L(E)C50-values (continued)

Organism	A	Test-type	Test sub. purity	Test-water.	pH	Hardness mg $CaCO_3$/l	Exp.-time	Crite-rion	Result µg/l	Reference
Chlorella vulgaris	-	S	--	n.m.	6.5	--	3-h	EC50	2,500	Hutchinson et al. '80
Ankistrodesmus falcatus	-	c-S	--	n.m.	8	--	4-h	$EC50_g$	3,022	Wong et al. '84
Crustaceans										
Daphnia magna < 1-d old	-	S	≥80%	r.w.w.	7.4-9.4	173	48-h	LC50	9,700 [3]	LeBlanc '80
Daphnia magna	-	c-S	>97%	s.w.	6-7	--	48-h	$EC50_i$	1,730	Bobra et al. '83
Daphnia magna	-	c-S	>97%	s.w.	-	--	48-h	$EC50_i$	860	Abernethy et al. '86
Fish										
Lepomis macrochirus	-	c-S	≥80%	r.w.	6.7-7.8	32-48	96-h	LC50	6,400 [4]	Buccafusco et al. '81
1,2,4,5 - tetrachlorobenzene										
Algae										
Ankistrodesmus falcatus	-	c-S	--	n.m.	8	--	4-h	$EC50_g$	4,965	Wong et al. '84
Crustaceans										
Daphnia magna < 1-d old	-	S	≥80%	r.w.w.	7.4-9.4	173	48-h	LC50	>530,000 [3]	LeBlanc '80
Fish										
Salmo gairdneri early fry	-	R	97%	s.w.	7.2	50	96-h	LC50	1,200 [2]	Van Leeuwen et al. '85
Lepomis macrochirus	-	c-S	≥80%	r.w.	6.7-7.8	32-48	96-h	LC50	1,600 [4]	Buccafusco et al. '81
pentachlorobenzene										
Algae										
Ankistrodesmus falcatus	-	c-S	--	n.m.	8	--	4-h	$EC50_g$	1,250	Wong et al. '84
Crustaceans										
Daphnia magna <24-h old	-	S	≥80%	r.w.w.	7.4-9.4	173	48-h	LC50	5,300 [3]	LeBlanc '80
Daphnia magna	-	c-S	>97%	s.w.	6-7	--	48-h	$EC50_i$	1,250	Bobra et al. '83
Daphnia magna	-	S	≥97%	s.w.	-	--	48-h	$EC50_i$	300	Abernethy et al. '86
Fish										
Lepomis macrochirus	-	c-S	≥80%	r.w.	6.7-7.8	32-48	96-h	LC50	250 [4]	Buccafusco et al. '81
hexachlorobenzene										
Algae										
Selenastrum capricornutum	+	c-S	ag	s.w.	-	--	3-h	EC50	30 [1]	Calamari et al. '83
							96-h	$EC50_g$	<30 [1]	Calamari et al. '83

Table 2.3 Freshwater organisms - short-term toxicity tests with chlorobenzenes: L(E)C50-values (continued)

Organism	A	Test-type	Test sub. purity	Test-water.	pH	Hardness mg $CaCO_3$/l	Exp.-time	Crite-rion	Result µg/l	Reference
Crustaceans										
Daphnia magna	+	c-S	ag	s.w.	-	--	24-h	$EC50_i$	<30 [1]	Calamari et al. '83
Fish										
Salmo gairdneri	+	c-S	ag	s.w.	7.4	320	48-h	LC50	<30 [1]	Calamari et al. '83
Branchydanio rerio	+	c-S	ag	s.w.	7.4	320	48-h	LC50	<30 [1]	Calamari et al. '83

rg = reagent-grade quality; ag = analytical grade quality; n.m. = nutrient medium; s.w. = standard water; r.w. = recontituted water; w.w. = well water; r.w.w. = reconstituted well water; r.s.w. = reconstituted soft water; i = immobility; g = growth.
For explanation, see "list of abbreviations tables 2.3 to 2.6".

[1] For all chlorobenzenes tested the loss of compound did not exceed 10% of the initial value, except for the Daphnia test in which it did not exceed 15%.

[2] Tests were performed with life stages from 0-77 days; egg 0-h, egg 24-h, early eyed egg 14-d, late eyed egg 28-d, sac fry 42-d and early fry 77-d. The early fry stage appeared to be the most critical stage, resulting in a 96-h LC50-value of 1,200 µg/l. For all other egg stages the 96-h LC50-values were 10,000 µg/l.

[3] The range of pH-values is based on all tests that were conducted (including those on other compounds). The vessels with test solutions were covered with a plastic wrap secured with an elastic band.

[4] The range of pH-values is based on all tests that were conducted (including those on other compounds). The range of dissolved oxygen concentration was 9.7 (at start) to 0.3 (after 96-h) mg/l. The acute toxicity of some chemicals was tested above their water solubility. Therefore in the tests with MCB, 1,3-DCB and 1,2,4,5-TeCB undissolved chemical was present in the test solution, whereas the test solution of 1,4-DCB, 1,2,3,5-TeCB, 1,2,4,5-TeCB and PeCB contained precipitates. The vessels were "capped" in an effort to control volatilization.

[5] On the basis of the same test Curtis and Ward (1981) reported 96-h LC50-values based on nominal concentrations of 57 and 30 mg/l for 1,2-DCB and 1,4-DCB, respectively. The concentrations of 1,2-DCB were not measured, therefore no reliable LC50-value can be given.

Table 2.4 Freshwater organisms - long-term toxicity tests with chlorobenzenes: NOE(L)C-values

Organism	A	Test-type	Test-subst. purity	Test-water.	pH	Hardness mg $CaCO_3$/l	Exp.-time	Crite-rion	Result µg/l		Reference
monochlorobenzene											
Crustaceans											
Daphnia magna	+	R	--	s.w.	-	--	16-d	$NOEC_r$	320	[4]	Hermens et al. '84
								$NOLC_r$	1,000		Hermens et al. '84
Daphnia magna	+	R	--	s.w.	-	--	16-d	$NOEC_g$	320	[6]	De Wolf et al. '88
								$NOEC_g$	1,000		De Wolf et al. '88
Daphnia magna	+	c-R	ag	s.w.	-	--	2-w	$NOEC_r$	1,050	[8]	Calamari et al. '83
Fish											
Salmo gairdneri	-	CF	--	w.w.	-	--	30-d	NOLC	2,900	[9]	Dalich et al. '82
Branchydanio rerio	+	R	>99	r.w.	7.4-8.4	210	28-d	NOEC	4,800 α		Van Leeuwen et al.'90
egg <1-d old --> fry								$NOLC_g$	8,500 α		Van Leeuwen et al.'90
1,2-dichlorobenzene											
Crustaceans											
Daphnia magna	+	c-R	--	tap	6.6-7.6	16	21-d	$NOEC_r$	505 α	[9]	Kühn et al. '89
								$NOLC_r$	505 α		Kühn et al. '89
Daphnia magna	+	$c\text{-}R_d$	ag	s.w.	-	--	2-w	$NOEC_r$	185	[8]	Calamari et al. '83
1,3-dichlorobenzene											
Crustaceans											
Daphnia magna	+	R	95-99	lake	6.6-7.9	45	28-d	$NOEC_r$	690 α		Richter et al. '83
								$NOEC_r$	690 α		Richter et al. '83
Daphnia magna	+	c-R	--	tap	6.6-7.6	16	21-d	$NOEC_g$	650 α	[9]	Kühn et al. '89
Daphnia magna	+	CF	98%	lake	7.4-6.9	42	28-d	$NOEC_r$	690		Call et al. '83
Fish											
Pimephales promelas	+	CF	98%	lake	7.3-7.6	44-46	32-d	NOEC	1,000 α		Carlson & Kosian '87
embryo->early juvenile								$NOLC_g$	2,400 α		Carlson & Kosian '87
1,4-dichlorobenzene											
Algae											
Selenastrum capricornutum	+	c-S	ag	s.w.	-	--	96-h	$NOEC_g$	570		Calamari et al. '83
Crustaceans											
Daphnia magna	+	c-R	--	tap	6.6-7.6	16	21-d	NOEC	400 α	[9]	Kühn et al. '89
Daphnia magna	+	c-R	ag	s.w.	-	--	8-d	$NOEC_r$	220		Calamari et al. '82
Daphnia magna	+	c-R	ag	s.w.	-	--	2-w	$NOEC_r$	320	[8]	Calamari et al. '83
Fish											
Pimephales promelas	+	CF	97%	lake	7.3-7.6	44-4	32-d	NOEC	570 α		Carlson & Kosian '87
embryo --> early juvenile								$NOLC_g$	570 α		Carlson & Kosian '87

Table 2.4 Freshwater organisms - long-term toxicity tests with chlorobenzenes: NOE(L)C-values (continued)

Organism	A	Test-type	Test-subst. purity	Test-water.	pH	Hardness mg $CaCO_3$/l	Exp.-time	Crite-rion	Result µg/l		Reference
Salmo gardneri eggs --> alevin	+	c-CF	ag	s.w.	-	--	60-d	$NOEC_{m,h}$	≥122	[3]	Calamari et al. '82
Branchydanio rerio eggs <1-d old --> fry	+	R	99%	r.w.	7.4-8.4	210	28-d	$NOEC_g$	650 α		Van Leeuwen et al.'90
								$NOLC_g$	2,100 α		Van Leeuwen et al.'90
1,2,3-trichlorobenzene											
Algae											
Selenastrum capricornutum	+	c-S	ag	s.w.	-	--	96-h	$NOEC_g$	110		Calamari et al. '83
Crustaceans											
Daphnia magna	+	c-R	ag	s.w.	-	--	2-w	$NOEC_r$	40	[8]	Calamari et al. '83
Fish											
Branchydanio rerio eggs <1-d old --> fry	+	R	99%	r.w.	7.4-8.4	210	28-d	$NOEC_g$	250 α		Van Leeuwen et al.'90
								$NOLC_g$	450 α		Van Leeuwen et al.'90
1,2,4-trichlorobenzene											
Algae											
Selenastrum capricornutum	+	c-S	--	s.w.	-	--	96-h	$NOEC_g$	190		Calamari et al. '83
Crustaceans											
Daphnia magna	+	R	95-99%	lake	6.6-7.9	45	28-d	$NOEC_r$	360 α		Richter et al.'83
								$NOEC_r$	360 α		Richter et al.'83
Daphnia magna	+	c-R	ag	s.w.	-	--	28-d	$NOEC_g$	190		Calamari et al.'83
Daphnia magna	+	R	--	s.w.	-	--	16-d	$NOEC_r$	100	[4]	Hermens et al. '84
								$NOLC_r$	320		Hermens et al. '84
Daphnia magna	+	R	--	s.w.	-	--	16-d	$NOEC_g$	100	[6]	De Wolf et al. '88
								$NOEC_r$	181		De Wolf et al. '88
Daphnia magna	+	CF	99%	lake	7.3-6.6	45	28-d	$NOEC_r$	360		Call et al. '83
Daphnia magna	+	c-R	ag	s.w.	-	--	2-w	$NOEC_r$	160	[8]	Calamari et al. '83
Fish											
Pimephales promelas embryo --> early juvenile	+	CF	--	lake	7.3-7.6	44-46	32-d	$NOEC_g$	500 α		Carlson & Kosian '87
1,2,3,4-tetrachlorobenzene											
Crustaceans											
Daphnia magna	+	R	98	s.w.	-	--	16-d	$NOEC_r$	10	[4]	Hermens et al. '84
								$NOLC_r$	100		Hermens et al. '84
Daphnia magna	+	R	--	s.w.	-	--	16-d	$NOEC_g$	55	[6]	De Wolf et al. '88
								$NOEC_r$	55		De Wolf et al. '88

Table 2.4 Freshwater organisms - long-term toxicity tests with chlorobenzenes: NOE(L)C-values (continued)

Organism	A	Test-type	Test-subst. purity	Test-water.	pH	Hardness mg $CaCO_3$/l	Exp.-time	Crite-rion	Result µg/l		Reference
Fish											
Pimephales promelas embryo --> early juvenile	+	CF	99%	lake	7.3-7.6	44-46	33-d	NOEC	250 α		Carlson & Kosian '87
								NOLC[g]	250 α		Carlson & Kosian '87
Branchydanio rerio eggs <1-d old --> fry	+	R	--	r.w.	7.4-8.4	210	28-d	NOEC	100 α		Van Leeuwen et al.'90
								NOLC[g]	310 α		Van Leeuwen et al.'90
pentachlorobenzene											
Crustaceans											
Daphnia magna P < 1-d old	-	R	≥98%	lake	8.1	225	3-w	NOEC[g]	56		Van Leeuwen et al.'87
								NOLC	100		Van Leeuwen et al.'87
								NOEC	100		Van Leeuwen et al.'87
Daphnia magna	+	R	--	s.w.	-	--	16-d	NOEC[r]	31	[6]	De Wolf et al. '88
								NOEC[g]	31		De Wolf et al. '88
Daphnia magna	+	R	--	s.w.	-	--	16-d	NOEC[r]	10	[4]	Hermens et al. '84
								NOLC[r]	100		Hermens et al. '84
Daphnia magna exponentially growing populations	+	CF	≥98%	lake	8.1	225	2-w	NOEC[y]	50 α	[2]	Van Leeuwen et al. '87
Fish											
Pimephales promelas embryo-early juvenile	+	CF	98%	lake	7.3-7.6	44-46	31-d	NOEC	≥55 α	[1]	Carlson & Kosian '87
								NOLC[g]	≥55 α		Carslon & Kosian '87
Branchydanio rerio eggs < 1-d old --> fry	+	R	98	r.w.	7.4-8.4	210	28-d	NOEC	34 α		Van Leeuwen et al.'90
								NOLC[g]	110 α		Van Leeuwen et al.'90
hexachlorobenzene											
Algae											
Selenastrum capricornutum	+	c-S	ag	s.w.	-	--	96-h	NOEC[g]	14	[7]	Calamari et al. '83
Worms											
Lumbriculus variegatus	+	CF	--	w.w.	7.0	25-35	49-d	NOEC	≥4.7		Nebeker et al. '89
								NOEC[g]	≥4.7		Nebeker et al. '89
								NOLC[r]	≥4.7		Nebeker et al. '89
Crustaceans											
Daphnia magna	+	CF	--	w.w.	7.0	25-25	7-d	NOLC	≥5		Nebeker et al. '89
Gammarus lacustris	+	CF	--	w.w.	7.0	25-35	28-d	NOLC	1.8		Nebeker et al. '89
Hyalella azteca	+	CF	--	w.w.	7.0	25-35	30-d	NOEC	≥4.7		Nebeker et al. '89
								NOEC[r]	≥4.7		Nebeker et al. '89
								NOLC[g]	≥4.7		Nebeker et al. '89
Fish											
Pimephales promelas embryo --> early juvenile	+	CF	97%	lake	7.3-7.6	44-46	32-d	NOEC	≥4.8 α	[1]	Carlson & Kosian '87
								NOLC[g]	≥4.8 α		Carlson & Kosian '87
Pimephales promelas	+	CF	--	w.w.	7.0	25-35	28-d	NOEC	≥3.8		Nebeker et al. '89
								NOLC[g]	≥3.8		Nebeker et al. '89

n.m. = nutrient medium; s.w. = standard water; w.w. = well water. g = growth; r = reproduction; m = mortality; h = histopathological changes; d = development; y = yield.
For explanation, see "list of abbreviations tables 2.3 to 2.6".

[1] Non-toxic at highest mean concentration that could be maintained in the test chambers.
[2] At 50 µg/l the yield (mean number of daphnids) was reduced 10%; the calculated EC50 was 120 µg/l.
[3] Concentrations ranging from 1.8 to 122 µg/l were tested. Neither macroscopic malformations nor histological changes were found at the time of hatching. The cumulative mortality of in treated groups was not increased as compared to the control groups.
[4] The decrease in concentrations during the tests, till renewing the solutions, were reported to be maximal 20%.
[5] Fish exposed to 2.1 and 2.9 mg/l did not show mortality, but changes in behaviour and liver toxicity (elevated GTP activity).
[6] The average decrease in concentration during the tests was 9%, with a maximum of 26%.
[7] A slight inhibition (12% in respect to control cultures) was seen at the maximum tested concentration; about 27 µg/l (90% of the solubility). The NOEC has been estimated using a factor 2.
[8] A 16% reproductive impairment was reported at 2,100 µg/l for MCB, 370 µg/l for 1,2-DCB, 640 µg/l for 1,4-DCB, 80 µg/l for 1,2,3-TCB and 320 µg/l for 1,2,4-TCB. The NOEC-values have been calculated from these EC16-values using a factor 2.
[9] The given NOEC-value is an average between the nominal NOEC-value and the "minimal" NOEC-value, representing the lowest analysed concentration obtained during the test.

Table 2.5 Freshwater organisms - long-term toxicity tests with chlorobenzenes: L(E)C50-values

Organism	A	Test-type	Test-subst. purity	Test-water.	pH	Hardness mg $CaCO_3$/l	Exp.-time	Criterion	Result µg/l		Reference
Monochlorobenzene											
Algae											
Selenastrum capricornumtum	+	c-S	ag	s.w.	-	--	96-h	$EC50_g$	12,500	[1]	Calamari et al. '83 Galassi & Vighi '81
Crustaceans											
Daphnia magna	+	c-R	--	s.w.	-	--	14-d	$EC50_r$	2,500		Calamari et al. '83
Daphnia magna	+	R	--	s.w.	-	--	16-d	LC50	4,000	[3]	Hermens et al. '84
							16-d	$EC50_r$	1,100		Hermens et al. '84
Fish											
Poecilia reticulata	-	R	--	s.w.	-	--	14-d	LC50	19,120		Könemann '79
Micropterus salmoides eggs <1-d old --> 4-d post-hatching	+	CF	--	r.w.	7.3-8.1	50	7.5-d	LC50	50		Birge et al. '79
Carassius auratus eggs <1-d old --> 4-d post-hatching	+	CF	--	r.w.	7.3-8.1	50	7.5-d	LC50	880		Birge et al. '79
1,2 - dichlorobenzene											
Algae											
Selenastrum capricornumtum	+	c-S	ag	s.w.	-	--	96-h	$EC50_g$	2,200	[1]	Calamari et al. '83 Galassi & Vighi '81
Crustaceans											
Daphnia magna	+	c-R	--	s.w.	-	--	14-d	$EC50_r$	550		Calamari et al. '83
Fish											
Poecilia reticulata	-	R	--	s.w.	-	25	14-d	LC50	5,850		Könemann '79
1,3 - dichlorobenzene											
Fish											
Poecilia reticulata	-	R	--	s.w.	-	25	14-d	LC50	7,370		Könemann '79
1,4 - dichlorobenzene											
Algae											
Selenastrum capricornumtum	+	c-S	ag	s.w.	-	--	96-h	$EC50_g$	1,600	[1]	Calamari et al. '83 Galassi & Vighi '81
Crustaceans											
Daphnia magna	+	c-R	--	s.w.	-	--	14-d	$EC50_r$	930		Calamari et al. '83

Table 2.5 Freshwater organisms - long-term toxicity tests with chlorobenzenes: L(E)C50-values (continued)

Organism	A	Test-type	Test-subst. purity	Test-water.	pH	Hardness mg $CaCO_3$/l	Exp.-time	Crite-rion	Result µg/l		Reference
Fish											
Pimephales promelas	+	CF	--	lake	-	43-49	8-d	LC50	3,530		Hall et al. '84
Poecilia reticulata	-	R	--	s.w.	-	25	14-d	LC50	3,960		Könemann '79
Salmo gairdneri alevins	+	c-CF	--	s.w.	-	--	14-d	LC50	800		Calamari et al. '82
1,2,3 - trichlorobenzene											
Algae											
Selenastrum capricornumtum	+	c-S	ag	s.w.	-	--	96-h	$EC50_g$	900	[1]	Calamari et al. '83 Galassi & Vighi '81
Crustaceans											
Daphnia magna	+	c-R	--	s.w.	-	--	14-d	$EC50_r$	200		Calamari et al. '83
Fish											
Poecilia reticulata	-	R	--	s.w.	-	25	14-d	LC50	2,340		Könemann '79
1,2,4 - trichlorobenzene											
Algae											
Selenastrum capricornutum	+	c-S	≥98%	s.w.	-	--	96-h	$EC50_g$	1,400		Calamari et al. '83 Galassi & Vighi '79
Crustaceans											
Daphnia magna	+	R	--	s.w.	-	--	16-d	LC50	560	[3]	Hermens et al. '84
							16-d	$EC50_r$	270		Hermens et al. '84
Fish											
Pimephales promelas	+	CF	--	lake	-	43-49	8-d	LC50	1,815		Hall et al. '84
Poecilia reticulata	-	R	--	s.w.	-	25	14-d	LC50	2,390		Könemann '79
1,3,5 - trichlorobenzene											
Fish											
Poecilia reticulata	-	R	--	s.w.	-	25	14-d	LC50	3,300		Könemann '79
1,2,3,4 - tetrachlorobenzene											
Crustaceans											
Daphnia magna	+	R	--	s.w.	-	--	16-d	LC50	320	[3]	Hermens et al. '84
							16-d	$EC50_r$	43		Hermens et al. '84
Fish											
Poecilia reticulata	-	R	--	s.w.	-	25	14-d	LC50	800		Könemann '79

Table 2.5 Freshwater organisms - long-term toxicity tests with chlorobenzenes: L(E)C50-values (continued)

Organism	A	Test-type	Test-subst. purity	Test-water.	pH	Hardness mg $CaCO_3$/l	Exp.-time	Crite-rion	Result µg/l		Reference
1,2,3,5 - tetrachlorobenzene											
Fish											
Poecilia reticulata	-	R	--	s.w.	-	25	14-d	LC50	800		Könemann '79
Pimephales promelas	+	CF	--	lake	-	43-49	8-d	LC50	800		Hall et al. '84
1,2,4,5 - tetrachlorobenzene											
Fish											
Poecilia reticulata	-	R	--	s.w.	-	25	14-d	LC50	300		Könemann '79
Pimephales promelas	+	CF	--	lake	-	43-49	8-d	LC50	300		Hall et al. '84
pentachlorobenzene											
Crustaceans											
Daphnia magna P < 1-d old	-	R	≥98%	lake	8.1	225	3-w	LC50	240		Van Leeuwen et al. '87
Daphnia magna P < 1-d old	-	R	≥98%	lake	8.1	225	3-w	$EC50_y$	120		Van Leeuwen et al. '87
Daphnia magna	+	R	--	s.w.	-	--	16-d	LC50	110	[3]	Hermens et al. '84
							16-d	$EC50_r$	25		Hermens et al. '84
Fish											
Poecilia reticulata	-	R	--	s.w.	-	25	14-d	LC50	180		Könemann '79
hexachlorobenzene											
Crustaceans											
Daphnia magna	+	c-R	--	s.w.	-	-	14-d	$EC50_r$	16		Calamari et al. '83
Fish											
Poecilia reticulata	-	R	--	s.w.	-	25	14-d	LC50	>300	[2]	Könemann '79

n.m. = nutrient medium; w.w. = well water; g = growth; r = reproduction; y = yield.
For explanation, see "list of abbreviations tables 2.3 to 2.6".

[1] For all chlorobenzenes tested the loss of compound did not exceed 10% of the initial value, except for the Daphnia test in which it did not exceed 15%.
[2] No mortality was observed at concentrations far more than its solubility in water.
[3] The decrease in concentrations during the tests, till renewing the solutions, were reported to be maximal 20%.

Table 2.6 Marine organisms - short- and longterm toxicity tests chlorobenzenes: L(E)C50- and NO(L)EC-values

Organism	A	Test-type	Test-subs. purity	Test-medium	Salinity o/oo	Exp.-time	Crite-rion	Result µg/l		Reference
1,2,4 - trichlorobenzene										
Amphibiens										
Branchiostoma caribaeum	+	CF	--	n.s.	-	96-h	NOLC	1,500	[1]	Clark et al. '87
	+	CF	--	n.s.	-	96-h	LC50	>1,500		Clark et al. '87
Crustaceans										
Palaemonetes pugio	+	CF	--	n.s.	-	96-h	LC50	540	[1]	Clark et al. '87
	+	CF	--	n.s.	-	96-h	NOLC	240		Clark et al. '87
Fish										
Cyprinodon variegatus (14-28 days old)	-	S	≥80%	n.s.	10-31	96-h	LC50	21,000		Heitmuller et al. '81
1,2,3,5 - tetrachlorobenzene										
Fish										
Cyprinodon variegatus (14-28 days old)	-	S	≥80%	n.s.	10-31	96-h	LC50	3,700		Heitmuller et al. '81
1,2,4,5 - tetrachlorobenzene										
Fish										
Cyprinodon variegatus (14-28 days old)	-	S	≥80%	n.s.	10-31	96-h	LC50	800		Heitmuller et al. '81
Cyprinodon variegatus	+	CF	--	n.s.	-	96-h	LC50	330 α		Ward et al. '81
Cyprinodon variegatus	+	CF	--	n.s	12-28	>28-d	NOEC	300 α		Ward et al. '81
eggs <1-d old --> 28 days post-hatching							NOLC^{g}	90 α		Ward et al. '81
							NOEC$_{h}$	≥520 α		Ward et al. '81
pentachlorobenzene										
Fish										
Cyprinodon variegatus (14-28 days old)	-	S	≥80%	n.s.	10-31	96-h	LC50	800		Heitmuller et al. '81

n.s. = natural seawater; g = growth; h = hatchability
For explanation, see "list of abbreviations tables 2.3 to 2.6".

[1] Measured concentrations were between 75% and 95% of nominal concentrations.

List of abbreviations tables 2.3 to 2.6

A	+ Test substance analysed in test solution
	- Test substance not analysed in solution or : no data
α	Value based on actual (measured) concentrations in test solutions, as mentioned explicitly in the literature source. Values not indicated by "α" are considered to be nominal concentrations.
> and $\geq$	Value indicated is highest concentration used in the test.
< and $\leq$	Value indicated is lowest concentration used in the test.
Test type	S: static; R: renewal; CF: continuous flow;
	c- : closed system
Test time	hr: hour(s); w: week(s); m: month(s)
Criterion	LC50: Lethal concentration for 50% of the organisms exposed
	EC50: Effect concentration for 50% of the organisms exposed
	NOLC: No-observed-lethal-concentration
	NOEC: No-observed-effect-concentration

CHAPTER 3 ECOTOXICITY - TERRESTRIAL ORGANISMS

3.1 ACCUMULATION

In a long-term experiment (11-w) using a sandy soil (pH=6.1, OM=1%) the BCF based on fresh weight of HCB in the earthworm *Lumbricus terrestris* was found to be about 2. In a soil with a higher OM (exact percentage not given) the BCF (based on fresh weight) was determined to be 0,5. After exposure of the snail *Deroceras reticulatum* to 1.0 $mg.kg^{-1}$ of HCB in soil, the snails contained 1.4 $\mu g.kg^{-1}$ bw (Ebing et al., 1984). BCF's in the earthworms *L. terrestris* and *Allolobophora longa*, about 55 days exposed to 1,2,3,5-TeCB and HCB in soil (2.6% OM, pH=5.1), were about 4 (Lord et al., 1980). In three wild mammals the HCB content in adipose tissues were determined. In animals known to feed on small animals (mice and invertebrates) higher HCB residues were found than in animals feeding exclusively on plant material. According to the authors this could be an indication of accumulation of HCB via the food chain (Koss and Manz, 1976). The disposition of four ^{14}C-labeled pesticides, including HCB, was examined as a seed-protectant coating in a terrestrial microcosm chamber, containing a synthetic soil medium, agricultural crops, numerous invertebrates and two gravid gray-tailed vole (*Microtus canicaudus)* . After 45 days the percentage total recovery was 61% for HCB. Some accumulation of HCB in plants was found, HCB was present mainly as extractable parent compound. Due to lack of parent material in the invertebrates, as well as poor recovery of the organisms, no index for "ecological magnification" (= whole body concentration/concentration in soil; EM) could be given. For the vole an EM of 118 was determined (Gille and Gillet, 1979).

3.2 TOXICITY

- Soil processes

The effects of HCB on soil processes were studied using a pine forest microcosm during 21 days. HCB-contaminated litter (0, 0.085, 0.730, 7.42 $mg.cm^{-3}$) was applied to replicate soils in filtered, flow-through microcosm

systems. The two studied parameters, CO_2 efflux and Ca loss, were affected by HCB: CO_2 efflux decreased and Ca loss increased (Ausmus et al., 1979).

- Invertebrates

The results of toxicity tests with earthworms resulting in L(E)C50-values are summarized in table 3.1.

Additional data

The toxicity of 1,4-DCB to the earthworms *Dendroboena rubida* and *Lumbricus terrestris* was determined using a soil containing 5% peat and 5% cow-dung (pH=7) which was repeatedly treated. The LC50-values for both earthworms were found to be 390 $mg.kg^{-1}$ dry weight. The oral LD50-value for the insect *Apis mellifera* has been reported to be >5 µg 1,4-DCB per insect (Caprioli et al., 1984). The effect of HCB on postembryonic stages of the free-living nematode *Panagrellus redivivus* was studied in a 96-h assay. Test animals were L2 juveniles (second-stage juvenile), which develop subsequently into the third stage (L3), the fourth stage (L4) and the adult stage. The testconditions were established such that 50% of the L2 animals will reach the adult stage in a 96-h growth period. HCB had no effect on "overall" (L2 ->adult) survival over the range tested (10^{-8} - 10^{-3} $mol.l^{-1}$). It was also reported that the lower but not the higher concentrations ($\leq 10^{-5}$) had effects on intermediate stages (L2-L3, L3-L4 and L4 to adult) (Samoiloff et al., 1980).

- Vertebrates

The quail *Coturnix coturnix* was given a single oral dose of 1,4-DCB, followed by an observation period of 14 days. The LD50-value was 2400 $mg.kg^{-1}$ bw (Caprioli et al., 1984).

After a single oral dose of 1,2,4-TCB (200 $mg.kg^{-1}$ bw or more) a significant increase in liver porphyrin levels and a liver enzyme was observed in adult Japanese quails. Repeated administration of 50 or 200 $mg.kg^{-1}$ bw significantly increased several liver enzymes, including cyt P-450 (Miranda et al., 1983).

Quails *Coturnix coturnix japonica* were given oral doses of 500 $mg.kg^{-1}$ bw HCB for 1, 2, 5, or 10 days. After one dose the birds already developed porphyria. Porphyrin levels were increased as well as the activity of some liver enzymes (including Cyt P450 enzymes). A decrease in body weight was observed (Carpenter et al., 1985a, Carpenter et al., 1985b). In another experiment an oral dose of 100 $mg.kg^{-1}$ bw HCB for 10 days caused an increase in liver enzymes and a slight increase in liver porphyrin concentrations in *C. coturnix japonica* . A consecutive treatment (same dose for 1, 5, 10, or 15 days) caused a further increase in porphyrin levels (Carpenter et al., 1985c). In a 90-day study quails were exposed to dietary concentrations of 0, 1, 5, 20 or 80 $mg.kg^{-1}$ (0, 0.1, 0.5, 2.2 or 8.8 $mg.kg^{-1}$ bw). At the highest dose an increased mortality and several toxic effects were seen. At a concentrations of 5 $mg.kg^{-1}$ diet and more an increased liver weight and slight liver damage was observed. The no-effect level was established at 1 $mg.kg^{-1}$ diet (which equals 0.1 $mg.kg^{-1}$ bw) (Vos et al., 1971). In a reproduction study minks and ferrets were fed HCB at dietary concentrations of 0, 1, 5, 25, 125 or 625 $mg.kg^{-1}$ (0, 0.04, 0.2, 1, 5, 25 $mg.kg^{-1}$ bw) for nearly one year. Diets containing 125 or 625 were lethal to the adults. Diets containing 1 $mg.kg^{-1}$ or more resulted in reduced reproductive performance, as indicated by decreased litter size, increased percentage of still births, increased kit mortality and decreased growth. Minks were more sensitive than ferrets. From cross-fostering experiments it appears that exposure via milk also increases kit mortality, although mortality was lower than among kits exposed in utero (Bleavins et al., 1984). Female mink were exposed to HCB at dietary levels of 0, 1 or 5 $mg.kg^{-1}$ and bred with males on the same treatments. Female offspring were allowed to mature to 16-17 weeks and killed. A profound effect on the survival of kits was found: 44% in the lowest dose group and 77% in the high dose group, versus 8% in the control group. At 17 weeks of age the only effect was enzym induction in the highest dose group (Rush et al., 1983).

Summary and conclusions "Terrestrial organisms"

- Accumulation

Data on the accumulation of terrestrial organisms from soil are very limited. Studies with earthworm species (2) exposed to HCB and 1,2,4,5-TeCB, resulted in BCF's of 2 and ±4. In a terrestrial laboratory microcosm, containing agricultural crops, numerous invertebrates and two voles, no indication of bioconcentartion was found.

- Toxicity

The long-term toxicity of 1,2,3-TCB to the earthworms *Eisenia andrei* and *Lumbricus rubellus* was determined in four different soils; humic sand, a very humic sand, an artificial (OECD) soil and a peaty soil. The 2-w LC50-values for *E. andrei* ranged from 134 to 547 $mg.kg^{-1}$ dry weight and those for *L. rubellus* from 115 to 563 $mg.kg^{-1}$ dry weight. The effects of 1,2,4-TCB were studied in 4 earthworm species using an artificial soil. LC50-values ranged from 127 to 251 $mg.kg^{-1}$ dry weight. The LC50-values of 1,4-DCB for the earthworms *Dendroboena rubida* and *L. terrestris* were found to be 390 $mg.kg^{-1}$ dry weight.

The effects of short- and longterm exposure of the quail *Coturnix coturnix* to chlorobenzenes, mostly HCB, was studied several times. An LD50-value of 2400 $mg.kg^{-1}$ bw was reported for 1,2-DCB, whereas subacute exposure to 50 $mg.kg^{-1}$ bw of 1,2,4-TCB induced liver enzyme activity. Long-term oral exposure of quails to HCB caused an increased mortality, toxic effects on the liver (increased liver weights and liver enzym induction) and porphyria, resulting in increased liver porphyrin concentrations. The dose without effect was 1 $mg.kg^{-1}$ diet, corresponding to 0.1 $mg.kg^{-1}$ bw.

In reproduction studies with ferrets and minks it appeared that the lowest tested dietary concentration (1 $mg.kg^{-1}$, corresponding to 0.04 $mg.kg^{-1}$ bw) caused adverse beffects on the reproductive performance (decreased litter size, increased percentage of still births, etc.). Minks were more sensitive than ferrets. The survival of kits from minks fed 1 $mg.kg^{-1}$ diet, also was significantly lower than those in the control group.

Table 3.1 Earthworms - toxicity tests with chlorobenzenes: LC50-values (laboratory studies)

Organism	Soil	pH	%OM	%Clay	Temp. °C	Exp.-time	Criterion	Result in test soil (mg/kg dry weight)	Calculated* value in 10% OM soil (mg/kg dry weight)
1,2,3,-trichlorobenzene									
Eisenia andrei	mod. humic sand	4.8	3.7	1.4	19	2-w	LC50	134	362
	very humic sand	5.3	6.1	2.4	19	2-w	LC50	240	393
	art.(OECD) soil	3.8	16	9	19	2-w	LC50	133	83
	peaty soil	6.5	8.1	8.1	19	2-w	LC50	547	675
Lumbricus rubellus	mod. humic sand	4.8	3.7	1.4	19	2-w	LC50	115	310
	very humic sand	5.3	6.1	2.4	19	2-w	LC50	207	340
	art.(OECD) soil	3.8	16	9	19	2-w	LC50	195	122
	peaty soil	6.5	8.1	8.1	19	2-w	LC50	563	695
								Van Gestel & Ma '90	
1,2,4-trichlorobenzene									
Eisenia fetida	art. soil	6.0	10	20	20	2-w	LC50	197	197
Allolobophora tuberculata						2-w	LC50	251	251
Eudrilus eugeniae						2-w	LC50	127	127
Perionyx excavatus						2-w	LC50	180	180
								Neuhauser et al. '86	

For explanation, see "list of abbreviations tables 3.1 and 4.1".

CHAPTER 4 AGRICULTURAL CROPS AND LIVESTOCK

4.1 AGRICULTURAL CROPS

- Accumulation

In experiments under outdoor conditions the toxicity of ^{14}C-labelled 1,2,4-TCB, PeCB and HCB to barley and cress plants was determined. The plants were grown for one vegetation period on a soil containing 2 $mg.kg^{-1}$ dry weight of the substances and analyzed after varying time intervals. The soil used contained 34% clay, 27% silt and 32% sand (pH= 6.4, OM=2.1%). After 11 days the BCF's (concentration in dry plant matter/ concentration in dry soil) varied between 2.1 (HCB in cress plants) and 36 (1,2,4-TCB in barley plants). In course of time (125 and 80 days for barley and cress plants, respectively) the BCF's were about a factor 10 lower. This effect is due to growth dilution, since the absolute amounts of radioactive substances in plants increased with time (Topp et al., 1989). In another study with the same plants the uptake of ^{14}C-labelled substances (by roots and by leaves via the air) was described. The same soil as described in the preceding study was used. After about 60 days the BCF's of PeCB and HCB were about 1. For the total group of substances a positive relationship was found between barley root BCF's and n-octanol/water partition coefficient. The uptake of chemicals via leaves correlated strongly to volatilization from the soil. For the cress plant these correlations were poor (Topp et al., 1986). In a laboratory soil-plant system the uptake of ^{14}C-labelled HCB by barley plants from a humus sand (pH=6.9, OM=2.3%) containing 2 $mg.kg^{-1}$ HCB was examined. The plants contained 3.6 $mg.kg^{-1}$, which resulted in a BCF of 1.9 (Kloskowski et al., 1981).

HCB residues may be present in lettuce and witloof- chicory as a result of earlier application of quintozene (a fungicide) to lettuce foliage or soil and to witloof-chicory soil. HCB is normally present as an impurity in technical grade quintozene in amounts varying between 1% and 6.2% (Dejonckheere et al., 1975, 1976).

- Toxicity

Toxicity studies with lettuce resulting in 2-w EC50- and NOEC-values are summarized in table 4.1.

Additional data

The toxicity of 1,2,4,5-TeCB on the germination and seedling vigor of barley, oats and wheat was studied using a sandy soil, a sandy loam, a clay loam and a clay soil (no % organic matter given). The crops were planted 1 to 125 days after treating the soil 6 times, resulting in a concentration corresponding to 12-980 $mg.kg^{-1}$. The lowest concentration was already detrimental after one day, except for the clay soil. In this soil effects were seen at concentrations $\geq$ 320 $mg.kg^{-1}$. The adverse effects decreased when the time between treatments of the soil and planting increased (Ameen et al., 1960)

Summary and conclusions "Agricultural crops"

- Accumulation

Data on accumulation of chlorobenzenes by agricultural crops are limited. In an outdoor experiment it was found that the BCF's of 1,2,4-TCB, TCB (isomer not given), PeCB and HCB in barley and cress varied between 2 (HCB in cress plants) and 36 (1,2,4-TCB in barley plants). In course of time (about 100 days) the BCF's were a factor of 10 lower. In another study with the same plants the uptake of PeCB and HCB by roots and by leaves via the air was studied. A positive correlation was found between barleys root BCF's and Kow-values. The uptake of chemicals via leaves correlated strongly to the volatilization from the soil. For cress these correlations were poor.

-Toxicity

Data on the toxicity of chlorobenzenes to agricultural crops are limited to one study with lettuce and one with cereals. In the first study the long-term toxicity of chlorobenzenes to *Lactuca sativa* was determined, resulting in 2-w EC50-values (based on growth) of 248 $mg.kg^{-1}$ for MCB, 1-4

mg.kg^{-1} for 1,2,3-TCB, 48 mg.kg^{-1} for 1,2,4-TCB, 123 mg.kg^{-1} for 1,3,5-TCB, 32 mg.kg^{-1} for 1,2,3,4-TeCB, 1.3 mg.kg^{-1} for 1,2,3,5-TeCB, 2 mg.kg^{-1} for 1,2,4,5-TeCB and 56 mg.kg^{-1} for PeCB. For a number of chlorobenzenes NOEC-values were reported as well: 10 mg.kg^{-1} for 1,4-DCB, 1 mg.kg^{-1} for 1,2,3-TCB, 10 mg.kg^{-1} for 1,2,4-TCB, 1,3,5-TCB, 1,2,3,4-TeCB and PeCB and 100 mg.kg^{-1} for HCB. Concentrations of $\geq$12 mg.kg^{-1} of 1,2,4,5-TeCB were toxic to cereals in several soils.

4.2 LIVESTOCK

- Accumulation

Growing chickens were exposed to HCB for 6 months at dietary levels of 0, 0.1, 1, 10 or 100 mg.kg^{-1} (0, 0.0125, 0.125, 1.25 or 12.5 mg.kg^{-1} bw). The amounts found in the tissues increased with the dietary level and were roughly proportional to the fat content of the tissues. After 6 months the concentrations in body fat, egg yolk, liver and muscle were 2,000, 450, 57 and 8.6 mg.kg^{-1}, respectively, at the highest dose (Avrahami and Steele, 1972c). Laying pullets were given dietary concentrations up to 100 mg.kg^{-1} HCB (12.5 mg.kg^{-1} bw) for 6 months. The concentrations in the fat were 20-30 times the dietary concentrations (up to 2,900 mg.kg^{-1} at the highest dose). Relative HCB concentrations in fat, yolk, liver and muscle were 75, 40, 4 and 1, respectively (Avrahami and Steele, 1972b).
HCB was fed to pigs at concentrations between 0.05 and 50 mg.kg^{-1} bw a day for 90 days. HCB accumulated in fat and blood at all doses; the concentrations in fat (mg.kg^{-1}) being about 300 times those administered (mg.kg^{-1} bw). Tissues of control animals also contained significant HCB concentrations, which was, according to the authers, due to cross contamination. The (lowest) dose groups could have been contaminated as well. Therefore, the concentration factor of 300, even for the lowest dose, is considered to be an overestimation (Tonkelaar, den et al., 1978). In growing swines, orally exposed to HCB for 13 weeks, HCB also accumulated in fat to concentrations 5-7 times the dietary concentration (0, 1, 10 or 100 mg.kg^{-1}) (Hansen et al., 1977). In lambs the HCB levels in fat reached a level approximately 10 times those in the diet (0, 0.01, 0.1 or 1 mg.kg^{-1})

at the end of the 90-day exposure period. The highest levels in other tissues were in the brain and in the liver (Mull et al., 1978). Sheep were dosed orally with HCB at 0.1, 1, 10 or 100 $mg.kg^{-1}$ (0.004, 0.04, 0.4 or 4 $mg.kg^{-1}$ bw HCB) a day during 18 weeks. The sheep stored HCB in their body fat to the extent of about 8 times the daily intake. In the blood the concentrations were about 1,000 times lower than in fat. The undosed controls were also found to accumulate HCB in their fat. The primary source of HCB in these controls could have been the faeces of the dosed sheep that grazed in the same paddocks (Avrahami and Steele, 1972a). HCB was fed to pregnant sows at concentrations of 0, 1 or 20 $mg.kg^{-1}$ diet (0, 0.025 or 0.5 $mg.kg^{-1}$ bw) a day throughout gestation and nursing (over 200 days). In the sows highest residue concentrations were found in fat and bone marrow, with levels of up to 7 and 90 for the lower and higher dietary levels, respectively. The pigs accumulated fat residues that were higher than those of the sows (Hansen et al., 1979). Two groups of 3 cows were fed either 5 or 25 mg of HCB per day for 60 days. Residues were determined in milk at 5-day intervals during the exposure period and for 60 days after dosing was stopped. The average concentrations in milk fat for 40th to 60th days of dosing were about 2 and 9 $mg.kg^{-1}$ for the low and high dose groups, respectively. The concentrations in subcutaneous body fat were about 2 and 35 for the low and high dose groups, respectively. After exposure had stopped the concentrations in declined rapidly (Fries and Marrow, 1975).

- Toxicity

Single oral doses of 800 $mg.kg^{-1}$ bw of MCB, 1,4-DCB or 1,2,4-TCB produced an increase in total porphyrin content of liver of one day-old chicks. The administration of similar concentrations to chick embryos failed to produce an induction of liver porphyrins (Miranda et al., 1984). Feeding of HCB at dietary levels up to 100 $mg.kg^{-1}$ (12.5 $mg.kg^{-1}$ bw) to growing chickens for 6 months did not cause any effects (Avrahami and Steele, 1972c). In another study, in which HCB was fed to laying pullets at concentrations up to 100 $mg.kg^{-1}$ (12.5 $mg.kg^{-1}$), no adverse effects were seen on the pullets nor on the egg fertility or hatchability (Avrahami and Steele, 1972b). Groups of laying hens were fed HCB at levels of 0, 1, 5, 125 or 625 $mg.kg^{-1}$ diet (0, 0.2, 0.9, 0,21.9 or 110 $mg.kg^{-1}$ bw) for 12 weeks. The highest dose caused

decreased body weight, increased relative liver weight and induced drug enzyme activity. No histopathological abnormalities were found (Kan et al., 1979). Laying pullets were given oral doses of HCB ranging from 1 to 100 $mg.kg^{-1}$ for 7 days. At the higher doses HCB ($\geq$10 $mg.kg^{-1}$) delayed the onset of full egg production but also appeared to offer protection against development of hemorrhagic fatty liver (Hansen et al., 1978).
Groups of growing swines were exposed to dietary concentrations of 0, 1, 10 or 100 $mg.kg^{-1}$ HCB (0, 0.04, 0.4 or 4 $mg.kg^{-1}$ bw) for 13 weeks. No toxic effects were observed. In the highest dose group larger livers with hypertrophy were observed (Hansen et al., 1977). In an 90-day test pigs were exposed orally to 0.05, 0.5, 5 or 50 $mg.kg^{-1}$ bw HCB a day. In the highest dose group clear signs of porphyria were seen. At 0.5 and 5.0 $mg.kg^{-1}$ bw an increased excretion of coproporphyrin and an induction of liver enzymes was found. An increased liver weight occurred at 5.0 $mg.kg^{-1}$ bw. The no-effect-level was judged to be 0.05 $mg.kg^{-1}$ bw a day for HCB (Tonkelaar, den et al., 1978).
Pregnant sows were exposed to dietary concentrations of 0, 1 or 20 $mg.kg^{-1}$ HCB (0, 0.025, 0.5 $mg.kg^{-1}$ bw) throughout gestation and nursing (over 200 days). No adverse effects were seen at the lower dose. The higher dose caused slight toxic effects (Hansen et al., 1979).

Three studies (6, 16 and 68 weeks) were conducted to study the effects of the addition of a mixture of organochlorine pesticides to the feed of broilers or laying hens. The total concentration of the pesticides was maximal 3.1 $mg.kg^{-1}$ diet, including 0.10 $mg.kg^{-1}$ HCB. No adverse effects were seen (Kan and Tuinstra, 1976, Kan and Jonker-den Rooyen, 1978, Kan et al., 1978).

Summary and conclusions "Livestock"

With regard to the accumulation of chlorobenzenes in livestock the only data that were available concern HCB. The accumulation of HCB after subchronic oral administration was examined in growing chickens, laying pullets, pigs, swines, lambs, sows and sheep. In general, the amounts of HCB found in the tissues increased with the dietary level and with the fat

content of the tissues. In growing chickens and laying pullets the fat contained between 20 and 30 times the dietary level. The concentrations in egg yolk was about 4 times the dietary level. In pigs fed HCB up to levels of 50 $mg.kg^{-1}$ bw a day the concentrations in the fat were about 500 times higher than those in blood (15,500 $mg.kg^{-1}$ in fat). Growing swines, lambs and sheep concentrated HCB in their fat to the extent of about 10 times the dietary levels. Other organs that contained higher levels were bone marrow, liver and brain.

Most data on the toxicity of chlorobenzenes to livestock concern HCB. The only data that were available on the toxicity of other chlorobenzenes indicate that single doses of 800 $mg.kg^{-1}$ bw of MCB, 1,4-DCB and 1,2,4-TCB produce an increase in prophyrin contents of the liver of one-day old chickens. HCB was tested in several domestic animals; chickens, laying hens, swines, lambs and sows. Feeding of HCB to chickens at levels up to 12.5 $mg.kg^{-1}$ bw for 6 months did not produce adverse effects. In cattle HCB caused effects on the liver, resulting in liver enzyminduction. Th dose-without effect was 0.025 $mg.kg^{-1}$ bw.

Table 4.1 Toxicity tests with chlorobenzenes: EC50- and NOEC-values (laboratory studies)

species	Soil	pH	%OM	%Clay	Temperature. °C	Exp.-time	Criterion	Result in test soil (mg/kg dry weight)	Calculated* value in 10% OM soil (mg/kg dry weight)	
1,4-dichlorobenzene										
Lactuca sativa	brook bed	7.8	1.4	12	20	2-w	$EC50_g$	248	1250	[1]
						7-d	$NOEC_g$	10	50	[1]
1,2,3-trichlorobenzene										
Lactuca sativa	brook bed	7.8	1.4	12	18-26	2-w	EC50	1	5	[2]
Lactuca sativa	brook bed	7.8	1.4	12	20	2-w	$EC50_g$	4	20	[1]
						2-w	$NOEC_g$	1	5	[1]
1,2,4-trichlorobenzene										
Lactuca sativa	brook bed	7.8	1.4	12	20	2-w	EC50	48	240	[1]
						2-w	$NOEC_g$	10	50	[1]
1,3,5-trichlorobenzene										
Lactuca sativa	brook bed	7.8	1.4	12	20	2-w	EC50	123	615	[1]
						7-d	$NOEC_g$	10	50	[1]
1,2,3,4-tetrachlorobenzene										
Lactuca sativa	brook bed	7.8	1.4	12	20	2-w	EC50	32	160	[1]
						2-w	$NOEC_g$	10	50	[1]
1,2,3,5-tetrachlorobenzene										
Lactuca sativa	brook bed	7.8	1.4	12	20	2-w	$EC50_g$	1.3	6.5	[1]
1,2,4,5-tetrachlorobenzene										
Lactuca sativa	brook bed	7.8	1.4	12	18-26	2-w	$EC50_g$	2	10	[2]
pentachlorobenzene										
Lactuca sativa	brook bed	7.8	1.4	12	20	2-w	EC50	56	280	[1]
						2-w	$NOEC_g$	10	50	[1]
hexachlorobenzene										
Lactuca sativa	brook bed	7.8	1.4	12	20	2-w	$NOEC_g$	100	500	[1]

g = growth
For explanation, see "list of abbreviations tables 3.1 and 4.1".

[1] Data evaluated by Denneman and Van Gestel (1990), RIVM
[2] Hulzebos et al. (1989)

List of abbreviations tables 3.1 and 4.1

Test time — hr: hour(s); w: week(s); m: month(s)

Criterion
- LC50: Lethal concentration for 50% of the organisms exposed
- EC50: Effect concentration for 50% of the organisms exposed
- NOLC: No-observed-lethal-concentration
- NOEC: No-observed-effect-concentration

Soil characteristics:
- OM: organic matter
- dw: dry weight

OECD artificial soil:
10% sphagnum peat, 20% kaolin clay, 69% fine sand, 1% calcium carbonate to adjust pH.
The indicated soil characteristics are based on measurements in several tests.

* Calculated value in 10% OM soil = Experimental value x 10/%OM-t
%OM-t = % organic matter in test soil.

5 RISK ASSESSMENT

5.1 RISK ASSESSMENT FOR MAN

Generally, a toxicological limit value is only established when a certain "minimum toxicological dataset" concerning genotoxicity, carcinogenicity, reproductive and/or teratogenicity and (sub)chronic toxicity is available. Consequently, a toxicological limit value for oral exposure could only be established for MCB, 1,2-DCB, 1,4-DCB and HCB. No limit values could be given for the remaining chlorobenzenes. However, because of the fact that a group of related substances is involved which behave rather similar or at least predictable (with respect to metabolism, toxicology and genotoxicity), it was decided to give indicative toxicological limit values for oral exposure for the other chlorobenzenes (1,3-DCB, 1,2,3-TCB, 1,2,4-TCB, 1,3,5-TCB, 1,2,3,4-TeCB, 1,2,3,5-TeCB, 1,2,4,5-TeCB and PeCB).
With respect to inhalatory exposure the data were for all chlorobenzenes insufficient to establish a (indicative) toxicological limit value.

The metabolic behaviour of the different chlorobenzenes changes gradually with the degree of chlorination. With an increase in the number of chloro-atoms the substances become more lipofile and accumulate to a greater extent in fat and fatty tissues. The biotransformation and elimination via the urine decrease with the number of chloro-atoms; the difference in halflife times between for example 1,4-DCB and HCB was estimated to be at least a factor of 10. Especially HCB is metabolized very slowly and the excretion is mainly via the faeces. The tissues contain predominantly unchanged HCB.
The toxicity of the chlorobenzenes, when administered repeatedly, also increases with the degree of chlorination. This may be partly explained by the decrease in elimination and the increase in accumulation.
Microsomal enzyme induction and the interference with the normal synthesis of porphyrines are considered to be sensitive toxicological parameters for all chlorobenzenes. Microsomal enzyme induction is already obvious after a relative short exposure period, and the sensitivity does not seem to increase after longer exposure periods. With respect to chlorobenzenes, enzyme induction was one of the studied parameters in nearly all subchronic

experiments. Instead, this parameter was generally not studied in the chronic experiments, which mostly concerned carcinogenicity. If possible, this evaluation was based on data on enzyme induction.
As was already stated, the chlorobenzenes might have genotoxic activities. This suspection was, however, based on only one study, in which MCB, DCB's and TCB's were tested for their potential to induce micronuclei in the bone marrow of mice. In all other testsystems, both *in vitro* as *in vivo*, the chlorobenzenes showed no or (hardly no) activity. The evidence for genotoxicity is therefore considered to be very weak.
From carcinogenicity experiments with a number of chlorobenzenes, it appeared that the development of tumours is mostly accompanied by toxicity in the target organ. In addition, it is striking that for the the most toxic chlorobenzene, HCB, the indications of carcinogenicity are most distinct. In three species exposed to HCB, toxicity (in the liver) was accompanied by the development of tumours. On the basis of the limited indications of genotoxicity and the correlation between toxicity and carcinogenicity it seems as yet justified to use a threshold extrapolation method for risk assessment.

- Oral exposure

Monochlorobenzene

On the basis of experimental studies there is no evidence of carcinogenicity of MCB in animals. There is limited evidence of genotoxicity. Oral reproductive or teratogenicity studies were not found.
A two-year (carcinogenicity-) study resulted in a dose without effect of 60 $mg.kg^{-1}$bw. From subchronic experiments it appeared that at similar doses slight effects were occurred in rats, mice and dogs (for example slight increases of heart- and splenic weights); the dose without effect was (±) 30 $mg.kg^{-1}$ bw. Taking into account a safety factor of 100 (for extrapolation from animal data to human beings) a maximal acceptable daily intake of 0.3 $mg.kg^{-1}$bw for was determined for lifetime exposure.

1,2-Dichlorobenzene

On the basis of experimental studies there is no evidence of carcinogenicity of 1,2-DCB in animals. There is limited evidence of genotoxicity. No oral reproductive or teratogenicity studies were found.

From a chronic (carcinogenicity-) study it appeared that only in the highest dose group (120 $mg.kg^{-1}$ bw) a siginicant effect (tubular regeneration of the kidneys) occurred. The lower dose (60 mg/kg bw) was without effect. Taking into account a safety factor of 100, a maximal acceptable daily intake of 0.6 mg/kg bw was calculated for lifetime exposure.

1,4-Dichlorobenzene

On the basis of experimental studies there is limited evidence of carcinogenicity of 1,4-DCB in animals. Based on the limited evidence of genotoxicity and the correlation between toxicity and carcinogenicity it seems justified to use a threshold extrapolation method as yet. There is no evidence of teratogenicity and an embryotoxic effect was reported at doses of 500 mg/kg bw or more.

In a chronic (carcinogenicity-) study the lowest tested dose resulted in effects on the liver and kidneys of rats. In another experiment with rats (exposed for circa 6 months) the lowest dose (19 $mg.kg^{-1}$bw) did not result in any effects. Because of the fact that in this experiment only increased liver- and kidneyweights were found at the next lowest dose, which was a factor of 10 higher than the dose-without effect, it was concluded that a safety factor of 100 was sufficient. Based on a dose of 19 $mg.kg^{-1}$bw a maximal acceptable daily intake of 0,2 $mg.kg^{-1}$ bw was calculated.

Hexachlorobenzene

On the basis of experimental studies there is sufficient evidence of carcinogenicity in animals. There is limited evidence of genotoxicity, but as yet a threshold extrapolation method is used. There is no evidence of a teratogenic effect or effects on the reproduction. Embryotoxicity occurred at doses of $\geq$40 $mg.kg^{-1}$bw.

An oral subchronic experiment with female rats resulted in a dose without effect of 2 $mg.kg^{-1}$bw for the induction of porphyria and liver enzymes. In a study with combined pre- and postnatal exposure the lowest dose (0.2

mg.kg^{-1}bw) resulted in effects on the immune sytem of rats. The dose-without effect for changes in liver cells of rats was 0.05 mg.kg^{-1}bw. A similar dose did also not cause effects in a small group of monkeys. It was not possible to derive a dose without effect from the chronic studies.
In spite of the fact that the dose without effect was derived from a subchronic experiment, a safety factor of 100 is considered sufficient because the parameters are considered to be toxicologically sensitive. The maximal acceptable daily intake thus becomes 0.5 μg.kg^{-1}bw for liftime exposure.

Other chlorobenzenes

For the other chlorobenzenes the data were limited; therefore only an indicative toxicological limit value can be derived. In the introduction of this section it was already stated that a threshold extrapolation method can be used (as yet) and that as much as possible data concerning enzym induction were used.

Trichlorobenzenes

At the end of a 13-week study with rats the lowest dose (10 mg.kg^{-1} bw) resulted in enzyminduction. After a 30-day "recovery" period this effect had disappeared. A study with monkeys (13 weeks exposed) resulted in a dose without effect of 25 mg.kg^{-1}bw. There was no evidence of teratogenic effects or effects on the reproduction. Embryotoxicity, which was accompanied by maternal toxicity, occurred at doses $\geq$360 mg.kg^{-1}bw.
In establishing an indicative limit value, a safty factor of 500 is used because of the fact that at a dose of 10 mg.kg^{-1}bw still effect were found. This results in a indicative value of 0.02 mg.kg^{-1}bw.

Tetrachlorobenzenes

With respect to toxicity (enzym induction) one subchronic study with rats was available; 1,2,4,5-TeCB appeared to be the most toxic isomer. The dose without effect was 5 mg.kg^{-1} in the diets (corresponding to 0.34 and 0.4 mg.kg^{-1}bw for males and females, respectively). There was no evidence of teratogenicity. Am embryotoxisch effect occurred at 200 mg.kg^{-1}bw of

1,2,3,4- and 1,2,3,5-TeCB. A similar dose of 1,2,4,5-TeCB caused mortality in nearly all mother-animals.
Using the dose without effect of 0.4 $mg.kg^{-1}$bw and a safety factor of 100 an indicative limit value of 4 $\mu g.kg^{-1}$bw for TeCB's was established.

Pentachlorobenzene
One subchronic and reproduction toxicity study with rats was available, which resulted in a dose without effect of 12.5 $mg.kg^{-1}$bw. However, suckling pups of mothers from this dose group developed tremors. The dose without effect was 6.3 $mg.kg^{-1}$bw.
Because of the fact that no data are available on enzyminduction of PeCB no indicative toxicological limit value is given.

5.2 RISK ASSESSMENT FOR THE ENVIRONMENT

5.2.1 Aquatic organisms

The extrapolation methods, which can be used in establishing toxicological limit values, are being discussed at the moment. At present, an "preliminary hazard assessment" method (modification of the EPA-method) will be applied when the available number of NOEC-values resulting from long-term studies is less than 4. When there are at least 4 NOEC-values (from at least three different taxonomic groups) an "refined hazard assessment" method will be applied.
For all chlorobenzenes the first extrapolation method had to be applied. The results of this method are summarized in table 5.1. In principle, lowest NOE(L)C- or L(E)C50-values were used. However, if more values based on the same parameter were available for the same test species, then the geometric mean of these values was used. No data from short-term toxicity tests were used, when three NOEC-values (for algae, crustaceans and fish) were available (see 1,4-DCB, 1,2,3-TCB, 1,2,4-TCB and HCB). Because of the limited number of data the calculated values have te be considered as indicative of maximally acceptable risk-levels (MTR's).
The data show an increasing toxicity with an increase in degree of chlorination. This has been confirmed by values estimated on the basis of

QSAR's. For example, on the basis of the chronic QSAR for crustaceans (De Wolf et al., 1988) the following NOEC-values were estimated: 940 $\mu g.l^{-1}$ for MCB, 540 $\mu g.l^{-1}$ for DCB's, 300 $\mu g.l^{-1}$ for TCB's, 170 $\mu g.l^{-1}$ for TeCB's, 90 $\mu g.l^{-1}$ for PeCB and 45 $\mu g.l^{-1}$ for HCB. The experimental data do not show a difference in toxicity between isomers with a similar number of chloro-atoms. Therefore, only one indicative MTR has been derived for isomers with a similar number of chloro-atoms. The indicative MTR's were in the first place based on that compound from which most data were available. In addition, the MTR's were influenced by the theoretical difference in toxicity, appearing from QSAR-data. This resulted in the following indicative MTR's: 30 $\mu g.l^{-1}$ for MCB, 20 $\mu g.l^{-1}$ for DCB's, 10 $\mu g.l^{-1}$ for TCB's, 5 $\mu g.l^{-1}$, 2.5 $\mu g.l^{-1}$ for PeCB and 0.2 $\mu g.l^{-1}$ for HCB.
The limited number of toxicity data on marine organisms are comparable to those of freshwater organisms. Therefore, the indicative MTR's for seawater are similar to those for fresh water.

5.2.2 Terrestrial organisms

For terrestrial organisms, the numbers of toxicity values are (very) limited. Therefore, the "preliminary hazard assessment" method (modification of the EPA-method) has been used. The results of this extrapolation method are summarized in table 5.2. The NOEC- and EC50-values from this table have been converted to a "standard soil" containing 10% organic matter, to correct for differences in toxicity caused by the use of different soils. Accordingly, the values calculated with the extrapolation method refer to a 10% OM standard soil. This results in indicative MTR's varying between 0.005 $mg.kg^{-1}$ to 0.4 $mg.kg^{-1}$ for 1,4-DCB, TCB's, TeCB's and PeCB and 50 $mg.kg^{-1}$ for HCB. The toxicity values for terrestrial organisms do not show a clear trend of increasing toxicity with increasing degree of chlorination, not even in identical tests. This may be the caused by different ways of applications (water soluble compounds in aqueous solution, not water soluble compounds as solids) and therefore variable bioavailability. For this reason a range of 0.01 to 1 $mg.kg^{-1}$ dry weight is given as indicative for MTR's, for individual compounds, in a 10% standard soil. It must be noted that plants seemed to be relative sensitive to some chlorobenzenes, such as 1,2,3-TCB and 1,2,3,5-TeCB.

Tabel 5.1. Calculated "acceptable" concentrations (μg/l) of chlorobenzenes in fresh water, according to the "preliminary hazard assessment" (PHA) method ("modification" of EPA-method; OECD Workshop, 1990).

Compound	Input (a)		result (μg/l)		
	lowest NOEC I (n)	lowest L(E)C50 II (n)	EPA-modification I (b)	II (c)	indicative "MTR"
HCB	320 (2)	660 (3)	32	6,6	30
1,2-DCB	340 (1*)	1230 (3)	34	12	20
1,3-DCB	680 (2)	3270 (3)	68	33	20
1,4-DCB	304 (3)		30		20
1,2,3-TCB	40 (3)		4		10
1,2,4-TCB	190 (3)		19		10
1,3,5-TCB	260 (**)	490 (1**)	26	4,9	10
1,2,3,4-TeCB	25 (2)	340 (2*)	2,5	3,4	5
1,2,3,5-TeCB	180 (**)	1580 (3)	18	15,8	5
1,2,4,5-TeCB	150 (**)	(d)	15		5
PeCB	35 (2)	250 (3)	3,5	2,5	2,5
HCB	1,8 (3)		0,18		0,2

"MTR": maximally acceptable risk-levels

(n) The number of taxonomic groups for which NOE(L)C- or L(E)C50-values were available. Numbers indicate experimental values, whereas (*) indicate the number of values estimated on the basis of QSAR's. The following QSAR's were used: log 1/EC50 = 0.69 log Kow - 3.18 and log 1/NOEC = 0,67 log Kow - 2,82 for crustaceans (De Wolf et al., 1988) and log 1/LC50 = 0,94 log Kow - 4,62 and log 1/NOEC = 1,06 Kow - 4,57 for fishes (Van Leeuwen et al., 1990).

(a) In principle, lowest NOE(L)C- or l(E)C50-values were used. If more values based on the same parameter were available for the same test species, then the geometric mean was used.

(b) An extrapolationfactor of 10.

(c) An extrapolationfactor of 100 is applied in case there is at least 1 "reliable" L(E)C50-values for each of the following taxonomic groups: algae, crustaceans and fish; in all other cases an extrapolationfactor of 1000 is applied.

(d) Toxicity values for 1,2,4,5-TeCB were equal to exceeded the water solubility threshold (560 μg/l).

Table 5.2. Calculated "acceptable" concentrations of chlorobenzenes according to the "preliminary hazard assessment" (PHA) method (modification of the EPA-method, OECD Workshop, 1990) (in mg/kg dry weight)

Compound	input (a)		results (mg/kg)		
	lowest NOE(L)C I (n)	lowest L(E)C50 II (n)	EPA-modification I (b)	II (c)	indicative "MTR"
HCB					
1,2-DCB					
1,3-DCB					
1,4-DCB	50 (1)	390 (1)	5	0.4	0.4
1,2,3-TCB	5 (1)	5 (2)	0.5	0.005	0.005
1,2,4-TCB	50 (1)	127 (2)	5	0.1	0.1
1,3,5-TCB	50 (1)	615 (1)	5	0.6	0.6
1,2,3,4-TeCB	50 (1)	160 (1)	5	0.2	0.2
1,2,3,5-TeCB		7 (1)		0.007	0.007
1,2,4,5-TeCB		10 (1)		0.01	0.01
PeCB	50 (1)	280 (1)	5	0.3	0.3
HCB	500 (1)		(50)		

(n) The number of taxonomic groups of which NOEC- or EC50-values were available.

(a) The experimental values (V_e) have been converted into estimated values (V_s) into a "standard soil" containing 10% organic matter (% OM-s = 10%), on the basis of the percentage of organic matter in the test soil (% OM-t), using the following equation:

$$V_s = V_e \times 10 / \%\ OM\text{-}t.$$

In the tests with plants, the % OM in the test soil was 1.4%, in these cases a percentage of 2% has been used in the equation.

(b) Extrapolationfactor of 10.

(c) Extrapolationfactor of 1000 is applied in all cases. (An extrapolationfactor of 100 is only applied in case at least one "reliable" L(E)C50-value for at least 3 of the following taxonomic groups: microbial processes, earthworms, plants and arthropods is available).)

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