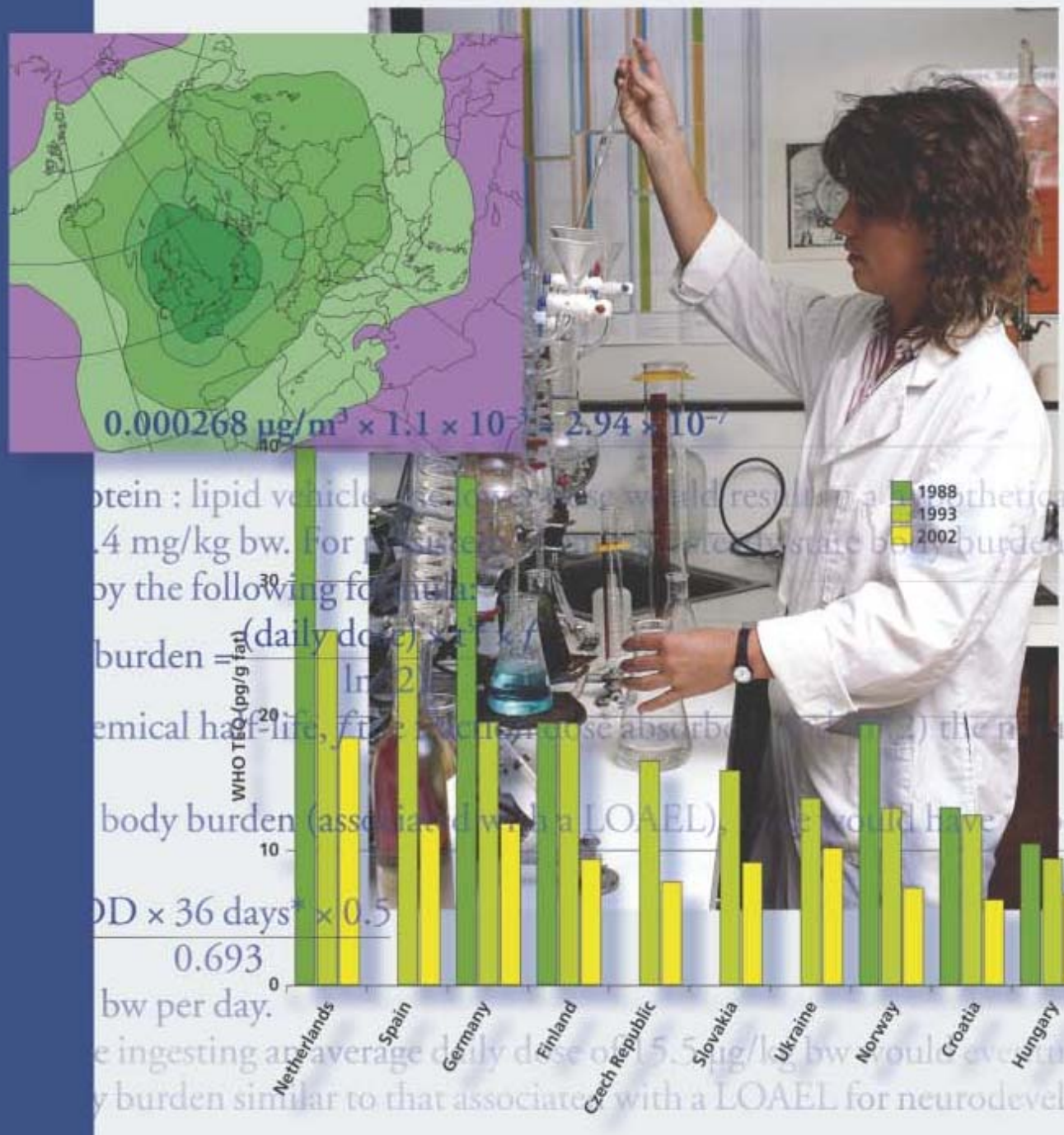
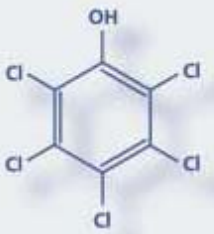
WORLD HEALTH ORGANIZATION
EUROPE

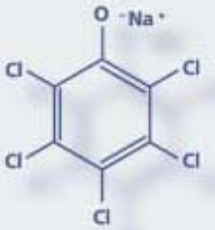
HEALTH RISKS OF PERSISTENT ORGANIC POLLUTANTS FROM LONG-RANGE TRANSBOUNDARY AIR POLLUTION



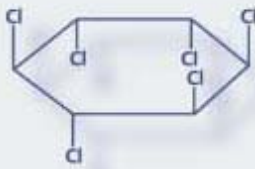
Persistent organic pollutants (POPs) are organic compounds of anthropogenic origin that resist degradation and accumulate in the food-chain. They can be transported over long distances in the atmosphere, resulting in widespread distribution across the earth, including regions where they have never been used. Owing to their toxicity, they can pose a threat to humans and the environment.

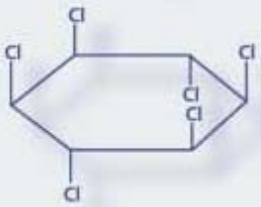


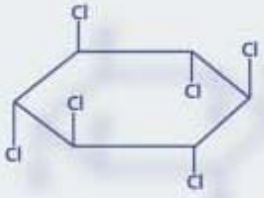
This publication, based on contributions from an international group of experts, provides a concise review of the available evidence on the characteristics of 13 groups of POPs (pentachlorophenol, DDT, hexachlorocyclohexanes, hexachlorobenzene, heptachlor, polychlorinated dibenzo-*p*-dioxins and dibenzofurans, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, polychlorinated terphenyls, polybrominated diphenylethers, polybrominated dibenzo-*p*-dioxins and dibenzofurans, short-chain chlorinated paraffins and ugilec). It reviews pathways of human exposure related to the long-range transport of the POPs through the atmosphere, and the potential hazards associated with them. The review concludes with an expert assessment of the risks to health associated with exposure due to the long-range transport of each of the pollutants.

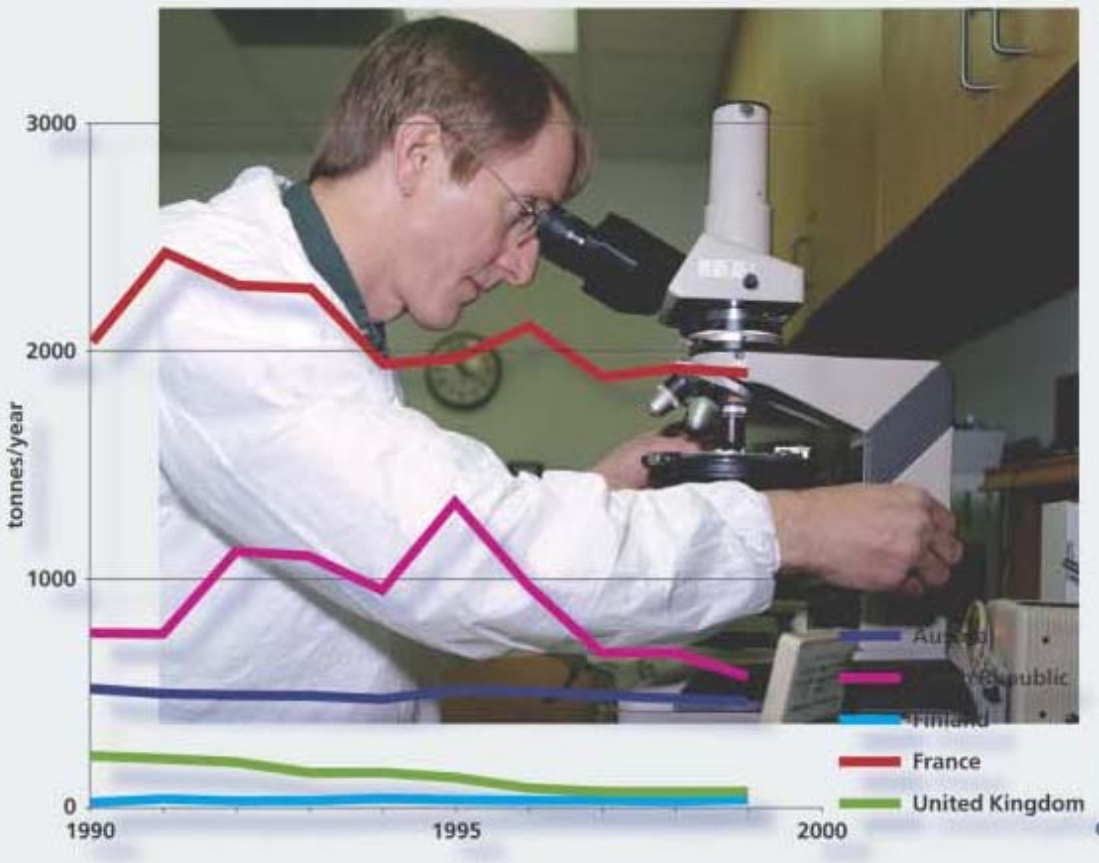


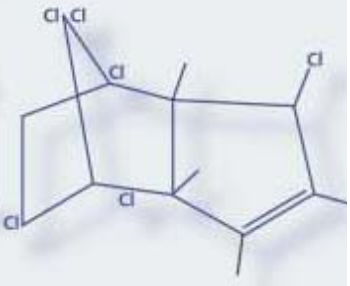
It is intended that the assessment will serve to strengthen the commitment of the parties to the Convention on Long-range Transboundary Air Pollution to improve air quality in Europe and to prevent adverse effects of air pollution on human health.











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JOINT WHO/CONVENTION TASK FORCE ON THE HEALTH ASPECTS OF AIR POLLUTION

HEALTH RISKS OF PERSISTENT ORGANIC POLLUTANTS FROM LONG-RANGE TRANSBOUNDARY AIR POLLUTION

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ABSTRACT

Persistent organic pollutants (POPs) are organic compounds of anthropogenic origin that resist degradation and accumulate in the food-chain. They can be transported over long distances in the atmosphere, resulting in widespread distribution across the earth, including regions where they have never been used. Owing to their toxicity, they can pose a threat to humans and the environment.

This publication, based on contributions from an international group of experts, provides a concise review of the available evidence on the characteristics of 13 groups of POPs (pentachlorophenol, DDT, hexachlorocyclohexanes, hexachlorobenzene, heptachlor, polychlorinated dibenzo-*p*-dioxins and dibenzofurans, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, polychlorinated terphenyls, polybrominated diphenylethers, polybrominated dibenzo-*p*-dioxins and dibenzofurans, short-chain chlorinated paraffins and ugilec). It reviews pathways of human exposure related to the long-range transport of the POPs through the atmosphere, and the potential hazards associated with them. The review concludes with an expert assessment of the risks to health associated with exposure due to the long-range transport of each of the pollutants.

It is intended that the assessment will serve to strengthen the commitment of the parties to the Convention on Long-range Transboundary Air Pollution to improve air quality in Europe and to prevent adverse effects of air pollution on human health.

FOREWORD

The long-range transport of air pollution has been recognized as an important factor affecting ecosystems and human populations. The UNECE Convention on Long-range Transboundary Air Pollution is a powerful international instrument that aims to reduce and prevent air pollution. The effects of the Convention can be assessed by the reduction in emissions of pollution by the countries that are Parties to the Convention. However, an important criterion of the effectiveness of the Convention is its ability to prevent or reduce the burden of long-range air pollution on the environment and human health.

The objective of the Protocol on Persistent Organic Pollutants to the Convention is to control, reduce or eliminate discharges, emission and losses of persistent organic pollutants (POPs). It is recognized that POPs resist degradation under natural conditions and are associated with adverse effects on human health and the environment. The Protocol describes the obligations of the Parties and, in particular, lists the substances that should be eliminated from production and use, or for which use should be restricted. It also provides guidelines on the best available techniques for controlling emissions of POPs.

Preventing health effects of POPs is a strong argument for the commitment of the Parties to the Convention to ratifying and implementing the Protocol. However, evidence of the role of long-range transport as a contributor to human exposure to POPs and related health risks has been dispersed and not readily available. Therefore, the Executive Body for the Convention, at its 17th Session held in Gothenburg on 29 November – 3 December 1999, requested the Joint WHO/Convention Task Force on the Health Aspects of Air Pollution to review the relevant scientific information and to provide the Convention with a concise, authoritative assessment.

The Task Force used existing reviews, such as the Environmental Health Criteria documents published by the International Programme on Chemical Safety, the WHO Air Quality Guidelines for Europe and other relevant publications, as the basis for the health hazard assessment of selected POPs. It also used existing information on the emission of POPs, their dispersal and levels in various environmental media provided by the European monitoring programmes (in particular, the Convention's Cooperative Programme for Monitoring and Evaluation of the Long-range Transmission of Air Pollutants in Europe, EMEP).

The report of the Task Force is based on contributions from its members, national experts nominated by their governments or international experts invited by the WHO European Centre for Environment and Health (ECEH). The WHO/ECEH, Bonn Office, acted as the secretariat of the Task Force. We are most thankful for all the expert contributions, and expect that the results presented in the report will strengthen the commitment to improving air quality in Europe.

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ABBREVIATIONS

ADI	Acceptable daily intake
AOPWIN	Atmospheric Oxidation Program for Microsoft Windows
ATSDR	Agency for Toxic Substances and Disease Registry
BaP	Benzo[*a*]pyrene
BCF	Bioconcentration factor
bw	Body weight
CLRTAP	Convention on Long-range Transboundary Air Pollution
DDA	2,2-bis (*p*-chlorophenyl) acetic acid
DDD	1,1-dichloro-2,2-bis (4-chlorophenyl) ethane
DDE	1,1-dichloro-2,2-bis (4-chlorophenyl) ethylene
DDT	1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane
EMEP	Cooperative Programme for Monitoring and Evaluation of the Long-range Transmission of Air Pollutants in Europe
HCB	Hexachlorobenzene
HCH	Hexachlorocyclohexane
IARC	International Agency for Research on Cancer
IC	Inhibiting concentration
JMPR	Joint Meeting on Pesticide Residues
K_{oc}	Organic carbon partition coefficient
K_{ow}	Octanol/water partition coefficient
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
LRTAP	Long-range transboundary air pollution
MSCE	Meteorological Synthesizing Centre – East
NaPCP	Sodium pentachlorophenoate
NOAEL	No observed adverse effect level
NOEL	No observed effect level
PAH(s)	Polycyclic aromatic hydrocarbon(s)
PBDDs	Polybrominated dibenzo-*p*-dioxins

PBDEs	Polybrominated diphenylethers
PBDFs	Polybrominated dibenzofurans
PCBs	Polychlorinated biphenyls
PCDDs	Polychlorinated dibenzo-*p*-dioxins
PCDFs	Polychlorinated dibenzofurans
PCNs	Polychlorinated naphthalenes
PCP	Pentachlorophenol
PCTs	Polychlorinated terphenyls
POPs	Persistent organic pollutants
PTDI	Provisional tolerable daily intake
SCCPs	Short-chain chlorinated paraffins
TCBT(s)	Tetrachlorobenzyltoluene(s)
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TDI	Tolerable daily intake
TEF	Toxic (TCDD) equivalency factor
TEQ	Toxic equivalent
TRI	Toxic release inventory
UNECE	United Nations Economic Commission for Europe
USEPA	US Environmental Protection Agency

EXECUTIVE SUMMARY

This report summarizes the results of the review of health risks of the persistent organic pollutants in relation to LRTAP performed by the Joint WHO/Convention Task Force on the Health Aspects of Air Pollution. The process involved expert review of accumulated evidence and a series of working group meetings, conducted between May 2000 and May 2002. The risks associated with the following groups of substances were reviewed: pentachlorophenol, DDT, hexachlorocyclohexanes, hexachlorobenzene, heptachlor, polychlorinated dibenzo-*p*-dioxins and dibenzofurans, polychlorinated biphenyls and polycyclic aromatic hydrocarbons. The conclusions related to the health implications in relation to LRTAP for this group of pollutants are summarized below. In addition, the Task Force performed a short hazard assessment for polychlorinated terphenyls, polybrominated diphenylethers, polybrominated dibenzo-*p*-dioxins and dibenzofurans, short-chain chlorinated paraffins and ugilec, identifying the main gaps in information necessary for risk assessment.

Pentachlorophenol / The health characterization of PCP indicates a potential for a number of human health effects associated with low-level chronic exposure via the oral route. Some of these effects have been seen as result of occupational exposure. It is also known that man-made PCPs introduced into the environment have the potential for long-range atmospheric transport, and may reach human foodstuffs and drinking-water. Nevertheless, further research is needed to assess the significance of LRTAP as a significant pathway leading to human exposure via the oral route.

DDT / Intake through the diet may approach or even exceed the PTDI, particularly in tropical and developing countries where DDT is still used for public health purposes (or even used illegally). In these countries, local use represents the main source of exposure. On the other hand, high levels of exposure also occur within the LRTAP Convention area. These include the Inuit populations of Arctic regions, where DDT has not been used for decades or has never been used. The main source of exposure in this case, and the consequent health implications, are mainly related to LRTAP.

Hexachlorocyclohexanes / Large reservoirs of HCH exist in the environment, which suggests that it potentially takes a long time for environmental levels to reflect any action taken. Health hazard characterization has identified a range of health effects related to exposure to γ-HCH by the oral route. Some might be relevant to observed environmental exposures. The oral route is the most relevant for LRTAP sources. Taking into account the uncertainties of the information, and specifically the level of exposure at which human health can be affected, HCH may be considered a possible risk to health through LRTAP.

Hexachlorobenzene / HCB is still released to the environment in the LRTAP Convention region, mainly as a result of unintentional emission from waste incineration and as a by-product of various manufacturing processes. Health hazard characterization has identified a number of effects potentially related to low-level chronic exposure via the oral route. Food is the most relevant means of exposure related to LRTAP-derived sources.

Heptachlor / It appears that the general population is not at risk from LRTAP-derived heptachlor, although highly exposed groups such as some breastfed infants and Inuit in the Arctic may be at risk. Long-range transport represents the most important source of heptachlor found in the terrestrial and aquatic food chains in remote regions, although the environmental concentrations in those regions are likely to be very low since contemporary use is limited.

Dioxins and dioxin-like polychlorinated biphenyls / As human exposure levels often exceed the TDI, the weight of evidence suggests an increased risk of harmful health effects in the general population, especially for breastfed infants and populations with specific diets. Since the chemical and physical properties of PCDD/PCDFs and dioxin-like PCBs make them susceptible to LRTAP, it is expected to contribute significantly to exposure and health risks.

Polychlorinated biphenyls / As human PCB exposure, including both dioxin-like and non-dioxin-like congeners, may reach estimated LOAELs for neurodevelopmental effects in infants, the weight of evidence suggests an increased health risk from current exposures. Lack of congener-specific exposure and toxicity data limits the possibilities for indicating which congeners are responsible for the effects. Since the chemical and physical properties of PCBs make them susceptible to LRTAP, they are expected to contribute significantly to exposure and health risks, especially in remote areas.

Polycyclic aromatic hydrocarbons / The weight of evidence from epidemiological studies based on inhalation and occupational exposure to PAHs suggests an increased risk of harmful health effects, mainly lung cancer. The excess lifetime risk of lung cancer that can be attributed to LRTAP is low compared to the risk due to exposure from local sources.

INTRODUCTION

Persistent organic pollutants (POPs) are organic compounds of anthropogenic origin that resist photolytic, biological or chemical degradation, leading to their bioaccumulation in the food chain. They can be transported over long distances in the atmosphere, resulting in widespread distribution across the earth including regions where they have never been used. Owing to their toxic characteristics, they can pose a threat to humans and the environment. In recent years, therefore, the international community has called for urgent global action to reduce and eliminate the release of POPs and to identify their possible risk to human health and the environment.

The Protocol on POPs to the UNECE Convention on Long-range Transboundary Air Pollution addresses several of those compounds, namely aldrin, chlordane, chlordecone, DDT, dieldrin, endrin, heptachlor, hexabromobiphenyl, hexachlorobenzene, hexachlorocyclohexanes, mirex, polyaromatic hydrocarbons, polychlorinated biphenyls, polychlorinated dibenzodioxins and dibenzofurans, and toxaphene. The Protocol describes the technical measures required to eliminate or restrict the production or use of these substances, and identifies the requirements to achieve that goal.

It is the objective of the Protocol to prevent adverse effects on human health or the environment. Therefore, the Executive Body for the Convention, at its seventeenth session held in Gothenburg in November/December 1999, requested the Joint WHO/UNECE Task Force on Health Aspects of LRTAP to provide a preliminary selection of priority POPs based on the assessment of potential health effects and on the potential contribution of long-range transport to population exposure and risk. Following this request the Task Force, at its meeting in May 2000, selected the following groups of substances for which the risk assessment would be conducted:

> pentachlorophenol, DDT, hexachlorocyclohexanes, hexachlorobenzene, heptachlor, polychlorinated dibenzo-*p*-dioxins and dibenzofurans, polychlorinated biphenyls and polycyclic aromatic hydrocarbons (UNECE 2000). In addition, a short hazard assessment was planned for polychlorinated terphenyls, polybrominated diphenylethers, polybrominated dibenzo-*p*-dioxins and dibenzofurans, short-chain chlorinated paraffins and ugilec.

This document presents the results of the evaluation requested by the Executive Body, as well as the background material for this evaluation. It was prepared by an international group of experts listed in Annex 1. The experts were invited based

on their known expertise as well as on the recommendations of the Parties to the Convention. Besides the experts drafting various parts of the text and participating in working group meetings, a group of external reviewers contributed comments on the drafts (see Annex 2).

THE PROCESS

First drafts of the background papers were reviewed at the fourth meeting of the Task Force on Health Aspects of LRTAP, held in Bonn, Germany, on 3–4 December 2001. Following the recommendations of the meeting, the Expert Group designated by the fourth meeting of the Task Force prepared a draft report entitled "Health risks of POPs from LRTAP". Comments on this draft were received both from members of the Expert Group and external reviewers. A small drafting group, meeting on 26 April 2002, proposed a uniform format of the review for each group of substances.

To finalize the assessment, the fifth meeting of the Task Force was convened in Bonn on 13–14 May 2002. The meeting reviewed the drafts, taking into account the comments received from the reviewers. The meeting prepared and approved executive summaries for all the substances reviewed, except ugilec. These summaries were presented to the Working Group on Effects for approval at its 21st Session on 28–30 August 2002 (UNECE 2002) and are also included in this document as Annex 3. The staff of the WHO European Centre for Environment and Health in Bonn, in close collaboration with the main authors of the chapters, carried out the final editing of the background material presented in the individual chapters of this document.

Evaluation of the health risks related to LRTAP for ugilec was not possible because of the incompleteness of the relevant information. The information collected by the Expert Group on this group of substances is, however, presented in this report.

The present assessment conducted by the Task Force is complementary to the work of the ad hoc group of experts on POPs under the LRTAP Convention. This group is reviewing the existing obligations on substances already in the 1998 UNECE/LRTAP Protocol on POPs and is advising national experts preparing preliminary risk profiles on substances that may be candidates for inclusion in the Protocol.

STRUCTURE OF THE REPORT

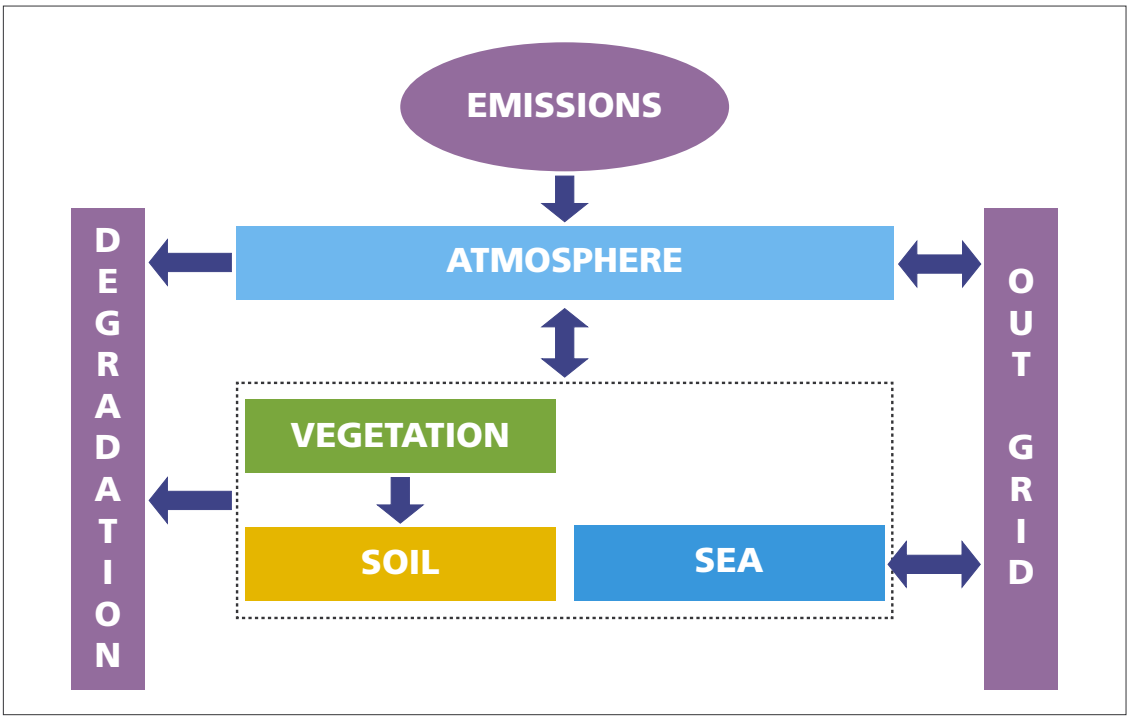
To assess the risk to human health related to long-range transport of the considered pollutants, the experts considered the ability of substances to be transported in the environment over long distances after their release to the environment, their potential to persist and accumulate in different environmental compartments, the pathways and opportunities for human exposure to the substance transmitted in the environment, and data characterizing the hazardousness of the substance. The discussion of the experts during the working group meetings concentrated on formulating the conclusions of the assessment. In the result, the assessment of each of

the substances or group of substances described in this document is presented in the following sections.

- Introduction (summarizing the sources and uses of the substance, as well as its status in the POPs Protocol).
- Characteristics of the substance(s)[1] as compound(s) with long-range transboundary potential (listing its/their chemical and physical properties, assessments of its/their concentrations in environmental media and ability to bioaccumulate).
- Pathways of human exposure and its relation to LRTAP, using results of available exposure assessment studies and models.
- Health hazard characterization based on existing toxicological (human and animal) data as well as, where available, epidemiological information. This section also includes the results of risk assessment performed by WHO, IARC or major national chemical safety and public health agencies and the relevant reference values.
- Human health implications relative to LRTAP, summarizing the evidence presented in earlier sections and providing conclusions of the assessment.

Assessing concentrations of POPs in the atmosphere and their environmental fate relies also on modelling. Several groups, using various methods over the past two decades, have attempted numerical modelling of long-range atmospheric transport of persistent organic pollutants. Several approaches have been used, which can be grouped in two broad types: generic box models based on the fugacity con-

Fig. 1. Simplified scheme of the EMEP/MSCE POPs model



[1] The plural is used for compounds whose chemical name implies a number of isomers or congeners.

cept (e.g. Mackay & Wania 1995; Wania & Mackay 1999) and dynamic transport models (Strukov et al. 2000).

Fig. 1 presents a simplified scheme of the EMEP/MSCE POPs model. It is a multi-compartment model with Eulerian-type advection scheme with spatial resolution 150 × 150 and 50 × 50 km. It includes the atmosphere, soil, sea water and vegetation. The model is able to assess the redistribution of POPs between these media and estimate concentration levels in them. Obviously, many uncertainties remain concerning, for instance, emission rates, degradation rates and the role of sediments. Results obtained from this model, or models similar to it, are used in various parts of this report for illustrative purposes as, despite their limitations, they do indicate the main features of large-scale atmospheric transport.

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CHAPTER 1/ PENTACHLOROPHENOL

1/ INTRODUCTION

Pentachlorophenol (PCP) is a white organic solid with needle-like crystals and a phenolic odour. It may be released to the environment as a result of its manufacture, storage, transport or use. One major use of PCP is as a wood preservative, primarily applied to protect timber from fungal rot and wood-boring insects, but it has also been used as a pre-harvest defoliant in cotton, as a general pre-emergence herbicide, and as a biocide in industrial water systems. Its sodium salt is used for similar purposes and readily degrades to PCP. At present, the most extensive use of PCP is the production of the ester, pentachlorophenyl laurate (PCPL), which is less toxic by an order of magnitude.

Production of PCP and sodium pentachlorophenate (NaPCP) ceased in the European Union in 1992, since when they have been imported to the European market from the United States. There is unconfirmed information that additional NaPCP may be imported from South-East Asia (EC 1998; OSPAR 2001). In 1996, a total of 378 tonnes of NaPCP and 30 tonnes of PCP were imported into the European Union (France, Portugal, Spain and the United Kingdom). Imported PCP is manufactured into PCPL in the United Kingdom (EC 1998; OSPAR 2001).

PCP has been one of the most heavily used pesticides in the United States: 42 million pounds in 1984; 38 million pounds in 1985; 32 million pounds in 1986 and 18.2 million pounds (9.1 thousand short tons) in 1996. About 24 million pounds were manufactured in 1987 by Vulcan Materials. More recent production data are not available (ATSDR 2001).

According to the TRI, an estimated 13 141 pounds of PCP, amounting to 54% of the total environmental release, was discharged to the atmosphere from manufacturing and processing facilities in the United States in 1991 (ATSDR 2001). The TRI data should be used with caution because only certain types of facility are required to report; the list of facilities is not exhaustive (ATSDR 2001).

PCP can be formed during the incineration of chlorine-containing waste material. Heeb et al. (1995) found that PCP constituted 8% of polychlorinated phenols formed in the flue gas and 10% of those formed in the stack gas during the incineration of chlorine-containing waste material. It may also be released in stack emissions as a result of pyrolysis of polyvinyl chlorides (Blankenship et al. 1994). Available measurements and calculations show that, for the period 1980–1996, about 37 tonnes of PCP per year are released from a municipal waste incinerator in Hungary (Kovács 2002).

Technical grade PCP has historically contained dioxins (e.g. tetra-, hexa- and octochlorodibenzo-*p*-dioxins) and hexachlorobenzene as manufacturing by-products. Technical grade PCP is typically about 86% pure.

PCP is a major product of the metabolism of hexachlorobenzene in mammals.

Actions on PCP are not included in the 1998 UNECE/LRTAP Protocol on POPs. However, PCP is identified in article 8 concerning research development, monitoring and cooperation. Hence PCP is one of the substances considered to be the most likely to be added to the annexes of the Protocol.

2/ POTENTIAL FOR LRTAP

2.1/ Physical properties allowing atmospheric transport

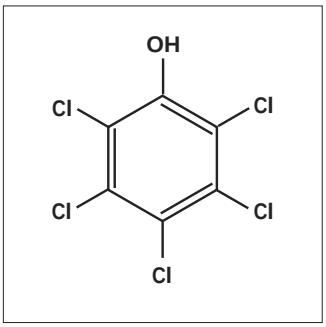

Fig. 1.1. Pentachlorophenol (C_6HCl_5O), CAS registry: 87-86-5

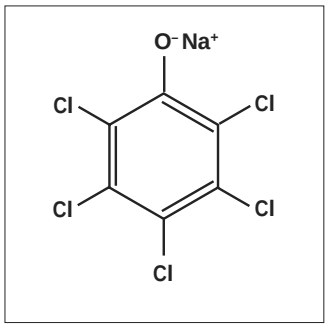

Fig. 1.2. Sodium pentachlorophenate (C_6Cl_5ONa), CAS registry: 131-52-2

The physical and chemical properties of the compound suggest limited evaporation to the atmosphere and that most of it will move with water and generally associate with soil particles. Movement of PCP in soils depends on soil acidity.

Table 1.1. Physical properties of PCP and NaPCP

Property	PCP	NaPCP
Molecular weight	266.35	288.34
Solubility in water	14 mg/l at 20 °C	330 000 mg/l at 25 °C
Log K_{ow}	3.32	No data
Log K_{oc}	4.5	No data
Vapour pressure at 25 °C	0.00011 mmHg	No data
Henry's law constant at 25 °C	3.4×10^{-6} atm·m³/mol	No data

Sources: ATDSR; Montgomery 1996.

2.2/ Persistence in water, soil and sediment

The photolysis of PCP in water is a significant process largely dependent on the pH. The ionized form is more sensitive to photodegradation than the protonated form. Weiss (1982) showed 90% degradation in 10 hours of PCP in surface water with a pH of 7.3, while at pH 3 the degradation was only 40% after 90 hours. Photolysis in water leads to the formation of substances such as 2,3-dichloromaleic acid, 2,3,5,6- and 2,3,4,6-tetrachlorophenol, tetrachlororesorcinol, tetrachlorocatechol, benzoquinones and potentially dioxins.

In wet soil, photolysis may be significant (Donaldson & Miller 1997). These authors showed 55% photodegradation of PCP added to a sandy clay loam soil over a 14-day period.

Increasing concentration tends to lengthen the process of biodegradation, probably owing to the possible toxicity of PCP for bacterial colonies. Maximum rates of degradation of 0.3–0.5 mg/kg per day in soils containing 30 mg/kg PCP and a degradation rate of 82% after 7 months have been reported by Miethling & Karlson (1996). Over the same period, less than 2% of the PCP added to the soil in a concentration of 100 mg/kg had degraded.

PCP released into the atmosphere from treated wood can be transported back to surface waters and soils via wet and dry deposition. Atmospheric PCP is transformed via photolysis; the compound may slowly undergo free radical oxidation with an estimated half-life of approximately 2 months (ATSDR 2001).

Atmospheric PCP probably undergoes photolysis in the absence of water, although mechanisms for this reaction are not well known (Crosby & Hamadad, 1971; Gäb et al. 1975). Photolysis of sorbed or film-state PCP in the presence of oxygen has also been observed (Gäb et al. 1975). The reaction products were similar to those found in aqueous photolysis. Bunce & Nakai (1989) estimated the rate of photolysis in the atmosphere based on measured quantum yields (254 nm) in the laboratory, molar absorptivity values and solar intensity values for mid-day in summer at a latitude of 40° N; the estimated loss of PCP to vapour-phase photolysis was 6.2% per hour. This rate represents the maximum rate at 40° N; the average rate of photolysis for PCP will be lower. No empirical data were found describing the reactivity of PCP to free radical oxidation in the atmosphere. Bunce & Nakai (1989) calculated the potential atmospheric degradation of PCP due to hydroxyl radical attack. The estimated loss rate was 1.5% per hour (half-life of 66 hours) as calculated from an estimated rate constant of 4.7×10^{-13} $cm^3 \cdot molec^{-1} \cdot s^{-1}$, assuming a peak noon summer hydroxyl radical concentration of 6.2×10^6 molec/cm^3 (ATSDR 2001).

Using the method of Meylan & Howard (1993), a half-life of 58 days for the vapour-phase reaction of PCP with hydroxyl radicals can be obtained from an estimated rate constant of 5.5×10^{-12} $cm^3 \cdot molec^{-1} \cdot s^{-1}$ and an average hydroxyl radical concentration of 5.5×10^5 molec/cm^3. Adsorption of PCP to particulate matter will, however, attenuate the rate of this process in the atmosphere (ATSDR 2001).

Volatilization from treated wood poles and other outdoor-use wood also occurs. Between 30% and 80% of the PCP applied to coniferous wood by dip or brush treatments may be lost by volatilization within 12 months (Bunce & Nakai 1989). Ingram et al. (1986) reported increased volatilization of PCP from treated wood with increased temperature; similar results with temperature change were seen with each of numerous solvent systems used to apply the compound.

2.3/ Bioaccumulation

The bioconcentration of PCP in aquatic organisms is high. Bioconcentration factors of 100–1000 have been reported by a number of authors (Bude et al. 1985;

Devillers et al. 1996; Lu & Metcalf 1975; Parrish et al. 1978). The bioconcentration depends on the pH and increases with falling pH (Kobayashi & Kishino 1980).

The toxicity is also largely dependent on the pH of the matrix tested. The acute toxicity of PCP was investigated at pH 4, 6 and 9 in *Chironomus riparius*; this experiment showed that toxicity was maximum at pH 4 and minimum at pH 9. The difference in toxicity was attributed to variations in the degree to which the substance penetrated the organism tested, since at pH 4 the PCP is entirely in protonated form and therefore lipophilic. Conversely, at pH 9 PCP is fully ionized, which reduces the potential for penetration into the organism, and at the same time reduces the potential for build-up and toxic effects (Fisher & Wadleigh 1986).

No reliable data have been found for the bioaccumulation of PCP in plants.

2.4/ Monitoring and modelling

Limited information is available on the levels of PCP in ambient air. USEPA (1980) estimated atmospheric concentrations of PCP using air models. A cumulative concentration estimate based on all emission sources was 0.5–136 ng/m^3. The lower end of this range coincides with the upper end of the range of computed air concentration estimates based on PCP concentrations in rainwater in Hawaii (0.002–0.063 ng/m^3), where PCP has been used extensively as an herbicide and wood preservative. A Canadian study (Cessna et al. 1997) reported the amount of PCP in air in Saskatchewan (Regina and Waskesiu) and Northwest Territories (Yellowknife). The concentrations of PCP in the vicinity of Yellowknife ranged from 0.43 to 3.68 ng/m^3 with a mean concentration of 1.53 ng/m^3. At both the Regina and Waskesiu sites, the concentrations ranged from 0.06 to 0.58 ng/m^3 with a mean value of 0.30 ng/m^3 (ATSDR 2001)

Two background air sampling stations in the mountains above La Paz, Bolivia, at 5200 m measured 0.93 and 0.25 µg PCP per 1000 m^3 of air, and four Antwerp (Belgium) samples varied from 5.7 to 7.8 µg PCP per 1000 m^3 of air. The level of PCP in Burlington, Ontario, rainwater was 10 µg/l in 1982 (Warrington 1996).

In the past, PCP concentrations as high as 25 000–150 000 µg/l in industrial effluent were reported; at one time, 30–40 tonnes were calculated to be transported by the Rhine each year (WHO 1998). Concentrations up to 10 500 µg/l have been reported locally in a river (Fountaine et al. 1976), but concentrations in water samples are usually below 10 µg/l (WHO 1987). Monitoring data showed that PCP concentrations generally decreased (from 0.07–0.14 µg/l in 1988 to 0.01–0.02 µg/l in 1993) in the River Elbe after PCP production was stopped in Germany in 1986 and its use was banned in 1989. Such a trend was not seen in the Rhine and its tributaries, where concentrations were even higher in 1990–1991 than in 1980–1989 (maximum levels up to 0.23 µg/l); the cause is not known, but it indicates continuing environmental contamination.

Concerning measurements in biota as evidence of transport to remote regions, the situation is complicated for two main reasons. On the one hand, PCP is me-

tabolized into other molecules and therefore its absence in animal tissues is not conclusive; on the other hand, it is a major product of the metabolism of hexachlorobenzene and other common pesticides in mammals, and therefore if it is found it does not mean it was taken up as such.

Fig. 1.3 and 1.4 present pilot calculations of PCP transport from Hungarian and United Kingdom emission sources (Shatalov et al. 2002). PCP emissions are adapted from Berdowski et al. 1997. From these figures it can be seen that PCP is capable of being transported over considerable distances.

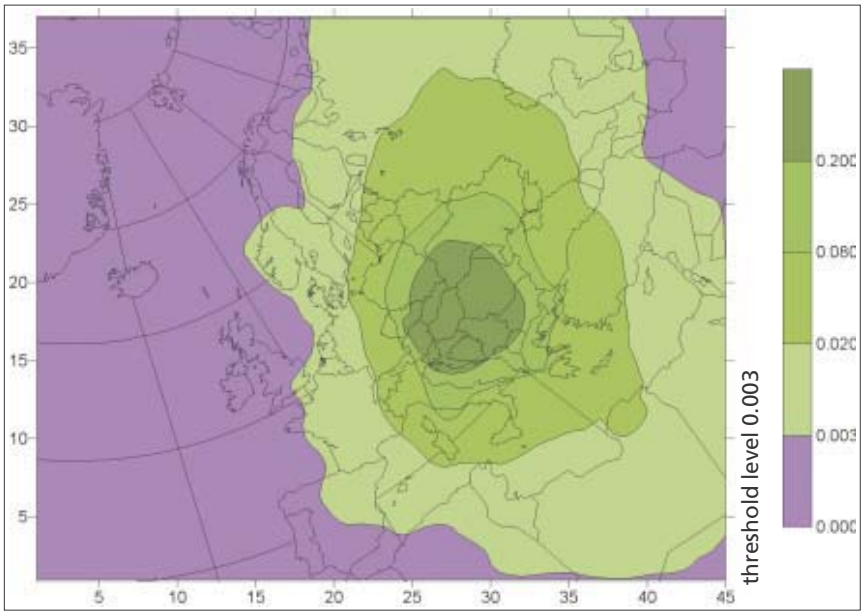

Fig. 1.3. Spatial distribution of PCP air concentrations (ng/m³) from Hungarian emission sources for 1990 (Berdowski et al. 1997). Violet means concentrations less than the 0.003 ng/m³ threshold level (Shatalov et al. 2002).

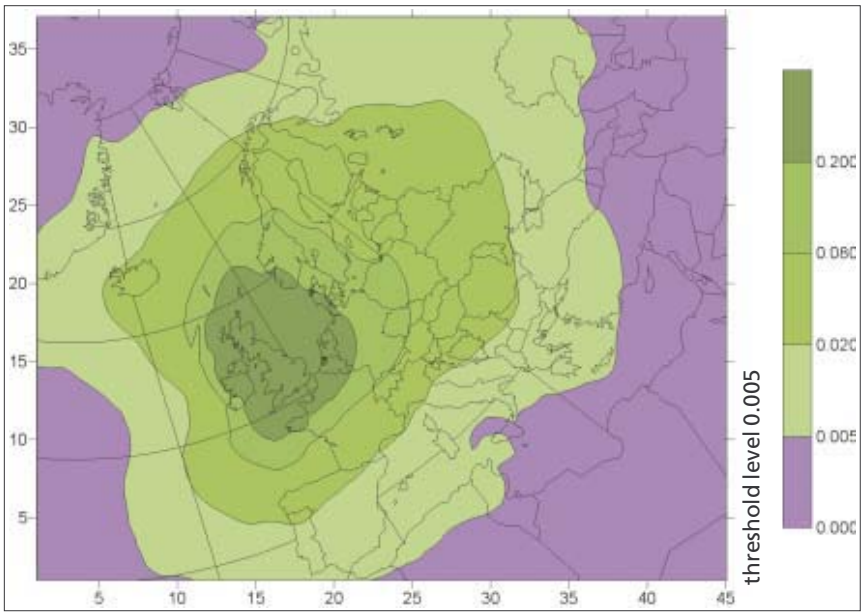

Fig. 1.4. Spatial distribution of PCP air concentrations (ng/m³) from United Kingdom emission sources for 1990 (Berdowski et al. 1997). Violet means concentrations less than the 0.005 ng/m³ threshold level.

2.5/ Conclusions regarding the LRTAP potential

The physical and chemical properties of the compound suggest limited evaporation to the atmosphere and that most of it will move with water and generally associate with soil particles. The mobility and availability of PCP in the environment depends on the acidity of the medium. The volatilization of PCP from treated

wood increases with temperature; similar results with temperature change were seen with all the numerous solvent systems utilized for the application of the compound.

In air, soil and surface water PCP is subjected to photolysis and hydroxyl degradation, with atmospheric half-lives ranging from hours to weeks.

PCP bioconcentrates in aquatic organisms and the BCF value increases with falling pH.

3/ PATHWAYS OF LRTAP-DERIVED HUMAN EXPOSURE

3.1/ Significant sources and magnitude of exposure

PCP is released to the air by evaporation from treated wood surfaces and factory (chemical manufacturing plants and wood preservation plants) waste disposal. It enters surface water and groundwater from factories, wood treatment facilities and hazardous waste sites. It also enters the soil as a result of spills, disposal at hazardous waste sites and its use as a pesticide. The compound can be present in fish or other species used for food, as demonstrated by the ongoing food monitoring programme of the US Food and Drug Administration. In air, soil and surface water, PCP lasts for hours to days. The compound is broken down in soil and surface water.

Chlorination of phenolic compounds during water treatment has been reported to produce detectable levels of PCP (Detrick 1977; Smith et al. 1976). In addition, common pesticides such as lindane, hexachlorobenzene, pentachlorobenzene and pentachloronitrobenzene are known to be metabolized to PCP by plants, animals and/or microorganisms, but the contribution of the metabolism of these pesticides to environmental levels of PCP is unknown (Dougherty 1978).

Even in those countries where the use of PCP has been abandoned, it continues to be an important environmental contaminant because it is imported via various materials treated with it.

The general population is exposed to PCP through the ingestion of drinking-water (0.01–0.1 µg/l) and food (up to 40 µg/kg in composite food samples) (WHO 1987). Apart from the daily dietary intake (0.1–6 µg/person per day) continuous exposure to hexachlorobenzene and related compounds in food, which are biotransformed to PCP, may be another important source. Daily net intake of PCP in the general population has been estimated to be 5–35 µg/day. The long-term average daily intake of PCP by the general population in the United States was estimated to be 16 µg/day using six-compartment environmental partitioning models; food, especially fruits, vegetables and grains, accounted for 99.9 % of the total exposure (Hattemer-Frey & Travis 1989). In Canada, the estimated daily intake is 0.05 µg/kg of body weight per day, mostly via food or indoor air. It seems likely that food accounts for most of the intake unless there is specific local chlorophenol contamination causing increased concentrations in drinking-water, or exposure from wooden homes treated with PCP.

The general population can be exposed to PCP in treated items such as textiles, leather and paper products and, above all, through inhalation of contaminated

indoor air. Alterations in the use pattern have taken place during the last 10 years as a result of increased concern about the potential health hazards from PCP and its impurities. Very limited data are available on exposure of the general population via these various routes.

3.2/ Significance of LRTAP as the source of total exposure

Humans will be exposed through three main routes: treated products, food and drinking-water. The latter two sources are relevant for LRTAP. The long-term average daily intake of PCP by the general population was estimated in 1989 to be 16 µg/day in the United States; in Canada the estimated daily intake is 0.05 µg/kg bw per day. It seems likely that food accounts for the majority of the intake unless there is specific local chlorophenol contamination causing increased concentrations in drinking-water, or exposure from wooden homes treated with PCP.

Concerning measurements in biota as evidence of transport to remote regions, the situation is complicated for two main reasons. On the one hand, PCP is metabolized into other molecules and therefore its absence in animal tissues is not conclusive; on the other hand, it is a major product of the metabolism of hexachlorobenzene and other common pesticides in mammals, and therefore if it is found it does not mean it was taken up as such.

4/ HEALTH HAZARD CHARACTERIZATION

All the toxicological information and data are taken essentially from papers published by WHO (1987), IARC (1986, 1991), ATSDR (1994, 2001) and HSDB (2000).

4.1/ Toxicokinetics

PCP is rapidly and completely absorbed by the digestive tract. After entering the blood, where it combines at least in part with plasma proteins, the highest concentrations of PCP are in the liver, kidneys and brain, but the tendency for bioaccumulation remains very low.

Results from human and animal studies indicate that PCP is not extensively metabolized, as shown by a large portion of the administered dose being excreted in urine unchanged after exposure by inhalation or by oral routes. The metabolism of PCP occurs in the liver, and the major pathways are glucuronide conjugation and oxidative dechlorination.

Whatever the species (including humans) and exposure route, the principal elimination route of PCP is the urine, in which it is found in free form or in conjugate glucide form (86% in humans, 60–83% in rodents and 45–75% in monkeys). Apart from the faeces, it is also accepted that some elimination takes place via plasma proteins, but the influence of plasma concentration on the overall elimination kinetics of PCP is not yet known.

Also it must be noted that the elimination time of PCP is largely determined by the form in which it is used. In humans, NaPCP has a half-life of 30 hours in the plasma and 33 hours in the urine, whereas in ethanol (40% solution) these

times are considerably longer, reaching 16 and 20 days, respectively, in plasma and urine.

4.2/ Effects on laboratory animals

4.2.1/ Systemic effects

Only experimental oral studies are available; the chronic toxicity of PCP by the oral route is very well documented.

In rodents, biochemical, functional and histopathological changes in the liver have been widely described for daily doses of 1–30 mg/kg over periods of 3–8 months (Johnson et al. 1973; Kimbrough & Linder 1978). The use of purified PCP reduces the extent of the lesions observed, although one research programme noted, over long periods of treatment (6 months), similar effects on the liver owing to the use of three more or less purified preparations of PCP (NTP 1989).

The more recent studies confirmed these effects. Evidence of biochemical (alterations in hepatic enzyme activities), gross (increased liver weight) and histopathological (hypertrophy, vacuolization, hyperplasia, fibrosis, necrosis and degeneration) effects is found following acute, intermediate and chronic oral exposure to PCP in rodents. At low dosages, the observed liver effects are characteristic of enzyme induction. Increase in liver weight and hepatocellular hypertrophy and vacuolization have been observed in mice exposed to pure PCP at 41 mg/kg bw per day for 2 weeks (Umemura et al. 1996), in rats exposed to pure or technical grade PCP at 1–40 mg/kg bw per day for an intermediate duration (Bernard et al. 2001b, Blakley et al. 1998, Kimbrough & Linder 1978, Knudsen et al. 1974; NTP 1999), in mice exposed to pure or technical-grade PCP at 9 mg/kg bw per day for 4–12 weeks (Kervliet et al. 1982; Umemura et al. 1996) and pigs exposed to pure PCP at 10 mg/kg bw per day for 30 days (Greichus et al. 1979).

Purified PCP (2 mg/kg bw per day, only dose tested, >99% pure with no detectable chlorinated dibenzo-*p*-dioxin impurities) also induced a small but significant increase in relative liver weight in rats exposed twice weekly for 28 days. Histological examination was not performed (Blakley et al. 1998). The National Toxicology Program (Chhabra et al. 1999; NTP 1997) conducted a 28-day dietary range-finding study with pure PCP (20–270 mg/kg bw per day, approximately 99% pure, containing tetrachlorophenol as a single impurity) in F344 rats. Significantly increased absolute or relative liver weights were seen at all dose levels. Hepatocyte degeneration and centrilobular hypertrophy were seen at 40 mg/kg bw per day and higher in males, and at 75 mg/kg bw per day and higher in females. The results of the study by Kimbourgh & Linder (1978) suggest that impurities found in technical grade PCP may influence its toxicity, but other studies that compared the hepatotoxicity of pure and technical grade PCP did not find differences in potency or type of liver effects (Kerkviet et al. 1982, NTP 1989).

Significant alterations in thyroid hormone levels have been observed in several chronic and intermediate-duration animal studies. A significant decrease in mean serum concentration of thyroxine and a significant increase in the mean serum concentration of insulin, compared with controls, was observed in female sheep

administered PCP at 2 mg/kg bw per day (only dose tested; 99.9% pure) by gavage twice weekly for 43 days. Mean serum concentrations were based on blood samples taken every hour for 6 hours after 36 days of PCP treatment (Rawlings et al. 1998). These results are confirmed on ewes and male lambs by Beard et al. (1999a, b). In a multigeneration study in mink, significant decreases in serum thyroxine levels were observed in the F_1 males and the F_2 males and females exposed to PCP at 1 mg/kg bw per day (purity not reported) (Beard & Rawlings 1998). A decrease in relative thyroid weight was also observed in the F_2 female mink.

A study of mice exposed in parallel to two preparations of PCP – one purified, one not – at 25 mg/kg bw per day for 10–12 weeks concluded that the impurities play an essential but non-exclusive role in immune system malfunctions (Kerkvliet et al. 1982), mainly deterioration of the T-cells. However, a recent study in rats provides evidence that pure PCP (> 99% pure with no detectable dioxin impurities) can affect immune function (Blakley et al. 1998).

The haematological effects appear to be due largely to the impurities present in industrial preparations of PCP (Johnson et al. 1973). Nevertheless, a fall in the white blood cell count has been described in pigs following administration of purified PCP (Greichus et al. 1979).

Hypothermia resulting from the decoupling of the oxidizing phosphorylation process is probably the reason for the neurological effects observed in animals. In rats, the administration of PCP in drinking-water (purity not specified) led after 14 weeks to a reduction of the glutathion level in nerve tissue, which is responsible for activating a number of enzymes (Savolainen & Pekari 1979). Again in rats, demyelinization of the sciatic nerve was observed after administration of PCP (1 and 3 mM) in drinking-water for three months.

4.2.2/ Effects on reproduction and growth

Only experimental oral studies are available.

Numerous data suggest that long-term exposure to PCP can decrease fertility, although the mechanism does not appear to be through histological damage to reproductive tissue. In a two-generation study, decreased fertility (significant decreases in the number of rats mated and in the ratio of pregnant rats to the number of rats in cohabitation) was observed in the first generation of rats exposed to 60 mg/kg bw per day PCP (purity not reported) administered by gavage (Bernard et al. 2001b). No alterations in fertility were observed in the F_1 generation exposed to 10 or 30 mg/kg bw per day or in the parent generation. The only other reproductive effects observed in this study were a significant decrease in testicular spermatid count, a decrease in absolute testes weight and in the ratio of testes weight to brain weight, and focal/multifocal mononuclear cell infiltrate in the epididymis in F_1 rats administered 30 or 60 mg/kg bw per day. Other alterations were observed on the F_1 generation in different studies where minks were exposed to 1 mg/kg bw per day PCP (purity not reported) in the diet for 3 weeks prior to mating (Beard & Rawlings 1998; Beard et al. 1997). The effects were not found in sheep exposed before mating (Beard & Rawlings 1999; Beard et al. 1999b). Several reproduc-

tive toxicity studies have reported histological alterations in reproductive tissues. Beard et al. (1999a) reported focal degeneration of the seminiferous tubules and decreased sperm density in the epididymis in sheep exposed to PCP (purity not reported) at 1 mg/kg per day in the diet during gestation, lactation and for 20 weeks postnatally. Chhabra et al. (1999) and NTP (1999) reported minimal to marked germinal degeneration and lack of spermatozoa in the seminiferous tubules of rats exposed to pure PCP at 270 mg/kg per day in the diet for 28 days. Beard et al. (1997) reported increased severity of cystic uterine glands in mink exposed to PCP (purity not reported) at 1 mg/kg per day prior to mating and during gestation and lactation. No histological alterations in reproductive tissues were observed in male or female rats chronically exposed to pure PCP at 30 mg/kg per day in the diet for 2 years (Chhabra et al. 1999; NTP 1999).

Administration of purified and unpurified PCP to gestating rats in doses of 5–50 mg/kg over periods of between 6 and 15 days demonstrated a dose-dependent increase in the incidence of subcutaneous oedema, urethric swelling and a number of bony anomalies in the skull, vertebrae, ribs and sternum (Schwetz et al. 1974).

The toxicity of PCP to rat embryos and fetuses has been confirmed in other studies (Bernard et al. 2001a, b; Exon & Koller 1982; Welsh et al. 1987). In a recent study, however, Bernard & Hoberman (2001) exposed Sprague Dawley rats by gavage to PCP at 0, 10, 30 and 80 mg/kg/day in corn oil from day 6–15 of presumed gestation. From this study they determined a NOAEL of 30 mg/kg/day for maternal toxicity in Sprague Dawley rats. A developmental NOAEL for PCP was also found to be 30 mg/kg/day and the LOAEL for PCP developmental toxicity of 80 mg/kg/day was associated with increased resorptions and reduced live litter size and fetal body weights, and caused increased malformations and variations. The authors concluded that PCP should not be identified as a selective developmental toxicant in the rat because adverse effects on development of rat conceptuses occurred only at dosages toxic to the mother.

In hamsters, oral administration of PCP at doses between 1.25 and 20 mg/kg resulted in fetal death in a number of groups (Hinkle 1973).

No developmental effects were observed in rabbits administered 88–89% pure PCP at up to 30 mg/kg/day by gavage on gestational days 6–18 (Bernard et al. 2001b).

4.2.3/ Carcinogenic effects

The IARC and USEPA classifications are based on a study on B6C3F1 mice of both sexes, in which oral administration at daily doses of 0, 100 and 200 ppm of two 90% pure preparations of PCP led to the development of a number of tumours, particularly in the males (adenomas and hepatocellular carcinomas, haemangiosarcomas and phaeochromocytomas) (NTP 1989).

A recent study confirms these effects: groups of male and female F344 rats were given diets that contained 0, 200, 400 or 600 ppm PCP (approximately 99% pure with one impurity, tetrachlorophenol) in the diet (equivalent to doses of 0, 10, 20 or 30 mg/kg/day) for 105 weeks (NTP 1999). A stop-exposure group was given

a diet that contained 1000 ppm PCP for 52 weeks (60 mg/kg/day) followed by a control diet through to 105 weeks. At 2 years, a significant increased incidence of malignant mesothelioma originating from the tunica vaginalis was present in males from the 60-mg/kg/day stop-exposure group compared with controls, and the incidence exceeded the historical control range. Nasal squamous cell carcinomas were present in one control male, three 10-mg/kg/day males, one 20-mg/kg/day male and five 60-mg/kg/day males at 2 years, and the incidence in 1000-ppm males exceeded the historical control range.

4.3/ Health effects in humans

As far as the oral route is concerned, there are few usable data for humans for systemic effects and effects on reproduction and growth.

Human epidemiological data address multiple exposure situations, where the significance of PCP exposure cannot easily be singled out (Colosio et al. 1985).

A study performed on 40 volunteers among workers who had been employed in the manufacture of PCP and its sodium salt for more than three years revealed signs of chloracne and minor disturbance of lipid metabolism. Although the study had many limitations, and the fact that chlorodibenzodioxin may have been implicated in the development of the symptoms, it seems that long-term occupational exposure to PCP and /or its by-products did not induce profound changes (Baxter 1984).

Another study was performed on 32 subjects with prolonged exposure to PCP in a wood factory and in 37 controls. The results suggested the absence of major laboratory and clinical signs of PCP-dependent immune deficiency. A weak effect of long-term exposure to PCP on the functional immune response could not be ruled out, because of the finding of a decreased response to 5% phytohaemagglutinin in the high-exposure group. A weak effect against hepatocyte membrane was evidenced by the finding of raised serum concentration of glycocholic, taurodeoxycholic and glycochenodeoxycholic acids in subjects directly exposed to PCP for more than 10 years (Colosio et al. 1993).

A recent study determined PCP, polychlorinated biphenyl, hydroxylated metabolites of polychlorinated biphenyl and octochlorostyrene in umbilical cord plasma samples from three different regions of Quebec. Geometric mean concentrations of PCP were 1670 pg/g (range 628–7680 pg/g) wet weight in plasma. The results suggested that PCP possibly alters thyroid hormone status in newborns, which could lead to neurodevelopmental effects in infants. But these effects could also be partly related to the other compounds measured in this study (Sandau et al. 2002).

4.4/ Critical outcomes and existing reference values

European Union: Category 3, substance of concern to humans owing to possible carcinogenic effects. The salts of PCP (NaPCP) are also classified in category 3.

IARC (1991): Group 2B, agents possibly carcinogenic to humans.

USEPA (IRIS 1993): Group B2, substances probably carcinogenic to humans. Adequate proof exists for animals but inadequate proof for humans.

WHO has assessed PCP in order to establish water quality guidelines. In 1993 a TDI of 0.003 mg/kg bw was set and, although a subsequent risk assessment was conducted in 1998 based on neoplastic effects, it is noted that the resultant water quality guideline was the same (9 µg/l). A summary of existing reference values is presented in Tables 1.2 and 1.3.

PCP is not classified as genotoxic by the European Union.

Table 1.2. Reference values for PCP

Biological media	Reference values
Blood	0.016–0.32 µg/ml
Urine	20–40 µg/l

Source: INERIS 2000.

The values presented in Table 1.2 refer to unexposed populations and are given by NIOSH (1994).

Table 1.3. Reference toxicological values for PCP

Source	Exposure route	Uncertainty factors used	Reference value[a]	Year of evaluation
WHO	Oral		Provisional guideline for drinking-water quality: 9 µg/l	1998
ATSDR	Oral: acute	1000	MRL: 0.005 mg/kg per day	1994
ATSDR	Oral: subchronic	1000	MRL: 0.001 mg/kg per day	2001
ATSDR	Oral: chronic	1000	MRL: 0.001 mg/kg per day	2001
USEPA	Oral: chronic	100	RfD: 0.03 mg/kg per day	1999
USEPA	Oral	–	ERU_o: 1.2×10^{-1} mg/kg per day	1991
USEPA	Oral	–	ERU_{water}: 3×10^{-6} mg/l per day	1993

[a] MRL = minimum risk level; ERU = excess unit risk.

Source: INERIS 2000.

5/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

PCP is rapidly absorbed by the digestive tract. The highest concentrations are in the liver, kidney and brain, but the tendency for bioaccumulation remains low. Regarding human health effects, the experimental data related to PCP are well documented for the oral low-dose chronic exposures and indicate:

- impact on the liver characterized by biochemical, functional and histopathological changes;
- impact on the immune system; and
- significant alteration of thyroid hormone levels at exposures of 1 or 2 mg/kg bw per day.

Data on occupationally exposed workers confirm effects on the immune system and liver.

The health characterization of PCP indicates a potential for a number of human health effects associated with low-level chronic exposure via the oral route. Some of these effects have been seen as a result of occupational exposure. It is also

known that man-made PCPs introduced into the environment have the potential for long-range atmospheric transport and may reach human foodstuffs and drinking-water. However, more research is needed to assess the significance of LRTAP as a significant pathway leading to human exposure via the oral route.

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CHAPTER 2/ DDT

1/ INTRODUCTION

DDT (1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane) was first synthesized by Zeidler in 1874, but the compound was not used until 1939, when Müiller and co-workers discovered its insecticidal properties. During the Second World War, DDT was widely used to protect troops and civilians from the spread of malaria, typhus and other vector-borne diseases. DDT was used for the first time for agricultural purposes in the United States in 1946, and a little later its agricultural use began in most other countries. DDT has been used in cotton, deciduous fruit, cereals and potatoes. In the United States, use of DDT increased up to 1959 (35 771 tonnes), since when it has gradually decreased so that in 1969 only 13 724 tonnes were sprayed in the environment. Nevertheless, owing to the export market, the American manufacture of DDT continued and reached a maximum in 1963 with a production of 81 154 tonnes. DDT was manufactured not only in the United States but in many parts of the world, including some developing countries: in 1974 world-wide production was around 60 000 tonnes. Because of its persistence and bioaccumulation in the environment, and the growing concern about adverse environmental and health effects, the use of DDT was banned in Sweden in 1970 and the United States in 1972, and later in many other countries (WHO 1979).

During the period when DDT was being extensively used, large quantities were released into the air during both agricultural and vector control applications. Emissions could also have resulted from the production, transport and disposal of the compound. Because the use of DDT was banned in the United States and in most European countries after 1972, release of DDT in recent years should be negligible in these countries.

The ability of DDT to cross international borders and travel long distances in air and water before entering a source point has made its elimination an international problem. In 2001, DDT was placed in Annex B of the Stockholm Convention on POPs and it has been given restricted use status. This means that the production and use of DDT is to be eliminated except in those countries that have to control vector-borne diseases, where its use must be in accordance with WHO recommendations and guidelines. The ultimate goal is the complete elimination of DDT use and its replacement with suitable alternative products, methods and activities, including resistance management strategies to ensure the continuing effectiveness of these alternatives (Stockholm Convention on POPs 2001).

2/ POTENTIAL FOR LRTAP

2.1/ Physical and chemical properties

When we refer to DDT, we are generally referring to *p,p'*-DDT, which was produced and used for its insecticidal properties. However, technical grade DDT that was generally used as an insecticide was composed of up to 14 chemicals, of which only 65–80% was the active ingredient, *p,p'*-DDT. The other components included 15–21% of the nearly inactive *o,p'*-DDT, up to 4% of *p,p'*-DDD and up to 1.5% of 1-(*p*-chlorophenyl)-2,2,2-trichloroethanol. The chemical formulae of *p,p'*-DDT and *p,p'*-DDE are shown in Fig. 2.1 and 2.2, and the identification numbers for *p,p'*-DDT, *p,p'*-DDE, *p,p'*-DDD, *o,p'*-DDT, *o,p'*-DDE and *o,p'*-DDD are given below. The latter five compounds are either impurities or metabolites of technical DDT (ATSDR 2000).

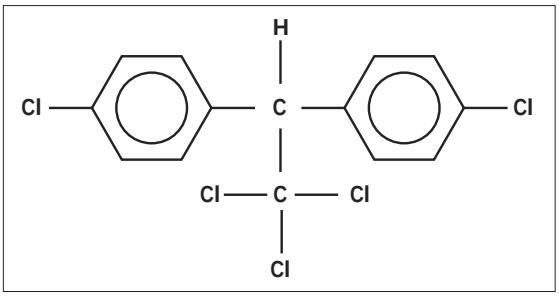


Fig. 2.1. *p,p'*-DDT, $C_{14}H_9Cl_5$ (CAS: 50 29 3)

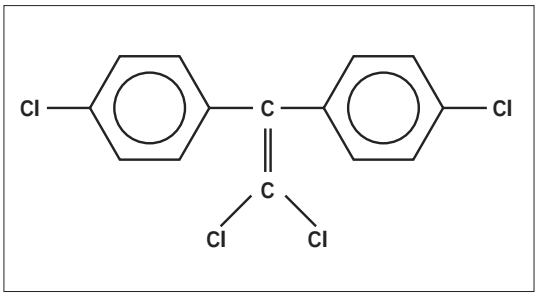


Fig. 2.2. *p,p'*-DDE, $C_{14}H_8Cl_4$ (CAS: 72 55 9)

p,p'-DDD	CAS: 72 54 8	$C_{14}H_{10}Cl_4$
o,p'-DDT	CAS: 789 02 6	$C_{14}H_9Cl_5$
o,p'-DDE	CAS: 3424 82 6	$C_{14}H_8Cl_4$
o,p'-DDD	CAS :53 19 0	$C_{14}H_{10}Cl_4$

The basic properties of the most common compounds are presented in Table 2.1.

Table 2.1. Physical and chemical properties of DDT, DDE and DDD

Property	*p,p'*-DDT	*p,p'*-DDE	*p,p'*-DDD
Molecular weight	354.49	318.03	320.05
Solubility in water	0.025 mg/l at 25 °C	0.12 mg/l at 25 °C	0.090 mg/l at 25 °C
Log K_{ow}	6.91	6.51	6.02
Log K_{oc}	5.18	4.70	5.18
Vapour pressure at 25 °C	1.60×10^{-7} torr at 20°C	6.0×10^{-6} torr at 25°C	1.35×10^{-6} torr at 25°C
Henry's law constant at 25 °C	8.3×10^{-6} atm-m^3/mol	2.1×10^{-5} atm-m^3/mol	4.0×10^{-6} atm-m^3/mol

Source: ATSDR 2000.

Nevertheless, DDT residues in bogs and peat lands across the mid-latitudes of North America indicate that DDT was still released even after it was banned for use in the United States (Rapaport et al. 1985). An analysis of peat cores, as well as rain and snow samples, indicated that DDT was still present in the atmosphere,

although levels were lower compared to those in the 1960s. The implication is that DDT is still being released to the atmosphere, either from its current production and use in other countries and transport to the United States, or from the volatilization of residues resulting from previous use. The estimated release of DDT into the atmosphere from the Great Lakes in 1994, excluding Lake Huron, was 14.3 kg (Hoff et al. 1996).

Historically, DDT was released to surface water when it was used for vector control in the vicinity of open waters. This source of release may still be occurring in countries that rely on DDT for insect pest control near open waters. DDT also enters surface water as a result of dry and wet deposition from the atmosphere and direct gas transfer. Atmospheric DDT deposited into tributaries will contribute to the loading in rivers, lakes and oceans. In 1994, the estimated loading of Σ DDT into the Great Lakes, as a result of dry and wet deposition, was estimated at 148 kg, down from 278 kg in 1988 (Hoff et al. 1996).

DDT and its metabolites may be transported from one medium to another by the processes of solubilization, adsorption, remobilization, bioaccumulation and volatilization. In addition, DDT can be transported within a medium by currents, wind and diffusion.

Organic carbon partition coefficients (Koc) of 1.5×10^5 (Swann et al. 1981), 5.0×10^4 (Sabljic 1984), and 1.5×10^5 (Meylan et al. 1992), reported for *p,p*'-DDT, *p,p*'-DDE and *p,p*'-DDD, respectively, suggest that these compounds adsorb strongly to soil. These chemicals are only slightly soluble in water, with solubilities of 0.025, 0.12 and 0.090 mg/l for *p,p*'-DDT, *p,p*'-DDE and *p,p*'-DDD, respectively (Howard & Meylan 1997). Therefore, loss of these compounds in runoff is primarily due to transport of particulate matter to which these compounds are bound. The amount of DDT transported into streams as runoff depends on the methods of irrigation used (USGS 1999). In the western United States, DDT concentrations in stream-bed sediment increased as furrow irrigation (as opposed to sprinkler or drip irrigation) increased. DDT can adsorb to free-moving dissolved organic carbon, a soluble humic material that may occur in the soil solution; this material behaves as a carrier and facilitates transport of DDT into subsurface soil (Ding & Wu 1997).

The use of DDT in Europe in 1980 was less than 7% of the amount used in 1970 (Fig. 2.3). In the mid-1990s, the reported use of DDT in Europe declined to zero (Table 2.2). Currently the most significant sources of DDT are re-emissions, stockpiles and emissions resulting from use in areas outside the UNECE area.

DDT released into water adsorbs to particulate matter in the water column and sediment. Sediment is the sink for DDT released into water, from which it is available for ingestion by organisms such as bottom feeders.

There is abundant evidence that DDT enters the atmosphere as a result of emissions or volatilization. The process of volatilization from soil and water may be repeated many times and, consequently, DDT may be transported long distances in the atmosphere by what has been referred to as a "global distillation" from warm source areas to cold polar regions. As a result, DDT and its metabolites are found in Arctic air, sediment and snow, with substantial accumulations in the food chain,

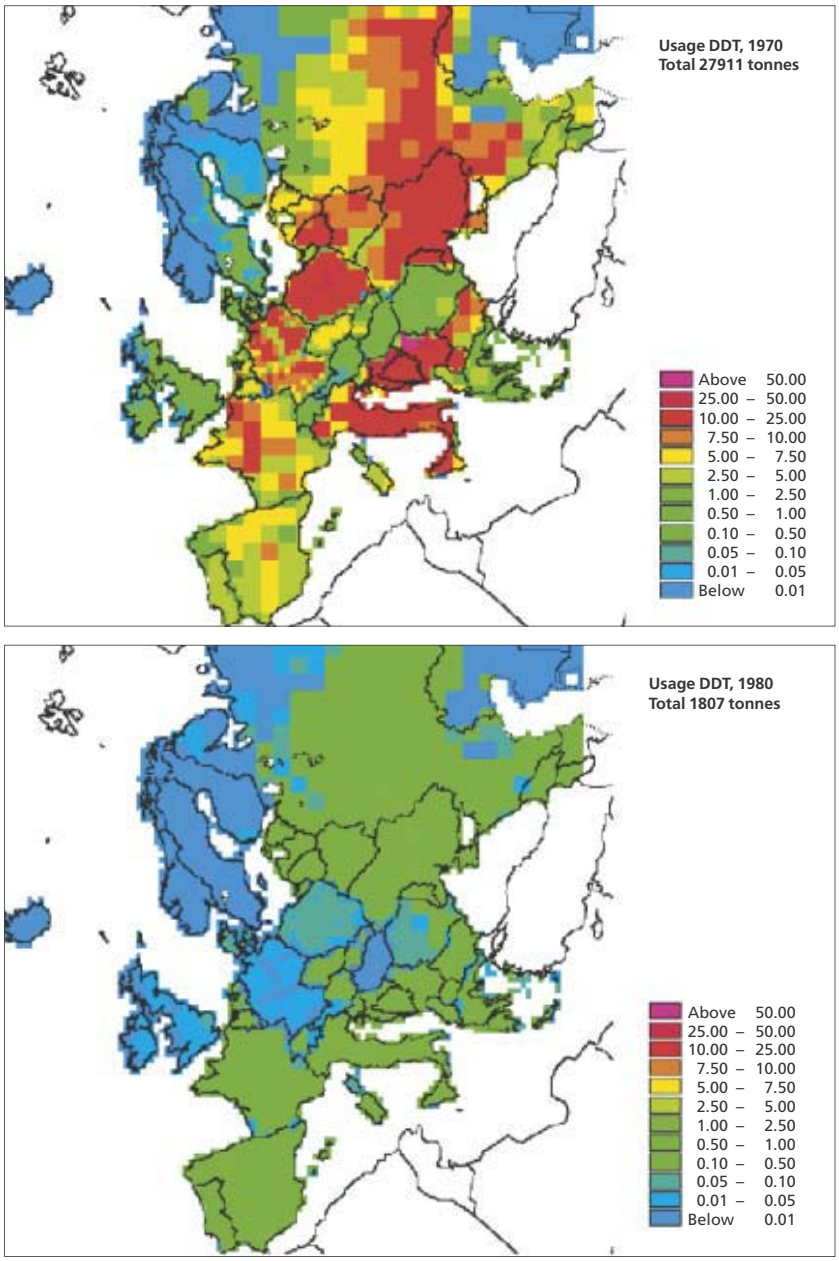


Fig. 2.3. Usage of DDT in European Countries in 1970 and 1980

Source: Pacyna 1999.

mammals and humans residing in these regions (ATSDR 2000). An analysis of sediment cores from eight remote lakes in Canada indicated that Σ DDT concentrations in surface sediments (0–l.3 cm depth) declined significantly with latitude (Muir et al. 1995). The maximum Σ DDT concentrations in core slices in mid-continent lakes date from the late 1970s to the 1980s, which is about 5–10 years later than the maximum for Lake Ontario.

2.2/ Persistence

There is evidence that DDT, as well as other molecules, undergoes an aging process in soil, whereby DDT is sequestered in the soil so as to reduce its bioavailability to microorganisms, extractability with solvents, and toxicity to some organisms (Alexander 1995 and 1997; Peterson et al. 1971; Robertson & Alexander 1998).

Table 2.2. Usage of DDT in European Countries (tonnes) (Pacyna, 1999)

Country	1970	1975	1980	1985	1990	1996
Albania	90.00	12.00	6.66	3.00	0	0
Austria	20.50	10.90	5.70	0	0	0
Belarus	872.25	95.22	67.19	29.07	12.21	0
Belgium	70.00	7.80	7.85	0	0	0
Bulgaria	600.00	63.00	59.20	27.70	0	0
Czechoslovakia	270.00	33.30	28.00	13.00		0
Czech Republic					0	
Slovak Republic					0	
Denmark	18.00	0.80	1.20	0	0	0
Estonia	106.08	11.58	8.17	3.54	1.49	0
Finland	6.10	0.62	0.67	0	0	0
France	1 800.00	200.34	108.53	31.29	0	0
Germany					0.65	0
eastern Germany	1 500.00	33.99	2.78	4.03		
western Germany	152	24.72	0	0		
Greece	235.00	239.30	27.04	13.81	0	0
Hungary	20.60	0.60	0	0	0	0
Ireland	9.00	0.90	0.56	0	0	0
Italy	2 178.00	1 569.50	196.48	103.20	54.72	0
Latvia	306.47	33.46	23.61	10.22	4.29	0
Lithuania	365.40	39.89	28.15	12.18	5.12	0
Luxemburg	0	0	0	0	0	0
Netherlands	130.00	14.13	9.44	0	0	0
Norway	1.73	1.24	0.99	1.46	0	0
Poland	2 528.00	16.70	8.78	0	0	0
Portugal	165.00	17.97	13.66	7.60	0	0
Republic of Moldova	695.44	75.92	53.57	23.18	9.74	0
Romania	196.00	26.20	12.00	0	0	0
Russian Federation	6 000.00	654.99	462.22	200.00	83.99	0
Spain	1 200.00	103.34	192.66	131.48	46.02	0
Sweden	13.80	0.94	0	0	0	0
Switzerland	10.00	10.00	2.70	0	0	0
Ukraine	5 150.97	562.31	396.81	171.70	72.11	0
United Kingdom	49.62	3.38	2.32	0.004	0	0
Yugoslavia	3 150.60	311.40	80.00	50.00	31.56	0
TOTAL	27 911.00	4 176.00	1 807.00	836.00	322.00	0

Long-term monitoring data have also indicated that aged and sequestered DDT is not subject to significant volatilization, leaching or degradation (Boul et al. 1994). The concentrations of DDT, DDE and DDD monitored at two sites in a silt loam in New Zealand declined from 1960 to 1980, but very little loss was evi-

dent from 1980 to 1989 (Boul et al. 1994). The lack of appreciable biodegradation as DDT ages in soil suggests that the compound is not bioavailable to microorganisms. Aging is thought to be associated with the continuous diffusion of a chemical into microspores within soil particles, where it is sequestered or trapped and is therefore unavailable to microorganisms, plants and animals (Alexander 1995). In the case of biodegradation, the aging process results in the gradual unavailability of substrate that makes the reaction kinetics non-linear.

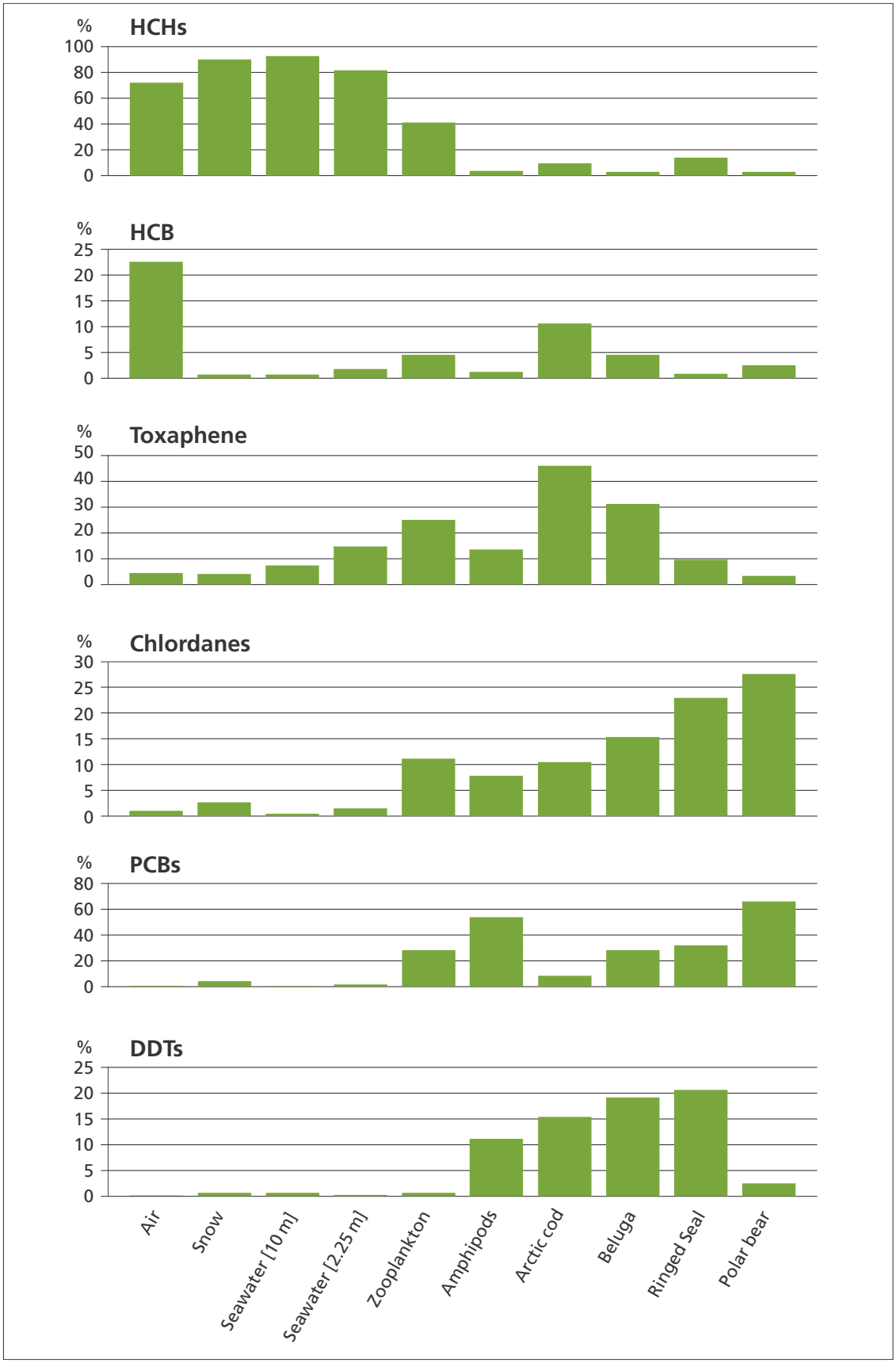
The volatilization rate of DDT from soil is significantly enhanced by temperature, sunlight and flooding of the soil (Samuel & Pillai 1990). DDT is removed from the atmosphere by wet and dry deposition and diffusion into bodies of water. The largest amount of DDT is believed to be removed from the atmosphere in precipitation (Woodwell et al. 1971). DDT is adsorbed to particulate matter to a large extent. Particulate-bound DDT prevails at low temperatures (e.g. in the upper troposphere) (Bidleman 1988). In the vapour phase, DDT reacts with photochemically produced hydroxyl radicals with an estimated rate constant of 3.44×10^{-12} cm^3/molecule-set, determined from a fragment constant estimation method (Meylan & Howard 1993). When atmospheric sampling of pesticides was performed at nine localities in the United States during a time of high DDT usage, DDT was mostly present in the particulate phase (Stanley et al. 1971).

Assuming an average hydroxyl radical concentration of 1.5 × 10~ per cm^3, its half-life will be 37 hours. Both DDE and DDD have higher vapour pressures than DDT, and a smaller fraction of these compounds will be adsorbed to particulate matter. The estimated half-lives of vapour-phase DDE and DDD are 17 and 30 hours, respectively. Direct photolysis may also occur in the atmosphere. DDT, DDE and DDD adsorbed on particulate matter are not expected to undergo photo-oxidation rapidly, and therefore may be subject to long-range transport.

2.3/ Monitoring and modelling

DDT is among the most frequently detected organochlorine insecticides (USGS 2002). *p,p*'-DDT, *p,p*'-DDE and *p,p*'-DDD have all been detected in the dissolved and particulate phases of fog-water and air and in rainwater (Millet et al. 1997). Fog-water samples were 1.5–30 times higher than rainwater samples, and the distribution between the dissolved and particulate phases appeared to be governed by the solubility of the chemical. The site of the measurements was a rural area in France between 1991 and 1993. DDT had not been used in the area since the 1970s. Ligocki et al. (1985) conducted concurrent rain and air sampling during rainfall in Portland, Oregon in 1984. In rain samples, no *p,p*'-DDT, *p,p*'-DDE or *p,p*'-DDD were detected, whereas in the gas phase associated with this rainfall *p,p*'-DDE was detected in five of seven samples. Levels detected in the samples ranged from non-detected to 20 pg/m^3. More recently, Poissant et al. (1997) reported that the mean concentration of *p,p*'-DDT in precipitation over a rural site near the St Lawrence river was 500 pg/l, with a 75% frequency of detection. Rapaport et al. (1985) measured DDT residues in rain and snow samples in Minnesota. Samples

Fig. 2.4. Levels of selected organochlorine contaminants (including DDT) in the Arctic



Source: AMAP 1998.

of snow taken in 1981–1982, 1982–1983 and 1983–1984 contained an average of 0.32, 0.60 and 0.18 ng/l of *p,p*'-DDT, respectively. Two rain samples taken in 1983 contained 0.2 and 0.3 ng/l of p,p'-DDT.

Regular measurements of DDT in air and precipitation are carried out in EMEP stations (Berg & Hjellbrekke 1998, 1999; Berg et al. 2000).

Modelling of long-range atmospheric transport of persistent organic pollutants has been attempted by several groups over the past two decades (e.g. Mackay & Wania 1995; Jones 1998; Pacyna 1999; Wania & Mackay 1996; Wania et al. 1999, 2000). Monitoring and modelling results indicate that long-range transport is indeed a very relevant factor in the global redistribution of DDT and that, although use is greatly restricted in many countries, there are still significant currently sources and large amounts in environmental media.

One new approach to investigating pesticide recycling from soil and water involves using enantiomers as tracers (Bidleman & Falconer 1999). This is feasible because several classes of insecticides and herbicides have members that are chiral compounds, having right- and left-handed molecular configurations, or enantiomers. Four of the eight organochlorine pesticides listed by the United Nations Environment Programme (*o,p*'-DDT, chlordane, heptachlor and toxaphene) are chiral. Pesticide enantiomers are useful as tracers of soil–air and water–air exchange processes. Although a few chiral pesticides are manufactured as single-enantiomer products, most are racemic mixtures having a (1 : 1) enantiomer ratio (ER). Enantiomers have the same physical and chemical properties. As a result, transport processes (leaching, volatilization and atmospheric deposition) and abiotic reactions (hydrolysis and photolysis) do not discriminate between the enantiomers – such processes leave ERs unaffected. In contrast, metabolism of pesticides by microorganisms in water and soil, and by enzymes in higher organisms, often proceeds enantio-selectively, leading to non-racemic residues and an alteration of the original ER (2 : 6). By examining ERs, it is possible to differentiate new sources of organochlorine pesticides from ghosts of the past. The technique provides a sensitive indicator of biological degradation and clues about the origins of pesticides found in the atmosphere.

Fig. 2.4 illustrates the distribution of organochlorine contaminants in Arctic air, snow and seawater and in the food chain of marine mammals. Data for the six major classes of organochlorines are plotted for each compartment or species as the percentage of organochlorines in that compartment or species, to demonstrate the changing importance of residue classes in the process of transfer among compartments and bioaccumulation in the food chain of marine mammals (AMAP 1998; Norstrom & Muir 1994).

2.4/ Conclusion regarding LRTAP potential

DDT and its breakdown products are semi-volatile and can be expected to partition into the atmosphere as a result, and precipitate at low temperatures; therefore, in addition to being found close to known sources, they can also occur at significant levels in remote areas. They are insoluble in water and soluble in most organic solvents.

Owing to these physicochemical properties, DDT and its metabolites are readily absorbed by organisms; the high lipid and low water solubility lead to the retention of the compounds in fatty tissues. Consequently, there is significant potential for biomagnification. The breakdown products of DDT, DDD and DDE, are present virtually everywhere in the environment and are more persistent than the parent compound.

3/ PATHWAY OF LRTAP DERIVED HUMAN EXPOSURE

3.1/ Significant sources and magnitude of human exposure

DDT and its metabolites are ubiquitous contaminants of the ecosystem, and can be absorbed readily by organisms. The high lipid solubility and the low water solubility lead to the retention of DDT and its stable metabolites in fatty tissue. The rates of accumulation into organisms vary with the species, the duration and concentration of exposure, and the environmental conditions. The high retention of DDT metabolites means that toxic effects can occur in organisms remote in time and geographical area from the moment of DDT use (WHO 1989).

These compounds are readily adsorbed to sediments and soils that can act as sinks and as long-term sources of exposure (e.g. for soil organisms). Organisms can accumulate these chemicals from the surrounding medium and from food, and there is clear evidence that the residues of DDT and its metabolites persist in the organism for long periods after exposure has ceased. In aquatic organisms uptake from the water is generally more important, whereas in terrestrial fauna food provides the major source (WHO 1989).

Both DDT and its degradation products tend to bioaccumulate and persist to varying degrees in tissue. *p-p'*-DDE, the main metabolite of DDT, is the major contaminant in human milk and persists longer than DDT. Where DDT use is banned, DDT levels in milk decline with time, and the ratio of *p-p'*-DDE to *p-p'*-DDT increases. A DDE/DDT ratio between 1 and 5 indicates recent exposure to parent DDT; a ratio greater than 5 indicates that the DDT residues arise from the food chain (Hooper et al. 1997).

3.1.1/ Human exposure in adults

DDT and its metabolites are detected in food samples in every country in the world, and absorption through digestive tract is likely the greatest source of exposure for the general population. Even in countries in North America and northern Europe, where DDT has been banned for over a decade, its residues are still found in food. This is because of environmental persistence, illegal use or importation of contaminated food from regions where DDT is still used. DDE was the second most frequently found residue (21%) in a recent survey of domestic animal fats and eggs in Ontario, with a maximum residue of 0.410 mg/kg. Residues in domestic animals, however, have declined steadily over the past 20 years. In a survey of Spanish meat and meat products, 83% of lamb samples tested contained at least one of the DDT metabolites investigated, with a mean level of 25 ppb. An average of 76.25 ppb *p,p'*-DDE was detected in fish samples from Egypt. DDT

was the most common organochlorine detected in foodstuffs in Viet Nam, with mean residue concentrations of 3.2 and 2.0 μg/g fat in meat and fish, respectively. Consumption of fish and marine mammals in the Artic appears to be a significant dietary contributor to human exposure to DDT (Laden et al. 1999). A 1982 study by the Michigan Department of Public Health found that people eating large quantities of fish from the Great Lakes had significantly higher serum DDT levels compared to non-fish-eating controls. Furthermore, fish consumption was a major predictor of exposure. A follow-up study in 1989 found that serum DDT levels were primarily a reflection of historical exposure and previously established

Table 2.3. Relative DDT intakes and comparison with ADI (FAO/WHO 1984) and PTDI (FAO/WHO 2000)

Country	Year	Daily intake (g/kg bw)	Percentage of ADI (0.02 mg/kg bw per day)	Percentage of PTDI (0.01 mg/kg bw per day)
Australia	1980	0.39	1.95	3.9
	1987	0.026	0.13	0.26
Egypt	1988	13.7	68.5	137.0
Finland	1984	0.041	0.21	0.42
	1986	0.026	0.13	0.26
Guatemala	1982	0.26	1.3	2.6
	1984	0.2	1.0	2.0
	1985	0.065	0.33	0.66
	1988	0.031	0.16	0.32
India	1981	3.9	19.5	39.0
	1983	3.6	18.0	36.0
Japan	1980	0.056	0.28	0.56
	1982	0.07	0.37	0.74
	1984	0.03	0.15	0.3
	1986	0.02	0.1	0.2
	1988	0.02	0.1	0.2
Netherlands	1984	0.004	0.02	0.04
	1985	0.004	0.02	0.04
New Zealand	1982	0.003	0.015	0.03
Switzerland	1983	0.03	0.15	0.3
Thailand	1980	1.6	8.0	16.0
	1987	0.0008	0.004	0.008
United Kingdom	1980	0.05	0.25	0.5
	1981	0.035	0.18	0.36
	1985	0.05	0.25	0.5
United States	1980	0.36	1.8	3.6
	1982	0.033	0.17	0.34
	1985	0.036	0.18	0.36
	1986	0.019	0.1	0.2

Source: WHO 1996.

body burden rather than recent exposure (Hovinga et al. 1992, 1993). Overall, the dietary intake of DDT is considerably higher in developing countries. In 1996, WHO estimated the daily intake for DDT in a number of countries and made a dietary risk assessment by determining the rate between estimated daily intake and the acceptable daily intake (ADI) established in 1984 by the Joint Meeting on Pesticide Residues (JMPR) (FAO/WHO 1984) (see Table 2.3). In 1994 JMPR converted the ADI to a provisional tolerable daily intake (PTDI) for several pesticides, including DDT, that are no longer used in agricultural practice but may be present in food commodities as contaminants (FAO/WHO 1994), and in 2000 the PTDI was reduced to 0.01 mg/kg per day (FAO/WHO 2000) Thus Table 2.3 shows relative DDT intakes and comparison are provided either with the ADI of 0.02 mg/kg per day or with the PTDI established in 2000. The ADI established in 1984 is never exceeded, but the PTDI established in 2000 is exceeded in Egypt and the estimated DDT absorption is very high in India.

3.1.2/ Human exposure in children

DDT transfers freely across the placenta from mother to fetus, and is also excreted in breast-milk. Harris et al. (1996) showed measurable amounts of residues of *p,p'*-DDE in the amniotic fluid of three out of nine pregnant women in Los Angeles.

Since it has been stated that concentrations of DDE in the amniotic fluid in the range of 0.01–0.63 ng/ml are sufficient to cause concern (Foster et al. 1999), further investigations are needed to better quantify and qualify the health risks of babies prenatally exposed to these compounds. A laboratory study carried out on pregnant or lactating Sprague-Dawley rats showed that DDE transfers across the placenta, but the comparison between exposed fetuses and breastfeeding neonates indicated that lactational exposure is quantitatively far more important than exposure *in utero* (You et al. 1999).

Once inside the body, DDT residues accumulate in fatty tissues and are slowly released. Lactation or significant weight loss increase the release of DDT to the blood, and therefore the presence of DDT in breast-milk raises serious concerns regarding potential health effects in developing infants. Generally, DDT and DDE are found in human breast-milk in concentrations higher than in cow's milk or other infant foods. As a result, breastfed infants may receive higher dietary exposure than those who are not breastfed. If a woman has been exposed to DDT in the past, her milk may contain high levels of DDT, which will be transferred to the child. Women exposed to high levels of DDT include Inuit and Indian women in Arctic regions, who eat a traditional diet comprising large amounts of fatty tissues from sea mammals, as well as women whose diet is mainly based on fish from highly contaminated rivers and lakes, such as the Yakima River (Marien & Laflamme 1995). In a general survey of 16 separate compounds in the breast-milk of lactating mothers in four remote villages in Papua New Guinea, DDT was detected in 100% of samples and was one of only two organochlorines detected (Spicer et al. 1993). DDT has also been detected in the breast-milk of Egyptian women. The average of total DDT levels was 57.59 ppb and the estimated daily

intake for breastfeeding infants was 6.90 µg/kg bw per day. This intake exceeds the PTDI of 0.01 mg/kg bw recommended by the Joint FAO/WHO Meeting on Pesticide Residues (FAO/WHO 2000). The mean DDT content in the breast-milk of women in the Odessa area of Ukraine was 0.69 mg/kg (Vashkulat 2000); the DDT content in the blood of rural teenagers was 0.05–11.53 µg/l, and in the hair the value ranged from 0.011 to 0.053 µg/g (Karakoshyan et al. 2000).

DDT and other organochlorine pesticides were measured in samples of breast-milk taken from 92 donors representative of the general population in southern Kazakhstan (Hooper et al. 1997). Levels of *p-p'*-DDE were between 240 and 10 540 ng/g fat, with a mean of 1960 ng/g fat. Levels of *p,p'*-DDT were between 75 and 1030 ng/g fat, with a mean near 300 ng/g fat. Data obtained from rural regions show higher DDE : DDT ratios, which, according to the authors, suggest the curtailed use of DDT on cotton crops and its persistence in the food chain. On the contrary, data obtained from an agricultural area with an elevated fish consumption show a low DDE : DDT ratio, which may be related to continuing exposures to DDT, possibly from pesticide-laden dust blowing from the dry lake bed.

Time trend information suggests that environmental concentrations and human exposure levels have fallen significantly in countries that have banned DDT use. In a study in Sweden, where the use of DDT has been banned since 1972, a 75–95% reduction of the levels of *p,p'*-DDT and *p,p'*-DDE in human breast-milk was observed between 1967 and 1985 (Noren 1988). In 28 studies from Canada and the United States, average DDT levels in breast-milk were about 4000–5000 ng/g lipid in the early 1970s and then steadily declined. For 13 studies from 1975 on, there was an 11–21% reduction in mean Σ DDT levels per year. Similar reductions have been also observed in western European Countries (ATSDR 2000).

3.2/ Potential for high exposure situations

DDT and its metabolites are ubiquitous in foods, particularly in fatty food of animal origin (meat, fish and dairy products) and in human milk. Globally, food is the main source of exposure for the general population. Estimates of current intake vary according to diet and geographical area, and in some countries the estimated daily intake may approach the acceptable daily intake. Since DDT and its metabolites are excreted through human milk, breast-fed children have to be considered as a high-exposure group. Pre-natal exposure may also take place, owing to the capacity of DDT and its metabolites to cross the placenta. Once absorbed, DDT is readily distributed to all body tissues, where the storage rate is proportional to the fat content of the organ.

3.3/ Significance of LRTAP as the source of total exposure

Intake through the diet may approach or even exceed the PTDI, particularly in tropical and developing countries where DDT is still used for public health purposes (or even used illegally). In these countries, local use represents the main source of exposure. On the other hand, high levels of exposure also occur within the LRTAP Convention area. These include the Inuit populations of Arctic re-

gions, where DDT has not been used for decades or has never been used. The main source of exposure in this case, and the consequent health implications, are mainly related to LRTAP.

4/ HEALTH HAZARD CARACTERIZATION

4.1/ Toxicokinetics

4.1.1/ Absorption

4.1.1.1/ Respiratory tract

Since most DDT dust is in a large size class (≥ 250 μm), most of the inhaled particles are deposited in the upper respiratory tract and then swallowed through mucociliary action (Smith 1991). Toxicological data also indicate that the relevance of the respiratory tract in DDT intake is very low.

4.1.1.2/ Dermal absorption

DDT is very poorly absorbed through the skin, even when dissolved in oil or water (WHO 1979).

4.1.1.3/ Gastrointestinal absorption

Available data show that DDT absorption from the gastrointestinal tract is low, but relevant compared to respiratory and dermal absorption. Laboratory toxicity studies show that DDT given intraperitoneally is four times more toxic than when administered orally and 40 times more toxic than when administered by the dermal route (Hayes 1982). Similarly, an intravenous injection of 50 mg/kg DDT to rats causes convulsions in 20 minutes, but convulsions occur only after 2 hours when DDT is administered orally at doses higher than the LD_{50} for the species under study (WHO 1979).

Gastrointestinal absorption can be inferred from animal studies. The presence of urinary metabolites in mice, rats and hamsters (Fawcett et al. 1987; Morgan & Roan 1971, 1974) and the presence of DDT and its metabolites in bile (Jensen et al. 1957) provide evidence of gastrointestinal absorption.

There is clear evidence that gastrointestinal absorption markedly increases when DDT is dissolved in a lipid matrix such as digestible oils (Keller & Yeary 1980). DDT dissolved in animal or vegetable fats is absorbed by the gastrointestinal tract of laboratory animals 1.5–10 times more effectively than undissolved DDT (WHO 1979). Experimental studies indicate that after an oral administration of DDT dissolved in vegetable oils, about 70–90% of the dose is absorbed by the rats under study (Keller & Yeary 1980; Rothe et al. 1957).

Absorption of DDT by humans following ingestion is evident from both measurements of DDT levels in serum and adipose tissue and measurements of DDA in urine (Hayes et el. 1971; Morgan & Roan 1971, 1974).

In subjects chronically exposed to oral doses of DDT of up to 20 mg/day (approximately 0.3 mg/kg bw per day), maximum serum DDT concentrations were reached 3 hours after ingestion. Serum levels decreased to near pre-dose values 24 hours after each dose (Morgan & Roan 1971).

4.1.2/ Distribution

Once absorbed, DDT is readily distributed via the lymph and blood to all body tissues and stored in the various organs. DDT is stored in all body tissues, but the storage rate is proportional to the fat content of the organ: the highest concentrations are usually found in adipose tissue (Smith 1991). Following repeated doses, storage in the fatty tissues increases rapidly at first and then more gradually until a plateau is reached (Laugh et al. 1950). It is recognized that repeated low doses could result in greater total storage of DDT in the fat compared to a single higher dose (Smith 1991). DDT uptake in tissues is a function of blood flow, the lipid content of the single tissue and the partition coefficient for DDT between blood and lipids in specific organs. The ratio of DDT concentration in adipose tissue to that in blood may remain relatively constant, although the amount of DDT from past exposures cannot be determined from present blood determinations. The amount of stored DDT related to environmental and occupational exposure is generally greater in warm climates, where the need for insecticides is larger than in temperate and cold countries. Measurements over a sufficiently long period have shown storage to decrease as the use of DDT has decreased (WHO 1979).

4.1.3/ Metabolism

4.1.3.1/ Laboratory animals

The metabolism of DDT has been studied in humans and other mammalian species. Metabolism in rats, mice and hamsters is similar to that in humans, though not all the intermediary metabolites identified in animals have been identified in man. The chemical nature of the chief metabolite excreted in the urine was first elucidated by White & Sweeney in 1945. Rabbits were given 100 mg/kg bw per day of DDT for 6 days per week and their urine was collected. It contained a considerable amount of organic chloride, whereas control rabbit urine did not. The authors isolated a crystalline material containing 25.37% chlorine and melting at 166–166.5 °C, which was shown to be 2,2-bis (*p*-chlorophenyl) acetic acid (DDA). Only 80–85% of the total organic chloride of the rabbit urine was found to be soluble in alkali and in bicarbonate. For this and other reasons, it was considered possible that DDA was not the only chlorinated organic compound present (WHO 1979). Studies carried out in mammals suggested that DDA is produced by a sequence of reductive dechlorination, dehydrochlorination, reduction, hydroxylation and oxidation of the aliphatic portion of the molecule. Peterson & Robinson (1964) explored the metabolic pathway of DDT in rats. DDT is initially reduced to 1,1-dichloro-2,2-bis(4-chlorophenyl)ethane (DDD). The DDD is then dehydrochlorinated to 1-chloro-2,2-bis(4-chlorophenyl)ethene (DDMU), which is finally converted to 2,2-bis-(4-chlorophenyl)ethanol (DDOH) via 2,2-bis(4-chlorophenyl)ethene (DDNU). The compound identified as "probable" intermediate aldehyde between DDOH and DDA was later synthesized and shown to be highly labile, confirming the suggestion by Peterson & Robinson that it is unlikely to accumulate in tissues in detectable amounts. Organ perfusion studies indicated that DDT, DDD and DDMU are metabolized in the liver, whereas

metabolism of DDNU occurs in both liver and kidney, although the kidney is the primary site (Datta 1970; Datta & Nelson 1970). Gold and co-workers (Gold & Brunk 1982; Gold et al. 1981) investigated the metabolic pathway of DDT in mice *in vivo*. The results differed from those obtained in previous studies, suggesting that DDMU can undergo epoxidation; the resulting mutagenic epoxide is hydrolysed and oxidized to 2-hydroxy-2,2-bis-(4-chlorophenyl)acetic acid (αOH-DDA), which is excreted in the urine. Another route of DDT metabolism, in both the mouse and the hamster, seems to be the production of DDA by hydroxylation of the C1-ethane side-chain carbon of DDD with the production of Cl-DDA. This compound is capable of reacting with cellular proteins or DNA, or to lose water to produce the major urinary metabolite, DDA (Smith 1991).

After the studies of Gold and co-workers, the metabolism of DDT in rats was re-examined and was concluded to be more similar to that described for hamsters and mice than previously believed. The conversion of *p,p'*-DDD to *p,p'*-DDA occurs primarily by hydroxylation leading to Cl-DDA, which on hydrolysis gives DDA. This acyl chloride may also be formed from DDE by epoxidation. Although DDMU is converted to DDA, it is doubtful whether it is an important intermediate in DDT metabolism. In addition, there is evidence to suggest that DDOH is a reduction product of DDCHO, formed directly from DDT, rather than a precursor.

In conclusion, although it has been studied for many years, the metabolism of DDT in laboratory animals is not completely understood (Smith 1991).

4.1.3.2/ Humans

Several studies have detected DDT metabolites in human urine, serum and adipose tissue. Since the most represented metabolites are similar to those detected in animals, it may be inferred that the metabolic pathways in humans and animals are similar. DDT ingested by humans undergoes reductive dechlorination to DDD, which is further degraded and readily excreted as DDA (Roan et al. 1971). DDT is also converted by dehydro-dechlorination to DDE, although at a much slower rate than in the DDT–DDD pathway: the conversion of DDT to DDE was estimated to be less than 20% over the course of a 3-year study (Morgan & Roan 1971). Further metabolism of DDE is apparently slow, and DDE is accumulated in adipose tissue (Hayes et al. 1971; Morgan & Roan 1971). According to Roan et al. (1971) and Morgan & Roan (1971), oral administration of DDT or DDD to volunteers resulted in an increased urinary excretion of DDA, but no increase in excretion of DDA above pre-dose values was noted after oral ingestion of DDE. The data indicate that DDD, and not DDE, is the precursor in humans and that little, if any, DDE is further converted to DDA.

4.1.4/ Elimination and excretion

4.1.4.1/ Laboratory animals

The faeces may be the principle route of excretion of DDT after ingestion of a high dose, also because part of the ingested compound is not absorbed and passes unal-

tered in the faeces. Only traces of unchanged DDT are found in the faeces when exposure is by any route other than the oral. The bile appears to be the main source of DDT metabolites in the murine faeces. When the bile duct was cannulated before intravenous injection of radioactive DDT, 65% of the dose was recovered in the bile, 2% in the urine and only 0.3% in the faeces, and the possibility of contamination of the faeces by urine could not be excluded. Moreover, following ligation of the bile duct in rats fed radioactive DDT, there was an increased urinary excretion of radioactive material. Although an enterohepatic circulation of DDT metabolites has not been directly demonstrated, these studies suggest that such a circulation does exist (Smith 1991).

Demonstration of DDT excretion in milk was firstly published by Woodard et al. (1945), who studied a dog fed with a dose of 80 mg/kg bw per day of DDT. Within a short time, excretion of DDT in milk was reported in rats, goats and cows, and in 1951 it was demonstrated in women. The proportion of the mother's DDT intake that could be recovered from milk varied from 12.6% to 30.2%, and averaged 24.6% in rats receiving the compound in their diet at an average dose of 32.4 mg/kg bw per day. Under these conditions, the dosage of the young was somewhat less than half that of their mothers (Smith 1991).

4.1.4.2/ Humans

The main route of excretion of DDT in humans is through the urinary tract, although it also occurs in the faeces (via biliary excretion) and breast-milk.

The excretion of the compound has been studied in subjects receiving 35 mg/day of DDT for up to 18 months (Hayes et al. 1971). Urinary excretion of DDA increased rapidly for the first few days up to a steady state level, characterized by the elimination of about 13–16% of the daily dose. When this level of excretion was reached, it remained stable for 56 weeks. Urinary excretion decreased rapidly after dosing ceased. It seems that a steady state for storage was reached within 12–18 months of daily dosing, after which humans were able to eliminate the entire daily dose of 35 mg/day.

Concentrations of DDT in human milk have been reported to be in the range of 0.01–0.10 mg/litre as DDT plus its metabolites, especially DDE, the concentration of which was the highest. In a few countries, however, average values for total DDT have been reported to range from 1 to 5 mg/litre, and the highest value observed has been 12.21 mg/litre. Especially high values were reported from Guatemala in 1970 (0.41–12.21mg/litre). Additional and more numerous samples taken only four years later in the same and other communities in Guatemala revealed entirely different results, and the highest single value observed for total DDT in 1974 was 5.69 mg/litre. The authors recognized the importance of the agricultural use of DDT as a potential source of the compound in human milk, but they attributed the change between 1970 and 1974 almost exclusively to the substitution of propoxur for DDT in residential spraying to combat malaria (WHO 1979).

4.2/ Effects on laboratory animals

4.2.1/ Acute toxicity

Acute effects of DDT were first described by Domenjoz (1944). The target organ for acute effects is the nervous system: the first perceptible effect is abnormal susceptibility to fear, with violent reaction to normally sub-threshold stimuli. With increasing doses, hyperirritability and fine tremors occur and, with lethal doses, epilectiform tonic–clonic convulsions and death. In non-fatal poisonings animals recover completely. The oral LD_{50} in animals ranges between 275 mg/kg bw (rabbit) and 2500 mg/kg bw (guinea pig).

4.2.2/ Subacute and subchronic toxicity

With repeated high doses animals are gradually debilitated, especially by malnutrition. If food intake is maintained, tremor may last for weeks or, intermittently, for months. If animals survive the recovery is complete (Smith 1991).

4.2.3/ Mutagenicity

Comprehensive summaries of the genotoxic effects of DDT and its metabolites have been published. Conflicting data were obtained with regard to some genetic end-points. DDT induced chromosomal aberrations in human blood cultures but, in most studies, did not induce genotoxic effects in rodent or human cell systems, nor was it mutagenic to fungi or bacteria. *p,p'*-DDE weakly induced chromosomal aberrations in cultured rodent cells and mutations in mammalian cells and insects, but not in bacteria (FAO/WHO 2000). DDT induced structural chromosomal aberrations in the spleen cells of mice 6, 24 and 48 hours after an intraperitoneal injection of DDT at a dose of 5.5 mg/kg bw. Maximal induction was found at 24 hours (Amer et al. 1996).

4.2.4/ Long-term toxicity

The hepatic effects of DDT in rats include increased liver weight, hypertrophy, hyperplasia, induction of microsomal enzymes (including cytochrome P450), cell necrosis, increased activity of serum liver enzymes and mitogenic effects, which might be related to a regenerative hepatic response to DDT. The potencies of DDT, DDE and DDD for induction of CYP2B are of the same order of magnitude. The effects on CYP2B and associated enzymes indicated that males have a lower threshold than females, which induced these enzymes to a greater extent (FAO/WHO 2000).

4.2.4.1/ Effects on growth and reproduction

The effects of *p,p'*-DDE on male sexual development in offspring of Sprague-Dawley and Long-Evans rats were tested by administrating 10 or 100 mg/kg bw from gestation day 14 to day 18. The higher DDE dose induced a reduction in male anogenital distance, an increase in retention of male thoracic nipples and alterations in expression of the androgen receptor in either one or both strains. A much weaker response was seen in the lower dose groups, suggesting that the developmental effects of *p,p'*-DDE on male rat sexual differentiation are minimal at maternal doses below 10 mg/kg bw per day (You et al. 1998).

There is some evidence that exposure of rats to DDT is associated with impaired fertility. The reproductive toxicity of DDT was investigated in adult male rats exposed to 50 and 100 mg/kg bw per day for 10 successive days. DDT administration led to a dose-dependent reduction of both testicular weight and the number of motile spermatozoa in the epididymis. The weight of the seminal vesicles dropped significantly, resulting from a decrease of testosterone production by the testes. Serum levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) increased after pesticide exposure. The authors suggest that DDT damages the male rats' fertility by acting directly on the testes and altering the neuro-endocrine function (Ben Rhouma et al. 2001).

Groups of adult male rats treated with DDT showed decreased levels of testosterone both in the serum and in the testis. According to the author, the observed damage to spermatogenesis induced by DDT is caused by a lack of androgens (Krause 1977).

Palanza et al. (1999a) examined the effects of prenatal exposure to *o,p'*-DDT and to diethylstilbestrol (as a positive control) on male reproductive organs. Between gestation days 11 and 17, female mice were treated with average concentrations of 0.018 and 0.18 ng/g bw of DES. Doses of *o,p'*-DDT were thus 18 and 180 ng/g bw, based on the prediction that the *in vivo* potency of *o,p'*-DDT would be approximately 1000 times lower than that of DES. Preputial glands in males exposed to the 0.018 ng/g dose of DES were significantly enlarged relative to controls. Males exposed to DDT (18 ng/g) had smaller testes than controls.

DDE, shown to be an androgen receptor antagonist, has been investigated as a factor in the etiology of erectile dysfunction in rats. Using the model of apomorphine-induced erections, Brien et al. (2000) studied the dose–response effects of *p,p*-DDE in comparison to the known androgen receptor antagonist flutamide. A single dose of flutamide (50 mg/kg bw, i.p.) was found to significantly reduce apomorphine-induced erections to less than 50% over 12 hours, with recovery of erectile response within 48 hours. In comparison, a single dose of *p,p*-DDE (500 mg/kg bw, i.p.) reduced apomorphine-induced erections for at least two weeks. The study confirms the role of *p,p*-DDE as an endocrine disrupter and suggests that this compound can markedly interfere with erectile function.

The female rabbit was used to study both the accumulation of lipophilic chlorinated hydrocarbons in genital tract tissues and the subsequent morphological and functional effects after long-term low-dose exposure. DDT (0.8 mg/kg bw) was administered to sexually mature rabbits over a period of 12–15 weeks. Accumulation of DDT was high in ovarian, oviductal and uterine tissue and in follicular fluid, and clearly detectable in uterine secretions. DDT-treated animals showed a significantly reduced ovulation rate ($P<0.002$). During early pregnancy, DDT decreased serum progesterone levels and changed the protein pattern of uterine secretion (Lindenau et al. 1994).

The relevance for human reproduction of slight changes in ovulation rate, the relative proportion of uteroglobin and progesterone concentrations in rabbits is not clear. After perinatal exposure to *p,p'*-DDE, there was some evidence of

impaired sexual development in male pups, including an increased frequency of thoracic nipple retention and a reduction in the male anogenital distance, with a NOAEL of 10 mg/kg bw per day. The Agency for Toxic Substances and Disease Registry concluded that the DDT complex could impair reproduction and/or development in mice, rats, rabbits, dogs and birds at doses ≥ 5 mg/kg bw per day. The lowest relevant NOAEL for developmental effects was reported to be 1 mg/kg bw per day in rats (ATSDR 1994). The PTDI for humans of 0.01 mg/kg bw is based on this NOAEL, with a safety factor of 100 (FAO/WHO 2000).

4.2.4.2/ Immunotoxicology

Since 1987, large-scale deaths of dolphins have been reported along the Atlantic coast of North America, in the Gulf of Mexico and in the Mediterranean Sea. Autopsied bottlenose dolphins, collected from the Atlantic coast in 1987 to 1988, showed opportunistic infections indicative of immune dysfunction. Since these animals had high levels of chlorinated hydrocarbons, such as PCBs and DDT, which can suppress immune functions, Lahvis et al. (1995) investigated the possible relationship between chemical contaminant exposure and immune function. Peripheral blood lymphocyte responses to concanavalin A and phytohaemagglutinin were determined *in vitro* and compared by regression analysis with contaminant concentrations in whole blood from a small subset of these animals (n = 5). A reduced immune response in the dolphins correlated with increasing whole blood concentrations of several contaminants. Specifically, concanavalin A-induced lymphocyte responses correlated inversely with *p,p'*-DDT, *o,p'*-DDE and *p,p'*-DDE.

Effects of *p,p'*-DDT and *p,p'*-DDE on immune functions were assessed in beluga whales. The two compounds significantly reduced the proliferative response of splenocytes cultured either with or without phytohaemoagglutinin A (De Guise et al. 1998).

The effects of different durations/intensities of stress on DDT-induced modulation of humoral immune response were evaluated in mice. DDT (20, 50 or 100 ppm for 4 weeks) did not *per se* influence the primary antibody response to sheep red blood cells (SRBC). However, when DDT-pretreated mice were exposed to single and multiple sessions of restraint stress (RS), the anti-SRBC antibody titres were lower than the control values and the most prominent effects were seen after 50 and 100 ppm DDT exposure in combination with a single intense stressor (24-hour RS) or repeated stress (1-hour RS × 5). In splenic plaque-forming cell assays, similar potentiations of DDT-induced immune suppression were seen at 50 and 100 ppm exposure levels in combination with single or multiple restraint stress (Banerjee et al. 1997).

In conclusion, numerous studies have been conducted on the effect of DDT on the immune system of laboratory animals. However, since no validated study protocols were used in different species at different doses, application periods and routes of exposure, available data do not allow any conclusion to be reached on DDT immunotoxicity.

4.2.4.3/ Neurobehavioural toxicity

Exposure to oestrogenic chemicals during critical periods in fetal life can alter the development of reproductive organs, the neuroendocrine system and subsequent behaviour. Palanza et al. (1999b) investigated these potential effects of DDT on mice treated with doses of *o,p'*-DDT ranging between 18 and 180 ng/g bw. Exposure of fetal mice to low doses of *o,p'*-DDT produced some behavioural changes. In particular, the rate of marking new territory by urinating increased, albeit marginally, in mice prenatally exposed to *o,p'*-DDT. The lower dose of DDT also tended to increase the proportion of males that exhibited aggression towards a male intruder. However, males exposed to *o,p*-DDT displayed a lower intensity of attack than controls.

DDT has been shown to be a potent neurotoxicant in both vertebrate and invertebrate species. Neonatal exposure to DDT affects the muscarinic cholinergic receptors (MAChR) in the cerebral cortex of neonatal mice, leading to permanent disturbances of the cholinergic system and in the behaviour of the adult animals. To determine whether there is a critical period for the development of these effects, 3-, 10- and 19-day-old mice were given a single low oral dose of DDT (0.5 mg/kg bw) (Eriksson et al. 1992). At adult age (4 months) the mice were tested for spontaneous behaviour ("locomotion", "rearing" and "total activity"), and were subsequently sacrificed to measure the density of MAChR and subpopulations of MAChR in the cerebral cortex. A significant increase in spontaneous motor behaviour and a significant decrease in MAChR density in the cerebral cortex were only observed in adult mice receiving DDT at the age of 10 days.

DDT may also act as a disruptor of sexual behaviour. Female rats were tested following treatment with *o,p'*-DDT or *p,p'*-DDT during either diestrus or proestrus. *o,p'*-DDT decreased lordosis only after treatment during diestrus, whereas *p,p'*-DDT disrupted sexual behaviour under all treatment conditions. *p,p'*-DDT disrupted sexual behaviour at doses as low as 25 mg/kg bw, while 100–200 mg/kg bw *o,p'*-DDT were required. The authors suggest that *o,p'*-DDT may have altered behaviour by disrupting the oestrous cycle, while *p,p'*-DDT had a major effect on the female's proceptivity and receptivity without modifying vaginal cyclicity (Uphouse & Williams 1989).

Hudson et al. (1985) investigated the effects of *p,p'*-DDT on the concentrations of neurotransmitters in rat brain and the related association on tremor and hyperthermia. A total of 344 adult rats were given various doses (25–100 mg/kg bw) of *p,p'*-DDT by oral gavage, and levels of biogenic amines, their metabolites and amino acid neurotransmitters, tremor activity and rectal temperature were measured at intervals of 2, 5, 12 and 24 hours after dosing. Dose-related increases in rectal temperature and tremor activity were observed at 50–100 mg/kg bw 12 hours after dosing. Tremorigenic doses increased the 5-hydroxyindoleacetic acid (5-HIAA) level in the hypothalamus, brainstem and striatum, whereas doses of 75 and 100 mg/kg bw increased the levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) in the hypothalamus and brainstem and 3,4-dihydroxydiphenylacetic acid levels in the striatum. Among the amino acids assayed, aspartate and glutamate showed

increased levels in the brainstem. The DDT-induced hyperthermia and tremor were associated with dose- and time-related increases in levels of 5-HIAA, MHPG, aspartate and glutamate. The authors suggest that an increase in the turnover rate of 5-hydroxytryptamine (5-HT) may be responsible for the DDT-induced hyperthermia, whereas increases in the metabolism of 5-HT and norepinephrine may be involved in the tremor.

Data of limited usefulness for human risk assessment indicated changes in spontaneous behaviour and brain muscarinic receptors in mice receiving DDT by a single oral dose of 0.5 mg/kg bw on postnatal day 10. Similar effects were not observed when this dose was administered on other postnatal days (FAO/WHO 2000).

Quantitative measurements of the transfer of DDE from pregnant or lactating rats or rabbits to their fetuses or suckling neonates showed that the concentrations in rabbit fetuses were much higher than those in blastocysts and that, in rats, lactation is quantitatively far more important than the transplacental route. The persistent DDT metabolite in animals, 3-methylsulfonyl-DDE, is a potent transplacental and trans-mammary adrenal toxicant in mice. Treatment of mice with a single dose of 3 mg/kg bw resulted in mitochondrial destruction in the adrenal zona fasciculata (FAO/WHO 2000).

4.2.4.4/ Carcinogenicity studies

Osborne-Mendel rats ingested 200, 400, 600 or 800 ppm DDT composed of 81.8% *p,p-* isomer and 18.2% *o,p-* isomer for periods up to 2 years. Both male and female rats developed highly significant incidences of hepatocellular carcinoma, which varied from well differentiated to undifferentiated. There was a highly significant increase in carcinomas of the ovary in treated female rats. Lymphosarcomas also increased in DDT-treated male rats (Reuber 1978).

The livers of male Balb/c mice fed on diets containing 10 ppm dieldrin and 100–175 ppm DDT were histologically and histochemically analysed after 2, 4, 8, 16, 36, 52 and 75 weeks of exposure. Treated mice initially responded with centrolobular hepatocytomegaly. between 52 and 75 weeks, foci of phenotypically altered hepatocytes were noted, including hepatocellular foci and adenomas, which may be potential precursors of mouse hepatocellular carcinomas (Lipsky et al. 1989). In contrast, no significant differences in liver tumour incidence were observed in Syrian golden hamsters fed a diet containing 0, 125, 250 and 500 ppm DDT (Cabral et al. 1982).

Rats fed diets containing 0.05% DDT for 72 weeks, after exposure to an initiating dose of diethylnitrosamine, developed an 85–100% incidence of hepatocellular carcinomas, suggesting that DDT acts as a promoter of liver tumorigenesis (Shivapurkar et al. 1986).

Carcinogenicity of DDT in mice was evaluated by oral and subcutaneous DDT treatment, which resulted in a significant increase in the incidence of tumours, mainly of the lymphoid tissues, lung and liver. The highest tumour incidence was recorded in the mice receiving DDT subcutaneously (Kashyap et al. 1977).

IARC has concluded that there is sufficient evidence in experimental animals for the carcinogenicity of DDT (IARC 1991).

4.3/ Health effects in humans

4.3.1/ Acute effects and overexposures

The health effects of DDT in humans have been reviewed (ATSDR 1989, 1994; Coulston 1985; Hayes 1982; USEPA 1979). In several studies, volunteers took diets containing DDT and DDE. A single dose of 6–10 mg/kg bw DDT resulted in sweating, headache and nausea, while a dose of 16 mg/kg bw led to convulsions. The volunteers usually recovered within 24 hours. Doses of 0.31–0.61 mg/kg bw per day for up to 21 months did not cause any noticeable effect (ATSDR 1989).

4.3.2/ Reproductive toxicity

Based on a review of available data, Coulston et al. (1985) and ATSDR (1989) concluded that there was no evidence of correlation between exposure to DDT and stillbirth, miscarriage or premature rupture of the fetal membranes.

In an ecologically designed study, based on *p,p'*-DDE concentrations in tree bark in 27 countries and 17 American states in 1992–1995, Cocco (1997) did not find evidence of any impairment of human fertility in relation to environmental exposure to DDT and its derivatives. However, the author stressed that more powerful studies in this field are needed in order to clarify any doubt and, according to him, these studies should be conducted in those countries were DDT contamination is still higher.

In conclusion, the few data available do not show an acceptable evidence of effects on human reproduction.

4.3.3/ Neurobehavioural effects

In 1965, memory impairment was described in 123 workers exposed to DDT for 1–10 years, accompanied by impairment of the peripheral nervous system (Model & Zaritskaja 1967).

No confirmed adverse health effects have been reported in infants exposed to DDT while suckling, even in communities where the reference level was frequently exceeded (WHO 1998). A total of 859 children in the United States were tested at 3, 4 or 5 years of age to evaluate the effects of exposure to DDT exposure, either through transplacental route or during breastfeeding. The study showed that DDT did not affect either psychomotor or mental behavioural patterns, tested on the McCarthy and Bayley scores, respectively, or measures of school performance in English and mathematics, even when the PTDI was exceeded (Gladen & Rogan 1991; FAO/WHO 2000). On the other hand, a study carried out in Costa Rica on 27 retired men engaged in malaria control activities and exposed to DDT for at least 2 years suggested that chronic occupational exposure to DDT is associated with a permanent decline in neurobehavioral functioning and an increase of neuropsychological and psychiatric symptoms (De Joode et al. 2001).

4.3.4/ Endocrine disruption

Animal studies suggest that *p,p'*-DDE has anti-androgenic properties and that *o,p'*-DDT is oestrogenic (Kurihara 2000). Activation of oestrogen receptors and inhibition of androgen receptors may be mechanisms of the action of DDT-related compounds that lead to the observed perturbations of reproductive function. The *p,p'*-DDE metabolite acts as an anti-androgen. DDE binds to the androgen receptor *in vitro* and inhibits 5-dihydrotestosterone-induced transcriptional activation with a potency similar to that of the anti-androgenic drug hydroxyflutamide. The results of competitive binding assays showed that *o,p'*-DDT, *o,p'*-DDD, *o,p'*-DDE and *p,p'*-DDT bind to the human oestrogen receptor but with an approximately 1000-fold weaker affinity than that of estradiol (FAO/WHO 2000).

The fact that exogenous hormones, including hormonal medicines such as diethylstilbestrol, have shown carcinogenic potential in humans and animals has raised concern as to whether endocrine-disrupting chemicals (EDCs) also have carcinogenic potentials at their target organs, such as the prostate, mammary gland, testis, uterus, ovary and thyroid. However, epidemiological studies have shown that no EDC clearly possesses carcinogenic potentials in humans, except dioxins and hormonal drugs (Imaida & Shirai 2000). The most recent studies have ruled out the hypothesis that DDT derivatives are responsible for excess risks of cancer of the reproductive organs, although the role of high-level exposure to *o,p'*-DDE in post-menopausal ER+ (oestrogen receptor-positive) breast cancer cannot yet be excluded. A vast amount of scientific effort and resources have been dedicated to exploring the risk of breast cancer associated with an internal dose of DDT derivatives. Of the 29 studies reviewed by Cocco (2002), the majority (21 out of 29) yielded negative results, and only five found a significant excess risk. According to the author, it may be concluded that there is no epidemiological evidence that an internal dose of DDT derivatives, mostly *p,p'*-DDE, is associated with an increase in breast cancer risk. Such a conclusion fits with the current experimental knowledge about *p,p'*-DDE as a potential anti-androgen. *o,p'*-DDE, the oestrogen derivative, derives from *o,p'*-DDT, which is only a contaminant of the technical grade DDT. The *o,p'*-DDT concentration may vary according to the producer, but is usually much lower than that of the *p,p'*-isomer. As a consequence, *o,p'*-DDE is frequently below the limit of detection in population studies, thus excluding it from making a significant contribution to increasing the risk of breast cancer. On the other hand, the author states that it is not possible to exclude a potential role of *o,p'*-DDE in breast cancer etiology if exposure were at a high level.

Apart from carcinogenic risk, since steroid hormone receptors control basic events in embryonic development and sex differentiation, the consequences of disrupting these processes can be particularly dangerous during development, owing to the critical role that hormones play in controlling transient and irreversible developmental processes. Concern is therefore growing about possible effects on fetal development, fertility and libido and on possible neurobehavioral effects.

Up to now, chemicals that mimic estrogens (so-called xenoestrogens) have been the main focus of endocrine disruption research. However, recent evidence suggests that many abnormalities in the male reproductive system may be mediated via the androgen receptor (Sohoni & Sumpter 1998). Despite the strong laboratory evidence of DDT effects on the endocrine system, only a few data are available on humans: aviation crop dusters handling DDT were found to have reduced sperm counts, and workers at a plant producing another chlorinated insecticide, Kepone (chlordecone), reported a reduction of libido and low sperm counts (Sonnenschein & Soto 1998).

Based on the available data, no firm conclusion can be drawn as to the capacity of DDT to cause endocrine disruption at the low doses typical for LRTAP, but the topic is a matter of serious concern, particularly in terms of effects on children and fetuses.

4.4/ Carcinogenesis

The carcinogenic risk from DDT was evaluated by WHO in 1991. The final evaluation states that there is inadequate evidence in humans and sufficient evidence in experimental animals of the carcinogenicity of DDT, and that therefore DDT is possibly carcinogenic to humans (group 2B) (IARC 1991). In two studies performed on workers employed at DDT manufacturing plants in the United States, a slight increase in the risk of lung cancer was observed, while no other cancers occurred in sufficient numbers for statistical analysis (Ditraglia et al. 1981; Wong et al. 1984). In a prospective cohort study (limited, in the authors' opinion, by the small size), Austin et al. (1989) concluded that "the evidence does not support the opinion that DDT is a human carcinogen". Details of these cohort studies are given in Table 2.4.

Non-Hodgkin lymphomas were strongly related to DDT exposure in a study from Washington State in the United States, but were not related to other agricultural exposures (Woods & Polissar 1989; Woods et al. 1987). A slight increase in the risk of leukaemia occurred among farmers in the United States reporting the use of DDT, but this also occurred with other agricultural exposures (Brown et al. 1990). Other types of cancer, such as soft-tissue sarcomas and primary liver cancer, did not show any association with DDT exposure (Hardell et al. 1984). Details of these case-control studies are given in Table 2.5.

Some authors have hypothesized a carcinogenic effect of DDT and its metabolites on the reproductive system, and suggested the prohibition of DDT use (Hileman 1996), while other studies failed to show any association between DDE exposure and testicular cancer (Hengster & Pernthaler 1996).

The IARC review (IARC 1991) concluded that the epidemiological data suggested cancer risks associated with DDT exposure, but that the overall evaluation was limited by several inconsistencies related to the assessment of exposure and to the weakness of the small excesses in risk. The slight excesses of respiratory cancer seen among cohorts exposed to DDT were based on differences of five or fewer cases between exposed and unexposed groups. In case-control studies of lymphatic

and haematopoietic cancers, exposures to agricultural pesticides other than DDT resulted in excesses as large as or larger than those associated with exposure to DDT. In most case-control studies, adjustment was not made for the potential influence of other exposures.

Since the IARC evaluation in 1991, several authors have studied the carcinogenicity of DDT to humans. The main findings of these studies are briefly reported.

4.4.1/ Cohort studies

A proportional mortality study was conducted on 1043 deaths among men who took part in an anti-malaria campaign in Sardinia from 1946 to 1950. DDT comprised 94% of the insecticide used during the campaign, and was sprayed over the soil of the entire region at an average concentration of 10 mg/m^2. The estimated levels of exposure were 170–600 mg/m^3 for indoor applications and 24–86 mg/m^3 for outdoor activities. The study showed a significant increase of risk among workers exposed to DDT, in application or inspection jobs, for liver and biliary tract cancer (PMR = 228, 95% CI = 143–345) and multiple myeloma (PMR = 341, 95% CI = 110–795) (Cocco et al. 1997). However, since the risk of these cancers also increased in workers who had no direct contact with DDT, and since no dose–response relationship was observed, the authors concluded that further research,

Table 2.4: Cohort studies of populations exposed to DDT

Reference	Cancer site	No. of cases	Relative risk	95% CI	Comments
Wong et al. (1984)	Lung	9	1.5	0.68–2.8	Workers at a DDT manufacturing plant; also exposed to other pesticides
	Leukaemia	2	2.1	0.24–7.6	Nested case-control analysis gave odds ratio = 0.74 for DDT exposure
Distraglia et al. (1981)	Respiratory system	4	1.3	0.34–3.2	Workers at a DDT manufacturing plant
	Lymphatic-haemopoietic system	0	–	–	No deaths from skin, brain or bladder cancer or leukaemia
Austin et al. (1989)	Respiratory tract	5 (low DDT)	1.0	0.5–4.9	Exposure levels based on serum levels of DDT (P for trend = 0.34)
		7 (medium)	1.5	0.5–6.2	
		7 (high)	1.8		Respiratory cancer in total cohort: SMR = 1.2

with expansions of the cohort, was needed to clarify the doubts. Earlier studies are summarized in Table 2.4.

An exploratory epidemiological study performed in the United States examined the association between DDE concentrations in adipose tissue from population samples stored in 1968 and mortality rates (between 1975 and 1994) for multiple myeloma, non-Hodgkin lymphoma (NHL) and cancer of the breast, corpus uteri, liver and pancreas. The study did not show any evidence of a consistent increase in mortality with increase of DDE concentration in fat. As for single cancers, liver cancer mortality increased significantly with adipose DDE levels among white subjects but not among African Americans, while breast cancer mortality was inversely correlated with adipose DDE levels in both races. The study did not show any association between adipose tissue levels of DDE and pancreatic cancer, multiple myeloma and NHL. Significant inverse correlations were also observed for uterine cancer only in white women, whereas no association was observed for African Americans (Cocco et al. 2000). In conclusion, this study did not show any association between past DDT exposure and pancreatic cancer, multiple myeloma, NHL, breast cancer and uterine cancer, while the authors suggest a deeper investigation be carried out into the association between liver cancer and DDE concentration in adipose tissue observed only in white people.

A cohort study of mortality among farmers and agricultural workers during the period 1972–1988 revealed a nom-statistically significant tendency towards an increased risk of lung cancer. Under 65 years of age, excess deaths were also found for lung cancer. Since farmers usually have a low lung cancer rate, the increased mortality in the young age group (0–24, SMR = 1.28) deserves consideration in relation to past exposure, in particular to DDT (Faustini et al. 1993).

The cancer morbidity in a large group of male agricultural workers exposed to several pesticides was investigated through a German retrospective cohort study. A total of 169 malignant tumours were diagnosed in 1658 men who began to work with pesticides between 1948 and 1972, and continued this activity for at least 5 years. The SMR of 2.0 for lung cancer among pesticide-exposed subjects with the same smoking habits as the general population was significantly higher than that for the general male population of the German Democratic Republic. A positive correlation between duration of employment and mortality from lung cancer (mainly undifferentiated and small-cell carcinomas) suggested a dose-effect relationship. Because the subjects had been exposed to different substances, the study does not permit any conclusions to be drawn in respect of the carcinogenicity of single pesticides. The increased mortality could be attributed to the additive effect of various active ingredients and contaminants (including chlorinated dibenzodioxins and DDT) (Barthel 1981).

The epidemiological findings on the association between DDT and breast cancer are inconclusive. However, the largest and best designed study has been interpreted as negative. The hypothesis that human exposure to environmental oestrogenic chemicals, including DDT, would favour an oestrogenic over-activity

leading to an increase in oestrogen-dependent formation of mammary tumours cannot be conclusively rejected on the basis of available data (Ahlborg et al 1995).

4.4.2/ Case-control studies

The levels of organochlorine pesticides in the bile of 60 patients (30 carcinoma of the gall bladder, 30 cholelithiasis) were measured to evaluate the association of exposure to these pesticides with carcinoma of the gall bladder. The mean biliary concentration of DDT was significantly higher in carcinoma of the gall bladder (0.14 ppm) than in cholelithiasis (0.0103 ppm) ($P < 0.03$), suggesting that the compound could be associated with gall bladder carcinogenesis (Shukla et al. 2001).

A case-control study (108 vs 82) was carried out in the San Francisco Bay area to evaluate the association between occupational exposure to DDT and pancreatic cancer. Median concentrations of DDE were significantly ($P = 0.05$) higher among cases than controls (Hoppin et al. 2000).

A nested case-control study held among chemical manufacturing workers with increased mortality from pancreatic cancer showed that DDT was associated with pancreatic cancer (RR= 4.8, 95% CI = 1.3–17.6). Among those who had a mean exposure to DDT of 47 months, the risk was 7.4 times that of those with no exposure. Two DDT derivates, ethylan and DDD, were additionally associated with pancreatic cancer, suggesting that DDT may cause pancreas cancer under circumstances of heavy and prolonged exposure (Garabrant et al. 1992).

A study was conducted to investigate the risks of exposure to DDT in the general population. A total of 66 subjects with cytologically diagnosed pancreatic cancer were identified as cases, and 131 controls were matched to these subjects for age, sex, ethnicity and county of residence. Lifetime exposure to pesticides was assessed using a questionnaire. No significant association was found between self-reported exposure to DDT and the risk of cancer (Fryzek et al. 1997). The apparent inconsistency of these findings with those of Garabrant et al. (1992) and Hoppin et al. (2000) may be due to the fact that the latter studies concerned very high levels of exposure, while the study of Fryzek et al. was aimed at low-level exposure of the general population.

A study carried out in Uruguay to provide information on the risk of lung cancer found significant increases in risk associated with DDT exposure (De Stefani et al. 1996). The study was aimed at providing information on the relationship of lung cancer with several risk factors such as asbestos, pesticides and other occupational exposures. Moreover, information on exposure levels was collect through a questionnaire, and the limits of this method of collection are well known and have already been discussed.

In contrast, a Brazilian study showed that agricultural workers are not a risk group for lung cancer (Algranti et al. 2001). However, this study was not aimed solely at DDT but at several risk factors, and agricultural activities do not necessarily imply exposure to DDT.

A case-control study evaluated the role of agricultural exposures in the development of lymphatic and haemopoietic tumours. The odds ratio (OR) of haematological malignancies for agricultural workers was 1.63 (95% CI = 0.69–4.34) in the whole sample and 6.00 (95% CI = 1.21–25.52) in the female group. A significant increase was found in cancer related to exposure to DDT (OR = 4.11; 95% CI = 1.16–14.55) (Assennato et al. 1995).

A study in western Washington State showed a small but significant increase of risk of non-Hodgkin lymphoma among workers with occupational exposure to organochlorine insecticides, including DDT (OR = 1.82, 95% CI = 1.04–3.2) (Woods et al. 1987).

A multicentre case-control study (517 vs 1506) performed in Canada identified an association between pesticide exposure and development of non-Hodgkin lymphoma. Pesticide exposure was investigated with a self-administered questionnaire and a telephone interview. The risk of disease significantly increased with exposure to carbamate, organophosphorus insecticides, amine fungicides and carbon tetrachloride. Using multivariate analysis, the authors found an increased risk of non-Hodgkin lymphoma associated with some individual compounds such as DDT (OR = 2.11; 95% CI = 1.21–3.69) (McDuffie et al, 2001).

A population based case-control study conducted in Italy investigated the association between chronic lymphocytic leukaemias, non-Hodgkin lymphomas and subtypes, and exposure to pesticides in farm-animal breeding workers. The two diseases together were found to be associated with insecticide exposure, including DDT, although the association was limited to chronic lymphocytic leukaemias and low-grade non-Hodgkin lymphomas. The independent effect of the variable "exposure" during childhood suggests that early exposures, including possible contact with animals, may play a role in the pathogenic process of these neoplasms (Nanni 1996).

A case-control study (275 vs 275) was conducted in Sweden to identify an association between multiple myeloma and several suspected environmental factors. Occupational exposure to chemicals and other potential carcinogens was evaluated by a questionnaire, which also included questions about potential carcinogenic co-factors. The study indicated some domestic animals and two types of pesticide (phenoxyacetic acids and DDT) as risk factors for multiple myeloma in farmers (Eriksson & Karlsson 1992).

A nested case-control study (74 cases vs 147 matched controls) investigated the association between non-Hodgkin lymphoma and serum organochlorine residues. Total lipid-corrected serum concentrations of DDT were not associated with risk of non-Hodgkin lymphoma (Rothman et al. 1997).

A summary of the results of some other case-control studies is presented in Table 2.5.

Most of the above-mentioned epidemiological studies were reviewed by FAO/WHO (2000). The main conclusions are that the association between exposure to DDT and/or DDE and breast cancer in women, suggested in some case-control studies, was not confirmed in later prospective studies. The results of studies of

Table 2.5. Case–control studies of cancers containing information on exposure to DDT

Reference	Cancer site	No. of cases/ controls	Relative risk	95% CI	Comments
Woods et al. (1987)	Non-Hodgkin lymphoma	Not reported	1.8	1.0–3.2	Not adjusted for other agricultural exposures
Woods and Polissar, (1989) United States		Not reported	1.7	0.9–3.3	Farmers
Hardell et al. (1981) Northern Sweden	Malignant lymphoma	22/26	1.8	1.0–3.2	Crude risk calculated from data in paper; not adjusted for other agricultural exposures
		7/11	1.6	0.6–4.1	Crude risk for DDT without exposure to phenoxyacetic acid herbicide
Hardell et al. (1984) Sweden	Primary liver	4/20	0.4	0.1–1.1	Crude risk calculated from data in paper; not adjusted for other agricultural exposures
		5/8	1.3	0.4–4.0	
Brown et al. (1990) United States	Leukaemia	35/75	1.2	0.7–1.8	DDT used on crops
		80/149	1.3	1.0–1.8	DDT used on animals Not adjusted for other agricultural exposures; risks increased with duration of use
	Chronic lymphatic leukaemia	36	1.5	0.9–2.3	
	Chronic myeloid leukaemia	10	1.9	0.9–4.2	

pancreatic cancer, multiple myeloma, non-Hodgkin lymphoma and uterine cancer did not support the hypothesis of an association with environmental exposure to the DDT complex, e.g. in food. Under circumstances of heavy, prolonged occupational exposure to technical-grade DDT, an increased risk for pancreatic cancer could not be excluded.

In conclusion, data provided by studies carried out after the evaluation performed in 1991 by IARC do not bring about the need to change what was

stated, i.e. that the evidence of DDT carcinogenicity in humans is inadequate. Nevertheless, very high and prolonged exposures to DDT, such as those observed in occupational settings, may bring about an additional risk of pancreatic cancer.

4.5/ Critical outcomes and existing reference values

In a detailed study in monkeys, conducted at the US National Cancer Institute, DDT was administered by gavage at a dose of 10 mg/kg bw per day for 11 years without any tumorigenic effect. A no-effect toxicological level of 10 mg/kg bw per day in monkeys was based on a seven-year diet study conducted by the US Food and Drug Administration. Therefore, 10 mg/kg bw per day may be taken as the level causing no toxicological effects in monkeys.

A lifespan carcinogenicity study in rats showed slight increases in the incidence of hepatomas in females given 250 and 500 ppm per day in the diet; the 125 ppm dose level was without effect, and males showed no increased tumorigenicity at any of these doses. Thus 125 ppm, equivalent to 6.25 mg/kg bw per day, may be taken as the no-effect level for tumorigenesis in the rat (FAO/WHO 2000).

DDT and DDE toxicity in humans was revised by JMPR in 1984. The conclusion was that available data on humans do not show causal relationships for carcinogenicity in any organ system or significant adverse health effects after repeated exposure to concentrations up to 0.25 mg/kg bw per day (FAO/WHO 1984).

In 1984 JMPR calculated an acceptable daily intake for humans of 0.02 mg/kg bw per day (FAO/WHO 1984), which was converted to a PTDI in 1994 (FAO/WHO 1994). In 2000, after assessing newer studies and reviews, JMPR changed the PTDI established in 1994; it derived a PTDI for humans of 0.01 mg/kg bw on the basis of the NOAEL of 1 mg/kg bw per day for developmental toxicity in rats and a safety factor of 100.

Since DDT is no longer used in agricultural practice but may be present in food commodities as a contaminant, peaks of acute dietary intake above the PTDI are not likely to occur, and therefore an acute reference dose was not allocated (FAO/WHO 2000).

5/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

It has been shown that DDT, like other POPs, resists degradation, bioaccumulates, is transported by means of air, water and migratory animals and birds across international boundaries, and is finally deposited far from the place of release where it accumulates in terrestrial and aquatic ecosystems (Stockholm Convention on POPs 2001). The clearest evidence for long-range transport derives from the high levels of DDT measured in the Arctic. Owing to long-range transport, DDT is nowadays a ubiquitous contaminant of the ecosystem, and it is able to enter the food chain. Therefore, most of the human population is exposed to this compound and its main metabolites. Moreover, since DDT passes from mother to fetus across the placenta, and from mother to newborn through breastfeeding, infants are at risk of harmful effects in the most critical period of their development.

Nowadays, about 50 years after the introduction of DDT, the scientific community is still trying to assess the real cost of its use considering the long-term effects in both the general population and exposed workers. This evaluation is the basis for a better understanding of the health risks related to the ubiquity of DDT in the environment. The uncertainty surrounding this question shows that whatever hazards appeared, they were at a sufficiently low level as not to be detected by the great number of epidemiological studies carried out so far. However, it is necessary to take account of the fact that most of these studies are carried out on subjects exposed to different chemical substances, with a consequent difficulty in the definition of the role of single compounds in the production of the observed effect, if any. Also, data on exposure levels are weak or lacking. The above-mentioned limits may affect the sensitivity of these studies.

The critical issues for human health concern the ability of DDT to cause carcinogenic effects, damage the nervous, reproductive and immune systems, and act as an endocrine disrupter.

To minimize the effects of DDT on both the environment and humans, the international community has begun a process of developing a global legally binding treaty to phase out and eliminate the production, use and sources of DDT and other POPs (Rother 2000). Nevertheless, despite the health risks related to exposure and the persistence of the compound in the environment, DDT is still considered important and necessary for vector control in developing countries, where malaria kills over one million people a year, most of them young children (WHO 1999a). Therefore, whereas a worldwide ban of the agricultural use of DDT is necessary, banning its use for public health purposes is not. For these reasons the Intergovernmental Negotiating Committee, convened by the United Nations Environment Programme, stated that the use and production of DDT shall be limited to disease vector control with a long-term goal of elimination, which must be at no cost to public health.

Countries requiring DDT to fight malaria are allowed to use the compound until effective and affordable alternatives become available. Use must be limited to indoor applications and bed-net treatment, in order to reduce the risk of large-scale releases to the environment. Up to now, no effective and cheap alternative has been found. A 1990 cost comparison by WHO found DDT considerably less expensive than other insecticides, especially pyrethroids, which cost 2–23 times more (Curtis & Mnzava 2000). Moreover, in some cases, owing to the resistance or the short-term duration of the effects, alternative methods have been demonstrated to be scarcely effective. South Africa, which had stopped applying DDT because of the elevated levels found in the blood and breast-milk of local people, has resumed its use owing to the resistance of mosquitoes to alternative chemicals (Bouwman 2000). According to the "Action plan for the reduction of reliance on DDT in disease vector control" (WHO 1999b), the alternatives are defined as (*a*) the use of alternative products for chemical and biological control, (*b*) alternative methods for the application of chemical and biological control and (*c*) alternative strategies, such as integrated vector management based on scientifically sound

criteria, cost–effectiveness analyses and delivery systems compatible with current trends in health sector reform.

Recommended activities to be carried out in the near future are monitoring campaigns aimed at measuring the concentration of DDT and its metabolites in body fluids, human milk and body fat in order to develop a map of the levels of DDT exposure in different countries and organize proper preventive activities. DDT concentrations in the environment and in food must also be assessed, especially in developing countries and countries in transition, where exposure data are poor or totally lacking.

6/ REFERENCES

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CHAPTER 3/ HEXACHLOROCYCLOHEXANES

1/ INTRODUCTION

γ-Hexachlorocyclohexane (γ-HCH or lindane) is used as an insecticide on fruit and vegetable crops (including greenhouse vegetables and tobacco), for seed treatment, in forestry (including Christmas trees) and for animal treatment. It is used also as a therapeutic scabicide, pediculicide and ectoparasiticide for humans and animals (Budavari et al. 1989). Other HCH isomers are still found in environmental samples owing to the former use of technical HCH as an insecticide.

The use of γ-HCH in Europe decreased from about 25 000 tonnes in 1970 to 671 tonnes in 1990 (see Fig. 3.4). Commercial γ-HCH production in the United States reportedly ended in 1976 (USEPA 1989). Its use was forbidden in France in 1998 and in the European Union in 2000.

Medically, γ-HCH is used topically for the treatment of head and body lice and scabies; it is available in 1% preparations as a lotion, cream or shampoo (Huff 1988). The γ-HCH used in human and veterinary medicinal and pharmaceutical products must be 99% pure (Budavari et al. 1989). However, the use of γ-HCH for the treatment of scabies can be replaced with permethrin, a pyrethroid insecticide with lower mammalian toxicity (Franz & Lehman 1996).

The use of technical HCH is restricted under the UNECE/LRTAP Protocol on POPs to the manufacture of other substances. γ-HCH is restricted to the following uses: seed treatment; soil application directly followed by incorporation into the topsoil; professional remedial and industrial treatment of timber and logs; a topical insecticide for public health and veterinary use; non-aerial application to tree seedlings; and indoor industrial and residential applications. All of these uses are to be reassessed under the Protocol no later than two years after its entry into force.

HCH is not covered by the Stockholm Convention, and the use of technical HCH and γ-HCH in other parts of the world is continuing.

2/ POTENTIAL FOR LRTAP

2.1/ Physical properties allowing atmospheric transport

Technical grade HCH consists of 65–70% α-HCH, 7–10% β-HCH, 14–15% γ-HCH (see Fig. 3.1–3.3) and approximately 10% of other isomers and compounds. Lindane contains > 99% γ-HCH. It is a solid with a low vapour pressure, and is poorly soluble in water but very soluble in organic solvents such as acetone and in aromatic and chlorinated solvents. Some physical properties of α-, β- and γ-HCH are listed in Table 3.1.

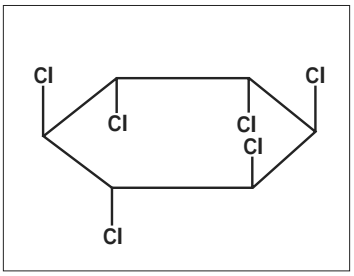

Fig. 3.1. α-HCH ($C_6H_6Cl_6$) CAS 319-84-6

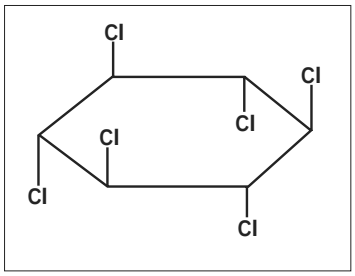

Fig. 3.2. β-HCH ($C_6H_6Cl_6$) CAS 319-85-7

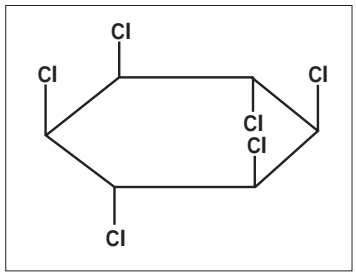

Fig. 3.3. γ-HCH $C_6H_6Cl_6$ CAS 58-89-9

Table 3.1. Physical properties of α-, β- and γ-HCH

Property	α-CH	β-HCH	γ-HCH
Molecular weight	290.83	290.83	290.83
Solubility in water	10 ppm; 69.5 mg/l at 28 °C	5 ppm	17 ppm; insoluble in water
Log K_{ow}	3.46–3.85	4.50; 3.78; 3.98	3.3–3.61
Log K_{oc}	3.57	3.57	3.0–3.57
Vapour pressure	0.02 mmHg at 20 °C	0.005 mmHg at 20 °C 2.8×10^{-7} at 20 °C	9.4×10^{-6} mmHg at 20 °C
Henry's law constant at 25 °C	4.8×10^{-6} atm·m³/mol 6.0×10^{-6} atm·m³/mol	4.5×10^{-7} atm·m³/mol	7.8×10^{-6} atm·m³/mol 3.2×10^{-6} atm·m³/mol

Source: ATDSR 1999.

HCH does not occur as a natural substance. The manufacture of technical grade HCH involves the photochlorination of benzene, which yields an isomeric mixture consisting of α-HCH, β-HCH, γ-HCH, δ-HCH, ε-HCH and inert S-isomers (IARC 1979); this reaction can be started by free radical initiators such as visual or ultraviolet light, X-rays or γ-rays (Kirk-Othmer 1985). Treatment with methanol or acetic acid, followed by fractional crystallization, concentrates γ-HCH to the 99.9% required in the technical grade of γ-HCH (IARC 1979); nitric acid is used to remove odour (SRI 1987, ATSDR 1999).

2.2/ Persistence in water, soil and sediment

γ-HCH present in soil can leach to groundwater, sorb to soil particulates or volatilize to the atmosphere. In general, the leaching of organic chemicals through soil is governed by the water solubility of the chemicals and their propensity to bind to soil. According to the results of a number of laboratory soil column leaching studies that used soils of both high and low organic carbon content as well as municipal refuse, γ-HCH is generally immobile in soils (Hollifield 1979; Melancon et al. 1986; Rao & Davidson 1982; Reinhart & Pohland 1991).

γ-HCH sorbed to the soil can partition to the atmosphere by wind erosion of surface soil particulates (Stanley et al. 1971) and via volatilization from treated agricultural soils and plant foliage (Lewis & Lee 1976). In tests conducted in a model laboratory system at 10 °C and 20 °C, Dorfler et al. (1991a) reported volatilization

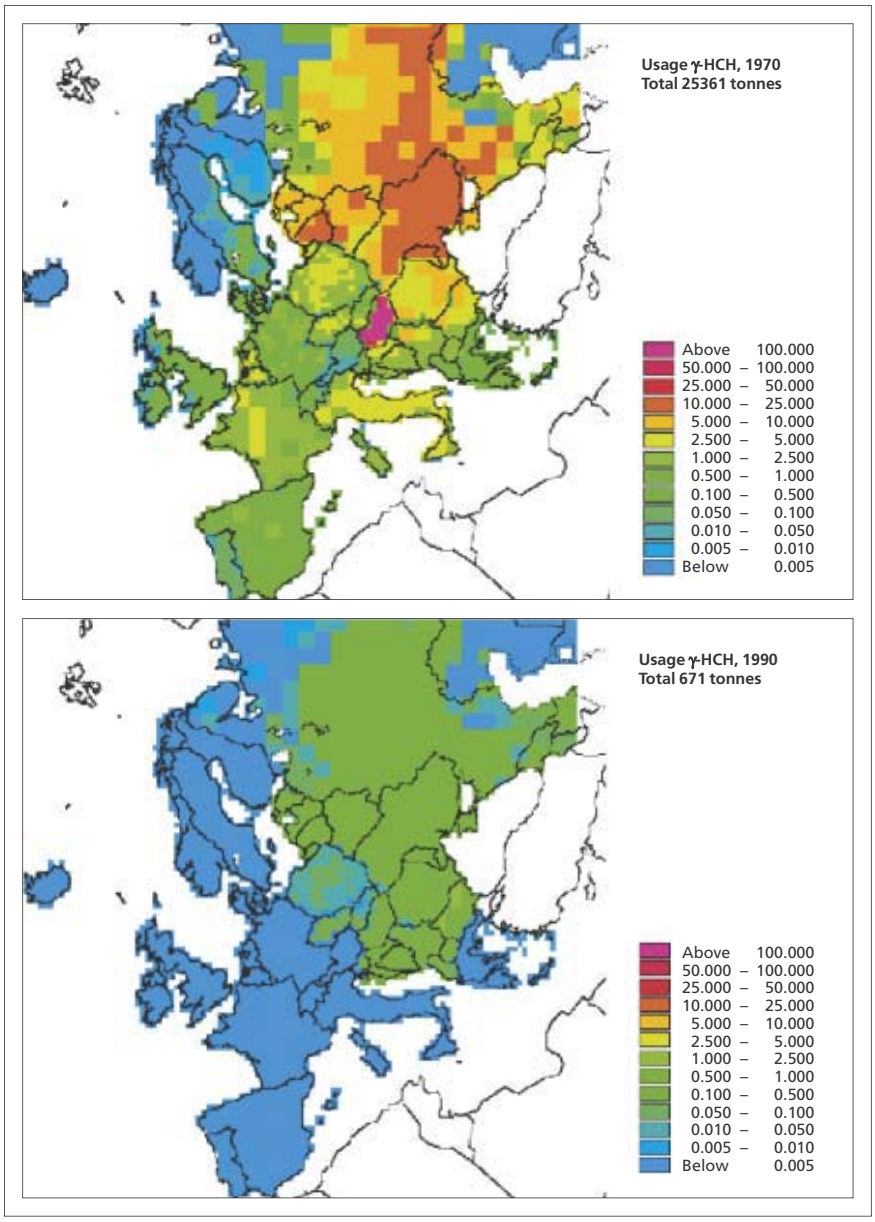

Fig. 3.4. Usage of γ-HCH in Europe in 1970 and 1990

Source: Pacyna 1999.

half-lives of γ-HCH from soil and oat plant surfaces of 2.3–24.8 days and 0.29–0.73 days, respectively. Half-lives were longer on dry, sandy soils versus peat soils; however, when moisture was added to the soils, the half-life was greater for the peat soil, while a higher temperature decreased the half-life under all soil and moisture conditions (Dorfler et al. 1991b).

In tests performed with a wind tunnel, a volatilization rate was determined of >20% for lindane from soil surfaces within a 24-hour period (Rüdel 1997). The volatilization rate from plant surfaces was 55% for lindane. Application of γ-HCH to fields of sunflowers and sugar beet resulted in a 54% evaporative loss of the pesticide within 24 hours (ATSDR 1999; Neururer & Womastek 1991).

β-HCH is the most persistent HCH isomer. Biodegradation and abiotic degradation (dechlorination) by ultraviolet irradiation occur in the environment and produce pentachlorocyclohexane, but at a much slower rate than in the case of γ-HCH.

2.3/ Bioaccumulation

Owing to the persistence of β-HCH, rapid bioconcentration takes place in invertebrates (the bioconcentration factor is approximately 125 within 3 days), fish (250–1500 on a dry weight basis or approximately 500 000 times on a lipid basis within 3–10 days), birds and humans (approximately 525). The bioconcentration is higher and the elimination slower for β-HCH than for the other HCH isomers (WHO 1991).

2.4/ Monitoring and modelling

In a study of global distribution and atmospheric transport of chlorinated hydrocarbons in the Western Pacific, Eastern Indian and Antarctic Oceans, Tanabe et al. (1982) confirmed the widespread distribution of HCH isomers. HCH residues were detected in all 79 air and water samples collected. The concentrations ranged from 1.1 to 2.0 ng/m^3 in air and from 3.1 to 7.3ng/l in water. Other monitoring studies include the detection of γ-HCH in the lower troposphere over the Southern Indian Ocean in 1986 at a mean concentration of 0.406 ng/m^3 (Wittlinger & Ballschmiter 1990), in the lower troposphere over Bermuda in 1988 at a mean concentration of 0.012 ng/m^3 (Knap & Binkley 1991), in ambient air samples collected at Axel Hieberg Island in the Canadian Arctic at 0.017–0.07 ng/m^3 (Hargrave et al. 1988) and in air over the Atlantic Ocean along a transect 50° N–70° S at 0–35 pg α-HCH/m^3 and 0–70 pg γ-HCH/m^3 (Lakaschus et al. 2002).

γ-HCH has also been detected in rainfall samples collected at College Station, Texas in 1979–1980 at a weighted mean concentration of 2.81 ng/l (range 0.30–7.8 ng/l) (Atlas & Giam 1988) and in Bermuda in 1983–1984 at a mean concentration of 0.126 ng/l (range 0.001–0.936 ng/l) (Knap et al. 1988). In rainfall samples collected at four sites in Canada in 1984, γ-HCH concentrations ranged from 0.46 to 34 ng/l (Strachan 1988). The mean concentration in rainfall samples

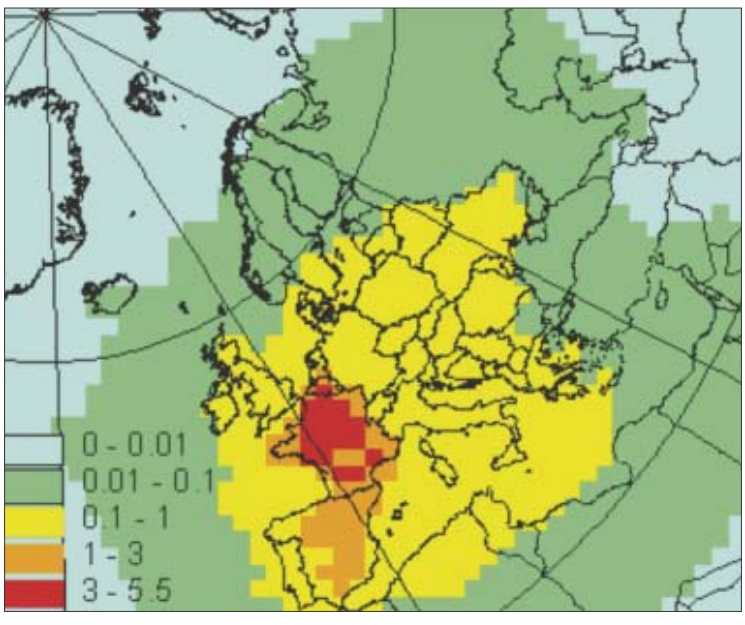

Fig. 3.5. γ-HCH air concentrations in 1997, ng/m^3

Source: Shatalov et al. 2002.

collected at Lake Superior during the 1984 wet season was 3.0 ng/l, with an annual loading of 2.0 μg/m^2 per year (Strachan 1988). These values were less than those determined in 1977, 1981 and 1983 (Strachan 1988). γ-HCH was detected in rain and snow water in Portland, Oregon in 1982 at mean concentrations of 0.45–11 ng/l (Pankow et al. 1984). Rainwater collected in Hawaii in 1970–1971 had a mean γ-HCH concentration of 5 ng/l, with concentrations ranging from 1 to 19 ng/l (Bevenue et al. 1972). Snow and ice samples collected at Axel Hiberg Island in the Canadian Arctic in 1986 contained γ-HCH at concentrations of 0.211–0.644 ng/l and 0.186 ng/, respectively (Hargrave et al. 1988). Rain samples collected in Germany between June 1990 and August 1991 contained γ-HCH at a mean concentration of 0.208 μg/l (range 0.020–0.833 μg/l; detection limit 0.5 pg) in 39 of 41 samples (ATSDR, 1999; Scharf et al. 1992).

In France, observation of pesticides in the atmosphere started at the end of the 1980s with three major zones being prospected (Brittany, Ile-de-France and Alsace-Vosges) (Bedos et al. 2002; Chevreuil et al. 1996; Granier & Chevreuil 1997; Millet et al. 1997). Atmospheric concentrations of γ-HCH in air (gaseous phase and particulate matter) were between 0.59 and 1.25 ng/m^3 in rural or remote sites, and between 1.53 and 2.7 ng/m^3 in urban sites (with predominance in the gaseous phase). The average concentrations observed in rainwater ranged from 0.029 to 0.16 μg/l, and the concentration was more important in fogwater (9.45 μg/l). In both rainwater and fogwater the particle-bound form is more important than the dissolved form. Estimates by EMEP indicate that the concentrations of γ-HCH in air tend to be higher in France than in the other regions of Europe (Fig. 3.5).

The α-HCH : γ-HCH ratio can be used as a tracer to detect the origin of the air masses, or may be an indicator of the age of the air masses because γ-HCH can isomerize to α-HCH by photochemical reaction (Millet et al. 1997).

An analysis of the concentrations of α-HCH and γ-HCH in air over southern Ontario suggested that high levels of γ-HCH were indicative of recent lindane usage (Hoff et al. 1992a). The levels of α-HCH were less variable throughout the year, ranging from 77 to 260 pg/m^3. During the winter, higher α-HCH : γ-HCH ratios reflect the movement of air containing the more persistent α-HCH isomer from the colder Arctic regions to the south, while the lower ratios in the summer reflect both increased lindane usage in the region and the lack of movement of Arctic air (Hoff et al. 1992a). γ-HCH is also seen to move with warm air during the summer months from the lower United States (or areas even further to the south) to the Great Lakes region, although a similar trajectory cannot be identified for the more ubiquitous α-HCH. Levels of α-HCH in air are not dominated by volatilization or partitioning to surfaces but depend on local temperature changes (Hoff et al. 1992b). α-HCH appears to have a long residence time in the atmosphere and is controlled primarily by transport (ATSDR 1999).

In a study by Atkins & Eggleton (1971), γ-HCH removal rates by rainfall and dry deposition were 2.5% and 3.3% per week, respectively, and the atmospheric residence time of γ-HCH is limited by wet deposition (owing to the molecule's

moderate water solubility, i.e. s = 7.4 mg/l at 298 K) and photochemistry (k_OH = $1.9.10^{-13}$ cm^3/molec/s which corresponds to about $t^{1/2}$ = 6d at c_OH = 5.10^5 molec/cm^3). The estimated residence time of γ-HCH in the atmosphere was 17 weeks.

α-HCH and γ-HCH were detected in 60–90% of the air samples collected in the vicinity of formulation plants in Arkansas and Tennessee in 1971 at mean levels of 1.0 and 1.3 mg/m^3, respectively (Lewis & Lee 1976). Quantitative estimates of the total quantities of γ-HCH released to the air from these sources were not located (ATSDR 1999).

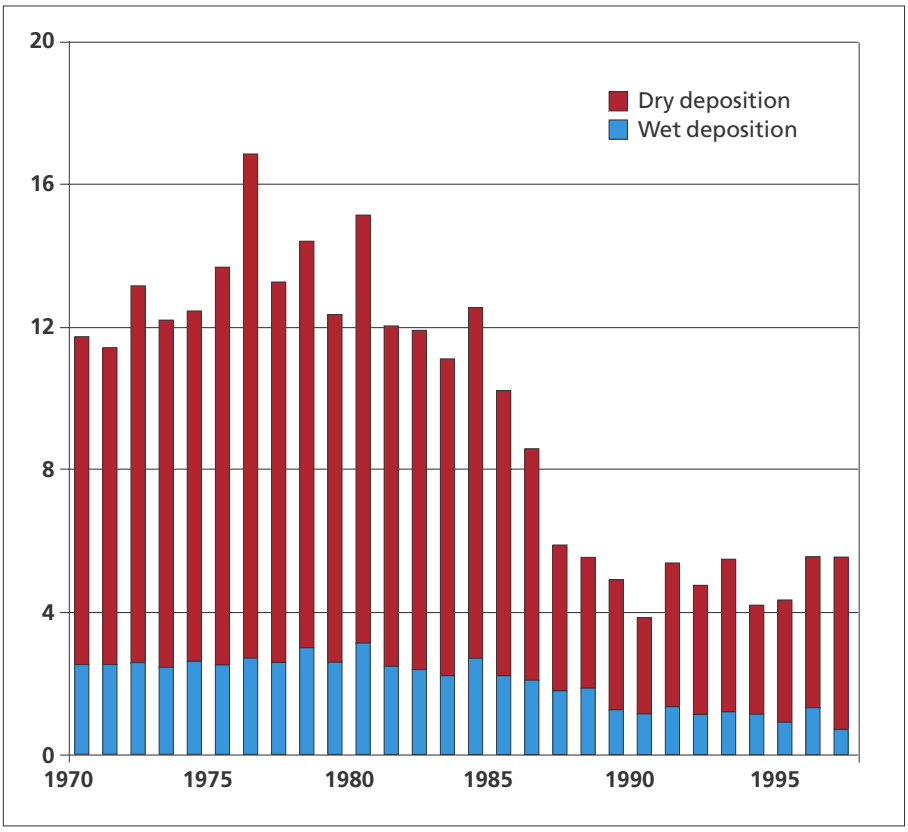

Fig. 3.6. Estimated γ-HCH deposition on the sea, µg/m^2 per year

Source: Shatalov et al. 2002.

According to EMEP, less than 1% of lindane in air is bound to particles, and dry deposition is superior to wet deposition (on average by a factor 2 on land and 4 at sea, although this strongly depends on the season (see Fig. 3.6)). γ-HCH concentrations in air are positively correlated with ambient air temperature, whereas concentrations of α-HCH are not. Removal by rainfall and dry deposition of atmospheric γ-HCH results in the contamination of surface soil and water in areas not directly exposed through pesticide application. The ocean becomes a major reservoir of γ-HCH since the half-life in this compartment is higher. EMEP estimated that during a 28-year calculation period about 60% of the emission is transported outside the European Region. (Shatalov et al. 2000).

2.5/ Conclusions regarding the LRTAP potential

α- and γ-HCH are relatively water-soluble and have little bioconcentration potential. γ-HCH is very prevalent in the marine environment and soils, but low levels are found in biota. A minor constituent of lindane is β-HCH, which has

reduced water solubility and hence a more significant bioconcentration factor than γ-HCH.

HCH residues are found in water and air samples all over the world. Often higher concentrations are found in the waters of northern regions than in major source regions in the mid-latitudes. The atmospheric long-range transport potential of γ-HCH far away from the source has been demonstrated, especially by EMEP for the European Region.

The presence of large quantities of γ-HCH in oceans and lakes introduces a delay in the response of atmospheric concentrations to reductions in emissions.

3/ PATHWAYS OF LRTAP-DERIVED HUMAN EXPOSURE

3.1/ Significant source(s) and magnitude of human exposure and its relation to LRTAP

Historically, the largest source of γ-HCH released to the air was the agricultural use of the pesticide lindane. All applications of γ-HCH are now forbidden in the European Union, and aerial applications of γ-HCH are now prohibited in the United States (USEPA 1985), and atmospheric releases from these sources are not expected.

Other air releases also occur during the manufacture of the pesticide and as a result of other uses or disposal. For example, wind erosion of contaminated soil may distribute pesticides into the atmosphere. γ-HCH can also be released to the atmosphere through volatilization from treated agricultural soils and plant foliage (Lewis & Lee 1976). Evaporative loss of γ-HCH from water is not considered a significant source of atmospheric γ-HCH because of its relatively high water solubility (Mackay & Leinonen 1975). Quantitative estimates of the amount of γ-HCH released from these sources were not found in the literature. Atmospheric release of γ-HCH from disposal sites or hazardous waste sites has not been documented, but is likely to occur given the physical and chemical properties of γ–HCH (ATSDR 1999).

γ-HCH can be detected in air, water, soil, sediment, aquatic and terrestrial organisms and food throughout the world, although the concentrations in these different compartments are generally low and are gradually decreasing. Humans are exposed daily through food, and γ-HCH has been found in blood, adipose tissue, and breast milk.

In the early 1980s, mean concentrations of γ-HCH in human adipose tissue in Czechoslovakia, the Federal Republic of Germany and the Netherlands were 0.086, 0.024–0.061 and 0.01–0.02 mg/kg, respectively, on a fat basis (WHO 1991). In total-diet and market-basket studies to estimate daily human intake of γ-HCH, clear differences were observed with time. Intake in the period around 1970 was up to 0.05 μg/kg bw per day, whereas by 1980 intake had decreased to 0.003 μg/kg bw per day or lower.

Daily intake of HCH isomers in adult diets in the United States in 1981–1982 was reported to be 10 ng/kg bw for total HCH (8 ng α-HCH) (ATSDR 1989). In the Netherlands, the daily intake from food has been calculated to be 1 μg for the α-, β-, and γ-isomers, or approximately 15 ng/kg bw (WHO 1991). Intake from air may be considerable for people living in houses treated for pest control purposes. A

maximal ADI for γ-HCH in humans was established at 0–0.008 mg/kg bw in 1989 (FAO/WHO 1990). This value is based on a NOAEL of 10 mg/kg bw in the diet.

Determinations of the γ-HCH content in body tissues in the general population have been made in a number of countries. The content in blood in the Netherlands was in the order of < 0.1–0.2 µg/l, but much higher concentrations were found in several countries where technical grade HCH was used. The mean concentrations in human adipose tissue in various countries ranged from < 0.01 to 0.2 mg/kg on a fat basis. Concentrations of lindane in human milk are generally low, at average concentrations of < 0.001 to 0.1 mg/kg on a fat basis; however, there has been a clear reduction over time.

Food is the main source of exposure to β-HCH for the general population. Reported concentrations in fat-containing food products ranged up to 0.03 mg/kg (on a fat basis), but in milk products levels up to 4 mg/kg (on a fat basis) were found. In non-fatty food items, the levels were < 0.005 mg/kg product. In general, levels are slowly decreasing. In total-diet studies in the United Kingdom, 0.003, 0.0005 and < 0.0005 mg/kg were found for the years 1966–1967, 1975–1977 and 1981, respectively. In the United States, the average daily intake of β-HCH in 1982–1984 was < 0.1–0.4 ng/kg bw for various age groups. β-HCH is circulating in the environment and present in terrestrial and aquatic food chains, giving rise to a continuous potential for human exposure. This exposure is low and is expected to decrease slowly in the coming years as technical HCH products are withdrawn.

β-HCH is the predominant HCH isomer accumulating in human tissues. Reported concentrations in adipose tissue found in Canada, Germany, Kenya, the Netherlands and the United Kingdom ranged up to 4.4 mg/kg (on a fat basis) (WHO 1991). β-HCH concentrations in adipose tissues are higher than those of other HCH isomers – a phenomenon that reflects the greater accumulative properties of β-HCH. There is, in general, no clear trend for a decrease in β-HCH concentrations over the period that studies have been made. There is a relationship between concentrations in adipose tissue and breast-milk and the consumption of meat products, animal fat and fatty fish. Reported concentrations in blood, serum and plasma varied between different countries and ranged up to 25 µg/l. In Canada, Germany, the Netherlands and the United Kingdom, breast-milk has been analysed and β-HCH levels of between 0.1 and 0.69 mg/kg (on a fat basis) have been found, whereas levels of γ-HCH ranged from <0.001 to 0.1 mg/kg (on a fat basis). The level in the milk of women living in rural areas appears to be higher than that in those living in urban areas.

3.2/ Significance of LRTAP as the source of total exposure

More than 90% of human exposure to all HCH isomers originates from food sources, particularly those that are animal-based (WHO 1991). The intake of lindane in food decreased by more than an order of magnitude in the 1970s, to levels at least 2 orders of magnitude below the ADI established by WHO in 1989. Intake from (indoor) air may be considerable for people living in houses treated for pest-control purposes.

β-HCH is the predominant HCH isomer accumulating in human tissues, as indicated *inter alia* by the levels in human milk. The intake of lindane from commercially produced food has decreased since the 1970s; this is a response to decreasing emissions, although this trend is not evident for those eating mainly marine foods, particularly marine mammals. There is a relationship between the HCH concentration in breast-milk and the consumption of meat products, animal fat and fatty fish.

4/ HEALTH HAZARD CHARACTERIZATION

All the toxicological information and data are taken essentially from papers published by WHO (1991), IARC (1979, 1987) and ATSDR (1999). Most of data correspond to γ-HCH exposure but there are also some studies on HCH exposure.

4.1/ Toxicokinetics

4.1.1/ Absorption

Evidence exists that humans absorb γ-HCH vapour or dust via inhalation. There are no specific studies that have quantified the rate or extent of absorption of the HCH isomers following inhalation exposure.

HCH is absorbed following oral exposure in humans and animals. Various studies have demonstrated the rapid absorption of γ-HCH from the gastrointestinal tract.

The proportion of the applied dose absorbed into the systemic circulation in 6 hours was 5% of the dose applied in acetone and 60% of the applied dose in a formulation based on white spirit (Dick et al. 1997a). γ-HCH absorption was reported to be 15–25% in 24 hours for the formulations that contained white spirit as the predominant solvent, 3% in 24 hours from an aqueous spray and <1 % in 24 hours for the acetone preparation (Dick et al. 1997b).

4.1.2/ Distribution

The distribution of HCH isomers in humans and animals is primarily in the adipose tissue but also in the brain, kidney, muscle, lungs, heart, spleen, liver and blood (Baumann et al. 1980; Siddiqui et al. 1981). Placental transfer of HCH in humans has been well documented (Saxena et al. 1981).

4.1.3/ Metabolism

In animals, γ-HCH appears to be transformed by hepatic enzymes to form chlorophenols, chlorobenzene, chlorocyclohexanes, chlorocyclohexanols and conjugates of mercapturic acid, glucuronide and sulfate (Chadwick & Freal 1972; Chadwick et al. 1978; Engst et al. 1979; Kujawa et al. 1977).

4.1.4/ Elimination and excretion

The excretion of HCH isomers and their metabolites is primarily through the urine. The isomers have also been detected in breast-milk (Ejobi et al. 1996;

Schoula et al. 1996) and semen (Szymczynski & Waliszewski 1981). The primary urinary metabolites are chlorophenols and epoxides.

The metabolites 2,3,5-, 2,4,6- and 2,4,5-trichlorophenol accounted for almost 57.7 % of the γ-HCH metabolites identified in the urine collected during the last 2 hours of workers' shifts. Other urinary metabolites identified included other trichlorophenols, dichlorophenols, tetrachlorophenols and dihydroxychlorobenzenes. Pentachlorophenol has also been identified as a urinary metabolite in humans following occupational exposure (Engst et al. 1979).

4.2/ Effects on laboratory animals

4.2.1/ Hepatic effects

Numerous studies have demonstrated hepatic effects of lindane on animals. An increase in cytochrome P-450 concentration has been reported in rats following inhalation of lindane aerosol (5 mg/m^3) for 90 days, but the level returned to control values after a 4-week recovery period (Oldiges et al. 1983).

Significant increases in hepatic microsomal cytochrome P-450 levels and increases in hepatic microsomal superoxide anion production and cytoplasmic superoxide dismutase activity and lipid peroxidation were found in Wistar rats fed diets containing 1.8 mg/kg bw per day γ-HCH for 15 or 30 days (Barros et al. 1991). Focal degeneration of hepatocytes was noted in rabbits given γ-HCH at a dose of 7 mg/kg bw per day by gavage for 4 weeks (Grabarczyk et al. 1990; Kopec-Szlezak et al. 1989). Rabbits treated with lindane at 4.21 mg/kg bw per day by gavage for 28 days exhibited a significant increase in plasma alkaline phosphatase and alanine aminotransferase activities immediately following initiation of dosing; these activities returned to control levels by day 14 (Ceron et al. 1995). Aspartate aminotransferase activity also increased immediately following dosing and remained elevated for up to 7 days post-exposure (day 35). Lindane residues were detected in the blood.

Exposure to lindane for 12 weeks resulted in increases in liver microsomal mixed-function oxidase activity in rats and mice and a significant increase in absolute and relative liver weights in female rats fed 10.6 and 32.3 mg/kg bw per day and male and female CF1 mice fed 21.1 mg/kg bw per day; histopathological examinations were not performed (Oesch et al. 1982). Liver centrilobular hypertrophy increased in a dose-dependent manner beginning at 0.4 mg/kg bw per day in Wistar rats exposed in their diet for 12 weeks (Suter 1983). Liver cell lipospheres were reported in rats fed γ-HCH at 2.5 mg/kg bw per day in the diet for 32 weeks (Ortega et al. 1957). In mice, administration of γ-HCH at 90 mg/kg bw per day in the diet for 24 weeks was reported to result in centrilobular hypertrophy (Ito et al. 1973).

Chronic exposure of rats to 7–8 mg/kg bw per day γ-HCH in the diet for 38–70 weeks was reported to result in liver necrosis and fatty degeneration (Fitzhugh et al. 1950). A dose-related increase in periacinal hepatocytic hypertrophy was seen in Wistar rats given lindane at 7–8 mg/kg bw per day in the diet for 104 weeks (Amyes 1990). However, no liver effects were reported in dogs exposed to 2.9 mg/kg bw per day for 104 weeks (Rivett et al. 1978).

4.2.2/ Neurotoxic effects

Neurotoxic effects have been reported in several animal species exposed by ingestion to a single dose of γ-HCH. Longer exposures to lower doses of γ-HCH were reported to result in significantly altered Skinner box behaviour (operant conditioning) in a small number of rats exposed to 2.5 mg/kg bw per day for 40 days (Desi 1974) and significantly reduced nerve conduction velocity in rats exposed to 25.4 mg/kg bw per day for 30 days (Muller et al. 1981). The latter study did not examine any behavioural parameters.

4.2.3/ Haematological effects

Animals appear to be less sensitive to induction of adverse haematological effects by γ-HCH, but comparison between humans and animals is difficult because limited data is available. No haematological effects were noted in beagles exposed to γ-HCH at 12.5 mg/kg bw per day in the diet for 32 weeks or to 2.9 mg/kg bw per day in the diet for 104 weeks (Rivett et al. 1978). Twelve-week studies on rats, using lower doses (10 mg/kg bw per day), support this finding (Suter 1983). In another study, however, following 10 days of exposure to 10 or 20 mg/kg bw per day, dose-dependent reductions were noted in bone marrow cellularity, granulocyte-macrophage progenitor cells and pluripotent bone marrow stem cells (Hong & Boorman 1993).

4.2.4/ Immunotoxic effects

Some evidence of possible immunotoxic effects of γ-HCH is available from animal studies. Immunosuppression, as measured by decreased agglutinin titres against typhoid vaccine and Salmonella vaccine, was reported in rats exposed by gavage to γ-HCH at 6.25 and 25 mg/kg bw per day for 5 weeks (Dewan et al. 1980) and in rabbits exposed by capsules five times each week to 1.5, 6 and 12 mg/kg bw per day for 5–6 weeks (Desi et al. 1978). The primary antibody response to sheep red blood cells was suppressed in albino mice after exposure to 9 mg/kg bw per day γ-HCH in the diet for 12 weeks (Banerjee et al. 1996). Suppression of secondary antibody response was also observed after 3 weeks' exposure to γ-HCH at 9 mg/kg bw per day and after 12 weeks' exposure to lindane at 5.4 mg/kg bw per day. A biphasic dose-dependent immunological effect of γ-HCH on components of cell- and humoral-mediated immunity, characterized by initial stimulation followed by immunosuppression, was reported in mice fed γ-HCH at 0.012, 0.12 or 1.2 mg/kg bw per day for 24 weeks (Meera et al. 1992). In addition, histological examinations revealed reduced lymphocyte populations in the thymus and lymph nodes and a reduction in overall cellularity in the spleen and necrosis of the thymus at 1.2 mg/kg bw per day. Based on immunological effects of γ-HCH on components of cell- and humoral-mediated immunity in mice, an intermediate MRL of 1.10^{-5} mg/kg bw per day has been calculated from the LOAEL of 0.012 mg/kg bw per day (Meera et al. 1992).

4.2.5/ Renal dysfunction

Male rats exposed for 2 years to lindane in their diet exhibited hyaline droplets in the renal proximal tubules at 0.07 mg/kg bw per day, and pale kidneys, increased kidney weights and urine volumes, and higher urinary protein excretions and tubular necrosis at 7 mg/kg bw per day (Amyes 1990). Hyaline droplet formation also occurred in a dose-dependant manner in rats treated with lindane at 0.02–10 mg/kg bw per day in their diets for 12 weeks (Suter 1983). Dose-dependent incidents of renal tubular distension and degeneration were seen in this study, beginning at a dose of 2 mg/kg bw per day. These results indicate that damage to male rat kidneys by γ-HCH may be caused by α-2-microglobulin, which is not present in humans. Thus, it is unlikely that humans are at risk of developing this type of pathology from γ-HCH (USEPA 1991).

4.2.6/ Reproductive effects

Female mink treated with 1 mg/kg bw per day γ-HCH in their diet from 6 weeks before mating until weaning showed a decrease in receptivity to a second mating and a decrease in whelping rate, although litter size was not affected (Beard et al. 1997). This decreased fertility effect was primarily a result of embryo mortality after implantation. Mouse dams treated with γ-HCH (6.2 mg/kg bw) during gestation days 6–12 had increased numbers of resorbed fetuses (Sircar & Lahiri 1989). A lack of implantation sites and pup deaths were observed following treatment with 10.8 mg/kg bw per day on gestation days 1–4 and 3.6 mg/kg bw per day on gestation days 14–19, respectively. Statistically significant increases in the glycogen content of the uterus, cervix and vagina (but no increase in organ weight) were reported in female rats exposed to γ-HCH at 20 mg/kg bw per day in the diet for 30 days (Raizada et al. 1980).

Anti-estrogenic properties were found in female rats given oral gavage doses of 10 mg/kg bw per day γ-HCH for 15 weeks (Chadwick et al. 1988). These responses were not seen at 5 mg/kg bw per day. Overiectomized rats exposed for 5 days and sexually immature female rats exposed for 7 days to 40 mg/kg bw per day lindane showed no effects on the number of estrogen and estrogen-dependent progesterone receptors (Laws et al. 1994). Thus, the anti-estrogenic effects of lindane in reproductive tissue do not appear to be due to direct action on estrogen receptors or its induction of progesterone receptors. Female rabbits exposed to γ-HCH at 0.8 mg/kg bw per day, 3 days per week for 12 weeks, had a reduced ovulation rate (Lindenau et al. 1994). However, rabbits given the same treatment regime followed by artificial insemination exhibited no effects on the fertilization rate or on pre- or post-implantation losses (Seiler et al. 1994). In male rats, oral administration of 6 mg/kg bw for 5 days or a single dose of 30 mg/kg bw of γ-HCH resulted in a reduction in the number of testicular spermatids and epididymal sperms of both treated groups 2 weeks after the last treatment. Histological examination by electron microscopy revealed ballooning of the Sertoli cells with fragmentation or loss of organelles. Similarly, Shivanandappa & Krishnakumari (1983) reported testicular atrophy, degeneration of seminiferous tubules and disruption of sperma-

togenesis in male rats fed 75 mg/kg bw per day γ-HCH for 90 days. Significant reductions in the relative weight of testicles and epididymis, spermatid and sperm counts and testosterone levels were observed in pubescent or adult rats fed milk as neonates from dams gavaged with 6mg/kg bw γ-HCH on lactation day 9 or 14 or 1 mg/kg bw on lactation days 9–14 (Dalsenter et al. 1997b). Histopathological observations included a reduction in Leydig cell numbers and spermatogenesis. However, fertility, measured by impregnation of female rats, was unaffected. Rats exposed to approximately 10 mg/kg bw per day for four generations showed no adverse reproductive effects (Palmer et al. 1978b).

4.2.7/ Developmental effects

When mink were treated with 1 mg/kg bw per day γ-HCH in their diet (Beard et al. 1997), the proportion of embryos lost after implantation was increased. In another study, γ-HCH was administered to pregnant mice by gastric intubation on day 12 of gestation. At doses of 30 and 45 mg/kg bw in C57BL/6J mice, significant decreases in fetal weight, fetal thymic weight and placental weight were observed (Hassoun & Stohs 1996a). When given to DBA/2J mice at a dose of 45 mg/kg bw, γ-HCH caused significant reduction in fetal and placental weight. No malformations in the fetuses of either strain of mice were observed, even though the administered doses caused maternal deaths. Increases in the production of lipid metabolites in maternal sera and amniotic fluids were found to parallel the observed fetotoxicities. Superoxide production, lipid peroxidation and DNA-single strand breaks increased in fetal and placental tissues 48 hours after administration of single dose of 30 mg/kg bw γ-HCH to pregnant mice on day 12 of gestation (Hassoun & Stohs 1996b). Significant increases in lipid peroxidation also occurred in fetal livers collected on day 18 of gestation. Thus, it was suggested that fetotoxic effects of γ-HCH may be due to induced oxidative stress, enhanced lipid peroxidation, and DNA-single strand breaks in the fetal and placental tissues of mice. In another study, γ-HCH given to rat dams during gestation and lactation did not cause developmental effects in the pups (Srinivasan et al. 1991). When lactating female rats were treated orally with a single dose of 6 mg/kg bw γ-HCH on day 9 or 14, or 1 mg/kg bw on days 9–14 of lactation, the testosterone level of the male offspring was reduced 50% at puberty (day 60) compared to the control group (Dalsenter et al. 1997a). When the offspring reached adulthood (day 140 post-natal), the relative testicular weight was significantly reduced. A dose-related increase in the incidence of fetuses with an extra 14th rib was reported in CFY rats exposed to 5, 10 or 20 mg/kg bw γ-HCH by gavage during gestation days 6–15; statistical significance was attained only at 20 mg/kg bw (Palmer et al. 1978a). The incidence of fetuses with an extra 13th rib was statistically increased in rabbits exposed to 20 mg/kg bw γ-HCH by gavage during gestation days 6–18 (Palmer et al. 1978a). In both rats and rabbits, the incidences of extra ribs were within or just greater than the ranges recorded for the control groups, and thus may not be sufficient evidence of teratogenicity caused by exposure to γ-HCH. No effects on embryonic development were seen in rabbits treated by oral gavage with 0.8 mg/kg

bw lindane three times per week for 12–15 weeks before artificial insemination and throughout gestation (Seiler et al. 1994). Regional changes in brain noradrenaline, serotonin and dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) levels were noted in suckling rats treated with 20 mg/kg bw per day γ-HCH as a single dose (Rivera et al. 1991). Alterations in levels of brain dopamine, serotonin, γ-aminobutyric acid, glutamate, glutamate decarboxylase and noradrenaline were seen in various areas of the brains of female rat pups treated with technical grade HCH at 10 mg/kg bw per day for 60 days (Nagaraja & Desiraju 1994). In addition, epileptiform seizures have been reported in male rats fed with milk from dams gavaged with 20 mg/kg bw γ-HCH on postnatal days 3–15 (Albertson et al. 1985). These data suggest that γ-HCH can be transferred in the dam's milk and elicit neurological effects in the offspring. It is not possible to determine the doses received by the pups. No clinical signs of behavioural effects were seen in suckling Wistar rats treated once with 20 mg/kg bw lindane by gavage at postnatal days 8, 15, 22 or 29, although regional changes in brain noradrenaline and serotonin were seen, with differential effects depending on age at the time of exposure (Rivera et al. 1991). No significant changes were seen in lipid peroxidation in brain tissue from rats treated for 90 days with 90 mg/kg bw per day lindane in food, indicating that the tonic convulsions observed throughout the exposure period were probably not brought on by oxidative stress in the brain (Arisi et al. 1994).

Exposure to low levels of lindane corresponding to those encountered in contaminated vegetables (80–250 µg/kg) or in contaminated tap water (0.02 µg/l) were studied in rats by Pages et al. (2000). Rats were exposed for 12 weeks at 1.7, 3.4, 6.8 µM in drinking-water *in utero*, during lactation or at weaning. No mortality was observed but growth rate was affected. Among rats exposed to 6.8 µM, only those contaminated *in utero* or during lactation showed a significantly lower body weight. The spermatozoid number was decreased, the mobility rate dropped to about 40%, and testosterone levels also showed a significant decrease.

4.2.8/ Carcinogenic effects

The carcinogenicity of lindane was tested by oral administration in six experiments in mice. It produced benign and malignant liver tumours in animals of both sexes in two experiments, one of which involved only small groups of animals. The results of a third experiment suggested hepatocarcinogenicity but were inadequately reported. The results of a fourth experiment also suggested hepatocarcinogenicity but were considered inadequate because of the low number of control animals used. The other experiments were considered inadequate for an evaluation of carcinogenicity. Lindane was also tested in three feeding studies in rats: two were considered inadequate, while in the other a slight excess of thyroid tumours was observed in females. Lindane was tested inadequately in mice by skin application and by subcutaneous and intraperitoneal administration (IARC 1979).

More recent studies have shown that information concerning the carcinogenic effects of γ-HCH following chronic feeding exposure is equivocal. No statistically significant increases in endocrine, thyroid, pituitary, adrenal gland, liver or ovary

tumours were observed in Wistar rats fed 0.07–32 mg/kg bw per day γ-HCH for 104 weeks (Amyes 1990); however, poor survival rates limit the significance of these results. On the other hand, hepatocellular carcinomas were reported in CF1 and B6C3F1 mice exposed to 13.6–27.2 mg/kg bw per day in the diet for 104 weeks (Wolff et al. 1987). In addition, hepatocellular carcinomas have been found in (YS/UY)F-1 mice exposed to 27.2 mg/kg bw per day in the diet for 96 weeks (Wolff et al. 1987); this strain of mouse has dominant mutation at the agouti locus (Avy) that results in an increased susceptibility to the formation of strain-specific neoplasms.

4.3/ Health effects in humans

Vomiting and nausea are the usual manifestations in humans following lindane ingestion (Sunder Ram Rao et al. 1988).

There are no data on hepatic effects reported for individuals who have inhaled or ingested γ-HCH or applied it to their skin.

In humans, the most commonly reported effects associated with oral exposure to γ-HCH are neurological. Most of the information is from case reports of acute γ-HCH poisoning. Seizures and convulsions have been observed in individuals who have accidentally or intentionally ingested γ-HCH in insecticide pellets, liquid scabicide or contaminated food (Davies et al. 1983; Harris et al. 1969; Munk & Nantel 1977; Powell 1980; Starr & Clifford 1972; Storen 1955).

Abnormal EEG patterns (increased variation in the frequency and amplitude of wave patterns or more serious changes without specific EEG signs) have been reported in 16 of 37 workers following exposure to γ-HCH for 0.5–2 years in a fertilizer plant (Czegledi-Janko & Avar 1970).

Human data suggest that γ-HCH has the potential to induce adverse haematological effects, but establishing a causal relationship has been difficult owing to a lack of personal exposure data. Aplastic anaemia was reported in a boy exposed to γ-HCH used as an insecticide in his home and in a man exposed at work (Rugman & Cosstick 1990). The anaemia was reversible and did not occur in other family members. The levels and routes of exposure are not known, although they are presumed to be inhalation and dermal. Other haematological abnormalities, including isolated instances of leukopoenia, leukocytosis, granulocytosis, eosinophilia, monocytosis and thrombocytopenia, have been reported following chronic human occupational exposure to γ-HCH (Brassow et al. 1981; Jedlicka et al. 1958). Exposure concentrations were not specified in these studies and concomitant dermal exposure probably occurred.

Aplastic anaemia was documented in a man who applied γ-HCH to his skin for 3 weeks for treatment of scabies (Rauch et al. 1990). Reduced haemoglobin and haematocrit values and a nearly complete absence of red blood cell precursors in the bone marrow were reported in a 2-year-old boy exposed to a family dog that was dipped regularly in mange treatment containing 12% γ-HCH (Vodopick 1975).

Evidence of renal dysfunction has not been observed in humans exposed to HCH by any route.

No studies could be found proving reproductive or developmental effects in humans following oral exposure to HCH.

No studies could be found regarding the carcinogenicity of the individual isomers of HCH or following ingestion by humans. The human oral carcinogenicity assessment for γ-HCH is currently under review (USEPA (IRIS) 1988).

4.4/ Critical outcomes and existing reference values

IARC (1987) has concluded that for the technical grade and α-HCH there is sufficient evidence for carcinogenicity in animals, whereas this evidence is limited for the β- and γ- isomers. There is inadequate evidence for their carcinogenicity in humans. HCHs are classified in group 2B as possibly carcinogenic to humans. However, the European Union and USEPA have not classified HCH as carcinogenic to humans.

JMPR established a temporary ADI of 0.001 mg/kg bw for lindane in 1997, based on a NOAEL of 0.5 mg/kg bw established in a two-year toxicity and carcinogenicity study in rats and using a safety factor of 500.

Lindane is not classified as genotoxic by the European Union.

Reference values for various exposures and their indicators are presented in Tables 3.2 and 3.3.

Table 3.2. Reference values for lindane

Biological medium	Reference values
Blood	20 µg/l [a]
Plasma or serum	25 µg/l [a]

[a] Moment of the sample: at the end of the exposure (INRS 1992, 1997, 2001).

Source: INERIS 2002.

Table 3.3. Reference toxicological values for lindane

Source	Exposure route	Uncertainty factor used	Reference value	Year of evaluation
ATSDR	Oral: acute	100	MRL: 0.01 mg/kg per day	1999
ATSDR	Oral: subchronic	1000	MRL: 1×10^{-5} mg/kg per day	1999
USEPA	Oral: chronic	1000	RfD:[a] 3×10^{-4} mg/kg per day	1988
JMPR		500	Temporary ADI: 0.001 mg/kg	1997

[a] RfD : Oral reference dose.

Source: INERIS 2002.

5/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

γ-HCH is rapidly absorbed by the oral route and undergoes extensive metabolism, mainly in the liver.

Animal studies have revealed neurotoxic, hepatic and reproductive effects and immunotoxicity in mice. In humans, poisoning incidents have generally been associated with significant misuse of the compound. The most common signs of toxicity following oral ingestion were seizures, convulsions, vomiting and dizziness. Human data suggest that γ-HCH has a potential to induce haematological effects (aplastic anaemia), but establishing a causal relationship has been difficult owing to a lack of personal exposure data.

It is known that large reservoirs of HCH exist in the environment, indicating a potentially long interval between any control action taken and its effects on environmental levels. The health hazard characterization has identified a range of health effects related to γ-HCH isomers by the oral route. Some might be relevant to observed environmental exposures. The oral route is the most relevant for LRTAP sources. Taking into account the uncertainties of the information, and specifically the level of exposure at which human health effects can happen, HCH may be considered a possible risk to health through LRTAP.

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CHAPTER 4/ HEXACHLOROBENZENE

1/ INTRODUCTION

Hexachlorobenzene (HCB) is a chlorinated hydrocarbon industrial chemical. Although it is not currently manufactured as a commercial end-product in the United States and other developed countries, it is formed as a waste product in the production of several chlorinated hydrocarbons such as tetrachloroethylene, trichloroethylene and carbon tetrachloride. In 1972, HCB produced as a by-product during the production of other chlorinated chemicals was estimated to range from 1 123 500 kg to 2 224 900 kg (IARC 1979). HCB is contained as a contaminant in some pesticides such as pentachloronitrobenzene and pentachlorophenol. Five major pesticides (chlorothalonil, chlorthal, pentachlorophenol, picloram and quintozene) in current use contain up to 0.3% HCB as an impurity. The presence of HCB in the environment is also due to its previous use as a fungicide (Beyer 1996).

HCB is also released into the environment through its contiuing use in developing countries and improper storage or disposal in developed countries (Dewailly et al. 1991).

Another minor source of HCB releases to the air comes from the use of pyrotechnic mixtures that produce white obscurant screening smokes (Karlsson et al. 1991). These screening smokes are used by the military to obscure vision and hide targets, and are used by civilian firefighters during training.

HCB is banned as a chemical for production and use, except in one country with an economy in transition. However, HCB also occurs as combustion by-product, and its emission and re-emission from soil and water are still relatively high in both Europe and North America.

Long-range transport plays a significant role as a means of redistributing HCB throughout the environment. Long-range global transport of HCB released anywhere in the world can occur via atmospheric or oceanic systems, and this transport plays a significant role in the HCB budget in the European Region. Similar transboundary transport is monitored in North America. Human health problems caused by HCB are of special concern owing to its various effects on different physiological systems, inducing mutagenic, teratogenic and carcinogenic phenomena. HCB is a very persistent environmental chemical owing to its chemical stability and resistance to biodegradation (ATSDR 2000). This substance is already included in the UNECE/LRTAP Protocol on POPs (Annexes 1 and 3).

2/ POTENTIAL FOR LRTAP

2.1/ Physicochemical properties allowing atmospheric transport

The structural formula of HCB is shown in Fig. 4.1 and some of its physical and chemical properties are listed in Table 4.1. At ambient temperature, HCB is a white crystalline substance that is virtually insoluble in water but soluble in ether, benzene and chloroform (NTP 1994). It has a high octanol/water partition coefficient, low vapour pressure, moderate Henry's Law constant and low flammability. Technical grade HCB is available as a wettable powder, liquid and dust (NTP 1994).

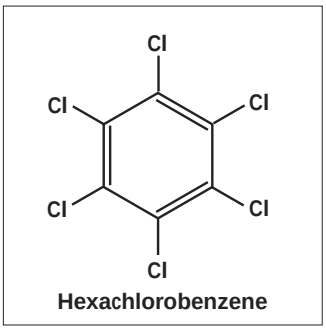

Fig. 4.1. Structural formula of HCB, CAS: 118 74 1

Table 4.1. Physical and chemical properties of HCB

Property	Value
Relative molecular mass	284.79
Melting point (°C)	230
Boiling point (°C)	322 (sublimates)
Density (g/cm^3 at 20 °C)	1.5691
Vapour pressure (Pa at 25 °C)	0.0023
Log octanol/water partition coefficient	5.5
Water solubility (mg/litre at 25 °C)	0.005
Henry's Law Constant (calculated)[a] (Pa· mol/m^3)	131
Conversion factors	1 ppm = 11.8 mg/m^3 1 mg/m^3 = 0.08 ppm

[a] The Henry's Law Constant was calculated using the tabled values for aqueous solubility and vapour pressure.

Source: ATSDR 1990; Mackay et al. 1992.

Technical grade HCB contains about 98% HCB, 1.8% pentachlorobenzene and 0.2% 1,2,4,5-tetrachlorobenzene (IARC 1979) and it is known to contain a variety of impurities, including hepta- and octachlorodibenzofurans, octachlorodibenzo-*p*-dioxin and decachlorobiphenyl (Goldstein et al. 1978; Villanueva et al. 1974).

2.2/ Persistence and bioaccumulation

HCB belongs to the most persistent environmental pollutants because of its chemical stability and resistance to degradation. If released to the atmosphere, HCB exists primarily in the vapour phase and degradation is extremely slow. Half-life es-

timations for HCB in the atmosphere are highly variable, ranging from 0.63 years in tropical/subtropical regions, to 1.94 years in temperate/boreal regions, to 6.28 years in polar regions. A calculated half-life of 1.69 years was attained from a measured hydroxyl rate constant (2.7×10^{-14} cm^3/molecule-second). Long-range global transport is possible from the temperate to the polar regions. Physical removal of HCB from the air may occur via washout by rainfall or snowfall, or through dry deposition. If released to water, HCB will partition from the water column into sediment and suspended particulate matter.

In water, HCB is a persistent chemical not readily degraded by either abiotic or biotic processes. The half-life of HCB is estimated to range from 2.7 to 5.7 years in surface water and from 5.3 to 11.4 years in groundwater. Volatilization from the water column is moderately rapid; however, the compound's strong adsorption to particulates and organic matter in water can result in long persistence in the sediment. If released to soil, HCB can volatilize from the soil surface relatively quickly, but will be strongly adsorbed to organic matter and is generally considered immobile with respect to leaching. Its half-life in soils is estimated to range from 3 to 6 years.

HCB is widely distributed in the environment, by virtue of its mobility and resistance to degradation, although slow photodegradation in air and microbial biodegradation in the soil-water-bottom sediment system do occur. It has been detected in air, water, sediment, soil and biota from around the world. HCB is a bioaccumulative substance (BCF values range from 375 to >35 000) and biomagnification of HCB through the food chain has been reported.

2.3/ Monitoring

HCB is moderately volatile, but is usually not detected in ambient air samples except at very low concentrations. Ambient air sampling was conducted by the EPA at selected locations in the United States from 1976 to 1979. In 1976, 49% of the 43 composite samples collected in four locations contained detectable concentrations of HCB, with a mean value of 0.1 ng/m^3. In 1977, 12% of the 34 samples collected in three locations contained HCB, with a mean concentration of 1.5 ng/m^3. In 1978, the compound was not detected in any of the 33 samples collected at three locations and in 1979, HCB was detected in 31% of the 89 samples collected in eight locations, with a mean of 0.5 ng/m^3 (detection limit 0.1 ng/m^3) (USEPA 1985). Eisenreich et al. (1981) reported atmospheric concentrations of HCB in the Great Lakes region ranging from 0.09 to 0.28 ng/m^3. Results of airborne samples collected between 1990 and 1993 from the Great Lakes region by the Integrated Atmospheric Deposition Network, provided by Hoff et al. (1996) are presented in Table 4.2.

From July 1988 to September 1989, 143 air samples were collected at Egbert, Ontario and analysed for PCB and organochlorine concentrations. HCB was detected at concentrations ranging from a minimum of 0.04 pg/m^3 to a maximum of 640 pg/m^3 (annual mean >54 pg/ m^3) (Hoff et al. 1992). Inhalation exposure was estimated to be 300 pg/m^3 in urban air (Burton & Bennett 1987). Poissant et al.

Table 4.2. Annual mean concentrations of HCB in airborne samples from the Great Lakes region (1990–1993)

Air sampling location	Annual mean gas-phase concentrations of HCB (pg/m^3)	Annual mean particulate-phase concentrations of HCB (pg/m^3)
Lake Superior near Eagle Harbor, Michigan	98	0.2
Lake Michigan near Sleeping Bear Dunes, Michigan	120	0.1
Lake Erie near Sturgeon Point, New York	80	0.2
Lake Ontario near Point Petre, Ontario	130	< 0.1

(1997) measured HCB in air in Villeroy, Quebec in 1992 and found mean and median concentrations of 36.68 and 30.94 pg/m^3, respectively, from 56 air samples.

Four air samples per day (taken at 6-hour intervals) were taken for 7 days in a meteorological station located in a semi-rural area outside Lancaster, England. The minimum, maximum and mean concentrations of HCB in these samples were < 28.8, 76.1, and 39.3 pg/m^3, respectively. The authors found an absence of a cycle in the concentrations of HCB, and concluded that the compound was breaking through the polyurethane foam plugs owing to its relatively high vapour pressure (Lee et al. 2000). HCB air concentrations have also been measured in urban and rural areas in France. Atmospheric fallout from an urban area (Paris) and a rural area (La Ferte-sous-Jouarre) was collected in raw form as bulk precipitation (Chevreuil et al. 1996). The results of the analysis are summarized in Table 4.3:

Table 4.3. HCB concentrations in atmospheric fallout from urban and rural areas in France

Sample	HCB concentration (ng/l)	
	February–July 1992	January– September 1993
Rural fallout	2.5–4.5	0.3–4
Urban fallout	1.8–17	0.3–5.6

The mean concentrations of HCB in precipitation samples collected in the Great Lakes region from 1986 to 1991 ranged from 0.145 ng/l at Sibley Park on Lake Superior, to 0.108 ng/l at Pelee Island in Lake Erie, to 0.174 ng/l at Wolfe Island in Lake Ontario (Chan et al. 1994). The mean and median concentrations of HCB from eight precipitation samples collected from Villeroy, Quebec in 1992 were 0.04 and 0.05 ng/l, respectively (Poissant et al. 1997). Precipitation samples collected between 1990 and 1993 from the Great Lakes region by the Integrated Atmospheric Deposition Network were analysed (Hoff et al. 1996). The annual mean concentration of HCB in these precipitation samples is presented in Table 4.4.

Extremely high concentrations of HCB in air have been detected in areas close to production and disposal sites in both outdoor and indoor air. Mann et al. (1974) measured HCB concentrations ranging from 70 to 23 296 ng/m^3 near chlorinated solvent and pesticide manufacturing facilities; air levels near a chemi-

Table 4.4. Annual mean concentrations of HCB in precipitation samples from the Great Lakes region (1990–1993)

Sampling location	Annual mean concentrations of HCB in precipitation samples (ng/l)
Lake Superior near Eagle Harbor, Michigan	0.1
Lake Michigan near Sleeping Bear Dunes, Michigan	0.06
Lake Erie near Sturgeon Point, New York	0.04
Lake Ontario near Point Petre, Ontario	0.3

cal waste landfill were as high as 16 000 ng/m^3 (USEPA 1975). HCB has been detected at 11 000 ng/m^3 in flue gas effluents from a municipal refuse-fired steam boiler in Virginia, and at 9.5 ng/m^3 in flue gas effluents from a refuse-derived fuel fired power plant in Ohio (Tiernan et al. 1985). Air concentrations of HCB inside industrial plants can be as high as 150 000 ng/m^3 (Currier et al. 1980); air concentrations inside a pesticide production facility were measured at 22 000 ng/m^3 (Davis & Morgan 1986).

Wet deposition (deposition via rain or snowfall) is the primary mechanism for transport of HCB from the atmosphere to aquatic and terrestrial systems in Canada (Eisenreich & Strachan 1992). For example, it is estimated that long-range transport and total deposition to the Canadian environment is approximately 510 kg/year, an amount that is similar to that from all other sources combined (Government of Canada 1993).

2.3.1/ Modelling

Spatial distribution and pollution levels in European countries were assessed by MSCE-POP model calculation (Shatalov et al. 2001). The highest levels of emissions are simulated in some regions of Germany and the Russian Federation. One should note, however, the considerable role played by the global transport of HCB in the formation of pollution in Europe. For example, HCB transport by sea currents is important in the formation of air concentrations. The average HCB contents in various environmental media and relevant emission and deposition densities on a per country basis are shown in Table 4.5. In fact, to a large extent the resultant deposition densities are due to the impact of long-range transport. The relationship between deposition densities and emissions may serve as an indication as to whether the deposition flux of a given country is caused by its own emissions or it is produced by transport from other European countries. For example, the high emission flux in Germany suggests that depositions in this country are essentially caused by its own emissions. At the same time, the emission flux in Finland appears to be considerably less than in Germany although the deposition flux is nearly the same. This suggests that long-range transport from other countries is of great importance in the formation of depositions in Finland. More accurate quantitative estimates of transboundary transport should be calculated in future by "country-to-country" matrices. Correction of emission values from countries may result in considerable re-thinking as to the character of long-range transport.

Table 4.5. Mean depositions (dry + wet) and concentrations in natural media of European countries calculated for 1998

Country	Air (pg/m^3)	Soil (pg/g)	Water (ng/m^3)	Vegetation (ng/g)	Deposition flux (g/km^2 per year)	Total depositions (kg/year)	Emission flux (g/km^2 per year)	Total emissions (tonnes/ year)
Albania	53	38	5.67	0.18	0.15	4.46	1.88	0.06
Armenia	69	30	-	0.18	0.12	3.63	1.63	0.05
Austria	67	101	-	0.83	0.32	27.42	0.96	0.08
Azerbaijan	69	15	5.62	0.29	0.06	5.20	2.15	0.19
Belarus	83	89	-	0.85	0.17	35.09	2.33	0.48
Belgium	59	60	7.09	0.48	0.22	6.86	2.40	0.07
Bosnia and Herzegovina	54	59	7.24	0.36	0.16	8.03	0.99	0.05
Bulgaria	76	68	7.75	0.33	0.14	15.33	2.74	0.30
Croatia	59	55	6.94	0.38	0.18	10.88	1.28	0.08
Cyprus	48	6	3.72	0.00	0.02	0.19	0.00	0.00
Czech Republic	69	67	-	0.54	0.17	13.32	2.75	0.22
Denmark	58	53	8.69	0.17	0.20	9.30	2.45	0.12
Estonia	73	89	11.17	0.99	0.22	10.04	1.56	0.07
Finland	51	122	9.56	2.08	0.25	83.35	0.38	0.12
France	56	62	5.73	0.57	0.21	113.91	2.34	1.29
Georgia	80	37	10.01	0.37	0.15	10.56	2.28	0.16
Germany	69	75	7.95	0.70	0.26	91.90	4.36	1.56
Greece	53	19	4.51	0.24	0.07	9.63	1.31	0.18
Hungary	71	96	-	0.45	0.31	28.58	3.31	0.31
Iceland	52	4	8.82	0.26	0.16	16.38	0.00	0.00
Ireland	43	54	6.14	1.43	0.13	9.81	0.63	0.05
Italy	60	58	4.96	0.29	0.16	48.33	2.61	0.80
Kazakhstan	45	10	4.65	0.19	0.01	5.17	1.21	0.74

Country	Air (pg/m^3)	Soil (pg/g)	Water (ng/m^3)	Vegetation (ng/g)	Deposition flux (g/km^2 per year)	Total depositions (kg/year)	Emission flux (g/km^2 per year)	Total emissions (tonnes/ year)
Latvia	77	86	12.34	0.95	0.20	12.81	1.99	0.13
Lithuania	76	75	9.46	0.84	0.19	12.64	2.67	0.18
Luxembourg	60	74	-	0.57	0.29	0.65	1.57	0.003
Malta	39	1	3.35	0.00	–0.04	–0.02	0.00	0.00
Netherlands	57	66	7.19	0.44	0.21	7.80	2.51	0.09
Norway	44	76	7.79	0.27	0.20	66.78	0.14	0.05
Poland	74	87	9.82	0.51	0.24	76.34	2.97	0.93
Portugal	50	49	4.36	0.30	0.06	5.42	1.61	0.15
Republic of Moldova	80	118	-	0.66	0.17	5.63	3.06	0.10
Romania	79	111	7.27	0.52	0.25	59.90	3.10	0.74
Russian Federation	68	99	9.44	1.84	0.18	657.52	2.64	9.85
Slovakia	72	90	-	0.48	0.33	15.97	2.43	0.12
Slovenia	65	90	9.45	0.63	0.31	5.68	0.84	0.02
Spain	57	42	4.47	0.28	0.11	52.90	2.34	1.17
Sweden	48	78	8.90	1.31	0.23	104.80	0.36	0.16
Switzerland	69	103	-	0.60	0.31	13.08	1.33	0.06
The former Yugoslav Republic of Macedonia	63	44	-	0.34	0.15	3.77	1.19	0.03
Turkey	66	8	6.61	0.03	0.05	37.65	0.00	0.00
Ukraine	82	157	7.39	0.53	0.21	123.45	3.48	2.10
United Kingdom	51	102	6.86	0.96	0.21	53.74	1.99	0.51
Yugoslavia	63	96	7.19	0.44	0.20	20.88	1.34	0.14

Source: Shatalov et al. 2001.

On the basis of model calculations for 1980–1998, the long-term dynamics of environmental compartment pollution was studied in different European countries. The analysis indicated that long-term accumulation processes and purification of natural media were strongly dependent on the geographical position of a country. To illustrate this dependence, a comparison of long-term variations of emissions and concentration in soil was carried out in the United Kingdom and the Czech Republic. The first country is an island to the west of other European countries and consequently less affected by prevailing winds, whereas the other is in the middle of the European continent. The reduction in soil concentrations in the United Kingdom is considerably slower than the reduction in emission (a 20-fold decrease in emissions during the period in question as opposed to an 8-fold decrease in soil concentrations). In the Czech Republic, on the other hand, the decrease in soil concentration is more rapid than the reduction in emissions (a 5-fold decrease in emissions versus a 10-fold reduction in soil concentrations). This fact can be explained by a drastic reduction in emissions in Austria and Germany to the west of the Czech Republic (the prevailing airborne transport being west to east (Holoubek et al. 2001).

3/ PATHWAYS OF LRTAP-DERIVED HUMAN EXPOSURE

3.1/ Significant sources and magnitude of human exposure

Based on estimates of mean exposure from various media, the general population is exposed to HCB principally through food (mean intakes for adults range from 0.0004 to 0.0028 μg/kg bw per day). Intakes are estimated to be considerably less for ambient air (3.4×10^{-5} to 2.1×10^{-4} μg/kg bw per day) and drinking-water (2.2×10^{-6} to 4.4×10^{-5} μg/kg bw per day).

Based on these intakes, it is estimated that the total average daily intake of HCB from food, air and drinking-water is between 0.0004 and 0.003 μg/kg bw per day.

Data on levels of occupational exposure to HCB are limited, but indicate that workers in some industries may be exposed to higher levels than the general population, particularly in the manufacture of chlorinated solvents and in the manufacture and application of chlorinated pesticides contaminated with HCB. In some instances, inappropriate manufacturing and waste management practices may expose nearby populations to higher levels of HCB than the general population. Exposures may also be elevated in some indigenous subsistence populations, particularly those that consume large quantities of food species near the top of the food chain.

Owing to the elimination of HCB in breast-milk, mean intakes by nursing infants are estimated to range from < 0.018 to 5.1 μg/kg bw per day in various countries.

4/ HEALTH HAZARD CHARACTERIZATION

4.1/ Toxicokinetics

4.1.1/ Absorption

There are few data on the absorption of HCB by humans. By comparing intake and faecal excretion of HCB in a single breast-fed infant, Abraham et al. (1994) estimated that absorption was virtually complete (greater than 99.7% at 1 month

of age and greater than 97% at 5 months). The concentrations of HCB in the diet and faeces of a single formula-fed infant were too low for reliable estimation of absorption (Abraham et al. 1994). The results of animal studies indicate that 80% or more of an oral dose of HCB (10–180 mg/kg bw) is absorbed if administered in an oil vehicle (Albro & Thomas 1974; Bleavins et al. 1982; Ingebritsen et al. 1981; Koss & Koransky 1975). In female rats treated with ^{14}C-HCB in oil, peak values of radioactivity were reached in 2–5 days. The absorption was poor (2–20%, depending on the dose) when the substance was given as an aqueous suspension (Koss & Koransky 1975). Little information was identified on dermal absorption, although it appears to be lower. Koizumi (1991) observed that after dermal application of approximately 2.5 mg ^{14}C-HCB in tetrachloroethylene to Fisher-344 rats for 72 hours, only 9.7% of the administered dose had been absorbed. No information on absorption via the lungs has been reported.

4.1.2/ Distribution

There are no experimental studies of tissue distribution of HCB in humans, although in a small autopsy study of members of the general population (Schechter et al. 1989) the highest levels were found in adipose tissue, the adrenals, bone marrow and liver, in that order. Laboratory studies in a number of animal species also indicate that the highest concentrations of HCB are accumulated in tissues with a high lipid content, such as adipose tissue, the adrenal cortex, bone marrow, skin and some endocrine tissues (thyroid, adrenals and ovaries) following ingestion or injection of HCB (Courtney 1979; Foster et al. 1993; Goldey et al. 1990; Ingebritsen 1986; Jarrell et al. 1993; Koss & Koransky 1975; Smith et al. 1987, 1994; Sundlof et al. 1982; Yang et al. 1978). No information was found on tissue distribution following inhalation or dermal exposure. HCB crosses the placenta, and is eliminated via the mother's milk in both animals and humans (Bailey et al. 1980; Bleavins et al. 1982; Courtney & Andrews 1985; Courtney et al. 1979; Goldey et al. 1990; Mendoza et al. 1975; Villeneuve et al. 1974).

4.1.3/ Metabolism

Metabolic transformation is not extensive in the wide range of species examined. The pathways of biotransformation of HCB have been reviewed by Debets & Strik (1979) and by Renner (1988). The metabolism of HCB operates via three distinct pathways. These are (*a*) oxidative pathways giving rise to phenolic metabolites including pentachlorophenol, tetrachlorohydroquinone and tetrachlorobenzoquinone; (*b*) a glutathione-conjugation pathway leading to pentachlorothiophenol, pentachlorothioanisoles and several other sulfur-containing metabolites; and (*c*) a minor pathway that yields lower chlorinated benzenes through reductive dechlorination. Metabolism occurs primarily in the liver, although dechlorination of HCB has also been demonstrated *in vitro* in enzyme preparations from the lung, kidney and small intestine (Mehendale et al. 1975).

The metabolism of HCB has been studied in rat, guinea-pig (Courtney 1979; Koss & Koransky 1976; Koss & Koransky 1978; Mehendale et al. 1975; Rozman

et al. 1981) and in monkey (Courtney 1979; Rozman et al. 1986). Dosing routes included gastric incubation and the intraperitoneal route, while dosing vehicles included oil and aqueous media. The monitoring for metabolic products of HCB has included excretory products and/or tissue residues for periods ranging from 28 to 40 days post-dosing. The findings were quite dissimilar among the studies. The most common finding was that less than 40% of the administered dose was recovered in the excretory products and the majority of the recovered dose was unchanged HCB.

4.1.4/ Elimination and excretion

The major metabolites found in the urine of rats, mice and guinea-pigs exposed to HCB by various routes in most studies are pentachlorophenol, tetrachlorohydroquinone and pentachlorothiophenol (Koss & Koransky 1978). (There is some question as to whether most of the latter compound detected in some studies was an analytical artefact from alkaline hydrolysis of the *N*-acetyl cysteine conjugate.) Other metabolites include tetra- and pentachlorobenzenes and thioanisoles, and tri- and tetrachlorophenols, both in free and conjugated forms. It has been reported that, after dietary exposure of male and female Wistar rats to HCB for 13 weeks, *N*-acetyl-*S*-(pentachloro-phenyl)cysteine was the most abundant metabolite via the conjugation pathway (89–92% of the total urinary metabolites collected over 24 hours, after one week of treatment). Mercaptotetrachlorothioanisole was also present, excreted as a glucuronide (Den Besten et al. 1994).

The excreta from male Wistar rats given 125 mg/kg bw on days 1 and 6 were collected for 12 days (Jansson & Bergman 1978). The faeces and/or urine contained HCB (about 4% of the total dose), pentachlorobenzene, pentachlorophenol, pentachlorobenzenethiol (both as such and as conjugates), methylthiopentachlorobenzene, tetrachlorobenzenedithiol and/or methylthiotetrachlorobenzenethiol (both as such and as conjugates), dichlorotetrakis(methylthio)benzene (trace amounts), hexakis(methylthio)benzene (trace amounts), bis(methylthio)tetrachlorobenzene, tetrachlorobenzenethiol (trace amounts) and methylthiotetrachlorobenzene (trace amounts). The compounds found in adipose tissue were HCB, pentachlorobenzene, pentachlorobenzenethiol, bis(methylthio) tetrachlorobenzene and pentachloroanisole.

Rizzardini & Smith (1982) administered 50 µmol HCB/kg bw to male and female rats by gavage in arachis oil for 103 days. Three urinary metabolites were identified, i.e. pentachlorophenol, 2,3,5,6-tetrachlorobenzene, 1,4-diol and pentachlorothiophenol (derived from mercapturate). The authors reported that female rats excreted several times more HCB metabolites than males.

Pentachlorophenol and pentachlorothiophenol have been detected in the urine of humans from the general population of Spain with high body burdens of HCB (To-Figueras et al. 1992).

A set of 53 individuals from a population highly exposed to airborne HCB were selected to study the elimination kinetics of this chemical in humans. The volunteers provided blood and 24-hour urine and faeces samples for analysis of

HCB and metabolites. The serum HCB concentrations ranged from 2.4 to 1485 ng/ml (mean ± SD, 124 ± 278), confirming that this population had the highest HCB blood levels ever reported. All analysed faeces samples contained unchanged HCB (range, 11–3025 ng/g dry weight; mean ± SD, 395 ± 629). The HCB concentration in the faeces strongly correlated with HCB in serum (r = 0.85; P < 0.001), suggesting a faeces/serum equilibrium compatible with a main pulmonary entrance of the chemical and low intestinal excretion of non-absorbed foodborne HCB. The equilibrium is also compatible with a non-biliary passive transfer of the chemical to the intestinal lumen. Two HCB main metabolites, pentachlorophenol and pentachlorobenzenethiol, were detected in 51% and 54% of faeces samples, respectively. All urine samples contained pentachlorophenol and pentachlorobenzenethiol. The comparison between faeces and urine showed that whereas daily urinary elimination of metabolites may account for 3% of total HCB in blood, intestinal excretion of unchanged HCB may account for about 6%, thus showing the importance of metabolism in the overall elimination of HCB. The elimination of HCB and metabolites by both routes, however, appears to be very small (< 0.05% per day) compared to the estimated HCB adipose depots. Features of HCB kinetics (i.e. nonsaturated intestinal elimination of HCB and excretion in faeces and urine of inert glutathione derivatives) may explain, in part, the absence of porphyria cutanea in this human population heavily exposed to HCB.

No reliable information on the elimination half-life of HCB in humans was found. Excretion of HCB by laboratory animals occurs mainly through the faeces regardless of the route of administration (ATSDR 1990; USEPA 1985). Both biliary excretion and non-biliary intestinal transfer contribute to faecal excretion (Ingebritsen et al. 1981; Richter & Schäfer 1981; Rozman et al. 1981; Sundlof et al. 1982). Reported half-lives for the elimination of an oral dose of HCB (doses were 3 mg/kg bw or less in these studies) are approximately one month in rats and rabbits, 10–18 weeks in sheep, pigs and dogs, and 2.5–3 years in rhesus monkeys (Avrahami 1975; Avrahami & Steele 1972; Rozman et al. 1981; Scheufler & Rozman 1984; Sundlof et al. 1982; Yamaguchi et al. 1986). HCB has been detected in the milk of several species, including humans, and the results of experiments with mice and ferrets indicate that the majority of the maternal body burden can be eliminated via the mother's milk (Bleavins et al. 1982; Courtney & Andrews 1985).

4.2/ Effects on laboratory animals

The critical effects induced by HCB in experimental animals comprise both non-neoplastic and neoplastic effects.

Repeated exposure to HCB has been found to cause a wide range of non-neoplastic effects in several species, with similar LOELs and NOELs for a number of end-points. In these studies, effects reported have included those on the liver in pigs and rats, on calcium metabolism in rats, on ovarian histopathology in monkeys, on immune function in mice and rats, on neurotransmitter levels in the hypothalamus of mink, on postnatal survival in mink and on neurobehavioural

development in rats. The range over which the various effects have been observed is quite narrow; the lowest LOELs range from 0.1 to 0.7 mg/kg bw per day, while the lowest NOELs range from 0.05 to 0.07 mg/kg bw.

Based on the induction of a variety of tumours in hamsters, rats and mice exposed by ingestion, there is sufficient evidence that HCB is carcinogenic in animals. The available evidence indicates that HCB has little or no genotoxic activity and is therefore unlikely to be a direct-acting (genotoxic) carcinogen. However, it was noted that tumours, some of which were malignant, have been induced in multiple species, at multiple sites, in some instances at doses that were not overtly toxic in other respects and that are within an order of magnitude of those that produce more subtle toxicological effects, or following subchronic exposure. Although there is some evidence to suggest that HCB may cause cancer by indirect mechanisms, the evidence is not definitive at this time and does not address all tumour sites.

4.3/ Health effects in humans

Most data on the effects of HCB on humans originate from accidental poisonings that took place in Turkey in 1955–1959, in which more than 600 cases of porphyria cutanea tarda were identified. In this incident, disturbances in porphyrin metabolism, dermatological lesions, hyperpigmentation, hypertrichosis, enlarged liver, enlargement of the thyroid gland and lymph nodes, and (in roughly half the cases) osteoporosis or arthritis were observed, primarily in children. Breast-fed infants of mothers exposed to HCB in this incident developed a disorder called pembe yara (pink sore), and most died within a year. There is also limited evidence that porphyria cutanea tarda occurs in humans with relatively high exposure to HCB in the workplace or in the general environment.

The few available epidemiological studies of cancer are limited by small size, poorly characterized exposures to HCB and exposure to numerous other agents, and are insufficient to assess the carcinogenicity of HCB to humans.

Grimalt et al. (1994) reported a small ecological study of cancer incidence (129 cases in all) in the inhabitants of a village in Spain located near a chlorinated solvents factory. There were statistically significant excesses of thyroid neoplasms and soft-tissue sarcomas in males, compared with the province as a whole, although these were based on only two and three cases, respectively. The exposures experienced by this population were somewhat unclear. Levels of HCB in ambient air and in the sera of volunteers were much higher in the village than in Barcelona (means of 35 ng/m^3 versus 0.3 ng/m^3 and 26 µg/litre versus 4.8 µg/litre, respectively) but the authors presented evidence that historical exposures had been much higher and indicated that all of the males with cancer for whom there were occupational histories had worked in the factory. Ambient air monitoring revealed that there were exposures to a variety of other compounds, including polychlorinated biphenyls, *p,p'*-DDE, chloroform, carbon tetrachloride, trichloroethylene and tetrachloroethylene, but at similar or lower levels than in the reference community.

There was no evidence of cutaneous porphyria in a cross-sectional study of the general population in Louisiana, United States, exposed to HCB through the im-

proper transport and disposal of hex waste. Nevertheless, plasma concentrations of HCB were significantly correlated with levels of coproporphyrin in the urine and of lactic dehydrogenase in the blood (Burns & Miller 1975).

No adequate epidemiological studies of cancer in populations exposed to HCB in the environment were found in the literature. Exposure to HCB as a cause of cancer in humans does not seem to have been reported, but exposure to this compound and other chlorinated aromatics should be included in future observations of porphyria cutanea tarda and cancer. The possibilities for good epidemiological studies of HCB exposure in relation to cancer and other effects seem to be limited.

4.3.1/ Occupational exposure

There have been case reports of workers developing porphyria cutanea tarda as a result of direct contact with HCB (Courtney 1979; Currier et al. 1980), although there was no association between exposure to HCB and porphyria cutanea tarda in three cross-sectional studies of very small populations of exposed workers (Burns et al. 1974; Currier et al. 1980; Morley et al. 1973).

Available epidemiological studies on the carcinogenicity of HCB in occupationally exposed humans are restricted to one study of a cohort of 2391 magnesium metal production workers in Norway. Although the incidence of lung cancer was significantly elevated compared to that of the general population, workers were exposed to numerous other agents in addition to HCB, including coal tar, asbestos and dust of metal oxides and chlorides (Heldaas et al. 1989).

Although infants may have a high intake of HCB via breast-milk for a short time, the TD_5 and TDI were considered to be protective of the health of this population (unless there are extreme exposures), because one of the long-term studies used in deriving these values included lactational exposure. However, it should be noted that the TD_5 and TDI values derived above should not be compared directly with intakes from breast-milk by nursing infants, since the guidance values are based on a lifetime intake whereas the duration of breast-feeding is relatively short.

4.3.2/ Critical outcomes and existing reference values

The WHO Task Group on Environmental Health Criteria for HCB (WHO 1997) concluded that the available data were sufficient to develop guidance values for non-neoplastic and neoplastic effects of HCB.

For non-neoplastic effects, based on the lowest reported NOEL (0.05 mg HCB/kg bw per day), for primarily hepatic effects observed at higher doses in studies on pigs and rats exposed by the oral route, and incorporating an uncertainty factor of 300 (× 10 for interspecies variation, × 10 for intraspecies variation and × 3 for severity of effect), a TDI of 0.17 µg/kg bw per day has been derived.

The approach for neoplastic effects is based on the tumorigenic dose TD_5, i.e. the intake associated with a 5% excess incidence of tumours in experimental studies in animals. Based on the results of the two-generation carcinogenicity bioassay in rats and using the multi-stage model, the TD_5 value is 0.81 mg/kg bw per day

for neoplastic nodules of the liver in females. Based on consideration of the insufficient mechanistic data, an uncertainty factor of 5000 was used to develop a health-based guidance value of 0.16 µg/kg bw per day.

IARC has classified HCB as a group 2B carcinogen (possibly carcinogenic to humans), based on inadequate evidence for carcinogenicity in humans and sufficient evidence for carcinogenicity in animals (IARC 1987).

A drinking-water guideline of 1 µg/litre was developed for HCB, based on an evaluation of the production of liver tumours in female rats and applying the linearized multi-stage model to calculate an excess life-time cancer risk of 10^{-5} (WHO 1993).

5/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

Long-range transport via atmospheric or oceanic systems plays a significant role in redistributing HCB throughout the environment, and is a very important item in the HCB budget throughout the European Region. Similar transboundary transport is found in North America. Accordingly, this pollutant must be considered within the framework of the UNECE/LRTAP Convention on POPs.

Alternatives should be found for any present uses of HCB. It is important to reduce the environmental burden of HCB by identifying the remaining sources and quantities of release to the environment from these sources, including point source emissions, waste disposal sites and production facilities, and applying appropriate manufacturing and waste disposal practices in order to decrease levels of HCB in the environment.

The health characterization of HCB has identified a number of human health effects of potential relevance for low-level chronic exposure via the oral route. To improve the risk assessment, more information is needed.

Human monitoring of HCB in blood and breast-milk should be undertaken to develop data representing exposure of the general population, in order to identify highly exposed populations and potential sources, and to enable interpretation of individual results in various European regions.

To gauge the efficacy of control measures, it would be valuable to monitor environmental levels and effects in locations where levels are higher than the global average. For assessing human health risk, the relevant end-point should be based principally on those neonatal effects in humans and other species that have been associated with ingestion of high doses of HCB through breast-milk.

It is recommended that techniques be developed to assess appropriately the risk to infant health from exposure to HCB and related compounds in breast-milk.

6/ ACKNOWLEDGEMENT

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CHAPTER 5/ HEPTACHLOR

1/ INTRODUCTION

Heptachlor is a non-systemic contact insecticide, used primarily against soil insects and termites. It has also been used against cotton insects, other crop pests and grasshoppers, and to combat malaria. Heptachlor is present as an impurity and is also a breakdown product of the pesticide chlordane. The use of heptachlor has been banned or severely restricted in many countries around the globe since the late 1970s, and current environmental concentrations are therefore principally the result of environmental recycling of historical use of the compound. Contemporary use of chlordane contaminated with heptachlor may be responsible for sporadic atmospheric inputs to the remote Arctic environment.

Heptachlor is already included in the UNECE/LRTAP Protocol on POPs, in the list of substances scheduled for elimination (Annex I).

2/ POTENTIAL FOR LRTAP

2.1/ Physical properties allowing atmospheric transport

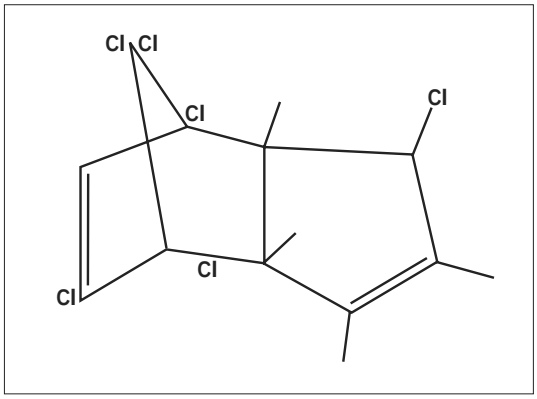

Fig. 5.1. Heptachlor (CAS: 76-44-8)

Table 5.1. Some physical properties of heptachlor and heptachlor epoxide

Property	Value	
	Heptachlor	Heptachlor epoxide
Water solubility (mg/l)	0.056	0.275
Vapour pressure (mmHg at 25 °C)	4.0×10^{-4}	
Henry's law constant	1.48×10^{-3}	3.2×10^{-5}
log K_{oc}	4.34	3.34–4.37
Log K_{ow}	4.4–5.5	

Heptachlor has low vapour pressure and low water solubility (Table 5.1). The experimental value for Henry's law constant suggests that heptachlor partitions somewhat rapidly to the atmosphere from surface water and that volatilization is significant. Heptachlor is also subject to long-range transport and wet deposition.

Based on the vapour pressure, heptachlor is expected to exist almost entirely in the vapour phase in ambient air.

The experimental value for Henry's law constant for heptachlor epoxide, which is the main breakdown product of heptachlor, suggests that it partitions slowly to the atmosphere from surface water (Lyman et al. 1982). Based on regression equations, the log K_{oc} for heptachlor epoxide was estimated to range between 3.34 and 4.37 (Lyman et al. 1982). These log K_{oc} values suggest a high sorption tendency, meaning that this compound is not mobile in soil and has a low potential to leach.

2.2/ Persistence in water, soil and sediment

Heptachlor is quite persistent in soil, where it is mainly transformed to its epoxide. Heptachlor epoxide is very resistant to further degradation. Heptachlor and heptachlor epoxide bind to soil particles and migrate very slowly (WHO, 1993).

Volatilization is an important mechanism of transport of heptachlor from land surfaces (Jury et al. 1987). When heptachlor was applied to orchard grass, approximately 90% was lost in 7 days. When it was applied to moist soil surfaces, 50% was lost in 6 days. When it was applied to dry soil surface, 14–40% was lost in approximately 2 days (50 hours). Volatilization was much less – only 7% in 167 days – when incorporated to a shallow depth of 7.5 cm (Jury et al. 1987). Temperature and humidity affect the persistence of heptachlor and total heptachlor (heptachlor plus heptachlor epoxide) in soil. An increase in temperature resulted in a decrease in the volatilization half-lives of heptachlor and total heptachlor. For example, at 18 ± 1 °C (90 ± 50% relative humidity (RH)) and 35 ± 1 °C (90 ± 5% RH), the half-lives of heptachlor (6 ppm) were 44.8 days and 38 days, respectively. Persistence of heptachlor and total heptachlor was found to be greater at higher humidity, irrespective of temperature. At the combination of higher temperature (25 ± 1 °C and low humidity (55 ± 5% RH), faster dissipation of heptachlor occurred (half-life = 24.67 days). At lower temperatures (18 ± 1 °C) and low humidity (55 ± 5% RH), greater persistence of heptachlor was found (40.67 days). Half-lives of total heptachlor (6 ppm) were longer because of the more persistent nature of heptachlor epoxide.

The log K_{oc} value indicates a very high sorption tendency, suggesting it will adsorb strongly to soil and is not likely to leach into groundwater in most cases. The leaching potential at 15 cm (concentration in soil water/concentration in soil) for heptachlor is 0.06, and the volatilization potential at 15 cm (concentration in soil air/concentration in soil) determined in laboratory studies is 5.5×10^{-3}, again suggesting that heptachlor is unlikely to leach appreciably in soil but has some volatilization potential. These are important properties, since heptachlor can remain deep in soil for years. The organic matter content of the soil is another factor affecting mobility.

Heptachlor epoxide is less likely to leach from soil with a high organic matter content. If released into water, it adsorbs strongly to suspended and bottom sediments. Heptachlor and heptachlor epoxide are subject to long-range transport and removal from the atmosphere by wet deposition. The organic matter content of soil affects the mobility of heptachlor epoxide.

2.3/ Bioaccumulation

The persistence of heptachlor, combined with a high partition coefficient (log K_{ow} = 4.4–5.5), provides the necessary conditions for it to bioconcentrate in terrestrial and aquatic foodchains.

2.4/ Monitoring

Levels of heptachlor in the Arctic atmosphere are usually at or below detection limits, probably because the majority of past use has been transformed in surface soils to the epoxide. Nevertheless, heptachlor and heptachlor epoxide has been regularly detected in Arctic air samples (Halsall et al. 1998). Mean concentrations of heptachlor in Arctic air ranged from 0.03 to 0.07 pg/m^3 between 1993 and 1994. Concentrations of heptachlor epoxide were higher, ranging from 0.92 to 1.47 pg/m^3. Recent evidence has highlighted sporadic inputs of heptachlor in the Arctic atmosphere, particularly during the winter months (Hung et al. 2002). This is likely to be the result of recent use of heptachlor or recent use of technical chlordane, which is contaminated with heptachlor.

Heptachlor epoxide was detected in rain samples at concentrations ranging from 0.03 to 1 ng/l at four widely separated sites in Canada from May to October in 1984. The sites are representative of overlake and shoreline locations. Snowpack samples representing snow accumulation for the winter of 1985–1986 were collected at a total of 12 widely distributed sites throughout the Northwest Territories, Canada, during the spring of 1986. Heptachlor epoxide was detected at 11 of the 12 sites at concentrations ranging from 0.2 to 0.41 ng/l. The only reasonable source for these compounds is long-range atmospheric transport and deposition. Heptachlor was detected in wet precipitation samples (rain/snow) from Lake Erie at a volume-weighted mean concentration (based on the total volume collected over the 1-month period) of 0.1 ng/l. (Chan & Perkins 1989; Gregor & Gummer 1989).

A study of nine households selected on the basis of high pesticide usage in an urban–suburban area in the south-eastern United States found outdoor air levels of heptachlor ranging from less than 0.0006 ppb to 0.003 ppb, with a mean of 0.001 ppb. Heptachlor was found in seven of nine households at levels in indoor air ranging from not detectable to 0.02 ppb, with a mean of 0.006 ppb. (Lewis et al. 1986).

2.5/ Conclusions regarding the LRTAP potential

The physicochemical properties (i.e. low water solubility, high stability and semivolatility) also favour its long-range transport, and as a result heptachlor and its

epoxide have been detected in Arctic air, water and a variety of aquatic and terrestrial organisms (WHO 1984). Long-range transport represents the most important source of these compounds found in the terrestrial and aquatic food chain in remote regions.

3/ PATHWAYS OF LRTAP-DERIVED HUMAN EXPOSURE

3.1/ Significant source and magnitude of human exposure

WHO (1993) suggests that food is the major source of exposure of heptachlor to the general population. A daily intake of 0.25 µg/person per day (for heptachlor and heptachlor epoxide combined, based on a 60-kg person) was estimated for Viet Nam, and of 0.07 µg/person per day (for heptachlor alone) for India. Based on a total diet study conducted by the US Food and Drug Administration, estimated daily intakes of heptachlor and heptachlor epoxide for men aged 25–30 were 0.007 µg and 0.184 µg, respectively in the early 1980s. Since the 1970s, dietary intake of heptachlor has declined significantly. For example, the daily intake of heptachlor epoxide from food in 1965 in the United States was 2 µg/day. In 1970, this figure was 1 µg/day. During the period 1971–1974 it was calculated that the daily human intake of heptachlor epoxide in the United States had fallen to between 0.29 and 0.64 µg/day.

A possibly additional area of exposure risk involves people, particularly military personnel, whose homes have been treated with heptachlor for termite control. People whose homes have been treated may continue to be exposed to this chemical through the air over long periods of time.

Heptachlor is generally not detectable in the human population, but heptachlor epoxide has been found in human fat, blood, organs and milk. Similar to many semi-volatile organic compounds, a significant source of heptachlor for infants is breast-milk, in which the levels of heptachlor can be considerably higher than those in dairy milk.

4/ HEALTH HAZARD CHARACTERIZATION

Heptachlor is readily absorbed via all routes of exposure, and is readily metabolized to heptachlor epoxide by mammals. Heptachlor epoxide is metabolized slowly and is the most persistent metabolite; it is mainly stored in adipose tissue, but also in the liver, kidney and muscle. There is limited information available on blood levels of heptachlor epoxide, but it has been confirmed that levels in the blood are several orders of magnitude lower than those found in adipose tissue. Because of the rapid transformation of heptachlor into heptachlor epoxide in the mammalian body, toxicity data concerning the two substances are discussed together.

Animal studies have reported effects on the liver, kidney and immune and nervous systems from oral exposure to heptachlor. The addition of heptachlor (up to 45 mg/kg diet) or its epoxide (up to 60 mg/kg diet) or both to the diet of rats for 140 days produced microscopic liver changes, e.g. enlarged centrilobular cells showing big nuclei with prominent nucleoli, cytoplasmic fat droplets and occasional cytoplasmic margination. It was demonstrated that these changes regressed after

withdrawal of the pesticide. The continuous exposure of rats to doses of either heptachlor or its epoxide exceeding 7 mg/kg increased the mortality rate of the pups during the suckling period, although 10 mg/kg fed to three generations of rats did not produce any adverse effects on reproductive capacity, growth or survival. (ATSDR 1993).

Heptachlor did not induce dominant lethal mutations in mice. In one study, it induced unscheduled DNA synthesis in human fibroblast cultures but not repair synthesis in cultured rodent cells. It inhibited intercellular communication in rodent cell systems but was not mutagenic in cultured rat liver cells. It did not induce sex-linked recessive mutations in *Drosophila* or gene conversion in yeast. It was mutagenic in plants but not in bacteria. In one study, positive results were reported for technical grade but not commercial grade heptachlor. (ATSDR 1993).

There is evidence that heptachlor and heptachlor epoxide are associated with infertility and improper development of offspring. Animal studies showed that females were less likely to become pregnant when both males and females were fed heptachlor. Reduced postnatal survival was reported in the progeny of rats fed 0.25 mg/kg bw per day heptachlor for 60 days and during pregnancy. Dosage of 6.9 mg/kg bw per day for 3 days significantly reduced fertility in rats and reduced the survival of young during the first weeks by one third. A dose of 1 mg/kg bw per day had no adverse effects on reproduction. No increase in fetal mortality or malformations occurred when pregnant rats were given up to 20 mg/kg bw per day on days 7–17 of gestation. Because the available data are inconclusive, it is not possible to make conclusions about possible reproductive effects of heptachlor in humans. (ATSDR 1993; WHO 1996).

Heptachlor has been shown to cross the placenta to the developing fetus in humans. However, inadequate information is available to determine whether heptachlor may cause developmental or reproductive effects in humans.

4.1/ Existing reference values

In 1991, IARC reviewed the data on heptachlor and concluded that the evidence for carcinogenicity was sufficient in animals and inadequate in humans, classifying it in group 2B.

JMPR has evaluated heptachlor on several occasions, and in 1991 established an ADI of 0.1 µg/kg bw on the basis of a NOAEL of 0.025 mg/kg bw per day from two studies in the dog, incorporating an uncertainty factor of 200 (100 for inter- and intra-species variation and 2 for the inadequacy of the database). With an allocation of 1% of the ADI to drinking-water, because the main source of exposure seems to be food, the guideline value is 0.03 µg/litre (WHO 1993).

5/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

Many registered uses of heptachlor around the world have been cancelled since the 1970s as a result of its potential cancer risk and its persistence and bioaccumulation throughout the food chain. Nevertheless, measured concentrations of heptachlor and heptachlor epoxide may be detected in remote atmospheres.

It appears that the general population is not at risk from LRTAP-derived heptachlor; however highly exposed groups such as some breast-fed infants and Inuit in the Arctic may be at risk. Long-range transport represents the most important source of heptachlor found in the terrestrial and aquatic food chain in remote regions, although the environmental concentrations of heptachlor in those regions are likely to be very low as a result of limited contemporary use.

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CHAPTER 6/
DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS

1/ INTRODUCTION

Polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDD/PCDFs), often called just "dioxins", consist of two groups of tricyclic aromatic compounds with similar chemical and physical properties. The number of chlorine atoms in each molecule can vary from one to eight. The number of chlorine atoms and their positions are of utmost importance for the toxicological potency of each congener. PCDD/PCDFs have never been produced intentionally, except for pure substances used as references in analytical and toxicological research, and have never served any useful purpose, unlike many other POPs such as polychlorinated biphenyls (PCBs) and DDT. PCDD/PCDFs are formed as unwanted by-products in many industrial and combustion processes. They have also been shown to be formed in the environment by forest fires and volcanoes, and also via enzymatically catalysed processes. The natural formation is in general of less importance compared to the anthropogenic.

Primary sources of environmental contamination with PCDD/PCDFs in the past were the production and use of organic chemicals containing chlorine. PCDFs were formed as inadvertent by-products in the production and use of PCBs and, in combination with PCDDs, in such high-temperature processes as waste incineration, the metal industry, home heating and other energy production processes. PCDFs are also found in residual waste from the production of vinyl chloride and the chlor-alkali process for chlorine production.

Factors favourable for the formation of PCDD/PCDFs are high temperatures, alkaline media, the presence of ultraviolet light, and the presence of radicals in the reaction mixture/chemical process (Fiedler 1999; Hutzinger & Fiedler 1993). Previous production of pentachlorophenol, as well as the bleaching process in pulp and paper mills, has been shown to be a major source. Changes in industrial processes have resulted in a reduction of PCDD/PCDFs concentration in products.

Whereas in the past the chemical industry and, to a lesser extent, the pulp and paper industry were considered to be the main sources of PCDD/PCDFs (and also the cause of many of today's contaminated sites in several industrialized countries), today's dioxin input is mainly due to thermal processes. There is still a considerable focus on waste incineration but, owing to requirements for dioxin reduction in stack gases set by several national authorities, the importance of this category has declined during the last years. Examples can be seen especially in the European

emission inventories (Fiedler 1999). An overview of combustion sources known to generate and emit PCDD/PCDFs (Fiedler 1999) is presented in Table 6.1.

PCDD/PCDFs are found not only in stack gases but also in solid residues from any combustion process such as bottom ash, slag and fly ash. With advanced technology and better burnout of the ashes and slag (characterized by a low content of organic carbon), PCDD/PCDFs concentrations have declined (Fiedler 1996, 1999).

Secondary sources of PCDD/PCDFs, their reservoirs, are those matrices where they are already present, either in the environment or as products. Product reservoirs include PCP-treated wood, PCB-containing transformers and sewage sludge, compost and liquid manure, which can be used as fertilizers in agriculture and gardens. Reservoirs in the environment are, for example, landfills and waste dumps, contaminated soils (mainly from former chemical production or handling sites), and contaminated sediments (especially in harbours and rivers with industries discharging directly to the waterways).

Table 6.1. Sources of emission of PCDD/PCDFs

Stationary sources	
Waste incineration	Municipal solid waste, clinical waste, hazardous waste, sewage sludge
Steel industry	Steel mills, sintering plants, hot-strip mills
Recycling plants	Non-ferrous metals (melting, foundry: Al, Cu, Pb, Zn, Sn)
Energy production	Fossil fuel power plants, wood combustion, landfill gas
Diffuse sources	
Traffic	Cars
Home heating	Coal, oil, gas, wood
Accidents	PCB fires, fires in building, forest fires, volcanic eruptions

Source: Fiedler, 1999.

Although these reservoirs may be highly contaminated with PCDD/PCDFs, the chemical and physical properties of these compounds imply that dioxins and furans will stay adsorbed to organic carbon in soils or other particles. On the other hand, mobilization can occur in the presence of lipophilic solvents (leaching into deeper layers of soils and/or groundwater) or in cases of erosion or run-off from topsoil (translocation into the neighbourhood). Experience has shown that transport of PCDD/PCDFs due to soil erosion and run-off does not play a major role in environmental contamination and human exposure (Fiedler 1995, 1999).

The polychlorinated biphenyls (PCBs) have been used commercially since 1929 as dielectric and heat exchange fluids and in a variety of other applications. The presence of PCBs in human and wildlife tissues was first recognized in 1966. Investigations in many parts of the world have since revealed widespread distribution of PCBs in the environment, including remote areas with no PCB production or use. There is evidence that the major source of PCB exposure in the

general environment is the redistribution of PCBs previously introduced into the environment. It is believed that large bodies of water, such as the Baltic Sea and the Canadian Great Lakes, may release significant amounts of PCB residues from previous uses into the atmosphere. The fact that PCB levels seem to decline in a similar way at different latitudes indicates that primary sources may play still an important role. The amount of dioxin-like PCBs might vary in the environment but the sources, transport and distribution, as well as persistence, show similarities with the general properties of PCBs.

For more general information on PCBs, see Chapter 7. PCDD/PCDFs and all PCBs are included in the UNECE POPs Protocol.

2/ POTENTIAL FOR LRTAP

PCDD/PCDFs are very persistent compounds; as their K_{ow} and K_{oc} are very high, they will intensively adsorb on to particles in air, soil and sediment and accumulate in fat-containing tissues. The strong adsorption of PCDD/PCDFs and related compounds to soil and sediment particles means that their mobility in these environmental compartments is negligible. Their mobility may be increased by the simultaneous presence of organic solvents such as mineral oil. The air compartment is probably the most significant compartment for the environmental distribution and fate of these compounds.

Some of the PCDD/PCDFs emitted into air will be bound to particles while the rest will be in the gaseous phase, which can be subject to long-range transport (up to thousands of kilometres). In the gaseous phase, removal processes include chemical and photochemical degradation. In the particulate phase, these processes are of minor importance and the transport range of the particulate phase will primarily depend on the particle size. PCDD/PCDFs are extremely resistant to chemical oxidation and hydrolysis, and hence these processes are not expected to be significant in the aquatic environment. Photodegradation and microbial transformation are probably the most important degradation routes in surface water and sediment.

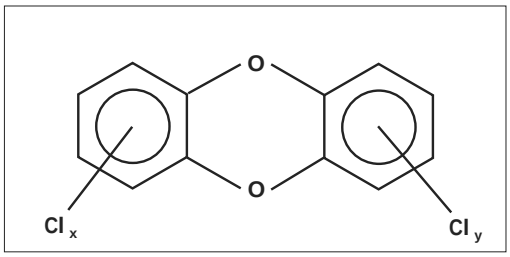


Fig. 6.1. Polychlorinated dibenzo-*p*-dioxins (PCDDs), general formula

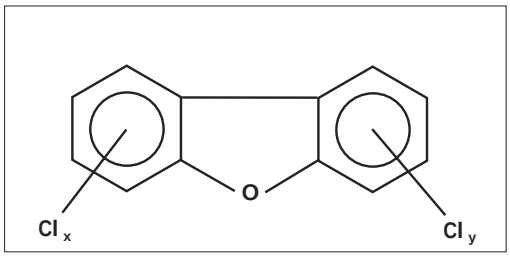


Fig. 6.2. Polychlorinated dibenzofurans (PCDFs), general formula

2.1/ Physicochemical properties allowing atmospheric transport

The number of chlorine atoms in each molecule can vary from one to eight. Among the possible 210 compounds, 17 congeners have chlorine atoms at least in the positions 2, 3, 7 and 8 of the parent molecule and these are the most toxic,

bioaccumulative and persistent ones compared to congeners lacking this configuration. All the 2,3,7,8-substituted PCDDs and PCDFs plus coplanar PCBs (with no chlorine substitution at the *ortho* positions) show the same type of biological and toxic response.

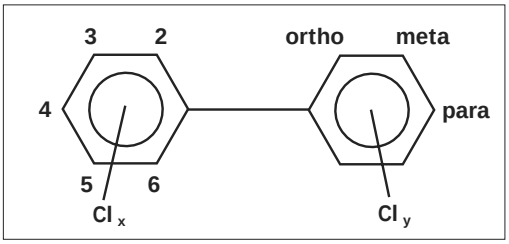


Fig. 6.3. Polychlorinated biphenyls (PCBs), general formula

Table 6.2. Physical properties of PCDD/PCDFs

Property	Value
Vapour pressure (mmHg at 25 °C)[a]	5.6×10^{-12}–4×10^{-8}
Log octanol/water partition coefficient[a]	5.6–8.0
Water solubility, TCDD, ng/l	19.3 (7.9–483)

[a] For tetra- to octa-substituted congeners. *Source*: Mackay et al. 1992.

PCDD/PCDFs are characterized by their lipophilicity, semi-volatility and resistance to degradation. The photodegradation of particle-bound PCCD/PCDFs in air was found to be negligible (Koester & Hites 1992). These characteristics predispose these substances to long environmental persistence and to long-range transport. They are also known for their ability to bioconcentrate and biomagnify under typical environmental conditions, thereby potentially achieving toxicologically relevant concentrations. The tetra–octa PCCD/PCDFs have lower vapour pressures than PCBs and are therefore not expected to undergo long range transport to the same extent (Mackay et al. 1992); nevertheless there is evidence for deposition in Arctic soils and sediments (Brzuzy & Hites, 1996; Oehme et al. 1993; Wagrowski & Hites 2000).

2.2/ Persistence in water, soil and sediment

Owing to their chemical, physical and biological stability, PCDD/PCDFs are able to remain in the environment for a long time. As a consequence, dioxins from so-called "primary sources" (formed in industrial or combustion processes) are transferred to other matrices and enter the environment. Such secondary sources are sewage sludge, compost, landfills and other contaminated areas (Fiedler 1999).

PCBs and PCDD/PCDFs are lipophilic (lipophilicity increases with increasing chlorination) and have very low water solubility. Because of their persistent nature and lipophilicity, once PCDD/PCDFs enter the environment and living organisms they will remain for a very long time, like many other halogenated aromatic compounds. As log K_{ow} (typically 6–8) or log K_{oc} are very high for all these compounds, they will intensively adsorb on to particles in air, soil and sediment. The strong adsorption of PCDD/PCDFs and related compounds to soil and sediment

particles causes their mobility in these environmental compartments to be negligible. Their mobility may be increased by the simultaneous presence of organic solvents such as mineral oil. The half-life of TCDD in soil has been reported as 10–12 years (Young 1983), whereas photochemical degradation seems to be considerably faster but with a large variation that might be explained by experimental differences (solvents used, etc). Highly chlorinated PCDD/PCDFs seem to be more resistant to degradation than those with just a few chlorine atoms.

2.3/ Bioaccumulation

The physicochemical properties of PCBs and their metabolites enable these compounds to be absorbed readily by organisms. The high lipid solubility and the low water solubility lead to the retention of PCCD/PCDFs, PCBs and their metabolites in fatty tissues. Protein binding may also contribute to their tissue retention. The rates of accumulation into organisms vary with the species, the duration and concentration of exposure, and the environmental conditions. The high retention of PCDD/PCDFs and PCBs, including their metabolites, implies that toxic effects can occur in organisms spatially and temporally remote from the original release.

Gastrointestinal absorption of TCDD in rodents has been reported to be in the range of 50–85% of the dose given. The half-life in rodents ranges from 12 to 31 days except for guinea-pigs, which show slower elimination ranging from 22 to 94 days. The half-life in larger animals is much longer, being around 1 year in rhesus monkeys and 7–10 years in humans.

2.4/ Monitoring

PCCD/PCDFs have been found to be present in Arctic air samples, e.g. during the winter of 2000/2001 in weekly filter samples (particulate phase) collected at Alert in Canada (Hung et al. 2002). PCDD/PCDFs have been monitored since 1969 in fish and fish-eating birds from the Baltic. The levels of PCDD/PCDFs in guillemot eggs, expressed as TEQ, decreased from 3.3 ng/g lipids to around 1 ng/g between 1969 and 1990. Since 1990, this reduction seems to have levelled off and today it is uncertain whether there is a decrease or not. Fish (herring) show a similar picture.

2.5/ Conclusions regarding LRTAP potential

Both physical characteristics and environmental findings support the long-range transport of PCCD/PCDFs and PCBs. There are differences, however, both between and within the groups regarding ability to undergo LRTAP.

3/ PATHWAYS OF LRTAP-DERIVED HUMAN EXPOSURE

For decades, many countries and intergovernmental organizations have taken measures to prevent the formation and release of PCDD/PCDFs, and have also banned or severely restricted the production, use, handling, transport and disposal of PCBs. As a consequence, release of these substances into the environment has decreased in many developed countries. Nevertheless, analysis of food and breast-

milk show that they are still present, although in levels lower than those measured in the 1960s and 1970s. At present, the major source of PCB exposure in the general environment appears to be the redistribution of previously introduced PCBs.

3.1/ Significant sources and magnitude of human exposure

PCDD/PCDFs are today found in almost all compartments of the global ecosystem in at least trace amounts. They are ubiquitous in soil, sediments and air. Excluding occupational or accidental exposures, most human background exposure to dioxins and PCBs occurs through the diet, with food of animal origin being the major source, as they are persistent in the environment and accumulate in animal fat.

Importantly, past and present human exposure to PCDD/PCDFs and PCBs results primarily from their transfer along the pathway: atmospheric emissions → air → deposition → terrestrial/aquatic food chains → human diet. Information from food surveys in industrialized countries indicates a daily intake of PCDD/PCDFs in the order of 50–200 pg I-TEQ/person per day for a 60-kg adult, or 1–3 pg I-TEQ/kg bw per day. If dioxin-like PCBs are also included, the daily total TEQ intake can be higher by a factor of 2–3. Recent studies from countries that started to implement measures to reduce dioxin emissions in the late 1980s clearly show decreasing PCDD/PCDF and PCB levels in food and, consequently, a lower dietary intake of these compounds by almost a factor of 2 within the past 7 years. Biota from the Baltic have, however, not shown any clear trend for dioxins or PCBs since 1990.

Occupational exposures to both PCDDs and PCDFs at higher levels have occurred since the 1940s as a result of the production and use of chlorophenols and chlorophenoxy herbicides and to PCDFs in metal production and recycling. Even higher exposures to PCDDs have occurred sporadically in relation to accidents in these industries. High exposures to PCDFs have occurred in relation to accidents such as the Yusho (Japan) and Yucheng (Taiwan) incidents, involving contamination of rice oil and accidents involving electrical equipment containing PCBs.

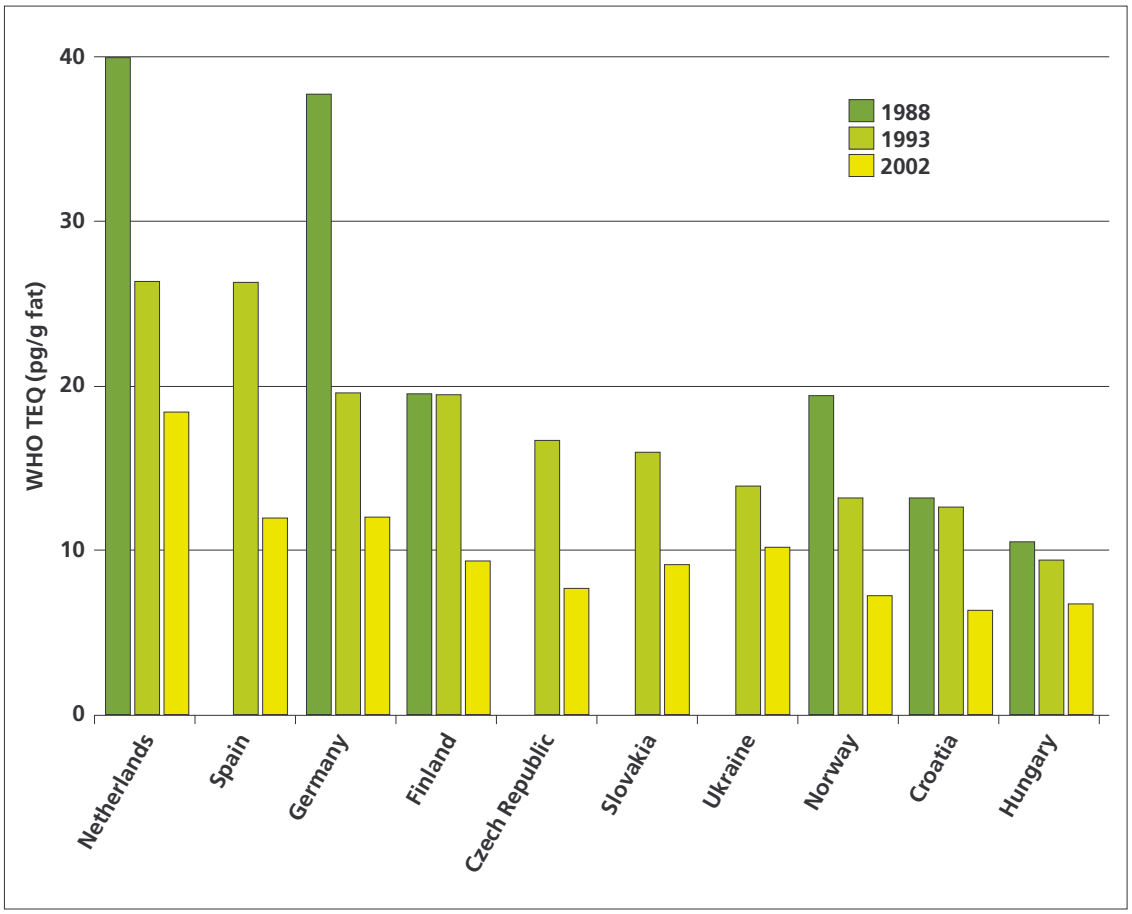
3.1.1/ Exposure levels in adults

PCDD/PCDFs accumulate in human adipose tissue, and the level reflects the history of intake by the individual. Several factors have been shown to affect adipose tissue concentrations/body burdens, notably age, the number of children and period of breastfeeding, and dietary habits.

Breast-milk represents the most useful matrix for evaluating time trends of dioxins and many other POPs. Several factors affect the PCDD/PCDFs content of human breast-milk, most notably the mothers age, the duration of breast-feeding and the fat content of the milk. Studies should therefore ideally be performed on samples from a large number of mothers, taking these variables into account.

The WHO Regional Office for Europe carried out a series of exposure studies aimed at detecting PCBs, PCDDs and PCDFs in human milk. The first round took

Fig. 6.4. Temporal trends in the levels of dioxins and furans in human milk in various countries participating in consecutive rounds of the WHO exposure study



Source: van Leeuwen et al. 2002.

place in 1987–1988 and the second in 1992–1992. In 2001–2002, a third round was organized in collaboration with the WHO Global Environmental Monitoring System/Food Contamination Monitoring and Assessment Programme (GEMS Food) and the International Programme on Chemical Safety (IPCS) (van Leeuwen et al. 2002). Results are currently available from 21 countries. Fig.6.4 presents the temporal trends of levels of PCDDs and PCDFs expressed in WHO-TEQ for those countries participating in all three rounds or in the last two rounds of the WHO study. A clear decline can be seen, with the largest decline for countries originally having the highest level of dioxin-like compounds in human milk.

The general population is mainly exposed to PCBs through common food items. Fatty food of animal origin, such as meat, certain fish and diary products are the major sources of human exposure. Owing to considerable differences in the kinetic behaviour of individual PCB congeners, human exposure to PCB from food items differs markedly in composition compared to the composition of commercial PCB mixtures.

PCB levels in fish have been decreasing in many areas since the 1970s, but the decrease has levelled off during the last couple of years. Today, the daily PCB intake is estimated to be around 10 ng/kg bw for an adult. More information on human exposure to PCBs is given in Chapter 7.

3.1.2/ Exposure levels in children (including prenatal exposure)

Once in the body, PCBs and PCDD/PCDFs accumulate in fatty tissues and are slowly released. Lactation or significant weight loss increases the release of the substances into the blood. PCBs can cross the placenta from mother to fetus, and are also excreted into the breast-milk. PCB and PCDD/PCDF concentrations in human milk are usually higher than in cow's milk or other infant foods. As a result, breastfed infants undergo higher dietary exposure than those who are not breastfed. This concerns particularly breastfed infants of women exposed to high levels of PCBs, including Inuit and women whose diet is mainly based on fish from highly contaminated rivers and lakes, such as the Great Lakes and the Baltic Sea. Time-trend information suggests that PCDD/PCDF and PCB concentrations in human milk have decreased significantly since the 1970s in countries that have taken measures against these substances. However, the decrease has levelled off during the last couple of years. Therefore, current fetal and neonatal exposures continue to raise serious concerns regarding potential health effects on developing infants.

Compared to adults, the daily intake of PCDD/PCDFs and PCBs by breastfed babies is 1–2 orders of magnitude higher. A recent field study showed higher mean levels of PCDD/PCDFs and PCBs in human milk in industrialized areas (10–35 pg I-TEQ/g milk fat) and lower levels in developing countries (< 10 pg I-TEQ/g milk fat). Very few studies have been performed on Arctic populations with respect to the exposure of children to these substances. It is likely, however, that the differences in exposure between children and adults demonstrated in many industrialized regions also exist in Arctic regions.

3.2/ Potential for high exposure situations

It has been shown that these substances, and especially PCBs, can occur in elevated concentration in Arctic fauna. As the diet of many Arctic populations relies to a vast extent on marine mammals that represent high trophic levels, human exposure has been shown to be considerably high compared to industrialized areas.

3.3/ Significance of LRTAP as a source of total exposure

There are clear connections between food habits and the levels of different POPs, including PCCD/PCDFs and coplanar PCBs, found in humans. The current substances, especially PCBs, have been shown to be capable of transport over long distances. Indigenous people who rely heavily on marine mammals will therefore face a comparably high exposure to different POPs, and atmospheric transport is likely to play an important role in their presence in these animals in remote areas.

4/ HEALTH HAZARD CHARACTERIZATION

4.1/ Toxicokinetics

The physicochemical properties of both PCDD/PCDFs and coplanar PCBs enable these compounds to be readily absorbed by organisms. The high lipid solubility and low water solubility of all congeners lead to the retention of the compounds

in fatty tissues. Once absorbed, the compounds are readily distributed to all body compartments, where the storage rate is proportional to the fat content of the organ. The metabolism and excretion of 2,3,7,8-substituted PCCD/PCDFs and PCBs is very slow.

The main route of excretion is via the faeces (biliary excretion), urine and breast-milk. Excretion through breast-milk results in transfer to breastfed infants, who therefore are highly exposed. There is also transfer across the placenta, thus causing fetal exposure. Perinatal exposure is a major concern with regard to human health effects, even at present background exposure levels.

4.2/ Effects on laboratory animals and the TEF-concept

As 2,3,7,8-substituted PCDD/PCDFs and coplanar PCBs are believed to act through a common toxicological mechanism, a toxic (or TCDD) equivalency factor (TEF) concept has been established. The concept is based on the observation that, even if the current substances act via a common mechanism, they do so with varying potency. A couple of different schemes have therefore been proposed whereby the toxic potencies of all substances are related to the most potent substance of the group, TCDD. The toxicity of TCDD is set to 1.0 and all the other substances are given individual toxicity factors, which are fractions of 1.0. Thus, the combined toxicity of all congeners in a sample, expressed as a toxic equivalent (TEQ) can be calculated by multiplying the amount or concentration of the individual substances with the respective TEF and adding the products.

The TEF concept has gained wide acceptance and many different schemes have been proposed. Nowadays, the use of the TEFs for dioxins, dibenzofurans and PCBs for humans and mammals suggested by WHO is often recommend (van den Berg et al. 1998). The TEF scheme includes a kind of safety factor, as the TEF values are rounded upwards.

However, no studies on fetal exposure are available for setting TEFs. Thus there is a need for dose–response studies of the critical effects, based on synthetic mixtures reflecting the human exposure situation. The WHO TEFs for dioxins, dibenzofurans and PCBs for humans and mammals are given in Table 6.3

4.2.1/ Non-cancer endpoints

A plethora of effects have been reported from multiple animal studies following exposure to PCDDs, PCDFs and PCBs. The most extensive data set on dose–response effects is available for 2,3,7,8-TCDD; less information is available for the other dioxin-like compounds. Therefore, the focus of the evaluation of the animal data is on the effects of 2,3,7,8-TCDD.

Among the most sensitive endpoints (on a body burden basis) are: endometriosis, developmental neurobehavioural (cognitive) effects, hearing loss, developmental reproductive effects (sperm counts, female urinogenital malformations) and immunotoxic effects, both adult and developmental. The most sensitive biochemical effects are CYP1A1/2 induction, hepatic retionid depletion, EGF-receptor down-regulation and oxidative stress.

4.2.2/ Carcinogenic effects

2,3,7,8-TCDD has been shown to be carcinogenic in several long-term studies at multiple sites in several species and in both sexes. Short-term studies observed a lack of direct DNA-damaging effects, including covalent binding to DNA by TCDD, which underscores that TCDD does not act as an initiator of carcinogenesis. However, secondary mechanisms may be important in the observed carcinogenicity of TCDD and related dioxin-like compounds. Several PCDDs, PCDFs, non-ortho and mono-ortho PCBs have also been shown to be tumour promoters.

The LOAEL of TCDD in the Kociba study was the development of hepatic adenomas in rats at an intake of 10 ng/kg bw per day, and the NOEL was 1 ng/kg bw per day. At the NOEL, the body burden was 60 ng/kg bw (WHO 2000).

TCDD also causes thyroid tumours in male rats. This has been shown to proceed through a mechanism that involves altered thyroid hormone metabolism and consequent increases in feedback mechanisms, TSH (thyroid stimulating hormone), which results in a chronic proliferative stimulation of thyroid follicular cells.

4.3/ Health effects in humans

There are many studies on the carcinogenicity of 2,3,7,8-TCDD in accidentally exposed workers. Epidemiological studies on people exposed in connection with the accident in Seveso have generated valuable information. Excess risks were observed for ovarian and thyroid cancers and for some neoplasia of the haematopoi-

Table 6.3. WHO TEF values for human risk assessment

Congener	TEF value	Congener	TEF value
Dibenzo-p-dioxins		***Non-ortho PCB***	
2,3,7,8-TCDD	1	PCB 77	0.0001
1,2,3,7,8-PnCDD	1	PCB 81	0.0001
1,2,3,4,7,8-HxCDD	0.1	PCB 126	0.1
1,2,3,6,7,8-HxCDD	0.1	PCB 169	0.01
1,2,3,7,8,9-HxCDD	0.1		
1,2,3,4,6,7,8-HpCDD	0.01		
OCDD	0.0001		
Dibenzofurans		***Mono-ortho PCB***	
2,3,7,8-TCDF	0.1	PCB 105	0.0001
1,2,3,7,8-PnCDF	0.05	PCB 114	0.0005
2,3,4,7,8-PnCDF	0.5	PCB 118	0.0001
1,2,3,4,7,8-HxCDF	0.1	PCB 123	0.0001
1,2,3,6,7,8-HxCDF	0.1	PCB 156	0.0005
1,2,3,7,8,9-HxCDF	0.1	PCB 157	0.0005
2,3,4,6,7,8-HxCDF	0.1	PCB 167	0.00001
1,2,3,4,6,7,8-HpCDF	0.01	PCB 189	0.0001
1,2,3,4,7,8,9-HpCDF	0.01		
OCDF	0.0001		

Source: Van den Berg et al. 1998.

etic tissue; these results were, however, based on small numbers. Epidemiological studies on the cohorts most highly exposed to 2,3,7,8-TCDD produced the strongest evidence of increased risks for all cancers combined, along with less strong evidence of increased risks for cancers of particular sites. The relative risk for all cancers combined in the most highly exposed and longer-latency sub-cohorts is 1.4 (Bertazzi et al. 1998).

Studies of non-cancer effects in children have indicated neurodevelopmental delays and neurobehavioural effects, including neonatal hypotonia. In children in Seveso who were highly exposed to TCDD, small, transient increases in hepatic enzymes, total lymphocyte counts and subsets, complement activity, and non-permanent chloracne were observed. Also, an alteration of the sex ratio (excess female to male) was observed in children born to parents highly exposed to TCDD.

4.4/ Critical outcomes and existing reference values

During the last two decades, a number of different risk assessments of dioxins and related compounds have been performed. Since the mid-1990s, coplanar PCBs have often been included in the assessments.

In 1997, WHO established an expert group on dioxins and related compounds. It proposed, based on the TEF scheme shown in Table 6.3, a TDI for dioxins and related compounds. The proposal was based on kinetic calculations of doses to body burden and vice versa. The body burden approach resulted in a reduced need for a safety factor for extrapolation between species. The two most important studies for estimating LOAEL were both published by Gray et al. (1997a, 1997b). The WHO expert group calculated that a reliable LOAEL probably could be found in the range of 14–37 pg/kg bw per day. By applying a safety factor of 10 to this range, it proposed a TDI of 1–4 pg/kg bw. The group emphasized that the TDI represents a tolerable daily intake for lifetime exposure, and that occasional short-term excursions above the TDI would have no health consequences provided that the averaged intake over long periods was not exceeded. In addition, it recognized that certain subtle effects may be occurring in some sections of the general populations of industrialized countries at current intake levels (2–6 TEQ/kg bw per day), but found it tolerable on a provisional basis since these reported subtle effects were not considered overtly adverse and there were questions as to the contribution of non-dioxin-like compounds to the observed effects. The group therefore stressed that the upper range of the TDI of 4 pg TEQ/kg bw should be considered a maximum tolerable intake on a provisional basis, and that the ultimate goal was to reduce human intake levels to below 1 pg TEQ/kg bw per day.

In 2001, the European Commission and the Scientific Committee for Food proposed a temporary TWI of 14 pg/kg bw for 2,3,7,8-PCDD/PCDFs and dioxin-like PCBs.

5/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

It has been demonstrated that dioxins and many PCBs resist degradation, bioaccumulate, are transported through air, water and migratory species across interna-

tional boundaries, and are finally deposited far from the place of release where they can accumulate in terrestrial and aquatic ecosystems. The clearest evidence for this long-range transport derives from the levels of PCDD/PCDFs and PCBs measured in the Arctic. Owing to long-range transboundary transport, these substances are nowadays ubiquitous contaminants of the ecosystem and are also present in the food chain. Therefore, most of the human population is exposed to PCDD/PCDFs and PCBs. Moreover, since dioxins and PCBs pass from mother to fetus through the placenta, and from mother to newborn through the breastfeeding, infants are at risk of harmful effects in the most critical period of their development. There are just a few reports of dioxins in humans from Arctic regions, but there are plenty of animal samples analysed for dioxins and PCBs that give information on human exposure through food. As many people living in the Arctic still practise hunting and fishing for an important part of their diet, their exposure to dioxins, PCBs and other contaminants could be elevated compared to people living in industrialized parts of the world.

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CHAPTER 7/
POLYCHLORINATED BIPHENYLS

1/ INTRODUCTION

Polychlorinated biphenyls (PCBs) are found in almost all compartments of the global ecosystem in at least trace amounts. PCBs are found in human tissues in many parts of the world, including remote areas with no PCB production or use.

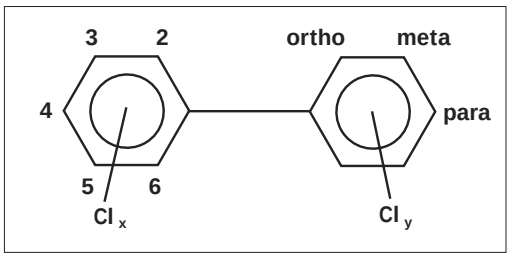

Fig. 7.1. Structural formula of PCBs

PCBs have been used commercially since 1929 as dielectric and heat exchange fluids, and in a variety of other applications. PCBs are aromatic chemicals not occurring naturally in the environment. They consist of the biphenyl structure with two linked benzene rings, in which some or all of the hydrogen atoms have been substituted by chlorine atoms.

In Sweden, the use of PCBs was restricted in 1972 for use only in closed systems. No new PCB-containing products have been allowed in Sweden since 1978, in Norway since 1980, in Finland since 1985, in Denmark since 1986 and in Iceland since 1988.

There are several health criteria documents concerning all aspects of PCB chemistry and toxicity from the early 1990s (Ahlborg et al. 1992; Rantanen et al. 1987; USEPA 1990; WHO 1993). Unless otherwise stated, it is these documents that are referred to here. A Concise International Chemical Assessment Document (CICAD) on PCBs is currently in preparation, and USEPA is currently involved in an assessment of non-cancer effects associated with exposure to PCBs. The CICAD is based on the recent ATSDR review of PCBs (ATSDR 2000).

The ability of PCBs to cross international borders and move long distances in air and water has made the elimination of PCBs an international problem. According to the Stockholm Convention on POPs, the development of a global legally binding treaty to phase out and eliminate the production, use and sources of PCBs is necessary to minimize the their effects on the environment and humans. To this end, PCBs were placed in Annex A of the POPs Convention and thereby given elimination status.

2/ POTENTIAL FOR LRTAP

PCBs are characterized by their semi-volatility and resistance to degradation. The water solubility is low. These characteristics predispose them to environmental persistence and to long-range transport.

2.1/ Physicochemical properties allowing atmospheric transport

The basic molecular structure, including the conventional numbering of the substituent positions, is shown in Fig. 7.1. Theoretically, 209 individual congeners are possible (7.1), but only about 130 of these have been identified in commercial products. Commercial PCB products are always a mixture of different congeners, and their absolute composition varies from batch to batch. Impurities such as polychlorinated dibenzofurans (PCDFs), naphthalenes (PCNs) and quaterphenyls (PCQs) have all been identified in commercial PCB products.

The chemical formula of PCBs is $C_{12}H_{10-n}Cl_n$, where n ranges from 1 to 10. The PCB congeners without chlorine atoms at the *ortho* positions can assume a coplanar conformation. The congeners 3,4,4',5-, 3,3',4,4'-, 3,3',4,4',5- and 3,3',4,4',5,5'-PCB (non-*ortho* PCB congeners), which are also substituted in both para and at least two meta positions, are in their coplanar conformation approximate stereoisomers of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic dioxin congener. Their mono-*ortho* analogues are less, and the di-*ortho* analogues even less, likely to assume a coplanar conformation and thereby structurally resemble TCDD.

PCBs are highly insoluble in water and are soluble in most organic solvents. They are semi-volatile and can be expected to partition into the atmosphere as a result. Their presence is ubiquitous in the environment, and residues have even been detected in the Arctic air, water and organisms. They form vapours heavier than air. Aqueous solubility, determined for 26 different congeners, ranges from 1.08×10^{-5} to 9.69×10^{-10} mol/litre and generally decreases with relative molecular mass. Henry's law constant, determined for 20 congeners, ranges from 0.3×10^{-4} to 8.97×10^{-4} atm-m^3/mol and increases with the degree of *ortho*-chlorine substitution within a relative mass class. Vapour pressure generally decreases with relative molecular mass and increases with increasing degree of *ortho*-chlorine substitution. Log K_{ow} values range from 4.46 to 8.18 for all congeners.

2.2/ Persistence in water, soil and sediment

All PCB congeners are lipophilic (lipophilicity increases with increasing degree of chlorination) and have very low water solubilities. On the basis of these properties, PCBs are highly persistent, and they can be expected to partition into the atmosphere and accumulate within food chains. These characteristics predispose them to environmental persistence and to long-range transport. They intensively adsorb on to particles in air, soil and sediment and accumulate in fat-containing tissues. The strong adsorption causes their mobility in soil and sediments to be negligible.

Degradation in the environment depends on the degree of chlorination. Persistence of PCB congeners increases as the degree of chlorination increases.

Air is probably the most significant compartment for environmental distribution. The presence of PCBs in humans and wildlife was first recognized in 1966. Since then, investigations in many parts of the world have revealed widespread distribution of PCBs in the environment, including remote areas (Macdonald et al. 2000; Schreitmüller & Ballschmiter 1994). It has been demonstrated that PCBs can be transported by currents, wind and atmospheric diffusion for long distances from source areas, including Arctic and Antarctic regions. In the atmosphere, water and soil, PCBs occur mostly adsorbed to particles; the tendency to adsorb increases with the degree of chlorination.

In the atmosphere, the vapour phase reaction of PCBs with hydroxyl radicals may be the dominant transformation process. Estimated half-lives for this reaction range from about 10 days for a monobiphenyl to 1.5 years for a heptachlorobiphenyl. In the aquatic environment, hydrolysis and oxidation do not significantly degrade PCB. Microorganisms degrade up to the tetrachlorobiphenyls, while higher chlorinated congeners are resistant to biodegradation. Chlorine substitution positions are important in determining the biodegradation rate.

2.3/ Bioaccumulation

The physicochemical properties of PCBs and their metabolites enable these compounds to be absorbed readily by organisms. The high lipid solubility and the low water solubility lead to the retention of PCBs and their metabolites in fatty tissue. Protein binding may contribute to tissue retention of PCBs and their metabolites. The rates of accumulation into organisms vary with the species, the duration and concentration of exposure, and the environmental conditions. PCBs have the ability to bioconcentrate and biomagnify under typical environmental conditions, thereby potentially achieving toxicologically relevant concentrations. The high retention of PCBs and their metabolites means that toxic effects can also occur in organisms remote in time and geographical area from the original PCB use. The bioconcentration factor (BCF) for Aroclor 1254 in aquatic organisms ranges from 0.24 to 165 000, in plants from 0.001 to 0.041, and in birds and mammals from 5.15 to 28.5. However, BCFs should be interpreted with caution, since they are simple ratios between the PCB concentration in an organism and the concentration in medium or food. The exposure concentration, therefore, makes a marked difference to the BCF obtained; very low exposure concentrations are likely to lead to high BCFs, since all the PCBs are absorbed, while high exposure concentrations will tend to minimize the BCFs.

2.4/ Monitoring and modelling

Modelling of environmental PCB data has so far failed to simulate their fate, because soil processes are not well understood (Cousins et al. 2001; Halstall et al. 1999) and usage and emission data are very uncertain (Breivik et al. 2001).

2.5/ Conclusions regarding the LRTAP potential

Both physical characteristics and environmental findings support the long-range transport of PCBs. There are, however, differences within the groups regarding their abilities to do so.

3/ PATHWAYS OF LRTAP-DERIVED HUMAN EXPOSURE

For decades, many countries and intergovernmental organizations have banned or severely restricted the production, usage, handling, transport and disposal of PCBs. Because of the ban in most developed countries, release of PCBs in recent years should be limited. Nevertheless, analysis of food and breast-milk show that PCBs are still present, although in levels lower than those measured in the 1960s, even in those countries where they have never been used or produced. Currently, the major source of exposure could be redistribution, but primary sources could also be of significant importance. It is believed that large surfaces of water, such as the Baltic Sea and the Canadian Great Lakes, may release significant amounts of PCB residues from previous use into the atmosphere.

3.1/ Significant sources and magnitude of human exposure

3.1.1/ Exposure levels in adults

The general population is exposed to PCBs mainly via common food items, particularly fatty foods of animal origin such as meat, certain fish and diary products. Recent estimated intake levels for adults in the western world are about 50 ng/kg bw per day. Data available from industrialized countries have shown a reduction in population exposure levels in the last few decades, but there are indications that this decline has levelled off. Owing to considerable differences in the kinetic behaviour of individual PCB congeners, humans experience a PCB exposure from food items that differs markedly in composition from the composition of commercial PCB mixtures. PCB levels in fish have been decreasing since the 1970s, but the decrease has levelled off during the last couple of years. The decrease observed in herring has averaged 4–7% per year since 1975 (Bernes 1998). Today the levels in fatty fish range from 2.6 to 137.8 µg/kg in samples from surveys from the Netherlands, Norway, Sweden and United Kingdom. The non-dioxin-like PCB congeners constitute a major part of the PCB congeners found in human tissues and food (Tables 7.1–7.3).

3.1.2/ Exposure levels in children (including prenatal exposure)

Prenatal and neonatal exposures are considered particularly important, as breastfed infants will exceed adult exposures by one to two orders of magnitude. Once in the body, PCBs accumulate in fatty tissues and are slowly released. Lactation and significant weight loss increase the release of PCBs to the blood. PCBs move freely across the placenta from mother to fetus, and are also excreted in breast-milk. PCB concentrations in human milk are higher than in cow's milk or other infant foods. Breastfed infants receive a higher dietary exposure than those who are not breastfed. Women exposed to high levels of PCBs include Inuit and those whose diet is

mainly based on fish from highly contaminated rivers and lakes, such as the Great Lakes and the Baltic Sea. Time trend information suggests that PCB concentrations in breast-milk have decreased significantly since the 1970s in countries that have banned PCB use. However, the decrease has levelled off during the last couple of years, and exposure of the fetus and neonate to PCB continues to raise serious concerns regarding potential health effects on developing infants.

3.2/ Potential for high exposure situations

It has been shown that PCBs can occur in elevated concentrations in Arctic fauna. As the diet of many Arctic populations to a vast extent relies on marine mammals that represent high trophic levels, human exposure has been shown to be considerably high compared to industrialized areas.

3.3/ Significance of LRTAP as source of exposure

In the absence of local sources of PCBs in Arctic and other remote locations, LRTAP appears to be an important element of the exposure pathways in those areas.

4/ HEALTH HAZARD CHARACTERIZATION

Among the 209 individual PCB congeners, some have a chemical structure that enables the molecule to fit into the ligand-binding domain of the Ah receptor. These congeners exhibit numerous biological effects similar to those caused by dioxins, and they are referred to as dioxin-like. Typically, dioxin-like PCB congeners have chlorine substituents in *para* and *meta* positions and at the most, in one *ortho* position (Fig 7.1 and Table 7.1). To date, there are twelve PCB congeners that have been assigned toxic equivalency factors (TEFs) in the dioxin TEF-scheme proposed by WHO (van den Berg et al. 1998) (Table 7.4). Health risks associated with exposure to these PCB congeners are thereby covered in the most recent dioxin risk assessments (European Commission 2000; van Leeuwen & Younes 2000; WHO 2000). For further information about the toxicology profile and the human health implications of dioxin-like PCB congeners relative to LRTAP, see Chapter 6.

Based on the induction of various cytochrome P-450 enzymes, PCB congeners have been assigned as CYP1A1/2 inducers (i.e. dioxin-like PCBs), CYP2B1/2 inducers (typically di-*ortho*-substituted) or of mixed type (typically *mono-ortho*-substituted) inducers (Table 7.5). Non-dioxin-like PCB congeners possess no or only negligible Ah-receptor-mediated activity, and are often considered to be less toxic than dioxin-like PCB congeners.

Non-dioxin-like PCB congeners are poorly characterized from a toxicological point of view. To date, toxic effects specific to non-dioxin-like PCB congeners have not been identified. The available toxicological information suggests that typical effects of PCB exposure, including the critical effects of carcinogenicity, immunotoxicity and neurobehavioural alterations, are caused by all PCB congener classes (i.e. by both the dioxin-like and the non-dioxin-like congeners). However, the

Table 7.1. IUPAC numbers and chlorine atom positions of all PCB congeners[a]

No.[b]	Structure	No.[b]	Structure	No.[b]	Structure
1	2	36	3,3',5	71	2,3',4',6
2	3	37	3,4,4'	72	2,3',5,5'
3	4	38	3,4,5	73	2,3',5',6
4	2,2'	39	3,4',5	74	2,4,4',5
5	2,3	40	2,2',3,3'	75	2,4,4',6
6	2,3'	41	2,2',3,4	76	2',3,4,5
7	2,4	42	2,2',3,4'	77*	3,3',4,4'
8	2,4'	43	2,2',3,5	78	3,3',4,5
9	2,5	44	2,2',3,5'	79	3,3',4,5'
10	2,6	45	2,2',3,6	80	3,3',5,5'
11	3,3'	46	2,2',3,6'	81*	3,4,4',5
12	3,4	47	2,2',4,4'	82	2,2',3,3',4
13	3,4'	48	2,2',4,5	83	2,2',3,3',5
14	3,5	49	2,2',4,5'	84	2,2',3,3',6
15	4,4'	50	2,2',4,6	85	2,2',3,4,4'
16	2,2',3	51	2,2',4,6'	86	2,2',3,4,5
17	2,2',4	**52**	**2,2',5,5'**	87	2,2',3,4,5'
18	2,2',5	53	2,2',5,6'	88	2,2',3,4,6
19	2,2',6	54	2,2',6,6'	89	2,2',3,4,6'
20	2,3,3'	55	2,3,3',4	90	2,2',3,4',5
21	2,3,4	56	2,3,3',4'	91	2,2',3,4',6
22	2,3,4'	57	2,3,3',5	92	2,2',3,5,5'
23	2,3,5	58	2,3,3',5'	93	2,2',3,5,6
24	2,3,6	59	2,3,3',6	94	2,2',3,5,6'
25	2,3',4	60	2,3,4,4'	95	2,2',3,5',6
26	2,3',5	61	2,3,4,5	96	2,2',3,6,6'
27	2,3',6	62	2,3,4,6	97	2,2',3',4,5
28	**2,4,4'**	63	2,3,4',5	98	2,2',3',4,6
29	2,4,5	64	2,3,4',6	99	2,2',4,4',5
30	2,4,6	65	2,3,5,6	100	2,2',4,4',6
31	2,4',5	66	2,3',4,4'	**101**	**2,2',4,5,5'**
32	2,4',6	67	2,3',4,5	102	2,2',4,5,6'
33	2',3,4	68	2,3',4,5'	103	2,2',4,5',6
34	2',3,5	69	2,3',4,6	104	2,2',4,6,6'
35	3,3',4	70	2,3',4',5	105**	2,3,3',4,4'

[a] Bold indicates so-called indicator congeners, readily detectable in abiota and biota by a variety of analytical techniques (i.e. PCBs 28, 52, 101, 118, 138, 153, 180).

[b]

* Non-ortho congener,

** mono-ortho congener,

*** di-ortho congener, also chlorinated in both para and at least two meta positions.

Source: Ballschmiter & Zell 1980.

No.[b]	Structure	No.[b]	Structure	No.[b]	Structure
106	2,3,3',4,5	141	2,2',3,4,5,5'	176	2,2',3,3',4,6,6'
107	2,3,3‘,4',5	142	2,2',3,4,5,6	177	2,2',3,3',4',5,6
108	2,3,3',4,5'	143	2,2',3,4,5,6'	178	2,2',3,3',5,5',6
109	2,3,3',4,6	144	2,2',3,4,5',6	179	2,2',3,3',5,6,6'
110	2,3,3‘,4',6	145	2,2',3,4,6,6'	**180*****	**2,2',3,4,4',5,5'**
111	2,3,3',5,5'	146	2,2',3,4',5,5'	181	2,2',3,4,4',5,6
112	2,3,3',5,6	147	2,2',3,4‘,5,6	182	2,2',3,4,4',5,6'
113	2,3,3',5',6	148	2,2',3,4',5,6'	183	2,2',3,4,4',5',6
114**	2,3,4,4',5	149	2,2',3,4‘,5',6	184	2,2',3,4,4',6,6'
115	2,3,4,4',6	150	2,2',3,4',6,6'	185	2,2',3,4,5,5',6
116	2,3,4,5,6	151	2,2',3,5,5',6	186	2,2',3,4,5,6,6'
117	2,3,4',5,6	152	2,2',3,5,6,6'	187	2,2',3,4',5,5',6
118**	2,3',4,4',5	**153*****	**2,2',4,4',5,5'**	188	2,2',3,4',5,6,6'
119	2,3',4,4',6	154	2,2',4,4',5,6'	189**	2,3,3',4,4',5,5'
120	2,3',4,5,5'	155	2,2',4,4',6,6'	190***	2,3,3',4,4',5,6
121	2,3',4,5',6	156**	2,3,3',4,4',5	191***	2,3,3',4,4',5',6
122	2',3,3',4,5	157**	2,3,3',4,4',5'	192	2,3,3',4,5,5',6
123**	2',3,4,4',5	158***	2,3,3',4,4',6	193	2,3,3',4',5,5',6
124	2',3,4,5,5'	159	2,3,3',4,5,5'	194***	2,2',3,3',4,4',5,5'
125	2',3,4,5,6'	160	2,3,3',4,5,6	195	2,2',3,3',4,4',5,6
126*	3,3',4,4',5	161	2,3,3',4,5',6	196	2,2',3,3',4,4',5,6'
127	3,3',4,5,5'	162	2,3,3',4',5,5'	197	2,2',3,3',4,4',6,6'
128***	2,2',3,3',4,4'	163	2,3,3',4‘,5,6	198	2,2',3,3',4,5,5',6
129	2,2',3,3‘,4,5	164	2,3,3',4‘,5',6	199	2,2',3,3',4,5,6,6'
130	2,2',3,3',4,5'	165	2,3,3',5,5',6	200	2,2',3,3',4,5',6,6'
131	2,2',3,3‘,4,6	166***	2,3,4,4',5,6	201	2,2',3,3',4',5,5',6
132	2,2',3,3',4,6'	167**	2,3',4,4',5,5'	202	2,2',3,3',5,5',6,6'
133	2,2',3,3',5,5'	168***	2,3',4,4',5',6	203	2,2',3,4,4',5,5',6
134	2,2',3,3‘,5,6	169*	3,3',4,4',5,5'	204	2,2',3,4,4',5,6,6'
135	2,2',3,3',5,6'	170***	2,2',3,3',4,4',5	205***	2,3,3',4,4',5,5',6
136	2,2',3,3',6,6'	171	2,2',3,3',4,4',6	206	2,2',3,3',4,4',5,5',6
137***	2,2',3,4,4',5	172	2,2',3,3',4,5,5'	207	2,2',3,3',4,4',5,6,6'
138***	**2,2',3,4,4',5'**	173	2,2',3,3',4,5,6	208	2,2',3,3',4,5,5',6,6'
139	2,2',3,4,4',6	174	2,2',3,3',4,5,6'	209	2,2',3,3',4,4',5,5',6,6'
140	2,2',3,4,4',6'	175	2,2',3,3',4,5',6		

Table 7.2. Relative percentage concentrations of individual PCB congeners in Clophen commercial mixtures and in human adipose tissue[a]

Congener	IUPAC No.[b]	Clophen A50	Clophen A60	Adipose tissue	Congener	IUPAC No.[b]	Clophen A50	Clophen A60	Adipose tissue
2,2',3,4	41[c]	1.2		0.66	2,2',3,3'4,6'	132	1.8	3.2	0.15
2,2',3,5'	44	1.9		1.1	2,2',3,3',5,6'	135	1.2	4.2	1.0
2,2',4,5'	49	1.4			2,2',3,3',6,6'	136	0.5	1.0	
2,2',5,5'	52	5.0			2,2',3,4,4',5'	138***	5.1	11.3	14.0
2,3,4',6	64[c]	2.1		0.56	2,2',3,4',5,5'	146	0.90	2.9	2.7
2,3',4',5	70	3.9		1.5	2,2',3,4',5',6	149	2.0	6.5	0.13
2,2',3,3',4	82	1.0			2,2',3,5,5',6	151	1.3	3.3	0.43
2,2',3,3',6	84	2.5	0.28	0.48	2,2',4,4',5,5'	153***	4.2	12.9	21.5
2,2',3,4,5'	87	5.4	1.4	2.3	2,3,3',4,4',5	156**	0.81	1.5	2.0
2,2',3,5,5'	92	2.2	1.1	1.2	2,3',4,4',5,5'	167**	0.47	1.0	0.49
2,2',3,5',6	95	4.4	2.9	1.2	2,2',3,3',4,4',5	170***	0.72	4.1	3.9
2,2',3',4,5	97	1.4			2,2',3,3',4,4',6	171	0.13	1.3	0.57
2,2',4,4',5	99	1.8		1.9	2,2',3,3',4,5,5'	172	0.23	0.90	1.2
2,2',4,5,5'	101	7.0	5.6	4.2	2,2',3,3',4,5,6'	174	0.33	3.7	
2,3,3',4,4'	105**	3.6		1.9	2,2',3,3',4',5,6	177	0.27	2.1	1.3
2,3,3',4',6	110	7.6	2.9	4.7	2,2',3,4,4',5,5'	180***	0.98	7.6	7.7
2,3',4,4',5	118**	5.0	1.6	5.4	2,2',3,4,4',5',6	183	0.17	1.8	2.5
2,2',3,3',4,4'	128***	1.3	2.0	0.81	2,2',3,4',5,5',6	187	0.39	3.3	3.5
2,2',3,3',4,5'	130	1.1	1.5		2,2',3,3',4,4',5,5'	194***	0.35	0.67	1.7

[a] Only those congeners constituting at least 1% of total PCB in either matrix are shown.

[b] ** Mono-ortho congener, *** di-ortho congener, also chlorinated in both para and at least two meta positions.

[c] Tentative structure.

Source: Jensen & Sundström 1974.

Table 7.3. Relative percentage concentrations of individual PCB congeners in an Aroclor commercial mixture and in human milk[a]

Congener	IUPAC No.[b]	Aroclor 1260	Human milk	Congener	IUPAC No.[b]	Aroclor 1260	Human milk
2,4,4’	28	0.04	8.8 [c]	2,2’,4,4’,5,5’	153***	9.6	12
2’,3,4	33	0.09	2.2	2,3,3’,4,4’,5	156**	0.45	4.87
3,4,4’	37	0.04	2.9	2,2’,3,3’,4,4’,5	170***	6.8	5.3
2,2’,3,4	41	0.25	1.3	2,2’,3,3’,4,4’,6/	171/202	1.2	0.37
2,2’,5,5’	52	0.25	1.9	2,2’,3,3’,4,5,6’	174	5.5	0.39
2,4,4’,5	74	0.03	11	2,2’,3,3’,4’,5,6	177	1.9	0.61
2,2’,3,5’,6	95	2.7		2,2’,3,3’,5,5’,6	178	1.2	
2,2’,4,4’,5	99	0.13	4.8	2,2’,3,4,4’,5,5’	180***	9.1	5.3
2,2’,4,5,5’	101	2.5	0.97	2,2’,3,4,4’,5’,6	183	2.3	1.4
2,3,3’,4’,6	110	1.7	1.0	2,2’,3,4,5,5’,6	185	4.1	0.11
2,3’,4,4’,5	118**	0.49	6.5	2,2’,3,4’,5,5’,6	187	4.5	1.5
2,2’,3,3’,6,6’	136	1.4		2,3,3’,4,4’,5,5’	189**	0.15	2.4
2,2’,3,4,4’,5’	138***	6.5	10	2,2’,3,3’,4,4’,5,5’	194***	1.7	0.48
2,2’,3,4,5,5’	141	2.5	0.29	2,2’,3,3’,4,4’,5,6	195	3.1	0.31
2,2’,3,4,5’,6/	144/135	1.5	0.51	2,2’,3,3’,4,4’,5,6’	196	2.5	0.18
2,2’,3,4’,5,5’	146	1.3	1.9	2,2’,3,3’,4,5,5’,6’	201	2.9	0.85
2,2’,3,4’,5’,6	149	7.4		2,2’,3,4,4’,5,5’,6	203	3.1	0.79
2,2’,3,5,5’,6	151	2.5	0.59				

[a] Only those congeners constituting at least 1% of total PCB in either matrix are shown.

[b] ** Mono-ortho congener, *** di-ortho congener, also chlorinated in both para and at least two meta positions.

[c] This congener constitutes only about 1.2% in Swedish mother’s milk (Norén & Lundén 1991).

Source: Safe et al. 1985.

underlying mechanisms involved are probably different. The toxicity data on PCB hydroxy- and methyl-sulfonyl metabolites indicate that these compounds have their own toxicity profiles, which include endocrine disturbances and respiratory tract toxicity.

4.1/ Toxicokinetics

The physicochemical properties of PCBs and their metabolites enable these compounds to be readily absorbed by organisms. The high lipid solubility and low water solubility of all PCB congeners lead to the retention of the compounds in fatty tissues. Once absorbed, PCBs are readily distributed to all body compartments, where the storage rate is proportional to the fat content of the organ. Several hydroxylated and sulfur-containing PCB-metabolites, which are retained in tissues and elicit biological effects, have been identified. Protein binding of PCBs and their metabolites contributes to tissue retention. The main route of PCB excretion is via the faeces (biliary excretion), urine and breast-milk. PCBs and their methyl-sulfonyl metabolites are excreted through human milk, and breast-fed infants are therefore highly exposed. PCBs and their methyl-sulfonyl metabolites may also cross the placenta. Perinatal PCB exposure is a major concern with regard to human health effects, owing to current background exposure levels.

4.2/ Effects on laboratory animals

Non-dioxin-like PCB congeners are poorly characterized from a toxicological point of view. To date, toxic effects specific to non-dioxin-like PCB congeners have not been identified, however, animal studies indicate that endocrine disturbances and developmental toxicity are end-points of major concern. The available toxicological information suggests that typical effects of PCB exposure, including the critical effects of carcinogenicity, immunotoxicity and neurobehavioural alterations, are caused by all PCB congener classes (i.e. by both the dioxin-like and the non-dioxin-like congeners) (WHO 2001). However, the underlying mechanisms involved are probably different.

The developing fetus and the neonate are thought to represent a potential "at risk" population owing to increased susceptibility. For further information about the toxicology profile and the human health implications of dioxin-like PCB congeners relative to LRTAP see Chapter 6. Toxicity data on the hydroxy- and methyl-sulfonyl metabolites of PCBs indicate that these compounds have their own toxicity profiles, which could include endocrine disturbances and respiratory tract toxicity.

4.3/ Health effects in humans and the TEF-concept

In 1992 a Nordic expert group concluded that the critical health effects related to PCB exposure are carcinogenicity, immunotoxicity, and neurobehavioural changes (Ahlborg et al 1992). While the carcinogenicity and immunotoxicity data sets were judged unsuitable for risk assessment, the neurobehavioural data were considered highly relevant. Behavioural effects following perinatal exposure were observed

both in animals (monkey, rat and mouse) and humans. Hyperactivity and impaired learning ability were reported for Rhesus monkey infants exposed *in utero* and during lactation. Similar and dose-related effects were reported for human infants whose mothers were exposed to PCBs through the intake of contaminated fish in Michigan in the United States. The effects recorded in these infants were slight, but were still regarded as adverse. Further supportive evidence came from a similar study performed in North Carolina, and from a study reporting similar but more pronounced effects in children born to mothers in Yu-Cheng, Province of Taiwan, who were poisoned via food oil contaminated with PCBs. Even if the Michigan study was not fully conclusive from an epidemiological point of view, owing to some potentially important confounding factors, it was used to calculate the LOEL for subtle neurotoxic effects in infants from exposed mothers of 0.014–0.9 μg /kg bw per day. This exposure is of the same order of magnitude as the present PCB exposure of the general population in many countries.

The same expert group also concluded that it was impossible, based on the available database, to reach a scientifically justified recommendation on a TDI of either PCB mixtures or of any individual non-dioxin-like PCB congener. Data based on the exposure to technical PCB mixtures was concluded to be of little relevance for the assessment of PCB exposure via common food items, owing to differences in congener composition. Also, many studies on commercial mixtures did not account for possible biochemical and/or toxic contributions from impurities, in particular PCDFs and PCNs.

The Nordic expert group emphasized that qualitative differences in the toxic properties of individual congeners introduces several problems in the health risk assessment of PCBs, problems that are more complicated than usually encountered when dealing with a group of chemicals. Finally, it was acknowledged that there are limited toxicity data on PCB metabolites and on interactions between various groups of PCBs, including the hydroxy- and methyl-sulfonyl metabolites.

On behalf of WHO, the German Federal Institute for Consumer Health Protection and Veterinary Medicine (BGVV) recently organized an international exploratory consultation to address the issue of non-dioxin-like PCB congeners and human health (WHO 2001). The scope of the consultation was to explore scientifically justified and practically feasible concepts of addressing the overall toxicological properties of non-dioxin-like PCB congeners in the context of risk assessment and regulatory decision-making. The meeting reached the following important conclusions

- In order to perform a scientifically justified health risk assessment, it is first necessary to compile and evaluate the existing exposure and toxicity data for major non-dioxin-like PCB congeners. Studies on individual non-dioxin-like PCB congeners, synthetic and/or natural environmental mixtures and PCB metabolites should be included in this compilation and evaluation process. A major goal of the process would be to define toxicological end-points specific for the non-dioxin-like PCB congeners, if present. The process will also serve to identify the major data requirements.

- Following the evaluation of all relevant scientific data with regard to hazard characterization, a decision can be made as to the necessity or possibility of conducting a separate risk assessment for non-dioxin-like PCB congeners. A major issue to explore is whether or not the present dioxin risk assessment covers the effects of non-dioxin-like PCBs, if present, in addition to the dioxin-like effects. If dioxin-like effects are the major part of PCB exposure, e.g. in food, then risk assessment can be performed by the WHO TEQ approach for dioxins (see Chapter 6). If additional critical effects are caused by non-dioxin-like PCB congeners, ignoring this exposure would result in an underestimation of the exposure effects, unless a separate risk assessment is performed for these congeners.

It is unlikely that a TEF concept corresponding to the one for dioxins can be applied to non-dioxin-like PCB congeners owing to the lack of major criteria, the most important being the lack of a common mechanism of action.

4.4/ Existing reference values, critical outcomes

The LOEL for subtle neurotoxic effects in infants following perinatal exposure is in the range 0.014–0.9 µg /kg bw per day. This exposure is of the same order of magnitude as the present PCB exposure of the general population in many countries.

Table 7.4. Dioxin-like PCB congeners that have been assigned toxic equivalency factors (TEFs) by WHO

PCB congener (IUPAC No.)	Chlorine substitution pattern	TCDD TEF
77 Non-ortho	3,3',4,4'	0.0001
81 Non-ortho	3,4,4',5	0.0001
126 Non-ortho	3,3',4,4',5	0.1
169 Non-ortho	3,3',4,4',5,5'	0.01
105 Mono-ortho	2,3,3',4,4'	0.0001
114 Mono-ortho	2,3,4,4',5	0.0005
118 Mono-ortho	2,3',4,4',5	0.0001
123 Mono-ortho	2',3,4,4',5	0.0001
156 Mono-ortho	2,3,3',4,4',5	0.0005
157 Mono-ortho	2,3,3',4,4',5'	0.0005
167 Mono-ortho	2,3',4,4',5,5'	0.00001
189 Mono-ortho	2,3,3',4,4',5,5'	0.0001

Source: van den Berg et al. 1998.

It has not yet been possible, based on the available data, to reach a scientifically justified agreement on a TDI of either PCB mixtures or of any individual non-dioxin-like PCB congener.

IARC (1987) has classified PCBs as probably carcinogenic to humans (group 2A).

Regarding the implications for human health of non-dioxin-like PCBs relative to LRTAP, the critical issues are carcinogenicity, immunotoxicity and neurobehavioural alterations. Endocrine disturbances and developmental toxicity are other

Table 7.5. Enzyme-inducing properties of individual PCB congeners

Congener	IUPAC No.	Category	Methylcholantrene-typeinduction	Phenemal-type induction
3,3',4,4'	77	Non-*ortho* [a]	+	–
3,4,4',5	81	Non-*ortho*	+	+
3,3',4',5	126	Non-*ortho* [a]	+	–
3,3',4,4',5,5'	169	Non-*ortho* [a]	+	–
2,3,3',4,4'	105	Mono-*ortho* [a]	+	+
2,3,4,4',5	114	Mono-*ortho* [a]	+	+
2,3',4,4',5	118	Mono-*ortho* [a]	+	+
2',3,4,4',5	123	Mono-*ortho* [a]	+	+
2,3,3',4,4',5	156	Mono-*ortho* [a]	+	+
2,3,3',4,4',5'	157	Mono-*ortho* [a]	+	+
2,3',4,4',5,5'	167	Mono-*ortho* [a]	+	+
2,3,3',4,4',5,5'	189	Mono-*ortho* [a]	+	+
2,2',3,3',4,4'	128	Di-*ortho* [a]	+	+
2,2',3,4,4',5	137	Di-*ortho* [a]	–	+
2,2',3,4,4',5'	138	Di-*ortho* [a]	+	+
2,2',4,4',5,5'	153	Di-*ortho* [a]	–	+
2,3,3',4,4',6	158	Di-*ortho* [a]	+	+
2,3,4,4',5,6	166	Di-*ortho* [a]	+	+
2,3',4,4',5',6	168	Di-*ortho* [a]	+	+
2,2',3,3',4,4',5	170	Di-*ortho* [a]	+	+
2,2',3,4,4',5,5'	180	Di-*ortho* [a]	–	+
2,3,3',4,4',5,6	190	Di-*ortho* [a]	–	+
2,3,3',4,4',5',6	191	Di-*ortho* [a]	–	+
2,2',3,3',4,4',5,5'	194	Di-*ortho* [a]	–	+
2,3,3',4,4',5,5',6	205	Di-*ortho* [a]	–	+
3,3'	11		–	(+) [b]
3,5	14		–	(+)
4,4'	15		–	(+)
3,4,4'	37		+	+
2,2',4,4'	47		–	+
2,2',5,5'	52		–	(+)
2,2',6,6'	54		–	(+)
2,3',4,4'	66		–	+
2,4,4',6	75		–	(+)
3,3',5,5'	80		–	(+)
2,2',3,4,5'	87		–	+
2,2',4,5,5'	101		–	+
2,3,4,4',6	115		–	+
2,3',4,4',6	119		+	+
2,2',3,3',5,5'	133		–	+
2,2',3,3',6,6'	136		–	(+)
2,2',3,5,5',6	151		–	(+)
2,2',4,4',5,6'	154		–	+
2,2',4,4',6,6'	155		–	(+)
2,3,3',4,5,5'	159		–	(+)
2,3,3',4',5,6	163		–	+
2,3,3',5,5',6	165		–	+
2,2',3,3',4,4',5,6	195		–	+

[a] Also chlorinated at both *para* and at least two *meta* positions.
[b] (+) = weak or non-inducer.

Source: McFarland & Clarke, 1989.

toxicological end-points of concern. For the human health implications of dioxin-like PCB congeners relative to LRTAP see Chapter 6.

5/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

As human exposure to PCBs, both dioxin-like and non-dioxin-like congeners, may reach estimated LOAELs for neurodevelopmental effects in infants, the weight of evidence suggests an increased health risk from current exposures. Lack of congener-specific exposure and toxicity data limits the possibilities of indicating which congeners are responsible for the effects.

It has been demonstrated that PCBs, similar to other POPs, resist degradation, bioaccumulate, are transported through air, water and migratory species across international boundaries and are finally deposited far from the place of release, where they accumulate in terrestrial and aquatic ecosystems. The clearest evidence for this long-range transport derives from the high levels of PCBs measured in the Arctic region. Owing to the long-range transboundary transport, PCBs are nowadays ubiquitous contaminants of the ecosystem and are able to enter the food chain. Therefore, most of the human population is exposed to PCBs and their metabolites. Moreover, since PCBs and their methyl-sulfonyl metabolites pass from mother to fetus through the placenta, and from mother to newborn through breastfeeding, infants are at risk of harmful effects in the most critical period of their development.

Nowadays, about 40 years after the first identification of PCBs in human and wildlife tissues, the scientific community is still trying to assess the long-term health effects from background exposure levels worldwide. The real cost of the contamination of the ecosystem by PCBs is unknown.

The chemical and physical properties of PCBs make them susceptible to LRTAP, they are expected to contribute significantly to exposure and health risks, especially in remote areas.

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CHAPTER 8/
POLYCYCLIC AROMATIC HYDROCARBONS

1/ INTRODUCTION

Polycyclic aromatic hydrocarbons (PAHs) are a group of compounds composed of two or more fused aromatic rings. PAHs are produced when organic matter containing carbon and hydrogen is exposed to temperatures exceeding 700 °C, i.e. pyrolytic processes and incomplete combustion.

Most direct releases of PAHs to the environment are to the atmosphere, both from natural and from anthropogenic sources, with emissions from human activities predominating. PAHs in the atmosphere are mostly associated with particulate matter; however, the compounds are also found in the gaseous phase. The primary natural sources of airborne PAHs are forest fires and volcanoes. The residential burning of wood is the largest source of atmospheric PAHs. Other important stationary anthropogenic sources include industrial power generation, incineration, the production of asphalt, coal tar and coke, petroleum catalytic cracking and primary aluminium production (in particular Södeberg technology). Stationary

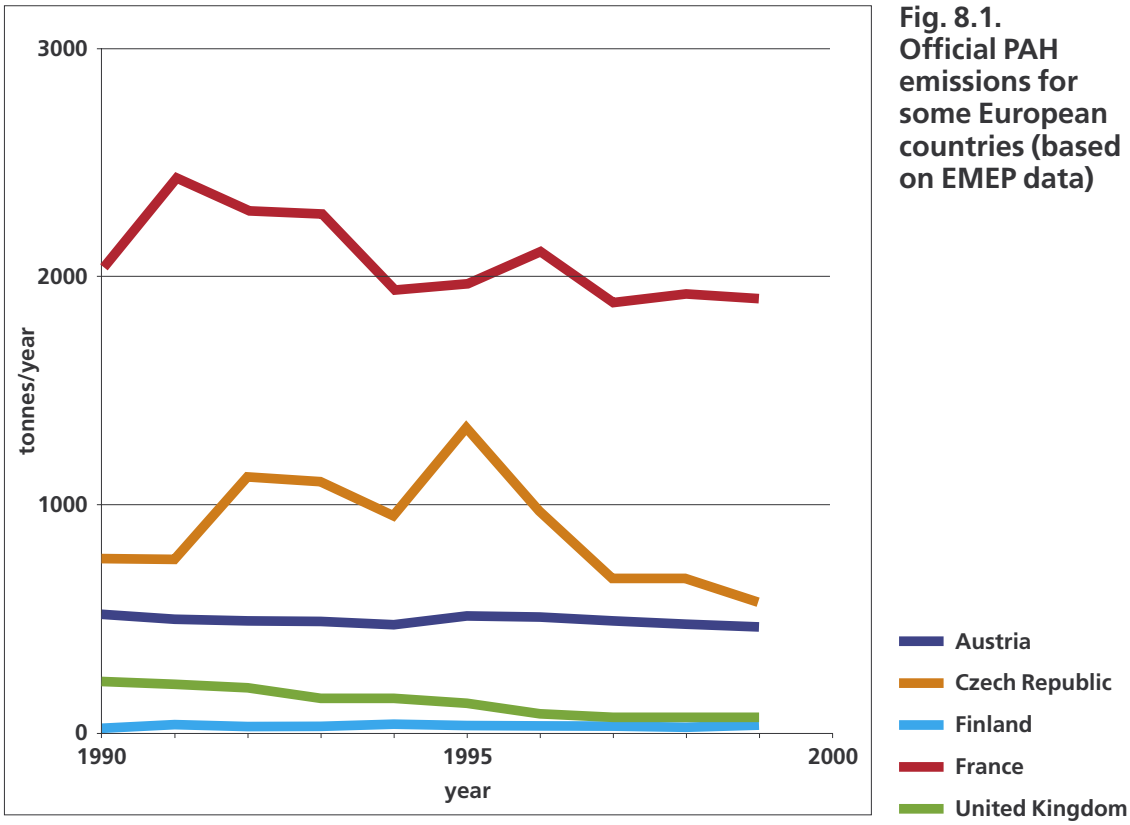


Fig. 8.1. Official PAH emissions for some European countries (based on EMEP data)

sources account for about 80% of total annual PAHs emissions; the rest are from mobile sources. The most important mobile sources are exhausts from gasoline and diesel-powered vehicle engines.

The emission of PAHs during industrial production and processing in developed countries are not thought to be important in comparison with the release of PAHs from incomplete combustion processes, since closed systems and recycling processes are usually used (WHO 1998).

The emissions of benzo[*a*]pyrene (BaP) into the air from several sources in the Federal Republic of Germany in 1981 were estimated to amount to 18 tonnes; about 30% was caused by coke production, 56% by heating with coal, 13% by motor vehicles and less than 0.5% by the combustion of heating oil and coal-fired power generation (WHO 2000). These figures may vary considerably from country to country.

In the Netherlands, the estimated release in 1985 was < 1 tonne (each) for benzo[*k*]fluoranthene and indeno[1,2,3-*c,d*]pyrene, < 10 tonnes (each) for anthracene, fluoranthene, benz[*a*]anthracene, chrysene and BaP, and 48–70 tonnes (each) for naphthalene and phenanthrene, mainly resulting from wood heating. The total PAH input, mainly from coal and wood heating, was about 63 tonnes in Norway and 130 tonnes in Sweden. In Canada in 1990, the total PAH release due to residential heating, mainly wood burning, was about 500 tonnes (WHO 1998).

Estimates of trends in emissions are available for a few countries. The reduction in the release of PAHs into the atmosphere from domestic heating resulting from the increasing use of oil and gas during the last 30–40 years was estimated in western Germany at 90–99% (WHO 1998). During the last 10 years there has been a relatively small decrease in reported PAH emissions for most of the European countries (Fig. 8.1). In the United Kingdom between 1990 and 1995, estimated total emissions of BaP decreased by over 50%, from 80.2 to 36.8 tonnes/year. The forecast emission for 2010 amounts to 16.4 tonnes/year.

2/ POTENTIAL FOR LRTAP

2.1/ Physicochemical properties allowing atmospheric transport

PAHs are a large group of compounds comprising two or more fused aromatic rings made entirely from carbon and hydrogen. The physical and chemical properties of the individual PAHs vary. Some physicochemical properties, as well as suggested half-life classes of PAHs in various environmental compartments, are presented in Table 8.1. While the physicochemical properties of PAHs vary considerably, the semi-volatile property of some PAHs makes them highly mobile throughout the environment, deposition and re-volatilization distributing them between air, soil and water bodies. A proportion of PAHs are subject to long-range atmospheric transport, making them a transboundary environmental problem.

Table 8.1. Physical and chemical properties of polycyclic aromatic compounds

Compound	Melting point (°C)	Boiling point (°C)	Vapour pressure (Pa at 25 °C)	n-Octanol : water partition coefficient (log Kow)	Solubility in water at 25 °C (µg/litre)	Henry's law constant at 25 °C (kPa)	Categories[a] of half-lives			
							Air	Water	Soil	Sediment
Acenaphthylene	92–93	279	8.9×10^{-1}	4.07	–	1.14×10^{-3}	2	4	6	7
Acenaphthene	95	295	2.9×10^{-1}	3.92	3.93×10^{3}	1.48×10^{-2}				
Fluorene	115–116	340	8.0×10^{-2}	4.18	1.98×10^{3}	1.01×10^{-2}	2	4	6	7
Phenanthrene	100.5	342	1.6×10^{-2}	4.6	1.29×10^{3}	3.98×10^{-3}	2	4	6	7
Anthracene	216.4	375	8.0×10^{-4}	4.5	73	7.3×10^{-2}	2	4	6	7
Fluoranthene	108.8	393	1.2×10^{-3}	5.22	260	6.5×10^{-4}	3	5	7	8
Pyrene	150.4	400	6.0×10^{-4}	5.18	135	1.1×10^{-3}	3	5	7	8
Benz[*a*]anthracene	160.7	448	2.8×10^{-5}	5.61	14	–	3	5	7	8
Chrysene	253.8	481	8.4×10^{-5}	5.91	2.0	–	3	5	7	8
Benzo[*b*]fluoranthene	168.3	480	6.7×10^{-5}	6.12	1.2 (20 °C)	5.1×10^{-5}				
Benzo[*j*]fluoranthene	165.4	480	2.0×10^{-6}	6.12	2.5	–				
Benzo[*k*]fluoranthene	215.7	496	1.3×10^{-8}	6.84	0.76	4.4×10^{-5} (20 °C)	3	5	7	8
Benzo[*a*]pyrene	178.1	536	7.3×10^{-7}	6.50	3.8	3.4×10^{-5}	3	5	7	8
Indeno[1,2,3-*c,d*]pyrene	163.6	524	1.3×10^{-8}	6.58	62	2.9×10^{-5}(20 °C)				
Dibenz[*a,h*]anthracene	266.6	594	1.3×10^{-8}	6.50	0.5 (27 °C)	7×10^{-6}	3	5	7	8
Dibenzo[*a,i*]pyrene	282	525	3.2×10^{-10}	7.30	0.17	4.31×10^{-6}				
Coronene	439		2×10^{-10}	–	5.4	0.14				

Class	Half-life (hours)	
	Mean	
1	17	10–30
2	55	30–100
3	170	100–300
4	550	300–1000

Class	Half-life (hours)	
	Mean	Range
5	1700	1000–3000
6	5500	3000–10 000
7	17 000	10 000–30 000
8	55 000	>30 000

[a] Suggested half-life classes of polycyclic aromatic hydrocarbons in various environmental compartments.

Source: WHO 1998.

2.2/ Behaviour in environment and persistence

The global movement of PAHs can be summarized as follows. PAHs released to the atmosphere are subject to short- and long-range transport and are removed by wet and dry deposition on to soil, water and vegetation. In surface water, PAHs can volatilize, photolyse, biodegrade or bind to suspended particles or sediments.

PAHs are present in the atmosphere in the gaseous phase or sorbed to particulates. In general, PAHs having two or three rings (naphthalene, acenaphthene, anthracene, fluorene, phenanthrene) are present in air, predominantly in the vapour phase. PAHs that have four rings (fluoranthene, pyrene, chrysene) exist both in the vapour and in the particulate phase, and PAHs having five or more rings (BaP, benzo[*g,h,i*]perylene) are found predominantly in the particle phase. Atmospheric residence time and transport distance depend on the size of particles to which PAHs are adsorbed and on climatic conditions. About 90–95% of particulate PAHs are associated with particle diameters < 3.3 µm. Particles with a diameter range of 0.1–3.0 µm, with which airborne PAHs are principally associated, are expected to have atmospheric residence times of a few days and, hence, can undergo long-range transport. Furthermore, based on field observations and laboratory studies with model aerosols, there are indications that abiotic degradation of PAHs on or in particles is hindered in the ambient atmosphere. A possible explanation is that PAHs diffuse partly from the particulates' surface into the particle volume, where degradation by the OH radical is not significant (Behymer & Hites 1988; Finizio et al. 1997; Masclet et al. 1995; McDow et al. 1996; Offenberg & Baker 2002; Reyes et al. 2000).

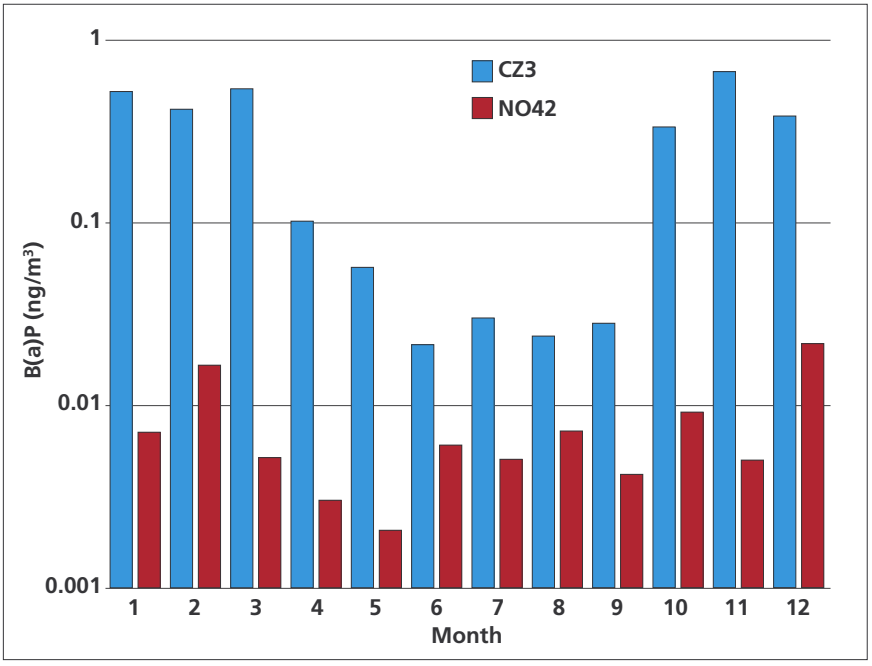


Fig. 8.2. Concentrations of BaP in air + aerosol at two EMEP stations in 1999: Kosetica, Czech Republic (CZ3) and Zeppelin, Spitsbergen, Norway (NO42)

Source: Berg et al. 2001.

Two types of chemical reaction are predominant: reactions between PAHs adsorbed on the particle surfaces and oxidant gases like NO_2, O_3 and SO_3; and photooxidation of PAHs under solar radiation (ATSDR 1995). The formation of

nitro-PAHs from the gas-phase reactions of fluoranthrene and pyrene with the OH radical in the presence of NO_X has been confirmed under both experimental (Arey et al. 1986) and environmental conditions (Ciccioli et al. 1996).

Photolysis is the most important factor in the decay of particle-sorbed PAHs in the atmosphere. In the absence of local sources, therefore, a pronounced seasonal trend is to be expected (Berg et al. 2001) (Fig. 8.2).

Half-lives in air are estimated to be in the range of a few minutes to one week, as determined by season (longer in winter), substance and particulate matter composition (European Commission 2001).

PAHs in soil can volatilize, undergo abiotic degradation (photolysis and oxidation) biodegrade, accumulate in plants or enter groundwater, and be transported within an aquifer. Based on experimental results, the half-lives (days) of the PAHs in soil were estimated (Table 8.2) (Park et al. 1990).

Table 8.2. Estimated half-lives of the PAHs in soil

Compound	Estimated half-lives (days)
Naphthalene	2.1–2.2
Anthracene	10–134
Phenanthrene	16–35
Fluoranthene	268–377
Pyrene	199–260
Chrysene	371–387
Benzo[*a*]pyrene	229–309
Dibenz[*a,h*]anthracene	361–420

Source: Park et al. 1990.

2.3/ Bioaccumulation

Aquatic organisms that metabolize PAHs to little or no extent, such as algae, molluscs and the more primitive invertebrates (protozoans, porifers and cnidaria) accumulate high concentrations of PAHs, as would be expected from their log K_{ow} values, whereas organisms that metabolize PAHs to a great extent, such as fish and higher invertebrates, accumulate little or no PAHs.

The concentration of PAHs in vegetation is generally considerably lower than that in soil, the bioaccumulation factors ranging from 0.0001 to 0.33 for BaP and from 0.001 to 0.18 for 17 other PAHs tested.

Biomagnification (the increase in concentration of a substance in animals in successive trophic levels of food chains) of PAHs has not been observed in aquatic systems and would not be expected to occur, because most organisms have a high biotransformation potential for PAHs. Organisms at higher trophic levels in food chains show the highest potential for biotransformation (WHO 1998).

2.4/ Monitoring and modelling

2.4.1/ Air

About 500 PAHs have been detected in the air, but most measurements have been made on BaP. Data obtained prior to the mid-1970s may be comparable only to a

limited extent with later data, because of different sampling and analytical procedures.

The natural background level of BaP (excluding forest fires) may be nearly zero. Present background levels of BaP on the island of Mallorca at an altitude of 1100 m (Simo et al. 1991) or on Spitsbergen at an altitude of 450 m (Shatalov et al. 2001a) amount to about 0.007 –0.1 ng/m^3 (Fig. 8.4)

In Europe in 1998, the highest emission of BaP took place in central and eastern European countries (the Czech Republic, Poland, the western Russian Federation and Ukraine) (Fig. 8.3). As a result, high levels of annual concentrations of BaP (more than 1 ng/m^3) were observed over vast areas of the Czech Republic, Poland and the Russian Federation. In these countries, high concentrations are determined mainly by internal BaP emissions. For most European countries, BaP concentra-

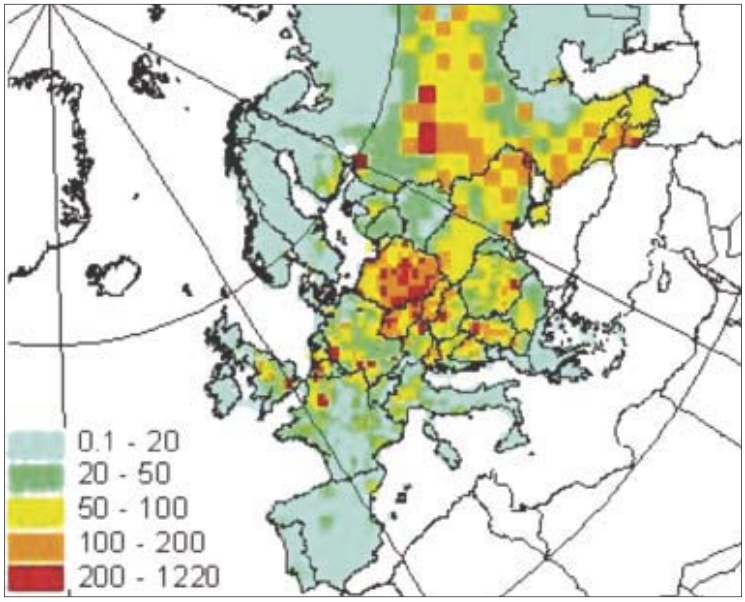


Fig. 8.3. Spatial distribution of BaP emissions used in calculations for 1998 (g/km^2 per year)

Source: Shatalov et al. 2001b.

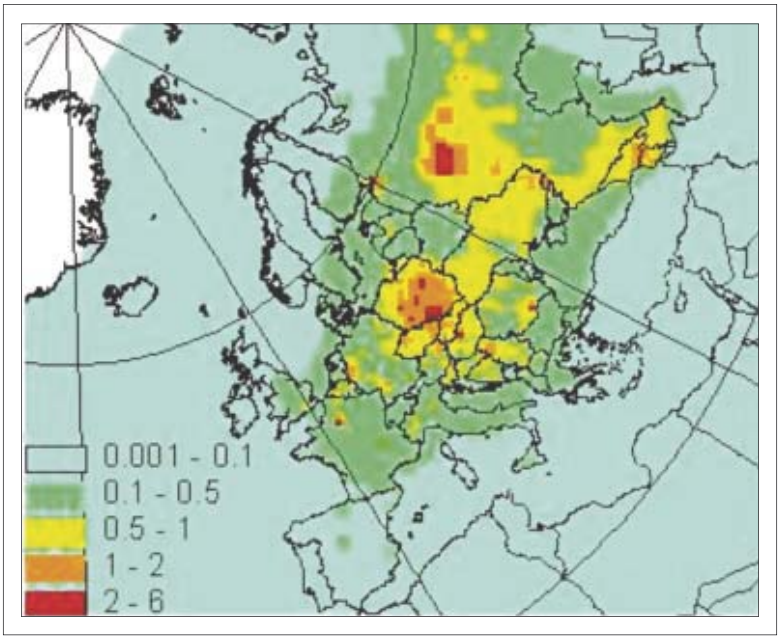


Fig. 8.4. Mean annual BaP air concentrations in 1998 (ng/m^3)

Source: Shatalov et al. 2001c.

tion values are within the range 0.1–1 ng/m^3 (Shatalov et al. 2001a), although concentrations from below 0.1 ng/m^3 to about 140 ng/m^3 in 30 different cities have been reported (WHO 1998). According to the map presented in Fig. 8.4, the influence of transboundary transport, assuming 0.1 ng/m^3 BaP as the threshold level for mean annual BaP air concentrations, can cover the area from western France to the Urals and from southern Scandinavia to Greece and Sicily.

The available data suggest that both emissions and concentrations of PAHs in the air are decreasing owing to modifications in heating systems and in the kinds of heating fuel used. In London, the concentration of BaP in the air fell from about 1.1 ng/m^3 in 1991 to about 0.3 ng/m^3 in 1999, and the sum of selected PAHs from about 140 ng/m^3 in 1991 to about 50 ng/m^3 in 1999 (European Commission 2001).

According to the data presented by EMEP, the mean annual concentrations of BaP in remote areas of the European region are within the range 0.001–0.1 ng/m^3. The lowest range of concentrations that can be contributed by LRTAP (e.g. over the Black Sea, Caspian Sea, southern Baltic or Adriatic Sea) amounts to 0.1–0.5 ng/m^3. The higher ranges, 0.5–6 ng/m^3, are generally connected with areas of high emission (Shatalov et al. 2001a)

2.4.2/ Soil

A rough distinction can be made between local sources of pollution (point sources) and diffuse sources. Point sources can give rise to significant local contamination of soil, whereas diffused sources usually affect more widespread areas. The annual deposition of BaP in Europe in 1998 wa between 0.1–10 g/km^2 (background level) and 80–213 g/km^2 in some areas of the Czech Republic, Poland and the Russian federation (Fig. 8.5).

Carcinogenic PAHs are found in all surface soil. Typical concentrations in forest soils range from 5 to 100 µg/kg. Substantial amounts of PAHs are transferred to

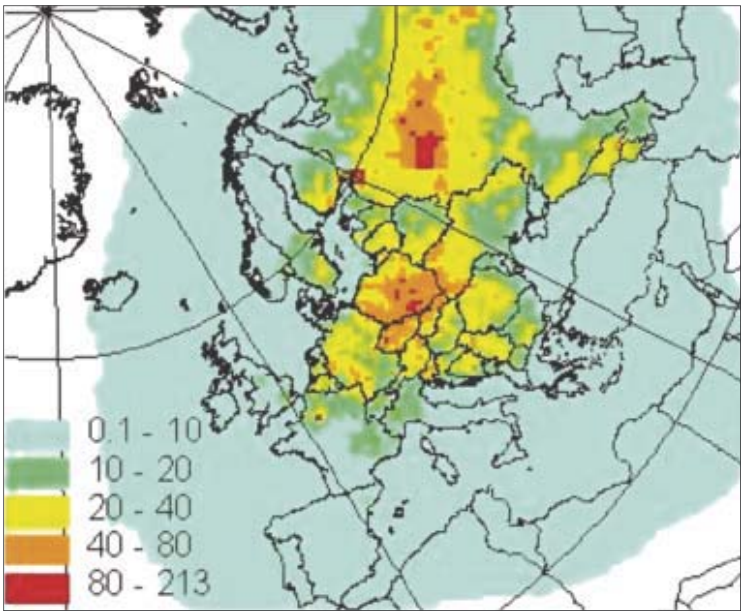


Fig. 8.5. Total deposition of BaP in 1998 (g/km^2 per year)

Source: Shatalov et al. 2001c.

forest soil from vegetative litter because the compounds are adsorbed from air to organic matter such as leaves and pine needles.

Rural soil contains carcinogenic PAHs at levels of 10–100 µg/kg, originating mainly from atmospheric fallout (WHO 1998). Metropolitan areas have higher PAH concentrations. The majority of urban soil concentrations fall in the range 600–3000 µg/kg. Higher values are likely near areas of heavy transportation and industrialization. Levels of 8000–336 000 µg/kg have been reported for road dust (WHO 2000).

Soil samples collected from Rothamsted Experimental Station in south-east England over a period of about 140 years (1846–1980) were analysed for PAHs. All of the soils were collected from the plough layer (0–3 cm) of an experimental plot for which atmospheric deposition was the only source of PAHs. The total PAH burden of the plough layer had increased by approximately five-fold since 1846. The concentrations of most of the individual PAHs (anthracene, fluorene, BaP, benzo[*e*]pyrene, fluoranthene, benzo[*b*]fluoranthene, phenanthrene and benz[*a*]anthracene) had increased by about one order of magnitude. For example, the BaP level was 18 µg/kg in 1846 and 130 µg/kg in 1980, and the anthracene level was 3.6 µg/kg in 1846 and 13 µg/kg in 1980. The levels of coronene, acenaphthylene, acenaphthene, perylene and benzo[*g,h,i*]perylene remained the same, whereas the naphthalene content decreased from 39 µg/kg in 1846 to 23 µg/kg in 1980 (WHO 1998).

The background deposition of BaP in the European region over sea and land remote from the main sources of emission of PAHs (southern Italy, Norway, Portugal, Spain and Turkey) amounted in 1998 to between 0.1 and 10 g/km^2 per year (Berg et al. 2002). Assuming that BaP is located in the upper 10 cm of soil, the annual deposition of BaP in soil can amount to between about 10 and 1000 µg/kg per year. The half-life of BaP is around 250 days (Park et al. 1990). According to the general toxicokinetic rules, the maximum concentration in the upper soil layer (A_∞) at a deposition of 100 µg/kg per year would amount to 100 µg/kg and the time necessary to attain this concentration would be 2.3 years. This value is similar to that (130 µg/kg) found in 1980 at Rothamsted.

2.4.3/ Water

Most of the PAHs in water are believed to result from urban runoff, from atmospheric fallout (smaller particles) and from asphalt abrasion (larger particles). In general, surface waters contain individual PAHs at levels up to 50 ng/l (WHO 1998). Collective concentrations of six PAHs (fluoranthene, benzo[*b*]fluoranthene, benzo[*k*]fluorathene, BaP, benzo[*g,h,i*]perylene and indeno[1,2,3-*c,d*]pyrene) in drinking-water did not exceed generally 0.1 µg/l, and in 90% samples were below 0.01 µg/l (WHO 2000).

Results of recent measurements indicate that most drinking-water samples contained 0.38–16 ng/l naphthalene and < 0.04–2.0 ng/l BaP (WHO 1998).

3/ PATHWAYS OF LRTAP-DERIVED HUMAN EXPOSURE

Raw food does not normally contain high levels of PAHs, but they are formed by processing, roasting, baking or frying. Vegetables may be contaminated by the deposition of airborne particles or by growth in contaminated soil. The levels of individual PAHs in meat, fish, dairy products, vegetables and fruits, sweets and beverages, cereals and their products, and animal and vegetable fats and oils were within the range 0.01–10 µg/kg. Concentrations of over 100 µg/kg were found in smoked meat and up to 96 µg/kg in smoked fish; smoked cereals contained up to 160 µg/kg (WHO 1998).

In a Dutch market-basket survey conducted from 1984 to 1986, the mean dietary daily intake of PAHs by 18-year-old males was estimated to range from 5 to 17 µg/day. The largest contribution of PAHs to the total diet came from sugar and sweets, cereal products, and oils, fats and nuts (de Vos et al. 1990).

From the average American diet, the intake of carcinogenic PAHs was estimated to be 1–5 µg/day, mostly from ingestion of unprocessed grains and cooked meats. The dietary intake estimate for people consuming diets with a large meat content was 6–9 µg/day, as a result of the additional contribution from charcoal-cooked or smoked meats and fish (Menzie et al. 1992).

Exposure via inhalation of ambient air was estimated to be 0.16 µg/day (median) with a range of 0.02–3 µg/day, assuming an inhalation rate of 20 m^3. Smoking one pack of unfiltered cigarettes per day increases exposure by an additional 2–5 µg/day (Menzie et al. 1992). Indoor air can be important source of human exposure to PAHs. Potential indoor combustion sources of PAHs include tobacco smoke, non-vented space heaters and food preparations. Environmental tobacco smoke was the most significant influence on indoor air PAH levels. In homes occupied by non-smokers, the highest average concentration of most PAHs were found in homes with gas cooking and heating appliances, followed by those with gas heating and electric cookers (Chuang et al. 1991).

Drinking-water exposure was estimated to be 0.006 µg/day (median), with a range of 0.0002–0.12 µg/day (2 litres of water daily). The estimated median soil intake of carcinogenic PAHs (50 mg soil/day) was 0.06 µg/day (range 0.003–0.3 µg/day). The total potential exposure to carcinogenic PAHs for adult males was estimated to be 3 µg/day (median), with a maximum value of 15 µg/day. Smoking of non-filtered cigarettes may double these estimates (Menzie et al. 1992).

4/ HEALTH HAZARD CHARACTERIZATION

4.1/ Toxicokinetics

4.1.1/ Absorption

PAHs are highly lipid-soluble. Like many other xenobiotic substances, they would be expected to be transported through the external and internal lipoprotein membranes of mammalian cells.

In humans, the major routes of uptake of PAHs are through the lungs and the respiratory tract after inhalation of PAH-containing aerosols or particulates, the

gastrointestinal tract after ingestion of contaminated food or water, and the skin as a result of contact with PAH-containing materials.

4.1.1.1/ Inhalation exposure

Studies on the lung retention of microcrystalline PAHs or PAHs in solution after intratracheal instillation to female rats have indicated that they are rapidly cleared from the respiratory tract. Clearance of PAHs from the lungs is best described as bi-phasic. For anthracene, benz[*a*]anthracene, 1-nitropyrene, BaP, 6-nitrobenzo[*a*]pyrene and dibenzo[*c,g*]carbazole, more than 85% of the initial dose was cleared with a half-time of less than 1 hour. The half-times for clearance of the residual radioactivity (1–15% of the dose) ranged from 26 to 63 hours (Weyand & Bevan 1986; Wolff et al. 1989a).

However, inhaled PAHs are mainly adsorbed on particles. After deposition in the airways, the particles can be eliminated by bronchial clearance. PAHs might be partly removed from particles during transport on the ciliated mucous and may penetrate into the bronchial epithelium cells, where they are metabolized (WHO 1987).

When BaP is absorbed on to particles, respiratory uptake is slower than after intratracheal instillation of pure compounds. When rats were exposed to radiolabelled BaP adsorbed on to diesel engine exhaust particles, lung clearance of radioactivity occurred in two phases. The half-life of the first phase was less than 1 hour. The second, long-term phase had a half-time of 18 days and represented 50% of the radioactivity that had initially been deposited in the lungs (Sun 1984). Similar results were obtained when BaP was adsorbed on to urban air particles (Tornquist 1985).

Inhalation of ^{14}C-BaP adsorbed on to carbon black particles resulted in 100-fold higher levels of ^{14}C in the lungs at the end of a 12-week exposure than did inhalation of pure BaP. The half-time for the decline in ^{14}C levels was 34 weeks for rats exposed to BaP adsorbed on to carbon black and 6 weeks for rats exposed to pure BaP (Wolf 1989a).

Inhalation absorption of BaP may be affected by the size of particles on to which it is adsorbed. The elimination of BaP from the lungs was studied in mice following intratracheal administration of pure BaP crystals or BaP coated on carbon particles of two size ranges (0.5–1.0 μm and 15–30 μm) (Creasia et al. 1976). Some 50% of the pure BaP crystals was cleared from the lungs within 1.5 hours and 95% within 24 hours, while only 50% of the BaP adsorbed on to the small particles cleared within 36 hours. Elution of BaP was even slower with the larger particle size (4–5 days).

The absorption of BaP may also be affected by the solubility of the vehicle used in administration. Approximately 70% of BaP administered with triethylene glycol was excreted 6 hours following intratracheal administration (Bevan & Ulman 1991). Excretion rates of BaP were only 58.4% and 56.2% with ethyl laureate and tricaprylin, respectively, within a 6-hour period.

Monkeys and dogs received nasal instillation of ^{14}C-BaP at doses of 0.16–0.21 mg/kg bw (Petridou-Fisher et al. 1988). Radiolabelled metabolites were detected in the nasal cavity, but little or no activity was detected in the blood and excreta

during the 48 hours after exposure. These results indicate that absorption of BaP and/or its metabolites was poor following nasal instillation.

4.1.1.2/ Oral exposure

Oral absorption of BaP in rats is incomplete and may be influenced by the presence of oils and fats in the gastrointestinal tract. Oral absorption of BaP was estimated to be 40% in rats infused intraduodenally to a total dose of approximately 0.5 µg/kg bw for 90 minutes (Foth et al. 1988). The extend of oral absorption in rats is enhanced when BaP is solubilized in a vehicle (triolein, soybean oils, high-fat diet) that is readily absorbed following low- and high-dose levels (Kawamura et al. 1988; O'Neil et al. 1991).

The intestinal absorption of PAHs is highly dependent on the presence of bile (Rahman et al. 1986). Conscious rats with bile duct and duodenal catheters were given tritiated BaP, phenanthrene, anthracene, 2,6-dimethylnaphthalene (DMN) and 7,12-dimethylbenz[*a*]anthracene (DMBA) with or without exogenous bile. The efficiencies of absorption without bile (as a percentage of absorption with bile) were: BaP 22.9%, phenanthrene 96.7%, anthracene 70.8%, DMN 91.6% and DMBA 43.4%. These differences correlated with water solubility. Those products with low water solubility are dependent on the creation of an intermediate phase of the products of lipolysis and bile salts.

There is evidence that BaP is orally absorbed in humans. Following ingestion of diets containing low levels of BaP, the metabolite 1-hydroxypyrene (1-HP) was detected in urine (Buckley & Lioy 1992). The concentration of BaP in human faeces was examined in eight volunteers who ingested broiled meat that contained approximately 9 µg of BaP. The faeces of these persons did not contain detectable levels of BaP (< 0.1 µg per person), which was similar to the excretion by the same volunteers following consumption of control meat that contained undetectable amounts of BaP (Hecht et al. 1979).

4.1.1.3/ Dermal exposure

Percutaneous absorption of ^{14}C-BaP in mice, rats, monkeys and guinea-pigs is rapid and high. A single dose of 7 µg/cm^2 BaP in acetone was applied to a 4-cm^2 area of the dorsal skin of female hairless guinea-pigs for 24 hours. Approximately 73% of the administered dose was absorbed within 7 days after application; most of the dose was absorbed by day 3. The skin wash at 24 hours of exposure contained about 10.6% of the dose (Ng et al. 1992). Seven days after exposure to 125 µg/cm^2 BaP, 80% of the total recovered activity was eliminated in the faeces of mice (Sanders et al. 1986). The percutaneous mechanism of absorption is not universal, however, since although almost all of the dose of ^{14}C-BaP applied to the mouse skin appeared in the faeces within 2 weeks, very little dibenz[*a,h*]anthracene was absorbed in this way and most was lost through epidermal sloughing (Heidelberger & Weiss 1951).

Evidence of percutaneous absorption of PAHs has also been obtained in humans *in vivo*. When 2% coal tar in petroleum jelly was applied topically, phenanthrene,

anthracene, pyrene and fluoranthene were detected in peripheral blood samples (Storer et al. 1984). Volunteers treated topically with creosote (100 µl) or pyrene (500 µg applied in toluene), and a psoriasis patient who used a coal-tar shampoo, excreted 1-HP in their urine. Maximum excretion occurred 10–15 hours after treatment (Viau & Vyskocil 1995).

Twelve workers from a coke plant participated in a monitoring programme for five consecutive 8-hours shifts. The mean concentration of total pyrene in the breathing zone air of the 12 workers ranged from 0.1 to 5.4 µg/m^3. The mean respiratory uptake of pyrene varied between 0.5 and 32.2 µg/day. Based on the estimates of the dermal and respiratory pyrene uptake, it is concluded that an average of 75% of the total absorbed amount of pyrene enters the body through the skin (Van Rooij et al. 1993b). The total excreted amount of urinary 1-HP as a result of exposure to PAHs during the five consecutive work shifts varied between 36 and 239 nmol. Analysis indicated that dermal absorption was most important in contributing to 1-HP excretion.

This observation was not confirmed during a well controlled human volunteer study (Brzeźnicki et al. 1997). Volunteers were exposed twice at the electrolysis department of an aluminium plant, where the source of PAHs was anode paste. During the first experiment, they breathed air containing PAHs and in the second, to eliminate pulmonary absorption, they inhaled PAH-free air through the facial masks. Efficiency of dermal absorption was evaluated on the basis of concentrations of pyrene in the air and excretion of 1-HP in urine. The results revealed that the dermal absorption of airborne pyrene could account for about 20% of the total absorbed dose.

4.1.2/ Distribution

Irrespective of the route of administration, PAHs are rapidly and widely distributed in the organism. In general, tissue distribution of BaPs following inhalation is qualitatively similar for different species (ATSDR 1995). The highest radioactivity was found in the caecum, small intestine, trachea, kidneys and stomach of rats following a 3-hour or 4-week inhalation exposure to 4.8 mg/m^3 ^{14}C-BaP (Wolff et al. 1989b). Tritiated BaP intratracheally administered to rats demonstrated that the highest fractions were distributed to the lung, liver, kidney, gastrointestinal tract and carcass (Weyand & Bevan 1986, 1987a). The concentration of BaP and its metabolites in the intestine increased with time, suggesting the occurrence of biliary excretion and enterohepatic circulation (Weygand & Bevan 1987b).

Tissue levels of BaP in rats were highest 2–8 days after initial oral exposure to multiple doses of 0.0005 mg tritiated BaP (Yamazaki & Kakiuchi 1989). The highest radioactivities were found in the kidney and testis. tritiated BaP was distributed to the protein fraction of the liver, lung and kidney (Yamazaki et al. 1987). The radioactivity in the protein fractions of these tissues increased gradually over time. In contrast, the radioactivity in the lipid fractions of these tissues accounted for 70% of the administered dose at 3 hours but decreased rapidly with time. The nucleic acid fraction maintained approximately 10% of total radioactivity. The

persistence of the radioactivity associated with the protein fractions suggests that protein binding may allow BaP and its metabolites to accumulate in certain tissues, thus increasing the likelihood of cytotoxicity, mutagenicity and carcinogenicity.

Pregnant Wistar rats inhaled ^{14}C-pyrene aerosol, head only, for 95 minutes. Concentrations of BaP amounted to 200, 350, 500, 650 or 800 mg/m^3. Concentrations of radioactivity in maternal blood sampled immediately after exposure were elevated 10-fold and concentrations in fetal blood were elevated 5-fold with a 4-fold increase in exposure concentration. Fetal tissue concentrations were 2–10 fold lower than the maternal concentration.

Single oral doses of 12 mg/kg bw ^{14}C-BaP were administered by gavage to pregnant mice on gestational days 11, 12, 13 or 18 (Neubert & Tapken 1988). Radioactivity was measured at 6, 24 and 48 hours after exposure. Maternal and embryo levels were highest with exposure on gestation day 11. In another experiment, mice were exposed to 24 mg/kg bw BaP for 3 consecutive days during early (days 9–11) or late gestation (days 15–17). After multiple dose administration, elimination appeared to be faster in maternal tissues but slower in embryonic tissues. Placental levels were always higher than those in embryonic tissue and therefore the levels in embryonic tissues of mice never reached levels found in maternal tissues.

4.1.3/ Metabolism

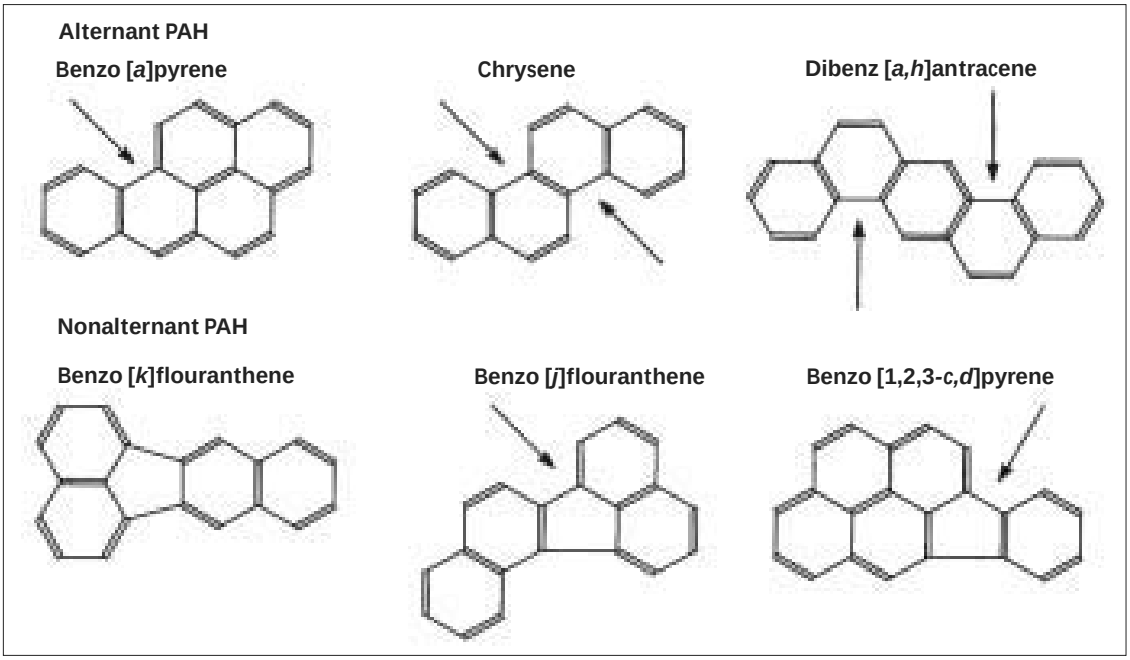
The metabolism of PAHs has been studied extensively. It occurs in all tissues and involves several possible pathways. The structural similarity of PAHs contributes to the similarities that exist in their biotransformation. BaP metabolism can be used as a model for alternant PAHs (such as benz[*a*]anthracene, chrysene and dibenz[*a,h*]anthracene) and metabolism of benzo[*b*]fluoranthene as a model for nonalterant PAHs (such as benzo[*k*]fluoranthene, benzo[*j*]fluoranthene and indeno[1,2,3-*c,d*]pyrene) (Fig. 8.6).

PAHs are metabolized initially by microsomal cytochrome P-450. CYP 1A1 appears to be the only enzyme with metabolic capability towards a wide variety of PAH molecules. It is expressed in various tissues but at a generally low constitutive level. PAHs can regulate their own metabolism by inducing CYP 1A1. After induction, CYP 1A1 expression may reach high levels, e.g. in the placenta, lung and peripheral blood cells. In the liver, however, the level of expression is low even after induction and another CYP appears to be more important, at least in the metabolism of BaP. The other members of the CYP family that can be involved in PAH metabolism are CYP 1A2, CYP 1B, CYP 2B, CYP 2C and CYP 3A (WHO 1998).

BaP is metabolized initially by the CYP-dependent mono-oxygenase system to epoxides (Fig. 8.7). Once formed, these epoxides may rearrange spontaneously to phenols, be hydrated to dihydrodiols in a reaction that is catalysed by epoxide hydrolase, or react covalently with glutathione, either chemically or in a reaction catalysed by glutathione S-transferase. Phenols and dihydrodiols can be conjugated to glucuronides and sulfate esters. In addition to being conjugated, the dihydrodiols

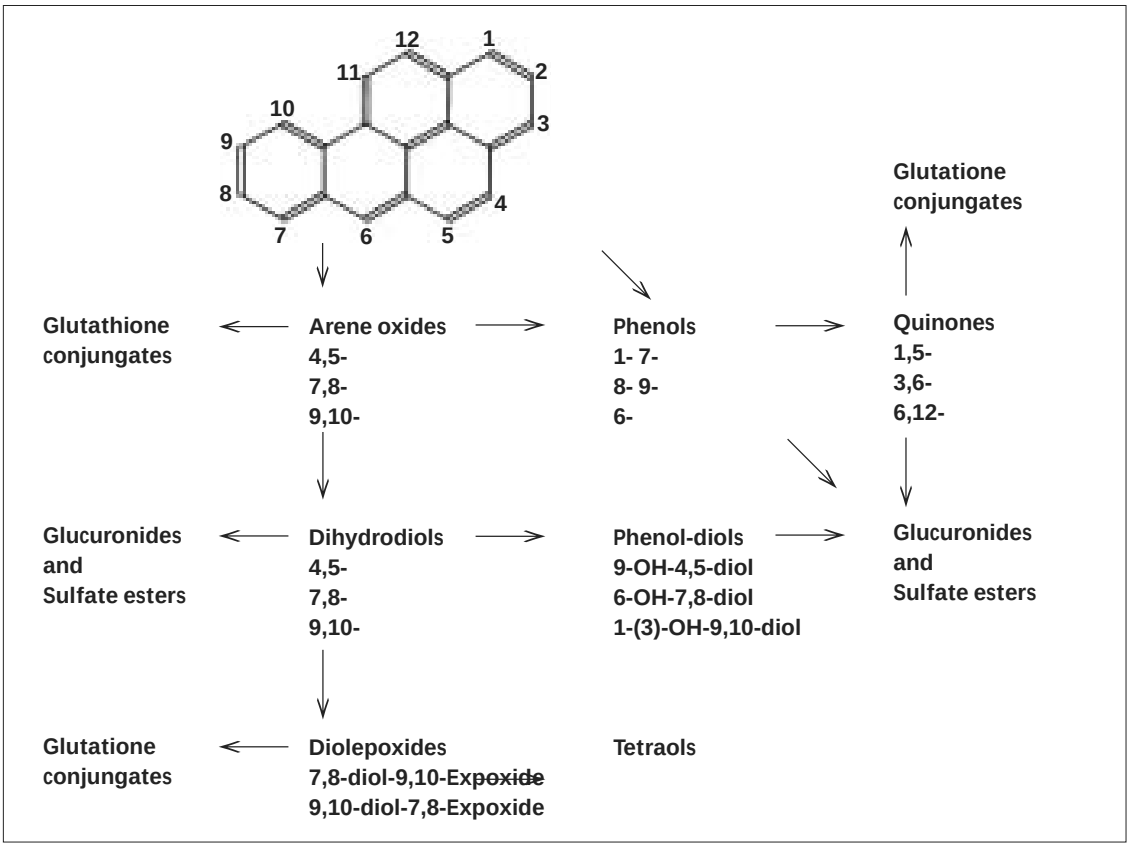
undergo further oxidative metabolism. The cytochrome P-450 system metabolizes BaP-4,5-dihydrodiol to a number of uncharacterized metabolites, while 9,10-dihydrodiol is metabolized predominantly to its 1- and/or 3-phenol derivatives with

Fig. 8.6. Alternant and nonalternant PAHs



Source: ATSDR 1995.

Fig. 8.7. Proposed metabolic scheme for BaP

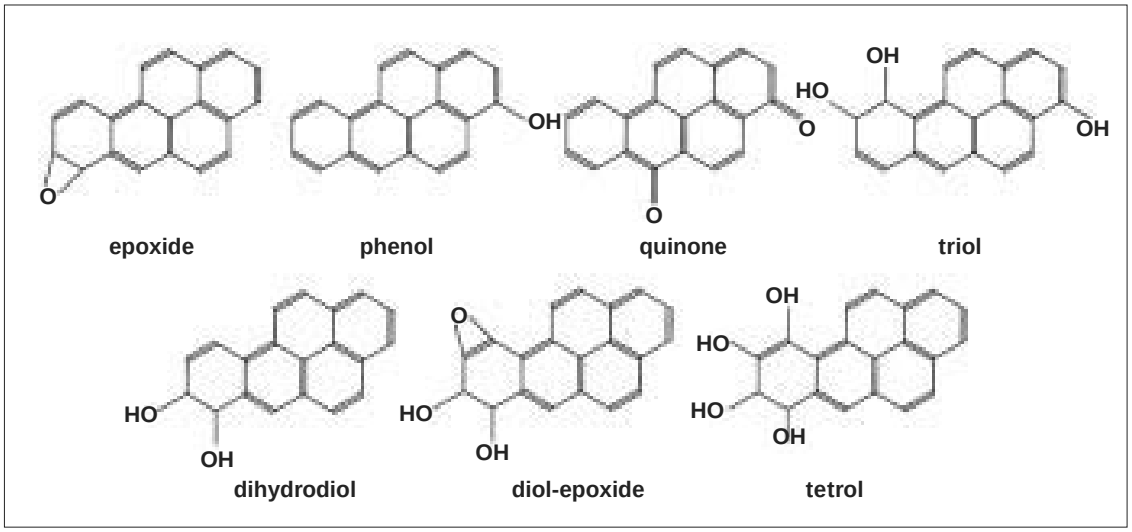


Source: ATSDR 1995.

only minor quantities of 9,10-diol-7,8-epoxide being formed. In contrast to the 9,10-diol, benzopyrene-7,8-diol is metabolized to 7,8-dihydrodiol-9,10-epoxide, an ultimate carcinogen, and phenol-diol formation is a relatively minor pathway. The diol epoxides can be conjugated with glutathione, either spontaneously or by a glutathione-S-transferase catalysed reaction. They may also hydrolyse spontaneously to tetrols. Structures of some types of BaP metabolite are presented in Fig. 8.8.

A proposed metabolic scheme for the metabolism of the nonalternant PAH benzo[*b*]fluoranthene is presented in Fig. 8.9. Nonalterant PAHs, in contrast to several alternant PAHs, do not appear to exert their genotoxic effect primarily through the metabolic formation of simple dihydrodiol epoxides. In the case of benzo[*b*]fluoranthene, there is evidence to suggest that metabolism to the dihydrodiol precursors to its bay-region dihydrodiol does occur, rather than this metabolite being converted to its dihydrodiol epoxide. However, it appears to be extensively converted to its 5-hydroxy derivative. It is the further metabolism of this phenolic

Fig. 8.8. Structures of some types of BaP metabolite



Source: WHO 1998.

dihydrodiol to 5,9,10-trihydroxy-11,12-epoxy-9,10,11,12-tetra-hydrobenzo[*b*] fluoranthene that has been linked to the genotoxic activity of benzo[*b*]fluoranthene in mouse skin (ATSDR 1995).

Nasal instillation of tritiated BaP (0.13 mg/kg bw) to hamsters resulted in the metabolism of this compound in the nasal cavity (Dahl et al. 1985). A large fraction of the metabolites was recovered from the epithelial surface, indicating that BaP was first absorbed in the mucosa, metabolized, and returned to the mucus.

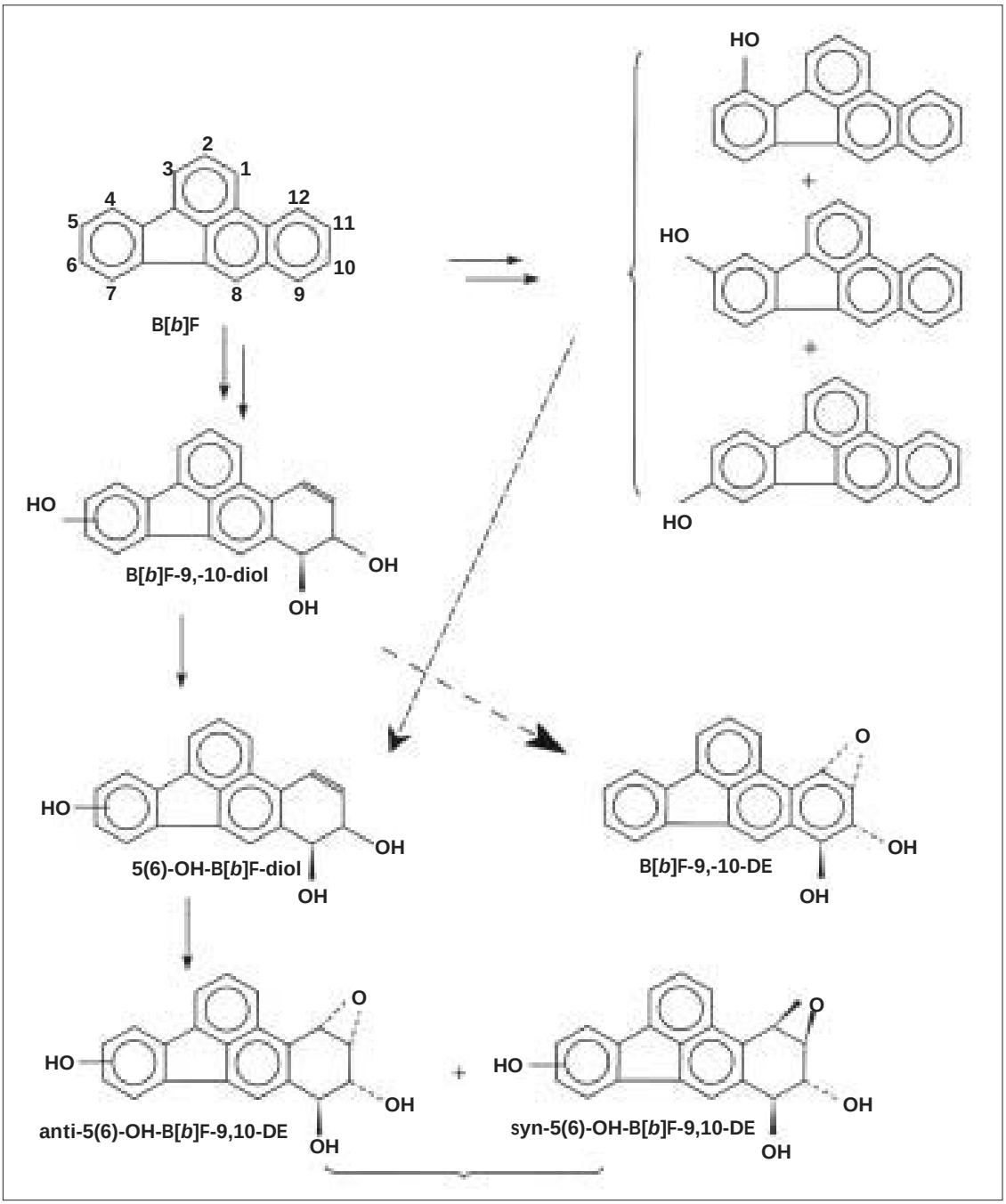
After instillation of a single spray bolus of tritiated BaP in the trachea of beagle dogs, BaP was slowly absorbed with a half-time of about 73 minutes, and led to local doses in the tracheal epithelium that were some 1000-fold those in other tissues (Gerde et al. 1997). The long retention of BaP in the epithelium provided the local metabolizing enzymes with high substrate levels over a long period, resulting in extensive metabolism. Three hours after exposure, 23% of the BaP-equivalent activity remained in the tracheal mucus. Of this fraction, 13% was the parent com-

pound, 28% was organic-extractable, 31% was water-soluble and 28% (7% of the instilled dose) was bound to tracheal tissues. These results explain the tendency of highly lipophilic carcinogens, such as BaP, to induce tumours at the site of entry.

4.1.4/ Excretion

Most metabolites of PAHs are excreted in the faeces and urine. As complete breakdown of the aromatic rings does not occur to any appreciable extent in higher organisms, very little of an administered dose of an unsubstituted hydrocarbon would be expected to appear as carbon dioxide in expired air.

Fig. 8.9. Proposed metabolic scheme for benzo[b]fluoranthene



Source: ATSDR 1995.

Both urinary excretion and the enterohepatic circulation have been studied. Detailed studies on the metabolism and excretion of PAHs in whole animals have been restricted mainly to the simpler compounds. Because of the complexity of their metabolism, most studies on the larger hydrocarbons have been carried out in hepatic homogenates or with cultured cells.

The excretion of BaP following low-level inhalation exposure is rapid and high in rats but low in dogs and monkeys. After nose-only inhalation of 4.8 mg/m^3 ^{14}C-BaP for a single exposure or daily for 4 weeks, excretion radioactivity in the faeces of rats was approximately 96% of the administered concentration. The excretion half-lives in the faeces and urine were 22 and 28 hours, respectively (ATSDR 1995). Rats eliminated a large amount of a single gavage dose of 0.22 mg/kg chrysene by 2 days post-exposure. The unchanged parent compound represented 0.17% and 13.9% in the urine and faeces, respectively. The recovery of the dose in excreta was 74% of the dose after 4 days. The major metabolites were 1- and 3-hydroxychrysene (33.1% and 17.87% of the administered dose), with about 100 times higher amounts in the faeces than in the urine (Grimmer et al. 1988). Male rats were given single oral doses of 2, 4, 6, 9 or 15 mg/kg ^{14}C-pyrene. Recovery of the dose in excreta was 82% for the low-dose groups and 50–63% for the other 2 days post-exposure groups. The urine and faeces contained 34–45% and 21–50% of the dose, respectively (Withey et al. 1991). Six hours after intravenous administration of 0.08 mg/kg ^{14}C-BaP to rabbits, 30% and 12% of the dose was excreted in the bile and urine, respectively. Excretion of activity into the bile was biphasic over a period of 30 hours, with half-lives of 0.27 and 4.6 hours for the rapid and slow phases, respectively (Chipman et al. 1982). The overall elimination of tritiated BaP following intravenous administration (0.001 mg/kg bw) best fits a tri-exponential model. The half-lives of the three phases were 1.5, 22.4 and 178 minutes (Weygand & Bevan 1986).

There have been several literature reports assessing the toxicokinetics of the urinary elimination of 1-HP after oral, dermal or inhalation exposure to PAHs in humans, but the results were not consistent. In experiment on human volunteers, ingestion of 250 g of broiled beef containing PAHs resulted in a 4–12-fold increase in urinary 1-HP concentration. Maximum excretion occurred approximately 6.3 hours after ingestion and declined thereafter, with an estimated half-life of 4.4 hours (Buckley & Lioy 1992). In another experiment, two human volunteers were exposed to 500 µg pyrene by ingestion or by dermal application. Following the absorption phase, 1-HP was excreted with an apparent half-life of 12 hours for both exposure routes (Viau et al. 1995).

Studies on the kinetics of 1-HP elimination after inhalation concerned workers employed in different technological processes. One study was carried out at a wood-preserving plant (Jongeneelen et al. 1988). Urine samples were collected up to 17 days after the end of the subjects' working week. The two-compartment toxicokinetic model, with half-lives of 1–2 days and 16 days for two phases of elimination, was found to describe the elimination process satisfactorily. While reporting on similar studies in a coke-oven plant, the same author suggested that the

half-life for the first phase of elimination was somewhere between 6 and 35 hours (Jongeneelen et al. 1990). The other studies were performed in coke-oven and graphite electrode manufacturing plants (Buchet et al. 1992). Urine samples of 15 workers were collected, starting from the end of a working week, at different times for up to 4 days. The authors described the elimination of 1-HP by the one-compartment model with a mean half-life of 18 hours. The values presented above, suggesting the possible accumulation of 1-HP (or its precursors) in the body, could nevertheless be influenced by contact dermal absorption. In a study whereby volunteers were exposed to PAHs in aluminium plants and contact dermal absorption was excluded, the half-life value of excretion of 1-HP in urine was 9.8 hours. More than 80% of the 1-HP was eliminated in urine during the first 24 hours following the onset of exposure (Brzeźnicki et al. 1997).

4.2/ Effects on laboratory animals

The acute toxicity of PAHs appears to be moderate to low. Naphthalene showed oral and intravenous LD_{50} values of 100–150 mg/kg bw in mice and mean oral LD_{50} of 2700 mg/kg bw in rats. The values for other PAHs are similar. Acute exposure to high concentrations of naphthalene induced bronchiolar necrosis in mice, rats and hamsters.

Short-term studies showed adverse haematological effects, expressed as myelotoxicity with BaP, hemolymphatic changes with dibenz[*a,h*]anthracene and anaemia with naphthalene.

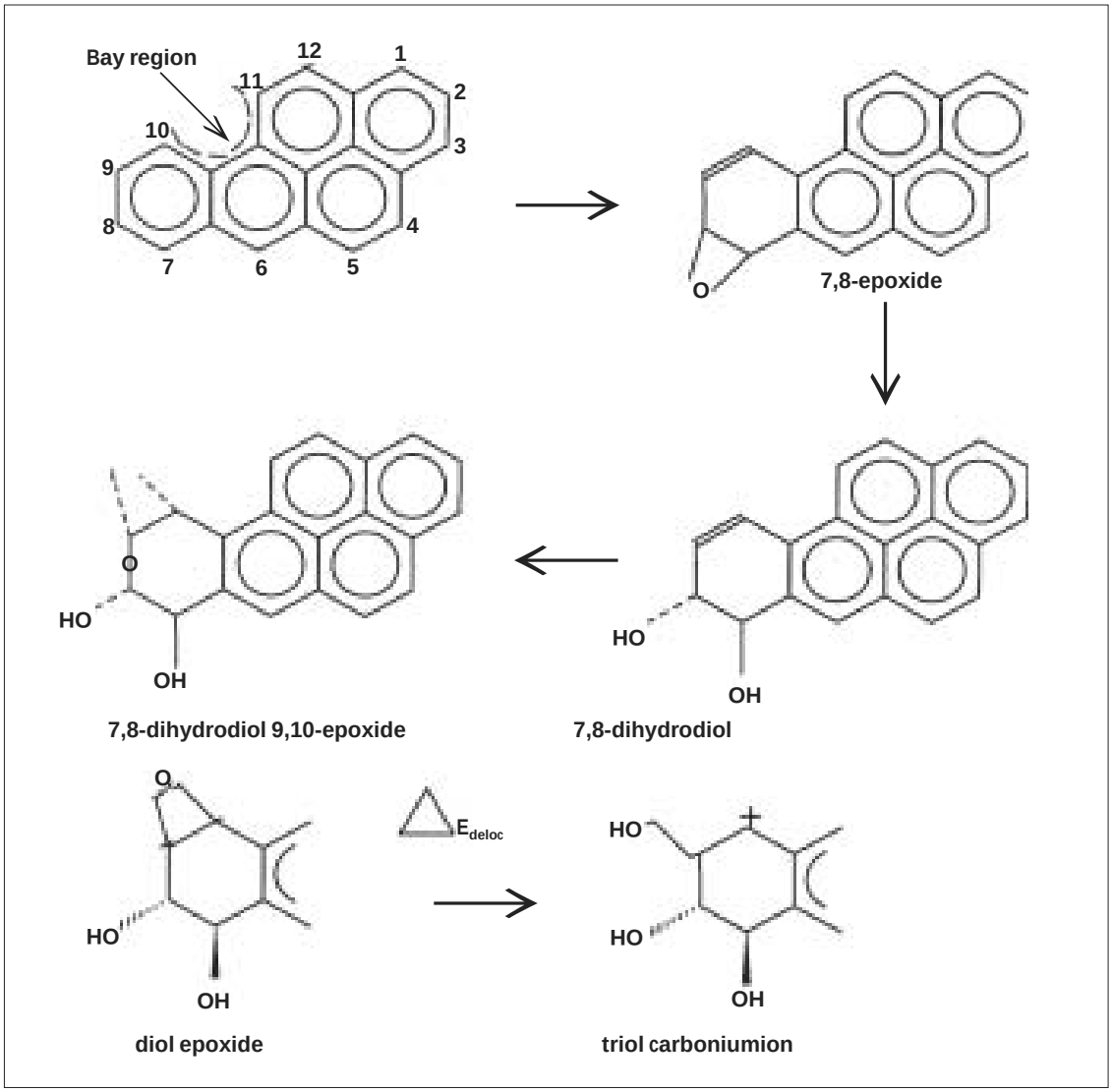
In studies of adverse effects on the skin after dermal application, non-carcinogenic or weakly carcinogenic PAHs were inactive, whereas carcinogenic compounds such as benz[*a*]anthracene, dibenz[*a,h*]anthracene and BaP caused hyperkeratosis. Anthracene and naphthalene vapours caused mild eye irritation.

Benz[*a*]anthracene, BaP, dibenz[*a,h*]anthracene and naphthalene were embryotoxic to mice and rats. BaP also had teratogenic and reproductive effects. Anthracene, BaP and some other PAHs were phototoxic to mammalian skin and in cell cultures *in vitro* when applied with ultraviolet radiation. PAHs have generally been reported to have immunosuppressive effects. After intraperitoneal treatment of mice with BaP, immunological parameters were strongly suppressed in the progeny for up to 18 months. Increased liver regeneration and an increase in liver weight have also been observed.

Most of the 32 PAHs covered by the International Programme on Chemical Safety (IPCS) in 1998 (WHO 1998) (Table 8.3) are genotoxic. Of the 32 compounds, 26 are or are suspected to be carcinogenic. According to the theory of reactive electrophiles in chemical carcinogenesis, PAHs are activated by microsomal enzymes to proximate and finally ultimate carcinogens, which are characterized by an electrophilic centre that can react with nucleophilic sites on macromolecules such as DNA, RNA and protein (WHO 1998).

The bay region theory states two prerequisites for carcinogenic potency: the epoxide group of an ultimate metabolite must be part of a bay region (Fig. 8.10), and the hydroxy groups of the diol epoxide are preferentially located in the "pre-

Fig. 8.10. The bay region dihydrodiol epoxide route of metabolism of BaP



Source: WHO 1998.

bay" region. The presence of the epoxide group on the saturated benzene ring in the bay region facilitates ring opening i.e. the delocalization energy forming the carbonium ion is higher. This is important for reactions with DNA via the carbonium ion, which is an alkylating agent. For example, the metabolic pathway of BaP is hypothesized to start with 7,8 oxidation, followed by hydrolysis to 7,8-dihydrodiol, and terminated by 9,10-oxidation, yielding the ultimate carcinogen 7,8-dihydrodiol-9,10-epoxide.

Besides the diol epoxide mechanism, other mechanisms of PAH carcinogenesis such as the radical–cation mechanism, the quinone mechanism and the benzylic oxidation mechanism have been proposed. Harvey (1996) concluded that current research provided evidence for all four. The second important property of certain PAHs is their affinity to the cytosolic aryl hydrocarbon or Ah receptor. Inappropriate activation of the Ah receptor by aromatic hydrocarbons induces a variety of biological effects. These include increased proliferation, inhibition of differentiation, endocrine disruption and tumour promotion in experimental

animals. Stimulation of growth seems to be the main component of promotion in chemical carcinogenesis; the ability of PAHs to act as promoters very strongly increases their carcinogenic potency, as shown by the high doses administered in animal cancer tests.

It is therefore in accordance with expectation that a multifactorial analysis of a number of bay-region PAHs shows the Ah receptor affinity to be a much stronger predictor of carcinogenicity than the mutagenic potency. In addition to

Table 8.3. Summary of results of tests for genotoxicity and carcinogenicity for 32 polycyclic aromatic hydrocarbons studied [a]

Compound	Genotoxicity	Carcinogenicity
Acenaphthene	(?)	?
Acenaphthylene	(?)	No studies
Anthracene	–	–
Benz[*a*]anthracene	+	+
Benzo[*a*]fluorene	(?)	(?)
Benzo[*a*]pyrene	+	+
Benzo[*b*]fluoranthene	+	+
Benzo[*b*]fluorene	(?)	(?)
Benzo[c]phenanthrene	(+)	(+)
Benzo[*e*]pyrene	+	?
Benzo[*g,h,i*]fluoranthene	(+)	(–)
Benzo[*g,h,i*]perylene	+	–
Benzo[*j*]fluoranthene	+	+
Benzo[*k*]fluoranthene	+	+
Chrysene	+	+
Coronene	(+)	(?)
Cyclopenta[*c,d*]pyrene	+	+
Dibenzo[*a,e*]pyrene	+	+
Dibenz[*a,h*]anthracene	+	+
Dibenzo[*a,h*]pyrene	(+)	+
Dibenzo[*a,i*]pyrene	+	+
Dibenzo[*a,l*]pyrene	(+)	+
Fluoranthene	+	(+)
Fluorene	–	–
Indeno[1,2,3-*c,d*]pyrene	+	+
1-Methylphenanthrene	+	(–)
5-Methylchrysene	+	+
Naphthalene	–	(?)
Perylene	+	(–)
Phenanthrene	(?)	(?)
Pyrene	(?)	(?)
Triphenylene	+	(–)

[a] + = positive;
– = negative;
? = questionable;
parentheses = result derived from a small database

Source: WHO, 1998.

promoting the carcinogenic process by interacting with the Ah receptor, PAHs may amplify the tumour promotion process via alternative mechanisms, such as induction of inflammatory processes and stimulated oxidative stress (Boström et al. 2002).

4.3/ Health effects in humans

Because of the complex profile of PAHs in the environment and in workplaces, human exposure to pure, individual PAHs has been limited to scientific experiments with volunteers, except in the case of naphthalene.

After dermal application, anthracene, fluoranthene and phenanthrene induced specific skin reactions, and BaP induced reversible, regressive verrucae that were classified as neoplastic proliferations.

The systemic effects of naphthalene are known from numerous cases of accidental intake, particularly by children. The lethal oral dose is 5000–15 000 mg for adults and 2000 mg taken over 2 days for a child. The typical effect after dermal or oral exposure is acute haemolytic anaemia, which can also affect fetuses transplacentally.

In aluminium plants, asthma-like symptoms, lung function abnormalities and chronic bronchitis have been observed.

Coke-oven workers were found to have decreased serum immunoglobin levels and decreased immune function. Occupational exposure to naphthalene for 5 years was reported to cause cataract.

The toxic effect of most concern from exposure to PAHs is cancer. Occupational exposure to soot as a cause of scrotal cancer was noted for the first time in 1775. Later, occupational exposure to tars and paraffins was reported to induce skin cancer. The lung is now the main site of PAH-induced cancer, whereas skin tumours have become more rare because of better personal hygiene.

Epidemiological studies have been conducted of workers exposed at coke ovens during coal coking and coal gasification, at asphalt works, foundries and aluminium smelters, and to diesel exhaust. Increased lung tumour rates owing to exposure to PAHs have been found in coke-oven workers, asphalt workers and workers in Södeberg potrooms of aluminium reduction plants. The highest risk was found for-coke ovens workers, with a standardized mortality ratio of 195.

4.3.1/ Quantitative cancer risk estimates

In principle, the cancer risk assessment of PAHs in ambient air can be performed in two ways. One approach is to add the risks from selected individual PAHs as determined from animal experiments. The other approach is to use BaP as an indicator of the mixture of carcinogenic PAHs in air and apply that to the dose–response relationship observed in epidemiological studies. Both of these approaches have considerable weaknesses. WHO has chosen epidemiological data on coke-oven workers for risk assessment in the revised Air Quality Guidelines for Europe (WHO 2000). The same approach has been chosen by the Working Group on Polycyclic Aromatic Hydrocarbons (European Commission 2001).

4.3.2/ Data produced by studies of carcinogenic effects of PAHs in experimental animals

PAHs occur in the environment as complex mixtures of many components with widely varying toxic potencies. The profile of compounds occurring in the air in different occupational environments and in the atmosphere in city agglomerations (e.g. the ratio sum of carcinogenic PAHs and BaP) can differ, as well as the carcinogenic potencies of the individual PAHs (Petry et al. 1996).

It has therefore been assumed that the development and establishment of potency equivalency factors (PEFs) for PAHs, similar to the concept used in the assessment of mixtures containing polychlorinated dibenzodioxins, dibenzofurans and biphenyls, could help to characterize more precisely the carcinogenic properties of PAH mixtures.

The approach adopted by USEPA (1980, 1984) as the basis for risk assessment was to separate the PAHs into two subclasses, consisting of the carcinogenic and non-carcinogenic PAHs, to apply a cancer slope factor derived from assays on BaP to the subclass of carcinogenic PAHs. Nisbet & LaGoy (1992) reviewed relative potency estimates and provided revised ones. The complex version of the application of PEFs was presented by Collins et al. (1998). The development of PEFs and application of the PEF scheme described in this paper is presented below.

Owing to the absence of chronic inhalation studies on PAH and the variety and uneven quality of data available on the carcinogenicity of PAH, an order of preference for the use of available data in assessing relative potency was developed (Table 8.4).

Table 8.4. Hierarchy for relative potency estimati

1.	Complete quantitative risk assessment (most preferred)
2.	"Expedited" quantitative risk assessment
3.	Tumour data from inhalation exposure
4.	Tumour data from intratracheal or intrapulmonary administration
5.	Tumour data from oral administration
6.	Tumour data from skin-painting studies
7.	Tumour data from subcutaneous or intraperitoneal administration
8.	Genotoxicity data
9.	Structure-activity information (least preferred)

Source: Collins et al. 1998.

According to Collins et al.(1991), the unit risk derived from hamster inhalation and mouse feeding data sets amount to 1.1×10^{-3} and 3.3×10^{-3}, respectively. Based on this order of preference, PEFs for cancer induction relative to BaP have been derived for a number of PAHs (Table 8.5).

PEF-adjusted concentrations and the unit risk for BaP are used for calculating lifetime cancer risk. An example of the application of PEFs is presented in Table 8.6. In the case of these data, an excess cancer risk amounts to:

$$\mathbf{0.000268\ \mu g/m^3 \times 1.1 \times 10^{-3} = 2.94 \times 10^{-7}}$$

According to the authors, the use of PEFs for estimating risk from exposure to PAHs is an improvement for those PAHs for which there are reliable collection and measurement techniques. Unfortunately, there is a large number of PAHs for which PEFs have not been developed. It should also be noted that the relative order of PAH potency might not be the same for the inhalation route as for the routes of exposure that formed the basis for establishing the TEF values.

4.3.3/ Data produced by epidemiological studies of the effects on humans following exposure to industrial mixtures that contain PAHs.

Table 8.7 summarizes unit risk estimates derived from both animal and epidemiological studies.

Unit risks derived from animal studies vary widely, by a factor of more than 1400. The unit risks derived from the epidemiological studies are remarkably consistent: the range is described by a factor of 18.7.

Of the unit risk estimates shown in the epidemiology part of Table 8.7, three are similar: the American coke-oven workers study (87×10^{-6}), the aluminium smelters study (90 × 10–6) and the RIVM "most appropriate" estimate of 100×10^{-6}.

WHO (1987) considered that the most appropriate indicator for the carcinogenic PAHs in air seems to be BaP concentrations, given present knowledge and the existing database. Assessment of risks to health of a given mixture of PAHs using this indicator approach would first entail measuring the concentration of BaP in a given mixture present in a medium such as air. Then, assuming that the given mixture resembles that from coke ovens, the unit risk estimate is applied in tandem with the measured BaP air concentration to obtain the lifetime cancer risk at this exposure level.

Risk estimates considered in the United States for coke-oven emissions were used in the Air Quality Guidelines for Europe (WHO 1987). Using a linearized multistage model, the most plausible upper-bound individual lifetime unit risk estimate associated with a continuous exposure to 1 μg/m^3 of benzene-soluble compounds from coke-oven emissions in ambient air was approximately 6.2×10^{-4}. Using BaP as an indicator of general PAH mixtures from emissions in coke ovens and similar combustion process in urban air, and a reported value of 0.71% BaP in the benzene-soluble fraction of coke-oven emissions, a lifetime risk of respiratory cancer of 8.7×10^{-5} per ng/m^3 was calculated. The same value was confirmed in the second edition of Air Quality Guidelines for Europe (WHO 2000).

The corresponding concentrations of BaP producing excess lifetime cancer risk of 1/10 000, 1/100 000 and 1/1 000 000 are 1.2, 0.12 and 0.012 ng/m^3, respectively (WHO 2000).

The disadvantage of using BaP as a surrogate for the PAH mixture in ambient air is that substituted PAHs are not well represented by BaP and they must be considered separately. Nevertheless, when some nitro-PAHs were considered in calculations from California, their relative contribution to the carcinogenicity of ambient air was minor compared to that of dibenzo[*a,l*]pyrene, BaP and benzofluoranthenes (Table 8.6).

Table 8.5. Relative potencies of indicator PAHs

Compound	Krewski et al. 1989	Nisbet & LaGoy 1992	Malcolm & Dobson 1994	Kalberlah et al. 1995	USEPA 1993	McClure & Schoeny 1995	Muller et al. 1995a, b, 1996	Larsen & Larsen 1998
1-Methylphenanthrene			0.001					
Acenaphthene		0.001	0.001	0.001	0			
Acenaphthylene		0.001	0.001	0.01				
Anthanthrene	0.320						0.28	0.3
Anthracene		0.01	0.01	0.01				0.0005
Benz[*a*]anthracene	0.145	0.1	0.1	0.1	0.1	0.1	0.014	0.005
Benzo[*a*]pyrene	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Benzo[*b*]fluoranthene	0.141	0.1	0.1	0.1	0.1	0.1	0.11	0.1
Benzo[*e*]pyrene	0.004		0.01				0	0.002
Benzo[*g,h,i*]perylene	0.022	0.01	0.01	0.01			0.012	0.02
Benzo[*j*]fluoranthene				0.1		0.1	0.045	0.05
Benzo[*k*]fluoranthene	0.061	0.1	0.1	0.1	0.01	0.1	0.037	0.05
Chrysene	0.0044	0.01	0.01	0.01	0.001	0.1	0.026	0.03
Coronene			0.001					
Cyclopenta[*c,d*]pyrene	0.023		0.1			0.1	0.012	0.02
Dibenzo[*a,e*]pyrene						1.0		0.2
Dibenz[*a,c*]anthracene[a]			0.1					
Dibenz[*a,h*]anthracene	1.11	5.0	1.0	1.0	1.0	1.0	0.89	1.1
Dibenzo[*a,l*]pyrene						100	100	1.0
Dibenzo[*a,e*]fluoranthene[a]							1.0	
Dibenzo[*a,h*]pyrene						1.0	1.2	1.0
Dibenzo[*a,i*]pyrene						0.1		0.1
Fluoranthene		0.001	0.001	0.01				0.05
Fluorene		0.001	0.001	0				

Compound	Krewski et al. 1989	Nisbet & LaGoy 1992	Malcolm & Dobson 1994	Kalberlah et al. 1995	USEPA 1993	McClure & Schoeny 1995	Muller et al. 1995a, b, 1996	Larsen & Larsen 1998
Indeno[1,2,3-*c,d*]pyrene	0.232	0.1	0.1	0.1	0.1	0.1	0.067	0.1
Naphthalene		0.001	0.001					
Perylene			0.001					
Phenanthrene		0.001	0.001	0			0.00064	0.0005
Pyrene	0.81	0.001	0.001	0.001			0	0.001

[a] Not evaluated by the Task Group.

Source: WHO 1998.

Table 8.6. Application of PEFs to PAH data from Riverside, California

PAH	Measured concentration (pg/m^3)	PEF	PEF-adjusted concentration (pg/m^3)
Benzo[*a*]pyrene	36.0	1.0	36.0
Benz[*a*]anthracene	39.0	0.1	3.9
Benzo[*b*+*j*+*k*]fluoranthenes	360.0	0.1	36.0
Dibenzo[*a,e*]pyrene	1.7	1.0	1.7
Dibenzo[*a,h*]pyrene	[< 0.5][a]	10.0	?
Dibenzo[*a,i*]pyrene	[< 0.5][a]	10.0	?
Dibenzo[*a,l*]pyrene	18.0	10.0	180.0
Indeno[1,2,3-*c,d*]pyrene	87.0	0.1	8.7
Chrysene	61.0	0.01	0.61
Dibenz[*a,h*+*a,c*]anthracene	8.2	0.1[b]	0.82
1-Nitropyrene	4.4	0.1	0.44
2-Nitrofluoranthene	36.0	0.01	0.36
4-Nitropyrene	[≤ 1.6][a]	0.1	?
1,6-Dinitropyrene	0	10.0	0
1,8-Dinitropyrene	No data		
6-Nitrochrysene	[≤ 5.4][a]	10.0	?
2-Nitrofluorene	0	0.01	0
Total carcinogenic PAHs	651.3		268.53

[a] Not included in total.
[b] Assumes equal PEF (0.1) for both dibenzanthracenes.

Source: Collins et al. 1998.

4.4/ Existing reference values

IARC considers several purified PAHs and PAH derivatives to be probable (group 2A) or possible (group 2B) human carcinogens (IARC 1987). Some mixtures containing PAHs, such as soot, are considered to be known human carcinogens (group 1) (Table 8.8) The USEPA has classified several PAHs in group B2 as being possibly carcinogenic in humans (Table 8.9). IARC (1987, 1989) has classified approximately 45 PAHs in group 3 (Table 8.10), a class of chemicals for which there are no data on carcinogenesis in humans and limited or inadequate data in animals.

4.5/ Biological indicators of exposure

Several methods exist to assess the internal exposure levels following intake of PAHs from the general or work environment. In most studies, metabolites of PAHs were measured in urine, 1-HP being widely used.

The genotoxic effects of PAH have been determined in tests for mutagenicity in urine and faeces, micronucleus formation, chromosomal aberration and sister chromatid exchange in peripheral blood lymphocytes, and adducts of BaP with DNA in peripheral lymphocytes and other tissues and with proteins such as albumin.

Table 8.7. Summary of unit risk estimates for BaP and for PAH with BaP as indicator substance (lifetime risk per ng/m³ BaP)

Basis for calculation	Unit risk	Reference
Animal experiments		
Inhalation of BaP in hamsters (Thyssen et al. 1981)	0.28×10^{-6} [a]	RIVM 1989
Inhalation of BaP in hamsters (Thyssen et al. 1981)	$0.37 - 1.7 \times 10^{-6}$ [b]	Collins et al. 1991; CARB 1994; Muller et al. 1997
Inhalation of BaP in mice (Knizhikow et al. 1982)	400×10^{-6} [a]	RIVM 1989
Intratracheal instillation of BaP in hamsters (Saffiotti et al. 1972; Feron et al. 1973)	4.4×10^{-6} [b] 4.8×10^{-6} [b]	Collins et al. 1991; CARB 1994 Collins et al. 1991; CARB 1994
Inhalation of coal tar/pitch aerosol with BaP as indicator substance	20×10^{-6} [b]	Heinrich et al. 1994
Epidemiology (PAH with BaP as indicator)		
American coke-oven workers	87×10^{-6}	WHO 1987, 2000
American coke-oven workers	23×10^{-6}	Muller et al. 1997
American coke-oven workers	50×10^{-6}	Pott 1985
American gas workers	430×10^{-6}	Pike 1983
Smoky coal indoors in China	67×10^{-6}	RIVM 1989
"Most appropriate" estimate	100×10^{-6}	RIVM 1989
Aluminium smelters	90×10^{-6}	Armstrong et al. 1994, converted from workplace exposure to continuous lifetime exposure

[a] Linear extrapolation.
[b] Linearized multistage model.
Source: Boström et al. 2002.

4.5.1/ Urinary metabolites

The metabolites measured in urine and faeces include urinary thioethers, 1-naphtol, β-naphtylamine, hydroxyphenanthrenes and 1-hydroxypyrene (WHO 1998).

No differences in thioether excretion in urine were observed between controls and coke-oven workers or workers in coke and graphite-electrode-producing plants. It was concluded that the determination of thioethers in urine is of little value, since smoking is a strong confounding factor (Ferreira et al. 1994a, b; Reuterwall et al. 1991). Becher & Bjorseth (1983) developed an analytical procedure to measure PAHs in human urine after reducing metabolites to parent compounds. Total PAHs, comparing to non-smokers, were elevated, although when individual PAHs were examined no significant differences were observed. Further application of this method to urine samples from workers at an aluminium plant (Venier et al. 1985) and from coke-oven workers (Haugen et al. 1986) did not show differences in PAH levels in urine between exposed workers and controls.

1-HP was introduced as a biomarker of exposure to PAHs by Jongeneelen et al. (1986) and has since been widely used. Its advantage is that pyrene is present in all

Table 8.8. IARC groupings of PAHs, PAH mixtures and PAH derivatives

Group 1	Group 2A	Group 2B
Coal-tar pitches	Benz[*a*]anthracene	Benzo[*b*]fluoranthene
Coal-tars	Benzo[*a*]pyrene	Benzo[*j*]fluoranthene
Coke production	Creosotes	Benzo[*k*]fluoranthene
Mineral oils	Dibenz[*a,h*]anthracene	Carbon black extracts
Shale oils		Dibenz[*a,h*]acridine
Soots		Dibenz[*a,j*]acridine
Tobacco smoke		7H-Dibenzo[*c,g*]carbazole
		Dibenzo[*a,e*]pyrene
		Dibenzo[*a,h*]pyrene
		Dibenzo[*a,i*]pyrene
		Dibenzo[*a,l*]pyrene
		Indenol[1,2,3-*c,d*]pyrene
		5-Methylchrysene
		5-Nitroacenaphthene
		1-Nitropyrene
		4-Nitropyrene
		1,6-Dinitropyrene
		1,8-Dinitropyrene
		6-Nitrochrysene
		2-Nitrofluorene

Source: Collins et al. 1998.

Table 8.9. USEPA groupings of PAHs

Group B2	Group D
Benz[*a*]anthracene	Acenaphthylene
Benzo[*a*]pyrene	Anthracene
Benzo[*b*]fluoranthene	Benzo[*g,h,i*]perylene
Benzo[*k*]fluoranthene	Fluorene
Chrysene	Fluoranthene
Dibenz[*a,h*]anthracene	Naphthalene
Indeno[1,2,3-*c,d*]pyrene	Phenanthrene

PAH mixtures in relatively high concentrations. Pyrene is metabolized predominantly to 1-HP, which can be measured easily. In contrast to other PAH metabolites, which are excreted mainly in the faeces, 1-HP is mainly excreted in the urine.

4.5.1.1/ General population

The background concentration of 1-HP in urine from the general population in different countries ranges from 0.12 to 0.3 μg/g creatinine (WHO 1998). No differences related to age or sex were seen (Zhao et al. 1992), and ethanol consumption did not influence 1-HP concentration (Van Rooij et al. 1994a).

Table 8.10. IARC group 3 PAHs and PAH derivatives

Chemical	Animal evidence	Chemical	Animal evidence
Acridine orange	Inadequate	l -Methylchrysene	Inadequate
5 -Aminoacenaphthene	Inadequate	2-Methylchrysene	Limited
2 -Aminoanthraquinone	Limited	3-Methylchrysene	Limited
Anthanthrene	Limited	4-Methylchrysene	Limited
Anthracene	Inadequate	6-Methylchrysene	Limited
Benz[*a*]acridine	Inadequate	2-Methylfluoranthene	Limited
Benz[*c*]acridine	Limited	1-Methylphenanthrene	Inadequate
Benzo[*g,h,i*]fluoranthene	Inadequate	1,5-Naphthalenediamine	Limited
Benzo[*g,h,i*] perylene	Inadequate	9-Nitroacenaphthene	Limited
Benzo[*c*]phenanthrene	Inadequate	9-Nitroanthracene	No adequate data
Benzo[*e*]pyrene	Inadequate	7-Nitrobenz[*a*]anthracene	Limited
Carbazole	Limited	6-Nitrobenzo[*a*]pyrene	Limited
Chrysene	Limited	3-Nitrofluoranthene	Inadequate
Cyclopenta[*c,d*]pyrene	Limited	1-Nitronaphthalene	Inadequate
Dibenz[*a,c*]anthracene	Limited	2-Nitronaphthalene	Inadequate
Dibenz[*a j*] anthracene	Limited	3-Nitroperylene	Inadequate
Dibenzo[*a,e*]fluoranthene	Limited	2-Nitropyrene	Inadequate
Dibenzo[*h,r,s,t*]pentaphene	Limited	Perylene	Inadequate
3,7-Dinitrofluoranthene	Limited	Phenanthrene	Inadequate
3,9-Dinitrofluoranthene	Limited	N-Phenyl-2-naphthylamine	Limited
1,3-Dinitropyrene	Limited	Pyrene	Inadequate
Fluoranthene	Inadequate	Triphenylene	Inadequate
Fluorene	Inadequate		

Source: Collins et al. 1998.

The intake of pyrene from cigarette smoking (12 nmol/day) is about the same as dietary intake from normal food (9.4 nmol/day) (Van Rooij et al. 1994a). Tobacco smokers who are not otherwise exposed to PAHs have about twice the level of 1-HP in their urine as non-smokers (0.23–0.63 µg/g creatinine), although no significant difference was found in some studies (WHO 1998).

Much higher levels were detected in persons living in areas contaminated with PAHs (1.1–2.9 µg/g creatinine) (WHO 1998). The concentrations can be twice as high in winter as in summer (Jongeneelen 1994; Ovrebo et al. 1995).

Very high exposure to PAHs occurs during the use of coal-tar ointments or shampoos by patients with eczema or psoriasis. The mean 1-HP concentration reached about 950 µg/g creatinine, and the maximum value was 9600 µg/g creatinine (Santella et al. 1994).

4.5.1.2/ Occupational exposure

1-HP concentrations have been measured in the urine of persons at various workplaces. The highest 1-HP excretion, up to 190 µg/g creatinine, was found in the urine of workers impregnating wood with creosote, although the PAH levels in

the air were quite low. The high exposure can be attributed to significant dermal uptake (Elovaara et al. 1995; Jongeneelen et al. 1988). Other workplaces where there is heavy exposure are coke ovens (1.4–26 µg/g creatinine), aluminium plants (1.1–77.2 µg/g creatinine) and the production of graphite electrodes (1.1–9.6 µg/g creatinine) (WHO 1998).

1-HP concentrations in urine correlated in most cases with PAH concentrations in air (Buchet et al. 1992; Levin et al. 1995; Mannschreck et al. 1996). The weak correlation between the levels of pyrene in air and 1-HP concentrations in urine was attributed to extensive dermal uptake of the PAHs (Ovrebo et al. 1995; Van Rooij et al. 1992). The 1-HP concentrations in urine correlated quite well with exposure of the skin, monitored by analysis of absorbent pads attached to the skin during shifts (Van Rooij et al. 1992, 1993a).

Significant dermal absorption, representing up to 95% of the total, was concluded from the several studies of workers exposed at coke ovens, in coal-liquefaction plants, in the petrochemical industry, in aluminium reduction plants, in graphite electrode plants and during road paving (WHO 1998). Workers impregnating wood with creosote had an estimated average dermal uptake 15 times higher than the estimated respiratory uptake (Van Rooij et al. 1993a).

4.5.1.3/ Suitability of 1-HP as a biomarker

When 1-HP was used as a biomarker for exposure to PAHs, the oral, dermal and inhalation routes were all shown to be important. Furthermore, low levels of exposure can be determined. A great advantage is that the determination of urinary 1-HP is easy and rapid and thus well suited for use in large-scale epidemiological studies.

Determination of 1-HP in urine can at present be used for evaluating exposure trends and the effectiveness of prophylactic measures. For example, the use of dermal protection in the form of impermeable polyvinyl chloride suits led to a substantial decrease in the urinary concentrations of 1-HP (Boogard & van Sittert 1994, 1995). Frequent changes of work clothes and underclothes reduced 1-HP excretion by 37–55% (Quinlan et al. 1995; Van Rooij et al. 1994b).

Comparison of different work environments may, however, be difficult because the proportion of pyrene in comparison to BaP and other potentially carcinogenic PAHs may vary. For example, the creosote oil used in a wood impregnation plant contained about 3.4% pyrene and less than 0.0004% BaP. Levels of 2–10% pyrene and 0.4–0.6% BaP are found in coal-tar, which is the main PAH contaminant in the coke industry, in the primary aluminium industry and during road paving with tar. Polluted ambient air contains about 6.5% BaP and 1.8–2.7% pyrene (WHO 1998).

Several authors have tried to establish admissible levels of 1-HP in urine for specific exposures. According to Jongeneelen (1992), a urinary concentration of 1-HP in coke-oven workers of 4.4 µg/g creatinine reflects concentrations of coal-tar pitch and BaP in the air of 0.2 mg/m^3 and 2 µg/m^3, respectively. A similar value of 4 µg/g creatinine was proposed by Levin et al. (1995). A higher value of 6.1 µg/g creatinine was suggested by Van Rooij et al. (1993b). In the case of aluminium reduction

plants, Tjoe Ny et al. (1993) assumed that exposure to 0.2 mg/m^3 coal-tar pitch or 5 µg/m^3 BaP would result in a urinary concentration of 1-HP of 8.6 µg/g creatinine.

On the basis of the logistical regression between the prevalence of abnormal serum high frequency cells PAHs in air or 1-HP in the post-shift urine of non-smoking workers exposed to PAHs, Buchet et al. (1995) concluded that the latter should be kept below 6.4 µg/m^3 and 2.7 µg/g creatinine, respectively.

It is not currently possible to assess risk presented by exposure to PAHs solely on the basis of urinary 1-HP concentrations. An indirect dose–response relationship between urinary 1-HP level and the relative risk for lung cancer has, however, been estimated for coke-oven workers: 4.4 µg 1-HP/g creatinine was estimated to be equal to a relative risk for lung cancer of approximately 1.3 (Jongeneelen 1992). Because of the varying composition of PAH mixtures, this risk estimation cannot be used for other workplaces or ambient air, where a correction factor may be necessary.

4.5.1.4/ Mutagen content of urine

The mutagen content of urine from persons exposed to PAHs has been assayed in a number of studies by the Ames test. Tobacco smoking resulted in mutagenic urine. No increase in mutagenic activity was found in most studies of workers exposed in occupational settings such as coking, coal-tar distillation, or aluminium, anode or graphite electrode plants (WHO 1998). Only the heavy exposure of patients with psoriasis to coal-tar application (Clonfero et al. 1989; Santella et al. 1994) and of coke-oven workers (Mielżyńska & Snit 1992) resulted in mutagenic urine.

The Ames test, therefore, appears not to be sensitive enough for detecting the presence of urinary mutagens caused by occupational exposure to low levels of PAHs.

4.5.2/ DNA adducts

DNA adducts with reactive metabolites (mainly diol epoxides) of BaP and other PAHs have been identified in numerous studies. For example, cigarette smokers have higher levels of adducts with PAHs in their lungs than non-smokers.

As binding of electrophylic PAH metabolites to DNA is thought to be a key step in the initiation of cancer, measurement of DNA adducts could be an indicator of exposure to PAHs and also of cancer risk. As a surrogate for lung tissue, which is an important target organ for PAHs in humans, the more easily accessible nucleated blood cells and blood proteins (haemoglobin, albumin) have been investigated.

In general, exposures that lead to the excretion of high concentrations of 1-HP in urine also lead to elevated DNA adduct levels. In all populations studied there was substantial inter-individual variation in PAH-DNA adduct levels after exposure by inhalation or orally, which is greater than that described for 1-HP excretion in urine. In one study, inter-individual variations of about 50-fold were reported among controls and of about 100-fold among coke-oven workers (Rojas et al. 1995). The variations are probably due to differences in the induction of aryl hydrocarbon hydroxylase (AHH) activity in lymphocytes and in the resulting detoxi-

fication of carcinogenic PAHs, the ability to repair DNA lesions and the turnover of damaged cells. These inter-individual variations result in a wide overlap in the ranges of values between exposed and unexposed subjects in all studies.

The levels of DNA adducts in control subjects range from 0.2 to about 10 per 10^8 nucleotides in leukocytes. Elevated DNA adduct levels have been detected in the general populations of industrialized areas in the Czech Republic and Poland, with levels up to 5 and 13 adducts per 10^8 nucleotides, respectively. The consumption of charcoal-grilled food leads to elevated DNA adduct levels; eating charcoal-grilled beef resulted in a 1.9–3.8-fold increase above the individual baseline adduct levels (Kang et al. 1995).

Workers exposed to PAHs had elevated mean levels of adducts and a higher percentage of positive samples than controls. In cases of high exposure, for example coke-oven workers, 5– 70 adducts per 10^8 nucleotides have been measured. Significant correlations with exposure concentrations have been found, although the level was no more than three-fold greater than in controls (Assennato et al. 1993; Hemminki et al. 1990a, b; Ovrebo et al. 1990).

The suitability of DNA adducts as biomarkers of exposure or risk has not been fully recognized. Concerning the use of lymphocytes as a surrogate for lung cells, inconsistent outcomes regarding the correlation between PAH-DNA adduct levels in human lungs and leucocytes have been reported (van Schooten et al. 1992; Wiencke et al. 1995). DNA adducts are much less sensitive for assessing human exposure than excretion of 1-HP in urine. Because of the large inter-individual differences in control and exposed groups, adduct levels can be compared only on a group basis. This method may, however, permit the identification of subjects who are highly susceptible to the DNA-damaging properties of PAHs and are therefore predisposed to lung cancer (WHO 1998).

5/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

After entering the atmosphere, PAHs are deposited in soil, water and vegetation and undergo degradation processes.

Accumulation of PAHs in the soil should not take place to a substantial extend. In the case of BaP, the time necessary to attain a steady state between deposition and elimination is 2.3 years. Bioaccumulation can take place only in primitive organisms, whereas organisms that metabolize PAHs accumulate little or no PAHs. Biomagnification has not been observed, because most organisms have a high biotransformation potential for PAHs.

Although food constitutes the main route of intake of PAHs, the Joint FAO/WHO Expert Committee on Food Additives was unable to establish a tolerable intake for BaP. Nevertheless, the large difference between the estimated oral human intake of BaP and the doses that induce tumours in animals suggests that any effects on human health are likely to be small (WHO 1998).

PAHs were assessed in the WHO Guidelines for Drinking-water Quality (WHO 1996). The resulting guidelines for BaP in drinking-water corresponding to excess lifetime risks for gastric cancer of 10^{-5} and 10^{-6} are 0.7 and 0.07 µg/l, re-

spectively. Current concentrations of BaP in drinking-water are below 0.002 µg/l (WHO 1998).

The toxic effect of most concern from exposure to PAHs is cancer. IARC considers several purified PAHs and PAH derivatives to be probable (group 2A) or possible (group 2B) human carcinogens. Some mixtures containing PAHs are known human carcinogens (group 1). Data obtained as a result of epidemiological studies under occupational conditions suggest that there is an association between lung cancer and exposure to PAHs. The most important exposure route for lung cancer appears to be inhalation. WHO (2000) considered the concentration of BaP in the air as a good index of the carcinogenic potential of the total fraction. A unit risk for BaP (lifetime exposure to a mixture represented by 1 ng/m^3 BaP) is estimated to be 8.7×10^{-5} (WHO 1987, 2000).

Available data for Europe published by Shatalov et al. (2001a) suggest that mean annual BaP air concentrations that could be attributed to long-range transport in 1998 were within the range of 0.1–0.5 ng/m^3. The corresponding excess lifetime cancer risk would amount to $8.7 \times 10^{-6} – 4.3 \times 10^{-5}$.

The weight of evidence arising from epidemiological studies based on inhalation and occupational exposure to PAHs suggests an increased risk of harmful health effects, mainly lung cancer. The excess lifetime risk of lung cancer that can be attributed to LRTAP is low compared to the risk owing to exposure from local sources.

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CHAPTER 9/
POLYCHLORINATED TERPHENYLS

1/ INTRODUCTION

Polychlorinated terphenyls (PCTs) are chlorinated aromatic compounds that are structurally and chemically similar to PCBs. The chemical and thermal stability and electrical properties of PCTs made them favoured for several industrial uses (de Boer 2000). PCTs were sold on the basis of their physical properties, which depend on the degree of chlorination within the molecules (WHO 1993). Several formulations of PCTs were manufactured for uses such as caulking compounds, vapour suppressants, sealants, carbonless copying paper, waxes, printing inks, fire retardants, plasticizers, hydraulic fluids and lubricants. Trade names for PCTs include: Aroclor (Series 54), Pydraul, Kanechlor C, Electrophenyl T-60, Clophen Harz (W) , Cloresil (A,B, 100), Leromoll, and Phenoclor (de Boer 2000; FAO/UNEP 1992).

PCTs were produced in the United States from 1929 to 1972 by the Monsanto Company under the trade name Aroclor. The Aroclors were composed of PCBs, PCTs or mixtures of both classes of compound. Approximately 52 000 tonnes of PCT were produced between 1959 and 1972 by Monsanto in the United States before production was discontinued owing to environmental concerns (Gallagher et al. 1993; Jamieson 1977; Pagano et al. 1999). In Canada, PCTs were imported and used commercially at one time, but all uses were terminated during the 1970s (Jamieson 1977); the use of PCTs in commercial, manufacturing and processing is banned in that country (FAO/UNEP 1992). PCTs were also produced in France, Germany, Italy and Japan, but their production has been discontinued (de Boer 2000). A total of some 60 000 tonnes of PCTs were produced worldwide during the period 1955–1980 (de Boer 2000). As a result of the widespread use of both PCTs and PCBs in Europe and the United States, both chemicals became global contaminants (de Boer 2000). All uses of PCTs are banned within the European Union, with the exception of preparations with a total PCT content of < 0.01% by weight, which are not restricted for use or sale (FAO/UNEP 1992).

PCTs are not included in emission inventories for Canada (National Pollutant Release Inventory) or the United States (Toxics Release Inventory).

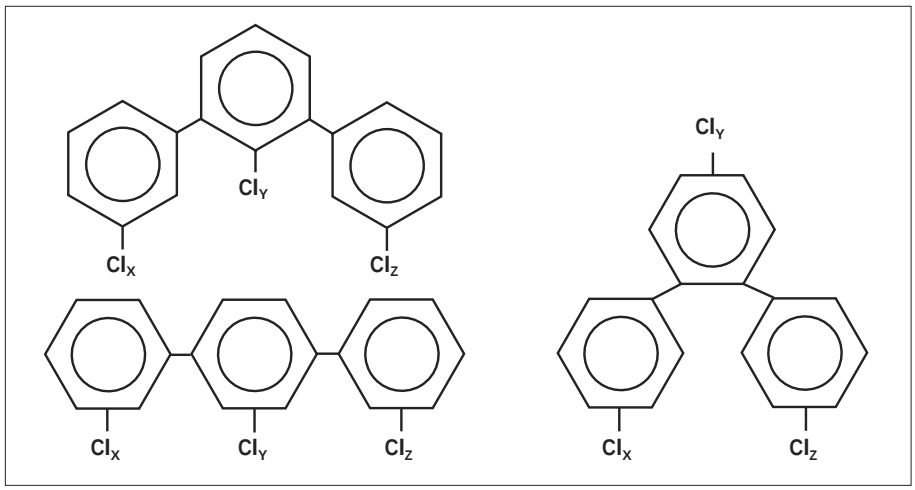
The production and use of PCTs will be reassessed under the POPs Protocol of the LRTAP Convention by 31 December 2004.

2/ POTENTIAL FOR LRTAP

2.1/ Physical and chemical properties

PCTs are composed of three chlorinated phenyl rings situated in one of three possible arrangements: *meta*, *para* and *ortho* (see Fig. 9.1). The maximum number of different congeners is 8149 (de Boer 2000; Jamieson 1977).

Fig. 9.1. Structural formulae of PCTs



Source: de Boer 2000; Jamieson 1977.

In general, PCTs are stable, non-flammable, yellow mixtures that are insoluble in water and soluble in various organic solvents and oils. They are also non-oxidizing, non-corrosive, thermoplastic and of low volatility (FAO/UNEP 1992; Jamieson 1977; Jensen & Jorgenson 1983). Refer to Table 9.1 for some chemical and physical properties. Within the temperature range of 300–800 °C, PCTs may

Table 9.1. Some chemical and physical properties of four Arocolor mixtures containing PCTs

Property	Aroclor 2565	Aroclor 4465	Aroclor 5442	Aroclor 5460
Chemical formula (n=number of chlorine atoms)	$C_{18}H_{14-n}Cl_n$			
CAS No.	61788-33-8			
Appearance	Black, opaque, brittle resin	Clear, light yellow resin	Clear yellow, sticky resin	Clear yellow/ amber, brittle resin or flakes
Distillation range (°C)	–	239–320 (4 torr)	215–300 (4 torr)	280–335 (5 torr)
Specific gravity (25°C)	1.734	1.670	1.470	1.670
Flash point (°C, open cup)	–	None to boiling point	247	None to boiling point
Fire point (°C, closed cup)	–	None to boiling point	> 350	None to boiling point
Refractive index (n 20 D)	–	1.664–1.667	–	1.660–1.665
Viscosity	–	90–150 (130 °C)	–	300–400 (98.9 °C)

Source: de Boer 2000; Jamieson 1977.

undergo thermolysis to produce polychlorinated dibenzo-*p*-dioxins and dibenzofurans (FAO/UNEP 1992).

PCTs are structurally and chemically similar to PCBs (Pagano et al. 1999) and are generally assumed to be similar to them with respect to environmental fate and transport processes and distribution as well (Jensen & Jorgenson 1983).

2.2/ Persistence and bioaccumulation

PCTs are resistant to both biodegradation and photodegradation. Owing to their lipophilicity and stability, PCTs can accumulate in organisms by means of the food chain (de Boer 2000; FAO/UNEP 1992).

A correlation between total PCT and total PCB concentrations has been found for both biota and sediment. High PCT : PCB ratios in sediment and fish samples indicate that PCTs may be more highly adsorbed to sediments and more persistent in fish tissues than PCBs (de Boer 2000).

PCTs have been identified in tissues of the common snapping turtle and in St Lawrence River sediment in a recent study. Historically, PCT was used as a hydraulic fluid by industries along the St Lawrence River. Sediment-bound PCT in samples taken in 1999 did not present any physicochemical or biological differences from an Aroclor 5432 standard, indicating that the PCTs remained unaltered for a period of at least 30 years. In the snapping turtle, PCTs were detected in adipose tissue, liver and eggs at levels of 42.2, 20.2 and 6.5 mg/kg (lipid basis), respectively. The PCT congeners found within these samples consisted mainly of the higher chlorinated congeners (chlorines at positions 4 and 5). As Aroclor 5432 consists of PCT molecules with 1–5 chlorines, it is suspected that the lower chlorinated congeners were metabolized and eliminated by the turtles, while the higher chlorinated molecules accumulated within various tissues (Pagano et al. 1999).

The relatively high PCT levels, ranging from 2800 µg/kg to 7400 µg/kg (wet weight basis), in white-beaked dolphins from the North Sea is indicative of the persistent nature of PCTs, given that these levels were found 20 years after PCT production was banned.

Aroclor 5432 was detected in salt marsh cordgrass, American oysters, fiddler crabs, wharf crabs and mummichogs (*Fundulus heteroclitus*) from a Virginia creek. Of these species, the highest accumulations of PCTs (18 000 µg/kg) were detected in oysters. The general trend observed within this study indicated that PCT concentrations decreased with distance downstream from a suspected source. PCTs have also been observed in wild populations of eels and oysters in the Netherlands, eider duck livers from the Wadden Sea, white-beaked dolphins and harbour porpoises from the North Sea (de Boer 2000) and white-tailed eagles and grey seals in Sweden (Gallagher et al. 1993). The detection of PCTs in sperm whales indicates that these substances have reached deep ocean waters (de Boer 2000).

2.3/ Monitoring and modelling

Atmospheric transport has been found to be a major pathway for PCT deposition into the Great Lakes (WHO 1993). Residues of PCTs have been detected in many

environmental samples (i.e. soil sediment and river water) and have been detected in fish, oysters, birds, wild dogs, cats, snakes, cow livers, pigeon fat, human milk and human fat/blood (de Boer 2000). Detection of PCTs in the sub-Antarctic area (Falkland Islands) is indicative of global PCT contamination (de Boer 2000).

Very little attention has been devoted to investigating the environmental presence and impact of PCTs in comparison to PCBs (de Boer 2000). While extensive monitoring and modelling data exist for PCBs, such data are unavailable or very limited for PCTs and have generally been collected only for the purpose of environmental monitoring of local contamination problems. In addition to the limited and dated data set for PCTs, the available information on PCTs should be used with caution because of the large variation in analytical procedures and calculation methods used at the time (de Boer 2000).

2.4/ Conclusions regarding LRTAP potential

Based on their persistence and their potential to bioaccumulate, PCTs satisfy the criteria of POPs with respect to LRTAP potential. PCTs are characterized by chemical and thermal stability and have low volatility and water solubility. Generally, PCTs are assumed to be similar to PCBs with respect to environmental fate and transport processes and distribution. However, very little attention has been devoted to investigating the environmental presence and impact of PCTs in comparison to PCBs. Atmospheric transport has been found to be a major pathway for PCT deposition into the Great Lakes.

The limited environmental data available indicate that PCTs are resistant to both biodegradation and photodegradation, which in combination with their lipophilicity and stability may indicate their ability to persist, bioconcentrate and biomagnify within the food chain. However, the database of literature for PCTs is both limited and dated.

3/ PATHWAYS OF LRTAP-DERIVED HUMAN EXPOSURE

3.1/ Significant sources and magnitude of human exposure

3.1.1/ Exposure in adults

PCTs have been detected in the environment, although usually at levels lower than PCBs within the same samples. PCTs have been detected in several species of fish and bird in various regions of Europe. In Japan, PCTs were found in fish and sediment samples at levels ranging from 0.0001 to 0.2 mg/kg, although they were not detected in water (Freudenthal & Greve 1973; WHO 1993).

In Canada, PCTs have been detected in food at levels of 0.01–0.05 ppm (FAO/UNEP 1992). Based on the intake of vegetables in Japan, the estimated human daily intake of PCTs is about 0.05 µg/day (FAO/UNEP 1992). Other sources of PCTs include paper products and food packaging materials (de Boer 2000; FAO/UNEP 1992; Jamieson 1977). One study reported PCT concentrations in 5.5% of 73 samples of food packaging materials ranging from 0.01 to 0.05 mg/kg total weight (de Boer 2000). Another study reported PCT concentrations in 100 paperboard samples of 0–163 ppm (Jamieson 1977).

Studies conducted during the 1970s noted the presence of PCTs in blood, liver, adipose tissue, kidney and brain at levels of 0.04–9.2 mg/kg on a lipid weight basis (de Boer 2000). A study conducted in Japan by Dogushi et al. (1974) demonstrated that PCTs have been detected in human fat samples at levels of 0.03–0.29 ppm.

As demonstrated by their lipophilicity and presence in human and animal tissues, PCTs are bioaccumulative and may accumulate in humans from exposure via food and other routes (de Boer 2000; Dogushi et al. 1974).

3.1.2/ Exposure in children

Studies conducted during the 1970s indicate the presence of PCTs in human milk in Dutch women at levels of 0.5–0.8 mg/kg and 0–0.22 mg/kg in Japanese women on a lipid weight basis (de Boer 2000). Children may therefore be exposed to PCTs *in utero* or during breastfeeding.

3.2/ Significance of LRTAP as a source of total exposure

PCTs have been detected in the environment, although usually at levels lower than PCBs within the same samples. Potential exposure to PCTs by the general population would primarily occur via consumption of meat, fish and dairy products. Young infants may be exposed to PCTs *in utero* or by consumption of breast milk. Although there are limited data on the toxicokinetics of PCTs, they are absorbed and readily distributed to all body compartments, with the highest concentration in the liver.

4/ HEALTH HAZARD CHARACTERIZATION

4.1/ Toxicokinetics

4.1.1/ Absorption

There is very limited information available on the rate of absorption of PCTs from the intestinal tract, although they have been shown to be absorbed (WHO 1993).

4.1.2/ Distribution

Once absorbed, PCTs are readily distributed to all body compartments, with the highest concentration in the liver. A feeding study involving diets containing Aroclor 5460 at levels of 10, 100 or 1000 mg/kg administered to rats for 7 days showed that the greatest concentration (611 mg/kg at 1000 mg/kg diet) was found in the liver, while the blood level was 5.85 mg/l at 1000 mg/kg diet (WHO 1993). Administration of PCTs did not affect body weight, but a significant increase in liver weight occurred in the rats fed 1000 mg/kg diet (WHO 1993). Table 9.2 presents a comparison of the tissue distribution of PCTs in rats fed 100 mg/kg Aroclor 5460 for 7 days and of PCBs in rats fed Aroclor 1254 at 100 mg/kg for 9 days.

Based on the data in Table 9.2, PCT tissue distribution is liver > heart > kidney > brain > blood, compared to PCB tissue distribution which is fat > liver ≅ kidney ≅ brain > blood (WHO 1993).

Table 9.2. Tissue distribution of PCTs in rats fed 100 mg/kg Aroclor 5460 for 7 days and of PCBs in rats fed Aroclor 1254 at 100 mg/kg for 9 days

Tissue	PCT tissue distribution (mg/kg wet weight)	PCB tissue distribution (mg/kg wet weight)
Blood	1.32	0.1
Liver	47.0	6.0
Brain	5.1	4.0
Kidney	15.1	5.0
Heart	21.5	–
Fat	–	180.0

4.1.3/ Metabolism (accumulation)

Cod (*Gadus morhua*) were dosed orally (by gavage) with Aroclor 5460 (in herring oil) at 0.5 g/ml; after one week of starvation, all tissues analysed contained PCTs. Uptake efficiency appeared to be low, with a total of 1–10 mg of Aroclor 5460 distributed throughout all tissues per gram administered. Liver was found to be the organ richest in PCTs, and probably contained most of the absorbed material (WHO 1993). PCTs were found in several cod tissues in an Aroclor 5460 feeding study approximately 70 days after exposure ceased (WHO 1993). The highest levels of PCTs were found in the liver, although they were also detected in the brain and gonads. Similarly, in mice exposed to 20–200 ppm PCTs for 3–6 months in the diet, PCTs were found to accumulate in the liver and adipose tissue. Other studies have demonstrated that the absorption, metabolism and accumulation of PCTs vary between the *meta*, *ortho* and *para* isomers (Jensen & Jorgenson 1983).

A bioaccumulation study (Pagano et al. 1999) using snapping turtles was completed in the area immediately adjacent to the General Motors (GM) facility on the St Lawrence River in Massena, New York. The GM site was designated a National Priority List "Superfund Site" in September 1983 owing to the historic landfilling of an estimated 30 000 cubic yards of PCB-contaminated hydraulic oil sludge. Snapping turtles were identified as biomonitors for bioaccumulation because they have a long life expectancy, are common to the Great Lakes, are non-migratory and have limited home ranges. Environmental data indicated that the PCT congeners found in sediment samples consisted mainly of the higher chlorinated congeners (chlorines at positions 4 and 5). As Aroclor 5432 consists of PCT molecules with 1–5 chlorines, it is suspected that the lower chlorinated congeners were metabolized and eliminated by the turtles, while the higher chlorinated molecules accumulated within various tissues.

4.1.4/ Elimination and excretion

PCT excretion is via the faeces as observed in the excreta of cod dosed orally with Aroclor 5460 and in rats after oral administration of a diet containing Aroclor 5460 (WHO 1993).

4.2/ Effects on laboratory animals

The toxicity of PCTs has not been extensively investigated and is considered to be very similar to that of PCBs, with the long-term toxicity being most important (Jensen & Jorgensen 1983). A general difficulty in toxicological studies of PCTs is the contamination of the PCT mixtures with PCBs. It is difficult to determine whether observed effects are caused by the PCTs or by the PCB contaminants (de Boer 2000).

4.2.1/ Acute toxicity

The oral LD_{50} values of the PCT mixtures Aroclor 5442 and Aroclor 5460 in rats were 10.6 and 19.2 g/kg bw, respectively (Jensen & Jorgensen 1983; WHO 1993). For 3 : 1 mixtures of PCBs and PCTs (Aroclor 4465 and Aroclor 2562) in corn oil, the LD_{50} values in rats were 16 and 6.3 g/kg bw, respectively (Jensen & Jorgensen 1983; WHO 1993). The acute toxicity of lower chlorinated PCBs is higher than that of higher chlorinated PCT mixtures (see Table 9.3). The LD_{50} values for PCBs in rats range from 4 to 11 g/kg bw, which is lower than for PCTs (Aroclor 5442 and Aroclor 5460) or the PCB and PCT mixture, presumably owing to a lower solubility and absorption in the body (de Boer 2000).

The skin minimum lethal dose of PCTs in rabbits seems to be higher than that of lower chlorinated PCBs, possibly owing to lower solubility and absorption in the body, but rabbits (and guinea-pigs) are generally more sensitive than rats. PCTs seem to be less acutely toxic than most PCBs, possibly owing to lower solubility and absorption in the body (de Boer 2000).

Table 9.3. Acute toxicity of PCTs and PCBs

	Aroclor 5442 (PCTs)	Aroclor 5460 (PCTs)	Aroclor 1221 (PCBs)	Aroclor 1248 (PCBs)	Aroclor 4465 (3 : 1 mixture PCB + PCT)	Aroclor 2565 (3 : 1 mixture PCB + PCT)
Oral $LD5_0$ (mg/kg), rats	10 600[a]	19 200[b]	3 980	11 000	16 000[a]	6 310[b]
Skin minimum lethal dose (mg/kg), rabbits	1 260[a]	7 940[b]	2 000	794	2 000[a]	2 000[b]

[a] Administered as a 50% solution in corn oil.
[b] Administered as a 33.3% solution in corn oil.
Source: Jensen & Jorgensen 1983.

4.2.2/ Short-term toxicity

Male Wistar rats showed increased relative liver weights as well as increased microsomal protein, cytochrome P-450 and specific activities of aniline hydroxylase and aminopyrine-N-demethylase when exposed to PCTs (as Aroclor 5460) at levels of up to 1000 mg/kg diet (equivalent to 50 mg/kg bw) for 7 days (WHO 1993). Several investigators have observed induction of mixed types of hepatic microsomal enzymes in rats exposed to PCTs (WHO 1993).

Male Wistar rats were fed diets with *ortho*-, *meta*- or *para*-PCTs at a level of 2000 mg/kg (equivalent to 100 mg/kg bw) for 2 weeks. *Ortho*- and *meta*-PCTs reduced growth and increased relative kidney weights, while only *meta*-PCTs decreased food intake and increased relative liver weights. All mixtures increased plasma, but not liver, cholesterol levels and produced evidence of adrenal hypertrophy (WHO 1993).

Male Sprague-Dawley rats gained less body weight than controls when exposed to PCTs at 10 g/kg in their daily diet (equivalent to 400 mg/kg bw) for 3 weeks (Jensen & Jorgensen 1983). PCTs may cause a dose-dependent increase in relative liver weight, a proliferation of the endoplasmic reticulum and formation of large concentric membrane arrays (de Boer 2000; WHO 1993).

4.2.3/ Sub-chronic toxicity

Mice gained less body weight than controls when exposed to PCTs in their daily diet (250 mg/kg and 550 mg/kg for 24 weeks) (Jensen & Jorgensen 1983). However, hens exposed to 20 mg/kg PCTs (as Aroclor 5442) for 9 weeks did not show any difference in body weight gain compared to controls (Jensen & Jorgensen 1983).

Six Rhesus monkeys showed retarded growth and increased relative liver weights compared to three controls when exposed to PCTs (as Aroclor 5460) at 5000 mg/kg in their daily diet (equivalent to 200 mg/kg bw) for over 3 months (WHO 1993). After 6 weeks of exposure, the toxic signs observed were similar to those found within 1 month in a group of monkeys exposed to 300 mg Aroclor 1248 per kg diet (equivalent to 12 mg/kg bw). Several macroscopic effects of PCTs resemble those of PCBs, but PCTs are less damaging within 6 weeks (de Boer 2000; WHO 1993). Effects include hair loss from the head, neck and back; swollen eyelids and lips; progressive generalized subcutaneous oedema; purulent discharge in the eyes and isolated acne-like lesions on skin areas devoid of hair. After exposure of both groups for 3 months, proliferation of the smooth endoplasmic reticulum was observed as well as hypertrophy and hyperplasia of the gastric mucosa (WHO 1993).

4.2.4/ Effects on enzyme systems

High doses of PCTs (Aroclor 5432, 5442 and 5460) have been reported to stimulate the hepatic microsomal enzyme system in test animals and *in vitro* systems. PCTs have been reported to increase levels of cytochrome P-450, aniline hydroxylase, aminopyridine-*N*-demethylase, esterases and nitroreductase; and to reduce levels of glucose-6-phosphatase and aromatic hydrolase (de Boer 2000; Jensen & Jorgensen 1983).

Some earlier data also show evidence of fatty degeneration in the liver and biochemical changes, including increases in microsomal protein and phospholipids, and a decrease in RNA and cholesterol (WHO 1993).

Hepatic enzyme induction was delayed in Japanese quail. A single oral dosing of Aroclor 5460 at 100 mg/kg bw initially increased the period of sleep induced by

pentobarbital, but 18 hours later the sleeping time was depressed in comparison to controls. The hepatic enzyme induction of PCTs was observed to be greater in males compared to females, where no significant induction was observed (Jamieson 1977; Jensen & Jorgensen 1983).

PCTs potently induced both phenobarbitol- and 3-methylcholanthrene-inducible forms of cytochrome P-450 in rat liver microsomes. However, 20% of the induction was due to PCB contamination of the PCT mixtures (up to 0.75%). Generally, PCBs were a more potent inducer (Jensen & Jorgensen 1983; de Boer 2000).

In vitro metabolism of benzo(*a*)pyrene to carcinogenic 7,8- and 9,10-dihydrodiol metabolites was increased by 10–20 times for both PCTs and PCBs (Jensen & Jorgensen 1983).

Both PCTs and PCBs caused a 30–40% inhibition of Na^+-K^+ ATPase in brain and kidney preparations of blue gills (*Lepomis machrochirus*) (de Boer 2000; Jensen & Jorgensen 1983).

In vitro testing of Aroclors, including Aloclor 5442 (PCTs), inhibited enzyme systems in beef heart mitochondria. The specific enzyme activity of PCT-treated mitochondria was depressed by 10–20% compared with controls for NADH oxidase, and by 15–30% compared with controls for succino oxidase (Jensen & Jorgensen 1983). PCTs were less potent than PCBs.

4.2.5/ Teratogenicity and reproductive effects

One teratogenicity study involved groups of 15 or 16 pregnant ddY mice fed PCTs at 0, 100, 500 or 2500 mg/kg diet during gestation. The animals were sacrificed on day 18 and examined for embryonic effects. The foetuses of dams receiving the 500 and 2500 mg/kg diets showed a higher incidence of cleft palate compared with controls. Pregnant ddY mice were administered PCTs at 0, 50 or 100 mg/kg diet, with corticosterone administered subcutaneously on days 11, 12 and 13. A significant increase was seen in corticosterone levels in the plasma in the PCT-treated animals on day 14. Adrenalectomy of pregnant ddY mice on day 10 did not suppress the development of cleft palate but metapyrone, an inhibitor of corticosterone synthesis, significantly reduced the incidence of cleft palate in the foetuses. The results suggested that cleft palate induced by PCTs was not a direct effect, but was due to an increase in the corticosterone level in the maternal plasma (WHO 1993).

Pregnant Wistar rats were fed PCTs at 0, 500 or 2500 mg/kg diet during gestation, and the animals were sacrificed on day 20. The fetuses of dams receiving 500 and 2500 mg/kg showed systemic oedema, but no cleft palate was observed (WHO 1993).

Increased incidence of abnormal embryos in White Leghorn chickens were observed after dietary intake of Aroclor 5460 at 20 mg/kg for 5–9 weeks, followed by 7 exposure-free weeks (de Boer 2000; Jamieson 1977).

White Leghorn laying hens were dosed with 20 mg/kg PCTs (Aroclor 5442), one polybrominated biphenyl (PBB) and six different PCBs. For all of the

compounds tested, there were no reported adverse effects on adult body weight gain, survival, egg weight, egg shell thickness or fertility after 9 weeks of feeding (Jamieson 1977). The hatchability of fertile eggs was not significantly affected, even after a 20-mg/kg diet of Aroclor 5442 for 9 weeks (de Boer 2000; Jamieson 1977; Jensen & Jorgensen 1983).

4.2.6/ Carcinogenicity

Six Rhesus monkeys fed PCTs for 3 months showed hyperplasia and dysplasia of the gastric mucosa (Jamieson 1977; Jensen & Jorgensen 1983). This indicated compromised gastric function and was suggestive of an eventual neoplastic transformation (Jamieson 1977; Jensen & Jorgensen 1983).

Groups of 35 male ICR mice were fed Kanechlor C (a mixture of 95% PCTs and 5% PCBs) at 0, 250 or 500 mg/kg diet (equivalent to 0, 36 and 70 mg/kg bw) for 24 weeks. The mice were sacrificed following 16 exposure-free weeks (a total of 40 weeks). The surviving animals in each group (numbering 28/35, 28/35 and 21/35 in the 0, 250 and 500 mg/kg groups, respectively) were autopsied. A dose-related reduction in body weight gain and a dose-related increase in absolute liver weights were observed. Nodular hyperplasia was found in the livers of 3/28 mice at 250 mg/kg diet and 6/21 mice at 500 mg/kg diet. Hepatocellular carcinomas were observed in 3/21 mice at 500 mg/kg diet. No neoplastic nodules were noted in the controls (de Boer 2000; Jensen & Jorgensen 1983; WHO 1993). A combination of PCBs and PCTs in the diet considerably enhanced the occurrence of nodules and carcinomas (de Boer 2000).

4.2.7/ Other effects

Aroclor 5442 (PCTs) was eight times more oestrogenically active in rats than some chlorinated PCBs, whereas highly chlorinated PCBs and PCTs were inactive (de Boer 2000). The potency was measured by an increasing glycogen level.

Data on endocrine disruption and immunotoxic, neurobehavioural or other effects were not found in the available literature.

4.3/ Health effects in humans

Data on health effects of PCTs in humans were not found in the available literature.

4.4/ Critical outcomes and existing reference values

Data on critical outcomes and reference values related to human health effects were not found in the available literature.

The toxicity of PCTs is considered to be very similar to that of PCBs, which suggests long-term toxicity might be critical, although chronic toxicity information is lacking. A general difficulty in toxicological studies of PCTs is the contamination of the PCT mixtures with PCBs. It is difficult to determine whether observed effects are caused by the PCTs or by PCB contamination. PCTs seem to be less acutely toxic than most PCBs. Effects in animals include dose-dependent increase in relative liver weights, reduced growth and proliferation of the endoplasmic re-

ticulum. High doses of PCTs have been reported to stimulate hepatic microsomal enzymes in *in vivo* and *in vitro* test systems. Owing to the limitations of the available data, the characterization of health hazards of PCTs is concluded to be limited.

The available data are inadequate for determining whether PCTs cause the same health effects as PCBs.

5/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

There is insufficient information to evaluate the health implications from long-term exposures to PCTs. Further studies are needed in order to be able to evaluate the human health impact of PCTs and their potential link to LRTAP. However, since the production and use of PCTs is banned in the UNECE regions, the likelihood of obtaining adequate toxicity data to meet LRTAP criteria is low.

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CHAPTER 10/
POLYBROMINATED DIPHENYL ETHERS

1/ INTRODUCTION

Polybrominated diphenyl ethers (PBDEs) can be described as a novel class of environmental contaminant with various physicochemical properties similar to PCBs (hydrophobic, lipophilic, low vapour pressure, high log K_{ow}). Commercial production and use of PBDEs as additive flame retardants began in the 1960s, with the majority of uses confined to the plastics (resins, polymers, substrates), textile, electronic, furniture and, to a lesser extent, paint industries (Hooper & McDonald 2000). Worldwide production of PBDEs in 1990 was estimated at up to 40 000 tonnes. In 1999, consumption in the European Union was some 7550 tonnes (de Wit 2000).

Trend analysis data are complicated by patterns of continued use and the presence of PBDE "sinks" in a variety of consumer products potentially available for environmental release through recycling, land filling and incineration. Agricultural use of sewage sludge can also be regarded as another potential environmental source of PBDEs (Rahman et al. 2001).

Although 209 possible congeners can theoretically be produced by direct bromination of the biphenyl oxide (Fig. 10.1, with the same IUPAC numbering system as PCBs) unlike PCBs, the commercial PBDEs usually only contain a limited number of congeners. For example, over 80% of Bromkal 70-5DE, a pentaBDE product, is accounted for by only three congeners: PBDE 47 (2,2',4,4'), PBDE 99 (2,2',4,4',5) and PBDE 100 (2,2',4,4',6). The major commercial preparations of PBDEs include tetraBDE (tetra=penta-substituted congeners; no longer produced), pentaBDE (penta> tetra-substituted congeners), octaBDE (hepta> octa> hexa=nona-substituted) and decaBDE (primarily PBDE 209 or 2,2',3,3',4,4',5,5',6,6'-decaBDE). Sales of the pentaBDEs in the United States in1999 have been estimated at approximately 8000 tonnes (Dodder et al. 2002). As the flame retardant properties for PBDEs are related to the degree of bromination, current use patterns favour the commercial decaBDE formulation.

Based on evidence of long-range atmospheric transport, environmental persistence and bioaccumulation in various species, including humans, PBDE congeners, mainly specific to the commercial penta-brominated diphenyl ether mixtures, appear to satisfy the criteria under which new chemicals can be considered for addition to the UNECE POP Protocol.

2/ POTENTIAL FOR LRTAP

2.1/ Physical properties allowing atmospheric transport

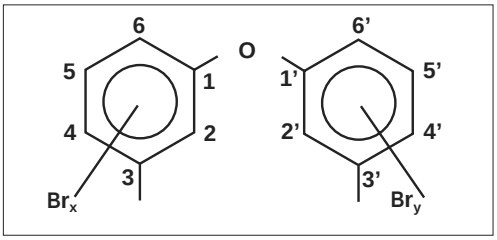

Fig. 10.1. Polybrominated diphenyl ethers, general formula

Table 10.1. Physical properties of PBDEs (petra, penta)

Property	Value
Molecular formula	$C_{12}H_6Br_4O$, $C_{12}H_5Br_5O$
Molecular weights	485.8–564.7
Water solubility	13.3 µg/l (pentaBDE), 10.9 µg/l (PBDE 47), 2.4 µg/l (PBDE 99)
Vapour pressure (at 25 °C)	4.69–7.5 × 10^{-5} Pa
Log K_{ow}	5.9–7.0

2.2/ Monitoring

PBDEs have been detected in a variety of environmental matrices, including air, water, sediment and biota, since the late 1970s. An analysis of biosolid samples from various regions in the United States found concentrations of PBDEs (penta-BDE equivalents) of up to 2.2 ppm (dry weight) (Hale et al. 2001a).

Analysis of air samples from remote northern locations has detected lower brominated congeners, in particular PBDEs 47, 99 and 100, at pg/m^3 concentrations, indicating that these substances are subject to long-range atmospheric transport (Darnerud et al. 2001). PBDEs in air samples collected from Alert, Canada in 1994 ranged from 10 to 700 pg/m^3, with PBDE congeners 99 and 47 predominating (Alaee et al. 1999). Similar and higher brominated PBDE congeners (i.e. PBDE 183 and 209) can be detected in emissions collected from the vicinity of electrical equipment and air samples from recycling/incineration facilities (Bergman et al. 1999).

Some of the earliest PBDE residue data from fish collected in Sweden reported that PBDE 47 was the most abundant congener present, making up 70–80% of the PBDE fraction (Andersson & Blomkist 1981). Of PBDEs detected in pilot whale blubber samples, congeners 47 and 99 accounted for on average over 70% of the total, with the former responsible for approximately 53% (Lindström et al. 1999). Similar results were found during analysis of fish from Washington State; tetraBDE and pentaBDE isomers predominated, with PBDE 47 accounting for up to 95% of the tetraBDE total and PBDE 99 a reported 80% of the pentaBDE (Johnson & Olson 2001). In salmon collected from Lake Michigan in 1996, total PBDEs ranged from 0.77 to 8.12 ppm (lipid based), with PBDE congeners 47, 99 and 100 accounting for on average 88% of the total and PBDE 47 approximately 65% (Manchester-Neesvig et al. 2001). In various species of fish collected

in 1998–1999 from the mid-Atlantic region of the United States (Virginia), sum PBDEs ranged from less than 5 μg/kg (detection limit) to the highest recorded value for PBDEs in edible fish tissue of 47.9 mg/kg (lipid based) (Hale et al. 2001b). PBDE 47 accounted for 40–70% of the sum PBDEs and, in certain fish, exceeded the concentration of PCB 153 and *p,p'*-DDE. Farmed salmon available on Scottish and European markets had lower concentrations of total PBDEs (1.1–85.2 ng/g lipid) but, as with the wild fish, PBDE congeners 47, 99 and 100 represented on average 77% of the total (Jacobs et al. 2001). In comparison, the same three PBDE congeners comprise almost 80% of the total PBDE fraction of Bromkal 70-5DE, a commercial pentaBDE but with congener PBDE 47 comprising only 37% of the total. Analysis of tissue samples from fish-eating birds has revealed similar PBDE congener patterns. Congeners 47, 99 and 100 were the major PBDEs detected in osprey from Sweden, with PBDE 47 contributing over 80% of the total (Sellström et al. 1993).

As an indication of long-range transport potential, PBDEs have been detected in fish and bivalve samples from southern Greenland (Christensen et al. 2002). The levels found in fish (1.2–12.0 ng/g wet weight) were orders of magnitude lower than fish samples collected from industrialized locations, and PBDE 47 accounted for up to 90% of the total. Further evidence of efficient atmospheric transport of PBDEs has been obtained from analysis of Arctic marine mammals. Average concentrations of total PBDEs in blubber samples collected from ringed seals in the Canadian high Arctic between 1981 and 2000 increased over 8-fold (0.572 vs 4.622 ng/g lipid) (Ikonomou et al. 2002). The major congeners detected included PBDEs 47, 99, 100, 153 and 154, with PBDE 47 on averaging accounting for approximately 74% of the total. The authors estimated that at the current rate of increase, PBDEs levels would surpass those of PCBs by 2050.

3/ PATHWAYS OF LRTAP-DERIVED HUMAN EXPOSURE

Although a variety of PBDEs are detectable in terrestrial samples (soil, sludge), it appears as though the aquatic environment represents the greatest potential for human exposure, especially waterways receiving direct input from industrial sources.

Levels of PBDEs in fish from Japanese markets ranged from 0.017 to 1.72 ng/g wet weight, with PBDE 47 (2,2',4,4') the predominant congener (approximately 60% of the total). PBDE 47 plus PBDE 99, 100 and 154 accounted for an average of 90% of the total PBDE (Ohta et al. 2002). Additional analysis of other food commodities (vegetables, meats) found significantly lower levels (6.25–134 pg/g wet weight) compared to fish. In women reporting the highest frequency of fish consumption (5–6 meals per week), breast-milk concentrations of PBDEs were significantly higher (1.7 ng/g lipid) compared to those reporting consuming only 1–2 fish meals per week (0.77 ng/g lipid). PBDE 47 was also the major congener in the breast-milk samples (40% of the total), while congeners 47, 99, 100 and 153 accounted for approximately 85% of the PBDE fraction. A similar association with PBDE congener 47 in blood was seen in Latvian men consuming fatty fish from the Baltic Sea (Sjödin et al. 2000). Men who reported consuming 12 or more

meals of fatty fish per month had plasma PBDE 47 levels more than 9-fold higher than men who consumed 0–1 fish meals per month (2.4 vs 0.26 ng/g lipid).

Although food survey data are limited, initial reports from Sweden have indicated that an estimated dietary intake of total PBDEs would be in the range of approximately 51 ng/person per day for adults, or less than 1 ng/kg bw per day (Darnerud et al. 2000). Preliminary market basket surveys in Canada have estimated the daily intake of total PBDEs from food to be approximately 44 ng/person, compared to an intake of total PCBs of 285 ng/person (Ryan & Paltry 2001). Major PBDE congeners found in various food commodities included PBDEs 47, 99, 100, 153, 154 and 183, with PBDE 47 (25%) and 99 (43%) comprising approximately 68% of the total. Analysis of butter samples collected from various locations worldwide has also shown the major PBDE congeners present to be PBDEs 47, 99 and 153, with PBDEs 47 and 99 occurring at approximately equal concentrations (Jones et al. 2001). Analysis of breast-milk samples collected up to 1996 in Sweden indicated mean PBDE concentrations of 4 ppb (lipid), with the major congeners including PBDEs 47 (over 50% of the total), 99, 153 and 100 (Lind et al. 2001). For the average breastfeeding infant, this would relate to an intake of approximately 11 ng/kg bw per day for PBDEs. Canadian human milk samples collected in 1992 contained on average 2.8 μg/kg (lipid) total PBDEs, with the major congeners present similar to those found in foods, i.e. PBDEs 47, 99, 153 and 100. PBDE 47 accounted for an average of 50% of the PBDE total, which was about 75-fold less than total PCBs.

In a limited sample of adipose tissues collected at autopsy from Swedish subjects (n = 5) the average total PBDEs was 5.4 ppb (lipid), with the major congeners present similar to those in breast-milk (Meironyté Guvenius et al. 2001). In a survey conducting with 23 samples of breast adipose tissue collected from women in the San Francisco area during the late 1990s, average total PBDEs was 85.7 ng/g lipid, with a range of 17.2–462 ng/g (She et al. 2002). For the majority of samples, PBDE 47 was the predominant congener (average 42%) with congeners 47 and 99 combined accounted for an average of 55% of the total (range 25–83%). In comparison to Bromkal 70-5DE, the hexabrominated congeners 153 and 154 were found at a substantially higher level in the human samples (less than 10% and 37%, respectively).

Additional estimations of maximum total daily intake of commercial pentaBDEs have been attempted, based both on releases from a local point source (polyurethane foam production) and general background levels in air, water and foods (European Commission 2000). Subsequent modelling estimations from multimedia exposure have provided values of between 2.0 and 53 μg/kg bw per day. In a similar exercise, theoretical chronic daily intakes were calculated for various age segments of the population, using Monte Carlo analysis of frequency distributions both for concentrations of PBDEs found in a variety of food commodities and for the associated ingestion rates (Wenning 2002). Based on the most prevalent congeners found in commercial pentaBDE mixtures, the average deterministic estimate was 0.85 μg/kg bw per day, while the probabilistic 50th and 95th percentiles were 1.47 and 2.73 μg/kg bw per day, respectively.

4/ HEALTH HAZARD CHARACTERIZATION

As abiotic and biotic residue patterns most closely resemble the congener composition of commercial pentaBDEs, the hazard characterization section of this report will focus primarily on that preparation.

4.1/ PentaBDE

Commercial mixtures of pentaBDE are usually composed mainly of tetraBDE (24–38%), pentaBDE (50–60%) and hexaBDE (up to 10%) isomers. For the majority of products, PBDE 47 (2,2',4,4') is the main tetraBDE, while PBDE 99 (2,2',4,4',5) is the major pentaBDE congener.

Although limited experimental data are available, the presence of PBDE congeners 47 and 99 in various environmental compartments, biota and humans indicates that these main constituents of commercial PentaBDEs are persistent and bioavailable. Following the total consumption of 672 ng of DE-71 by male rats over a period of 21 days (approximately 120 ng/kg bw per day), an average of 36% of the dose based on the total of major congeners was detected in the carcass and liver (Hakk et al. 2001). Mice and rats administered PBDE 47, one of the main congeners found in commercial pentaBDEs, retained 47% (mice) and 86% (rats) of the dose after 5 days (Örn & Klasson-Wehler 1998). In a similar study, approximately 39% of a single oral dose of 2.2 mg PBDE 99 (2,2',4,4',5-pentaBDE) was found to be retained by rats 72 hours after the dose (Hakk et al. 1999).

Dosing of male Sprague-Dawley rats by gavage with 0.1 mmol/day of commercial pentaBDE (24.6% tetraBDE, 58.1% pentaBDE, 13.3% hexaBDE) for 14 days (approximately 56.5 mg/kg bw per day) resulted in significant induction of various phase I and II hepatic enzymes, including total cytochrome P-450, and increased relative liver weights (65%) (Carlson 1980a). When exposure to the same commercial pentaBDE was subsequently increased to 90 days (0–14.12 mg/kg bw per day), significant induction of the same hepatic enzymes was observed, which at the higher doses persisted following a 60-day withdrawal period (Carlson 1980b). The lowest dose tested in these studies, 0.44 mg/kg bw per day, resulted in hepatic enzyme induction that persisted into a 30-day recovery period, but with no evidence of histopathological alterations. Sprague-Dawley rats were maintained on diets formulated to provide DE-71 at doses of 0, 2, 10 or 100 mg/kg bw per day for 90 days. Significant effects, including decreased body weights, increased relative liver weights, increased serum cholesterol, decreased serum T4 and increased liver and urine porphyrins levels were generally restricted to the two highest dose groups. In a satellite group held for 24 weeks following termination of dosing, slight hepatocytomegaly was still apparent even though liver weights had returned to control values (WHO 1994). Although the incidence and severity of histopathological effects in liver were described as dose-dependent, a subsequent study in which the same rat strain was exposed to DE-71 in the diet at 0, 0.01, 0.05, 0.1, 0.5 or 1.0 mg/kg bw per day for 30 days revealed no treatment-related effects (European Commission 2000). Relative liver weight increases and hepatic

histological changes were also noted in CD rats fed diets containing 100 or 1000 mg/kg of a commercial pentaBDE mixture for 28 days.

In repeat dose studies, C57BL/6J female mice were dosed by gavage with a single dose of DE-71 at 0, 0.8, 4.0, 20, 1000 or 5000 mg/kg bw or a total dose of 0, 250, 500 or 1000 mg/kg bw over 14 days (approximately 0, 18, 36 or 72 mg/kg bw per day, respectively) and assessed for general toxicity and indications of immunotoxicity (Fowles et al. 1994). A dose-related increase in relative liver weight and decrease in plasma free and total T4 concentrations was observed along with induction of hepatic enzymes (cytochrome P-450 IA1 and IIB1) in the 14-day study, while relative liver weight increases and hepatic enzyme induction were seen only in the highest-dose group from the acute study. Total serum T4 was reduced in all dose groups from the acute study, except at 100 mg/kg bw, and not in a dose-dependent manner as with the repeat dose study. The only indication of immunotoxicity was a 33% decrease in the plaque-forming cell response to sheep erythrocytes (SRBC) in the highest-dose group from the 14-day study.

In weanling female Long-Evans rats exposed to DE-71 at 0, 0.3, 1, 3, 10, 30, 100 or 300 mg/kg bw per day by gavage for 4 consecutive days, a dose-dependent increase in relative liver weight was observed (≥10 mg/kg bw per day dose groups) (Zhou et al. 2001). Significant decreases in serum total T4 (≥ 30 mg/kg bw per day) were also seen (an 80% reduction in the highest-dose group), with smaller reductions in serum T3 levels (30% reduction in the two high-dose groups only).Various hepatic enzyme activities (ethoxy-, pentoxy-resorufin (EROD, PROD) and uridinediphosphate-glucuronosyltransferase (UDPGT)) were also significantly increased (≥ 3 mg/kg bw per day, EROD and PROD; ≥ 10 mg/kg bw per day UDPGT). The dose corresponding to the 95% lower confidence limit for serum T4 reduction was estimated at 6.95 mg/kg bw per day. In a similar study, female Sprague-Dawley rats and C57BL/6N mice were administered by gavage daily doses of either Bromkal 70-5 DE (0, 18 or 36 mg/kg bw per day) or PBDE 47 (2,2',4,4') (0 or 18 mg/kg bw per day) for 14 days and then sacrificed 24 hours after the last dose (Hallgren et al. 2001). Relative liver weights were increased in all dose groups, along with dose-dependent decreases in plasma free and total T4 concentrations. Hepatic vitamin A (retinol and retinyl esters combined) concentration and total amount per liver were reduced by both doses of Bromkal 70-5 DE in rats (average of 25% and 13%, respectively), while only the highest dose caused a reduction in hepatic vitamin A in mice (μg/g liver). As previously seen, various hepatic phase I enzyme activities (EROD, PROD, methoxyresorufin-O-demethylase (MROD)) were significantly increased by either technical PBDE in rats and mice or PBDE 47 in mice, while UDPGT activity was increased only by the highest dose of Bromkal 70-5 DE in rats. A lower dose of Aroclor 1254 (10 mg/kg bw per day) induced similar but more pronounced effects. From a mechanistic perspective, *in vitro* conversion of various PBDEs by liver microsomal preparations from phenobarbital (CYP2B)- and, to a lesser extent, 8-naphthoflavone (CYP1A)-induced animals produces metabolites that can effectively displace T4 from human transthyretin (Meerts et al. 2000). This could

theoretically result in increased glucuronidation of free T4 and subsequent biliary elimination.

Pregnant Sprague-Dawley rats were dosed with Saytex 115 (commercial pentaBDE) at 0, 10, 100 or 200 mg/kg bw per day on gestational days 6–15, and all fetuses were collected on gestation day 20 for evaluation. While reduced maternal body weight gain was noted in the two highest dose groups, no fetal developmental anomalies were seen (WHO 1994). In a similar study, pregnant Long-Evans rats were dosed by gavage with DE-71 at either 0, 1, 10 or 30 mg/kg bw per day from gestation day (GD) 6 through to postnatal day (PND) 21 (Zhou et al. 2002). There were no treatment-related effects on any measured reproductive parameter, maternal or offspring body weights or time to pup eye opening. Relative maternal liver weight was significantly increased (8%) in the high-dose group on GD 20 (first observation time) and PND 22 (last observation time) while pup liver weights were also significantly increased in the middle- and high-dose groups on PND 4 (25% and 35%, respectively) and in the high-dose group only on PND 14 (39%). All offspring liver weights returned to control levels by PND 36. Associated with the observed increased liver weights were significant increases in hepatic EROD and PROD activities in the middle- and high-dose groups of the dams, and beginning on GD 20 for the pups (high-dose group), continuing through PND 4–14 (middle- and high-dose groups) and PND 36 (high-dose group). By PND 90, all offspring hepatic enzyme activities measured had returned to control levels. Exposure of the maternal animals to DE-71 also caused a significant decrease in serum T4 levels in the high-dose group (average 44%) compared to the controls, while T4 levels in pups decreased from GD 20 to PND 36 (highest decrease 66% on PND 14) in the middle- and high-dose groups, before returning to control levels by PND 36. Hepatic T4-UDPGT activity was significantly increased in the high-dose dams at both observation times and in high-dose pups from PND 4–14, returning to control values by PND 36. No effects were noted in either dams or offspring for serum total T3 levels.

Two major congeners present in various pentaBDE formulations, PBDE 47 and 99, have been tested for potential developmental neurotoxicity in mice. Male NMRI mice were treated with a single gavage dose of PBDE 47 (0, 0.7 or 10.5 mg/kg bw) or PBDE 99 (0, 0.8 or 12.0 mg/kg bw) on postnatal day 10 and tested for aspects of spontaneous behaviour and spatial learning ability at 2–5 months of age (Eriksson et al. 2001). Both doses of PBDE 99 and the highest dose of PBDE 47 affected spontaneous behaviour, while only mice treated with the highest PBDE 99 dose exhibited reductions in learning and memory functions as assessed by a swim maze.

While no *in vivo* studies have been conducted to address the potential mutagenicity/genotoxicity of pentaBDEs, commercial mixtures (Bromkal 70-5 DE, Saytex 115) have tested negative in standard bacterial reverse mutation assays (European Commission 2000). In addition, pentaBDE did not induce chromosomal aberrations in human peripheral blood lymphocytes following *in vitro* exposure.

Although PBDEs are structurally similar to various "dioxin-like" contaminants (dioxins, furans, PCBs) and EROD induction has been observed under various experimental conditions, pure synthetic congeners tested in established animal and human cell lines exhibited EROD induction potencies approximately 3–6 orders of magnitude lower than TCDD (Chen et al. 2001). For certain congeners, this was within the same potency range of mono-orthosubstituted PCBs. The commercial PBDEs tested, penta-, octa- and decaBDE, were generally inactive in inducing EROD activity, indicating the possible contribution of "dioxin-like" contaminants in various preparations (brominated dioxins/furans). Whereas various pure and hydroxylated PBDEs have also been shown to possess estrogenic activity, as determined by the *in vitro* ER-CALUX bioassay, their relative potency is limited (at least 4 orders of magnitude less than estradiol) (Meerts et al., 2001).

Concentrations of PBDE 47 (2,2',4,4') were found to be higher in adipose/blood samples collected from Swedish patients diagnosed with Non-Hodgkin lymphoma (NHL) as compared to age-matched controls (Hardell et al. 2001). In 82 patient samples, mean PBDE 47 levels were 8.2 ng/g lipid (range 0.1–134 ng/g) compared to 2.4 ng/g lipid (range 0.05–28 ng/g) in 83 controls. Patients were also grouped according to their PBDE levels (less than or equal to the control median value of 0.65 ng/g lipid or greater than the median value) and then further subdivided according to whether their Epstein-Barr virus early antigen (EA) titres (associated with certain types of NHL) were less than or equal to 80 or greater than 80. Patients with high levels of both PBDE and EA had a greater odds ratio (OR) for NHL than those with high PBDE levels and lower EA levels. The OR and 95% confidence interval (CI) for these two groups were 21 (CI = 4.6–124) and 13 (CI = 3.0–71), respectively.

4.2/ Risk assessment

4.2.1/ Scenario 1

A number of specific PBDE congeners can be detected in all environmental trophic levels, including biota and humans. Based on results from limited market basket surveys and human residues, the commercial mixtures that most closely reflect actual exposures are the pentaBDEs (e.g. Bromkal 70-5 DE, DE-71, Saytex 115). Hazard characterization for pentaBDEs is not only limited in scope but confounded by a lack of accurate identification of congener composition and impurities. In terms of the most sensitive experimental endpoints, pentaBDEs have consistently and in a dose-dependent manner induced a variety of effects in the liver (relative weight increases, vitamin A reduction, cytological alterations, enzyme inductions) and thyroid (slight hyperplasia, T3/T4 decreases). The lowest LOEL identified to date for liver effects is 0.44 mg/kg bw per day for 90 days, which resulted in persistent enzyme induction (Carlson 1980b). This finding is supported by the estimated lower confidence limit on a benchmark dose of DE-71 for CYP 2B induction of 0.54 mg/kg bw per day (4-day exposure) in a different rat strain (Zhou et al. 2001). A chronic NOEL could be estimated at a dose 10-fold lower than the LOEL, or 44 μg/kg bw per day. Although hepatic enzyme induction would not be

considered an adverse effect, justification for setting the NOEL at this level can be provided based on the persistent and bioaccumulative nature of PBDE congeners found in commercial pentaBDEs. In addition, dose-dependent increases in relative liver weight and hepatocytomegaly, potentially more adverse end-points, have been observed in rats following ingestion of DE-71 at ≥ 2 mg/kg bw per day for 90 days (European Commission 2000). In addition, a benchmark dose of DE-71 for neonatal thyroid hormone effects in rats has recently been estimated at 0.94 mg/kg bw per day (Zhou et al. 2002). When the chronic NOEL is compared to environmental exposures for adults from "worse-case" scenario modelling exercises, margin of safety values would be only 0.8–22, or unacceptably low taking into account current deficiencies in the toxicological database.

4.2.2/ Scenario 2

Exposure of weanling mice to a single dose of PBDE 99 (2,2',4,4',5) (0, 0.8 or 12.0 mg/kg bw) results in persistent deficits in spontaneous behaviour that appear to worsen with age (Eriksson et al. 2001). Based on an average absorption value of 50% from the protein : lipid vehicle, the lower dose would result in a hypothetical body burden of 0.4 mg/kg bw. For persistent chemicals, steady state body burdens can be estimated by the following formula:

$$\text{steady state body burden} = \frac{(\text{daily dose}) \times t^{1/2} \times f}{\ln (2)}$$

where $t^{1/2}$ is the chemical half-life, f the fraction dose absorbed, and ln (2) the natural logarithm.

To achieve this body burden (associated with a LOAEL), mice would have to be exposed to:

$$0.4 \text{ mg/kg bw} = \frac{\text{DD} \times 36 \text{ days}^* \times 0.5}{0.693}$$

DD = 15.5 µg/kg bw per day.

Therefore, mice ingesting an average daily dose of 15.5 µg/kg bw would eventually achieve a body burden similar to that associated with a LOAEL for neurodevelopmental effects. If the DD was reduced 10-fold to approximate a NOAEL (1.55 µg/kg bw per day), this would result in margin of safety values of only 0.03–1.1 when compared to the European Union's probabilistic exposure estimates. (*Note*: PBDE 99 was assigned 40% of the total PBDE intake estimation.)

4.3/ Previous risk assessments

USEPA has established oral reference doses for commercial deca-, octa- and pentaBDEs of 10.0, 3.0 and 2.0 µg/kg bw per day, respectively. To address the issue of contaminated fish, an interim reference dose for tetra-BDE has been suggested at 1.0 µg/kg bw per day.

* $t^{1/2}$ value cited for PBDE 99 in rodents (Hooper & McDonald 2000).

5/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

While uncertainties in the current exposure and toxicological database hinder an accurate risk characterization, there are indications that margin of safety estimates may be unacceptably low, especially considering the environmental persistence and bioaccumulative nature of PBDEs.

A scientifically defensible risk assessment for PBDEs is hampered by a variety of data deficiencies. What can be determined is that various PBDEs in the environment are persistent and bioaccumulate, resulting in residues in biota and humans. While a quantitative risk assessment has been attempted, further effort should be directed towards:

- identifying and controlling environmental sources;
- conducting additional exposure studies (market basket surveys, human residues);
- extending initial neurobehavioural observations to *in utero* exposure studies with multiple dose groups reflecting environmental PBDE mixtures and human body burdens; and
- obtaining additional toxicokinetic data under chronic exposure conditions.

The developing fetus and breast-fed infant are considered to be the main "at risk" groups from potential adverse effects due to exposure to PBDE congeners found in commercial penta-brominated diphenyl ether mixtures.

The overall contribution of LRTAP to daily PBDE exposure depends on the region, but would be substantial for more remote locations.

6/ REFERENCES

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CHAPTER 11/ POLYBROMINATED DIBENZO-*P*-DIOXINS AND DIBENZOFURANS

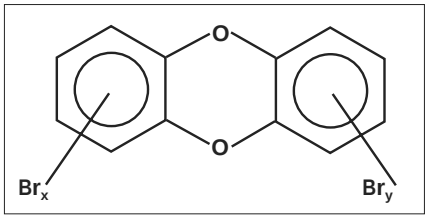

Fig. 11.1. Polybrominated dibenzo-*p*-dioxins (PBDDs)

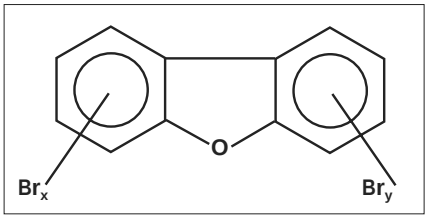

Fig. 11.2. Polybrominated dibenzofurans (PBDFs)

1/ INTRODUCTION

Polybrominated dibenzo-*p*-dioxins and polybrominated dibenzofurans (PBDD/PBDFs) consist of two groups of tricyclic aromatic compounds with similar chemical and physical properties (Fig. 11.1 and 11.2). The number of bromine atoms in each molecule can vary from one to eight. The number of bromine atoms and their positions are important for the toxicological potency of each congener. PBDD/PBDFs exist as unintentional by-products in chemical processes, but can also be formed during various combustion processes and photolytic degradation of PBDEs and bromophenols (WHO 1998).

Among the possible 210 compounds, 17 congeners have bromine atoms at least in positions 2, 3, 7 and 8 of the parent molecule, and these are very toxic compared to molecules lacking this configuration. All the 2,3,7,8-substituted PBDDs and PBDFs show the same type of biological and toxic response as PCDD/PCDFs. It is also known that mixed chlorine–bromine dioxins/furans can be formed. Thus, 1550 mixed dioxins and 3050 mixed furans are theoretically possible. Owing to the paucity of analytical reference standards, a very limited number of these congeners have been analysed so far. These substances are not included in the LRTAP POPs Protocol.

PBDD/PBDFs have high molecular weights compared to PCDD/PCDFs, high melting points, low vapour pressures and low water solubility. PBDD/PBDFs are more readily degraded photochemically compared to PCDD/PCDFs.

There are very few data available on environmental transport and distribution. Generally, their physicochemical properties suggest similarities to PCDD/PCDFs. Therefore, they would most probably accumulate in carbon- or fat-rich compartments.

Lower brominated congeners (mono-tetra) have been found close to motorways on pine needles and grass. So far, however, only one study has reported lev-

els of PBDD/PBDFs in biota. In this study (Choi et al. 2002), 2,3,7,8-TBDD, 1,2,3,7,8-PBDD, 2,3,7,8-TBDF and 2,3,4,7,8-PBDF are reported in human adipose tissue from the general population. The median total amount of the four substances is reported to be around 5 pg/g lipid. This is slightly lower than levels reported for the corresponding PCDD/PCDFs in similar samples.

The kinetics and metabolism of PBDD/PBDFs have been investigated in a limited number of studies. PBDD/PBDFs show obvious similarities with their chlorinated analogues concerning metabolism, elimination and biological half-lives. Also, in the limited number of effect studies performed, PBDD/PBDFs show similarities with PCDD/PCDFs. They are believed to share a common mechanism of action with PCDD/PCDFs and other related hydrocarbons. Binding to the Ah-receptor has been confirmed for several PBDD/PBDFs and the mixed CL–Br compounds. Also, the receptor-binding capacity has been reported to be similar to that of the chlorinated analogues.

There are no data on effects on humans.

2/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

Based on the physical and chemical similarities with PCDD/PCDFs, it is possible that PBDD/PBDFs could resist degradation, bioaccumulate and be transported through the air across international boundaries. Nevertheless, there is a great need for data that could further confirm the presence of PBDD/PBDFs in biota, as well as studies that could clarify the risk associated with exposure to these substances. It is likely that some PBDD/PBDFs and the corresponding mixed CL–Br compounds could cause "dioxin-like" effects. If so, the risk posed by the brominated dioxins and dibenzofurans should be added to the risk posed by PCDD/PCDFs and dioxin-like PCBs. However, the human health implications relative to LRTAP of PBDD/PBDFs could not be judged on the current data.

3/ REFERENCES

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CHAPTER 12/
SHORT-CHAIN CHLORINATED PARAFFINS

1/ INTRODUCTION

Chlorinated paraffins (CPs) are chlorinated derivatives of n-alkanes, having carbon chain lengths ranging from 10 to 38 and a chlorine content ranging from about 30% to 70% by weight. Commercial products, of which there are over 2000 (Serrone et al. 1987) are complex mixtures of homologues and isomers. The products vary in the distribution, range and possibly type of chain lengths, and in the degree of chlorination. They have been produced since the 1930s to the extent of some 300 kilotonnes per year in the western world. The main applications of short-chain CPs (SCCPs) are in metal working, as plasticizers in paints, as sealants, as flame retardants in textiles and in leather processing. Their greatest use is in the metal working industry, generally as high-temperature, high-pressure lubricating or cutting oils (European Commission 2000).

CPs are divided into three main categories, short- (C_{10}–C_{13}), medium- (C_{14}–C_{17}) and long-chain (C_{18}–C_{30}), and further by their degree of chlorination: low (< 50%) and high (> 50%). Because of their relatively high assimilation and accumulation potential, the SCCPs have been the most widely studied. Total annual production, based on 1994 Euro Chlor figures, was estimated at less than or equal to 15 000 tonnes per year.

It is confirmed that SCCPs are still produced in some European countries (the Czech Republic and the United Kingdom) and in the United States. The 2001 OSPAR background document on SCCPs (OSPAR 2001) cited a 1999 report indicating that in 1997 total production of short-, medium- and long-chain CPs in China was about 100 000 tonnes. According to 1995 data, there are no Canadian producers of SCCPs. Total imports of SCCPs into Canada in 1994 were estimated to be approximately 538 tonnes.

The incineration of products or wastes containing SCCPs can result in the creation of PCBs and PCNs.

The complexity of SCCP mixtures makes it difficult to provide an analytical method for their precise and specific quantitative determination. Technical SCCP mixtures consist of several thousand components and, owing to the large number of isomers, complete chromatographic separation seems impossible at this point. This analytical challenge has resulted in different approaches to the analysis of SCCPs; nevertheless, the number of relevant monitoring results is still limited.

These substances are not included in the LRTAP Protocol.

2/ POTENTIAL FOR LRTAP

2.1/ Physical properties allowing atmospheric transport

SCCPs have vapour pressure values (2.8×10^{-7} to 0.5 Pa) that are in the range of some persistent organic pollutants that are known to undergo long-range atmospheric transport (Tomy et al. 1998). Henry's law constants for $C_{10–12}$ SCCPs range from 0.7 to 18 Pa·m^3/mol (Drouillard et al. 1998), which is similar to the range for some chlorinated pesticides (e.g. hexachlorocyclohexane, toxaphene) and implies partitioning from water to air or from moist soils to air, depending on environmental conditions and prevailing concentrations in each compartment.

The melting point of CPs increases with increasing carbon chain length and with increasing chlorine content. Consequently, at room temperature, CPs range from colourless to yellowish liquids at about 40% chlorine to white solids (softening point about 90 °C) at 70% chlorine. Chlorinated paraffins have very low solubilities in water, ranging from 22.4 to 994 mg/l for some of the short-chain mixtures. Log octanol/water partition coefficients (K_{ow}s) for SCCPs range from 5.85 to 7.14 (Tomy et al. 1998).

The very low solubility in water and low vapour pressure of SCCPs would predict low mobility, but monitoring data in Sweden and the United Kingdom indicate widespread low levels of contamination in water, sediments, aquatic and terrestrial organisms and even commercial foods (Government of Canada 1993). Some airborne dispersion does therefore occur.

2.2/ Persistence

Estimates of atmospheric half-lives for SCCPs using the AOPWIN and European Union methodologies are greater than 2 days, which would classify them as having the potential for long-range transboundary atmospheric transport pursuant to the UNECE POPs Protocol.

CPs are generally considered persistent. In the aqueous phase, rates of hydrolysis, photolysis with visible or near UV radiation, oxidation and volatilization are insignificant under ambient temperatures (Government of Canada 1993). Nevertheless, studies have shown that degradation by microorganisms is possible. Madeley & Birtley (1980) reported that the ability of aerobic microorganisms to oxidize a range of chlorinated paraffins depended on their previous acclimatization, the chain length and degree of chlorination. In another study, 70 enrichment cultures of microorganisms were found to be incapable of using CPs as the sole carbon source (Omori et al. 1987).

2.3/ Bioaccumulation

In laboratory studies, individual SCCP congeners had half-lives in juvenile rainbow trout *(Oncorhynchus mykiss)* ranging from 7 to about 53 days (Fisk et al. 1998a). These half-lives were shorter than those for PCB congeners (2,4-substituted) in studies under the same conditions (Fisk et al. 1998b).

Bioaccumulation factors (BAFs) for SCCP homologue groups in western Lake Ontario lake trout *(Salvelinus namaycush)* range from 21 250 to 114 444 (Table

Table 12.1. Bioaccumulation factors for SCCPs in lake trout of western Lake Ontario

Homologue	Concentration in water (ng/l)	Concentration in lake trout [a] (ng/g wet weight)	BAF_{ww}
C_{10}	0.16	3.4	21 250
C_{11}	0.48	18.3	38 125
C_{12}	0.98	33.6	34 286
C_{13}	0.09	10.3	114 444
ΣC_{10}–C_{13}	1.8	65.7	36 500

[a] Concentrations in whole fish (wet weight). *Source*: Muir et al. 2000.

12.1) Chlorinated dodecanes (C_{12}) are the most prominent SCCPs in lake water and fish. The highest BAFs are seen for the tridecanes (C_{13}). The overall BAF for SCCPs ($C_{10–13}$) in lake trout from western Lake Ontario is 36 500. Reported bioconcentration factors (BCFs) calculated from laboratory studies for SCCPs vary widely among different species, and range from < 1 in marine algae *(Skeletonema costatum)* to 140 000 in the common mussel *(Mytilus edulis)* (Tomy et al. 1998). Log octanol/water partition coefficients (K_{ow}s) for SCCPs calculated according to Lyman et al. (1990) range from 5.06 to 8.12 (Tomy et al. 1998).

The European Union assessment also describes several accumulation studies in fish and molluscs (Madeley & Maddock 1983 a, b; Fisk at al. 1996; Madeley et al. 1983; Madeley & Thompson 1983).

2.4/ Monitoring

Tomy et al. (1998), Peters et al. (2000) and Borgen et al. (2000) (see Table 12.2) detected measurable amounts of SCCPs in Arctic and remote air samples. The samples were enriched with the lower chlorinated lower-chain-length congeners, owing to their higher vapour pressure and Henry's law constant. No experimental data are available on the fate of any chlorinated paraffin that volatilizes into the atmosphere.

Table 12.2. SCCP concentrations in ambient air (from)

Location	Period	SCCP concentration (pg/m^3)
Alert, Nunavut, Canada	September and December 1992	< 1– 8.5
Egbert, Ontario, Canada	May–July 1990	65–924
Lancaster, United Kingdom	May 1997–June 1998	< 15–1085
Mt Zeppelin, Svalbard, Norway	March–May 1999	9.0–57

Source: Borgen et al. 2000; Peters et al. 2000; Tomy et al. 1998.

SCCPs have been detected in sediments from Hazen Lake in the Arctic at a level of 7 ng/g dry weight (Tomy et al. 1998).

Tomy et al. (2000) reported SCCPs in the blubber of ringed seal *(Phoca hispida)* from Eureka, Nunavut, Canada, beluga whales *(Delphinapterus leucas)* from north-west Greenland and the Mackenzie Delta, Northwest Territories, Canada, and walrus *(Odobenus rosmarus)* from north-west Greenland at concentrations ranging

from 110 to 770 ng/g wet weight (Table 12.3). It was also noted that the concentration profiles for the Arctic marine mammals show a predominance of the shorter carbon chain length congeners, i.e., the C_{10} and C_{11} formula groups. This is significant, because Drouillard et al. (1998) have shown that these congeners are the more volatile components of SCCP mixtures, which show a trend of decreasing vapour pressures with increasing carbon chain length and degree of chlorination. Stern & Tomy (2000) noted that Arctic animal formula group profiles showed higher proportions of the lower chlorinated congeners (Cl_5–Cl_7), suggesting that the major source of contamination to the Canadian Arctic is via long-range atmospheric transport. Tomy et al. (2000) concluded that, although only a few samples were analysed in their study, it was clear that SCCPs are present in Arctic food webs and are being transported to these remote regions either in the atmosphere or in ocean currents.

SCCPs were detected in water samples collected in Bermuda. The distribution of SCCPs through the water column down to a depth of 1200 m was investigated. There was 50 µg/l in the surface film; at depths of 15, 250, 900 and 1200 m the concentrations were near the detection limit of 3 ng/l; and at a depth of 350 m a concentration of 0.02 µg/l was measured. SCCPs were not found in water from the Maldives. Both of these sites are considered to be remote from industry. It was concluded that the occurrence of SCCPs in Bermuda is mainly the result of atmospheric transport and partly of transport by sea currents (Kraemer et al. 1987).

2.5/ Conclusions regarding the LRTAP potential

SCCPs are complex mixtures that vary in chain length and in the degree of chlorination. The vapour pressure values, Henry's law constants and atmospheric half-lives are in the same range as for other persistent organic pollutants and imply a significant potential for long-range atmospheric transport.

Table 12.3. Concentrations of $C_{10–13}$ SCCPs and other persistent organic pollutants in blubber of marine mammals from the Arctic

			Concentration (ng/g wet weight) [a]			
Species	Location	Year	Σ DDT	Σ PCB	Σ toxaphene	Σ SCCP
Ringed seal	Eureka, Nunavut, Canada	1994	400–1040	760–1600	380–610	370–770
Beluga whales	North-west Greenland	1989	1350–2570	2430–4310	2590–3420	110–250
Beluga whales	Mackenzie Delta, Canada	1995	3090–4490	3830–5750	1920–4550	140–300
Walrus	North-west Greenland	1978	26–39	115–200	220–330	360–490
Ringed seal	Svalbard, Norway	1981	2550	1320	560	114 [b]

[a] Σ DDT: sum of p,p'-DDD, p,p'-DDE, p,p'-DDT and o,p'-DDT; Σ PCB: sum of all detected congeners; Σ toxaphene: sum of 20 congeners; Σ SCCP: sum of all congeners.
[b] Cl6–Cl16, unspecified chain length.

Source: Jansson et al. 1993; Tomy et al. 2000.

Estimates of atmospheric half-lives for SCCPs are greater than 2 days, which would classify them as having the potential for long-range transboundary atmospheric transport pursuant to the UNECE POPs Protocol. Also, the detection of the more volatile shorter carbon chain length congeners of SCCPs in Arctic air, biota and lake sediments in the absence of significant sources of SCCPs in this region, together with the detection of SCCPs in the water column around Bermuda, suggests that these residues are present owing to long-range atmospheric transport.

Based on the BAFs/BCFs in fish and mussels, and the log K_{ow} range found for SCCPs, it is concluded that SCCPs are bioaccumulative substances.

3/ PATHWAYS OF LRTAP-DERIVED HUMAN EXPOSURE

3.1/ Significant sources of human exposure

Chlorinated paraffins, including SCCPs, are not known to occur naturally (Government of Canada 1993). As described above, the two major sources of release of SCCPs into the environment are during their production and during their use in metalworking. During production, most emissions are to wastewater, *although emissions to air are also possible* (European Union assessment). The OSPAR Report (OSPAR Commission 2001) has noted that SCCPs can reach the marine environment via rivers and *via the atmosphere*. The main compartments to which releases occur were identified as sediment and surface waters in rivers, lakes, seas, air and soil spread with sewage sludge.

The main environmental source of human exposure is food and, to a lesser extent, drinking-water. The lack of monitoring data hampers reliable exposure estimation. Levels in food in the range of 30 to several thousand µg/kg have been measured.

In an analysis of carp (*Cyprinus carpio*) collected from Hamilton Harbour and lake trout (*Oncorhynchus mykiss*) collected from two locations in western Lake Ontario in 1996, SCCPs were detected in all samples (Table 12.4).

In the United States, yellow perch, catfish and zebra mussels from the Detroit River, Michigan, had measured mean SCCP concentrations of 1.1, 0.3 and 1.2 µg/g, respectively (Tomy et al. 1997).

SCCPs have been detected at concentrations ranging from 110 to 770 ng/g wet weight in marine mammals in Canada (see Table 12.3). To date, very limited information is available on SCCPs in tissues of terrestrial mammals. In Sweden, Jansson et al. (1993) reported SCCP concentrations in rabbit (Revingeshed, Skåne), moose (Grismsö, Västmanland), reindeer (Ottsjö, Jaämtland) and osprey (various regions in Sweden) to be 2.9, 4.4, 0.14 and 0.53 µg/g, respectively.

The presence of SCCPs in Arctic environmental samples and remote terrestrial samples is mainly due to long-range atmospheric transport. The risk for human exposure related to long-range transboundary atmospheric transport is difficult to quantify, but obviously not negligible. The European Union assessment (European Commission 2000) considered a human uptake value of 20 µg/kg bw per day a reasonable worst-case value.

Table 12.4. SCCP concentrations in different food samples

Species	Location	Year	SCCP concentration (ng/g wet weight)	Reference
Carp	Lake Ontario	1996	2630	Muir et al. 2000
Lake trout	Lake Ontario	1996	58.8–72.6	Ditto
Yellow perch	Detroit River, MI, USA	1996	1100	Tomy et al. 1997
Catfish	Detroit River, MI, USA	1996	300	Ditto
Zebra mussel	Detroit River, MI, USA	1996	1200	Ditto
White fish	Lake Storvindeln, northern Sweden	1986	6.6 [a]	Jansson et al. 1993
Arctic char	Lake Vättern, central Sweden	1987	30 [a]	Ditto
Herring	Bothnian Sea	1986	76 [a]	Ditto
Herring	Baltic Proper	1987	66 [a]	Ditto
Herring	Skagerrak	1987	51 [a]	Ditto
Plaice	United Kingdom waters		ND–200 [b]	Campbell & McConnel 1980
Pouting	Ditto		ND–200 [b]	Ditto
Common mussel	Ditto		100–12 000 [b]	Ditto
Pike	Ditto		ND–50 [b]	Ditto
Dairy products	United Kingdom		300 [b]	Ditto
Vegetable oils	Ditto		150 [b]	Ditto
Fruit and vegetables	Ditto		5 [b]	Ditto
Rabbit muscle	Sweden	1986	32 [a]	Jansson et al. 1993
Moose muscle	Ditto	1986	90 [a]	Ditto
Reindeer suet	Ditto	1986	80 [a]	Ditto

[a] $Cl_6 - Cl_{16}$, unspecified chain length.
[b] $C_{10} - C_{20}$.

4/ HEALTH HAZARD CHARACTERIZATION

4.1/ Toxicokinetics

In general, there is very limited information on the toxicokinetics of SCCPs and there is no information with respect to differing chain length and degree of chlorination. With respect to oral exposure, only limited studies on SCCPs are available. Significant absorption (up to about 60% of the administered dose) does occur following oral administration. One study indicated that absorption is greater for SCCPs with lower chlorination states. Absorbed CPs have been shown to distribute preferentially to tissues of high metabolic activity and/or high rate of cell proliferation following oral dosing. No attempts have been made to identify any metabolites of chlorinated paraffins, although cytochrome P450 oxidation to carbon dioxide has been demonstrated. Chlorinated paraffins and/or their metabo-

lites are excreted via exhaled air, urine and faeces, with up to approximately 60% of the administered dose being excreted in the air and urine in 12 hours.

4.2/ Single-exposure studies

There is no information available on the effects of acute exposure to SCPPs in humans, but the limited information available from animal studies clearly demonstrates that SCCPs are of very low acute toxicity. No toxicity occurring in rats following 1-hour exposure to a vapour or aerosol of 3300 mg/m3 or with a dermal dose of 2.8 g/kg bw, and there were some signs of systemic toxicity with oral doses of up to 13 g/kg bw in rats and 27 g/kg bw in mice. A very high, unsubstantiated rabbit dermal LD50 of approximately 13 g/kg bw has been reported. The nature and degree of effects were independent of degree of chlorination.

4.3/ Repeat-exposure studies

There is no information available on the effects of repeated exposure to SCCPs in humans. All available oral studies in animals were conducted using 52–60% chlorinated SCCPs, and therefore it is not possible to establish directly from data whether different degrees of chlorination would alter the toxicity. The liver and thyroid were identified as target organs in the oral studies in rats and mice. Small increases in liver weight are likely to be due to a response to xenobiotic metabolism, which is not of toxicological significance. Larger increases in liver weight and hepatocellular hypertrophy have been shown to be a reflection of peroxisome proliferation. Humans are not susceptible to peroxisome proliferation, and hence the liver effects are considered not to be relevant to human health. Increases in thyroid weight and follicular cell hypertrophy have been shown to be caused by stimulation of the thyroid via a negative feedback mechanism, initiated by increased excretion and plasma depletion of T_4. The depletion of T_4 is a result of increased liver enzyme (UDPG transferase) activity, which may be related to peroxisome proliferation. Also, humans and rodents show different T_4-globulin binding characteristics, which results in humans being less susceptible to plasma T_4 depletion and hence to thyroid stimulation. Overall, the thyroid effects seen in rats and mice are considered unlikely to be relevant to human health. Other signs of toxicity, such as reductions in body weight gain and increases in kidney weight, were observed in several 14- and 90-day studies in rats at doses greater than 100 mg/kg bw per day. In mice, general signs of toxicity were observed in a 90-day study at doses greater than 1000 mg/kg bw per day. Therefore, NOAELs of 100 and 1000 mg/kg bw per day were observed in rats and mice, respectively, for effects that are considered to be relevant to human health.

4.3.1/ Mutagenicity

There are relatively few data available on the genotoxicity of these substances, particularly considering the varying chain length and degree of chlorination of the different compounds in this family. However, the limited information in bacteria indicate that 50–60% chlorinated SCCPs are not mutagenic in these systems. No

standard *in vitro* cytogenetic studies are available, but a gene-mutation assay was negative for a $C_{10–13}$, 56% chlorinated SCCP. Two well conducted *in vivo* studies suggested that SCCPs do not produce mutagenicity in somatic (bone marrow) or germ cells. Overall, the data available and a consideration of the generally unreactive nature of these substances indicate that SCCPs (as a group) are not mutagenic.

4.3.2/ Carcinogenicity

No information is available on studies in human populations potentially exposed to SCCPs. The only studies available in animals investigated the effects of a C_{12}, 60% chlorinated paraffin. In rodent carcinogenicity studies, the CP tested produced toxicologically significant, dose-related increases in the incidence of several tumour types. Dose-related increased incidence of adenomas and carcinomas of the liver and thyroid were observed in mice. There was an indication of similar effects in a poor-quality study in rats. These findings reflect, in the case of the liver, chronic tissue damage caused by peroxisome proliferation and, for the thyroid, long-term hormonal stimulation. From consideration of the probable underlying mechanisms involved, it is likely that these carcinogenicity observations are not relevant to human health. Male rats also showed an increased incidence of kidney tubular cell adenomas. This was not seen in female rats or in mice of either sex. Although hyaline droplets were not directly observed, the pattern of results in male rats is consistent with tumour formation following kidney damage caused by hyaline droplet formation, which is a male-rat-specific phenomenon. This is suggestive that the benign tumours observed in the kidney of male rats are not likely to be relevant for human health.

It is recognized that the current evidence on the mechanism underlying the development of the kidney tumours is not definitive. Given that the SCCPs are not genotoxic, it is considered that there would be no risk of kidney tumour development associated with exposures lower than those required to produce chronic toxicity in this target organ. A NOAEL for kidney toxicity in male rats has been previously set at 100 mg/kg bw per day.

4.3.3/ Toxicity for reproduction

In relation to fertility, there is no information available in humans and there are no animal studies specifically investigating such effects. However, no changes were seen in the reproductive organs in rats and mice treated for 13 weeks with up to 5000 and 2000 mg/kg bw per day, respectively, of a C_{12} 60% chlorinated paraffin. In terms of developmental effects, there is no information available in humans, although in a well conducted study in rats a $C_{10–13}$, 58% chlorinated paraffin produced developmental effects at a dose that also caused severe maternal toxicity (2000 mg/kg bw), but no developmental effects at lower doses (500 mg/kg bw and below). No developmental effects were observed in a study in rabbits, although doses toxic to the mothers were not tested. There is no information on SCCPs with higher and lower chlorine contents.

4.4/ Critical outcomes and existing reference values

When compared with other chlorinated organics such as PCBs and pesticides, SCCPs appear to exhibit fewer of the less acute and chronic toxic effects (Tomy et al. 1998). SCCPs show lower reproductive and embryo toxicity in mammals and birds. It is clear from limited experimental data and structural features of the molecules that SCCPs are not cytochrome P450 1A1 mixed-function oxidation inducers, nor do SCCPs or their probable oxidative degradation products (OH- or COOH-substituted chloroalkanes) structurally resemble compounds associated with endocrine or thyroid dysfunction in mammals and fishes, such as hydroxy-PCBs or alkylphenols. There is no information in the case of immunotoxicity or neurotoxicity as manifested by a number of chlorinated aliphatic and aromatic compounds. The main target organs for repeated doses of SCCPs seem to be the liver, kidney and thyroid. SCCPs show neoplastic effects in the liver of mice and rats, but the relevance of this evidence for humans is uncertain. More information is needed on the sublethal toxicity of SCCPs. Ideally, this information should be developed for a range of specific congeners to develop structure-activity relationships, so that effects of complex mixtures in various CP products can be better assessed.

The European Union assessment (European Commission 2000) identified a NOAEL for general toxicity of 100 and 1000 mg/kg bw per day in rats and mice, respectively.

In 1996, WHO recommended that daily doses of SCCPs for the general population should not exceed 11 µg/kg bw for neoplastic effects.

5/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

There is a very limited database regarding environmental fate, levels in food and toxicology of SCCPs. The European Union risk assessment report (European Commission, 2000) concludes with that there is no significant risk to humans exposed via the environment. Compared to other chlorinated organic pollutants, SCCPs seem to have lower acute and chronic toxicities. However, it is noted that the European Union's worst-case human uptake estimate is greater than the guideline value established by WHO.

Long-range transboundary atmospheric transport is an important aspect of the global distribution of SCCPs and is responsible for their occurrence in remote northern food chains. Uptake via food is the main route for human exposure to SCCPs.

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CHAPTER 13/ UGILEC

1/ INTRODUCTION

Ugilec 141 and Ugilec 121 (or 21/C21) have been marketed since the early 1980s as less hazardous substitutes for PCBs. They were used as dielectric fluids in capacitors and transformers and as hydraulic fluids in coal mines. They were considered less harmful in case of fire owing to a much lower potential to form chlorinated dioxins/furans. Available information on the uses of Ugilec 141 and Ugilec 121 in Europe is very limited at the moment. However, based on the similarity of their toxic effects to those of PCBs, and their accumulation in fish and mussels in recipient waters in coal mining areas, they were not recommended as safe substitutes for PCBs.

In 1991 the European Community, in Council Directive 91/339/EEC, prohibited the marketing and use of Ugilec 141 (from 18 June 1994) and Ugilec 121, including preparations and products containing it (with some temporary exemptions, such as in the case of plants and machinery already in service on that date until they were disposed of) (EEC 1991). In Germany the manufacture, processing and use of Ugilec 141 and Ugilec 121 have been prohibited since 1993; they are classified as hazardous waste and require supervision under the provisions of the Waste Disposal Act (AbfG). Under the UNECE/LRTAP Protocol on POPs, the parties have agreed to reassess the production and use of polychlorinated terphenyls and Ugilec by 31 December 2004.

2/ POTENTIAL FOR LRTAP

2.1/ Physical properties allowing atmospheric transport

The structural formulas of Ugilec 141 and Ugilec 121 are shown in Fig. 13.1 and 13.2, respectively, and their physicochemical properties are set out in Table 13.1.

Tetrachlorobenzyltoluenes (TCBTs) are physicochemically similar to PCBs with respect to conformational aspects and dimensions. Log K_{ow} of tetra- or higher-chlorinated PCBs range from 5 to 7 and for TCBTs they range from 6.5 to 7.6.

No measured data are available for direct photolysis of Ugilec in the gas phase or in solution. This applies also to indirect photolytic breakdown caused by oxygen transients in the atmosphere, predominantly hydroxy radicals. To overcome this deficiency, a structure-activity relationship (SAR) method derived from more volatile compounds was employed. From model calculations on reactions with hydroxy radicals, a rate constant of 6.4×10^{-12} [$cm^3\,molec^{-1}\,s^{-1}$] was derived for Ugilec 141, while for Ugilec 121 a rate constant of 13.37×10^{-12} [$cm^3\,molec^{-1}\,s^{-1}$] was esti-

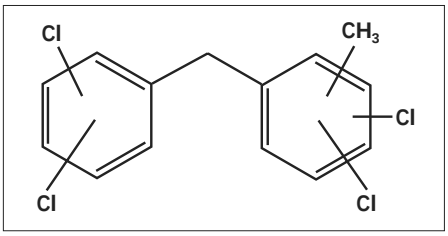

Fig. 13.1. Ugilec 141 (tetrachlorobenzyltoluenes, mixture of (theoretically) 69 isomers)

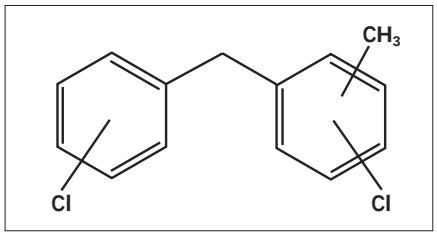

Fig. 13.2. Ugilec 121 or 21 (C21, for use in capacitors) (dichlorobenzyltoluenes, mixture of isomers)

Table 13.1. Physicochemical properties of Ugilec 141 and Ugilec 121 or 21

Property	Ugilec 141	Ugilec 121 or 21 (C21 for use in capacitors)
Molecular formula	$C_{14}H_{12}Cl_4$	$C_{14}H_{12}Cl_2$
Molecular weight	320.05	251.16
CAS No.	76253-60-6	None
Water solubility	5 µg/l at 20 °C	< 1 µg/l at 20 °C
Vapour pressure	< 10 Pa at 20 °C	0.005 Pa at 20 °C
log K_{ow} (estimated)	6.725–7.538[a]	5.85 (value was estimated by means of the QSAR program KOWIN v1.66 (USEPA 2000)
log BCF (estimated)	1.67–2.68 l/kg (fish) 4.43–5.19 l/kg (mussel)	3.81 (BCF = 6396) (value estimated according to QSAR equation log BCF = 0.77 K_{ow} – 0.70) Measured BCF data at 0.5 ppm are in the order of 10 000

[a] These K_{ow} values cover eight individually determined isomers at a standard deviation of between 0.089 and 0.356. For the mixture, log K_{ow} values of between 6.030 and 6.435 were determined.

Source: UNECE 2002.

mated. Assuming a globally annual averaged radical concentration of [OH] = 5×10^5 cm^{-3} in the troposphere layer, half-lives of 2.6 days for Ugilec 141 and 1.2 days for Ugilec 121 were calculated from these rate constants. No data were available on environmental concentrations of Ugilec from remote areas (UNECE 2002).

2.2/ PERSISTENCE IN WATER, SOIL AND SEDIMENT

No valid laboratory tests on biodegradability, performed according to standardized guidelines, are available. The outcome of tests submitted by the manufacturer of Ugilec 121 nevertheless indicated "moderate" biodegradability after adaptation of the inoculum. On the other hand, there is evidence of persistence of Ugilec 141 in river sediments in the vicinity and downstream of coal mines in Germany that used Ugilec. Contamination caused by leakage from hydraulic devices entered the rivers via mine effluents. While PCBs were found in sediments down to depths of 1.5 m, Ugilec took their place in the top layers, temporally coincident with the companies' switch from PCBs to Ugilec (UNECE 2002).

2.3/ Bioaccumulation

Measured values for log K_{ow} reported in the literature for Ugilec 141 samples are in the range 6.725–7.538. Bioconcentration studies, including those on eight isomers of Ugilec 141 in Zebra mussels (*Dreissena polymorpha*) resulted in log BCF values of 4.43–5.19 l/kg on a wet weight basis. For guppy fish (*Poecilia reticulata*) log BCF values ranged from 1.67 to 2.68 l/kg on a wet weight basis. These considerably lower values for fish were attributed to higher biotransformation rates compared to mussels. After 4 weeks' application of 500 mg/kg per day to rats, levels of < 100 µg/g fatty tissue and < 5 µg/g liver were found. Two weeks later, the concentrations had dropped by 90–97.5% (UNECE 2002).

After an exposure of fish over periods of 17–25 days in a flow-through system at 1 mg/l Ugilec 121, a bioaccumulating factor of 12 500 was determined by the manufacturer. No clearance time could be determined in this experiment owing to a 74% mortality rate after 30 days (UNECE 2002).

Ugilec was found in eel from the Rur river at levels 0.1–1.2 µg/g of fat. A decreasing trend in levels was found (Wammes 1997).

From *in vitro* studies on hepatic microsomes, transformation rates for Ugilec 141 are reported in the literature to range from 0.96 to 4.14/hour for rats and from 0.009 to 0.017/hour for trout (Kramer 2001).

Levels of TCBTs of between 0.1 and 25 mg/kg bw were found in fish in rivers in the vicinity and downstream of coal mines in Germany. These levels were comparable to those of PCBs, suggesting that the two substances have a similar accumulation pattern (Kramer 2001).

3/ HEALTH HAZARD CHARACTERIZATION

3.1/ Toxicokinetics

Given that TCBTs are physicochemically comparable to PCBs, similarities between TCBTs and PCBs can be expected in terms of their toxicokinetics, including a slow elimination of TCBTs from the organism and accumulation in adipose tissue. Thus TCBTs can pose risks similar to those posed by PCBs and other polyhalogenated hydrocarbons, e,g, Arochlor 1254 and 3,3',4,4'-tetrachlorobiphenyl inducing comparable biochemical changes, such as enzyme induction, in both mice and rats (although the effects were less pronounced for Ugilec 141). It has been suggested that the limited accumulation and limited cytochrome-P450 (CYP) induction are explained by a relative rapid biotransformation of TCBTs. TCBTs are much more rapidly metabolized than PCBs. Thus TCBTs show a lower potential than PCBs for accumulation in humans (Kramer 2001).

3.2/ Effects on laboratory animals (UNECE 2002)

Toxicity. According to data supplied by a manufacturer of Ugilec 141, its oral LD_{50} in rats (14-day study) was 3300 mg/kg. For rabbits the dermal LD_{50} (14-day study) was > 2000 mg/kg. In a subchronic toxicity study on rats, effects were observed at doses of 500 mg/kg per day over a 28-day period; a mortality rate of 20% was observed at this concentration. After 24 hours of exposure an IC_{50} of 0.4 mg/l was

observed for *Daphnia* spp. For algae, IC_{50} values of 5–25 mg/l were determined (depending on the species), while for fish no mortality was observed up to concentrations of 400 mg/l and an exposure period of 48 hours (UNECE 2002).

The LC_{50} for Ugilec 121 in fish was reported to be > 400 mg/l after a 48-hour exposure. No 96-hour value was determined in this study. The LC_{50} for *Daphnia* spp. was determined at 0.2–0.5 mg/l after 24 hours. This decreased slightly to 0.17 mg/l after 48 hours of exposure (UNECE 2002).

For algae an IC_{50} value of 0.66 mg/l was determined for Ugilec 121 (dispersed) and of 0.1–0.2 mg/l when the substance was dissolved in water (acetone as solvent). Subacute 90-day studies on rats resulted in a NOEL of 5.0 mg/kg per day. It should be noted that most of the results were not obtained in tests compatible with international guidelines. Their outcome should therefore be considered as indicative (UNECE 2002).

4/ HUMAN HEALTH IMPLICATIONS RELATIVE TO LRTAP

In June 1993, a German assessment report (Umweltbundesamt 1993) suggested that the oligochlorobenzyltoluenes (Ugilec 141, Ugilec T and Ugilec 121) were unsafe substitutes for PCBs on ecotoxicological, toxicological and safe-handling grounds. Significant environmental contamination has already been documented in the vicinity of mines where these substances have been used as hydraulic fluid.

In the event of a fire involving any equipment containing Ugilec 141 or 121, highly toxic substances including PCDFs and PCDDs may be given off.

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ANNEX 3/
EXECUTIVE SUMMARY OF THE REPORT

Prepared by the Joint WHO/Convention Task Force on the Health Aspects of Air Pollution

This summary contains the conclusions of the Joint WHO/Convention Task Force on the Health Aspects of Air Pollution. Basic information on pollutant characteristics, population exposure pathways and toxicity characterization precede the conclusions. This summary is also available as UNECE document http://www.unece.org/env/documents/2002/eb/wg1/eb.air.wg.1.2002.14.e.pdf

1/ PENTACHLOROPHENOL

1.1/ Introduction

Pentachlorophenol (PCP) can enter the environment as a by-product of various chemical manufacturing processes, through its use as a wood preservative, general purpose herbicide or biocide in industrial water systems, and as a result of incineration of chlorine-containing waste. Its sodium salt is used for similar purposes and readily degrades to PCP.

Actions on PCP are not included in the 1998 UNECE/LRTAP Protocol on POPs. However, PCP may be identified through article 8 concerning research development, monitoring and cooperation. Under this article, priority is given to substances most likely to be considered to be submitted under the provisions that allow substances to be added.

1.2/ Potential for LRTAP

The physical and chemical properties of the compound suggest that evaporation to the atmosphere is limited and that most of it will move with water and generally associate with soil particles. The mobility and availability of PCP in the environment depends on the acidity of the medium. The volatilization of PCP from treated wood increases with temperature; similar results with temperature change were seen with all the numerous solvent systems utilized for the application of the compound.

In air, soil and surface water, PCP is subjected to photolysis and hydroxyl degradation, with atmospheric half-lives ranging from hours to weeks.

PCP bioconcentrates in aquatic organisms and the BCF value increases with falling pH.

1.3/ Pathways of LRTAP-derived human exposure

Humans will be exposed through three main routes: treated products, food and drinking-water. The latter two sources are relevant for LRTAP. The long-term average daily intake of PCP by the general population was estimated in 1989 to be

16 µg/day in the United States; in Canada the estimated daily intake is 0.05 µg/kg bw per day. It seems likely that food accounts for the majority of the intake unless there is specific local chlorophenol contamination causing increased concentrations in drinking-water, or exposure from wooden homes treated with PCP.

Concerning measurements in biota as evidence of transport to remote regions, the situation is complicated for two main reasons. On the one hand, PCP is metabolized into other molecules and therefore its absence in animal tissues is not conclusive; on the other hand, it is a major product of the metabolism of hexachlorobenzene and other common pesticides in mammals, and therefore if it is found it does not mean it was taken up as such.

1.4/ Health hazard characterization

PCP is rapidly absorbed by the digestive tract. The highest concentrations of PCP are found in the liver, kidney and brain, but the tendency for bioaccumulation remains low. Regarding human health effects, the experimental data related to PCP are well documented for the oral low dose chronic exposures and indicate:

- effects on the liver characterized by biochemical, functional and histopathological changes;
- effects on the immune system, and
- significant alteration of thyroid hormone levels at exposures of 1–2 mg/kg bw per day.

Data on occupationally exposed workers confirm the effects on the immune system and the liver.

IARC has classified PCP in group 2B as an agent possibly carcinogenic to humans.

WHO has assessed PCP in order to establish water quality guidelines, and in 1993 set a TDI of 0.003 mg/kg bw. Although a risk assessment based on neoplastic effects was subsequently conducted in 1998, the resulting water quality guideline was the same (9 µg/l).

1.5/ Human health implications relative to LRTAP

The health characterization of PCP indicates a potential for a number of human health effects associated with low-level chronic exposure via the oral route. Some of these effects have been seen as result of occupational exposure. It is also known that man-made PCPs introduced into the environment have the potential for long-range atmospheric transport, and may reach human foodstuffs and drinking-water. Nevertheless, further research is needed to assess the significance of LRTAP as a significant pathway leading to human exposure via the oral route.

2/ DDT

2.1/ Introduction

DDT (1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane) was first synthesized in 1874. Technical grade DDT is composed of up to 14 chemical compounds, of which only 65–80% is the active ingredient *p,p'*-DDT. Worldwide production

reached its maximum in the 1960s. DDT is still being released into the atmosphere from current production and use in some developing countries. Oceans and large bodies of fresh water may release significant amounts of DDT (residues from previous uses and breakdown products) into the atmosphere.

The 1998 Protocol on POPs bans the production and use of DDT in the LRTAP Convention area, except as an intermediate chemical in the production of dicofol or for public health purposes (e.g. malaria control). The former is to be reassessed within two years of entry into force, and the latter is accompanied by special conditions. In addition, the Parties are committed to eliminating all production once available and feasible alternatives have been identified, and for this purpose consultation with health agencies, including WHO, is necessary. These provisions acknowledge that DDT remains important and necessary for vector control in developing countries.

2.2/ Potential for LRTAP

DDT and its breakdown products are semi-volatile and can be expected to partition into the atmosphere and precipitate at low temperatures. Thus, in addition to being found close to known sources, they can also occur at significant levels remote from the source. They are insoluble in water and soluble in most organic solvents. Owing to these physicochemical properties, DDT and its metabolites are readily absorbed by organisms, and their high lipid- and low water-solubility lead to their retention in fatty tissues. Consequently, there is significant potential for biomagnification. The breakdown products of DDT – DDD and DDE – are present virtually everywhere in the environment and are more persistent than the parent compound.

2.3/ Pathways of LRTAP-derived human exposure

DDT and its metabolites are ubiquitous in foods, particularly in fatty food of animal origin (meat, fish and dairy products) and in human milk. Globally, food is the main source of exposure for the general population. Estimates of current intake vary according to diet and geographical area, and in some countries the estimated daily intake may approach the acceptable daily intake. Since DDT and its metabolites are excreted through human milk, breast-fed children have to be considered as a high-exposure group. Pre-natal exposure may also take place, owing to the capacity of DDT and its metabolites to cross the placenta. Once absorbed, DDT is readily distributed to all body tissues, where the storage rate is proportional to the fat content of the organ.

2.4/ Health hazard characterization

The critical issues associated with the levels of lifetime chronic exposure to DDT typically reported in literature are as follows.

Carcinogenicity. There is inadequate evidence in humans and sufficient evidence in experimental animals of the carcinogenicity of DDT. IARC has therefore classified DDT in group 2B as an agent possibly carcinogenic to humans.

Endocrine disruption. p,p'-DDE exhibits anti-androgenic properties, and the isomer *o,p'*-DDT is estrogenic. Even if it is not clear whether an endocrine effect can be observed in humans, the possibility of endocrine disruption has to be taken into account, mainly because exposure may involve fetuses and newborn infants at critical periods of their development.

Neurobehavioural changes. Although poorly researched, DDT neurotoxicity must be investigated, especially because neurobehavioural effects may result from endocrine disruption.

Fertility. Little research has been carried out, although some data are available suggesting the capacity of DDT and its metabolites to affect fertility.

Immunotoxicity. Although no firm conclusions can be reached, some data are available suggesting that DDT and its metabolites act as immunosuppressive agents.

Developmental toxicity. The provisional tolerable daily intake (PTDI) for humans is 0.01 mg/kg bw. This has been established based on a NOAEL of 1 mg/kg bw per day for developmental toxicity in rats, with a safety factor of 100.

2.5/ Human health implications relative to LRTAP

Intake through the diet may approach or even exceed the PTDI, particularly in tropical and developing countries where DDT is still used for public health purposes (or even used illegally). In these countries, local use represents the main source of exposure. On the other hand, high levels of exposure also occur within the LRTAP Convention area. These include the Inuit populations of Arctic regions, where DDT has not been used for decades or has never been used. The main source of exposure in this case, and the consequent health implications, are mainly related to LRTAP.

3/ HEXACHLOROCYCLOHEXANES

3.1/ Introduction

γ-Hexachlorocyclohexane (γ-HCH or lindane) is used as an insecticide on fruit and vegetable crops (including greenhouse vegetables and tobacco), for seed treatment, in forestry (including Christmas trees) and for animal treatment. Other HCH isomers are still found in environmental samples owing to the former use of technical HCH as an insecticide.

The use of technical HCH is restricted under the UNECE/LRTAP Protocol to the manufacture of other substances. γ-HCH is restricted to the following uses: seed treatment; soil application directly followed by incorporation into the topsoil; professional remedial and industrial treatment of timber and logs; a topical insecticide for public health and veterinary use; non-aerial application to tree seedlings; and indoor industrial and residential applications. All of these uses are to be reassessed under the Protocol no later than two years after its entry into force.

HCH are not covered by the Stockholm Convention, and the use of technical HCH and γ-HCH in other parts of the world is continuing.

3.2/ Potential for LRTAP

α- and γ-HCH are water-soluble and have little bioconcentration potential. γ-HCH is very prevalent in the marine environment and soils, but low levels are found in biota. A minor constituent of γ-HCH is β-HCH, which has reduced water solubility and hence a more significant BCF than γ-HCH.

HCH residues are found in water and air samples all over the world. Higher concentrations are often found in waters at northern latitudes than in major source regions in the mid latitudes. The presence of HCH in the environment remote from sources is considered to be due to LRTAP.

The presence of large quantities of γ-HCH in oceans and lakes introduces a delay in the reduction of atmospheric concentrations following decreases in emissions.

3.3/ Pathways of LRTAP-derived human exposure

More than 90% of human exposure to all HCH isomers originates from food sources, particularly those that are animal-based. Intake of γ-HCH from food decreased by more than an order of magnitude in the 1970s, to levels at least two orders of magnitude below the ADI established by WHO in 1989. Intake from (indoor) air may be considerable for people living in houses treated for pest control purposes.

β-HCH is the predominant HCH isomer accumulating in human tissue as indicated, for example, by levels in human milk. Levels of β-HCH in human milk range from 0.1 to 0.69 mg/kg, and those of γ-HCH from < 0.001 to 0.1 mg/kg (on a fat basis). The intake of γ-HCH derived from commercially produced food has decreased since the 1970s in response to decreasing emissions, although this trend is not evident for populations consuming marine foods, particularly marine mammals. There is a relationship between the HCH concentration in breast-milk and the consumption of meat products, animal fat and fatty fish. Levels in human milk appear to be higher in women living in rural areas than in those living in urban areas.

3.4/ Health hazard characterization

γ-HCH is rapidly absorbed by the oral route and undergoes extensive metabolism, mainly in the liver.

Animal studies have revealed neurotoxic, hepatic and reproductive effects, as well as immunotoxicity in mice. In humans, poisoning incidents have generally been associated with significant misuse of the compound. The most common signs of toxicity following oral ingestion were seizures, convulsions, vomiting and dizziness.

Human data suggest that γ-HCH has a potential to induce haematological effects (aplastic anaemia), but establishing a causal relationship has been difficult owing to a lack of personal exposure data.

IARC has concluded that for technical grade HCH and α-HCH there is sufficient evidence for carcinogenicity in animals, whereas this evidence is limited for

the β and γ isomers. There is inadequate evidence for their carcinogenicity to human beings. HCH are therefore classified in group 2B as possibly carcinogenic to humans. It should be noted, however, that the European Union and USEPA have not classified HCH as carcinogenic to humans.

JMPR established a temporary ADI for γ-HCH in 1997 of 0.001 mg/kg bw, based on a NOAEL of 0.5 mg/kg bw established in a two-year toxicity and carcinogenicity study in rats and using a safety factor of 500.

3.5/ Human health implications relative to LRTAP

Large reservoirs of HCH exist in the environment, which suggests that it potentially takes a long time for environmental levels to reflect any action taken. Health hazard characterization has identified a range of health effects related to exposure to γ-HCH by the oral route. Some might be relevant to observed environmental exposures. The oral route is the most relevant for LRTAP sources. Taking into account the uncertainties of the information, and specifically the level of exposure at which human health can be affected, HCH may be considered a possible risk to health through LRTAP.

4/ HEXACHLOROBENZENE

4.1/ Introduction

Hexachlorobenzene (HCB) is introduced to the environment as a seed fungicide, through industrial production (by-products) and during incineration of waste. Another minor source of release to the air is the use of pyrotechnic mixtures that produce white screening smokes. The production and use of HCB is banned in many developed countries. HCB is today found in almost all parts of the global ecosystem in at least trace amounts, and is already included in the CLRTAP Protocol (Annexes 1 and 3).

4.2/ Potential for LRTAP

HCB is very persistent in the environment, owing to its chemical stability and resistance to biodegradation. Long-range transport plays a significant role in its redistribution throughout the environment in the atmosphere and oceans. In the atmosphere, HCB exists primarily in the vapour phase and degradation is extremely slow.

4.3/ Pathways of LRTAP-derived human exposure

HCB has the ability to bioconcentrate and biomagnify under typical environmental conditions. It is estimated that more than 91% of the total exposure of the general population to HCB originates from common food items, both of animal (e.g. meat, certain fish and dairy products) and plant origin. Intakes are considerably less from ambient air (about 7%) and drinking-water (about 1% of the total intake). The total average daily intake of HCB from food, air and drinking-water in the general population in Europe and North America is between 0.0004 and 0.003 µg/kg bw per day. HCB has been detected in the milk of several species, including humans.

4.4/ Health hazard characterization

The most sensitive organ for HCB is the liver, where the target effect resulting from low-level chronic exposure is a disturbance of porphyrin metabolism. In the case of high-level exposure, this will lead to skin lesions (erythema, bullae), hyperpigmentation and enlargement of the liver. In animal experiments, a range of effects have been observed at levels close to that causing liver effects, such as disturbance of immune function, neurobehavioural development, calcium metabolism and ovarian morphology. There is sufficient evidence of carcinogenicity in experimental animals but insufficient evidence in humans; HCB is therefore placed by IARC in group 2B as possibly carcinogenic to humans. For human risk assessment, WHO has derived TDI of 0.17 µg/kg bw per day for non-neoplastic effects and a guidance value of 0.16 µg/kg bw per day for neoplastic effects. Since HCB crosses the placenta and is present in breast-milk, there is concern that effects may result from prenatal and neonatal exposure.

4.5/ Human health implications relative to LRTAP

HCB is still released to the environment in the LRTAP Convention region, mainly as a result of unintentional emission from waste incineration and as a by-product of various manufacturing processes. Health hazard characterization has identified a number of effects potentially related to low-level chronic exposure via the oral route. Food is the most relevant means of exposure related to LRTAP-derived sources.

5/ HEPTACHLOR

5.1/ Introduction

Heptachlor is a non-systemic contact insecticide, used primarily against soil insects and termites. It has also been used against pests of cotton and other crops, grasshoppers and mosquitos in the fight against malaria. Heptachlor is present as an impurity in the pesticide chlordane. The use of heptachlor has been banned or severely restricted in many countries since the late 1970s, and current environmental concentrations are therefore principally the result of recycling following previous use of the compound. Contemporary use of chlordane contaminated with heptachlor may be responsible for sporadic atmospheric inputs to the remote Arctic environment. This substance is already included in the list of substances scheduled for elimination in the CLRTAP Protocol.

5.2/ Potential for LRTAP

Heptachlor is characterized by its semi-volatility, resistance to degradation and low water solubility. These characteristics predispose it to high environmental persistence and to long-range transport. The persistence of heptachlor and its oxidation product, heptachlor epoxide, combined with a high octanol : water partition coefficient, provides the necessary conditions for it to bioconcentrate in terrestrial and aquatic food chains. Air is probably the most significant compartment for global environmental distribution.

5.3/ Pathways of LRTAP-derived human exposure

The general population is exposed to heptachlor and heptachlor epoxide mainly via food items, particularly fatty foods of animal origin (e.g. meat, fish and dairy products). Heptachlor is generally not detectable in the human population, but the epoxide has been found in human fat, blood, organs and milk. Since the 1970s, dietary intakes of heptachlor and heptachlor epoxide have declined significantly in industrialized countries as the use of the compound has been reduced. Current values in the UNECE region range from 0.02 to 1.2 µg/day. Breastfeeding results in infants being exposed to levels exceeding those in adults. The presence of heptachlor and heptachlor epoxide in remote locations points to the significance of LRTAP as an important element of the exposure pathway in those areas.

5.4/ Health hazard characterization

Heptachlor is absorbed via all routes of exposure and is readily metabolized to heptachlor epoxide by mammals. Heptachlor epoxide is metabolized slowly and is the most persistent metabolite; it is stored mainly in adipose tissue, but also in the liver, kidney and muscle. Animal studies have reported effects on the liver, kidney and the immune and nervous systems from oral exposure to heptachlor. Heptachlor has been shown to cross the placenta to the developing fetus in humans. Based on consistent findings of neoplastic effects in experimental animals, IARC has classified heptachlor as a possible human carcinogen (group 2B). Inadequate information is available to determine whether heptachlor may cause developmental or reproductive effects in humans. JMPR has established an ADI for heptachlor of 0.1 µg/kg bw.

5.5/ Human health implications relative to LRTAP

It appears that the general population is not at risk from LRTAP-derived heptachlor, although highly exposed groups such as some breastfed infants and Inuit in the Arctic may be at risk. Long-range transport represents the most important source of heptachlor found in the terrestrial and aquatic food chains in remote regions, although the environmental concentrations in those regions are likely to be very low since contemporary use is limited.

6/ DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS

6.1/ Introduction

Polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDD/PCDFs) are today found in almost all compartments of the global ecosystem in at least trace amounts. PCDD/PCDFs are formed as unwanted by-products in many industrial and combustion processes, and are also generated in forest fires and volcanoes. The polychlorinated biphenyls (PCBs) have been used commercially since 1929 as dielectric and heat exchange fluids and in a variety of other applications. These three substance classes are found in human tissue in many parts of the world, including remote areas with no production or use. At present, the major source of exposure could be redistribution, but primary sources could also be of significant

importance. PCDD/PCDFs and dioxin-like PCBs are considered to act via a common mechanism of toxicity. These substances are already included in the CLRTAP Protocol, and PCBs were given elimination status (Annex A) by the Stockholm Convention on POPs, whereas PCDD/PCDFs are Annex C substances (Article 5: Measures to reduce or eliminate releases from unintentional production) in the same Convention.

6.2/ Potential for LRTAP

PCDD/PCDFs and dioxin-like PCBs are characterized by their semi-volatility and resistance to degradation. The water solubility is low. These characteristics predispose them to environmental persistence and to long-range transport. They intensively adsorb on to particles in air, soil and sediment, and accumulate in fat-containing tissues. The strong adsorption results in their negligible mobility in soil and sediments. Air is probably the most significant compartment for environmental distribution. They have the ability to bioconcentrate and biomagnify under typical environmental conditions, thereby potentially achieving toxicologically relevant concentrations.

6.3/ Pathways of LRTAP-derived human exposure

The general population is mainly exposed to PCDD/PCDFs and dioxin-like PCBs via common food items, particularly fatty foods of animal origin (e.g. meat, certain fish and dairy products). Estimated average current intake levels are in the range of 1-3 pg TEQ/kg bw per day. Data available from industrialized countries have shown a reduction of population exposure levels in the few last decades, but there are indications that this decline has levelled off. Prenatal and neonatal exposure are considered particularly important, as breastfed infants exceed adult exposures to PCDD/PCDFs and PCBs by 1–2 orders of magnitude. As a result of LRTAP and dietary habits, human exposure to dioxin-like PCBs in many Arctic regions is considerably higher compared to that in industrialized areas. This, as well as the presence of dioxins in remote locations, points to the significance of LRTAP as an important element of the exposure pathway in those areas.

6.4/ Health hazard characterization

As 2,3,7,8-substituted PCDD/PCDFs and dioxin-like PCBs are believed to act through a common toxicological mechanism, a TEF concept has been established, allowing calculation of the combined toxicity in a mixture of PCDD/PCDFs and dioxin-like PCBs. As it is likely that other substances, such as polychlorinated naphthalenes, could act through the same mechanism, it has been proposed that they could also be included in the TEF scheme and add to the estimated toxicity. Critical health outcomes include cancer, immunosuppression, behavioural changes and reproductive effects. The developing fetus and the neonate are thought to represent a potential "at risk" population owing to their increased susceptibility. WHO recommends a TDI of 1–4 pg TEQ/kg bw, but stresses that the upper *limit* of the range should be considered a maximum tolerable intake, which should be

reduced to below 1 pg TEQ/kg bw per day. The Scientific Committee on Food of the European Commission has proposed a temporary tolerable weekly intake of 14 pg TEQ/kg bw, while JECFA has suggested a provisional tolerable monthly intake of 70 pg TEQ/kg bw. IARC has classified TCDD as a human carcinogen (group 1). PCBs are classified as probably carcinogenic to humans (group 2A).

6.5/ Human health implications relative to LRTAP

As human exposure levels often exceed the TDI, the weight of evidence suggests an increased risk of harmful health effects in the general population, especially for breastfed infants and populations with specific diets. Since the chemical and physical properties of PCDD/PCDFs and dioxin-like PCBs make them susceptible to LRTAP, it is expected to contribute significantly to exposure and health risks.

7/ POLYCHLORINATED BIPHENYLS

7.1/ Introduction

Polychlorinated biphenyls (PCBs) are found in almost all compartments of the global ecosystem in at least trace amounts. PCBs have been used commercially since 1929 as dielectric and heat exchange fluids and in a variety of other applications. PCBs are found in human tissues in many parts of the world, including remote areas with no production or use. Currently, the major source of exposure could be redistribution, but primary sources could also be of significant importance. Based on biological activity, PCBs have been divided into non-dioxin-like and dioxin-like congeners. Dioxin-like PCB congeners are considered to act through the same mechanism of toxicity as the PCDD/PCDFs. PCBs are scheduled for elimination under both the CLRTAP Protocol and the Stockholm Convention on POPs.

7.2/ Potential for LRTAP

PCBs are characterized by their semi-volatility and resistance to degradation. The water solubility is low. These characteristics predispose them to environmental persistence and to long-range transport. They intensively adsorb on to particles in air, soil and sediment and accumulate in fat-containing tissues. The strong adsorption results in their negligible mobility in soil and sediments. Air is probably the most significant compartment for environmental distribution. PCBs have the ability to bioconcentrate and biomagnify under typical environmental conditions, thereby potentially achieving toxicologically relevant concentrations.

7.3/ Pathways of LRTAP-derived human exposure

The general population is exposed to PCBs mainly via common food items, particularly fatty food of animal origin (e.g. meat, certain fish and dairy products). Recent estimated intake levels for adults in the western world are about 50 ng/kg bw per day. Data available from industrialized countries have shown a reduction of population exposure levels in the last few decades, but there are indications that this decline has levelled off. Pre-natal and neonatal exposure is considered particularly important, as breastfed infants will exceed adult exposures by 1–2 orders of

magnitude. As a result of LRTAP and dietary habits, human exposure to PCB in many Arctic regions is considerably higher compared to that in industrialized areas. This, as well as the presence of PCBs in remote locations, points to the significance of LRTAP as an important element of the exposure pathways in those areas.

7.4/ Health hazard characterization

Typical effects of PCB exposure, including the critical effects of carcinogenicity, immunotoxicity and neurodevelopmental alterations, are caused by both the dioxin-like and the non-dioxin-like congeners. Nevertheless, the underlying mechanisms involved are probably different. The developing fetus and neonate are thought to represent a potential "at risk" population owing to increased susceptibility. (For further information about the toxicology profile and the human health implications of dioxin-like PCB congeners relative to LRTAP, see Chapter 6.) To date, toxic effects specific to non-dioxin-like congeners have not been identified, although endocrine disturbances and developmental toxicity are end-points of major concern. Toxicity data on PCB hydroxy- and methyl-sulfonyl metabolites indicate that these compounds have their own toxicity profiles, which could include endocrine disturbances and respiratory tract toxicity. The LOEL for subtle neurotoxic effects in infants following perinatal exposure is 0.014–0.9 µg/kg bw per day. This is in the same order of magnitude as the present PCB exposure of the general population in many countries. It has not yet been possible, based on the available data, to reach a scientifically justified agreement on a TDI of either PCB mixtures or of any individual non-dioxin-like PCB congener. IARC has classified PCBs as probably carcinogenic to humans (group 2A).

7.5/ Human health implications relative to LRTAP

As human PCB exposure, including both dioxin-like and non-dioxin-like congeners, may reach estimated LOAELs for neurodevelopmental effects in infants, the weight of evidence suggests an increased health risk from current exposures. Lack of congener-specific exposure and toxicity data limits the possibilities for indicating which congeners are responsible for the effects. Since the chemical and physical properties of PCBs make them susceptible to LRTAP, they are expected to contribute significantly to exposure and health risks, especially in remote areas.

8/ POLYCYCLIC AROMATIC HYDROCARBONS

8.1/ Introduction

Polycyclic aromatic hydrocarbons (PAHs) are a large group of compounds that consist of two or more fused aromatic rings made entirely from carbon and hydrogen. Most direct releases of PAHs to the environment from both natural and anthropogenic sources are to the atmosphere, with predominant emissions from human activities. The primary natural sources of airborne PAHs are forest fires and volcanoes. The residential burning of wood is the largest source of atmospheric PAHs. Other important stationary anthropogenic sources include industrial power generation, incineration, the production of asphalt, coal tar and coke, petroleum

catalytic cracking and primary aluminium production (Sodeberg technology in particular). Stationary sources account for about 80% of total annual emissions of PAHs. The most important mobile sources are vehicle exhausts from gasoline and diesel-powered engines. PAHs are subject to emission controls specified in Annex 3 of the CLRTAP Protocol.

8.2/ Potential for LRTAP

PAHs are present in the atmosphere in the gaseous phase or sorbed to particulates with relatively low degradation rates. Fine particles can remain airborne for a few days or longer and can be transported over long distances, and therefore a portion has LRTAP potential. Air is probably the most significant compartment for environmental distribution.

The cumulating of PAHs in the soil is not significant. Bioaccumulation is limited and biomagnification has not been observed because most organisms have a high biotransformation potential for PAHs.

8.3/ Pathways of LRTAP-derived human exposure

In the average American diet the intake of carcinogenic PAHs has been estimated to be 1–5 µg/day, mostly from unprocessed grains and cooked meats. The estimate was 6–9 µg/day for persons with diets that included a lot of meat, and resulted from the additional contribution of charcoal-cooked or smoked meats and fish. Exposure through inhalation of ambient air was estimated to be 0.16 µg/day (median) with a range of 0.02–3 µg/day, assuming an inhalation rate of 20 m^3/day. Exposure via drinking-water was estimated to be 0.006 µg/day (median), with a range of 0.0002–0.12 µg/day (2 litres of water daily).

Available data for Europe reported by EMEP in 2001 suggest that the mean annual air concentration of benzo[*a*]pyrene (BaP), one of the substances belonging to PAH group that could be attributed to long-range transport in 1998, ranged from 0.1 to 0.5 ng/m^3. Available data suggest that during last 20 years, both the emission and concentration of PAHs in the air decreased owing to modifications in heating systems and in the kind of heating fuel used, except for a few countries with an increasing number of mobile sources.

8.4/ Health hazard characterization

The toxic effect of most concern from exposure to PAHs is cancer. IARC considers several purified PAHs and PAH derivatives to be probable (Group 2A) or possible (Group 2B) human carcinogens. Some mixtures containing PAHs are known human carcinogens (Group 1). Data obtained as a result of epidemiological studies in occupational settings suggest that there is an association between lung cancer and exposure to PAHs. The most important exposure route for lung cancer appears to be inhalation. WHO considered BaP concentration in the air as a good index of the carcinogenic potential of the total fraction. A unit risk for BaP (lifetime exposure to a mixture represented by 1 ng/m^3 BaP) is estimated to be 8.7 x 10^{-5}, or roughly 90 cases per million people exposed. Consequently, the excess lifetime risk

of cancer corresponding to the mean BaP levels from LRTAP would be between 8.7×10^{-6} and 4.3×10^{-5}, or approximately 9–50 cases per million people exposed.

Food constitutes the main route of PAH intake. Nevertheless, according to FAO and WHO, the large difference between estimated human intake of BaP and the doses that induce tumours in animals suggests that any effects on human health as a result of oral intake are likely to be small or insignificant.

The WHO guidelines for BaP in drinking-water corresponding to an excess lifetime risk for gastric cancer of 10^{-5} and 10^{-6} are respectively 0.7 and 0.07 µg/l. The current concentrations of BaP in drinking-water are below 0.002 µg/l.

8.5/ Human health implications relative to LRTAP

The weight of evidence from epidemiological studies based on inhalation and occupational exposure to PAHs suggests an increased risk of harmful health effects, mainly lung cancer. The excess lifetime risk of lung cancer that can be attributed to LRTAP is low compared to the risk due to exposure from local sources.

9/ POLYCHLORINATED TERPHENYLS

9.1/ INTRODUCTION

Polychlorinated terphenyls (PCTs) are chlorinated aromatic compounds that are structurally and chemically similar to polychlorinated biphenyls (PCBs). PCTs were produced in the United States (from 1929 to 1972), France, Germany, Italy and Japan, but their production was discontinued owing to environmental concerns. Commercial PCT mixtures frequently contain PCBs. PCTs have been used since 1929 in a variety of applications, including as heat-exchange fluids owing to their chemical and thermal stability. Approximately 60 million tonnes of PCTs were produced between 1959 and the mid-1970s. Being chemically and physically similar, PCTs may be expected to behave like PCBs in the environment. The production and use of PCTs will be reassessed under the UNECE/LRTAP Protocol on POPs by 31 December 2004.

9.2/ Potential for LRTAP

Based on their persistence and their potential to bioaccumulate, PCTs satisfy the criteria of a POP with LRTAP potential. PCTs are characterized by their chemical and thermal stability; they have low volatility and water solubility. Generally, PCTs are assumed to be similar to PCBs with respect to environmental fate and transport processes and distribution. However, the long-range transport of PCTs has not been as extensively studied as that of PCBs. Atmospheric transport has been found to be a major pathway for PCT deposition into the Great Lakes in North America.

The limited environmental data available indicate that PCTs are resistant to both biodegradation and photodegradation, which in combination with their lipophilicity and stability may indicate their ability to persist, bioconcentrate and biomagnify within the food chain. However, the database of literature for PCTs is both limited and dated.

9.3/ Pathways of LRTAP-derived human exposure

PCTs have been detected in the environment, albeit usually at levels lower than those of PCBs within the same samples. Potential exposure to PCTs by the general population would primarily occur through the consumption of meat, fish and dairy products. Infants may be exposed to PCTs *in utero* or through breastfeeding. Although there is limited data on the toxicokinetics of PCTs, they are absorbed and readily distributed to all parts of the body, with the highest concentration in the liver.

9.4/ Health hazard characterization

The toxicity of PCTs is considered to be very similar to that of PCBs, which suggests long-term toxicity might be critical, although chronic toxicity information is lacking. A general difficulty in toxicological studies of PCTs is the contamination of the PCT mixture with PCBs. It is difficult to determine whether observed effects are caused by the PCTs or by the PCB contamination. PCTs seem to be less acutely toxic than most PCBs. Effects in animals include dose-dependent increase in relative liver weights, reduced growth, and proliferation of the endoplasmic reticulum. High doses of PCTs have been reported to stimulate hepatic microsomal enzymes in *in vivo* and *in vitro* test systems. Owing to the limitations of the available data, the characterization of health hazards of PCTs is limited.

The available data are inadequate to determine whether PCTs cause the same health effects as PCBs. However, since the production and use of PCTs is banned in the UNECE regions, the likelihood of obtaining adequate toxicity data to meet LRTAP criteria is low.

9.5/ Human health implications relative to LRTAP

There is insufficient information to evaluate the health implications from long-term exposures to PCTs. Further studies are needed in order to be able to evaluate the health impact of PCTs and their potential link to LRTAP.

10/ POLYBROMINATED DIPHENYL ETHERS

10.1/ Introduction

Polybrominated diphenyl ethers (PBDEs) belong to a family of diverse chemicals employed in various industrial/consumer product applications as flame retardants. Commercial production and use of PBDEs as additive flame retardants began in the 1960s, with the majority of uses confined to the plastic (resins, polymers, substrates), textile, electronic, furniture and, to a lesser extent, paint industries. Annual worldwide production of all PBDEs in 1990 was estimated at 40 000 tonnes, with a continued market demand in 1999 of 42 000 tonnes for the Americas and Europe. Based on evidence of long-range atmospheric transport, environmental persistence and bioaccumulation in various species, including humans, PBDE congeners (mainly specific to the commercial penta-brominated diphenyl ether mixtures) appear to satisfy the criteria under which new chemicals can be considered for addition to the UNECE Protocol.

10.2/ Potential for LRTAP

The PBDE congeners typical of commercial penta-brominated diphenyl ether mixtures, have certain physicochemical and structural properties similar to polychlorinated biphenyls (hydrophobic, lipophilic, low vapour pressure, high log K_{ow}), which make them generally resistant to environmental degradation, susceptible to long range transport processes and able to bioaccumulate. These PBDEs have been detected in both abiotic and biotic samples collected from remote locations, with some evidence that concentrations have been increasing over the last two decades. From 1981 to 2000, the concentration of PBDEs in ringed seals collected from the Canadian Arctic increased by almost an order of magnitude (from 0.6 to 4.6 ng/g) suggesting efficient atmospheric transport. This is in contrast to PCB levels, which over the same time period have either stabilized or begun to decline.

10.3/ Pathways of LRTAP-derived human exposure

The vast majority of the population is exposed to PBDEs through food consumption. Although market basket survey data are limited, preliminary indications estimate daily intakes of approximately 1 ng/kg bw per day. Persons consuming large quantities of fish have been shown to accumulate higher levels of PBDEs. As with other POPs, breastfed infants ingest quantities almost 1–2 orders of magnitude higher. Estimations of intake attempted near sites at which PBDEs are used industrially range up to 1 µg/kg bw per day. Based on the dietary practices of certain indigenous populations, it could be assumed that LRTAP is responsible for the majority of their exposure.

10.4/ Health hazard characterization

Initial results from experimental animals indicate that certain PBDEs are efficiently absorbed from the gastrointestinal tract; they can stimulate various liver enzymes and cause organ changes and endocrine-related effects. While there is limited evidence to suggest PBDEs are reproductive toxicants, individual congeners found in the commercial penta-brominated diphenyl ether mixtures can induce neurodevelopmental alterations (in learning, memory and spontaneous behaviour) in neonatal mice. While uncertainties in the current exposure and toxicological data hinder an accurate risk characterization, there are indications that margin of safety estimates may be unacceptably low, especially considering the environmental persistence and bioaccumulative nature of PBDEs.

10.5/ Human health implications relative to LRTAP

The developing fetus and breastfed infants are considered to be the main “at risk” groups from potential adverse effects due to exposure to PBDE congeners found in commercial penta-brominated diphenyl ether mixtures. The overall contribution of LRTAP to daily PBDE exposure depends on the region, but would be substantial for more remote locations.

11/ POLYBROMINATED DIBENZO-*P*-DIOXINS AND DIBENZOFURANS

11.1/ Introduction

Polybrominated dibenzo-*p*-dioxins and dibenzofurans (PBDD/PBDFs) consist of two groups of tricyclic aromatic compounds. PBDD/PBDFs exist as unintentional by-products in chemical processes but can also be formed during various combustion processes and photolytic degradation of PBDEs and bromophenols. Among the possible 210 congeners, 17 have bromine atoms at least in positions 2, 3, 7 and 8 of the parent molecule, and these are very toxic compared to molecules lacking this configuration. All the 2,3,7,8-substituted PBDD/PBDFs show the same type of biological and toxic response as the corresponding PCDD/PCDFs. It is also known that mixed chlorine–bromine dioxins/furans can be formed. Thus 1550 mixed dioxins and 3050 mixed furans are theoretically possible. Owing to the paucity of analytical reference standards, a very limited number of these congeners have been studied and analysed so far. These substances are not included in the LRTAP Protocol.

11.2/ Potential for LRTAP

There are very few data available on environmental transport and distribution. PBDD/PBDFs are more readily degraded photochemically than PCDD/PCDFs. Generally, the physicochemical properties of PBDD/PBDFs suggest similarities to PCDD/PCDFs. Therefore, they would be expected to accumulate in carbon- and/or fat-rich compartments.

11.3/ Pathways of LRTAP-derived human exposure

There are no quantitative data on levels of the current substances in food or wildlife. Lower brominated (mono–tetra) congeners have been found close to motorways on pine needles and grass.

11.4/ Health hazard characterization

The kinetics and metabolism of PBDD/PBDFs have been investigated in a limited number of studies. PBDD/PBDF congeners show obvious similarities with their chlorinated analogues concerning metabolism, elimination and biological half-lives. Also, in the limited number of effect studies performed, PBDD/PBDF congeners show similarities with their PCDD/PCDFs analogues. They are believed to share a common mechanism of action with PCDD/PCDFs and other related hydrocarbons. Binding to the Ah-receptor has been confirmed for several PBDD/PBDFs and the mixed chlorine–bromine compounds. Also, the receptor-binding capacity has been reported to be similar to that of the chlorinated analogues. There are no data on effects in humans.

11.5/ Human health implications relative to LRTAP

Based on the physical and chemical similarities with PCDD/PCDFs, it is possible that PBDD/PBDFs could resist degradation, bioaccumulate and be transported

through air across international boundaries. However, there is still a lack of data to confirm the presence of PBDD/PBDFs in biota. The human health implications relative to LRTAP could not be judged on present data.

12/ SHORT-CHAIN CHLORINATED PARAFFINS

12.1/ Introduction

Chlorinated paraffins (CPs) are straight-chain alkanes with varying degrees of chlorination. They have been produced since the 1930s at an estimated 300 kilotonnes per year in the western world. CPs have been used as high-temperature, high-pressure lubricants as well as secondary plasticizers and flame retardants in plastics and paints.

CPs are divided into three main categories, short- (C10–C13), medium- (C14–C17) and long-chain (C18–C30), and further by their degree of chlorination, i.e. low (<50%) and high (>50%). Because of their relatively high assimilation and accumulation potential, the short-chain chlorinated paraffins (SCCPs) have been the most widely studied.

The complexity of SCCP mixtures makes it difficult to provide an analytical method for their precise and specific quantitative determination. A technical SCCP mixture consists of several thousand components and, owing to the large number of isomers, complete chromatographic separation seems impossible at present. This analytical challenge has resulted in different approaches to the analysis of SCCPs, but the number of relevant monitoring results is still limited.
These substances are not included in the LRTAP Protocol.

12.2/ Potential for LRTAP

SCCPs are complex mixtures, which vary in chain lengths and in the degree of chlorination. The vapour pressure values, Henry's law constants and atmospheric half-life values are in the same range as for other persistent organic pollutants and imply a significant potential for long-range atmospheric transport. SCCPs have been detected in Arctic air, biota and lake sediments, and in the water column around the Bermuda Islands. This is despite the absence of significant sources of SCCPs in these regions, which suggests that these residues are present owing to long-range atmospheric transport.

SCCPs are clearly fulfilling the criteria for bioconcentration and there is some evidence for biomagnification.

12.3/ Pathways of LRTAP-derived human exposure

The main environmental source of human exposure is food and, to a lesser extent, drinking-water. The risk for human exposure related to long-range transboundary atmospheric transport is difficult to quantify, but clearly should not be neglected. The lack of monitoring data hampers reliable exposure estimation. Levels in food in the range of 30 to several thousand µg/kg have been measured. The EU risk assessment report considers a human uptake value of about 20 µg/kg bw per day as a reasonable worst-case value.

12.4/ Health hazard characterization

Compared to PCBs and chlorinated pesticides, SCCPs appear to exhibit fewer toxic effects. SCCPs show lower reproductive and embryo toxicity in mammals and birds. The main target organs for repeated doses of SCCPs seem to be the liver, kidney and thyroid. SCCPs show neoplastic effects in the liver of mice and rats, but the relevance of this for humans is uncertain.

In 1996, WHO recommended that daily doses of SCCPs for the general population should not exceed 11 μg/kg bw for neoplastic effects.

12.5/ Human health implications relative to LRTAP

Long-range transboundary atmospheric transport is an important aspect of the global distribution of SCCPs and is responsible for their occurrence in remote areas. The EU risk assessment report concludes that there is no significant risk to humans exposed to SCCPs via the environment. However, it is noted that the EU worst-case human uptake estimate is greater than the guideline value established by WHO.