IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Environmental Health Criteria 140

Polychlorinated Biphenyls and Terphenyls (Second Edition)

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization

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Environmental Health Criteria 140

POLYCHLORINATED BIPHENYLS AND TERPHENYLS (SECOND EDITION)

First draft prepared by Dr S. Dobson, Institute of Terrestrial Ecology, United Kingdom, and Dr G.J. van Esch, Bilthoven, The Netherlands

World Health Organization
Geneva, 1993

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

WHO Library Cataloguing in Publication Data

Polychlorinated Biphenyls and Terphenyls. — 2nd ed.

(Environmental health criteria ; 140)

1.Environmental exposure 2.Environmental pollutants 3.Polychlorinated biphenyls - adverse effects 4.Polychlorinated biphenyls - toxicity 5.Polychloroterphenyl compounds - adverse effects 6.Polychloroterphenyl compounds - toxocity I.Series

ISBN 92 4 157140 3 (NLM Classification: QV 633)
ISSN 0250-863X

Printed in Finland
93 0845 — Vammala 5500

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RESUMEN 657

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NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria monographs, readers are kindly requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone no. 7988400/ 7985850).

ENVIRONMENTAL HEALTH CRITERIA FOR PCBs AND PCTs

A WHO Task Group on Environmental Health Criteria for PCBs and PCTs met in Brussels from 28 May to 1 June 1990. The meeting was convened in the Institute of Hygiene and Epidemiology in Brussels and sponsored by the Belgian Ministry of Health. Mrs A.-M. Sacré-Bestin of the Ministry opened the meeting and welcomed the participants on behalf of the host country. Dr G.J. van Esch welcomed the participants on behalf of the Heads of the three IPCS cooperating organizations (UNEP/ILO/WHO). The Group reviewed and revised the draft Environmental Health Criteria monograph and the companion Health and Safety Guide and made an evaluation of the risks for human health and the environment from exposure to PCBs and PCTs.

The first draft of the EHC monograph was prepared by Dr S. Dobson (environmental aspects) and Dr G.J. van Esch (other sections) and was based on contributions from several authors and countries. It was prepared in close cooperation with the WHO Regional Office for Europe, in Copenhagen.

The second draft was prepared by Dr G.J. van Esch, incorporating comments received following the circulation of the first draft to the IPCS contact points for Environmental Health Criteria monographs. Dr K. Jager, Central Unit, IPCS, was responsible for the scientific content of the final monograph and Mrs M.O. Head, Oxford, for the editing.

The efforts of all who helped in the preparation and finalization of the documents are gratefully acknowledged.

INTRODUCTION

The commercial production of the polychlorinated biphenyls (PCBs) began in 1930, and, during the 1930s, cases of poisoning were reported among men engaged in their manufacture. The nature of this occupational disease was characterized by a skin affection with acneiform eruptions; occasionally the liver was involved, in some cases with fatal consequences. Subsequent safety precautions appear largely to have prevented further outbreaks of this disease in connection with the manufacture of PCBs, but, since 1953, cases have been reported in Japanese factories manufacturing condensers.

The distribution of PCBs in the environment was not recognized until Jensen started an investigation in 1964 to ascertain the origins of unknown peaks, observed during the gas-liquid chromatographic separation of organochlorine pesticides from wildlife samples. In 1966, he and his colleagues succeeded in attributing these to the presence of PCBs. Since then, investigations in many parts of the world have revealed the widespread distribution of PCBs in environmental samples.

The serious outbreaks of poisoning in humans and in domestic animals from the ingestion of food, accidentally contaminated with PCBs, have stimulated investigations into the toxic effects of PCBs on animals and on nutritional food chains. This has resulted in the limitation of the commercial exploitation of PCBs and polychlorinated terphenyls (PCTs), and in regulations to limit the residues in human and animal food.

In recent years, many industrial nations have taken steps to control the flow of PCBs into the environment. PCBs and PCB-containing formulations are restricted (an exception is sometimes made for mono- and dichloro-PCBs) for most uses. Now they are almost entirely restricted to use in closed systems, such as isolating oils in transformers, capacitors, and other electrical systems, and as a heat transfer medium and hydraulic liquid. The most influential forces leading to these restrictions have probably been the 1973 and 1987

decision-recommendations from the Organisation for Economic Co-operation and Development (OECD).

The environmental impact of the PCBs and PCTs has been discussed at a number of regional and international meetings and has been the subject of several reviews, including: ATSDR (1989), DFG (1988), IARC (1978), IRPTC (1988), Kimbrough (1987), Lorenz & Neumeier (1983a,b), NIOSH (1987), NTIS (1972), OECD (1982), Slorach & Vaz (1983), WHO (1985a,b, 1986a,b) & WHO/EUR (1987).

In 1976, the World Health Organization published Environmental Health Criteria 2: Polychlorinated biphenyls (PCBs) and terphenyls (PCTs) (WHO, 1976), discussing and evaluating the data then available on exposure levels and the effects of PCBs and PCTs on human beings, and, to a lesser extent, on the environment.

Since then, a wealth of new information has become available.

The IPCS decided to update the above-mentioned EHC and also to produce a Health and Safety Guide (HSG) and to do this in close coordination with the WHO Regional Office for Europe, which prepared "PCBs, PCDDs and PCDFs, prevention and control of accidental and environmental exposures" as No. 23 of their Environmental Health Series (WHO/EURO, 1987). This publication includes a set of guidelines to assist Member States in the development of strategies to reduce the probability of accidents involving the environmental release of PCBs, PCDDS, and PCDFs and also the severity of their hazardous effects, should such accidents occur. In particular, it is intended to guide occupational safety and health personnel and other staff, in workplaces and environments where PCBs and/or PCB-containing equipment are in use, to develop adequate safety measures, contingency planning, effective and relevant accident response, and appropriate rehabilitation.

Within the scope of the present EHC on PCBs and PCTs, the PCDDs and PCDFs have been mentioned where relevant. Full discussion of these compounds and evaluation, however, can be found in the IPCS EHC 88: Polychlorinated dibenzo-*para*-dioxins and dibenzofurans (WHO, 1989).

1. SUMMARY AND EVALUATION, CONCLUSIONS, RECOMMENDATIONS

1.1 Summary and evaluation

1.1.1 Introduction

Polychlorinated biphenyls (PCBs) were discovered before the turn of the century and their usefulness for industry, because of their physical properties, was recognized early. The PCBs have been used commercially, since 1930, as dielectric and heat-exchange fluids and in a variety of other applications. They have become widely distributed in the environment throughout the world, and are persistent and accumulate in food webs. Human exposure to PCBs has resulted largely from the consumption of contaminated food, but also from inhalation and skin absorption in work environments. PCBs accumulate in the fatty tissues of humans and other animals and have caused toxic effects in both, particularly if repeated exposure occurs. The skin and liver are the major sites of pathology, but the gastrointestinal tract, the immune system, and the nervous system are also targets. Polychlorinated dibenzofurans (PCDFs), which are contaminants in commercial PCB mixtures, contribute significantly to their toxicity. The results of studies on rodents suggest that some PCB congeners may be carcinogenic and that they can promote the carcinogenicity of other chemicals.

It is clear from available data on polychlorinated biphenyls (PCBs) and polychlorinated terphenyls (PCTs) that, in an ideal situation, it would be preferable not to have these compounds in food at any level. However, it is equally clear that the reduction of PCBs or PCTs exposure from food sources to "zero" or to a level approaching zero, would mean the elimination (prohibition of the consumption) of large amounts of important food items, such as fish, but more importantly breast milk. National and international scientific committees have to decide where the proper balance lies between providing an adequate degree of public health protection and avoiding excessive losses of food.

No levels of PCBs or PCTs exposure that can provide an absolute assurance of safety can be identified on the basis of the available data.

1.1.2 Identity, physical, and chemical properties

PCBs are mixtures of aromatic chemicals, manufactured by the chlorination of biphenyl in the presence of a suitable catalyst. The chemical formula of PCBs can be presented as $C_{12}H_{10-n}Cl_n$, where n is a number of chlorine atoms within the range of 1–10.

Theoretically, 209 congeners are possible, but only about 130 congeners are likely to occur in commercial products. In addition, PCBs may contain polychlorinated dibenzofurans (PCDFs) and chlorinated quarterphenyls as impurities. These impurities are relatively stable and resistant to chemical reactions, under normal conditions. All congeners of PCBs are lipophilic and have a very low water solubility. As a result, they easily enter the food chain and accumulate in fatty tissues.

Commercial PCB mixtures contain PCDFs at levels ranging from a few mg/kg up to 40 mg/kg. Polychlorinated dibenzo-*p*-dioxins (PCDDs), are not found in commercial PCBs. However, when PCBs are mixed with other chlorinated compounds, such as the chlorobenzenes used in transformers, PCDDs can be found in the case of accidental fires and during incineration.

Commercial PCB mixtures are light yellow or dark yellow in colour. They do not crystallize, even at low temperatures, but turn into solid resins. PCBs are, in practice, fire resistant, with rather high flash points. They form vapours heavier than air, but they do not form any explosive mixtures with air. They have very low electrical conductivity, rather high thermal conductivity, and extremely high resistance to thermal break-down. PCBs are chemically very stable under normal conditions; however, when heated, other toxic compounds, such as PCDFs, can be produced.

1.1.3 Analytical methods

In 1966, the discovery of PCBs in environmental samples raised interest in the analysis of these compounds and their toxicity for human beings and their environment.

Because of differences in the analytical methodology used, existing data are not directly comparable; nevertheless, they can be used for the establishment of control and preventive measures and for the preliminary assessment of health and environmental risks associated with these chemicals.

PCBs have been determined using gas chromatography (GC) techniques with electron capture detection, often using packed columns, though more sophisticated methods, such as capillary column and GC coupled with mass-spectrometry (GC-MS), have been used in recent studies to identify the individual congeners, to improve the comparability of the analytical data from different sources, and to establish a basis for toxicity assessment.

An extensive quality assurance programme is required for these analyses and intercalibration studies have been implemented and recommended. The quality and utility of the analytical data depend critically on the validity of the sample and the adequacy of the sampling. Furthermore, it is essential to have a planned and well documented sampling programme; a detailed sampling procedure is described in WHO/EURO (1987).

1.1.4 Production and uses

The commercial production of the PCBs began in 1930. They have been widely used in electrical equipment, and smaller volumes of PCBs are used as fire-resistant liquid in nominally closed systems.

By the end of 1980, the total world production of PCBs was in excess of 1 million tonnes and, since then, production has continued in some countries. Despite increasing withdrawal of the use, and restrictions on the production, of PCBs, very large amounts of these compounds continue to be present in the environment, either in use or as waste.

In recent years, many industrialized countries have taken steps to control and restrict the flow of PCBs into the environment. The most influential force leading to these restrictions has probably been a 1973 recommendation from the Organisation for Economic Co-operation and Development (OECD) (WHO, 1976; IARC, 1978; OECD, 1982). Since then, the 24 OECD member countries have restricted

the manufacture, sales, importation, exportation, and use of PCBs, as well as establishing a labelling system for these compounds.

Current sources of PCB release include volatilization from landfills containing transformer, capacitor, and other PCB-wastes, sewage sludge, spills, and dredge spoils, and improper (or illegal) disposal to open areas. Pollution may occur during the incineration of industrial and municipal waste. Most municipal incinerators are not effective in destroying PCBs. Explosions or overheating of transformers and capacitors may release significant amounts of PCBs into the local environment.

PCBs can be converted to PCDFs under pyrolytic conditions. The highest yield of PCDFs under laboratory conditions was obtained at a temperature between 550 and 700 °C. Thus, the uncontrolled burning of PCBs can be an important source of hazardous PCDFs. It is therefore recommended that destruction of PCB-contaminated waste should be carefully controlled, especially with regard to the burning temperature (above 1000 °C), residence time, and turbulence.

1.1.5 Environmental transport, distribution, and transformation

In the atmosphere, PCBs exist primarily in the vapour phase; the tendency to adsorb on particulates increases with the degree of chlorination. The virtually universal distribution of PCBs suggests transport in air.

At present, the major source of PCB exposure in the general environment appears to be the redistribution of PCBs, previously introduced into the environment. This redistribution involves volatilization from soil and water into the atmosphere with subsequent transport in air and removal from the atmosphere via wet/dry deposition (of PCBs bound to particulates) and then re-volatilization. Concentrations of PCBs in precipitation range from 0.001 to 0.25 μg/litre. Since the volatilization and degradation rates of PCBs vary between congeners, this redistribution leads to an alteration in the composition of PCB mixtures in the environment.

In water, PCBs are adsorbed on sediments and other organic matter; experimental and monitoring data have shown that PCB

concentrations in sediment and suspended matter are higher than those in associated water columns. Strong adsorption on sediment, especially in the case of the higher chlorinated PCBs, decreases the rate of volatilization. On the basis of their water solubilities and *n*-octanol-water partition coefficients, the lower chlorinated PCB congeners will sorb less strongly than the higher chlorinated isomers. Although adsorption can immobilize PCBs for relatively long periods in the aquatic environment, desorption into the water column has been shown to occur by both abiotic and biotic routes. The substantial quantities of PCBs in aquatic sediments can therefore act as both an environmental sink and a reservoir of PCBs for organisms. Most of the environmental load of PCBs has been estimated to be in aquatic sediment.

The low solubility and the strong adsorption of PCBs on soil particles limits leaching in soil; lower chlorinated PCBs will tend to leach more than the highly chlorinated PCBs.

Degradation of PCBs in the environment is dependent on the degree of chlorination of the biphenyl. In general, persistance of PCB congeners increases as the degree of chlorination increases. In the atmosphere, the vapour phase reaction of PCBs with hydroxyl radicals (which are photochemically formed by sunlight) may be the dominant transformation process. Estimated half-lives for this reaction in the atmosphere range from about 10 days for a monochlorobiphenyl to 1.5 years for a heptachlorobiphenyl.

In the aquatic environment, hydrolysis and oxidation do not significantly degrade PCBs. Photolysis appears to be the only viable abiotic degradation process in water; however, available experimental data are not sufficient to determine its rate or importance in the environment.

Microorganisms degrade mono-, di-, and trichlorinated biphenyls relatively rapidly and tetrachlorobiphenyls slowly, whilst higher chlorinated biphenyls are resistant to biodegradation. Chlorine substitution positions on the biphenyl ring appear to be important in determining the biodegradation rate. PCBs containing chlorine atoms in the *para* positions are preferentially biodegraded. Higher chlorinated congeners are biotransformed anaerobically, by a reductive

dechlorination, to lower chlorinated PCBs, which may then be biodegradable by aerobic processes.

Several factors determine the degree of bioaccumulation in adipose tissues: the duration and level of exposure, the chemical structure of the compound, and the position and pattern of substitution. In general, the higher chlorinated congeners are accumulated more readily.

Experimentally determined bioconcentration factors of various PCBs in aquatic species (fish, shrimp, oyster) range from 200 up to 70 000 or more. In the open ocean, there is bioaccumulation of PCBs in higher trophic levels with an increased proportion of higher chlorinated biphenyls in higher ranking predators.

Transfer of PCBs from soil to vegetation takes place mainly by adsorption on the external surfaces of terrestrial plants; little translocation takes place.

1.1.6 Environmental levels and human exposure

Because of their high persistence, and their other physical and chemical properties, PCBs are present in the environment all over the world.

Globally, PCBs are found in air concentrations of 0.002 up to 15 ng/m^3. In industrial areas, levels are higher (up to μg/m^3). In rain water and snow, PCBs are found in the range of nd (1 ng)–250 ng/litre.

Under occupational conditions, the levels in the air may be much higher. Under certain conditions, for instance, in the manufacturing of transformers or capacitors, levels of up to 1000 μg/m^3 have been observed. In acute emergencies, concentrations of up to 16 mg/m^3 have been measured. In case of fires and/or explosions, soot may be produced that contains high levels of PCBs. Levels of 8000 mg PCBs/kg soot have been found. In the latter situation, PCDFs will also be present. Polychlorinated dioxins (PCDDs) will be found in accidents with transformers containing chlorinated benzenes, as well as PCBs.

In these emergency situations, ingestion, skin contamination, or inhalation of soot particles may occur and result in serious exposure

of personnel. However, the exposure of the general population via air will be very low.

Surface water may be contaminated by PCBs from atmospheric fallout, from direct emissions from point sources, or from waste disposal. Under certain conditions, levels of up to 100–500 ng/litre water have been measured. In the oceans, levels of 0.05–0.6 ng/litre have been found.

In non-contaminated areas, drinking-water contains less than 1 ng PCBs/litre, but levels of up to 5 ng/litre have been reported. Soil and sediments in different areas and depending on local conditions, contain levels of PCBs ranging from <0.01 up to 2.0 mg/kg. In polluted areas, the levels have been much higher, i.e., up to 500 mg/kg.

In past years, many thousands of samples of different foodstuffs have been analysed in several countries for contaminants including PCBs. Most samples have been taken from individual food items, especially fish and other foods of animal origin, such as meat and milk. Human food has become contaminated with PCBs by 3 main routes:

(*a*) uptake from the environment by fish, birds, livestock (via food-chains), and crops;

(*b*) migration from packaging materials into food (mainly below 1 mg/kg, but,in some cases, up to 10 mg/kg);

(*c*) direct contamination of food or animal feed by an industrial accident.

The levels for the most important PCB-containing food items were: animal fat, 20–240 μg/kg; cow's milk, 5–200 μg/kg; butter, 30–80 μg/kg; fish, 10–500 μg/kg, on a fat basis. Certain fish species (eel) or fish products (fish liver and fish oils) contain much higher levels, up to 10 mg/kg. Vegetables, cereals, fruits, and a number of other products contained levels of <10 μg/kg. The major foods in which contamination with PCBs needs consideration are fish, shellfish, meat, milk, and other dairy products. Median levels in fish, reported in various countries, are of the order of 100 μg/kg (on a fat basis). When comparisons have been made, it appears that the levels of PCBs in fish are slowly decreasing.

PCBs concentrate in human adipose tissue and breast milk. The concentrations of PCBs in the different organs and tissues depend on their lipid contents, with the exception of the brain. PCB residues in the adipose tissue of the general population in industrialized countries range from less than 1 up to 5 mg/kg, on a fat basis.

The average concentrations of total PCBs in human milk fat are in the range of 0.5–1.5 mg/kg fat, depending on the donor's residence, life-style, and the analytical methods used. Women who live in heavily-industrialized, urban areas, or who consume a lot of fish, especially from heavily-contaminated waters, may have higher PCB concentrations in their breast milk.

The composition of most PCB extracts from environmental samples does not resemble that of the commercial PCB mixtures. It has also been shown, using high-resolution gas chromatography analysis, that the congener composition and the relative concentrations of the individual components in adipose tissues and breast milk differ markedly from those in the commercial PCBs. The GC patterns of PCBs in human adipose tissue and breast milk contain relatively high concentrations of mainly the higher chlorinated PCBs, such as: 2,4,5,3',4'-pentachlorobiphenyl; 2,4,5,2',4',5'-hexachlorobiphenyl, and 2,3,4,2',4',5'-hexachlorobiphenyl; 2,3,4,5,2',4',5'-hepta- and 2,3,4,5,2',3',4'- heptachlorobiphenyl. A few other PCB congeners are present in much lower quantities, such as the most toxic, coplanar PCBs: 3,4,3',4'-tetra-, 3,4,5,3',4'-penta-, and 3,4,5,3',4',5'-hexachlorobiphenyl.

It has been calculated that the daily intake of PCBs by infants from breast milk, is of the order of 4.2 μg/kg body weight (5.2 μg/100 Kcal consumed) (WHO/EURO, 1988). The average total of ingested PCBs from breast milk, during the first 6 months of life, is 4.5 mg compared with the calculated intake of 357 mg of PCBs over the subsequent life-time (0.2 μg/kg per day from the diet of a 70-kg person over a 70-year life-time). Therefore, the nursing period contributes about 1.3% of the life-time intake, which is not large, in the light of the benefits of breast-feeding (WHO/EURO, 1988).

On the basis of the evaluated background data, for adults the average dietary intake of PCBs amounts to a maximum of 100 μg per week, or approximately 14 μg/person per day. For a 70-kg person, this is

an intake equivalent to a maximum of 0.2 μg/kg body weight per day (WHO/EURO, 1988).

1.1.7 Kinetics and metabolism

Animal studies have been reported involving mainly oral, inhalation, and dermal exposures to both PCB mixtures and individual congeners. In general, PCBs appear to be rapidly absorbed, particularly by the gastrointestinal tract after oral exposure. It is clear that absorption does occur in humans, but information on the rates of human absorption of PCBs is limited.

From the available studies, the data on the distribution of PCBs, suggest a biphasic kinetic process with rapid clearance from the blood and accumulation in the liver and the adipose tissue of various organs. There is also evidence of placental transport, fetal accumulation, and distribution to milk. In some human studies, the skin contained a high concentration of PCBs, but the concentration in the brain was lower than that expected on the basis of the lipid content.

Mobilization of PCBs from fat appears to depend largely on the rates of metabolism of the individual PCB congeners. Excretion depends on the metabolism of PCBs to more polar compounds, such as phenols, conjugates of thiol compounds, and other water-soluble derivatives. Metabolic pathways include hydroxylation, and conjugation with thiols and other water-soluble derivatives, some of which can involve reactive intermediates, such as the arene oxides. Rates of metabolism have been shown to depend on the PCB structure and reflect both the degree and position of chlorine substituents. The polar metabolites of the more highly chlorinated PCBs appear to be eliminated primarily in the faeces, but excretion in the urine can also be significant. An important elimination route, is via (breast) milk. Certain PCB congeners can also be eliminated via hair.

The available kinetic studies indicate that there is a wide divergence in biological half-life among the individual congeners and this can reflect differences in structure-dependent metabolism, tissue affinities, and other factors affecting mobilization from storage sites.

Persistence in tissues is not always correlated with high toxicity, and differences in toxicity between PCB congeners may be associated with specific metabolites and/or their intermediates.

1.1.8 Effects on organisms in the environment

PCBs are universal, environmental contaminants and are present in most environmental compartments, abiotic and biotic, throughout the world. Since many countries have controlled both use and release, new input into the environment is on a reduced scale compared with the past. However, the available evidence suggests that the cycling of PCBs is causing a gradual redistribution of some congeners towards the marine environment. There is a trend for the highest chlorinated congeners to accumulate preferentially. While much of the PCB is adsorbed on to particulates in sediment, it is still bioavailable to organisms and will continue to be accumulated in higher trophic levels.

1.1.8.1 Laboratory studies

Effects of PCB mixtures on microorganisms are highly variable with some species adversely affected by a level of 0.1 mg/litre and others unaffected by 100 mg/litre; effects on different species do not vary consistently with the degree of chlorination of the mixtures. Almost all of the studies of the effects of PCBs on aquatic organisms have been concerned with Aroclor mixtures. Results have been extremely variable with no consistent relationship between percentage chlorination or environmental conditions and toxicity, even with closely-related organisms. Over 96 h, under static conditions, LC_{50} values have ranged between 12 μg/litre and > 10 mg/litre for various aquatic invertebrate species and different Aroclor mixtures. Flow-through conditions increased the toxicity of the PCBs. Generally, the most toxic mixtures were Aroclors in the mid-range of chlorination; low and high percentage chlorination mixtures were less toxic. This was also true for sub-lethal effects, such as reproduction effects in *Daphnia*. Crustaceans seem to be more susceptible to PCBs during moult. In model populations, the community structure of estuarine species changed on exposure to Aroclor 1254, with the numbers of amphipods, bryozoans, crabs, and molluscs decreasing and those of annelids, brachyopods, coelenterates, echinoderms, and nemerines

unaffected. Too few of the groups have been included in acute tests to determine whether the results represent variation in susceptibility to PCBs or differences in interaction between species.

There is a similar variation in the toxicity of PCB mixtures for fish, with 96-h LC_{50}s varying between 0.008 and > 100 mg/litre. Long-term tests have shown that acute exposure, particularly in static conditions, considerably underestimates the toxicity of the PCB. Rainbow trout was particularly susceptible, with embryo-larval stages showing a 22-day LC_{50} of 0.32 μg/litre for Aroclor 1254 and a no-observed-effect level (NOEL) over 22 days of 0.01 μg/litre for Aroclors 1016, 1242, and 1254.

Freshwater fathead minnow showed NOELs of 5.4, 0.1, 1.8, and 1.3 μg/litre for Aroclors 1242, 1248, 1254, and 1260, respectively; the estuarine sheephead minnow showed NOELs of 3.4 and 0.06 μg/litre for Aroclors 1016 and 1254, respectively.

Experimental evidence has confirmed field observations demonstrating reproductive impairment in seals fed on fish containing PCBs accumulated in the wild. The effect occurs late in reproduction, preventing implantation of the embryo in the uterine wall.

In short-term tests, the toxicity of Aroclor for birds increased with increasing percentage chlorination; 5-day dietary LC_{50}s ranged from 604 to > 6000 mg/kg diet. The main reproductive effects of PCBs on birds were reduced hatchability of eggs and embryotoxicity. These effects continued after dosing ended, as the hens reduced their PCB load via the eggs. There is no evidence that Aroclors cause egg-shell thinning, directly; effects on the food consumption and body weight of hens have an indirect effect on shell thickness. Sub-lethal effects on behaviour and hormone secretion have been reported.

The acute toxicity of Aroclors for mink decreases with increasing percentage chlorination, acute oral LD_{50}s varying between > 750 and 4000 mg/kg body weight; the ferret is less sensitive. Aroclor reduces food consumption and, thus, the growth rate of young mink. Reproduction of mink is reduced or eliminated by Aroclors, either given directly or as natural contaminants in fish. Higher percentage chlorinated Aroclors (notably 1254) have a greater effect. The reproductive rate returns to normal after cessation of feeding with Aroclor.

Bats are susceptible to Aroclor released from fat during migration.

Because the great majority of laboratory tests on aquatic and terrestrial organisms were carried out using PCB mixtures, it is not possible to identify which specific components of the mixtures were responsible for effects. Similarly, because tests were conducted in environmentally unrealistic conditions (e.g., beyond the solubility of congeners and without sediment present in aquatic tests), it is difficult to extrapolate from laboratory to field. However, it can reasonably be assumed that any effects on populations of organisms, likely to occur more generally in the environment in the future, will already have been observed in local populations exposed to high PCB levels in the past.

1.1.8.2 Field studies

Results suggesting effects of PCBs on fish populations in the field are inconclusive. Interpretation of field data on birds is difficult, since residues of many different organochlorines are also present. Most authors have shown a correlation between effects (embryotoxicity) and total organochlorine residues. Of the organochlorine compounds present, PCB residues correlate best with the effects on embryos, but the results cannot be regarded as proved field effects of the PCBs.

There is evidence (confirmed in laboratory studies) that PCBs reduce the reproductive capacity of sea mammals. The effect is on the implantation of the embryo, but there can also be physical changes in the female reproductive tract.

Extrapolation from laboratory, acute and short-term tests to effects at the population level in the field is not possible. Uncertainties about which components of the PCB mixtures cause effects, the specific congeners present in the environment, and the bioavailability of PCB components to organisms, all combine to make estimates of likely environmental exposures and effects difficult. The effects on sea mammal populations can be regarded as proved, but the component(s) of the PCB mixtures that are responsible are not yet known.

Given the trends towards increased contamination of the marine environment, attention should be concentrated on the effects on marine organisms. There is clear laboratory and field evidence of

reproductive effects on populations of sea mammals in heavily-polluted areas. The residues and effects of PCBs on other populations of sea mammals are likely to increase in the future. It is less clear whether effects will be seen in other organisms, such as birds feeding on marine prey.

Population and community effects on lower organisms, phyto-plankton, and zooplankton, would be expected to occur on the basis of laboratory experiments. Both the extent and significance of such changes are difficult to assess. From currently available information, effects on fish populations would not be expected, though fish will act as a route of exposure of fish-eating mammals and birds.

Previously reported effects on terrestrial species, fish-eating, freshwater mammals and migratory bats, for example, should be less evident as residues of PCBs are redistributed. Residues in terrestrial biota currently show little decline overall, but information on changes in congeners is scarce or absent. Declines in higher chlorinated congeners would be expected to be slow.

1.1.9 Effects on experimental animals and in vitro *systems*

1.1.9.1 Single exposure

The acute toxicity of Aroclors, after a single oral exposure, is generally low in rats. Young animals appear to be more sensitive (LD_{50}: 1.3–2.5 g/kg body weight) than adults (LD_{50}: 4–11 g/kg body weight). The lowest LD_{50} reported for Aroclor 1254 in adult rats was 1.0 g/kg body weight. No differences between the sexes were observed.

The dermal LD_{50} in rabbits ranged from >1.26 to <2 g/kg body weight for Aroclor 1260 (in corn oil) and from 0.79 to <3.17 g/kg body weight for some other undiluted PCB mixtures. With intra-venous application, an LD_{50} of 0.4 g/kg body weight for Aroclor 1254 was shown in rats; the LD_{50} after intraperitoneal injection in the mouse varied from 0.9 to 1.2 g/kg body weight.

1.1.9.2 Short-term exposure

The main targets in mammals, with short-term, oral exposure to PCB mixtures or congeners, were the liver, the skin, the immune system, and the reproductive system. The Rhesus monkey was the most sensitive species tested, females being more sensitive than males. Adult female Rhesus monkeys exposed to a diet containing Aroclor 1248 at a level of 2.5 mg/kg, or 0.09 mg/kg body weight per day, for 6 months, showed an increased mortality rate, growth retardation, alopecia, acne, swelling of the Meibomian glands, and possibly immunosuppression. Microscopically, enlarged fatty liver with focal necrosis, and epithelial hyperplasia, and keratinization of hair follicles were found. At higher exposure levels, microscopic changes have also been observed in other epithelial tissues, such as the sebaceous and Meibomian glands, the gastric mucosa, gall bladder, bile duct, nail beds, and the ameloblast. Serum levels of total lipid triglycerides and cholesterol were decreased. Short-term exposure to commercial PCB mixtures induced an increase in the concentrations of total lipids, triglycerides, cholesterol, and/or phospholipids in the liver. Among the PCB congeners, 3,4,3',4'-tetrachlorobiphenyl 3,4,5,3',4',5'-, and 2,4,6,2',4',6'-hexachlorobiphenyl were the most potent. Aroclor 1254, at a dose level of 0.2 mg/kg body weight per day, also showed several other effects, such as lymphoreticular lesions, fingernail detachment, and gingival effects, but no acne and alopecia. A NOEL for the general toxicity of Aroclor 1242 of 0.04 mg/kg body weight per day was established in Rhesus monkeys. Relatively mild effects were shown in suckling Rhesus monkeys, exposed to a much higher dose of Aroclor 1248 of 35 mg/kg body weight per day. Effects in the liver have been best investigated in rats and include hypertrophy, fatty degeneration, proliferation of the endoplasmic reticulum, porphyria, adenofibrosis, bile-duct hyperplasia, cysts, and preneoplastic and neoplastic changes. In studies on rats and mice, individual PCB congeners caused effects in the liver, spleen, and thymus, the planar congeners being most toxic. In monkeys, planar congeners, at doses of 1–3 mg/kg diet, induced effects similar in character and severity to those produced by Aroclor 1242, at a dose of 100 mg/kg diet, and Aroclor 1248, at a dose of 25 mg/kg diet.

Following dermal exposure of rabbits and mice, PCB mixtures and some congeners caused effects on the skin and liver, similar to those found after oral exposure. In rabbits, thymic atrophy, a reduction of germinal centres of the lymph nodes, and leukopenia were also observed.

1.1.10 Reproduction, embryotoxicity, and teratogenicity

1.1.10.1 Reproduction and embryotoxicity

Comprehensive reproduction and teratogenicity studies have not been conducted. In a 2-generation reproduction study on rats, a NOEL of 0.32 mg/kg body weight, based on reproductive parameters (Aroclor 1254) and a NOEL of 7.5 mg/kg body weight (Aroclor 1260) were established. However, the lowest tested dose of 0.06 mg/kg body weight resulted in increased relative liver weights in weanlings.

In Rhesus monkeys exposed to Aroclor 1016, a NOEL of 0.03 mg/kg body weight was established, on the basis of reproductive parameters. However, at this level, decreased birth weight was observed and the lowest dose tested, of 0.01 mg/kg body weight, resulted in skin hyperpigmentation.

For Aroclor 1248 (containing PCDFs), a NOEL of 0.09 mg/kg body weight was established in Rhesus monkeys, 1 year after exposure ceased.

1.1.10.2 Teratogenicity

Available studies on rats and monkeys did not indicate any teratogenic effects, when animals were dosed orally during organogenesis. A NOEL of 50 mg/kg body weight for Aroclor 1254 was demonstrated in rats with regard to pup weight, and a LOEL of 2.5 mg/kg body weight, on the basis of fetotoxicity (lesion in thyroid follicular cells) could be assumed.

In teratogenicity tests with individual congeners on mice, rats, and Rhesus monkeys, no NOEL was demonstrated. In Rhesus monkeys a dose of 0.07 mg/kg body weight resulted in maternal toxic effects (3,4,3',4'-tetrachlorobiphenyl).

1.1.11 Mutagenicity

PCB mixtures did not cause mutation or chromosomal damage in a variety of test systems. Chromosome breakage was induced in human lymphocytes *in vitro* by 3,4,3',4'-tetrachlorobiphenyl. High concentrations of PCB mixtures may cause primary DNA damage, as evidenced by DNA single strand breaks in alkaline elution assays.

1.1.12 Carcinogenicity

The interpretation of the available animal data involving commercial PCB mixtures is often complicated by lack of information concerning the presence, or contribution, of chlorinated dibenzofuran impurities as well as variations in congener composition.

A number of long-term carcinogenicity studies have been carried out on mice and rats. The PCB mixtures used were Kanechlors 300, 400, and 500, Aroclors 1254 and 1260, and Clophens A30 and A60. The Clophens were reported to be free of PCDFs, but no data were provided on the purity of the other PCB mixtures.

A significant increase in hepatocellular adenomas and/or carcinomas was observed in mice fed a diet containing Kanechlor 500 and Aroclor 1254 at dose levels of approximately 15–25 mg/kg body weight. No neoplasms could be detected in mice treated with Kanechlors 300 and 400.

In rats, an increase in hepatocellular adenomas and/or carcinomas was noted in studies on Aroclors 1254 and 1260, and Clophen A30, with an exposure period of more than one year. The increase in the incidence of tumour-bearing animals in these studies was not considered to be statistically significant, however, it was in the case of 2 other studies. An increase in the incidence of hepatocellular (trabecular) carcinomas and adenocarcinomas was demonstrated with Aroclor 1260 and Clophen A60 administered at a dose level of approximately 5 mg/kg body weight.

The liver tumours concerned were considered to be non-aggressive (benign or of low malignancy, no metastasis) and not life shortening. Adenofibrosis, a preneoplastic lesion and/or neoplastic nodules in the liver were reported in some of the studies. In one test with Aroclor 1254, a dose-related increase in intestinal metaplasia and

adenocarcinomas of the glandular stomach was demonstrated in the rat.

There is a substantial body of evidence to support the enhancing effects of PCBs on liver carcinogenesis in rodents pretreated with hepatocarcinogens. There is weak evidence for the initiating activity of PCB-mixtures in rodents. From the genotoxicity studies reported, it can be concluded that PCB-mixtures can be regarded as non-genotoxic. These results imply that the association of liver tumours with the administration of PCBs in rodents is attributable to some epigenetic mechanisms involving enforcement of cell proliferation in the liver and other manifestations of liver toxicity, hence a threshold approach can be followed in the evaluation of PCB toxicity. The possibility that PCBs might enhance carcinogenesis in tissues other than the liver, in animals pre-exposed to various tissue-specific carcinogens, needs to be addressed. The anticarcinogenic activity of PCBs shown in some studies, where PCBs were given to animals during, and prior to, the administration of carcinogens, may be related to the microsomal, enzyme-inducing properties of PCBs resulting in an increase in detoxification.

Overall, there is reason to exercise caution in extrapolating the available animal data on the carcinogenic potential of PCBs to humans.

1.1.13 Special studies

Lesions induced after exposure to PCB mixtures or individual congeners concern the liver, skin, immune system, reproductive system, oedema and disturbances of the gastrointestinal tract, and thyroid gland.

PCBs are able to induce various enzymes in the liver. This has been demonstrated, in rats, mice, guinea-pigs, rabbits, dogs, and monkeys, for Aroclors 1248, 1254, 1260, and Kanechlor 400 (induction of cytochrome P450 and P448). The inducing ability increases with the chlorine content in the molecule. It is also dependent on the congener composition, congeners with chlorine in the *para*- and *meta*- position inducing the P450 enzyme. For AHH induction, the position of the chlorine seems to be more important than the degree of chlorination. Congeners with both *para*- and at least two *meta*- positions substituted

by chlorine, are the most potent inducers of AHH. Distinct inter-species variations have been demonstrated. The lowest NOEL (0.025 mg/kg body weight) was found for Aroclor 1260 in Osborn-Mendel rats.

Effects on the endocrine system are seen as alterations in hormonal receptor binding and in steroid hormone balance. Direct and indirect evidence for a weak estrogenic activity was observed for various Aroclors. Decreased levels of gonadal hormones and increased relative testes weight were found in rats exposed to 75 mg Aroclor 1242/kg diet for 36 weeks. Decreased plasma corticosteroid levels without increased adrenal weight, was found in female mice exposed to Aroclor 1254 (25 mg/kg diet) for 3 weeks. Increased adrenal weight was found in another strain given a diet containing 200 mg/kg for 2 weeks.

PCB mixtures have shown an immunosuppressive effect in various animal species, monkeys and rabbits being the most sensitive. The lowest NOEL in monkeys was 0.1 mg/kg body weight, and, in rabbits, 0.18 mg/kg body weight.

Depressed motor-activity was seen in mice administered a single oral dose of 500 mg Aroclor 1254/kg body weight. This was probably in relation to inhibition of the uptake and release of neurotransmitters.

PCB mixtures were found to decrease the levels of vitamins A and B_1 in the blood and liver of rats. Decreased levels of vitamins A, B_1, B_2, and B_6 were seen in rats and mice exposed to PCB mixtures.

1.1.14 Factors modifying toxicity, mode of action

Commercial PCBs show a spectrum of toxic responses, partly resembling that of PCDDs and PCDFs. In addition, the analogous structure-activity relations of PCB congeners, with respect to most of their toxic responses and to their potency in inducing P448-dependent AHH, indicate that PCB congeners that are approximate stereoisomers of 2,3,7,8,-TCDD are the most active. These findings suggest a common mechanism of action based on the affinity of these compounds for the cytosolic AH-receptor protein. Toxic equivalence factors relating to 2,3,7,8-TCDD have been proposed for these coplanar PCB congeners. The nature of the likely interactions

between PCBs, PCDFs, and PCDDs has not been adequately investigated. As PCBs can stimulate microsomal enzyme activity, they can influence the action of other chemicals that undergo microsomal metabolism. Other so-called, non-planar PCB congeners may cause other more subtle toxicities. In addition, PCB congeners, especially the lower chlorinated ones, may be metabolized through arene oxide intermediates and methylsulfonyl metabolites.

1.1.15 Effects on humans

The toxicological evaluation of PCBs presents many problems. PCBs usually occur as mixtures of many congeners, and many of the data on the toxicity of the PCBs are based on the testing of these mixtures. Some components of the mixtures are more easily degraded in the environment than others. Thus, the general population may be exposed to mixtures that are different from those to which workers, working with PCBs, are exposed.

The general population is exposed to PCBs mainly through contaminated food (aquatic organisms, meat and dairy products). The daily intake of PCBs is of the order of some micrograms per person for most of the industrialized countries. Such exposures have not been associated with disease. The infant is exposed to PCBs through its mother's milk. Daily intake of PCBs may be some micrograms/kg body weight.

There are great difficulties in assessing human health effects separately for PCBs, PCDFs, or PCDDs, since, quite frequently, PCB mixtures contain PCDFs. The presence of PCDDs has also been seen occasionally, in accidents with certain mixtures. Commercial PCBs have been shown to be contaminated with PCDFs and, therefore, in many cases, it is not clear which effects are attributable to the PCBs themselves and which to the much more toxic PCDFs. Thus, much of the data that can be retrieved from large episodes of intoxication in humans, e.g., the Yusho-, Yu-Cheng, and other intoxications, probably reflect effects of exposure to both PCDFs and PCBs.

The signs of intoxication in Yusho and Yu-Cheng patients were hypersecretion of the Meibomian glands of the eyes, swelling of the eyelids and pigmentation of the nails and mucous membranes,

occasionally associated with fatigue, nausea, and vomiting. This was usually followed by hyperkeratosis and darkening of the skin with follicular enlargement and acneiform eruptions. Furthermore, oedema of the arms and legs, liver enlargement and liver disorders, central nervous disturbances, respiratory problems e.g., bronchitis-like disturbances, and changes in the immune status of the patients were also observed. In children of Yusho- and Yu-Cheng patients, diminished growth, dark pigmentation of the skin and mucous membranes, gingival hyperplasia, xenophthalmic oedematous eyes, dentition at birth, abnormal calcification of the skull, rocker bottom heel, and a high incidence of low birth weight were observed. Whether or not a correlation existed between the exposure and the occurrence of malignant neoplasms in these patients could not be definitely concluded, because the number of deaths was too small. However, a statistically significant increase was observed in male patients, with regard to mortality from all neoplasms, liver and lung cancer.

Under occupational conditions, skin rashes occurred a few hours after acute exposure. Furthermore, itching, burning sensations, irritation of the conjunctivae, pigmentation the fingers and nails, and chloracne were found after exposure to high PCB concentrations. Chloracne is one of the most prevalent findings among PCB-exposed workers. Besides these dermal signs of intoxication, different authors have found liver disturbances, immunosuppressive changes, transient irritation of the mucous membranes of the respiratory tract, neurological and unspecific psychological or psychosomatic effects, such as headache, dizziness, depression, sleep and memory disturbances, nervousness, fatigue, and impotence. The overall conclusion is that continous occupational exposure to high PCB and PCDF concentrations may result in effects on the skin and liver.

Two large mortality studies were carried out on cohorts of workers. When exposure to Aroclor 1254, 1242, and 1016 occurred, increased mortality from cancer of the liver and gall bladder was observed in one study and from neoplasms and cancer of the gastrointestinal tract in the other. None of the available epidemiological studies provide conclusive evidence of an association between PCB exposure and increased cancer mortality, because of the small number of deaths in

exposed populations, the lack of dose-response relationships, and the problem of contaminants in the PCB mixtures.

1.2 Conclusions

1.2.1 Distribution

Because of their physical and chemical properties, PCBs have become dispersed globally, throughout the environment.

PCBs are almost universally present in organisms in the environment and are readily bioaccumulated. Biomagnification in food chains has also been demonstrated.

Higher chlorinated congeners accumulate preferentially.

1.2.2 Effects on experimental animals

The results of animal studies suggest that PCBs are immunosuppressive, as assessed by alterations in gross measures of immune function (spleen weight, thymus weight, and lymphocyte counts). NOELs in monkeys have been estimated at 100 μg/kg for Aroclor 1248 and < 100 μg/kg body weight for Aroclor 1254. Immunosuppression appears to be a congener-specific effect.

Reproductive toxicity is, in general, only seen at doses producing systemic toxicity in the mother. Neonates feeding on contaminated mother's milk (in monkeys and other animal species, used as models) appear to be particularly sensitive to PCBs and show reduced growth with other toxic symptoms. The NOEL for Aroclor 1016 on reproductive effects is 30 μg/kg body weight for monkeys; no NOEL could be established for the reproductive effects of Aroclor 1248.

PCBs are not genotoxic and there is inconclusive evidence for action as tumour initiators. PCBs do act as tumour promoters. It can be concluded that the toxicity of PCB mixtures can be evaluated on a threshold basis.

1.2.3 Effects on humans

Exposure of the general population to PCBs will be principally through food items. Babies will be exposed through the mother's milk.

Two large episodes of intoxication in humans have occurred in Japan (Yusho) and Province of Taiwan (Yu-Cheng). The main symptoms in Yusho and Yu-Cheng patients have frequently been attributed to contaminants in the PCB mixtures, specifically, to PCDFs. The Task Group concluded that symptoms may have been caused by the combined exposure to PCBs and PCDFs. However, some of the symptoms, principally, the chronic respiratory effects, may have been caused specifically by the methylsulfone metabolites of certain PCB congeners.

1.2.4 Effects on the environment

While there have been reports of effects on local populations of birds, the most important effect of PCBs on organisms in the environment has been reproductive failure in sea mammals. This has been observed principally in semi-enclosed seas and has led to population declines, locally. The prediction that residues of PCBs in the environment will gradually be redistributed towards the marine environment indicates an increasing hazard for sea mammals in the future.

1.3 Recommendations

- International agreement on analytical procedures to improve the comparability of results of monitoring programmes is recommended. Methodology for congener-specific analysis should continue to be developed, though the value of analysis based on mixtures is recognized.
- In order to ensure the reliability of analytical data, inter-laboratory quality control studies are strongly recommended. It is also recommended that an international network of technical support and supervision is established, to allow developing countries to participate in monitoring.

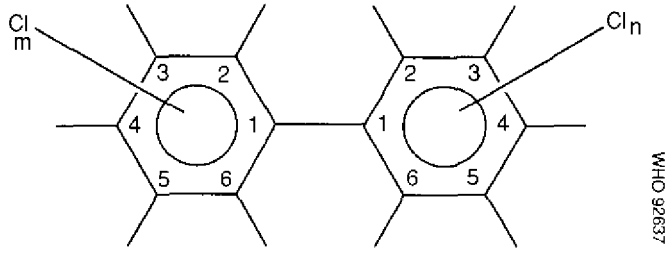
- Long-term studies using specific congeners, and studies on the mechanism of action of constituents of PCBs mixtures, with special regard to tumour promotion, are recommended to improve the precision of the risk assessment of PCBs.
- Epidemiological studies to better assess the risk to neonates are required, since new-born infants appear to be the most vulnerable sector of the general population, because of high exposure through milk.
- Sensitive and specific biomarkers for some of the more subtle types of PCB toxicity (such as reproductive, immunological, and neural toxicity) should be developed for use in future epidemiological studies.
- Disposal of PCBs should be carried out by incineration in properly designed and run facilities that can guarantee the constant high temperatures (above 1000 °C), residence time, and turbulence necessary to ensure complete breakdown.
- Methods to remove PCBs already contained in landfills should be investigated.
- Monitoring of PCBs in the environment and in wildlife should be encouraged globally, to follow the expected redistribution of residues already present.
- Marine mammals are susceptible to reproductive failure as a result of PCB contamination. Studies on the population size and reproductive success of cetaceans should be encouraged, together with further research to establish which congeners are responsible for the effects.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

2.1.1 Chemical formula and structure

The chlorination of biphenyl can lead to the replacement of 1–10 hydrogen atoms by chlorine; the conventional numbering of substituent positions is shown in the diagram:



The chemical formula can be presented as $C_{12}H_{10-n}Cl_n$, where n, the number of chlorine atoms in the molecule, can range from 1 to 10.

2.1.2 Relative molecular mass

The relative molecular mass depends on the degree of substitution.

Monochlorobiphenyl has a relative molecular mass of 188, while completely chlorinated biphenyl ($C_{12}Cl_{10}$) has a relative molecular mass of 494 (US EPA, 1980).

2.1.3 Common name

Common name;	polychlorinated biphenyls (PCBs)
CAS Registry number:	1336-36-3
RTECS Registry number:	TQ 1350000

2.1.4 Chemical composition

The PCBs are chlorinated hydrocarbons, manufactured commercially by the progressive chlorination of biphenyl in the presence of a suitable catalyst (e.g., iron chloride). Depending on the reaction conditions, the degree of chlorination can vary between 21 and 68% (w/w). The yield is always a mixture of different isomers and congeners. Thus, a total of 209 theoretically different chemical components exist, but only about 130 of these are likely to occur in commercial products or mixtures of such compounds (Safe, 1990).

Seventy-eight out of the possible 209 PCB congeners can exist as rotational isomers that are enantiomeric to each other. Nineteen PCBs, of which 9 are components of commercial PCB formulations, have been predicted to be stable at room temperature (Kaiser, 1974).

Püttmann et al. (1988) separated the atropisomers of 2,3,4,6,2',4'-hexachlorobiphenyl and demonstrated that they possess different biological effects with regard to *in vivo* enzyme induction (aminopyrine *N*-demethylase, aldrin epoxidase, cytochrome P-450 content, morphine UDP-glucuronosyl transferase) in Sprague-Dawley rats.

Unlike the dioxins or dibenzofurans, the phenyl rings of a PCB are not constrained through ring fusions and have relatively unconstrained rotational freedom. Chlorines at the *ortho* (2,2', 6,6') positions introduce constraints on rotational freedom that can hinder coplanarity of the phenyl rings. X-ray crystallographic studies (McKinney & Singh, 1981) indicate that the preferred conformation for all PCBs, including those without *ortho*-substituents, is noncoplanar. The proportion of molecules of a particular congener assuming a coplanar configuration becomes increasingly small as the degree of *ortho*-substitution and the energetic cost of conforming increases. However, PCBs without *ortho*-substitution are often referred to in the biological literature as the planar (or coplanar) PCBs and all others as the nonplanar (or noncoplanar) PCBs. This terminology, though somewhat misleading, is also used throughout this publication for convenience and ease of referring back to the published literature. It is widely recognized that certain biological activities of the PCBs vary, at least quantitatively, with stereochemical differences in the congeners.

Individual manufacturers have their own system of identification for their products. In the Aroclor series, a 4-digit code is used; biphenyls are generally indicated by 12 in the first 2 positions, while the last 2 numbers indicate the percentage by weight of chlorine in the mixture; thus, Aroclor 1260 is a polychlorinated-biphenyl mixture containing 60% of chlorine. An exception to this generalization is Aroclor 1016, which is a distillation product of Aroclor 1242 containing only 1% of components with 5 or more chlorine atoms (Burse et al., 1974). With other commercial products, the codes may indicate the approximate mean number of chlorine atoms in the components; thus Clophen A60, Phenochlor DP6, and Kanechlor 600 are biphenyls with an average of about 6 chlorine atoms per molecule (equivalent to 59% chlorine by weight).

Ballschmiter & Zell (1980) proposed a numbering system for the PCB congeners, that was later adopted by the International Union of Pure and Applied Chemists (IUPAC). The number, structure, and isomer group are given for each congener in the paper of McFarland & Clarke (1989) (see Appendix A). In the literature, the structure of a congener is given in 2 ways; for example 2,2',5,5' or 2,5,2',5' (No 52).

Individual PCBs have been synthesized for use as reference samples in the identification of gas-liquid chromatographic peaks, for toxicological investigations, and for studying their metabolic fate in living organisms, for which purpose they have been prepared labelled with carbon-14 (Hutzinger et al., 1971; Jensen & Sundström, 1974a; Sundström & Wachtmeister, 1975).

The proportions of PCBs with 1–9 chlorine substituents in the Aroclors are shown in Table 1.

It is apparent, from gas chromatographic analyses of commercial products, that PCB mixtures differ with respect to the individual congeners present and their relative concentrations (Jensen & Sundström, 1974a; Albro & Parker, 1979; Ballschmitter & Zell, 1980; Albro et al., 1981; Mullin et al., 1984; Safe et al., 1985a; Alford-Stevens, 1986).

There have been several investigations to identify individual PCBs in commercial products. The components of the Aroclors were separated by column and gas-liquid chromatography and many of the

Table 1. Approximate percentages (w/v) of Aroclors with different degrees of chlorination[a]

Number of chlorine atoms in molecule	Chlorine weight (%)	Aroclor						
		1221	1232	1016	1242	1248	1254	1260
0	0	10	-	-				
1	18.8	50	26	2	3			
2	31.8	35	29	19	13	2		
3	41.3	4	24	57	28	18		
4	48.6	1	15	22	30	40	11	
5	54.4				22	36	49	12
6	59.0				4	4	34	38
7	62.8						6	41
8	66.0							8
9	68.8							1

[a] From: WHO/EURO (1987).

peaks characterized by high-resolution mass spectrometry and nuclear magnetic resonance, and also by comparison with synthesized PCBs (Table 2) (see also DFG, 1988).

Jensen & Sundström (1974a) recognized that conventional gas-liquid chromatography was not suitable for separating all the components, so they devised a preliminary fractionation on a charcoal column, which separated the component PCBs according to the number of chlorines in the 2,6,2' or 6' positions in the molecule (*o*-chlorines). They compared the gas-liquid chromatographic peaks with those of 90 synthesized PCBs, and were able to characterize and quantify 60 components of Clophens A50 and A60.

2.1.5 Technical product

Major trade names

The PCBs manufactured commercially are known by a variety of trade names including: Aroclor, Pyranol, Pyroclor (USA), Phenochlor, Pyralene (France), Clophen, Elaol (Germany), Kanechlor, Santotherm (Japan), Fenchlor, Apirolio (Italy), and Sovol (USSR). Table 3 contains the most common trade names for

commercial products, some of which are not in use any more (Brinkman & De Kok, 1980; WHO/EURO, 1987).

2.1.6 Purity and impurities

Commercial PCBs are not sold according to a composition specification, but according to their physical properties. The composition of Aroclors and Clophens has been presented in recent papers; the composition of 5 Aroclors is shown in Tables 1 and 2. In Table 1, the approximate composition is expressed as the percentage of chlorine weight, and, in Table 2, the composition of the chlorine substitution pattern is expressed in mol % (Albro & Parker, 1979; Albro et al., 1981; Jones, 1988). The composition of the chlorine substitution pattern for 4 Clophens is described by Duinker & Hillebrand (1983) and Jones (1988). It should be kept in mind that nothing can be said about the variations in the different lots of these mixtures. Impurities known to be present in commercial PCBs are chlorinated dibenzofurans and chlorinated naphthalenes (Vos et al., 1970; Bowes et al., 1975; Albro & Parker, 1979; Albro et al., 1981; Duinker & Hillebrand, 1983; Rappe et al., 1985a). The concentrations of PCDFs in Aroclor, Clophen, Phenoclor, and Kanechlor are summarized in Tables 4 and 5.

Table 2. PCB compositions of aroclors in mol %[a]

IUPAC No.	Chlorine substitution pattern	Aroclor 1242	1016	1248	1254	1260
	BP	0.01	0.50			
1	2	0.68	0.80			
2	3	0.04	0.10			
3	4	0.22	1.00			
4	2.2'	3.99	4.36	0.25		
6	2.3'	1.24	1.37	0.69	0.07	
7	2.4	1.04	1.16			
8	2.4'	8.97	10.30	0.18		
9	2.5	0.31	0.34	trace		
10	2.6ŦŦ 0.13	0.20				
12	3.4	0.09	0.11			
13	3.4'	0.12	0.12			

Table 2 (*continued*)

IUPAC No.	Chlorine substitution pattern	Aroclor 1242	1016	1248	1254	1260
14	3.5	0.35	0.37			
15	4.4′	0.99	1.07			
16	2.3.2′	3.25	3.50	0.84		
17	2.4.2′	2.92	3.14	0.19		
18	2.5.2′	9.36	10.87	9.95	0.07	
19	2.6.2′	0.97	1.08			
20	2.3.3′	3.64	3.99			
22	2.3.4′	2.64	2.80	1.24	trace	trace
25	2.4.3′	1.68	1.79			
26	2.5.3′	0.55	0.62	0.75		
27	2.6.3′	0.54	0.58			
28	2.4.4′	13.30	14.48	trace		
31	2.5.4′	4.53	4.72	9.31	0.72	
32	2.6.4′	2.15	2.31	1.46		
33	3.4.2′	2.83	3.08			
35	3.4.3′	0.66	0.38			
37	3.4.4′	1.62	1.89	1.28	0.20	0.09
39	3.5.4′	1.03	1.08			
40	2.3.2′.3′	0.15	0.18	1.12	0.26	0.04
41	2.3.4.2′	1.67	2.00			
42	2.3.2′.4′			7.05	2.18	0.66
43	2.3.5.2′	0.44	0.47			
44	2.3.2′.5′	1.06	1.14			
45	2.3.6.2′	0.90	1.00	5.73	0.15	
46	2.3.2′.6′	0.31	0.33			
47	2.4.2′4′	1.65	1.8	3.18	0.52	0.88
48	2.4.5.2′	1.33	1.41			
?	2.5.2′.4′	-	-	3.81	1.63	0.44
49	2.4.2′.5′	3.28	3.48			
52	2.5.2′5′	4.08	4.35	8.36	4.36	1.91
53	2.5.2′6′	0.97	1.07	6.30	0.13	
54	2.6.2′6′	0.17	0.19			
55	2.3.4.3′			0.11	0.43	0.12
56	2.3.3′4′	0.60	trace	0.18	0.03	
60	2.3.4.4′	0.21				
66	2.4.3′.4′	0.81	0.14	4.95	2.24	0.22
70	2.5.3′.4′	1.11		6.38	4.75	0.85
71	2.6.3′.4′			0.65		
72	2.5.3′.5′	0.33		2.10	1.01	0.28
74	2.4.5.4′	2.02	1.35	0.25	0.30	0.09

Table 2 (*continued*)

IUPAC No.	Chlorine substitution pattern	Aroclor 1242	1016	1248	1254	1260
75	2.4.6.4'	2.18	2.40			
76	3.4.5.2'	trace		trace	0.18	0.01
77	3.4.3'.4'	0.34		0.47	0.12T0.04	
78	3.4.5.3'	0.52				
79	3.4.3'.5'	0.24	Ttrace	0.23	0.04	
80	3.5.3'.5'T		trace	trace	trace	
81	3.4.5.4'	0.28				
83	2.3.5.2'.3'			trace	0.32	0.09
84	2.3.6.2'.3'	0.38	0.01	0.71	1.72	0.69
85	2.3.4.2'.4'	0.40		0.55	2.15	0.31
?	2.3.4.3'.5'			0.02	0.55	0.14
87	2.3.4.2'.5'	0.09		1.05	3.81	1.10
91	2.3.6.2'.4.'	trace		1.78	5.00	3.22
92	2.3.5.2'5'	0.12	0.20	0.63	0.21	
95	2.3.6.2'.5'	0.53	0.18			
97	2.4.5.2'.3'			0.78	2.59	0.63
98	2.4.6.2'.3'	0.13	0.04			
99	2.4.5.2'4'	0.55		2.52	6.10	0.82
101	2.4.5.2'.5'	0.27		1.50	6.98	5.04
102	2.4.5.2'.6'			trace	trace	trace
105	2.3.4.3'.4'	0.25				
106	2.3.4.5.3'				0.40	0.06
108	2.3.4.3'.5'	0.46	0.16			
110	2.3.6.3'.4'			1.69	8.51	3.57
113	2.3.6.3'.5'	0.39	0.01	3.10	trace	0.01
114	2.3.4.5.4'				0.25	0.03
118	2.4.5.3'.4'				8.09	2.00
120	2.4.5.3'.5'	0.31		trace	0.15	3.01
121	2.4.6.3'.5'	0.92		4.32	3.51	0.57
123	3.4.5.2'.4'	0.36				
?	3.4.5.2'.3'			trace	0.76	1.88
126	3.4.5.3'.4'	0.03			0.16	1.59
127	3.4.5.3'.5'	0.05				
128	2.3.4.2'.3'.4'				1.31	0.47
131	2.3.4.6.2'.3'				0.14	0.01
132	2.3.4.2'.3'.6'			trace	2.00	2.77
133	2.3.5.2'.3'.5'			1.13	0.03	0.06
134	2.3.5.6.2'.3'			0.11	0.38	1.01
135	2.3.5.2'.3'.6'		T	0.20	0.29	
136	2.3.6.2'.3'.6'			0.20	0.34	1.12

Table 2 (*continued*)

IUPAC No.	Chlorine substitution pattern	Aroclor 1242	1016	1248	1254	1260
138	2.3.4.2'.4'5'	0.08		0.19	4.17	5.01
143	2.3.4.5.2'.6'	0.07				
148	2.3.5.2'.4'.6'			0.12	0.07	0.06R
149	2.4.5.2'.3'.6'			0.77	3.59	9.52
151	2.3.5.6.2'.5'			trace	0.33	0.06
153	2.4.5.2'.4'.5'	0.02		0.13	3.32	8.22
154	2.4.5.4'.6'				0.14	
156	2.3.4.5.3'.4'					0.41
157	2.3.4.3'.4'.5'				0.18	0.03
158	2.3.4.6.3'.4'				0.46	0.18
159	2.4.5.2'.3'.5'				0.75	1.48
163	2.3.5.6.3'.4'					trace
167	2.4.5.3'.4'5'				0.21	0.17
168	2.4.6.3'.4'.5'			0.56	4.23	0.59
170	2.3.4.5.2'.3'.4'				0.43	0.62
171	2.3.4.6.2'.3'.4'		T	0.30	4.31	
174	2.3.4.5.2'.3'.6'				trace	0.09
176	2.3.4.6.2'.3'.6'			0.09	trace	0.57
177	2.3.5.6.2'.3'.4'					trace
179	2.3.5.6.2'.3'6'				0.56	0.83
180	2.3.4.5.2'.4'.5'				0.76	7.20
181	2.3.4.5.6.2'.4'				0.28	2.72
182	2.3.4.5.2'.4'6'				trace	0.47
183	2.3.4.6.2'.4'.5'				1.16	2.58
185	2.3.4.5.6.2'.5'				1.11	5.65
186	2.3.4.5.6.2'.6'			trace	trace	0.37
187	2.3.5.6.2'.4'.5'				0.48	1.12
189	2.3.4.5.3'.4'.5'					0.13
190	2.3.4.5.6.3'.4'					0.02
192	2.3.4.5.6.3'.5'				0.20	0.97
193	2.3.5.6.3'.4'.5'				2.30	
194	2.3.4.5.2'.3'.4'.5'					2.21
195	2.3.4.5.6.2'.3'.4'					trace
196	2.3.4.5.2'.3'.4'6'					0.79
197	2.3.4.6.2'.3'.4'.6'.					0.30
198	2.3.4.5.6.2'.3'.5'				1.00	0.15
199	2.3.4.5.6.2'.3'.6'					0.38
200	2.3.4.6.2'.3'.5'.6'.				trace	0.15
202	2.3.5.6.2'.3'.5'6'				trace	0.31
203	2.3.4.5.6.2'.4'.5'					0.08

Table 2 (*continued*)

IUPAC No.	Chlorine substitution pattern	Aroclor 1242	1016	1248	1254	1260
204	2.3.4.5.6.2'.4'.6'				trace	0.13
205	2.3.4.5.6.3'.4'5'					0.01
206	2.3.4.5.6.2'.3'.4'5'					0.51
207	2.3.4.5.6.2'3'.4'6'					1.15
208T2	.3.4.5.6.2'.3'.5'.6'					1.64
?	2.3.4.5.6.2'.3'.5'.6'					0.18

[a] From: Albro & Parker (1979); Albro et al. (1981).

Table 3. The trade marks of PCB products and mixtures containing PCBs[a]

Aceclor (t)	Disconon (c)	PCBs
Apirolio (t,c)	Dk (t,c)	Phenoclor (t,c)
Aroclor (t,c)	Duconol (c)	Polychlorinated biphenyl
Arubren	Dykanol (t,c)	Polychlorobiphenyl
Asbestol (t,c)	EEC-18	Pydraul [c]
Askarel	Elemex (t,c)	Pyralene (t,c)
Bakola 131 (t,c)	Eucarel	Pyranol (t,c)
Biclor (c)	Fenchlor (t,c)	Pyroclor (t)
Chlorextol (t)	Hivar (c)	Saf-T-Kuhl (t,c)
Chlorinated Biphenyl	Hydol (t,c)	Santotherm FR [b]
Chlorinated Diphenyl	Inclor	Santovac 1 and 2
Chlorinol	Inerteen (t,c)	Siclonyl (c)
Chlorobiphenyl	Kanechlor (t,c)	Solvol (t,c)
Clophen (t,c)	Kennechlor	Sovol
Clorphen (t)	Montar	Therminol FR [b]
Delor	Nepolin	
Diaclor (t,c)	No-Flamol (t,c)	
Dialor (c)	PCB	

[a] From: WHO/EURO (1987).

[b] Previous products (FR-series) used as pressure oil contained PCBs, but current products are a different series and do not contain PCBs.

[c] Previous products (A-serie) e.g., PYDRAUL A-200 contained PCBs, but current commercial products are B, C, or D-series and do not contain any chlorinated compounds.

(t) Used in transformers.
(c) Used in capacitors.

Table 4. Concentrations of chlorinated dibenzofurans [a] in Aroclor, Clophen, and Phenoclor [b]

PCB	4-Cl	5-Cl	6-Cl	Total
Aroclor 1248 (1969)	0.5 (25)	1.2 (60)	0.3 (15)	2.0
Aroclor 1254 (1969)	0.1 (6)	0.2 (12)	1.4 (82)	1.7
Aroclor 1254 (1970)	0.2 (13)	0.4 (27)	0.9 (60)	1.5
Aroclor 1260 (1969)	0.1 (10)	0.4 (40)	0.5 (50)	1.0
Aroclor 1260 (lot AK3)	0.2 (25)	0.3 (38)	0.3 (38)	0.8
Aroclor 1016 (1972)	ND	ND	ND	
Clophen A-60	1.4 (17)	5.0 (59)	2.2 (26)	8.4
Phenoclor DP-6	0.7 (5)	10.0 (74)	2.9 (21)	13.6

[a] Expressed as mg PCB/kg. Values in parentheses represent quantity as percentage of total dibenzofurans.

[b] From: Bowes et al. (1975).
ND = not detected (0.001 mg/kg).

Table 5. Concentrations of chlorinated dibenzofurans in Kanechlors [a]

Kanechlor	Chlorodibenzofurans						Concentration (mg/kg)	
	Di-	Tri-	Tetra-	Penta-	Hexa-	Hepta-	b	c
300			+	+			1	1.5
400	+	+	+	+			18	17
500		+		+	+	+	4	2.5
600			+	+	+	+	5	3

[a] From: Nagayama et al. (1975).

[b] Calculated from peak heights.

[c] Calculated by perchlorination method.

Different authors have examined the presence of PCDFs in PCB mixtures. Bowes et al. (1975) found 0.8–2.0 mg/kg in samples of Aroclor 1248 and 1260, but none in Aroclor 1016, 8.4 mg/kg in Clophen A60, and 13.6 mg/kg in Phenoclor DP-6. Rappe et al. (1985a) and Bentley (1983) found levels of PCDFs up to 40 mg/kg in a number of commercial PCBs. Recently, Wakimoto et al. (1988)

found a number of extremely toxic PCDFs in several Japanese and American commercial PCB preparations. These isomer-specific analyses revealed the 2,3,7,8-tetra-, 1,2,4,7,8-penta-, 1,2,3,7,8-penta-, 2,3,4,7,8-penta-, and 1,2,3,6,7,8-hexachlorodibenzofurans. The concentrations in unused Kanechlor 300, 400, 500, and 600, were 7.5, 26, 7.2, and 5.4 mg/kg, respectively, and those in Aroclors 1242, 1248, 1254, and 1260, were 0.6, 3.7, 4.2, and 7.5 mg/kg, respectively. Brown et al. (1988) found that the electrical use of PCB dielectric fluids in transformers and capacitors did not increase the PCDFs content significantly.

More data about the occurrence of PCDFs in the different commercial PCB mixtures are summarized in WHO/EURO (1987).

There are no reports on the presence of PCDDs in commercial mixtures (Bowes et al., 1975). Wakimoto et al. (1988) could not find PCDDs in the above samples of Kanechlors and Aroclors with a detection limit of < 2 μg/kg.

2.2 Physical and chemical properties

Individual pure PCB congeners are colourless, often crystalline compounds, but commercial PCBs are mixtures of these congeners with a clear, light yellow or dark colour. They do not crystallize at low temperatures, but turn into solid resins. Because of the chlorine atoms in the molecule, their density is rather high. PCBs are, in practice, fire resistant with rather high flash-points (170–380 °C). They form vapours heavier than air, but do not form any explosive mixtures with air. They possess very low electrical conductivity and an extremely high resistance to thermal breakdown, and it is on the basis of these properties that they are used as cooling liquids in electrical equipment (US EPA, 1980; WHO/EURO, 1987; DFG, 1988).

PCBs have a high degree of chemical stability under normal conditions. They are very resistant to a range of different oxidants and other chemicals. According to laboratory tests, they stay chemically unchanged, even in the presence of oxygen or some active metals at high temperatures (up to 170 °C) and for protracted periods (WHO/EURO, 1987).

PCBs are practically insoluble in water, whereas they dissolve easily in hydrocarbons, fats, and other organic compounds and they are readily absorbed by fatty tissues (WHO/EURO, 1987).

Some physical and chemical data for a number of Aroclors are presented in Table 6.

Foreman & Bidleman (1985) estimated the liquid phase vapour pressures, at 25 °C, of 134 PCB congeners found in 5 Aroclor fluids, using a capillary gas chromatographic method in conjunction with published retention indices of PCBs.

Burkhard et al. (1985) predicted Henry's Law Constants from the ratio of the liquid (or subcooled liquid) vapour pressure and aqueous solubility for PCB congeners. The predicted values were in fair agreement with experimental values and the error for these constants was estimated to be a factor of 5 in the temperature range of 0–40 °C. For the PCB congeners, Henry's Law Constants were independent of the relative molecular mass and increased approximately an order of magnitude with a 25 °C increase in temperature.

Aqueous solubility is considered an essential parameter for predicting the fate and transport of organic chemicals in the environment. As already stated, some physical and chemical data are given for 6 Aroclor mixtures in Table 6 (Alford-Stevens, 1986). However, during the last 5 years, much more information on aqueous solubility, melting points, entropies of melting, Henry's law constants, and vapour pressures has become available. This information concerns not only PCB mixtures but also individual congeners.

Opperhuizen et al. (1988) studied the aqueous solubilities of 45 chlorinated biphenyls and the relationships between activity coefficient and chemical structure parameters (total surface area (TSA) and total molecular volume (TMV)) of hydrophobic chemicals, to understand the nature of hydrophobicity. The aqueous solubilities of PCBs showed a linear relationship between logarithms of aqueous activity coefficients or TSA and TMV.

Dickhut et al. (1986) studied the solubilities of 6 higher chlorinated biphenyl congeners at different temperatures and found that the solubility increased exponentially with temperature in the range of 0.4–80 °C. From the temperature dependence of solubility,

Table 6. Physical and chemical properties of a number of Aroclors[a]

Substance Aroclor	Water solubility (mg/litre) 25 °C	Vapour pressure (torr) 25 °C	Density (g/cm^3) 25 °C	Appearance	Henry's Law constant ($atm\text{-}m^3/mol$ at 25 °C)[b]	Refractive index	Boiling point (distillation range) (750 torr, °C)
1016	0.42	4.0×10^{-4}	1.33	Clear, mobile oil	2.9×10^{-4}	1.6215-1.6235 (at 25 °C)	325-356
1221	0.59[c]	6.7×10^{-3}	1.15	Clear, mobile oil	3.5×10^{-3}	1.617-1.618 (at 20 °C)	275-320
1232	0.45	4.1×10^{-3}	1.24	Clear, mobile oil	unknown	unknown	290-325
1242	0.24	4.1×10^{-3}	1.35	Clear, mobile oil	5.2×10^{-4}	1.627-1.629 (at 20 °C)	325-366
1248	0.054	4.9×10^{-4}	1.41	Clear, mobile oil	2.8×10^{-3}	unknown	340-375
1254	0.021	7.7×10^{-5}	1.50	Light yellow viscous oil	2.0×10^{-3}	1.6375-1.6415 (at 25 °C)	365-390
1260	0.0027	4.0×10^{-5}	1.58	Light yellow sticky resin	4.6×10^{-3}	unknown	385-420

[a] From: IARC (1978); WHO/EURO (1987); ATSDR (1989).

[b] These Henry's Law Constants were estimated by dividing the vapour pressure by the water solubility. The first water solubility given in this table was used for the calculation. The resulting estimated Henry's law constant is only an average for the entire mixture; the individual chlorobiphenyl isomers may vary significantly from the average. Burkhard et al. (1985) estimated the following Henry's Law Constants ($atm\text{-}m^3/mol$) for various Aroclors at 25 °C: 1221 (2.28×10^{-4}), 1242 (3.43×10^{-4}), 1248 (4.4×10^{-4}), 1254 (2.83×10^{-4}), 1260 (4.15×10^{-4}).

[c] At 24 °C.

enthalpies of solution were calculated. The same results were found by Doucette & Andren (1988), who determined the aqueous solubilities of a few PCBs, using a generator-column technique, at temperatures of 4.0, 25.0, and 40.0 °C.

The dissolution of extremely hydrophobic chemicals that may be associated with a relatively constant endothermic enthalpy of solution and an endothermic enthalpy of fusion that is proportional to the solute's melting point is discussed by Opperhuizen et al. (1987) and Dickhut et al. (1987).

Dunnivant & Elzerman (1988) estimated the aqueous solubilities and Henry's Law Constants (HLC) for 26 selected PCB congeners for the evaluation of quantitative structure-property relationships (QSPRs). Aqueous solubilities (as solids at 25 °C, column generation technique), determined for the 26 congeners, ranged from 1.08×10^{-5} to 9.69×10^{-10} mol/litre and generally decreased with relative molecular mass. HLCs (25 °C, gas purge technique), determined for 20 congeners, ranged from 0.3×10^{-4} to 8.97×10^{-4} atm.m^3/mol. Measured HLCs were not correlated with relative molecular mass, but increased with the degree of *ortho*-chlorine substitution within a relative molecular mass class.

Vapour pressures calculated from the product of solubility (mol/m^3) and HLC (atm.m^3/mol) data, generally decreased with relative molecular mass and increased with increasing degree of *ortho*-chlorine substitution (Dunnivant & Elzerman, 1988; Hawker, 1989). Westcott et al. (1981) used a semimicro gas saturation method to determine the vapour pressures of 3 PCB isomers and 2 Aroclor mixtures.

Experimental data were tabulated and the relationships between the environmentally relevant physical chemical properties of the PCBs critically reviewed by Shui & Mackay (1986). Aqueous solubility, vapour pressure, Henry's law constant, and octanol-water partition coefficient were discussed and recommended values given for 42 of the 209 congeners; procedures were suggested for estimating the properties of the other congeners.

2.2.1 Log n-octanol/water partition coefficient

The environmental fate of PCBs is governed primarily by the partitioning process. Partitioning processes that are of particular interest with regard to environmental problems include: the octanol/water partition coefficient and the aqueous solubility. The octanol/water partition coefficient is a measure of the hydrophobicity of a substance and, in this respect, it has been used to predict the extent of bioconcentration of organic pollutants in organisms. Miller et al. (1984) studied the octanol/water partition coefficients for 16 PCBs and Hawker & Connell (1988) for 13 PCB congeners, using the generator column method. These partition coefficients were used to confirm a highly significant linear relationship between log K_{ow} and the logarithm of the relative retention time on a nonselective gas chromatographic stationary phase. The total surface areas (TSA) for all the PCB congeners were determined by assuming planar molecules, van der Waal's radii for component atoms, and appropriate values for solvent radius, bond angles, and distances. The TSA was highly significantly correlated with log K_{ow} and the relationship was used to calculate log K_{ow} values for all the PCB congeners. In the report of Hawker & Connell (1988), log K_{ow} values are summarized for all 209 PCB congeners. These log K_{ow} values range from 4.46 to 8.18.

2.2.2 Conversion factors [a]

Aroclor	
1016	1 mg/m^3 = 0.095 ppm
1221	1 mg/m^3 = 0.12 ppm
1232	1 mg/m^3 = 0.105 ppm
1242	1 mg/m^3 = 0.092 ppm
1248	1 mg/m^3 = 0.008 ppm
1254	1 mg/m^3 = 0.075 ppm
1260	1 mg/m^3 = 0.065 ppm

[a] These air conversion factors were calculated by using the average molecular mass at 25 °C.

2.3 Analytical methods

Reviews have been published on the methods used for the determination of organochlorine compounds including PCBs in environmental samples (Panel on Hazardous Trace Substances, 1972; Holden, 1973; US DHEW, 1978; Slorach & Vaz, 1983; Jensen, 1984, 1985; Erickson 1985; Alford-Stevens, 1986; NIOSH, 1987; DFG, 1988; WHO/EURO, 1987, 1988). No two laboratories used identical methods, though all the methods have features in common. The techniques appear to be those previously developed for the determination of organochlorine pesticides, with appropriate modifications for the presence of PCBs, and the studies on PCBs sometimes form part of a wider programme for monitoring persistent organochlorine compounds in the environment. In the past, the major difficulty in the determination of PCBs was to obtain a single quantitative figure from a variable mixture of components. The PCBs were chlorinated with antimony pentachloride to decachlorobiphenyl, which was measured as a single peak (Greve & Wegman, 1983; Tuinstra, 1983). At the moment, chemists and toxicologists are no longer trying to derive a single quantitative figure, preferring instead to quantify individual congeners. The legislation in certain countries is now based on quantifying a few selected congeners, instead of reporting "total PCBs". It is also felt that for pinpointing areas with high levels of contamination, in order to rank them into low, medium, or high priority areas for action, highly accurate laboratory analyses are not necessary; instead, analytical competence and the use of adequate controls and standards, resulting in consistent, reasonably accurate results would be enough. Of course, for complicated research, especially involving laboratories in different countries, standardization of techniques through collaborative and comparative studies would be necessary.

Jones (1988) and Safe et al. (1985a) studied the occurrence of specific PCB congeners in commercial formulations or mixtures. The congener composition of commercial formulations differs from batch-to-batch, between manufacturing processes, and with the level of chlorination. The presence of congeners in the environment will depend on the eventual use of commercial formulations, the quantity of each formulation manufactured, as well as on the isomer composition of the source.

On the basis of a literature review of the occurrence of PCB congeners in environmental and biological samples and human tissues, and consideration of the relative toxicity and persistence of the congeners, suggestions were made by Jones (1988), with regard to the most relevant components to be quantified in human foodstuffs and tissues, using a selective analytical approach.

The congeners reported (Safe et al., 1985a; Duinker et al., 1988; McFarland & Clarke, 1989) as being the most abundant in human tissues and which are most important, are compounds with IUPAC numbers 28, 52, 74, 77, 99, 101, 105, 118, 126, 128, 138, 153, 156, 169, 170, 179, and 180 (comprising >70% of total PCBs and being of greatest toxicological significance). Because of their reported occurrence or toxicity, congeners with IUPAC numbers 8, 37, 44, 49, 60, 66, 70, 82, 87, 114, 158, 166, 183, 187, and 189 might also be considered. Duinker et al. (1988) were also of the opinion that toxicity should be considered as a criterion for the selection of PCB congeners for analysis in environmental samples. Most of these congeners can be accurately determined with the application of the multidimensional, high-resolution GC-ECD techniques.

PCB reference materials are necessary for the qualitative and quantitative calibration of analytical apparatus and methods (e.g., determination of retention times, response factors, and reference spectra in chromatographic and spectroscopic analyses) and for the study of biological activity. Lindsey & Wagstaffe (1989) described the production and certification of 10 high-purity PCBs with IUPAC numbers 8, 20, 28, 35, 52, 101, 118, 138, 153, and 180.

Mes et al. (1989a) described an analytical method to determine 34 isomers of PCB congeners in fatty foods. A sample was extracted with an acetone:hexane mixture and the extracts washed and dried; this was followed by a clean-up and determination by gas chromatography. GC/MS was used for confirmation.

Environmental PCB residues are often expressed in terms of relative Aroclor composition. Schwartz et al. (1987) assessed the similarity of Aroclors with class models derived for fish and turtles, to ascertain if the PCB residues in the samples could be described by an Aroclor or Aroclor mixture. The PCB residues in fish and turtles were analysed with Soft Independent Modelling of Class Analogy, a

principal components analysis (PCA) technique. Using PCA, it was inappropriate to report these samples as an Aroclor or Aroclor mixture.

2.3.1 Sampling strategy and sampling methods

The quality and usefulness of analytical data, especially in the microgram-nanogram range, or even lower, depend critically on the validity of the sample and the adequacy of the sampling programme. The purpose of sampling is to obtain specimens that represent the situation being studied. Sampling plans may require that systematic samples be obtained at specified times and places, or simple random sampling may be necessary. Generally, the sample should be an unbiased representative of the situation of interest (WHO/EURO, 1987). Slorach (1984) described the problems encountered with the sampling and determination of PCBs in breast milk (see also WHO/EURO, 1985, 1988).

All aspects of a sampling programme should be planned and documented in detail, and the expected relationship of the sampling protocol to the analytical result should be defined. A sampling programme should include reasons for choosing sampling sites, the number and type of samples, the timing of sample acquisition, and the sampling equipment used. A detailed sampling procedure should include a description of the sampling situation, the sampling methodology, labelling of samples, field blank preparation, pretreatment procedures, transportation, and storage (WHO/EURO, 1987).

The quality assurance programme should include means to demonstrate that containers or storage procedures do not alter the qualitative or quantitative composition of the sample. Special transportation and storage procedures (refrigeration or exclusion of light) should be described (WHO/EURO, 1987).

Because environmental samples are typically heterogeneous, a sufficiently large number of samples (10 or more) must be analysed to obtain meaningful composition data. The number of individual samples that should be analysed will depend on the kind of information required. If an average composition value is required, a number of randomly selected individual samples may be obtained,

combined, and blended to provide a homogeneous composite sample, from which a sufficient number of subsamples are analysed. If composition profiles, time trends, or the variability of the sample population is of interest, many samples need to be collected and analysed individually.

If field blanks are not available, efforts should be made to obtain blank samples that best simulate a sample that does not contain the analyte. In addition, measurements should be made to ascertain whether, and to what extent, any reagent or solvent used may contribute or interfere with the analytical results (laboratory and solvent blanks). The recovery tests are frequently used and are necessary to evaluate the analytical methodology. Uncontaminated samples from control sites that have been spiked with the analyte of interest provide the best information, because they simulate any matrix effect. When feasible, isotopically labelled (^{13}C, ^{37}Cl) analytes spiked into the sample provide the greatest accuracy, since they are subjected to the same matrix effects as the analytes. The ^{13}C-labelled compounds can be used to:

(*a*) validate sampling (sampling surrogate);

(*b*) validate analytical waste (clean-up surrogate);

(*c*) validate quantification (internal standard).

Only a small number of laboratories in the world have access to, and experience in working with, these complicated analyses. In order to be able to compare data generated in different laboratories, the same quantitative standard compounds should be used. Interlaboratory calibrations, or "round-robin" studies, have been performed in a few cases (WHO/EURO, 1987).

2.3.1.1 Extraction procedures

Air

The sampling device used to collect and determine PCBs in air consists of a glass fibre filter and a Florisil stick. The glass fibre filter, held in a stainless steel holder, removes particles larger than 0.3 μm. The air passes from the filter to the Florisil stick, which is made in 2 sections, to provide information on migration and trapping efficiency for PCBs. Each section contains 0.4 g of Florisil preceded

and followed by a glass wool plug. The front and back sections are separated by 2 plugs of glass wool. The front is spiked with 0.1 μg of p,p'-DDE as a surrogate for recovery measurement and as an indication of analyte migration. The detection limit for PCBs in air is reported to be 0.3 ng/m^3 (Anon., 1985; WHO/EURO, 1987; NIOSH, 1987).

Particulate fallout from air has been trapped on 200 μm nylon net coated with silicone oil, and the PCBs then extracted with hexane (Södergren, 1972). Separate determinations of particulate and vapour phase PCBs in air have been made by passing a large volume of air through a filter followed by an impinger containing hexane or toluene (Rappe et al., 1985c), a polyurethane plug (Bidleman & Olney, 1974), or ceramic saddles coated with OV 17 silicone (Harvey & Steinhauer, 1974) to absorb the vapour.

Surface sampling

Surface sampling of PCBs can be carried out using a wet-wipe procedure with a cotton gauze pad that has been dampened with hexane before collecting the sample. The sampled area is 0.25 m^2. The wet-wipe sampling procedure collects both the contaminants from the surface and the contaminants that can be extracted from pores in the material. Materials such as waxes and plasticizers may interfere with the chemical analysis (WHO/EURO, 1987).

Another sampling method has been described by Rappe et al. (1985c), where a dry filter paper or Kleenex tissue is used first, for wiping, followed by a wet wipe with water-dampened material.

Water

PCBs have been extracted from water by passing a sample through a filter of undecane and Carbowax 400 monostearate supported on Chromosorb W (Ahling & Jensen, 1970) or a porous plug of polyurethane coated with a suitable gas-liquid chromatographic stationary phase, or Amberlite XAD-2 resin (Harvey et al., 1973) followed by elution of the PCBs with a solvent. Ahnoff & Josefsson (1974, 1975) have described liquid-liquid extraction into cyclohexane.

Soil and sediment

In a study by Huckins et al. (1988), sediment samples were thawed at room temperature and placed in a hexane-rinsed foil pan and air dried for 5 days. The sediment was broken up, homogenized, and mixed with anhydrous disodium sulfate until dry, for column extraction. The samples were extracted with methylene chloride. PCB residues were enriched by adsorption column chromatography on silica gel and sulfuric acid silica gel. Prior to GC analysis, nitric acid-rinsed copper wool was added to the sediment extract to remove elemental sulfur. An aliquot of the PCB residues was diluted in a mixture methylene chloride : cyclohexane (1:1) and the bulk of the *o,o*-Cl substituted PCB components eliminated by eluting the column with different solvents. The different PCB congeners were determined by GC-ECD.

The feasibility of cleaning PCB-contaminated soils using a solvent extraction method was studied by Reilly et al. (1986). Compared with direct incineration of the sludge, the solvent extraction route has a number of shortcomings; the detailed design of the extraction plant as well as its operation will be quite challenging as an extremely leak-tight operation is essential, considering the nature of the material handled. Direct incineration will clean the solids much more thoroughly than is feasible by solvent extraction under ambient conditions. Furthermore, it is inevitable that some residual solvent will remain in the solids after processing. The solvent extraction process costs essentially the same as direct incineration.

Biological samples

Most analysts have used standard methods, developed for organochlorine pesticides, in which the PCBs are extracted together with the fat; the sample is ground with anhydrous sodium sulfate and extracted with petroleum ether or hexane. Porter et al. (1970) studied the optimal conditions for this procedure. A dehydrating solvent may be included to facilitate the breakdown of cell structures; ethanol (Norén & Westöö, 1968) and acetone (Jensen et al., 1973) have been used.

Reznicek (1987) described a method to extract and determine PCBs in blood. The sensitivity of the method was 10 μg/litre.

2.3.1.2 Sample clean-up

Diverse extraction and clean-up procedures have been devised to preferentially remove co-extractives that are present in different matrices and interfere with routine quantitative gas chromatographic and gas chromatographic-mass spectrometric analysis.

The analysis of lipid-containing matrices for residues of organochlorine pesticides and PCBs is a common procedure. All the methods require the separation of the residues from the lipids prior to the determination of the PCBs by gas chromatography. The removal of the lipids is usually carried out by low-resolution column chromatography using an adsorbent, such as silica, alumina, or Florisil as the stationary phase. Low-resolution gel permeation chromatography has also been used. An electron-capture detector is the most commonly used detector, but clean-up procedures may still leave electron-capturing species in the extract, so the identities of the eluting peaks must be confirmed. In order to overcome some of these problems, perchlorination of the PCBs has been used, giving rise to one GC peak (decachlorobiphenyl), which is well removed from most interfering peaks, but this technique has been found to be qualitatively and quantitatively unreliable and unsatisfactory. Seymour et al. (1986b,c) attempted to simplify clean-up procedures by using high performance liquid chromatography (HPLC) coupled with gas chromatography-mass spectroscopy. This latter technique is less expensive than it used to be and is the only technique that can possibly identify each peak as a PCB before quantification is carried out, thereby improving the quality of the result. It is also capable, when used in the selective ion monitoring mode (SIM), of detecting only PCBs, even in the presence of pesticides, so that sample clean-up is further simplified.

Seymour et al. (1986a) described a clean-up procedure, with a preparative, high-performance liquid chromatographic (HPLC) separation method for selected pairs of chlorobiphenyl isomers, produced by Cadogen coupling in the preparation of individual congeners, to be used as standards in congener-specific determination using capillary GC methods.

A routine method for the determination of PCBs in breast milk, described by Seymour et al.(1987), is less labour-intensive and more

cost effective than the traditional methods. These advantages were achieved by adsorption of the milk on a polar substrate prior to Soxhlet extraction, using a polymeric HPLC column for the clean-up of the extract, followed by highly selective capillary GC-MS analysis.

Methods for the removal of fat from the extract include solvent partitioning between hexane and acetonitrile or dimethylformamide, or treatment with strong sulfuric acid or ethanolic potassium hydroxide. Gel permeation has also been used (Stalling et al., 1972), and Holden & Marsden (1969) removed fat on dry, partially deactivated, alumina columns. Certain pesticides, such as dieldrin, are destroyed by the sulfuric acid treatment, so this method cannot be used if such pesticides are to be determined together with PCBs (Jensen et al., 1973).

Huckins et al. (1988) described the clean-up of fish samples. Tissue samples were thawed, mixed, dried with sodium sulfate, and extracted in glass columns with methylene chloride. The extract was evaporated and the lipid content was determined gravimetrically. Gel permeation chromatography was used for removal of lipid from fish sample extracts. PCB residues were enriched by adsorption column chromatography on silica gel and sulfuric acid silica gel, eluted with a mixture of methylene chloride and cyclohexane, and determined by GC-ECD.

PCBs can be separated from organochlorine pesticides by column chromatography on Florisil (Mulhern et al., 1971), silica gel (Holden & Marsden, 1969; Armour & Burke, 1970; Collins et al., 1972) or on charcoal (Berg et al., 1972; Jensen & Sundström, 1974a). Several laboratories have reported difficulties in repeating results obtained by other investigators; the ease of separation appears to depend on the characteristics of the absorbent, of the eluting solvent, and of the sample extract, though there does not appear to be any difficulty in separating all interfering substances, except DDE, a metabolite of DDT. Thin-layer chromatography has been used for separation by Norén & Westöö (1968), Bagley et al. (1970), and Reinke et al. (1973).

In many environmental samples, DDE is present in larger amounts than the PCBs, and must be removed before their quantitative determination. Oxidation procedures have been used to convert DDE

to dichlorobenzophenone; recommended oxidants are potassium dichromate and sulfuric acid (Westöö & Norén, 1970b) and chromium (II) oxide and acetic acid (Mulhern et al., 1971). Jensen & Sundström (1974a), who were interested in determining DDT/PCB ratios in environmental samples, preferred sodium dichromate in acetic acid with a trace of sulfuric acid. They claimed that this does not destroy DDT and its metabolite DDD, which may be present in extracts after clean-up with strong sulfuric acid, and that using this mixture makes possible the quantitative determination of the dichlorobenzophenone from the oxidation of DDE.

Conversion of DDT to DDE can be achieved by treatment with ethanolic potassium hydroxide, which also removes interference from elemental sulfur (Ahling & Jensen, 1970). Sulfur may also be removed by activated Raney nickel (Ahnoff & Josefsson, 1975) or by metallic mercury.

Beck & Mathar (1985) used gel permeation chromatography to clean extracts of food of animal origin.

2.3.2 Separation and identification

2.3.2.1 Chromatographic separation

Numerous gas chromatographic studies using packed or capillary columns have confirmed the complexity of all commercial PCB formulations. The accuracy in determining PCB levels is highly variable and matrix dependent. Many factors including: the water solubility, volatility, and biodegradability of individual PCBs, will alter the composition of a commercial PCB preparation introduced as a pollutant into the environment. Thus, the composition of PCB extracts from environmental matrices will vary widely and often do not resemble any commercial mixture. Quantitative analyses on these mixtures is usually determined by pattern- or peak-matching methods, using artificially reconstituted mixtures of different commercial formulations. High-resolution, glass capillary gas chromatographic analysis can provide a solution. Capillary gas chromatography columns, currently in use, are made of fused silica, chemically bonded with various stationary phases, to achieve a range of different selectivities towards complex samples. In general, packed columns

have been replaced by capillary columns, because of their far superior efficiency. The identities of the individual peaks must then be determined by using synthetic standards and by retention index addition methods. This latter technique predicts the relative retention times (RRT) of specific PCBs and has been used to assign the structures of individual PCB congeners. The method relies on the RRT values that have been determined for synthetic PCB standards. On this basis, Safe et al. (1985a) reported the first congener-specific analysis of a PCB preparation and PCBs in human milk.

Some workers use GC with mass selective detection (MSD), which quantifies the level of chlorination in a sample extract (Alford-Stevens, 1986). Tanabe et al. (1987) and Kannan et al. (1987) described a method to determine the 3 toxic, non-*ortho*-chlorine-substituted, coplanar PCBs, 3,4,3',4'-tetra, 3,4,5,3',4'-penta-, and 3,4,5,3',4',5'-hexachlorobiphenyl, which are biologically active congeners. The method comprised alkali digestion, carbon chromatography, and high-resolution gas-chromatography. Using this method, it is possible to determine ppt levels of these toxic residues in biological samples. Duinker et al. (1988) used multidimensional gas chromatography with ECD to determine levels of all congeners in some Clophen and Aroclor mixtures and found considerable differences between their composition of congeners and those in an extract of a seal blubber sample. Using this technique, congeners were identified that had, hitherto, been undetected, using other analytical techniques. It was possible to identify the toxic congeners in the samples studied, even when the relative contribution of each congener to the cluster was as low as 0.01%.

2.3.2.2 *Gas-liquid chromatography*

Most analysts use gas-liquid chromatography with an electron-capture detector for the separation of PCBs from the extract after clean-up. Stationary phases commonly used are silicones or their derivatives, for example, DC 200, SF 96, OV 1, and QF 1, or Apiezon L. Jensen & Sundström (1974a) stated that, with a mixture of SF 96 and QF 1, 14 peaks could be obtained from Clophen A50, but that Apiezon L gave much better resolution. They obtained better peak separation by prior fractionation on a charcoal column, which separated the PCBs according to the number of *o*-chlorine

substituents; they regarded such refinements as unnecessary in PCB residue analysis, but they may be of value in the study of the selective, environmental degradation of PCBs. Column temperatures used ranged between 170 °C and 230 °C. Glass capillary columns are superior to packed columns giving better separation of closely-related congeners; they also give good separation of PCBs from DDT and its metabolites (Zell et al., 1977; Dunn et al., 1984; Beck & Mathar, 1985; Alford-Stevens, 1986; Tanabe et al., 1987; Duinker et al., 1988).

A gas chromatography/electron impact mass spectrometry (GC/EIMS) method was used by Erickson et al. (1988) for the determination of by-product (non-Aroclor) PCBs. In this method, the recovery of 4 ^{13}C-labelled PCBs was measured to assure adequate recovery of the native PCBs from diverse matrices. The complexity of the matrices and the high probability of chlorinated organic interferents precluded the use of GC/ECD. The best available technique for universal application to commercial products, and associated waste, is GC/EIMS. During the validation work, the anticipated difficulty of qualitative and quantitative data interpretation was confirmed. In addition to the inherent problems resulting from extrapolation from 11 standards to 209 analytes, interpretation of the complex peak clusters is tedious.

2.3.3 Quantification

An electron-capture detector (ECD) is the most commonly used instrument for the quantification of PCBs. However, the response of this detector varies according to the number and location of the chlorine atoms in the PCB molecule, resulting in difficulties when the sample under investigation contains PCBs that have degraded (Zitko et al., 1971).

Various principles have been used to quantify PCB residues:

- comparison of a single peak in the residue with the corresponding peak in a commercial reference PCB (Aroclor, Clophen);

- comparison of the total response for several peaks in the residue with the total response of the corresponding peaks in a reference standard;
- comparison of the response of all peaks in the sample with those in the reference standard;
- perchlorination of PCBs to decachlorobiphenyl followed by quantification of this single compound.

The results obtained using these various methods differ; consequently, the precision in these analyses is not very good. Recently, Dunn et al. (1984) described a method for the quantification of PCBs using gas chromatography data, based on a pattern recognition technique and partial least squares in latent variables. The data to which it was applied were gas chromatograms of Aroclor 1242, 1248, 1252, and 1260. This technique also allows the classification of unknown samples (WHO/EURO, 1987).

Fait et al. (1989) investigated whether the results obtained for total PCBs using FSCGC/ECD (see section 2.3), differed significantly from those determined using packed column gas chromatography electron capture (PCGC/ECD) techniques, within 3 exposure groups. The concentrations of individual PCBs were determined in both the serum and adipose tissue from 35 transformer repair workers and 17 previous repair workers, exposed mainly to Aroclor 1260, in comparison with 56 non-exposed workers. Eighty-nine PCB peaks were identified. The total serum PCBs determined by FSCGC/ECD greatly exceeded that from standard PCGC/ECD. The median concentrations in serum were: 43.7, 30.0, and 16.1 μg/litre, and the median concentrations in adipose tissue were: 3180, 888, and 821 μg/kg, respectively. In all workers, hexachlorinated and heptachlorinated congeners predominated followed by octachlorinated and pentachlorinated species. The 7 major peaks in serum and adipose tissue were 2,3,5,6,3',4',5'/ 2,3,4,5,2',4',5'/ 2,3,4,5,2',3',4'-heptachloro-; 2,3,4,2',3',5'-hexachloro-; 2,4,6,3',4',5'/ 2,4,5,2',4',5'-hexachloro-; 2,3,4,5,2',3',5',6'/ 2,3,4,5,6,2',3',5'-octachloro-; 2,4,5,3',4'/ 3,4,5,2',3'-pentachloro- and 2,3,4,2',3',4'/ 2,3,5,6,2',4',5'/ 2,3,4,5,2',4',6' multichlorobiphenyls.

The response of the electron capture detector is not equal for all PCB components, being much affected by the degree of chlorination, as already mentioned (Zitko et al., 1971). This does not lead to difficulties when the sample under investigation has been directly contaminated by a commercial PCB mixture, as this mixture can be used as a standard. Difficulties are encountered when the PCBs in the sample have undergone selective environmental degradation. Several investigators have noted that the pattern of peaks from such samples resembles fairly closely that of one or other of the higher chlorinated PCB mixtures, such as Aroclor 1254, and they have compared the total area of the peaks with that of the nearest commercial product, in order to determine the amount of PCBs in the sample (Armour & Burke, 1970; Tuinstra, 1983). Collins et al. (1972) observed that, under their conditions, the area of peaks usually encountered in extracts of tissue samples was very similar to that of an equivalent amount of DDE, thus, DDE could be used for calibration. In order to overcome the uncertainties of these procedures, Rote & Murphy (1971) divided the peaks into groups according to the number of chlorine atoms in the molecule, as determined from mass spectrographic data, and calculated the PCB content of each group from the theoretical response of the detector to chlorine content. Jensen et al. (1973) selected a commercial PCB that included all the peaks from the extract; they determined the PCB content of each peak by combined mass spectrometry and coulometry, and determined the total PCBs in the sample by comparing the height of each peak obtained with the extract with those obtained with the reference sample. Simpler methods have been used including that of Koeman et al. (1969), who compared the height of a single peak, obtained with the extract, with that of a peak with the same retention time obtained with a commercial PCB mixture, and those of others who averaged out more than one peak for this calculation (Reynolds, 1971; Reinke et al., 1973). Rote & Murphy (1971) calculated that such procedures may give more than double the values obtained by a more accurate method.

In the characterization of PCB components in PCB mixtures, the retention properties of the components of the mixtures, as well as a great number of synthesized components, were used to predict a complete analysis of mixtures as Aroclors 1242, 1254, and 1260.

Jensen & Sundström (1974a) synthesized a large number of reference substances and were able to identify almost 60 components in Clophen A50 and A60.

Attempting to account for unidentified peaks, authors have used the chromatographic retention indices of available components to calculate such data for missing ones. The identity of many peaks could not, however, be determined unambiguously. Some of these uncertainties have been resolved by the application of techniques other than the comparison of retention times e.g., MS, NMR, and IR. The efficiency of packed columns in GLC is not sufficient to allow their use for the accurate analysis of complex mixtures, in most cases. Another approach to the use of packed columns involves the use of columns with various selectivities. In this way, complete analysis of all components in Aroclors has been claimed with the use of up to 12 columns. The strongly increased GLC separation offered by capillary columns has been used to advantage in the analysis of technical formulations, in some cases the eluate was analysed by MS. To identify individual congeners, gas-liquid (using glass capillaries with different coatings) chromatography (GLC) was used by Albro & Parker (1979) and Albro et al. (1981). Hydrogen flame ionization detection (HFID) and electron capture detection (ECD) and MS were used by Duinker & Hillebrand (1983).

2.3.4 Accuracy of PCB determinations

A group of 8 analysts, engaged in an investigation of pollution in the North Sea, undertook a collaborative study to determine the PCB content of a sample of fish oil, using the methods currently employed in their laboratories (International Council for the Exploration of the Sea, 1974). The PCB values obtained ranged from 1.0 to 3.9 mg/kg with a mean of 1.97 mg/kg and a standard deviation of 0.93 mg/kg. Better agreement was obtained with the same fish oil fortified with PCBs at a concentration of 10 mg/kg; the mean of the results for the fortified sample was 10.0 mg/kg with a standard deviation of 1.1 mg/kg.

A probable source of error is incomplete initial extraction of PCBs from a sample (Holden & Marsden, 1969). Another source of variation between laboratories lies in the method used to quantify

gas-liquid chromatographic peaks; Van Hove Holdrinet (1975) considered this to be the major source of error.

It is evident that caution should be exercised in accepting the analytical results from a laboratory, particularly for samples with a low PCB content, until the competence of the laboratory has been established by an inter-laboratory collaborative study (Tuinstra, 1983).

Schulte & Malisch (1984) described a method to determine the real PCB contents of environmental samples. A technical PCB mixture of known composition was used for calibration. The PCB concentrations were determined in samples of human milk and butter and the calculated contents were 50% and 40% lower, respectively, than the values obtained by the usual calculation based on evaluation of some higher peaks of technical PCB mixtures.

2.3.5 *Confirmation*

Since Jensen first identified as PCBs hitherto unknown substances that interfered in the glass-liquid chromatographic determination of organochlorine pesticides using mass spectrographic data, other investigators have confirmed the presence of PCBs in environmental samples by combining gas-liquid chromatography with mass spectrometry (Bagley et al., 1970) and with coulometry, to measure the chlorine content. The conversion of PCBs to bicyclohexyl and decachlorobiphenyl is further confirmation (Berg et al., 1972). The widespread distribution of PCBs is now well established, and, as adequate methods are available to remove interference from organochlorine pesticides, there is no evidence of the presence of other interfering substances in the types of sample that have so far been analysed, down to a limit of detection of around 0.01 mg/kg. This does not necessarily apply to other types of sample, particularly when very low levels are being sought; Ahnoff & Josefsson (1973) reported a number of unknown interfering substances, when measuring PCBs in water at levels below 1 ng/litre. One of these substances was subsequently identified as elemental sulfur. They recommend confirmation by mass fragmentography for such samples.

2.3.6 Detection limits

The limits of determination using low or high resolution mass spectrometry are 0.01–1 pg per injection of each congener. The detection levels in samples depend on the sample size and matrix. Using an air sampling device described by Rappe et al. (1985b), a detection level of 0.05 pg/m^3 per congener could be determined in ambient air (WHO/EURO, 1987).

In general, other substances are not considered to interfere at levels of about 0.01 mg/kg. In river water and air, levels of 1 ng/litre and 0.3 ng/m^3, respectively, are reported to be the detection limits of PCBs (WHO/EURO, 1987). Tuinstra (1983) found a limit of detection for individual chlorobiphenyls in environmental and biological samples, of less than 1 μg/kg (see Table 7).

The results for sewage sludge, eel, grass, cow's milk, and human fat are given in Table 7 (Tuinstra, 1983). Individual chlorobiphenyls were also estimated in the monitoring programme for environmental and biological samples in the Netherlands.

2.4 Codex questionnaire on analytical methods

2.4.1 Interpretation and comparability of data

Monitoring data are available from many sources in many countries. They have been obtained using various methodologies, such as different sampling techniques and different methods of analysis and quantification. Limits of determination reported vary by a factor of 1000 or more.

Given this situation, data on levels of PCBs have to be interpreted with the greatest care. Comparisons can only be made between data from the same laboratory, using the same validated technique over a long period. Comparisons between data from different laboratories have to be limited to the very few cases, where very strict inter-laboratory checks have been made on the basis of the same sampling and analytical techniques. Indications about trends can only be obtained when taking into account these basic considerations (Beck & Mathar, 1985; Tuinstra et al., 1985b,c).

Table 7. Typical values of individual chlorobiphenyls in Dutch environmental and biological samples. Peak numbering according to IUPAC rules [a]

PCB compound	Structure	Sewage sludge µg/kg (dm) [b]	Eel µg/kg product	Grass µg/kg (dm) [b,c]	Cow's milk µg/kg fat [c]	Human fat µg/kg fat
28 [d]	2,4,4'	60	35	- [c]	- [c]	45
52 [d]	2,5,2'5'	22	110	0.4	2.1	10
44	2,3,2'5'	20	34	0.2	0.9	10
95	2,3,6,2'5'	58	130	0.7	1.6	30
101 [d]	2,4,5,2'5'	30	85	0.6	3.1	15
151	2,3,5,6,2'5'	9	24	0.2	0.6	10
149	2,3,6,2'4'5'	42	90	0.6	2.5	15
118	2,4,5,3'4'	20	110	0.3	- [c]	80
153 [d]	2,4,5,2'4'5'	54	180	0.7	13	295
141	2,3,4,5,2'5'	10	40	0.2	0.6	< 5
138 [d]	2,3,4,2'4'5'	45	200	0.7	11	235
128	2,3,4,2'3'4'	7	20	<0.1	1.2	15
180 [d]	2,3,4,5,2'4'5'	33	80	0.5	6.4	205
170	2,3,4,5,2'3'4'	10	30	0.2	1.8	90
201	2,3,4,5,2'3'5'6'	<5	10	<0.1	<0.5	20

[a] From: Tuinstra (1983).

[b] dm = dry matter.

[c] nd = not determined.

[d] Monitoring compounds.

In June 1985, a questionnaire was distributed to all Codex Contact Points with the aim of providing background information on PCBs for the ad hoc working group on contaminants to compare such factors as methods of analysis, quantification, monitoring, etc. Eighteen out of 22 countries responded to the questionnaire.

In some cases, the information given was incomplete, but it is apparent that a variety of clean-up methods is employed. Where good laboratory practices are followed and tests indicate close to 100% recovery of standards from spiked samples, the main effect of different clean-up procedures will be on the limit of detection.

For gas chromatography, 6 countries reported that they used capillary columns as alternative or confirmatory systems. Among the

respondents, the Netherlands and the Federal Republic of Germany routinely used capillary columns and specific PCB isomers as regulatory standards. The types of packed column materials used varied considerably. With respect to quantification, pattern comparison with standards of various PCB formulations was the method most favoured, though some countries specified the use of certain combinations of peaks. In several cases, the methods being used were stated to have been collaboratively tested, or checked by inter-laboratory ring tests.

During the sixties, packed column chromatography was the most widely used method in the determination of PCBs. Results obtained with this technique varied widely between laboratories, and were much influenced by the method of quantification chosen and by the PCB mixture used as a standard. Chemical conversion methods, especially perchlorination, have also been used. These methods are quite sensitive, but do not allow for peak pattern identification. Another drawback of perchlorination is that conversion of less chlorinated biphenyls is not quantitative.

Sensitivity is sufficient, if adequate clean-up methods are used. Combined gas chromatography/mass spectrometry has a somewhat lower sensitivity, needs more expensive equipment, and is not considered suitable for routine work. The results obtained using these techniques may vary widely and most of them can only be used as rough estimates.

When capillary columns are used with temperature programming, almost all PCB isomers and congeners normally present in samples can be identified. This method is now considered to be the best available technique. However, it is important to decide which isomers should be used as guiding substances.

2.5 Activities of the WHO Regional Office for Europe

The WHO Regional Office for Europe (WHO/EURO) has an ongoing programme related to PCBs, as well as to other chlorinated hydrocarbons, including polychlorinated-*para*-dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). Within this programme, practical guidelines to prevent and control accidental and environmental exposures to these chemicals have been published in

the Environmental Health Series of WHO/EURO (1987). The other important project within this programme dealt with the assessment of the health risks to infants associated with contamination of mother's milk. This assessment was completed by a WHO/EURO Expert Consultation held in Abano Terme, Italy, in 1987, and the output of this consultation has been published in the Environmental Health Series of WHO/EURO (1988). In order to produce more data on exposure levels through human milk, WHO/EURO has been coordinating analytical field studies in which several countries have participated. The results of these studies have been published in the Environmental Health Series of WHO/EURO (1989). This document also includes the results of interlaboratory quality control studies on levels of PCBs, PCDFs, and PCDDs in human milk. In the first series of studies, 12 laboratories were involved. The second round of the quality control studies has been completed, with the participation of additional laboratories, and the results will be published. Furthermore, the repetition of the analytical field studies on the levels of PCBs, PCDFs, and PCDDs in human milk will be implemented in 1991 and coordinated at WHO/EURO.

2.6 Appraisal

Since the congener composition and relative concentrations of the individual components in PCB extracts from environmental and biological samples differ markedly from those in commercial PCB mixtures, the quantitative determination of the PCB contents of such samples presents a special problem. Various approaches to the quantitative determination of PCBs have been reported including: attempts to determine the total PCB concentration through perchlorination of the mixture; identification of selected chromatographic peaks through gas chromatographic techniques with packed columns using certain commercial products as standards; as well as attempts to carry out congener-specific analysis, based on high resolution chromatographic separation followed by identification and quantification by mass spectrometry using synthetic standards. This last method is considered the best at present, though it is not feasible for all laboratories. Although the concentration values obtained from the various methods might be similar, such comparison will be limited and is of questionable value for most purposes. The occurrence of

specific PCB congeners in various samples and a consideration of the relative toxicity and persistence of the congeners have been suggested as a basis for a congener-specific analytical approach. While this approach can be useful, particularly in risk/hazard assessment exercises, it must be realized that it is based on the present knowledge about the occurrence, persistence, and toxicity of specific congeners. It does not take into consideration potentially unrecognized toxicities associated with the same or different congeners, which may be present in a sample, also it is not feasible in some countries. Therefore, further research in this area should continue to improve the basis for monitoring programmes and for a congener-specific approach.

In the selection of areas with high levels of contamination, in order to establish priorities for action, it is considered that analytical competence and the use of adequate controls and standards is more important than highly accurate laboratory analysis. Also, the quality and usefulness of analytical data depend critically on the validity of the samples and the adequacy of the sampling programme. A quality assurance programme and collaborative studies should be part of any long-term study on PCBs, since there are several possible sources of error. In this situation, data on levels of PCBs have to be interpreted with the greatest care and, in general, definitive comparison can only be made between data from laboratories using the same techniques and interpretation of results.

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural occurrence

Polychlorinated biphenyls are aromatic chemicals that do not occur naturally in the environment.

3.2 Man-made sources

3.2.1 Production levels and processes, uses

The first chlorinated biphenyl was synthesized in 1864, but it was not until 1929/1930 that the PCBs were produced commercially for use:

(*a*) as dielectrics in transformers and large capacitors;

(*b*) in heat transfer and hydraulic systems;

(*c*) in the formulation of lubricating and cutting oils and wax extenders;

(*d*) as plasticizers in paints, and as ink solvent/carriers in carbonless copy paper, adhesives, sealants, flame retardants, and plastics (Hutzinger et al., 1974; Pomerantz et al., 1978).

An extensive review of the uses of PCBs is given in DFG (1988).

3.2.1.1 World production figures

Over one million tonnes of PCBs have been produced commercially under a number of trade names, such as Aroclor, Fenclor, Clophen, and Kanechlor.

Details of the production and uses of PCBs in the USA have been released, and have been summarized by Nisbet & Sarofim (1972). Annual production increased steadily from 1930 and reached a maximum in 1970 of 33 000 tonnes. Of this, 56% was used as a dielectric (36% in capacitors and 20% in transformers). Various plasticizer outlets accounted for 30%, hydraulic fluids and lubricants, 12%, and heat transfer liquids, 1.5%. During this peak year, 65%

of the production was of the 42% chlorinated type, 25% was less chlorinated, and the remainder more chlorinated. After 1970, production decreased sharply owing to the voluntary limitation of sales by the Monsanto Company, the major manufacturer in the USA.

Following the restriction of sales for dissipative uses, the percentage of PCBs sold as dielectrics rose to 77% in 1971 and the proportion of highly chlorinated products was considerably reduced; Aroclor 1016 replaced Aroclor 1242. In Japan, 44 800 tonnes of PCBs were used from 1962 to 1971; of this, 65.4% was used in the electrical industry, 11.3% in heat exchangers, 17.9% in carbonless copying paper, and 5.4% for other dissipative uses (Ishi, 1972).

During the period 1980-84, the production in EEC member states was as follows: France, 16 200; Federal Republic of Germany, 24 200; Italy, 4500; and Spain, 3400 tonnes. After 1984, production was continued only in France and Spain (Bletchly, 1985; WHO/EURO, 1987).

Table 8. Estimated usage of PCBs in transformers and large capacitors in a number of OECD countries in 1930-80 (in tonnes)[a]

Country	Usage in transformers	Usage in capacitors	Total
France	50 700	8 800	59 500
Federal Republic of Germany	44 400	17 700	62 100
Italy	10 400	1 500	11 900
Japan	37 200[b]		37 200
Spain	20 100	3 400	23 500
United Kingdom	5 800	8 100	13 900
United States of America	125 800	130 400	256 200
Total	294 400	169 900	464 300

[a] From: WHO/EURO (1987).

[b] Includes the usage in both transformers and capacitors

By the end of 1980, the total amount of PCBs produced was 1 054 800 tonnes (of which approximately half was used in transformers and capacitors, see Table 8), divided between the following countries (in

tonnes): USA, 647 700; Federal Republic of Germany, 130 800; France, 101 600; United Kingdom, 66 800; Japan, 59 300; Spain, 25 100; and Italy, 23 500 (Bletchly, 1983).

In addition, Czechoslovakia and the USSR have manufactured PCBs for their domestic market under the trade names of Delor and Sovol, respectively, but the data on production quantities are not available.

According to an OECD report, transformers and capacitors provided the major outlets for PCBs in most OECD countries in 1971. In 1972, several countries restricted sales; in Sweden the importation and use of PCBs were restricted by law; in the United Kingdom, as in the USA, sales were voluntarily restricted to the lower chlorinated PCBs for use as dielectrics in enclosed systems, and, in the USA in 1979, manufacture, use, handling, storage, and disposal were promulgated. As late as 1985, a final rule concerning the restriction and conditions on the use of PCB transformers was published (USEPA, 1985). In Japan, the production and use of PCBs were banned in 1972.

The 24 OECD countries adopted a Decision in 1973, limiting the use of PCBs to certain specific applications and asking for the control of the manufacture, import, and export of bulk PCBs, for adequate waste treatment and for a special labelling system for PCBs and PCB-containing products. On 13 February 1987, the Council of the Organization for Economic Co-operation and Development (OECD) adopted a further Decision-Recommendation (C(87)2(final)) on "Further measures for the protection of the environment by control of polychlorinated biphenyls". With this Decision-Recommendation, the OECD Member countries committed themselves to ban virtually all new uses of PCBs, accelerate the phasing out of PCBs from existing uses, control PCBs in contaminated products, articles, or equipment, and ensure appropriate disposal methods for PCB-containing waste. The uses of PCBs have been virtually restricted to those in "closed systems". In 1976, an EEG Directive made the limitations of the use compulsory for the EEG Member States. Other Directives, such as those on waste treatment and disposal, followed (van der Kolk, 1984a, Personal communication).

3.2.1.2 Manufacturing processes

Industrial manufacturing of PCBs is based on the chlorination of biphenyl by anhydrous chlorine, under heated reaction conditions and in the presence of suitable catalysts (e.g., iron-chloride). Depending on the reaction conditions, a degree of chlorination varying between 21% and 68% (weight percentage, w/w) can be achieved.

The yield is always a mixture of different compounds and congeners. Commercial mixtures generally have been purified by filtration and fractional distillation, but, in spite of this, they have been found to contain many impurities (WHO/EURO, 1987). In general, commercial PCB products contain impurities, mainly polychlorinated dibenzofurans (PCDFs).

Rappe et al. (1985d) cf. WHO/EURO (1987) analysed a series of commercial PCBs, using a new clean-up technique based on reverse-phase chromatography on a carbon column followed by a fluorosil column. In all PCB products, PCDFs were found at levels varying from a few mg/kg up to 40 mg/kg. The chlorination pattern of the PCDFs was found to vary with the chlorination level of the PCBs. In most products, 2,3,7,8-substituted tetra-, penta-, and hexa-CDFs were the major constituents.

3.2.2 Uses

PCBs have been widely used in electrical equipment, such as capacitors and transformers. These have often been considered to be closed systems, though small amounts of PCBs can frequently be found on the outer metal surface of such equipment.

Smaller volumes of PCBs have often been used as fire-resistant liquid in nominally closed systems, such as hydraulic and heat exchange systems (WHO/EURO, 1988).

Broadhurst (1972) reviewed the many technical applications of PCBs that appear in the literature and in patent specifications, and indicate the possibility of a widespread, non-occupational, low-level exposure to PCBs, other than that derived from the diet. PCBs are used in the home in ballast capacitors for fluorescent lighting, and exposure from pressure-sensitive copying paper has not been limited to office workers. The valuable properties of PCBs as plasticizers has led to

their use in furnishings, interior decoration, and building construction; examples are surface treatment for textiles, adhesive for waterproof wall coatings, paints, and sealant putties. PCBs have been used as plasticizers for plastic materials and in the formulation of printing inks.

The value of PCBs for industrial applications depends on their chemical inertness, resistance to heat, non-flammability, low vapour pressure (particularly with the higher chlorinated compounds), and high dielectric constant.

Data on the usage of technical PCB mixtures in Europe are scarce. In the 1960s and early 1970s, PCBs were used in (WHO/EURO, 1987):

(*a*) completely closed systems;
(*b*) nominally closed systems;
(*c*) open-ended applications.

3.2.2.1 *Completely closed systems*

PCBs have been widely used in electrical equipment, such as capacitors and transformers, which are considered to be completely closed systems. Historically, capacitors are the single largest PCB-use category. The PCB mixtures used for this purpose are, for example, Pyralene 3010, Aroclor 1016, 1221, and, earlier, also Aroclor 1242 and 1254. The amounts used in a number of OECD countries are presented in Table 8 (OECD, 1982; Bletchly, 1983; Callahan et al., 1983).

Since the late 1970s and the beginning of the 1980s, PCB-filled capacitors have largely been superseded by capacitors with a non-PCB dielectric fluid. The tendency for this substitution varies from country to country, for example, it started in Sweden and Finland in 1982, and in Norway in 1985.

The technical PCB mixtures used in transformers are mostly highly chlorinated like Aroclor 1254 and 1260. In general, the PCBs are used in combination with tri- and tetrachlorobenzenes as mixtures called *Askarel*.

The amounts of PCBs used in transformers differ in different countries. In France, where most transformers are placed indoors,

the major dielectric fluid is PCBs or *Askarels*, which are both flame retardants, while in Scandinavia, where most capacitors are placed outdoors, mineral oils (with a lower melting point) are frequently used.

During the 1980s, there has been a marked interest in replacing the PCBs, mainly in indoor transformers, as a result of serious accidents, for example, in Binghamton, San Francisco, Miami in the USA, and Reims in France. Various products are used for this exchange, such as mineral oils, silicone oils, perchloroethylene, and other chlorinated products (WHO/EURO, 1987).

3.2.2.2 Nominally closed systems

Smaller volumes of PCBs have frequently been used as fire- resistant liquid in nominally closed systems, such as hydraulic and heat transfer exchange systems (for example, trade names Pydraul and Therminol FR, containing Aroclor 1242, 1248, 1254, and 1260). PCBs are used as a working fluid in vacuum pumps (Aroclor 1248, 1254), which can also be considered as nominally closed systems (WHO/EURO, 1987).

3.2.2.3 Open-ended applications

With open-ended applications of PCB, both the emissions into the environment and the levels of occupational exposure are more pronounced. The major open-ended applications include use as a plasticizer (in PVC, neoprene, and other artificial chlorinated rubbers). Other open-ended uses, such as surface coatings, paints, inks, adhesives, pesticide extenders, microencapsulation of dyes, and carbonless copy paper contribute smaller volumes into the environment. PCBs have also been used in immersion oils for microscopes, as catalysts in the chemical industry, in casting waxes in the iron/steel industry (decachlorobiphenyl), and in cutting and lubricating oils (WHO/EURO, 1987).

3.2.2.4 Contamination of other compounds

In addition to the above uses of PCBs, numerous halogenated compounds may contain PCBs in small amounts as a contaminant (US EPA, 1983).

3.2.3 Loss into the environment

PCBs are dispersed into the environment through atmospheric transport and, on a more regional scale, following release into water. PCBs are also mobilized in the soil or landfills, but the rates of dispersion and subsequent transfer to biota and humans are difficult to estimate.

More highly chlorinated forms become most prevalent in compartments further along the pathway chains. The analytical methods used to quantify PCBs in the environment and biota vary greatly within, and between, countries. Thus, comparisons can only be made in a very broad sense and could, to some extent, be erroneous (WHO/EURO, 1988).

An overview of prevention and control measures of accidental and environmental exposures is given in WHO/EURO (1987).

3.2.3.1 Routes of environmental pollution

Surveys of the sources of environmental pollution with PCBs were made before production and use became limited, and the information available may not now apply in North America and elsewhere. Only 20% of the annual production in the USA can be regarded as a net increase in current usage, and the remainder is balanced by a loss to the environment. More than one-half of this entered dumps and landfills and it has been calculated that 0.3 million tonnes of PCBs have accumulated in such locations in North America, since 1930 (Nisbet & Sarofim, 1972). Much of this was originally enclosed in containers, such as capacitors, or was in plasticized resins and will not be released until the containing medium decays. The diffusion of PCBs from landfills is likely to be slow, on account of their low volatility and low water solubility. Carnes et al. (1973) found little leaching from the one site that they tested.

The concentration of PCBs in emissions from several municipal sanitary landfills and refuse and sewage sludge incinerators were determined in the Midwest of the USA. Sanitary landfills continuously emit the gaseous products of anaerobic fermentation together with other volatile materials into the atmosphere. A projection, based on the amount of methane generated annually from

landfills and a PCB to methane ratio of 0.3 μg PCBs/m^3 of methane found from the landfills sampled, indicates that the annual PCB emissions from sanitary landfills in the USA are of the order of 10–100 kg/year. The concentrations of PCBs from the incinerator stacks ranged from 0.3–3 μg/m^3 and the annual emissions per stack were 0.25 kg/year. These estimates are very small in comparison with the 900 000 kg PCBs/year estimated to cycle through the atmosphere over the USA, annually (Murphy et al., 1985).

Scrap transformer fluid containing PCBs has been used in the USA in amounts of about 10 tonnes/year in pesticide formulations (Panel on Hazardous Trace Substances, 1972, cf. WHO/EURO, 1988), and this unauthorized use has led to the local contamination of milk supplies.

Pressure sensitive duplicating paper (carbonless copying paper) containing PCBs has found its way into waste paper supplies and has been recycled into paper and board used as food packaging materials, but not since 1970; paints for coating the bottom of ships contained 3–5% of PCBs, about 3% of the annual quantity imported into Sweden has been used for this purpose, and this has been a source of plankton contamination (Jensen et al., 1972a).

Schecter (1987) described the contamination of drinking-water by the use of submersible water pumps which, in certain instances, contained PCBs in the oil. When the pumps leak, PCBs may be released into the drinking-water.

In addition, the US EPA, in 1980, estimated that over 1 000 000 wells in the USA may have PCB capacitors in the well motors. Levels recorded in drinking-water range from 0.26 to 57 μg/litre compared with 1 μg/litre considered safe in the guidelines for New York State. The oil from these pumps contained 630 000–24 000 000 μg/kg of PCBs.

Stehr et al. (1985) studied the possibility of contamination with PCBs of oils and oil-filled devices used by amateur radio operators. Two of 77 oil samples contained more than 50 mg/kg.

3.2.3.2 Release of PCBs into the atmosphere

There appears to be little atmospheric contamination during the manufacture and processing of PCBs, but this can occur during their subsequent use and disposal. Although PCBs have a low volatility, there may be an appreciable loss to the atmosphere during the lifetime of a PCB-plasticized resin, particularly of the lower chlorinated products. Further pollution may occur during the incineration of industrial and municipal waste. Most municipal incinerators are not very effective in destroying PCBs; efficient incinerators can be designed for this purpose (Oehme et al., 1987), though the higher chlorinated PCBs are more resistant to pyrolysis. Secondary sources of atmospheric pollution are volatilization from soil, and the drying of sewage sludge. Furthermore, there is evidence that, even at ambient temperatures, PCBs will enter the atmosphere by volatilization from soils and water bodies, landfill sites etc. (section 4.1.1).

3.2.3.3 Leakage and disposal of PCBs in industry

Eschenroeder et al. (1986) analysed PCB risks using estimates of human intake of PCBs originating from accidental spills from electrical equipment. Equipment spills without controls resulted in a human intake of PCBs of, at the most, 2 ng/day via the water exposure pathway. This was negligible in comparison with the intakes calculated on the basis of fish comsumption. The inhalation exposure of approximately 100 persons living in the vicinity of a spill in Southern California was determined to equal the PCB intakes of a fish-eating population.

3.2.4 Thermal decomposition of PCBs

It has been found by Buser et al. (1978a,b) that PCBs can be converted to PCDFs under pyrolytic conditions. The pyrolysis of a commercial PCB mixture in a sealed quartz ampoule, in the presence of air, yielded a mixture including about 30 major and more than 30 minor PCDF congeners.

Buser & Rappe (1979) studied the pyrolysis (at 600 °C) of 15 individual PCB isomers and demonstrated the presence of PCDFs via intramolecular cyclizations, where m+n varies from 4 to 8 (Fig. 1). The thermochemical generation of PCDFs from PCBs was found to

follow 4 general reaction routes including loss of *ortho*-Cl; loss of HCl involving a 2,3-chlorine shift at the benzene nucleus; loss of *ortho*-HCl and loss of *ortho*-H (Buser, 1985; Hutzinger et al., 1985).

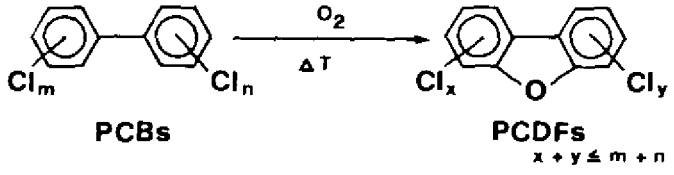


Fig. 1. Formation of PCDFs from PCBs.

The maximum yield of PCDFs was about 10%, calculated on the amount of PCBs decomposed, and the optimal temperature was between 550 and 650/700 °C (Bentley, 1983). Thus, the uncontrolled burning of PCBs can be an important occupational and environmental source of toxic and hazardous PCDFs and it is recommended that all destruction of PCB-contaminated waste should be carefully controlled, especially with regard to the burning temperature (above 1000 °C), residence time, and turbulence (Bentley, 1983; WHO/EURO, 1987).

In the temperature range 300-400 °C, Morita et al. (1978) reported that the yield of conversion seemed to be in the mg/kg range. However, Nagayama et al. (1981) reported a dramatic increase in the levels of PCDFs at these rather low temperatures, in the presence of stainless steel or nickel.

No, or very low levels of, PCDDs have been reported from the pyrolysis of PCBs. However, pyrolysis of a mixture of PCBs and chlorobenzenes (product *Askarel*) can yield both PCDFs and PCDDs (Buser, 1979).

Rappe et al. (1985b) found that various types of industrial incinerators, such as copper smelters and steel mills generate PCDFs and

PCDDs. Pyrolysis of chlorinated polymers like polyvinylchloride (PVC) and Saran also generate these compounds and exhaust gases of motor cars and their motor oil may contain PCDDs and PCDFs (WHO/EURO, 1987).

In a State Office Building in the centre of Binghamton, New York, a fire, in conjunction with several explosions, occurred in the basement mechanical room, in 1981. Approximately 750 litres of *Askarel*, a dielectric fluid composed of 65% PCBs (Aroclor 1254) and 35% polychlorinated benzenes, leaked from a transformer and caught fire. Pyrolysis of the *Askarel* led to the formation of a fine oily soot that spread throughout the building via 2 ventilation shafts. Samples taken several days after the fire showed average concentrations of PCBs in the air of the building of 1.5 $\mu g/m^3$. The average result for surfaces ranged from 4.6 to 162.2 $\mu g/m^2$. TCDFs and PCDDs were also present. The soot samples were analysed for pyrolysis products. They contained average levels of 3 mg TCDD/kg and 199 mg 2,3,7,8-TCDF/kg (Fitzgerald et al., 1989). Achilles (1983) reported the following levels in the deposited smut; 2160 mg PCDFs/kg and 20 mg PCDDs/kg (including 0.6 mg 2,3,7,8-TCDD/kg).

In the soot from the Binghamton, Reims, and Stockholm accidents, high levels of polychlorinated biphenylenes (PCBPs) were identified as well as the PCDFs (Fig. 2) (Rappe et al., 1982, 1985).

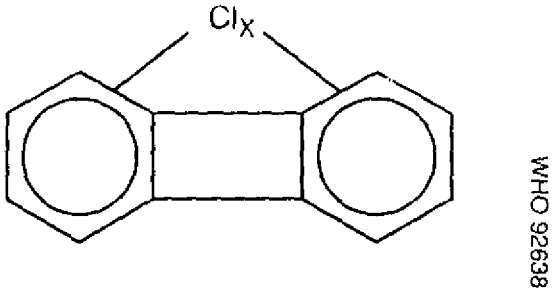


Fig. 2. Structure of PCBPs.

Between 1981 and 1985, a number of accidents in electrical equipment were reported from different countries; 28 accidents were mentioned in WHO/EURO (1987) including actual capacitor explosions, capaci- tor fires, and transformer accidents. In all cases, the accident site was contaminated by PCDFs, average levels of total PCDFs being in the range of 1–5 $\mu g/m^2$.

Hutzinger et al. (1985) also mentioned the presence of polychlorinated pyrenes (PCPYs).

In the period 1977–85, particulates and flue gas from municipal incinerators and hazardous waste incinerators in Canada, Denmark, Netherlands, Sweden, and Switzerland were investigated. It was found that emissions from incinerators contained many different PCDF and PCDD isomers. The total levels ranged from ng/m^3 to $\mu g/m^3$. Fly-ash contained levels of 0.1–0.6 mg/kg (Buser & Bosshardt, 1978; Rappe et al., 1985c; WHO/EURO, 1987).

Rappe et al. (1985b) studied the emissions of the municipal solid waste incinerator in Umea, Sweden. The levels of PCDDs and PCDFs varied under different burning conditions. The amount of dioxins formed seems to be dependent on the chlorine content in the waste, as well as the construction of the incinerator. The critical parameters seem to be temperature, residence time, turbulence, and excess air (oxygen).

The 2,3,7,8-tetra-CDD was always found to be a very minor constituent, whereas the 1,2,3,7,8-penta-CDD in all samples gave a medium-sized peak. The 2,3,7,8-substituted PCDFs were always middle or major components (WHO/EURO, 1987).

The fact that PCBs may be thermally converted to PCDFs has raised concern that similar conversions might occur in electrical equipment, such as capacitors and transformers, in which the dielectric fluids used are subjected to modest temperature rises accompanied by electrical stress. Brown et al. (1988) investigated the presence of PCDFs in both used and unused capacitors and transformers and did not find any evidence of an increase in PCDFs levels in the heavily used capacitor or the transformer PCBs compared with levels in unused samples.

For a number of years, concern has been expressed regarding the release of PCBs and other dangerous compounds when fluorescent light ballasts "burn out". The breakdown products may contain vapours and condensed particles of PCBs and asphalt. In response to concern at a school, the US EPA met with officials of Blaine Elementary School, because of material leaking from some fluorescent light fixtures. It was determined that the leaking material ("oil") contained PCBs (Aroclor 1242 or 1260). Air samples collected following the burn out of such lights, at different distances from the light fixture, gave concentrations of 0.166 and 0.012 mg/m^3, respectively, 1 and 6 m from the light. Three days later, levels of 0.004–0.001 mg/m^3 were still found. In a second series of tests, both burn-out and non-burn-out ballasts were heated to 150 °C, 300 °C, and 400 °C, in a chamber. No PCBs were detected at 150 °C. At 300 °C, concentrations ranged from 0.55 to 1.70 mg/m^3 and, at 400 °C, 2.54 to 28.2 mg/m^3. Wipe samples were taken in schoolrooms after burn-outs; average concentrations of Aroclor of 0.34 and 1.22 $\mu g/cm^2$ were found. It is obvious that PCBs and asphalt contamination, both surface and atmospheric, can occur when fluorescent lamp ballasts burn out.

The most serious potential contamination results when thermal runaway takes place. Thermal runaway volatilizes the asphalt potting compound and may rupture the capacitor. When the potting compound and the PCBs are exposed to high temperatures, some of both materials vapourizes. As the vapours pass through the atmosphere they condense into finely divided aerosols, less than 1 μm in diameter. Much of the visible fumes results from volatilization of the asphalt (Anon., 1987).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

4.1 Transport and distribution between media

A more detailed review of transport mechanisms can be found in Jury et al. (1987).

4.1.1 Transport in air

The virtually universal distribution of PCBs throughout the world, including the arctic and other remote areas, suggests that PCBs are transported in air (Risebrough & de Lappe, 1972). The ability of PCBs to co-distill, volatilize from landfills into the atmosphere (adsorption to aerosols with particle size of less than 0.05–20 μm), and resist degradation at low incinerating temperatures, makes atmospheric transport the primary mode of global distribution within the troposphere and stratosphere (Nisbet & Sarofim, 1972; Eisenreich et al., 1981). PCBs have been measured in air samples at Eniwetok Atoll in the North Pacific Ocean (Atlas & Giam, 1981), over the North Atlantic (Giam et al., 1978), and in the Gulf of Mexico (Giam et al., 1978, 1980). Murphy et al. (1985) estimated that approximately 18 000 kg of PCBs are present in the atmosphere over the USA, at any given time. The authors also estimated that, if these PCBs had an atmospheric residence time of one week, then about 900 000kg/ year of PCBs cycle through the atmosphere of the USA.

Nisbet & Sarofim (1972) suggested that most of the airborne PCBs will be adsorbed on any particles present. The half-life of particles in the air will depend greatly on the size of the particles and the extent of atmospheric precipitation. Most will be deposited within 2–3 days in their areas of origin (usually urban), the small amount attached to fine particles will last in the atmosphere for longer periods and can be transported to more remote regions.

Södergren (1972) collected airborne fallout in southern Sweden and found regional differences in PCB levels, with mean monthly levels ranging from 620 ng/m^2 per month to 10 510 ng/m^2 per month. The

lowest level was in a remote forest area. Industrialized areas had high levels but so too did some agricultural regions. Higher levels were generally found in the western part of the study region, suggesting that some PCB fallout may have originated from further afield and be dependent on the prevailing winds. Seasonal variations in fallout correlated well with precipitation. Lower levels of PCB precipitation were found in Iceland by Bengtson & Södergren (1974). The highest level was found in Northern Iceland at 1050 ng/m^2 per month and, like other sites sampled, showed a seasonal trend with highest levels in the summer.

Harvey & Steinhauer (1974) measured PCBs in the atmosphere over the western North Atlantic. They found that concentrations decreased exponentially with distance from land and concluded that wind transport is the major method of transport over the oceans. They also suggested that PCBs are transported primarily in the vapour phase.

4.1.1.1 Dry deposition

Atmospheric input into the Great Lakes has been studied extensively, because the lakes, as a whole, represent the largest surface area of any freshwater body in the world, with the lake surface area comprising from 27% (Ontario) to 64% (Superior) of the total basin area, and ranging from 19 000 km^2 (Ontario) to 82 100 km^2 (Superior). Eisenreich et al. (1981) estimated that more than 80% of the annual mean total input of PCBs in Lake Michigan originated from the atmosphere. They estimated that approximately 56% of the 9000 kg/year of PCB input in Lake Michigan was in the form of wet deposition and that 30% of the 6600–8300 kg/year input in Lake Superior was also in this form. However, Andren (1982) calculated a precipitation input of 650 kg/year for Lake Michigan, again assuming that all PCBs were on 0.5 μm airborne particles. Even assuming the lowest estimate for the annual input of PCBs into the lake, approximately 60% of the total input might be atmospheric deposition.

Andren (1982) also measured the input of PCB into an isolated lake (Crystal Lake, Wisconsin), to calibrate a dry deposition model. The model was then applied to Lake Michigan and the author concluded

that, assuming all particulate inputs of PCB are associated with 0.5 mm particles, dry deposition inputs were significantly less than wet inputs.

Manchester-Neesvig & Andren (1989) collected and analysed air samples from a remote site in the Great Lakes watershed during 1984 and 1985. Total PCB concentrations varied from 1.82 ng/m^3 in the summer to 0.135 ng/m^3 in the winter. They found that, on average, 92% of the PCBs detected were in the vapour phase. When these data were compared with data collected over the previous 7 years, no significant changes in PCB concentrations were found. The authors concluded that, on the basis of the short residence time and the relatively constant annual average levels of PCBs, repeated cycling between earth and atmosphere takes place.

Murphy (1984) reviewing data from the Great Lakes region on the relative distribution of airborne PCBs between particulate matter and vapour, concluded that they are transported predominantly in vapour. He stated that there was reasonable evidence to suggest that the atmosphere is the major source of the PCBs found in Lakes Michigan, Superior, and Huron, Siskiwit Lake on Isle Royale, and probably in the upper Great Lakes too.

Using liquid-coated collecting plates in near-shore areas of Lakes Huron and Michigan, close to urban centres, more PCBs were found on the upper plates suggesting that much of the dry deposit of PCBs was associated with large particles (20 μm). This sampling technique also indicated that, for the areas studied, dry deposition inputs were higher than wet inputs (Murphy, 1984).

Duinker & Bouchertall (1989) analysed filtered air, particulates, and rain, in the city of Kiel, Federal Republic of Germany for 14 different PCB congeners. They found that congeners with a low degree of chlorination were dominant in filtered air, whereas, congeners with a high degree of chlorination dominated in aerosols and rainfall. The vapour phase represented up to 99% of the more volatile congeners (i.e., those with a lower degree of chlorination). The particulates were found to carry relatively more of the less volatile congeners. Particle scavenging was the dominant source of PCBs in rain water despite the small contribution of particulate PCBs to the overall atmospheric concentration of PCBs (only 1 or 2%).

In a study by Södergren (1973), most of the PCB deposited on a south Swedish lake was in the form of dry deposit, with 11% as particulate matter in the precipitation and 2% from precipitation water. McClure (1976) stated that, on the basis of flux measurements and model calculations, most of the PCB fallout is in the form of dry deposition and that most of the dry deposition of aerosol PCB introduced into the troposphere falls within 100 km of its source.

4.1.1.2 Precipitation deposition

Precipitation scavenging of chlorinated hydrocarbons in the atmosphere is complex. Scavenging of particles by cloud droplets and by rain drops in, and below, clouds, and the scavenging of the vapour phase by rain occurs (Murphy 1984). Thus chlorinated hydrocarbons are concentrated in precipitation rather than in the atmosphere, resulting in rainfall levels of many ng/litre. Swain (1978) and Strachan & Huneault (1979) measured levels in rainfall ranging between 0 (not detectable) and 230 ng/litre in the Great Lakes area.

Murphy (1984) pointed out that variables, such as the amount of particulate material and PCBs in the atmosphere, the type of rain, and the rate of rainfall, will affect the precision of precipitation estimates.

Levels of PCBs in the rainfall throughout Canada during 1984 were monitored by Strachan (1988). Levels ranged from nd to 17 ng/litre, no geographical trends were apparent.

4.1.2 Transport in soil

PCBs in soil, derive from particulate deposition (often concentrated in urban areas), wet deposition, the use of sewage sludge as a fertilizer, and leaching from landfill sites.

Significant amounts of PCBs are deposited on soil by particulate deposition (see previous section). Fujiwara (1975) analysed soil samples in Japan, and found that the main sources of PCB contamination of agricultural soils are the industries using PCBs. Other sources include treatment of soil with sewage sludge and accidental spills. The 15% of soil samples in Indiana (USA) that contained more

than 50 mg/kg had been treated with PCB-contaminated dried sludge (Bergh & People, 1977).

Tucker et al. (1975a) found that, during a 4-month period following the addition of Aroclor 1016 to soil, the PCBs were not readily leached by percolating water and that only the lower chlorinated isomers were leached. The ease of leaching from different soils was in the order sandy loam > silty loam > silty clay loam.

The behaviour of ^{14}C-labelled PCB in flooded soils was studied by Ogiso et al. (1976). The amounts of PCB volatilized occurred in the following order: water > subsoil > soil. The addition of compost powder to soil reduced the amount that volatilized.

Haque et al. (1974) studied the adsorption of Aroclor 1254 on various soil particle types in an aqueous solution of 56 μg PCB/litre. Delmonte sand and silica gel did not adsorb any PCB. Woodburn soil adsorbed the highest amount followed by illite, montmorillonite, and kaolinite clays, in decreasing order. The high adsorptive capacity of Woodburn soil was attributed to the presence of organic matter and lipophilic or hydrophobic materials. Moza et al. (1976a) found that, 2 years after the application of ^{14}C-labelled dichlorobiphenyl to a loamy sand soil at 1 mg/kg, most of the detectable PCB was in the top 10 cm of the soil and only 0.2% had reached a depth of 40 cm. In another study, Suzuki et al.(1977) found that Aroclors 1242 and 1254 did not move upwards through uncontaminated sand deposited over contaminated soil. The leaching of water from soil may lead to a downward movement of PCBs, depending on the soil type and clay content (Pal et al., 1980).

A large spill of *Askarel* (containing 70% Aroclor 1254 and 30% tri- and tetrachlorobenzenes) occurred at a transformer-manufacturing facility in Canada, in 1976. Condie silt from near the site of the spill was studied with respect to the sorption partition coefficients and the transport retardation factors. The sorption partition coefficient values for 2,5,2',5'-tetrachloro-, 2,4,5,2',5'-pentachloro-, and 2,4,5,2',4',5'-hexachlorobiphenyl were 5000, 9400, and 26 000, respectively. The mean transport retardation factors for these 3 congeners were 2.7 E+04, 5.0 E+04, and 1.4 E+05, respectively. This implies that dissolved PCBs will move only very slowly through unfractured Condie silt (Anderson & Pankow, 1986).

4.1.3 Transport in water

PCBs enter water mainly from discharge points of industrial and urban wastes into rivers, lakes, and coastal waters. In static water, PCBs are more concentrated in the surface micro-layer than in subsurface samples (Bidleman & Olney, 1974). This is probably due to deposition from the air rather than redistribution in the water. On account of their low water solubility and high specific activity, it is expected that most of the PCBs discharged will be adsorbed by sediment at the bottom of rivers or lakes and transport will be mainly via waterborne particles (Nisbet & Sarofim, 1972). The bulk of the PCBs will sink to the bottom sediments. The sinking rate of PCBs from the surface to deeper layers in the open ocean is relatively slower in tropical waters than in high-latitude waters (Tanabe, 1985).

Oloffs et al. (1973) added 0.1 mg Aroclor 1260/litre to water samples in the presence of sediment. After 6 weeks, all of the PCBs had been adsorbed by the sediment, none being given off to the atmosphere. The degree of PCBs sorption is inversely related to the size of the particles (Haque et al., 1974) and the solubility of PCBs in water (Haque & Schmedding, 1975). Smaller particles have a relatively larger surface area and so adsorb more PCBs (Steen et al., 1978). Nau-Ritter et al. (1982) found the adsorption and retention of PCBs to be directly related to the particle organic content. A significant correlation was found by Larsen et al. (1985) between PCB levels and total organic carbon in the deepwater sediments of the Gulf of Maine, PCBs were concentrated on finer grain particles. Organic carbon and, therefore, the PCB concentration were also correlated with depth. Wildish et al. (1980) found that estuarine sediments, especially those containing higher levels of organic matter, readily adsorbed Aroclor 1254. The PCBs were found to be tightly bound to the sediment with virtually no desorption. Horzempa & Di Toro (1983) found that the adsorption of hexachlorobiphenyl was correlated with both sediment surface area and organic content. Adsorption was found to be significantly greater at 40 °C than at 1 °C. Hexachlorobiphenyl is strongly adsorbed on sediment and weakly desorbed. There is no simple reversible reaction.

Fisher et al. (1983) found that the rate of release of PCBs from contaminated sediment was a function of sediment PCB

concentration, chlorine substitution pattern, and degree of chlorination. In the absence of disturbance, even very low deposition rates of new sediment will quickly remove PCB-contaminated sediments from diffusional communication with overlying water. Little change was found (Nimmo et al.,1971a) in the PCB concentration in sediment at a point downstream of a contamination source over a period of 9 months. The very small amounts of PCBs leached from sediment into overlying water may be taken up by organisms.

Hom et al. (1974) stated that the annual inputs of PCBs into the southern California bight from waste water and from surface runoff in 1970-71 were estimated to be 10 and 0.25 tonnes, respectively.

Sewage treatment appears to remove PCBs from waste water, concentrating them in the sludge. However, often, the sludge is then discharged into open water (Ahling & Jensen, 1970). Holden (1970) found an average of 3 mg PCBs/kg in wet sewage sludge dumped in the Clyde estuary, in the United Kingdom, and calculated that this would be equivalent to approximately one tonne per year. A similar annual discharge of PCBs in the sludge on the Californian coast was calculated by Schmidt et al.,(1971).

Dredging of inland rivers and harbours may lead to a significant transfer of PCBs from contaminated sediments, especially when dumped at sea (Nisbet & Sarofim, 1972). Rice & White (1987) found that there was an increase in water concentrations of PCBs immediately following the dredging of sediment in the Shiawassee River, Michigan. The availability of PCBs for clams and fish, as measured by an increase in uptake, was found for up to 6 months following dredging.

4.1.4 Transport between media

In a model ecosystem, Södergren & Larsson (1982) found that the presence of bottom-living organisms, such as *Chironomus* and *Tubifex*, resulted not only in the uptake of PCBs from the sediment but also in the release of PCBs into the water and to the surface microlayer, compared with a system without organisms. PCBs were transported to the air via jet drops from bursting bubbles in the surface microlayer.

A similar pattern was found using large outdoor artificial ponds (Larsson, 1985a). Following the addition of Clophen A50 to sediment, the transport of PCBs from sediment to water followed a seasonal cycle, with higher levels in the summer than in the winter. The processes that transfer PCBs across the sediment/water interface (bioturbation, desorption, and gas convection) are positively related to temperature. Transfer from water to air was probably dominated by volatilization with maximum concentrations of PCBs in air at the highest water concentrations, lower chlorinated biphenyls achieving the highest concentrations in air. The majority of the airborne phase was presumed to be in the gaseous phase as it passed through particle filters. In the same ponds, Larsson & Okla (1987) measured the rate at which PCBs volatilized from water to air. PCB compounds volatilized at a rate of 0.9 to 9.6 ng/m^2 per h, the rate increasing with the temperature of the water and the concentration of PCBs. The transport rate during the day exceeded the rate at night and was positively correlated with the air temperature (Okla & Larsson, 1987).

Larsson (1985b) added Clophen A50 to the sediment in a model ecosystem comprising sediment, water, benthic macroinvertebrates, and fish. PCBs were detected in the water. The transport of PCBs from the water to air included at least 2 routes, volatilization and jet drop transport. Both routes were of the same magnitude (0.2–1.0 μg/week). However, though the PCBs transported by volatilization consisted of lower chlorinated isomers, those transported by jet drops were identical to those in the sediment and water.

In an earlier study, Larsson (1984) measured the uptake of PCBs from sediment by chironomid midge larvae and the concentrations of PCBs from larva to adult. In the field, chironomid larvae contained 114 μg/kg fresh weight at a sediment concentration of 39 μg/kg wet weight. Different sediments affected the amount of PCBs available to the organisms. Adult chironomids sampled near a sewage plant contained 251 μg/kg fresh weight. The chironomid larval population was estimated to be 9900 per m^2 and the authors calculated that these would move 20 μg PCB/m^2 per year into the terrestrial compartment of the environment.

A model, based on the fugacity concept, was described and illustrated by applying it to the time-varying fate of PCBs in Lake Ontario over the period 1940-2000. Expressions are included for a great number of variables, such as loadings and the partitioning of the contaminant between the phases of air, aerosols, water, suspended and bottom sediments, various trophic levels of aquatic organisms, and gull eggs. Also included are expressions for transformation rates, and transport rates for diffusion between water and sediment, and water and air wet and dry atmospheric deposition, sediment deposition, burial, and resuspension, and water and the inflow and outflow of suspended matter. The results obtained by numerical integration and by assuming reasonable loading and air concentrations were in accordance with data. It was shown that PCBs cycle appreciably between the atmosphere and water by wet and dry deposition and volatilization, and between water and sediment by deposition, resuspension, and diffusion. Biomonitors were shown to be particularly valuable indicators of contamination levels in the ecosystem (MacKay, 1989).

4.2 Biotransformation

4.2.1 Biodegradation

Nissen (1973) did not find any alteration in Aroclor 1254 after a 9-week incubation period in soil. Iwata et al. (1973) added Aroclor 1254 to various soil types. They did not find any change after one year in soils containing high amounts of organic matter (10.8–19.5%). Biotransformation had occurred, causing the disappearance of the lower chlorinated biphenyls, in soils with a low organic matter content (0.1–3.3%), as diverse as loamy sand and clay. The authors concluded that, after one year, the material remaining in loamy sand (0.1% organic matter) consisted of mainly penta- and hexachlorobiphenyl isomers.

4.2.1.1 Bacteria

The biodegradation of PCB isomers, which is possible with some aerobic bacteria, depends on the degree of chlorination and the position of chlorine substitution. Degradation decreases with increasing chlorination. Dechlorination of PCBs occurs in anaerobic

sediments. Here bacterial activity is preferentially targeted towards PCB congeners with higher levels of chlorination. Products of dechlorination are, therefore, more readily degraded by aerobic systems.

Early experiments were carried out to study the biodegradation of PCBs using activated sludge inocula; some degradation was found (Baxter et al., 1975). However, the presence of PCBs in sewage sludge shows that they are not all readily transformed by micro-organisms. Fries (1972) analysed silage containing PCBs (Aroclor 1254) that had undergone normal fermentation. The gas chromatogram of the standard was identical to that of the silage sample. The authors suggested that, if anaerobic degradation had taken place, it would have been unlikely to have been uniform for all components. They stated, however, that this test may not have been a good indication of possible anaerobic degradation because DDT showed much less degradation, under the same conditions, compared with other degradation test systems.

Lunt & Evans (1970) postulated a metabolic pathway, used by microorganisms, for biphenyl oxidation, which was later confirmed by the findings of Gibson et al. (1973) using a bacterium isolated from a polluted stream. Lunt & Evans (1970) found that a Gram-negative bacterium oxidized biphenyl to phenylpyruvic acid with the intermediary formation of 2,3-dihydroxybiphenyl and α-hydroxy-β-phenylmuconic semialdehyde. Catelani et al. (1971) found that the metabolism of biphenyl by *Pseudomonas putida* was different, in that, though the intermediate products were the same, benzoic acid was isolated, not phenylpyruvic acid. Ahmed & Focht (1973a) isolated 2 species of *Achromobacter* from sewage effluent using biphenyl and *p*-chlorobiphenyl as the sole carbon source. They found that both sources were rapidly degraded, biphenyl being oxidized to benzoic acid and both mono and dichlorinated biphenyls to *p*-chlorobenzoic acid. In a second study, Ahmed & Focht (1973b) investigated the biodegradation of other isomers of PCBs, with 2–5 chlorine atoms. The extent of oxidation seemed to be somewhat dependent on the presence of unsubstituted biphenyl rings. Because of the absence of chloride in all the supernatants, they concluded that the bacterium was unable to dechlorinate the PCBs. The fact that increasing chlorine substitution rendered the molecule more resistant

to microbial attack was used to support this argument. However, Kaiser & Wong (1974), studying the degradation of Aroclor 1242 by a bacterial culture, isolated from lake water, showed that the PCBs were degraded into several metabolites (aliphatic and aromatic hydrocarbons), none of which contained chlorine. Dechlorination had already taken place at an early stage of metabolism.

Wong & Kaiser (1975) found that lake water bacteria could use both Aroclor 1221 and 1242, but not 1254, as a sole carbon source for growth, but that only 1% of the bacterial culture had this ability. The authors then followed the degradation of Aroclor 1221. After one month, the mixture had been totally degraded to several compounds of low relative molecular mass. Unchlorinated biphenyls were degraded faster than chlorinated forms.

Tucker et al. (1975b) observed the degradation rates of Aroclors 1221, 1016, 1242, and 1254, and MCS 1043 (a non-commercial mixture). They found a clear relationship between the level of chlorination and the relative degradability, when degradation rate was plotted against percentage chlorine by weight. Volatilization rates fell within the 95% confidence limits of overall disappearance rates and so could be ruled out. Analysis of the Aroclors, following exposure to the activated sludge, revealed a redistribution of the dominant PCBs. For example, the chromatograms for Aroclor 1221 and 1242 were very similar showing that the lower chlorinated biphenyls were more rapidly degraded. Furthermore, since Aroclor 1221 was found to be rapidly degraded, a closer study was performed that showed that most of the degradation occurred within 24 h.

The degradation of polychlorinated biphenyls by either *Nocardia* spp. or *Pseudomonas* spp. was studied by Baxter et al. (1975). They found that, under experimental conditions, many of the lower chlorinated biphenyls (≤ 3 chlorine atoms/molecule) were degraded very readily and some biphenyls containing as many as 6 chlorine atoms could be degraded, if the conditions were suitable. When PCB mixtures Aroclor 1016 and 1242 were used, a different pattern of degradation was observed with an enhanced ability of the microorganisms to degrade. For example, 4,4'-dichlorobiphenyl degraded to 50% in about 2 days, when presented to *Nocardia* spp. as a component of Aroclor 1242, but it was virtually unaffected after 12 days exposure

as the pure isomer. The authors suggested that mutual solubilization might play some part.

Sayler et al. (1977) found that an estuarine *Pseudomonas* sp. was able to degrade both mixtures of PCBs (Aroclor 1254) and pure isomers of hexachlorobiphenyl. Degradation was dependent on incubation time and the purity and degree of chlorination of the biphenyl. Appreciable degradation occurred at all substrate concentrations of the Aroclor (10, 100, and 1000 μg/litre) within 22 days. Although, over this 22-day period, only 9% had been degraded at the lowest concentration compared with 30–40% for the other concentrations, after 60 days, this was reversed with 84% being degraded at 10 μg/litre, 70% at 100 μg/litre, and 63% at 1000 μg/litre. When compared with the pure isomer, degradation of the Aroclor mixture proceeded at a slower rate. Even though average chlorination was less, the authors speculated that this could be owing to the substitution positions of the chlorines. Chromatographic tracings showed that degradation of the lower chlorinated components of the Aroclor occurs before degradation of the more highly chlorinated biphenyls.

Furukawa et al. (1978a,b) examined 31 PCB isomers (mono to pentachlorobiphenyl) for biodegradability by 2 bacterial species, *Alcaligenes* and *Acinetobacter*. They found the following relationship between chlorine substitution and biodegradability.

i. Degradation decreased as chlorine substitution increased.

ii. Isomers containing two chlorines at the *ortho* position of either a single ring or on both rings showed very poor degradability.

iii. Isomers, in which all the chlorines were on one ring, were generally degraded faster.

iv. Molecules with non-chlorinated rings or rings with few chlorines underwent preferential ring fission.

v. The 4'-chloro-substituted PCBs formed and accumulated a yellow intermediate during degradation.

vi. Only with respect to 2,4,6-trichlorobiphenyl was there a significant difference in ability to degrade between the 2 bacteria. This compound was mostly metabolized within 1 h by *Acinetobacter*, but was degraded very slowly by *Alcaligenes*.

It was demonstrated by Carey & Harvey (1978) that mixed cultures of marine bacteria were capable of metabolizing both pure isomers (tri- and tetrachlorobiphenyl) and mixtures (Aroclor 1254). They isolated and partially characterized an acid lactone metabolite. They did not find any change in the chromatogram trace for the Aroclor but suggested that this might be related to the insensitivity of the method, since even if each of the isomers in the mixture had been metabolized to the same extent as pure isomers, this would still not have been detectable on the trace. The authors also found that no metabolism occured when a chlorobiphenyl isomer in an anaerobic marine mud was incubated for 6 weeks. Degradation of Aroclor 1242 by mixed microbial cultures, isolated from soil and river water samples, was demonstrated by Clark et al. (1979). The predominant organisms in the cultures were *Alcaligenes odorans*, *Alcaligenes denitrificans*, and an unidentified bacterium. The lower chlorinated isomers were not only degraded at a faster rate but were also more completely utilized by the bacteria. In general, the rate of degradation was much faster than in previous studies. Co-metabolism in the presence of sodium acetate was studied; greatly enhanced degradation was found for the more highly chlorinated isomers. Liu (1980) found that sodium ligninsulfonate also greatly enhanced the biodegradation of commercial PCB mixtures.

The same author found that a *Pseudomonas* sp. could oxidize Aroclors 1221, 1016, 1242, and 1254, at a rapid rate. A kinetic study using resting cells revealed that Aroclor 1221 was degraded much faster (980 μg/h per mg cell dry weight) than Aroclor 1254 (43 μg/h per mg cell dry weight). The degradation of the higher chlorinated PCB (Aroclor 1254) could be enhanced by the addition of Aroclor 1221. Liu (1981) observed that the oxidation of Aroclor 1221 by the bacteria was 10 times faster than with sewage. Two possible explanations for this difference were that the sewage contained toxic chemicals that inhibited the bacteria, but this was found not to be the case, or, the bacteria preferred Aroclor 1221 to the other substrates. This second explanation is a possibility, for glucose, a substrate used readily by most bacteria was poorly oxidized by this bacterium. *Pseudomonas* oxidized Aroclor 1221 readily between 15 and 35 °C, the rate increasing with temperature. Reducing the temperature to 4 and 10 °C drastically retarded, but did not halt, degradation. Adjusting

the concentrations of phosphorus and nitrogen from 2 mg to 20 mg/litre (the lower concentration being that found normally in sewage) did not alter the rate of degradation by *Pseudomonas* spp. in raw sewage. But increasing nitrogen and phosphorus gave more reproducible results, suggesting that the compounds are on the border of limiting degradation rates in raw sewage. The oxygen content was found not to affect degradation at concentrations over 1 mg/litre (oxygen levels are generally maintained at between 2 and 3 mg/litre in activated sludge reactors, under the operational conditions of sewage-treatment plants). Liu (1982) found that, under a limited substrate supply, *Pseudomonas* spp. degraded all 7 of the major components of Aroclor 1221. However, with excessive amounts of nutrient, preferential degradation of certain components was observed. The author stated that one of the main factors influencing this selective biodegradability was the position of chlorine substitution on the biphenyl.

4.2.2 Biodegradation; individual congeners

4.2.2.1 Bacteria

In a study by Parsons & Sijm (1988), the co-metabolism was investigated of several different mono-, di- and tetrachlorobiphenyls in chemostat continuous cultures of a *Pseudomonas* strain (JB1). They found that chemostat conditions favoured degradation compared with exposure of the *Pseudomonas* in batch culture, where little or no degradation was recorded. Using benzoate as the carbon source, results varied widely, with repeat incubations showing different degrees of degradation of chlorobiphenyls and, sometimes, no breakdown at all. In cultures that did degrade the materials, the monosubstituted 4-chlorobiphenyl was rapidly degraded. Of the disubstituted dibiphenyls, 3,5-dichlorobiphenyl was more readily broken down than 2,5-dichlorobiphenyl. Changing the carbon source available to the *Pseudomonas* sp. improved the reproducibility of the results. The authors reviewed the literature relative to their own findings and concluded that repeated culture on benzoate leads to the loss of the ability of the *Pseudomonas* sp. to degrade biphenyl by *meta* cleavage; *ortho* cleavage is retained. Coding for the *meta* cleavage resides on plasmids, which can be lost, whereas coding for

the *ortho* cleavage is chromosomal. Growth of the *Pseudomonas* sp. on a 3-methylbenzoate substrate improved degradation of the biphenyls. 3-Methylbenzoate can only be degraded by a *meta* cleavage favouring retention of the plasmid. Comparison of degradation of 4 tetrachlorobiphenyls showed the influence of the positions of the chlorine substitutions. The relative degradability of the 5 compounds, shown in Fig. 3, was: 2,3,2',3'-tetrachloro- >2,5,3',4'-tetrachloro- >2,5,2',5'-tetrachloro- ~2,6,2',6'-tetrachloro- ~3,4,3',4'-tetrachlorobiphenyl. The authors stated, from the liter- ature, that the first reaction in the degradation of chlorobiphenyls is, in most cases, 2,3-dioxygenation, eventually leading to the formation of chloro- benzoates. Chlorines in the *ortho* and *meta* positions will, therefore, offer steric hindrance to this reaction.

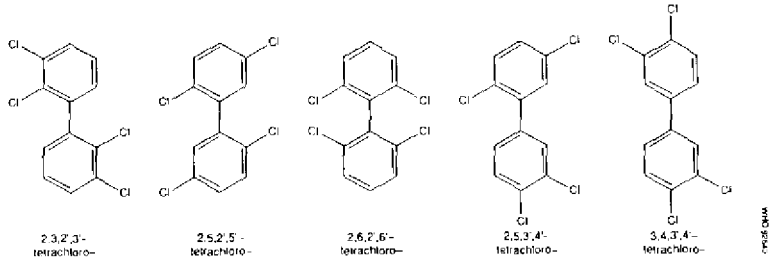


Fig. 3. Structures of tetrachlorobiphenyls used in the Parsons & Sijm (1988) study.

The low degradation rate of 3,4,3',4'-tetrachlorobiphenyl is not explained by this mechanism, since it has 2 adjacent unoccupied 2,3 positions, but is more likely explained by its toxicity. Steric influence on enzyme binding is offered as an explanation in this case. Similarly, Furukawa et al. (1978a) did not find any degradation of this compound in initial studies, though they did find degradation to a dichlorobenzoic acid by *Acinetobacter* in a later study (Furukawa et al., 1978b; Rogers, undated(a)).

Brown et al. (1987a,b) examined patterns of PCB congeners remaining in sediments after spills of commercial mixtures of Aroclor. Sediment from 5 different sites was examined. Shifts in gas chromatographic peak distribution were indicative of dechlorination of congeners by anaerobic bacteria in the sediment. Analysis of sediment from different depths indicated less difference from the original traces in superficial layers and the greatest shift in deeper layers of the sediment cores. They concluded that dechlorination had taken place and deduced several different processes involved by comparison between sites. Six of these processes have been characterized in detail, each presumed to be mediated by different populations of anaerobic bacteria, with different selectivity for different congeners in the PCB mixture. The point of most interest was that congeners with high degrees of chlorination were selectively dechlorinated by these anaerobic organisms. Whilst dechlorination still leaves the mass of PCB intact, congeners with lower chlorination can be more readily degraded by aerobic bacteria. This anaerobic dechlorination, therefore, enables further degradation to take place elsewhere and contributes significantly to the detoxification of the PCBs. While the combined *meta- para* selective dechlorinating/oxidizing action of sediment microbes for PCB residues is likely to be detoxifying, with respect to dioxin-like effects, there are reservations about whether this action would be detoxifying in respect of other, more subtle toxic effects of PCBs and their degradation products, known (such as the potential reproductive toxicity of the hydroxylated, *ortho*-enriched PCBs from sediment microbe action) and unknown. This is why it is important to study not only the disappearance of PCBs, but also the exact nature and amounts of the degradation products (McKinney et al., 1990). Two broad categories of transformation have been observed: the first dechlorinates in the *ortho, meta,* and *para* positions and the potential for the dechlorination of biphenyls is related to the reduction potential of the compound, the second dechlorinates only in the *meta* and *para* positions, and the reactivities of the congeners relate to the molecular shape. The second category suggested to the authors an active site on a dechlorinating agent that would be roughly conical with a reducing or hydrogenating site at the apex. In this schema, *para*-substituted molecules could enter the site directly, enough rotation of the molecule would be possible for the accommodation of *meta,* but

not *ortho*, substitution. Quensen et al. (1988) demonstrated this dechlorinating capacity of anaerobic bacteria from Hudson River sediments in the laboratory. Dechlorination occurred primarily from the *meta* and *para* positions; *ortho*-substituted congeners accumulated selectively. The fastest rate of dechlorination occurred at the highest exposure used (700 mg Aroclor 1242/kg); 53% of the total chlorine was removed over a 16-week incubation period. During incubation, the proportion of mono- and dichlorobiphenyls increased from 9 to 88%. The authors believed that a sequential anaerobic to aerobic system could be devised for the biological degradation of PCBs.

4.2.2.2 Fungi

Wallnofer et al. (1973) incubated a soil fungus *Rhizopus japonicus* in a medium containing ^{3}H-labelled 4-chlorobiphenyl or 4,4'-dichlorobiphenyl. After incubation for 1 week, the fungal mycelium was filtered out. Scans of TLC plates indicated a hydroxybiphenyl derivative present in the filtrate of both cultures. To further identify the metabolite, larger amounts of unlabelled 4-chlorobiphenyl were added to a similar culture. The NMR and mass spectra were identical to a synthetic sample of 4- chloro-4'-hydroxybiphenyl; mixed melting point determination showed no depression. Further positive identification of the product was not possible, because of limited material, but the experiment indicates the probability of degradation of biphenyl to a hydroxy derivative by a fungus.

4.2.3 Photodegradation

Several authors have reported that simple chlorinated biphenyls, as well as complex commercial PCB mixtures, undergo photoreduction in organic solvents (Safe & Hutzinger, 1971; Hustert & Korte, 1972; Ruzo et al., 1972, 1974, 1975; Sawai & Sawai, 1973; Koshioka et al., 1987) and aqueous systems (Crosby & Moilanen, 1973; Bunce, 1978) in the laboratory. Herring et al. (1972) found that PCBs degraded faster in hexane solution than in aqueous solution and slower in benzene solution.

Bunce et al. (1978) posed the question of the environmental significance of the photodegradation of PCBs and tried to estimate the likely degree of photolysis under real environmental conditions,

rather than in solution in organic solvents at high concentrations. The current best estimate suggests that significant amounts, particularly of higher chlorinated PCB congeners, might be degraded in water by the action of sunlight.

4.2.4 Bioaccumulation, distribution in organisms, and elimination

Polychlorinated biphenyls accumulate in almost all organisms, be-cause of their high lipid solubility and slow rate of metabolism and elimination. They accumulate preferentially in fat-rich tissues.

Bioconcentration factors (BCFs) should be interpreted with caution, since they are simple ratios. 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, whilst high exposure concentration will tend to minimize the BCFs.

Experimental data on the bioconcentration of PCB mixtures and pure chlorinated biphenyls are presented in Table 9 for microorganisms, Table 10 for aquatic organisms, and Table 11 for plants, birds, and mammals.

4.2.4.1 Microorganisms

Uptake of both pure chlorinated biphenyl isomers and commercial PCB mixtures by microorganisms is rapid, and high bioconcentration factors are achieved. While there is a suggestion in studies on some species that PCB congeners with higher levels of chlorination are taken up preferentially, in the majority of studies, all PCBs appear to be taken up equally. Uptake is true absorption; adsorption onto the surface of the organisms represents little of the uptake. Since resistant forms of microorganisms take up less PCBs than sensitive forms and dead cells accumulate more PCBs than live ones, there is some capacity to exclude the compounds.

Harding & Phillips (1978b) studied the uptake of ^{14}C-labelled 2,4,5,2',5'-pentachlorobiphenyl, at concentrations of 0.31 or 9.86 µg/litre water, by 11 marine phytoplankton species including: diatoms, green algae, chrysophytes, haptophytes, and dinoflagellates. The cell density of each culture was maintained at 106–109 cells/litre.

Table 9. Bioaccumulation of PCBs: Microorganisms

Organism	Biomass (cells/ml)	Temperature (°C)	PCB type	Duration	Exposure (μg/litre)	Bioconcentration factor[a]	Reference
Green alga *Chlorella pyrenoidosa*	2×10^6	20-25	TeCB	1 h	10	3200	Urey et al. (1976)
	2×10^6	20-25	HeCB	1 h	10	7000	Urey et al. (1976)
	2×10^6	20-25	OcCB	1 h	10	1600	Urey et al. (1976)
	2×10^6	20-25	DeCB	1 h	10	5200	Urey et al. (1976)
Algae *Fragilaria crotonensis*	3.2×10^5		HeCB	19 h	1	117 000[b]	Lederman & Rhee (1982)
	1.6×10^5		HeCB	19 h	1	313 000[b]	Lederman & Rhee (1982)
Algae *Ankistrodesmus falcatus*	3.4×10^5		HeCB	6 h	1	619 000[b]	Lederman & Rhee (1982)
	1.7×10^5		HeCB	6 h	1	959 000[b]	Lederman & Rhee (1982)
	8.5×10^4		HeCB	6 h	1	1 207 000[b]	Lederman & Rhee (1982)

Table 9 (continued)

Organism	Biomass (cells/ml)	Temperature (°C)	PCB type	Duration	Exposure (μg/litre)	Bioconcentration factor[a]	Reference
Algae	1.1×10^6		HeCB	6 h	1	129 000[b]	Lederman & Rhee
Mycrocystis sp.	5.5×10^5		HeCB	6 h	1	170 000[b]	(1982)
	2.8×10^5		HeCB	6 h	1	264 000[b]	Lederman & Rhee (1982)
							Lederman & Rhee (1982)
Fungus		22-25	Aroclor 1254	24 h	0.007 mg/kg	1327[b,c]	Pinkney et al. (1985)
Fusarium oxysporum		22-25	Aroclor 1254	48 h	0.007 mg/kg	1144[b,c]	Pinkney et al. (1985)

[a] Concentration of PCBs in organism/concentration of PCBs in medium or food; bioconcentration factors calculated on a wet weight basis unless otherwise stated.

[b] Calculated on a dry weight basis.

[c] Radioactive isotope used to calculate bioconcentration factor.

Table 10. Bioaccumulation of PCBs: Aquatic organisms

Organism	Stat/ flow[a]	Organ[b]	Temper- ature (°C)	PCB Type	Dura- tion	Exposure (µg/litre)	Bioconcen- tration factor[c]	Reference
American oyster	flow	WB		Aroclor 1016	96 h	0.6	6666	Hansen et al. (1974b)
Crassostrea		WB		Aroclor 1254	56 d	0.01	165 000	Parrish (1973)
virginica		WB		Aroclor 1254	392 d	0.01	89 000	Parrish (1973)
Polychaete	stat	WB		Aroclor 1254	5 d	1.1	236	Courtney & Langston
Arenicola marina	stat	WB		Aroclor 1254	5 d	1 mg/kg[d]	0.24	(1978)
Polychaete	stat	WB		Aroclor 1254	5 d	1.1	373	Courtney & Langston
Nereis diversicolor	stat	WB		Aroclor 1254	5 d	1 mg/kg[d]	0.36	(1978)
Water flea *Daphnia magna*	flow	WB	20-22	Aroclor 1254	96 h	1.1	47 000[e*]	Sanders & Chandler (1972)
Amphipod (M)	stat[f]	WB		Aroclor 1254	24 h	0.03	8700	Pinkney et al. (1985)
Gammarus tigrinus	stat[f]	WB		Aroclor 1254	24 h	195.8 mg/kg	0.118	Pinkney et al. (1985)
Scud	flow	WB	20-22	Aroclor 1254	96 h	1.6	24 000[e*]	Sanders & Chandler
Gammarus pseudolimnaeus	flow	WB	20-22	Aroclor 1254	21 d	1.6	27 000[e]	(1972)
Glass shrimp	flow	WB	20-22	Aroclor 1254	96 h	1.3	12 300[e*]	Sanders & Chandler
Palaemonetes kadiekensis	flow	WB	20-22	Aroclor 1254	21 d	1.3	16 600[e*]	(1972)

Table 10 (continued)

Brown shrimp *Penaeus aztecus*	flow	WB		Aroclor 1016	96 h	0.9	4222	Hansen et al. (1974b)
Grass shrimp	flow	WB	17-28	Aroclor 1254	7 d	2.3	11 000	Nimmo et al. (1974)
Palaemonetes	flow	WB	17-28	Aroclor 1254	16 d	1.3	14 000	Nimmo et al. (1974)
pugio	flow	WB	17-28	Aroclor 1254	28 d	0.62	17 450	Nimmo et al. (1974)
	flow	WB	17-28	Aroclor 1254	35 d	0.62	26 580	Nimmo et al. (1974)
	flow	WB		Aroclor 1016	96 h	0.4	2750	Hansen et al. (1974b)
Crayfish	flow	WB	20-22	Aroclor 1254	96 h	1.2	1700[e*]	Sanders & Chandler
Orconectes nais	flow	WB	20-22	Aroclor 1254	21 d	1.2	5100[e*]	(1972)
Stonefly	flow	WB	20-22	Aroclor 1254	96 h	2.8	2500[e*]	Sanders & Chandler
Pteronarcys	flow	WB	20-22	Aroclor 1254	21 d	2.8	2800[e*]	(1972)
dorsata								
Dobsonfly	flow	WB	20-22	Aroclor 1254	96 h	1.1	4600[e*]	Sanders & Chandler
Corydalus	flow	WB	20-22	Aroclor 1254	21 d	1.1	6800[e*]	(1972)
cornutus								
Phantom midge *Chaoboruspuncti pennis*	flow	WB	20-22	Aroclor 1254	96 h	1.3	23 600[e*]	Sanders & Chandler (1972)
Mosquito larvae *Culex tarsalis*	flow	WB	20-22	Aroclor 1254	96 h	1.5	18 000[e*]	Sanders & Chandler (1972)

Table 10 (continued)

Organism	Stat/ flow[a]	Organ[b]	Temperature (°C)	PCB Type	Duration	Exposure (µg/litre)	Bioconcentration factor[c]	Reference
Mayfly *Ephemera danica*	flow	WB	8	Clophen A50	6 d	0.526	2940	Södergren & Svensson (1973)
Pinfish	flow	WB		Aroclor 1016	96 h	0.8	2750	Hansen et al. (1974b)
Lagodon	flow	WB		Aroclor 1016	28 d	1 n	25 000	Hansen et al. (1974b)
rhomboides	flow	WB		Aroclor 1016	56 d	1 n	17 000	Hansen et al. (1974b)
Sheepshead	flow[g]	WB		Aroclor 1016	33 d	1 n	26 000	Hansen et al. (1975)
minnow	flow[g]	WB		Aroclor 1016	28 d	1 n	54 000	Hansen et al. (1975)
Cyprinodon variegatus	flow[g]	WB		Aroclor 1016	28 d	1 n	22 000	Hansen et al. (1975)
Spot	flow	WB		Aroclor 1254	7 d	1 n	7200	Hansen et al. (1971)
Leiostomus	flow	WB		Aroclor 1254	14 d	1 n	17 000	Hansen et al. (1971)
xanthurus	flow	WB		Aroclor 1254	28 d	1 n	37 000	Hansen et al. (1971)
	flow	WB		Aroclor 1254	56 d	1 n	27 000	Hansen et al. (1971)
Atlantic salmon *Salmo salar*	flow	WB	10-15	Aroclor 1254	33 d	10 mg/kg	0.39	Zitko (1974)

Table 10 (continued)

Coho salmon	flow	WB	17	Aroclor 1254	112 d	0.048 mg/kg	9.79	Mayer et al. (1977)
Oncorhynchus	flow	WB	17	Aroclor 1254	112 d	4.8 mg/kg	0.79	Mayer et al. (1977)
kisutch		WB		TeCB	17 d	1 mg/kg	0.144	Gruger et al. (1976)
		WB		TeCB	35 d	1 mg/kg	0.139	Gruger et al. (1976)
		WB		PeCB	35 d	1 mg/kg	0.162	Gruger et al. (1976)
		WB		HeCB	35 d	1 mg/kg	0.151	Gruger et al. (1976)
Channel catfish	flow	WB	26	Aroclor 1232	150 d	2.4 mg/kg	1.875	Mayer et al. (1977)
Ictalurus	flow	WB	26	Aroclor 1232	193 d	2.4 mg/kg	1.3	Mayer et al. (1977)
punctatus	flow	WB	26	Aroclor 1248	193 d	2.4 mg/kg	0.79	Mayer et al. (1977)
	flow	WB	26	Aroclor 1254	193 d	2.4 mg/kg	2	Mayer et al. (1977)
	flow	WB	26	Aroclor 1260	193 d	2.4 mg/kg	1.46	Mayer et al. (1977)
	flow	WB[h]	24-26	Aroclor 1242	130 d	20 mg/kg	0.72	Hansen et al. (1976a)
	flow	WB		Aroclor 1248	77 d	5.8	56 370*	Mayer et al. (1977)
	flow	WB		Aroclor 1254	77 d	2.4	61 190*	Mayer et al. (1977)

Table 10 (continued)

Organism	Stat/ flow[a]	Organ[b]	Temper- ature (°C)	PCB Type	Dura- tion	Exposure (µg/litre)	Bioconcen- tration factor[c]	Reference
Fathead (M)	flow	WB	25	Aroclor 1248	250 d	3	~60 000	DeFoe et al. (1978)
minnow (M)	flow	WB	25	Aroclor 1260	250 d	2.1	~160 000	DeFoe et al. (1978)
Pimephales(F)	flow	WB	25	Aroclor 1248	250 d	3	~120 000	DeFoe et al. (1978)
promelas(F)	flow	WB	25	Aroclor 1260	250 d	2.1	~270 000	DeFoe et al. (1978)

d = Days; M = Male; F = Female; DiCB = dichlorobiphenyl; TeCB = tetrachlorobiphenyl; PeCB = pentachlorobiphenyl; HeCB = hexachlorobiphenyl; OcCB = octachlorobiphenyl; DeCB = decachlorobiphenyl.

[a] Stat = static conditions (water unchanged for duration of experiment); flow = flow-through conditions (PCB concentration in water continously maintained).

[b] WB = whole body.

[c] Bioconcentration factor = concentration of PCBs in organism/ concentration of PCBs in medium or food; bioconcentration factors calculated on a wet weight basis unless otherwise stated. * Radioactive isotope used to calculate bioconcentration factor.

[d] Sediment.

[e] Calculated on a dry weight basis.

[f] Static conditions, but test solution changed at intervals.

[g] Intermittent flow-through conditions.

[h] Not including stomach.

Equilibrium between water and cell concentrations of biphenyl was reached very rapidly after 0.5–2 h; small motile forms reached equilibrium within 1 h and large centric diatoms after approximately 2 h. Exposure concentration and cell density, within the range given above, had little effect on the time-course of uptake. Substantial interspecies differences in adsorptive capacity were shown by differences in the Freundlich adsorption constant (log K). A large centric diatom, *Coscinodiscus* sp., had the highest log K. *Nitzschia longissima*, a penate diatom that has been shown to be resistant to PCBs (Harding & Phillips, 1978a), had the lowest log K value. The flagellates, with the exception of *Monochrysis lutheri*, which has been shown to be very sensitive to the effects of PCBs, had much lower log K values than diatoms. Concentration factors, calculated from the Freundlich adsorption isotherms, ranged between 12 300 and 2 410 000.

Biggs et al. (1980) exposed mixed species of estuarine phytoplankton (numerically dominated by the diatom *Skeletonema costatum*) to ^{14}C-labelled PCB (approximately 54% chlorine by weight) at concentrations of 5.8 or 11.6 μg/litre. At a particle concentration of 25 mg/litre, 19–22% of the labelled-PCB was sorbed on the particles after a 1-h exposure, with 70–72% in the water. At 4 times the above particle concentration, 66–69% was sorbed on particles and only 22–23% was retained in the water. Doubling the amount of ^{14}C-PCB doubled the mean amount of labelled-PCB in both the particles and the water. The authors calculated an index of sorption (the ratio of ^{14}C-PCB sorbed on particles to that in an equal volume of water) at an average of $2 \pm 1 \times 10^4$. The authors suggested that the higher uptake (88%) of PCBs found by Södergren (1971) was probably the result of an unnaturally high cell concentration. Phytoplankton sampled in the surface waters of Long Island Sound, USA, varied seasonally in concentration from about 0.5 to 30 mg/litre.

Lederman & Rhee (1982) calculated bioconcentration factors for 3 species of Great Lakes planktonic algae (Table 9). In the case of *Fragilaria crotonensis*, the uptake of hexachlorobiphenyl into the frustule (the siliceous wall of the diatom) was investigated. The bioconcentration factors for frustules were lower by an order of magnitude than the factors for live and dead cells. It appears,

therefore, that adsorption on the cell surface contributes only a little to the bioaccumulation of hexachlorobiphenyl.

Södergren (1971) maintained the unicellular freshwater green alga *Chlorella pyrenoidosa* in water (at a cell concentration of approximately 900 mg/litre) with added nutrient medium containing 3.7 μg Clophen A50/litre, over a period of 7 days. By the end of the experiment, 88% of the PCBs had been taken up by the alga. The remaining PCBs were detected in the water, none being found in the air samples taken. In another study, Urey et al. (1976) found that both tetrachloro- and hexachlorobiphenyl isomers, at 10 μg/litre, were concentrated by dead *Chlorella pyrenoidosa* cells by 6000 and 15 000 times, respectively, after a 1-h exposure. These concentration factors are approximately twice those for living cells (Table 9). Similar findings have been noted with other species of algae (Biggs et al., 1980; Lederman & Rhee, 1982).

The ciliate *Tetrahymena pyriformis* was exposed to Aroclors 1248 (0.01, 0.1, and 1 mg/litre) and 1260 (0.001, 0.01, 0.1, and 1 mg/litre) for 7 days (Cooley et al., 1973). Uptake of the toxicant increased linearly with increasing concentration. Concentration factors ranged from 14.8 to 40.6 for Aroclor 1248 and from 21 to 79 for Aroclor 1260. Approximately 15–20% of Aroclor 1248 was absorbed at each concentration compared with means of 37–53%, with increasing concentration, for Aroclor 1260. If the data from Cooley et al. (1972) on the uptake from Aroclor 1254 is included, it is clear that *T. pyriformis* accumulates more PCBs with increasing degree of chlorination.

Dive et al. (1976) studied the accumulation of 16 pure isomers of PCB and one commercial product, Pyralene 3010, by the ciliate protozoan *Colpidium campylum*, at concentrations of 0.1, 1, or 10 mg/litre for 43 h. The amount of PCBs taken up at 0.1 mg/litre was very similar for each of the PCB isomers and the commercial product, ranging from 29.4 to 49%. The percentage uptake did not change greatly for the higher exposures.

4.2.4.2 Plants

Uptake of PCBs into plants from soil is positively correlated with the soil concentration of the PCBs. Roots accumulate more than stems

and foliage. Bioconcentration factors are low. More lower chlorinated congeners of the PCBs are taken up, probably because of their greater mobility in the soil. Much of the uptake is adsorption on the surfaces of roots and there is little translocation. PCBs found in leaves have volatilized from the soil. Uptake on root surfaces can be reduced or eliminated by adding activated charcoal to the soil.

Lawrence & Tosine (1977) found that plants took up significant amounts of PCBs (30–140% of the applied PCB concentration) from soil treated with sewage sludge. In a waste PCB spill besides a North Carolina highway, levels as high as 4700 mg/kg were recorded in the top 3 cm of soil. Seven months later, the PCB concentrations were unchanged; the authors believed that this was because the PCBs were bound to activated carbon that had been used to treat the spill (Pal et al., 1980).

Strek & Weber (1982) analysed statistically the data from several literature sources (Iwata et al., 1974; Wallnofer & Koniger, 1974; Wallnofer et al., 1975; Iwata & Gunther, 1976; Moza et al., 1976a, 1979a,b; Weber & Mrozek, 1979) on PCB uptake by plants, with the following conclusions.

i. The PCB content of the plant is significantly dependent on the soil PCB concentration.

ii. There is a significant difference between plant species, carrots taking up more PCBs than other plants.

iii. There appears to be a limit of the PCB concentration in the soil at which no detectable PCBs are taken up by the plants.

iv. Roots take up more PCBs than tops.

v. most of the PCBs in roots may, in fact, be adsorbed on the surface and not actually taken up.

vi. There is a general trend of increasing PCB content with decreasing chlorination, for pure PCB congeners.

vii. The amount of chlorination seems to have an effect on the mobility of PCBs within plant parts. Since lower chlorinated PCBs have been reported to be more mobile in soils than highly chlorinated PCBs, they may be more readily transported and available for plant uptake.

Table 11. Bioaccumulation, of PCBs: Plants, birds, and mammals

Organism	Organ	PCB type	Duration	Exposure (mg/kg)	Bioconcentration factor[a]	Reference
				Soil[b]		
Beet *(Beta vulgaris)*	plant top	Aroclor 1254	39 days	20	0.041[c]	Strek et al. (1981)
Sorghum *(Sorghum bicolor)*	plant top	Aroclor 1254	39 days	20	0.003[c]	Strek et al. (1981)
Peanut *(Arachis hypogaea)*	plant top	Aroclor 1254	78 days	20	0.024[c]	Strek et al. (1981)
Corn *(Zea mays)*	plant top	Aroclor 1254	13 days	20	0.001[c]	Strek et al. (1981)
Carrot	root	DiCB[d]	112 days	0.118	2[c]	Moza et al. (1976a)
	leaves	DiCB[d]	112 days	0.118	0.92[c]	Moza et al. (1976a)
				Food		
White pelican *(Pelecanus erythrorhynchos)*	carcase	Aroclor 1254	70 days	144	14.8	Greichus et al. (1975)

Table 11 (continued)

Organism	Organ	PCB type	Duration	Exposure (mg/kg)	Bioconcentration factor[a]	Reference
Chicken	fat	Aroclor 1242	28 days	100	2.83	Harris & Rose (1972)
	fat	Aroclor 1254	28 days	100	5.15	Harris & Rose (1972)
	fat	Aroclor 1260	28 days	100	4.82	Harris & Rose (1972)
Big brown bat *(Eptesicus fuscus)*	carcase	Aroclor 1254	37 days	9.4	6.6	Clark & Prouty (1977)
Mink *(Mustela vison)*	fat	Aroclor 1254	~56 days	1.5	16.5	Hornshaw et al. (1983)
	fat	Aroclor 1254	~126 days	1.5	28.5	Hornshaw et al. (1983

[a] Bioconcentration factor = concentration of PCBs in organism/concentration of PCBs in medium or food; bioconcentration factors calculated on a wet weight basis, unless otherwise stated.

[b] Calculated on a dry weight basis.

[c] Radioactive isotope used to calculate bioconcentration factor.

[d] DiCB = dichlorobiphenyl.

Larsson (1987) maintained the macroalga *Cladophora glomerata* in a flowing-water, outdoor pool. Sediment contaminated with Clophen A50 at 2.7 mg/kg dry weight was added and PCB residues in the alga were monitored. The algal concentration was 3.55 mg/kg dry weight within 3 months. Residues had fallen a year later to 0.2 mg/kg, reflecting the water levels of PCBs. The authors concluded that a partitioning process governed the uptake of PCBs by *C. glomerata* in this experiment, because the alga accumulated the same PCBs and the same proportion of PCBs that were present in the water.

Red mangrove (*Rhizophora mangle*) seedlings were grown for 6 weeks in soil treated with Aroclor 1242 at concentrations of between 0.038 and 6 mg/kg (Walsh et al., 1974). Low levels (detection limit was 0.1 mg/kg) of the PCBs were detected in the roots at exposure concentrations of 3 or 6 mg/kg, during the exposure period, but no residues were found in the stems. Residues were detected in both the hypocotyls and leaves at application rates of 0.3 mg/kg or more. Leaf residues did not change with time, but PCB concentrations in the hypocotyls showed an increase. The highest mean residues of 1.5 mg/kg were found in the hypocotyl in the highest exposure group.

Iwata et al. (1974) treated soil with Aroclor 1254, at a concentration of 100 mg/kg, and sowed carrots in the plot 7 months later. The carrots were harvested 3 or 4 months after seeding. The authors found that the lower chlorinated biphenyls were more readily taken up from the soil into the carrot root. Analysis of the carrot peel revealed approximately 97% of the PCB residue, showing that there is little translocation within the plant; 23 months after sowing carrots in soil contaminated with 100 mg/kg Aroclor 1254, dissipation from soil appeared to parallel the degree of chlorination (Iwata & Gunther, 1976). Analysis of the soil revealed that the lower chlorinated biphenyls were slowly dissipated while the more highly chlorinated biphenyls appeared to be unaffected. Small amounts of PCBs were found in carrot foliage and the authors suggested that the PCB composition indicated that they came from soil dust. Suzuki et al. (1977) also found that lower chlorinated biphenyls were preferentially taken up by plants, following exposure of soybean sprouts to soil contaminated with Aroclor 1254 or 1242 at 100 mg/kg.

Moza et al. (1976a) found that carrot bioconcentrated 2,2'-dichlorobiphenyl (0.118 mg/kg soil) from soil by a factor of 2 (Table 11). No bioaccumulation was found in sugar beet, but the soil residue was only 0.029 mg/kg. Carrots were grown in soil amended with either ^{14}C-labelled 2,5,4'-trichlorobiphenyl at 1.28 kg/ha or 2,4,2',4',6-pentachlorobiphenyl at 1.12 kg/ha for one season (Moza et al., (1979a). Only 32.5% of the trichlorobiphenyl was recovered, the rest being lost through volatilization. The carrots had taken up 3.1% of the applied ^{14}C, representing a concentration factor of 2.8. For the pentachlorobiphenyl, 58.5% was recovered, 1.4% of which had been taken up by the carrots. Sugar beet grown in the soil the following year accumulated only 0.4% of the applied ^{14}C.

In a study by Weber & Mrozek (1979), ^{14}C-labelled Aroclor 1254 was applied to Lakeland soil at a rate of 20 mg/kg. Activated carbon was mixed with half the pots at a rate of 3.7 t/ha (3333 mg/kg). The pots were seeded with either soybean or fescue. After harvesting at 16 days for soybean and 50 days for fescue, the amounts of labelled-PCBs, recovered from the plant tops, were 0.016% and 0.17% for the 2 species, respectively. The addition of activated carbon to the soil reduced the uptake of ^{14}C-PCBs, the recovery of labelled-PCBs being 0.001% and 0% for soybean and fescue, respectively. Strek et al. (1981) also applied ^{14}C-labelled Aroclor 1254, at the same rate, to Lakeland soil; several species of crop plants were grown in the soil and bioaccumulation factors, calculated (Table 11). Addition of activated carbon (3.7 t/ha), equivalent to 3333 mg/kg to replicate pots, reduced the uptake of the labelled-PCBs by 80–100%.

When approximately 1 mg ^{14}C-labelled Aroclor 1254/kg was applied to the centre leaflet of the first trifoliate leaf of 18-day-old soybean plants, only 6.7% was recovered from the plant after 12 days, 76% of which was still present in the treated leaf (Weber & Mrozek, 1979).

Mrozek & Leidy (1981) transferred the marsh plant *Spartina alterniflora* from the field into soil containing 1 mg Aroclor 1254/kg (dry weight) and harvested the plants after a growth period of 90 days. The plants were found to take up selectively the lesser chlorinated biphenyls. The authors stated that a further shifting of the chromatographic pattern of PCBs towards the lesser chlorinated components in aerial tissues suggested that some alteration of the PCB mixture

occurs in the plant. Mrozek et al. (1982) also found that *Spartina* accumulates PCBs from both contaminated sand and mud–soil systems. The total ^{14}C-radioactivity accumulated in plants grown in sand systems was higher than that in plants grown in mud. The level of radioactivity accumulated in the green parts of the plants was similar in both soil systems.

Moza et al. (1976b) applied 76 mg/kg of ^{14}C-labelled 2,5,4'-trichlorobiphenyl or 133 mg/kg of labelled 2,4,6,2',4'-pentachlorobiphenyl to the leaves of the marsh plant *Veronica beccabunga*. Six weeks later, the total recovery from plant, water, and soil was 3.7 and 18.3%, respectively, 86 and 95% of which was recovered from the plant. In an earlier study, Moza et al. (1974) applied ^{14}C-labelled 2,2'-dichlorobiphenyl in water or soil to 2 higher water plant species (*Ranunculus fluitans* and *Callitriche* sp.) at concentrations of 13.7 and 14.5 mg/kg, respectively. Four weeks after application, the results showed that the dichlorobiphenyl was metabolized more readily after addition to water; the authors suggested the involvement of aquatic bacteria. When applied in soil, 1.2% of the dichlorobiphenyl was metabolized. This was contributed to the plant.

Moza et al. (1979b) grew 3-year-old spruce trees (*Picea abies)* in soil containing ^{14}C-labelled PCBs at approximately 4.2 mg/litre in sewage sludge. When analysed 4 years later, only 0.8% (0.5% in needles, 0.3% in stems) of the applied radioactivity was found in the trees. Leaching of radioactive substances from the soil was less than 0.1% in the first 2 years and undetectable for the remainder of the study.

In another study, Fries & Marrow (1981) grew soybean (*Glycine max*) in pots, to determine residue contamination in plant tops from ^{14}C-labelled 2,5,2'-trichlorobiphenyl, 2,5,2',5'-tetrachlorobiphenyl or 2,4,5,2',5'-pentachlorobiphenyl, applied to the surface or subsurface soil. Each compound was added to the soil at a rate of 2–3 mg/kg and the plants were harvested after a period of 52 days. Detectable residues were only found in plants grown in surface-treated soil, and concentrations in the plants increased with increasing chlorination. Little of the labelled PCBs was lost from subsurface-treated soil, but 20–30% of the surface-treated PCBs were lost through volatilization. The authors concluded that the PCB residues in the plant tops were, therefore, due to foliar contamination from

vapour rather than the uptake from the soil via the roots. Miyazaki et al. (1975) came to the same conclusion when they found no absorption or translocation of PCBs in sesame or rice seeds, following the application of 4 types of Kanechlor (KC300, 400, 500, and 600) at rates of between 0.1 and 100 mg/kg. But the rice straws contained PCB levels of 0.02–0.08 mg/kg, which were the same as levels found in plants from untreated soils.

Beets (*Beta vulgaris* L.), turnips (*Brassica rapa* L.), and beans (*Phaseolus vulgaris* L.) were grown (Sawhney & Hankin, 1984) in soil to which lake sediment contaminated with PCBs had been added. The plants were exposed to Aroclor 1248 at a concentration of 80 μg/kg, Aroclor 1254 at 1880 μg/kg, and Aroclor 1260 at 14 440 μg/kg. When beets and turnips were grown in the soil for 6 months, the plants showed greater uptake in the leaves than in the roots. For example, beet roots contained 15, 16, and 35 μg/kg of Aroclors 1248, 1254, and 1260, respectively, while beet leaves contained 22, 94, and 52 μg/kg, respectively. Total concentrations of the 3 Aroclors in beet roots and leaves and in turnip roots and leaves were 66 and 168 μg/kg, respectively, and 66 and 99 μg/kg, respectively. During a second growing season, turnips and beans were grown for 6 months without any additional PCB-contaminated sediment. Comparing PCB levels in turnips between the 2 growing seasons showed a decrease in Aroclor 1248 uptake relative to Aroclors 1254 and 1260. This was primarily because of a large reduction in the amount of Aroclor 1248 in the soil after 1 year, due to degradation and volatilization. In beans, higher PCB levels were found in the leaves and pods than in the stems and seeds.

Ten sludge application sites were selected within the Ontario area to determine background heavy metal and PCB concentrations in the soils and crops. Control sites (without sludge application) were adjacent to the sludge application sites. Grab samples of liquid sludges applied at each of the sites were taken for analysis. The soil samples were taken at a depth of 15 cm. Twenty core samples were taken at 20-m intervals and combined to form 1 sample. Eight of the application sites were cropped with corn, one with oats, and one was left without a crop. At the control sites, 7 were cropped with corn, 1 with oats, and 2 left without a crop. PCB concentrations in the sludges ranged from 0.13 to 1.61 mg/kg dry solids. PCB concen-

trations were in the range of 0.007–0.025 mg/kg in the soil without sludges, and in the range of 0.018–0.453 mg/kg air-dry weight in the soil with sludges. The PCB levels in the crops were close to the control values (Webber et al., 1983).

Bacci & Gaggi (1985) assessed the influence of translocation on the concentrations of PCBs in the foliage of different plant species. Beans, broad beans, tomatoes, and cucumbers were grown, either in soil with a nominal added concentration of 500 mg/kg Fenclor 64 (similar to Aroclor 1260), or in clean sand, for 28 days, enclosed in a glass box with a constant turnover of air. The plants grown in clean sands were exposed to PCBs by volatilization from other pots containing PCBs, which were in the same growing box. The PCB peak pattern of both sand and roots was similar to that of Fenclor 64, whereas the peak pattern for foliage and air had moved towards lesser chlorinated congeners. The concentrations of PCBs in the roots of tomatoes grown in contaminated soil ranged from 105 to 168 mg/kg dry weight. But translocation through the plants does not seem to be very likely since there was no significant difference in foliage uptake of PCBs between plants grown in contaminated soil and plants grown in clean soil. Foliar uptake ranged from 13.8 to 42.6 mg PCB/kg (dry weight) for the different species in PCB-fortified soil and from 11.8 to 47.1 mg/kg for plants grown in clean soil.

4.2.4.3 *Aquatic invertebrates*

Bioconcentration factors are high for PCBs taken up by aquatic invertebrates exposed to either pure chlorinated biphenyl isomers or commercial mixtures in the water. Since PCBs are strongly bound to sediments, this method of exposure is unrealistic. Addition of sediment to test tanks decreases the uptake of PCBs, particularly by organisms living in the upper water. However, there is clear evidence that PCBs can also be readily absorbed into invertebrates from both sediment and food. For organisms living on or in, sediment, uptake can take place from the sediment, via food organisms that have absorbed the PCBs, and from interstitial water or water immediately above the sediment layer. A high content of organic matter in sediment decreases the availability of PCBs for organisms. Uptake is rapid in most cases and equilibrium is often reached in hours, though it may take weeks in other examples. Uptake increases with

increasing temperature. The route of uptake is often via the gills, but varies among species. Loss of PCBs is slow, but residues do decrease on cessation of exposure. PCB uptake by aquatic invertebrates is transferred to predators and can also be transferred to the terrestrial environment.

(*a*) *Uptake from water*

Vreeland (1974) exposed American oysters (*Crassostrea virginica*) to various PCB isomers at concentrations of 5.5, 17, or 60 ng/litre (which is within the range found in coastal waters) for 65 days. Equilibrium was reached after approximately 1 month of exposure, with concentration factors ranging from 1200 to 48 000 for PCB isomers with 2–6 chlorine atoms/molecule. The PCB concentration, after equilibrium had been reached, was directly proportional to the amount of PCBs added to the water. Lowe et al. (1972) found a linear pattern of uptake in young American oysters exposed to Aroclor 1254 at 5 μg/litre for 24 weeks, followed by a further 32 weeks in clean water. The oysters already contained 17 mg/kg from a previous exposure and, by the end of the 24-week exposure period, had accumulated 425 mg/kg (a steady state was not established). By the end of the 32-week period in clean water, no PCB residues could be detected. In another study on uncontaminated young oysters, concentration factors of up to 101 000 were achieved after a 25-week exposure to 1 μg Aroclor 1254/litre. After 12 weeks in clean water, whole-body residues were reduced to 0.2 mg/kg.

Courtney & Denton (1976) fed hard clams (*Mercenaria mercenaria*) Aroclor 1254 adsorbed on the surface of alumina particles, at 1.25 and 12.5 μg/litre, for 21 days. The maximum concentration factor was 1800 for visceral mass, when the clams had been exposed to 1.25 μg/litre for 18 days. The visceral mass accumulated a 1.4–5.3 times greater concentration of PCBs per unit time than the muscular foot. Tissue samples contained relatively more lower chlorinated isomers than the Aroclor 1254 standard and, faeces and mud samples contained more higher chlorinated isomers. Following exposure, clams from the lowest dose group showed little change in PCB content after 3 months in clean seawater. However, at the higher dose level, there was a significant reduction in the PCB levels found in the foot

after 1 month, but PCB residues in the visceral mass remained unchanged for 6 months.

Pink shrimp (*Penaeus duorarum*) were exposed to Aroclor 1254 at a concentration of 2.5 μg/litre, in flowing water, for 22 days (Nimmo et al., 1971b). Accumulation was linear for the hepatopancreas and whole body, but a plateau was reached after 2 days in muscle. Residues in the hepatopancreas reached 510 mg/kg over the exposure period, representing a concentration factor of 204 000; over the same period, 50% of the shrimps died. In a separate study, the shrimps were exposed to 7.5 μg/litre for 16 days followed by an elimination period of 5 weeks in clean water. When calculated on the basis of the total tissue burden of PCBs, an 80% reduction in the hepatopancreas was found, concomitant with a doubling of the PCB levels in remaining tissues. However, when data were presented as a concentration, a linear loss from the hepatopancreas was seen, with the concentration in other tissues remaining constant. The authors calculated a half-life for loss of PCBs from the hepatopancreas of 17 days.

Nimmo et al. (1975) sampled shrimp from Pensacola estuary, USA, and measured the relative concentration of PCBs in the various tissues. The hepatopancreas contained the greatest amounts (50–75%) followed by the ventral nerve. The authors studied the uptake of PCBs by pink shrimp, experimentally, using various regimes with dosed food or dosed water. They found the same tissue distribution in pink shrimp that had been exposed to 0.2 μg Aroclor 1254/litre, in water, for 50 days. They concluded that most of the PCBs were taken up directly from the water in both the "wild" and laboratory situation. However, they did not exclude the possibility of some PCBs being taken up from food, which was found under some of the laboratory regimes.

To determine whether there was a concentration below which shrimps would be unable to accumulate PCBs, grass shrimp (*Palaemonetes pugio*) were exposed to flowing water concentrations of 0.04, 0.09, or 0.62 μg/litre. Whole-body residues of 0.2, 1.0, and 10 mg/kg, respectively, were accumulated within 3–5 weeks. Even at the lowest dose, shrimps accumulated more PCBs than the residues found in control shrimp. Concentrations in the shrimp did not reach equili-

brium during the 5-week exposure, but the rate of accumulation decreased towards the end of the exposure. When transferred to clean water, the shrimps lost most of the PCBs within 4 weeks (Nimmo et al., 1975).

Gammarus oceanus were exposed by Wildish & Zitko (1971) to Aroclor 1254 concentrations of 2.5, 10, or 20 mg/litre for up to 6 h. Uptake increased with increasing PCB concentration. Uptake decreased to half of the initial rate after 4–6 h exposure at 20 mg/litre. There was little or no uptake by dead animals. Although uptake was related to branchial surface area, branchiae were not necessary sites of uptake, since uptake could occur at an unchanged rate following branchial removal. The authors did not find any change in the rate of uptake during the intermoult stage.

Zhang et al. (1983) exposed *Daphnia magna* to ^{14}C-labelled 2,2'-dichlorobiphenyl, 2,5,4'-trichlorobiphenyl, 2,4,6,2'-tetrachlorobiphenyl, or 2,4,6,2',4'-pentachlorobiphenyl at 50 μg/litre. Equilibrium was reached after 20 h for all except the pentachlorobiphenyl, which had not reached equilibrium within 24 h. Bioaccumulation factors at equilibrium ranged from 3741, for the dichlorobiphenyl, to 18 144, for the trichlorobiphenyl. Concentration factors were not significantly related to the water solubility or chlorine content of the biphenyl, but there was a tendency for the bioaccumulation factor to increase with chlorine content and decreasing water solubility. The authors studied the rate of depuration and found it to increase with increasing water temperature between 2 and 22 °C. The rate of depuration was also faster for the dichlorobiphenyl than for the pentachlorobiphenyl; after 48 h, the amount of PCBs remaining in *Daphnia* was 22% and 77% (at 10–11 °C) for the 2 chlorobiphenyls, respectively.

(*b*) *Uptake from sediment*

Sediment was collected from the field and spiked with Phenochlor DP-5 to achieve a final PCB concentration of 0.65 mg/kg dry weight, compared with 0.2 mg/kg in unspiked sediment (Elder et al., 1979). Worms (*Nereis diversicolor*) were then added to aquaria containing the sediment under flowing seawater. Equilibrium was reached within 40–60 days, by which time both groups had concentrated the PCBs by 3.5 times. Upon transfer from spiked to unspiked sediment,

the worms took 2 months to attain body levels of PCBs comparable with those of the unspiked group. A half-life of approximately 27 days was calculated for incorporated PCBs.

Fowler et al. (1978) exposed *Nereis diversicolor* to spiked sediment containing 9.3 or 80 mg Phenochlor DP-5/kg (dry weight), for 120 days, compared with 0.11 mg PCB/kg in unspiked sediment. At the beginning of the study, worms in the unspiked sediment had body residues of 0.59 mg/kg dry weight and reached a steady state at 1.2 mg/kg. Those exposed to spiked sediment reached a steady state after a period of approximately 2 months, with concentration factors ranging from 3 to 4. The worms maintained at the highest level of PCBs all died within a 90-day exposure period. When transferred to unspiked sediment for a 2-month period, the worms that had taken up PCBs from the unspiked sediment lost PCBs exponentially. In a separate study, worms were exposed to PCBs in water alone at a concentration of 0.57 μg/litre. A steady state was reached much more quickly (2 weeks) than it was in the presence of sediment, with a concentration factor of approximately 800. By comparing these results with field monitoring, the authors calculated the relative importance of the 2 media. They stated that approximately 99% of the PCBs in these studies was taken up from the sediment. When the water overlying the spiked sediment was monitored, 28 ng PCBs/litre was measured (not leached, but a contaminant in the experimental system) reducing the figure of uptake from sediment to 89%.

In a study by Courtney & Langston (1978), 1.1 mg Aroclor 1254/kg was incorporated into intertidal sand. Specimens of 2 intertidal polychaetes (*Arenicola marina* and *Nereis diversicolor*) containing mean residues of 0.017 and 0.11 mg PCBs/kg (wet weight), respectively, were collected. After 5 days in the spiked sediment, they contained 0.24 and 0.36 mg/kg, and, after a further 5 days, 0.39 and 0.49 mg/kg, respectively. During a 3-week post-exposure period, there was no significant loss of these PCB residues. The authors achieved comparable PCB residues in these polychaetes after exposure to 1 μg/litre water or 1 mg/kg sediment.

McLeese et al. (1980) exposed the polychaete worm (*Nereis virens*) and the shrimp (*Crangon septemspinosa*) to sediment containing 0.016–0.58 mg Aroclor 1254/kg (dry weight) for 32 days. Uptake

was found to be dependent on the exposure concentration and, in the case of the worms, on the exposure period. The accumulation of PCBs was inversely related to animal size; at 32 days, concentration factors for worms ranged from 10.8 for 0.6-g worms to 3.8 for 4.7-g worms following exposure to 0.17 mg PCB/kg. Factors of 3.5 and 1.9 were found for shrimps weighing 0.1 and 2.9 g, respectively, after exposure to 0.13 mg Aroclor/kg. Shrimps were found to accumulate, on average, 60% less PCBs than worms per unit weight. During the 26 days following exposure, there was not any obvious loss of PCBs from the worms.

Rubinstein et al. (1983) collected sediments containing various levels of pollutants (PCBs, 0.46–7.28 mg/kg dry weight; Cd; Hg) and organic matter (5.5–22.3%). During a 100-day exposure period, only small increases in PCB concentrations were detected in hard clam (*Mercenaria mercenaria*) and grass shrimp (*Palaemonetes pugio*). Higher concentrations of PCBs were accumulated by *Nereis virens*. Uptake was found to be more dependent on the organic content of the sediment than on the exposure concentration. Concentration factors ranged from 1.59 in a low organic sediment to 0.15 in a high organic sediment. The authors also calculated the maximum water exposure concentration eluted from each of the sediments. On the basis of a concentration factor of 800, calculated by Fowler et al. (1978) for the uptake from water of *Nereis* sp., body residues of between 0.007 and 0.034 mg PCBs/kg (wet weight) would have been expected if accumulation were dependent purely on direct partitioning from water. However, whole-body residues of PCBs were found to be 0.4–0.63 mg/kg, suggesting that pathways other than direct uptake from water (e.g., ingestion and sorption) con- tributed significantly to the accumulation of PCBs by the polychaete.

Freshwater prawns (*Macrobrachium rosenbergii*) and clams (*Corbicula fluminea*) were exposed to contaminated sediments for 48–50 days (Tatem, 1986). Prawns were exposed to sediment containing approximately 62 mg PCBs/kg (dry weight) and to the same sediment diluted with sand to 50 and 10% of the original. Clams were exposed to 100, 50, or 10% of another sediment containing approximately 2 mg PCBs/kg at 100%. The amount of PCBs accumulated was related to the exposure concentration, with the highest concentration factors at the lowest exposure (10%) level.

Bioaccumulation factors for prawns ranged from 0.1 to 0.9 for Aroclor 1242 and from 0.2 to 2.4 for Aroclor 1254, relative to sediment concentrations. Exposed clams accumulated PCBs (Aroclors 1242 and 1254) at concentration factors of 0.54–12.52, relative to sediment. When tissues were analysed for Aroclor 1242 and 1254, maximum concentrations in prawns were attained at 7 and 40 days for the 2 Aroclors, respectively. Exposure of prawns at 100 and 50% dilution of sediment killed all the animals after 62 and 70 days, respectively. Clams survived exposure.

Clark et al. (1986) investigated the accumulation of sediment-bound PCBs by fiddler crabs (*Uca pugilator*) and (*Uca minax*). Mud and mud/sand sediments were used; both were naturally contaminated with PCBs and no further PCBs were added. Both species were exposed to a mud sediment containing 1.04 mg PCBs/kg and to a mud/sand sediment containing 0.37 mg/kg (dry weight). Concentration factors, after a 28-day exposure, were 0.19 and 0.79, for *U. minax*, and 0.2 and 0.59, for *U. pugilator*, for the 2 sediments, respectively. In a second study, using mud with 0.97 mg PCBs/kg and mud/sand with 0.55 mg PCBs/kg, *U. pugilator* showed concentration factors of 0.58 and 0.71, respectively, after 28 days. The authors did not find any detectable PCBs in the overlying water, suggesting that the PCBs are tightly bound to the sediment and leach out only very slowly. Following transfer to uncontaminated sediment on day 42, no PCB residues were detected in *U. pugilator* on day 56, or in *U. minax* on day 63.

Lynch & Johnson (1982) exposed the amphipod (*Gammarus pseudolimnaeus*) to 2,4,5,2',4',5'-hexachlorobiphenyl added to sediment in flow-through bioassays. Water overflowing from the tank containing the contaminated sediment was directed into a second tank where further amphipods were exposed without sediment. The hexachlorobiphenyl was labelled with ^{14}C and added to the sediment at 1 mg/kg; the system was allowed to equilibrate for 7–15 days prior to addition of amphipods, which were sampled from the tanks after 24, 48, 96, and 192 h. In the initial studies, the specific activity of the labelled hexachlorobiphenyl was insufficient to detect the hexachlorobiphenyl concentrations in water. However, it was clear that amphipods in the tank with the sediment accumulated more hexachlorobiphenyl than animals exposed only to the water overflow

(8.8–10.5 times more PCBs). Removal of organic matter from the sediment, by combustion, before addition of the PCB, increased uptake of the hexachlorobiphenyl by increasing the availability of the material to the *Gammarus*. In later studies, specific activity was increased and water concentrations could be measured. These were very low, ranging between 11 and 35 ng/litre in the upper tank and 9 and 25 ng/litre in the lower tank. The lower end of this range was found later in the exposure period suggesting that less hexachlorobiphenyl was released over time. There was little difference in concentration between water taken from the surface and that sampled close to the sediment suggesting rapid mixing of the overlying water. In this later series of studies, the authors demonstrated that both the organic matter content of the sediment and the presence of smaller particle sizes (silt and clay) reduced uptake of hexachlorobiphenyl by the amphipods. Organic matter was the more important factor. Adding maple leaves, to give about 70% organic content in the sediment, reduced hexachlorobiphenyl uptake to between 10 and 20% of that in sediment without organic matter. Very high bioconcentration factors were calculated relative to the very low water concentrations of hexachlorobiphenyl (ranging between 27 000 and 1 000 000 in the upper tank and 2000 and 460 000 in the lower tank, increasing with exposure period). These factors would be very low relative to sediment concentrations of the PCB. However, it is clear that the amphipod can accumulate hexachlorobiphenyl, leaching in very small amounts from contaminated sediment.

Cores of lake sediment complete with overlying water were taken by Larsson (1984) and transported back to the laboratory, still in the sampling tube. PCBs were introduced at different dose levels by injection through silicon septa in the walls of the tubes and spread evenly 10 mm below the surface. The cores were allowed to stabilize in the dark for 1 week at which time 80–100 chironomid larvae were introduced. After 8 weeks, the systems were moved and kept at 20 °C in the light. After 2 days, the chironomid larvae began to pupate and emerge. The study was terminated after 10 weeks. PCBs were measured in sediment, larvae, adults, and exuviae (discarded skins after emergence). Ranges of PCBs in sediment were between 0.5 and 14 mg/kg giving rise to residues in larvae, exuviae, and adults directly related to sediment concentrations. There was "biomagni-

fication" between larvae and adult. There was loss of body weight between the final larval stage and the adult, but little loss of PCBs (only 17% was retained in the exuviae). The author stated that the low variation in uptake between animals is an indication of passive physicochemical factors being involved in the handling of PCBs by chironomids. Active uptake via ingestion would be expected to lead to more variation in results. Meier & Rediske (1984) also monitored the uptake of PCBs from contaminated sediment into chironomid larvae (*Glyptotendipes barbipes*). Concentration factors for Aroclor 1242 from sediment ranged between 20 and 130 for exposures of between 0.01 and 1.0 mg/kg, considerably lower than concentration factors relative to water (10 000 for these organisms) (Sanders & Chandler, 1972). Addition of oil, commonly found in polluted areas where PCBs spills are likely, reduced the uptake of PCBs from the sediment.

(*c*) *Uptake from food*

A detritus diet containing 17 μg Aroclor 1242/kg (wet weight) was fed to male fiddler crabs (*Uca pugnax*) for 34 days (Marinucci & Bartha, 1982). The *Spartina* detritus was placed in the culture system at the start of the study and, because of rapid depletion, was renewed after 19 days of exposure. Since PCBs leached continually from the food source into the water, a second study was carried out to examine the uptake of PCBs from water alone. Contaminated detritus was mixed thoroughly with water and allowed to equilibrate for 24 h. Water levels were found to be 14–15 μg/litre. Aroclor 1242 was accumulated at a more rapid rate from PCB-laden detritus than from water alone. The linear accumulation rate from litter was calculated to be 1 μg PCBs/day per animal whereas, from water alone, the uptake was 0.1 μg PCBs/day per animal. Aroclor 1242 was highly concentrated in the hepatopancreatic tissue. It was found that the PCB residue in the crabs was inversely related to their weight. Comparison of the concentrations of PCBs in animals of the same weight shows that, at the end of the 34 day exposure, those exposed to water alone had taken up approximately half of the PCBs of those exposed to detritus. The authors concluded that the crabs in the study accumulated a similar amount of PCBs from both the food and the water.

Pinkney et al. (1985) exposed the amphipod *Gammarus tigrinus* to Aroclor 1254 (^{14}C-labelled) in fungus (*Fusarium oxysporum*) as a food item. The fungus contained 195.8 mg Aroclor/kg dry weight. Accumulation of PCBs was rapid, reaching a constant level in the amphipods of 23 mg/kg after 9–24 h. Similar exposure of the amphipods, but with exclusion from direct contact with the fungus by Teflon mesh (to monitor uptake of PCBs leached into the water), resulted in residues of between 0.16 and 3.3 mg/kg (from concentrations in the water at 0.03 μg/litre), representing between 0.6 and 13.9% of uptake from water and food combined. The PCB residues in the amphipods were also monitored over 144 h on uncontaminated food to measure the elimination rate. The water was changed every 24 h. Within this period, 57% of the accumulated PCBs was eliminated.

(d) Comparison of different routes of uptake

In a study by Wyman & O'Connors (1980), the uptake by the marine copepods *Acartia tonsa* and *Acartia clausi* of ^{14}C-labelled Aroclor 1254 from water, inorganic sediment, and food, was monitored over a period of 48 h. *Acartia* were exposed to water concentrations of 10 μg PCBs/litre. An asymptotic uptake curve was observed; equilibrium was reached after 36 h, corresponding to whole-body residues of 248 mg PCBs/kg (dry weight) for *A. tonsa* and 223 mg/kg for *A. clausi*. During exposure, water concentrations fell rapidly to 5 or 6 μg/litre. A similar pattern of uptake was found after exposure to sediment contaminated with 20 mg PCBs/kg with maximum levels of PCBs in *A. tonsa* of 22 mg/kg after 30 h. As in the water exposure, levels of PCBs in sediment fell rapidly from 20 mg/kg to 14 mg/kg and then slowly to 7 mg/kg at the end of the study. Water levels were initially 0.62 μg/litre and fell to 0.15 μg/litre. Uptake of PCBs by *A. tonsa* from phytoplankton contaminated with 80 mg PCBs/kg (wet weight) was very rapid and reached a maximum after 5 h at 61 mg/kg, but subsequently declined after exhaustion of the food supply. PCB concentrations in water were similar to those found when copepods were exposed to contaminated sediment, copepods exposed to these water concentrations alone accumulated significantly less PCBs than those fed PCB-dosed phytoplankton.

McManus et al. (1983) exposed the marine copepod *Acartia tonsa* to ^{14}C-Aroclor 1254 either in the food, as phytoplankton containing approximately 1.3 mg PCBs, or in water at 1.5 μg/litre, for a period of 30 h. For copepods exposed to contaminated phytoplankton, PCB levels ranged from 117 to 163 mg/kg dry weight. For copepods exposed to contaminated water alone, levels ranged from 82 to 104 mg/kg. When transferred to clean water, the authors found that copepods lost PCBs at a significantly faster rate if they were fed during depuration; after 36 h, PCB concentrations in copepods fed during depuration were 10 mg/copepod whereas those starved contained 30 mg/copepod. No significant difference in depuration rate was found between those exposed via food and those exposed via water. In a second study, elimination in males and females was compared. Although both sexes contained similar residues at the start of depuration (117 mg/kg and 95 mg/kg, respectively), after 36 h, females contained significantly lower levels of PCBs than males. During depuration, faecal pellets and eggs were analysed; similar levels of PCBs were found in both male and female faecal pellets during this period, but levels of PCBs more than four times that in the females were found in eggs (407.5 mg/kg dry weight after 4 h), indicating that egg production is an important route for PCB elimination.

4.2.4.4 *Fish*

Fish of all life stages have been shown to take up PCBs readily from water; bioconcentration factors are high. Time taken to reach equilibrium is variable, but often long, in excess of 100 days. PCBs with greater chlorination are more readily taken up and retained. PCB body burden tends to increase with age and levels are higher in fish with a greater lipid content. The accumulated PCBs are concentrated in lipid-rich tissues. PCBs of lower chlorination are eliminated more rapidly. Loss of PCBs is evident when exposure ends; an initial rapid loss is followed by a slower rate of loss. Half-life estimates, therefore, vary greatly, from a few weeks to several years. Reproduction, with the production of a large mass of eggs or sperm, allows loss of substantial amounts of the PCB residue. Depending on the species, habitat, and behaviour, PCBs can be taken up from water, sediment, or food to different degrees.

(*a*) Uptake from water

Califano et al. (1980) maintained larval striped bass (*Morone saxatilis*) in Hudson river water (filtered and unfiltered) contaminated with ^{14}C-Aroclor 1254 at 1.36 μg/litre for a period of 48 h. Whole-body residues for filtered and unfiltered water were not significantly different at 5 mg/kg and 5.9 mg/kg, respectively. Uptake between 34 and 48 h was very slow, suggesting a steady state had already been reached. Exposure of fish for a further 72 h in unfiltered water, supported this theory. Elimination was slow, only 18% being lost in 48 h following a 24-h exposure.

The PCB uptake pattern in lake trout (*Salvelinus namaycush*) sac fry was studied by Mac & Seelye (1981) by exposing them to a nominal concentration of 50 ng Aroclor 1254/litre for 48 days. Patterns of accumulation were similar, regardless of how the data were expressed (wet weight, dry weight, or body burden). PCBs levels increased slowly, reaching a peak after 32 days (just before completion of yolk absorption), and then decreased by day 48.

Hansen et al. (1975) exposed different life-stages of sheepshead minnow (*Cyprinodon variegatus*) to Aroclor 1016 (Table 10). After a 4-week exposure to nominal concentrations of 1, 3.2, or 10 μg/litre, adult fish laid eggs containing on average 4.2, 17, and 66 mg/kg, respectively. DeFoe et al. (1978) exposed fathead minnow (*Pimephales promelas)* to Aroclor 1248 or 1260 at concentrations of 0.1–3 μg/litre, for 240 days (life cycle). Bioconcentration factors for the uptake of PCBs were independent of the PCB concentration in the water. Residues in the fish reached an apparent steady state within about 100 days of exposure and growth. Females accumulated about twice as much PCBs as males, because of their higher body lipid content. The variability of residues in females reflected the variability of their lipid content. Although mechanisms for uptake were similar for both Aroclors, greater body burdens were always achieved with exposure to Aroclor 1260. Bioconcentration factors ranged from 60 000 to 160 000 for males and from 120 000 to 270 000 for females. After transfer to clean water, 18% of Aroclor 1248 was lost within 28 days and 15% of Aroclor 1260 in 42 days. The authors stated that, because of variations between fish, this

10–20% decline in total body burden of PCBs was insufficient to indicate definite PCB elimination over this period.

De Kock & Lord (1988) exposed an estuarine fish, the Cape stumpnose (*Rhabdosargus holubi*) to a flowing water concentration of 1 μg Aroclor 1260/litre for 90 days followed by a 90-day period in clean water. Equilibrium was reached at 90 days with a concentration factor of 24 000. The depuration rate was calculated to be 0.014 days, producing a half-life of 50 days.

Goldfish (*Carassius auratus*) were exposed to Clophen A50 at levels of 0.01, 0.05, 0.1, or 0.5 mg/litre for 18 days (Hattula & Karlog, 1973). Rapid uptake was observed with concentration factors of over 1000 at 18 days, but equilibrium was not achieved within this period. Nearly all the fish exposed to 0.5 mg/litre died within 7 days. After transfer to clean water, fish that had been exposed to 0.1 mg/litre for 13 days and had attained body residues of 70 mg/kg lost half of the PCBs within 3 weeks, but still retained levels of approximately 15 mg/kg, after 70 days.

Yoshida et al. (1973) exposed carp (*Cyprinus carpio*) to ^{14}C-PCBs (equivalent to Aroclor 1254) in water or in food. By measuring the radioactivity, they found similar tissue patterns of uptake from both water and diet. PCBs were localized in the gall bladder, adipose tissue, and hepatopancreas and, in particular, the adipose tissue of the skull.

Hansen et al. (1971) exposed spot (*Leiostomus xanthurus*) to Aroclor 1254 at 1 μg/litre, for 56 days. Maximum tissue levels of PCBs were achieved between days 14 and 28. Highest levels were found in the liver (210 mg/kg, after 28 days) followed by the gills, whole fish, heart, brain, and muscle. Aroclor 1254 was slowly lost from tissues; after 84 days in clean water, levels of PCBs had dropped by 73%.

In a study by Braun & Meyhofer (1977), rainbow trout (*Salmo gairdneri*) fingerlings were exposed to water concentrations of 2 or 20 μg Clophen C/litre, for 8 weeks. Tissue PCB concentrations for gills, muscle, and liver were found to be 0.62, 0.82, and 3.47 mg/kg, respectively, for the lower dose and 12.3, 7.6, and 10.6 mg/kg, for the higher dose. When fish were held in clean water for 10 weeks, following exposure to 2 μg/litre for 8 weeks, residues decreased by

half in the liver and had disappeared completely from the gills, but there was no change in the PCB levels in muscle.

Rainbow trout (*Salmo gairdneri*) were exposed by Guiney et al. (1977) to ^{14}C-labelled 2,5,2',5'-tetrachlorobiphenyl at 0.5 mg/litre for 36 h. The tissue distribution of ^{14}C was measured at regular intervals after transfer to clean water. Carcase, muscle, skin, lower gastrointestinal tract, and fat contained most of the radioactivity (88%). During the first 14 days after exposure, radioactivity increased in adipose tissue, carcase, and eyes. Elimination from most tissues appeared to be biphasic with a 30% loss within 2 weeks followed by a loss of only 6% in the following 126 days. Losses from the bile and blood were very rapid and nearly complete within 14 days. Based on the initial rate of loss, the authors calculated a half-life of 1.55 days, however, the second phase of eliminated PCBs suggested a half-life at 2.66 years. In a similar study, Guiney et al. (1979) calculated half-lives of 1.76 and 1.43 years for female and male rainbow trout, respectively, based on fish sampled 2-34 weeks after exposure. For both sexes the half-life of elimination was recalculated to 0.52 and 0.54 years between weeks 38 and 52 after exposure (the spawning season). The increased elimination appeared to be because of loss via eggs and sperm. Vodicnik & Peterson (1985) found a similar result after dosing yellow perch (*Perca flavescens*); an elimination half-life of 22 weeks was calculated. This was later recalculated to be <0.7 weeks during spawning, returning to 16.3 weeks after the completion of spawning.

(*b*) *Uptake from sediment*

The uptake of Aroclor 1254 from suspended solids by juvenile Atlantic salmon (*Salmo salar*) was studied by Zitko (1974). Aroclor 1254 was mixed with suspended solids (simulated by SilicAR CC7) in hexane at 5 mg/ml. Fish were exposed to contaminated solids at 1 g/litre for up to 144 days. Over this exposure period, the salmon accumulated 134 mg Aroclor 1254/kg.

Stein et al. (1984) exposed English sole (*Parophrys vetulus*) to a sediment concentration of 1 mg ^{14}C-Aroclor 1254/kg (dry weight). Seawater was allowed to flow over the sediment for 6 days before the fish were added. A steady state of PCBs accumulated in the tissues of the fish was achieved after 10 days of exposure. Highest residue

concentrations were found in the bile and the liver. Concentration factors were 10 for the bile and 4 for the liver, with other tissues individually concentrating PCBs by factors of 3 or less. Simultaneous exposure of sole to PCBs and ^{3}H-benzo[*a*]pyrene (3 mg/kg, dry weight) reduced the amount of PCBs accumulated. Stein et al. (1987) collected urban sediment containing aromatic hydrocarbons and PCBs at 32 mg/kg and 2.2 mg/kg dry weight, respectively. English sole accumulated hepatic concentrations of 1.4 mg PCBs/kg (wet weight) over a period of 108 days exposure to the urban sediment. This was 8 times the PCBs accumulated by sole exposed to the control sediment, which did not contain any detectable PCBs. In another study, the same authors added a ^{14}C-labelled PCBs tracer to the urban sediment. The concentration of PCB-derived radioactivity in the liver reached a steady state after 14 days of exposure; the steady state concentration in the carcase was found to be significantly lower.

(c) *Uptake from food*

Lieb et al. (1974) fed rainbow trout *Salmo gairdneri* on a diet containing 15 mg Aroclor 1254/kg for 16 or 32 weeks. PCB levels in the lipid fraction increased rapidly for the first 8 weeks, reaching equilibrium at about 95 mg/kg. The absolute quantity of PCBs continued to increase as the fish grew. The trout had retained 68% of the total PCBs ingested at equilibrium. No elimination was found after transfer to uncontaminated food at 16 weeks (for a period of 16 weeks), or after starving the fish for 8 weeks following exposure for 32 weeks. Reductions in PCB levels were found, but these were cancelled out by concomitant reductions in lipid content.

Coho salmon (*Oncorhynchus kisutch*) parr were fed 10 mg chlorobiphenyls/kg (containing equal parts by weight of 3,4,3',4'-tetrachlorobiphenyl, 2,4,5,2',4',5'-hexachlorobiphenyl, and 2,4,6,2',4',6'-hexachlorobiphenyl) for up to 165 days (Gruger et al., 1975). Most of the PCBs were accumulated in the adipose tissue of the salmon (51.1 mg/kg total chlorobiphenyls after 165 days). Tissue levels of tetrachlorobiphenyl were about half those of either of the two hexachlorobiphenyls throughout the exposure period. When fish were starved for 48 days, the data indicate mobilization or transformation, with, for example, chlorobiphenyls in the spleens lowered by half and in adipose tissue increased 5-fold. Most tissues

showed an increase in PCB levels, especially blood levels. In contrast, when a second group of salmon were fed on a clean diet, chlorobiphenyls were released from adipose tissue and levels increased in some other tissues, such as the lateral line dark muscle tissue. The ratio of the different chlorobiphenyls remained unchanged during both of these post-exposure treatments. Gruger et al. (1976) fed juvenile coho salmon diets containing a mixture of 2,5,2',5'-tetrachlorobiphenyl, 2,4,5,2',5'-pentachlorobiphenyl, and 2,4,5,2',4',5'-hexachlorobiphenyl at 1, 2, and 12 mg/kg, for up to 72 days. A steady state appeared to have been reached between 17 and 35 days at the lowest dose (a whole body concentration of approximately 0.45 μg/kg (wet weight)); steady state was not achieved at the other 2 dose levels. All 3 chlorobiphenyls were accumulated to similar levels. Comparing these data with the study by Gruger et al. (1975), suggests that the position of the chlorine substitution is an important factor.

Hansen et al. (1976a) fed channel catfish (*Ictalurus punctatus*) on a diet contaminated with 20 mg Aroclor 1242/kg. The total burden of PCBs (μg PCB/fish) increased exponentially with exposure time. When fish were placed on a clean diet (from day 84 for 56 days) a slight net decrease in body burden was observed, but levels remained constant when fish were placed on a clean diet for 56 days after 140 days exposure. On return to a PCB-contaminated diet, accumulation rates returned to those previously observed. The authors noted that, during PCB-free periods, there was a shift in residues from edible carcase to offal.

Mayer et al. (1977) fed fingerling coho salmon with Aroclor 1254 at concentrations ranging between 1.45 and 14 500 μg/kg body weight. Equilibrium was reached after 112 days at concentrations of 1.45, 14.5, and 145 μg/kg, with whole body residues of 0.47, 0.5, and 3.8 mg/kg, respectively. A steady state was reached at the 2 highest dose levels of 1450 and 14 500 μg/kg after 200 days, with corresponding residues of 57 and 659 mg/kg. In another study, channel catfish (*Ictalurus punctatus)* were exposed to Aroclors 1232, 1248, 1254, and 1260 in the diet at concentrations of 48 or 480 μg/kg body weight, for 193 days. Equilibrium was only achieved at the lowest exposure dose of Aroclor 1232, within 150 days, with a whole-body burden of 4.5 mg/kg. Similar whole-body residues were

achieved at the lowest dose of the other Aroclors, but no steady state was reached. At the higher dose, accumulation increased in the order Aroclor 1232 = 1248 < 1254 < 1260, with residues ranging from 13 to 32 mg/kg after 193 days.

When Zitko (1974) fed juvenile Atlantic salmon (*Salmo salar*) diets containing 10 or 100 mg Aroclor 1254/kg, accumulation reached equilibrium within 30 days at the lower dose, with a whole-body residue of approximately 3.8 mg/kg. Equilibrium was not reached within 200 days at 100 mg PCBs/kg. A whole-body residue of 30 mg/kg was recorded at 181 days.

Zinck & Addison (1974) administered a mixture of 2-, 3-, and 4-chlorobiphenyl to thorny skate (*Raja radiata*) and winter skate (*Raja ocellata*) by intravenous injection. All three congeners were cleared rapidly from blood plasma, 3-chlorobiphenyl consistently being cleared more rapidly than the other two. Less than 6% of 3-chlorobiphenyl remained in the plasma after 15 min compared with 30% for the other chlorobiphenyls. All three accumulated in the other tissues of *R. radiata*, principally in the liver and muscle. Tissue levels of 3-chlorobiphenyl were consistently less than the others during the 53-h sampling period.

In a study by Guiney & Peterson (1980), both yellow perch (a non-fatty fish) and rainbow trout (a fatty fish) were dosed with 0.8 μg of ^{14}C-labelled 2,5,2',5'-tetrachlorobiphenyl, either orally or by intraperitoneal injection. Whole-body elimination was found to be similar for both species and routes. A 20–30% elimination was observed after 3–4 days with virtually no more PCBs being eliminated during the rest of the 32-day sampling period. Tissue distribution varied between the 2 species; uptake in the perch was mainly concentrated in the viscera and carcase, whereas, in the trout, skeletal muscle and carcase were the major sites of uptake.

Niimi & Oliver (1983) calculated the biological half-life of 31 dichloro- to decachlorobiphenyl congeners, 105 days after a single oral dose of 46–261 mg/kg was administered to rainbow trout (*Salmo gairdneri*). Whole-body half-lives increased from 5 days to > 1000 days as the number of chlorines on the biphenyl increased. From structure-activity analysis of half-lives in whole fish, the authors concluded that elimination was enhanced for congeners with a lower

chlorine content and no chlorine substitutions in the *ortho* positions, and for those with 2 unsubstituted carbons adjacent on the biphenyl.

4.2.4.5 Birds

PCBs are taken up from contaminated food or water and concentrated in the fatty tissues of birds. PCBs of higher chlorination levels are accumulated to a greater extent. Egg-laying females can lose substantial amounts of PCBs from body tissues by transferring the PCBs to the eggs. Redistribution of residues occurs on starvation (of significance during the migration of birds in the wild). Expressed as a whole-body concentration, PCB residues fall during starvation. However, expressed as a concentration in fat, residues rise. Most critically, PCB residues in the brain increase during starvation and this may kill the birds without further intake of PCBs.

Brunström et al. (1982a) injected the yolk of developing hens' eggs, on day 4 of incubation, with ^{14}C-labelled 2,4,2',5'-tetrachlorobiphenyl at a concentration of 5 mg/kg. One hour after injection, radioactivity was found in the sub-blastodermic fluid, the highest concentrations being in amniotic membranes. None was present in the yolk, albumen, or embryonic tissues. Uptake was uniform throughout the embryo, after one day, and, as tissues developed, became concentrated in certain of them, such as the liver, kidney, and fluid brain vesicles, by day 7. ^{14}C was found uniformly in the yolk after 11–14 days and was highly concentrated in the first bile produced on day 11. The labelled PCBs accumulated in fatty tissue as it developed from day 14 onwards. In the hatched chick, large amounts of radioactivity were found to be concentrated in the gall bladder, intestine, cloaca, and the coiling of the gizzard. When either 3,4,3',4'-tetrachlorobiphenyl or 2,4,2',5'-tetrachlorobiphenyl was injected into the air sac of hens' eggs on day 14 of incubation at 0.4 mg/kg, no difference in distribution pattern was observed 1–5 days later (Brunström & Darnerud, 1983). The highest amounts of radioactivity were found in the fatty tissue, liver, kidneys, and the gall bladder, ^{14}C was also found in the bone marrow, the adrenals, and the gonads, but to a lesser extent. The yolk contained less radioactivity than the yolk analysed in the previous study by Brunström et al. (1982a), because the PCBs were administered via the air sac.

White leghorn hens were exposed to 50 mg Aroclor 1254/litre in their water for 6 weeks (Tumasonis et al., 1973). PCB residues in the yolks of eggs laid increased during the exposure period to a peak, after 6 weeks, of approximately 205 mg/kg. When hens were given clean water, the yolk levels of PCBs quickly dropped within 5 weeks to approximately 100 mg/kg, and then more slowly until, after 20 weeks without Aroclor 1254 in their water, the hens laid eggs containing 0.7 mg/kg.

During a 4-week exposure to Aroclor 1242, 1254, or 1260, in the feed of one-day-old chicks, Harris & Rose (1972) found that PCBs accumulated in the fat and that this accumulation increased with increasing exposure concentrations of 100, 200, and 400 mg/kg. At the 2 highest dose levels, the hens accumulated more of Aroclor 1260 than of the other 2 Aroclors (i.e., 482, 1427, and 2151 mg Aroclor 1260/kg at the 3 exposure concentrations, respectively). At the highest dose, there was high mortality during exposure to Aroclor 1242 and 1254 and this might have affected the residues found.

Greichus et al. (1975) fed white pelicans (*Pelecanus erythrorhynchos*) on a fish diet containing 100 mg Aroclor 1254/ day, for 10 weeks. PCB residues were measured in the carcase, liver, feathers, and brain; mean residues found were 2130, 290, 120, and 110 mg/kg wet weight, respectively.

In a study by Dahlgren et al. (1972), 11-week-old pheasant (*Phasianus colchicus*) were dosed with one capsule per day containing 210 mg of Aroclor 1254. Birds that died between days 1 and 5 contained, on average, PCB residues of 520 mg/kg in the brain, 2500 mg/kg in the liver, and 140 mg/kg in muscle. Birds that were sacrificed over the same period had mean brain, liver, and muscle PCB levels of 370, 1900, and 83 mg/kg, respectively. All birds dosed with only 10 mg of Aroclor 1254 per day died within 180 days and contained average brain and liver residues of 360 and 1200 mg/kg, respectively.

Södergren & Ulfstrand (1972) fed robins (*Erithacus rubecula*) meal-worms containing 1 μg of Clophen A50/day for 15 days. Brain, breast muscle, and carcase were analysed and contained mean PCB residues of 0.35, 0.55, and 4.5 mg/kg fresh weight, respectively. A second group of robins was starved following dosing and all died

within 48 h. PCB levels were higher in the brain and breast muscle at 1.1 and 1.3 mg/kg, respectively, but carcase PCB levels were lower on a fresh weight basis at 2.6 mg/kg. When the carcase lost some of its fat content during starvation, PCB levels in terms of fresh weight decreased. Consequently, because of the low remaining fat content, residue levels in terms of fat weight increased. Another group of birds were fed both PCBs and DDT (10.5 μg/day) for 15 days and then starved. PCB levels in all 3 tissues analysed were higher than those in birds administered PCBs alone followed by starvation; residues were: brain, 9.3 mg/kg fresh weight, breast muscle, 8.8 mg/kg, and carcase, 4.5 mg/kg.

Cormorants (*Phalacrocorax carbosinensis*) were kept on a fish diet contaminated with PCBs for one month, followed by gelatin capsules of PCBs administered daily for the remainder of the exposure (Koeman et al., 1973). After 14 weeks, the dose rate of Clophen A60 was increased periodically during the exposure period from 200 to 500 mg/kg. The birds died between days 55 and 124, and overall residues of PCBs increased in the tissues, the longer the birds survived. Total-body residues ranged from 850 to 2750 mg PCBs/kg (wet weight) at death. Brain and liver residues ranged from 76 to 180 mg/kg and from 210 to 290 mg/kg, respectively. The fat of 2 birds was analysed for PCBs and was found to contain 10 300 and 20 500 mg/kg.

Harris & Osborn (1981) dosed wild puffins (*Fratercula arctica*) by implantation with 30–35 mg of Aroclor 1254. PCBs were quickly taken up in fat, with concentrations rising to 10–14 times that in control birds (highest fat residue 654 mg/kg wet weight), and remaining at this level for up to 10 months. Levels slowly declined, but were still twice those of controls after 34 months. PCB concentrations in the liver and muscle tissue were highest shortly after dosing (48.4 and 25.2 mg/kg, respectively) and declined until, after 16 months, no PCBs were detectable. Levels of PCBs in the kidneys and brain were variable with no consistent trends.

Common grackles (*Quiscalus quiscula*), starlings (*Sturnus vulgaris*), red-winged blackbirds (*Agelaius phoeniceus*), and brown-headed cowbirds (*Molothrus ater*), were fed diets containing 1500 mg Aroclor 1254/kg over an 8-day period (Stickel et al., 1984). PCB

residues in the brains of birds that died were found to be higher than those in birds that were sacrificed over a similar period. PCB residues ranged from 349 to 763 mg/kg in birds that died and from 54 to 301 mg/kg in birds sacrificed. Liver and whole-body residues tended to be higher in birds that died, but they overlapped to a large extent. PCB residues in whole bodies on a lipid basis showed the most clear-cut difference, ranging from 22 600 to 98 600 mg/kg for birds that died and from 6690 to 22 500 mg/kg for those sacrificed. PCB residues in grackles declined slowly, when the birds were placed on a clean diet. From a whole-body level of 1300 mg/kg, residues declined to 169 mg/kg, 224 days later. The rate of decline was irregular, but a half-life was estimated at 89 days over this period of loss.

4.2.4.6 Mammals

Olsson et al. (1979) fed mink (*Mustela vison*) on a diet containing 11 mg PCBs/kg for 66 days. Mink accumulated 310 mg PCBs/kg in extractable fat over the exposure period. Control mink were found to contain 14 mg PCBs/kg, and, when the control feed was analysed, it was found to contain 0.05 mg PCBs/kg. The authors also found a significant increase in cadmium uptake in the kidneys of PCB-treated animals compared with controls. In another study on mink (*Mustela vison*), Hornshaw et al. (1983) administered various PCB-contaminated fish diets containing between 0.21 and 1.5 mg PCBs/kg. Adipose tissue samples were taken after 6–8 weeks and after 18 weeks exposure (Table 11). The amount of PCBs accumulated was directly related to the amount of PCBs in the diet; mean PCB residues ranging from 4 to 24.8 mg/kg after 6–8 weeks and from 8.1 to 42.8 mg/kg after 18 weeks. When expressed as individual congeners, it can be seen that the mink showed the highest accumulation of the PCBs with the chromatographic peak corresponding to 2,4,5,2',4',5'-hexa-chlorobiphenyl. To determine the rate of PCB elimination, male mink that had been on a fish diet containing 1.5 mg PCBs/kg for 10 weeks were transferred to a control diet. Over this period, adipose tissue residues of 32 mg PCBs/kg had accumulated. Over the 16-week elimination period, 60.3% of the total PCB burden of the adipose tissue was eliminated. This consisted of a loss of 87.2% of 2,5,2',5'-tetrachlorobiphenyl, 88.9% of 2,3,6,2',5'-pentachloro-

biphenyl, and 55.4% of the hexachlorobiphenyl. The half-life for total PCBs in mink adipose tissue was calculated to be 98 days.

Wren et al. (1987a,b) fed mink on a commercial mink food supplemented with 1 mg Aroclor 1254/kg for a period of 6 months. Male mink had liver residues of 1.98 mg PCBs/kg after 118 days and 2.8 mg/kg after 183 days exposure. The liver of a female, analysed on day 161 contained a residue of 3.1 mg PCBs/kg. Liver PCB levels in 5-week-old kits were similar to those in adult mink fed the experimental diet for several months. Bleavins et al. (1981) measured the relative importance of placental transfer and milk in the transfer of PCB residues from mother mink to offspring. Newborn kits contained less than 0.1% of a dose of PCBs injected into the mother mink. At 2 weeks of age, the kits contained 1.2% of the dose given to the mother, suggesting that lactation is a major route of exposing the young to PCBs and a major route for the loss of PCBs from the mother. Placental transfer of PCBs was greater in the ferret than in the mink (Bleavins et al., 1984). The ratio of placental to mammary transfer was 1:15 for offspring whose mothers were dosed during the first trimester of pregnancy and 1:7 for mothers exposed during the last trimester.

Big brown bats (*Eptesicus fuscus*) were fed on mealworm diets containing 9.4 mg Aroclor 1254/kg for up to 37 days (Clark & Prouty, 1977). In bats sacrificed on day 37, residues ranged from 29 to 121 mg PCBs/kg (wet weight) for the carcase and from not detectable to 4.2 mg/kg in the brain. Bats that were starved following exposure showed a significant correlation between increasing brain PCB concentrations and carcase lipid concentrations. The authors stated that PCBs increased in brain tissue as carcase fat was metabolized. Clark (1978) exposed pregnant big brown bats to a mealworm diet containing 6.36 mg Aroclor 1260/kg for approximately 18–28 days, until the young were born. Mean carcase levels of PCBs were 20.34 mg/kg in parent females and 4.38 mg/kg in litters. Levels of PCBs in both adults and young continued to rise throughout the sampling period; the longer the gestation time, the higher the PCB level in the sample.

4.2.5 Appraisal

Experimental work on mammals has been concentrated on terrestrial species. Problems with PCB toxicity are important for marine mammals, but these are less convenient for experimental study. Results in this section, therefore, have to be related to field observations on marine species.

Mink take up more chlorinated components of PCB mixtures and can accumulate large residues of PCBs. On cessation of exposure, more tetrachloro- and pentachlorobiphenyls were eliminated than hexachlorobiphenyl. The half-life for total PCBs was calculated to be 98 days. PCB residues are transferred from mother to offspring. The relative importance of transplacental transfer and transfer in milk varies between species. Redistribution of residues takes place on starvation, which is of significance for migratory species; brain residues, which may be fatal with no further intake of PCBs, increase as animals are starved.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Levels in the environment

PCBs were detected in the environment in the late 1960s (Risebrough et al., 1968; Jensen et al., 1969) and, within a short time, were reported as contaminants in almost every component of the global ecosystem including air, water, soil, fish, wildlife, human blood, adipose tissues, and milk (Holdrinet et al., 1977; Wassermann et al., 1979; Ballschmitter et al., 1981; Buckley, 1982; Safe, 1982b; Bush et al., 1985; Kannan et al., 1988; Tanabe, 1988).

The lipophilic properties of PCBs are the basis of the bioaccumulation and biomagnification that has been demonstrated and, thus, numerous sources within the environment can lead to human exposure.

High-resolution, gas-chromatographic analysis has shown that the congener composition and relative concentrations of the individual components in many PCB extracts from environmental samples differ markedly from those in the commercial PCBs (Jensen & Sundström, 1974a; Wolff et al., 1982a; Safe et al., 1985a; Brown et al., 1987a,b).

A major problem with data concerning PCB levels in environmental samples is that they normally are only available for "total PCBs" and that there are much fewer data on actual "PCB patterns". Moreover, when comparing results produced from different laboratories or from the same laboratory at different times, an additional difficulty may arise from differences in the sampling and analytical techniques used. It is difficult, if not impossible, to compare data obtained with different analytical methods, from different laboratories, and countries. Nowadays, the older data seem less reliable, especially in the light of the use of improved analytical methods and better sampling techniques (WHO/EURO, 1987). A comprehensive review of world PCB levels was published by Wassermann et al. (1979).

5.1.1 Air

PCB concentrations in air differ markedly from location to location, with the lower levels found over the oceans or over non-industrialized regions, such as the Canadian Northwest territories. In general, levels over industrialized areas or over landfills are the highest. Apparently, these levels influence PCB levels in rainwater and there is a gradient of values in air from industrial to rural areas. Some typical values can be found in Table 12.

MacLeod (1981) described a method for the analysis of PCBs using low-volume, indoor air sampling to estimate the presence of PCBs in indoor air in work-places and homes in the USA. Three facilities, an industrial research facility, an academic facility, and a shopping complex were sampled. The periods of sampling ranged from 2 days up to 6 months. The average concentrations (calculated as Aroclor 1242 plus Aroclor 1254) ranged from 44 up to 240 ng/m^3. Outdoor levels of up to 18 ng/mg^3 were found. In the homes, air samples from 14 areas (of which 9 were kitchens) were also analysed. The average concentrations in the kitchens ranged from 150 up to 500 ng/m^3 and, in the other rooms, from 39 to 170 ng/m^3. In a library, a level of 400 ng/m^3 was found.

The levels of PCB exposure that may occur in buildings in the USA were determined by Oatman & Roy (1986). Air samples and surface wipe samples were taken in 5 state-owned, office buildings and 2 elementary schools. The average levels of airborne PCBs in buildings with PCB transformers were nearly twice the levels in buildings without transformers, i.e., 457 ± 223 and 229 ± 106 ng/m^3, respectively. The mean of the surface wipes taken in buildings without PCB transformers was 0.17 and that in the buildings with transformers 0.23 μg/100 cm^2. There was a wide variation between the different buildings and, as shown above, the presence of transformers influenced the indoor PCB concentrations.

5.1.1.1 Rain and snow

In the Netherlands, at Bilthoven, the PCB-concentrations in rainwater ranged from 0.01 to 1.5 μg/litre (van Zorge, cf. WHO/EURO, 1985). In the Federal Republic of Germany, concentrations of 0–4 ng/litre were found (DFG, 1988).

Table 12. PCB levels in air in several countries

Country	Location and/or type of sample	PCB levels average and/or range	References
Canada	Northwestern territories	0.002-0.07 ng/m^3	Bidleman et al. (1978)
Germany	Industrial area (Ruhr area) Non-contaminated area	3.3 ng/m^3 0.003 ng/m^3	DFG (1988)
Japan	Within industrial plants:- PCB vapours - PCBs on airborne particulates	13-540 μg/m^3 4-650 μg/m^3	Tatsukawa & Watanabe (1972)
	North Pacific, South Pacific, Indian, Antarctic and South Atlantic Oceans	0.1-0.3 ng/m^3	Tatsukawa & Tanabe (1983)
	North Atlantic Ocean	0.5 ng/m^3	Tatsukawa & Tanabe (1983)

Table 12 *(continued)*

Country	Location and/or type of sample		PCB levels average and/or range	References
Sweden	Several locations		0.8[a]-3.9 ng/m^3	Ekstedt & Odén (1974)
USA	Near the North-East Coast Over the Atlantic Ocean, 2000 km away from the industrial complex		5 ng/m^3 0.05 ng/m^3	Harvey & Steinhauer (1974)
	several locations		1-50 ng/m^3	Panel on Hazardous Substances (1972) cf WHO/EURO (1988)
Yugoslavia	Bela Krajina:	- 300 m from an industrial plant - air near a waste landfill - over the River Kruga	4-7 µg/m^3 45 µg/m^3 2-5 µg/m^3	Jan et al. (1988b)

[a] Limit of determination.

5.1.1.2 Natural gas

PCBs were first identified in gas pipelines in January 1981, when a PCB-containing oil condensate was found in the gas meters of some residential customers in Long Island, New York. Voluntarily monitoring of condensate and natural gas by 33 transmission companies, showed the presence of PCBs in 12 companies. PCBs were also found in gas pipelines. Condensate is a mixture of heavier hydrocarbons and other liquids, such as water, that condenses, because the gas is transmitted under pressure. This condensate tends to collect in pools in the pipes. In the period 1981–83, 1841 samples of condensate from gas pipelines were analysed: 659 (35.8%) of the samples contained <25mg/kg; 65.8% of the samples contained <1000 mg/kg, and 0.4%, >10 000 mg/kg. The maximum level that was found was 42 394 mg/kg (Versar Inc., 1984).

In the period 1981-83, 138 samples of natural gas in transmission were analysed. In 29 samples, PCBs were found with a minimum concentration of $<0.004\ \mu g/m^3$ and a maximum concentration of $1050\ \mu g/m^3$. Natural gas in distribution lines was also analysed in the same period. Out of 528 samples, 224 did not contain any PCBs. The levels ranged from <0.02 to $51\ \mu g/m^3$.

Indoor concentrations (kitchens, etc.) were measured in 419 samples in the period 1981-83. No PCBs could be detected in 49 samples, but, in the others, levels ranged from <0.01 to $1.08\ \mu g/m^3$ (Versar Inc., 1984).

5.1.2 Water

Surface water may become contaminated with PCBs from atmospheric fall-out or from direct emissions from point sources. Because of adsorption on suspended particles, PCB concentrations in heavily contaminated waters may be several times greater than their solubility. Södergren (1973) reported a seasonal variation, which was attributed to aerial fall-out.

It has been shown that polluted rivers, lakes, and estuaries have higher PCB values than non-polluted waters (Table 13). On the basis of scanty information on PCBs and reinforced by extensive analogue information on DDT, it has been estimated that, for the Great Lakes

Table 13. PCB levels in water in several countries

Country	Location and/or type of sample	PCB levels average and/or range	References
Germany	Several rivers	5-103 ng/litre	Lorenz & Neumeier (1983)
Netherlands	River Rhine (1976/1977)	100-500 ng/litre	Wegman & Greve (1980)
Sweden	Water entering a treatment plant	0.5 ng/litre	Ahling & Jensen (1970)
	Tap water produced at the plant	0.33 ng/litre	Ahling & Jensen (1970)
	Several rivers	0.1-0.3 ng/litre	Ahnoff & Josefsson (1974)
USA	Polluted coastal area Lake Michigan (1970)[a]	100-450 ng/litre	Panel on Trace Hazardous Substances (1972) (cf. WHO/EURO, 1988)
	Distribution system feeding the Fort Edwards reservoirs in New York (1978)	<12-160 ng/litre	Brinkman et al. (1980, 1981)
	Hudson River at Fort Edward	up to 530 ng/litre	Brinkman et al. (1980, 1981)

[a] Followed by a marked decrease in 1971.

of North America, non-polluted freshwaters might contain less than 5 ng/litre, moderately polluted rivers and estuaries, 50 ng/litre, and highly polluted rivers, 500 ng/litre . These values can be used to evaluate those reported by several authors and presented in Table 13.

5.1.3 Soil

Soil may become contaminated with PCBs from atmospheric fall-out or from direct emissions from point sources. The presence and behaviour of these compounds in the soil depend on substance (congener)-specific characteristics and on a number of soil parameters. Sorption and condensation processes in the soil also play a role in the removal of PCBs. Some values of PCB levels in soil can be found in Table 14.

Klein (1983) found that PCBs accumulate in the sediments of rivers and lakes in the Federal Republic of Germany and that these levels indirectly reflect the contamination of water by PCBs. Some values for PCBs in sediments can also be found in Table 14.

An important, though localized, source of PCB contamination of soil, can be the use of sewage sludge as a fertilizer in agriculture. PCB levels varying from 0.1 to 765 mg/kg (dry weight) have been reported in sewage sludge from different countries, the usual range being 0.1 to 9.0 mg/kg (WHO/EURO, 1987). In the USA, 16 sewage sludge samples from cities contained a mean Aroclor 1254 concentration of 5.2 mg/kg dry weight (range 0.01–23.1 mg/kg). Other authors reported a range of 1.5–27.3 μg/litre in 36 raw sewage sludges. Some levels that have been found for PCBs in sludges are presented in Table 14 (WHO/EURO, 1987).

Five sediment samples were collected from the Waukegan Harbour of Lake Michigan, Illinois, in 1978. Residues of 3,4,3',4'-tetrachlorobiphenyl ranged from 0.005 to 27.5 mg/kg and residues of 2,3,4,3,'4'-pentachlorobiphenyl, from 0.102–131 mg/kg. The total PCB contents of the sediment ranged from 10.6 to 13 360 mg/kg (Huckins et al., 1988).

Table 14. PCB levels in soils, sediments, and sewage sludge in several countries

Country	Location and/or type of sample	PCB levels average and/or range	References
Germany	Soil without sewage sludge	0.02-0.08 mg/kg [a]	Markard (1988)
	Soil with sewage sludge	0.05-3.0 mg/kg [a]	
	Sewage sludge	nd [b]-19 mg/kg	
	Sediments of contaminated waters	0.1-1.0 mg/kg [a]	Klein (1983)
	Sediments of several rivers	0.16-0.59 mg/kg	DFG (1988)
	Agricultural soil	0.03 mg/kg	DFG (1988)
Japan	Agricultural soil	<1 mg/kg	Fukada et al. (1973)
	Soil near a factory making electrical components	510 mg/kg	Fukada et al. (1973)
Netherlands	Sediments from several surface waters	<0.01-1.2 mg/kg [a]	Greve & Wegman (1983)
United Kingdom (Scotland)	Soil from a waste disposal area with chemical treatment and incineration facilities	4.5-44.8 µg/kg	Eduljee et al. (1986); Badsha et al. (1986);
	Grass samples from the same area (foliage)	2.9-64.7 µg/kg	Badsha & Eduljee (1986)
	Soil of rural areas	8 µg/kg [a] (1-23)	
	Grass if rural areas	9 µg/kg [a] (7-16)	
	Soil of urban areas	52 µg/kg (11-141)	
	Soil of industrial locations	41 µg/kg (20-67)	

Table 14 (*continued*)

Country	Location and/or type of sample	PCB levels average and/or range	References
United Kingdom (Wales)	Surface soil	2.5 μg/kg (0.2-12.2)	Jones (1989)
USA (Florida)	Sediments near a point of accidental release of PCBs	1.4-61 mg/kg	Nimmo et al. (1971a)
Escambia river	Sediments 16 km downstream of this point	0.6 mg/kg	
Escambia Bay	Soil samples from the bank, 6.5 km downstream from the point	1.4-1.7 mg/kg	

[a] Dry weight.
[b] Not detectable.

5.1.4 Aquatic and terrestrial organisms

PCBs have been measured in a wide variety of biota from many different locations throughout the world. Only a few illustrative examples are given here, more comprehensive lists of PCB residues can be found in reviews by Risebrough et al. (1968); Peakall (1975); and Eisler (1986). Tanabe et al. (1987) reported that the highly toxic, coplanar PCBs are as widely spread as general PCB pollution.

In the biota of a small upstate New York public water supply system, which is near the polluted section of the Hudson River and a disposal site of PCB-containing waste, PCBs were found in detectable concentrations (Table 13). Five samples of algae showed Aroclor 1254 levels of <25 (nd)–120 μg/kg dry weight, macro-invertebrates showed levels between <200 and 3800 μg/kg and vertebrates, between <25 and 1100 μg/kg dry weight (Brinkman et al., 1980, 1981).

Serious environmental contamination has been documented in enclosed water bodies close to urban and industrialized areas, such as the Great Lakes, the Baltic Sea, and Tokyo Bay. PCB levels in aquatic organisms reflect these localized high concentrations.

Nimmo et al. (1971a) reported that PCB levels in shrimp from Escambia Bay, Florida (contaminated by an industrial plant on the Escambia River) contained between 0.6 and 120 mg Aroclor 1254/kg in 1969 and fiddler crabs, collected in 1970, contained 0.45–1.5 mg/kg.

When fish, sampled throughout the USA, were analysed by Schmitt et al. (1983,1985), the highest levels of PCBs were found in the North-eastern industrialized areas. Delfino (1979) reported concentrations ranging from 26 to almost 1000 mg PCBs/kg in fish collected from the Sheboygan River, Wisconsin, contaminated by a die-casting plant.

Wiemeyer et al. (1975) analysed osprey eggs in 1968-69 and found average levels of 2.6 mg/kg in Maryland compared with an average level of 15 mg/kg in eggs from Connecticut. PCB residues in

Connecticut eggs had not changed significantly compared with those collected in 1964.

Buckley (1982) analysed aspen, sumac, and golden rod plants growing at various distances (< 1200 m) and in different directions from a PCB dump in New York State, USA. All the plants were growing beyond a natural drainage ravine, which prevented contamination of soil and water by PCBs. Downwind of the site, PCB levels in the plants were found to be approximately 100 mg/kg dry weight (over 600 times background levels in plants). Levels above background concentrations were also found in directions from the site less obviously contaminated by airborne dust.

Eggs of terrestrial birds collected in a rural environment in Canada contained lower PCB levels than those sampled from urban areas (Frank et al., 1975).

In the Great Lakes, the highest levels of PCBs were found in Lakes Michigan and Ontario for fish (Delfino, 1979) and Lake Ontario for birds (Weseloh et al., 1979); both lakes receive input from industrial and urban sites. Glooschenko et al. (1976) found concentrations of up to 8.1 mg/kg in microorganisms from the middle of Lake Huron.

Weseloh et al. (1983) found that the PCB levels in double-crested cormorant eggs, collected from Lake Superior during 1972 (average of 23.8 mg/kg fresh weight), were higher than those in cormorant eggs analysed in other Canadian colonies. Mineau et al. (1984) found that the locations of herring gull colonies with the greatest mean levels of PCBs, in each of the Great Lakes, corresponded with the locations of major sources of the contaminant, as indicated by elevated residues in sediment.

Muir et al. (1988) determined PCB levels in pooled Arctic cod muscle (*Boreogadus saida*) and polar bear fat (*Ursus maritimus*), and in the blubber and liver of ringed seals (*Phoca hispida*) from 3 locations in the East/Central Canadian Arctic. The mean arithmetic concentrations of total-PCBs in the muscle of Arctic cod of 2 locations were 3 and 5 μg/kg wet weight. The mean concentrations shown in the tabulation below were found in the blubber and liver of ringed seals.

Year	Number of samples (blubber)	Sex	Arithmetic mean ±SD (μg/kg wet weight)
1972	3	female	639 ±249
1975/76	5	female	600 ±99
1983	10	male	794 ±879
	16	female	308 ±138
1984	19	male	568 ±287
	14	female	375 ±172
	(liver)		
1984	19	male	6 ±4
	14	female	4 ±3

The presence of PCBs in polar bears (*Ursus maritimus*) was studied by Norström et al. (1988) in the Northwest territories of Canada. Liver and adipose tissue specimens were obtained by Inuit hunters from 12 zones over the period 1982-84. A total of 121 samples was obtained. The mean concentrations of total PCBs in pooled samples ranged from 3.24 to 8.25 mg/kg, on a lipid weight basis. The adipose tissue of polar bear (10 pooled samples collected in 1982 and 10 samples, in 1984) contained 4.42 and 4.57 mg/kg wet weight, respectively. From these results, biomagnification factors for the food-chain of the Arctic cod/ringed seal/polar bears were calculated. For total PCBs, these factors ranged from 3.7 to 8.8 for fish to seal; from 7.4 to 13.9 for seal to bear, and 49.2 for fish to bear. For individual PCB homologues, for instance, for fish to bear, these factors ranged from <0.5 (tetra-chlorinated PCBs) to 263.4 for heptachlorinated PCBs.

Niimi & Oliver (1989b) monitored the presence of 92 monochloro- to decachlorobiphenyl congeners in brown and lake trout, small and large rainbow trout, and small and large coho salmon from Lake Ontario. Each sample consisted of 8–12 fish. The highest concentrations were among the penta- and hexachlorobiphenyl homologues, with 2,4,5,2',4',5'-hexachlorobiphenyl the most common congener.

Total congener concentrations ranged from 1 to 10 mg/kg in whole fish and from 0.3 to 4 mg/kg in muscle. The 10 most common PCB isomers were 84, 87/97, 101, 110, 118, 138, 149, 153, and 180, and represented 52% of the total content. This value did not appear to be influenced by species or by total concentration.

Huckins et al. (1988) collected fish (1–6 fish of 7 species) from the Waukegan Harbour of Lake Michigan, Illinois in 1978. The fish samples were analysed for the presence of 3,4,3',4'-tetrachloro- and 2,3,4,3',4'-pentachlorobiphenyl. Total PCB congener residues averaged 33.4 (2.4–56.6) mg/kg. The concentrations of 3,4,3',4'-tetrachlorobiphenyl averaged 45.3 μg/kg (2–89 μg/kg) in the whole body. The concentrations for 2,3,4,3',4'-pentachlorobiphenyl averaged 229 μg/kg (80–483 μg/kg).

Five times as much PCBs were found in herrings caught in industrialized areas of Sweden (near Stockholm) compared with those caught in the cleaner waters off the Swedish west coast. Levels in plankton fell progressively with increasing distance from industrialized areas (Jensen et al., 1972a).

Holden (1973) found levels of up to 235 mg/kg in the blubber of seals sampled in the polluted coastal areas of the United Kingdom compared with lower levels (2 mg/kg) from unpolluted areas. Higher levels, (up to 88 mg/kg) were found in the blubber of toothed whales sampled in the North Sea, but none was detectable in similar species sampled off New Zealand and Surinam (Koeman et al., 1972).

Peakall (1975) mapped out the global distribution of PCB levels in marine plankton. The values for the open North Atlantic (300–450 mg/kg lipid) were found to be very similar to those collected from polluted areas, such as the Baltic sea and the Firth of Clyde, in the United Kingdom. Values in the South Atlantic (12–64 mg/kg) were considerably lower. The highest values shown were for the Eastern coast of the USA (up to 3050 mg/kg). There were no values for the Pacific Ocean.

When monitoring PCB levels in fish from the Mediterranean, Albaiges et al. (1987) found that territorial species reflected local inputs of the pollutant, but migratory species had baseline levels.

Risebrough & de Lappe (1972) reported PCB levels higher than 3 mg/kg in fish from the industrialized areas of Tokyo Bay and New York Sound.

Tanabe et al. (1986a) analysed Antarctic minke whales and found that they contained lower PCB levels than those caught in the Northern hemisphere (Tanabe et al., 1983). McClurg (1984) also found low levels of PCB in the Antarctic; Ross seals contained 0.09 mg/kg (in blubber). Mean levels of 0.69 mg PCB/kg (wet weight), found by Smillie & Waid (1987) in Australian fur seal blubber, were much lower than levels found in seals from the temperate Northern hemisphere. Similarly, Antarctic fish had very low PCB residues, ranging from 0.08 to 0.77 μg/kg wet weight (Subramanian et al., 1983).

PCB residues in biota are usually highest near industrial sources, but this geographical distribution is becoming less pronounced. In fact, O'Shea et al. (1980) and Tanabe et al. (1988) found PCB levels in small oceanic cetaceans to be higher than those reported for terrestrial mammals and birds. For example, Tanabe et al. (1988) found the mean level of PCBs in the fatty tissue of the striped dolphin to be 36 mg/kg wet weight.

Subramanian et al. (1986) analysed subcutaneous fat from Adelie penguins from the Antarctic and found PCB levels of 0.05 mg/kg fat weight. This is a factor of 100 lower than that in auks caught in the northern North Pacific (Tanaka & Ogi, 1984) and a factor of 10 000 lower than residues found in the pectoral muscle (on a lipid weight basis) of herring gulls in the Baltic (Lemmetyinen et al., 1982).

5.1.4.1 *Effect of dredging-contaminated sediment on organisms*

Dredging to remove contaminated sediments from the Shiawassee River, Michigan, increased the availability of PCBs, and, thus, residue levels, in freshwater clams (64.5–88 mg/kg dry weight) and in fish (fathead minnow; 13.8–18.3 mg/kg), both during dredging and up to 6 months afterwards (Rice & White, 1987).

5.1.4.2 Relationship to lipid content of organisms

PCBs are accumulated in lipid-rich tissues and care must be taken when interpreting results between species with different amounts of body fat. Jensen et al. (1969) found that PCB levels in herring and cod, from the same area of the Baltic Sea, were 0.27 and 0.033 mg/kg, on a wet weight basis, respectively, even though the cod is at a higher trophic level. The 2 species were found to have body fat contents of 4.4 and 0.32%, respectively, and when the PCB residues were recalculated on a lipid weight basis, herring contained 6.8 mg/kg and cod, 11 mg/kg.

PCBs are particularly accumulated in animals with large amounts of fat, such as seals, dolphins, porpoises, and whales (Tanabe, 1988) and in Arctic and Antarctic birds and mammals. Subramanian et al. (1986) found PCBs in all Adelie penguins sampled in the Antarctic, an area known to be relatively low in PCBs; the PCBs were mainly concentrated in fat-rich tissues. Kawai et al. (1988) measured PCBs in striped dolphins and found that the tissue level of PCBs depended entirely on their lipid content and, especially, on the amount of triglycerides in tissues.

Redistribution of PCBs, from fat to other tissues, occurs in animals during periods of enforced starvation, such as seasonal food shortage, hibernation, migration, incubation, and the feeding of offspring. Subramanian et al. (1986) found that, as individuals Adelie penguins starved during incubation, residues of PCBs increased with declining fat reserves concomitant with tissue redistribution. Llorente et al. (1987) found that migratory duck species had a smaller percentage of the body burden of PCBs in adipose tissue than a resident species. A similar redistribution during starvation has been shown in the laboratory in European robins (Södergren & Ulfstrand, 1972) and big brown bats (Clark & Prouty, 1977) (see sections 4.2.4.5 and 4.2.4.6).

5.1.4.3 Residues in different trophic levels and effects of diets

In a study by Shaw & Connell (1982), bioaccumulation was increasingly evident in upper trophic level organisms, such as gulls and pelicans, in an Australian estuary compared with organisms from lower trophic levels. Veith et al. (1977) found typical PCB concen-

trations in Lake Superior biota to be 0.1 mg/kg for large zooplankton, 0.3 mg/kg for bottom fish, such as sculpins, and 1 mg/kg for pelagic fish.

When various insects were sampled for PCB residues (Morse et al., 1987), levels in honey bees ranged from <0.1 to 1.5 mg/kg dry weight. PCB residues in other species ranged from <0.1 to 2.6 mg/kg, with predatory wasps containing the highest residues.

Prestt et al. (1970) analysed the livers from various bird species in the United Kingdom. The highest PCB residues were found in freshwater, fish-eating species (up to approximately 900 mg/kg). The authors did not find any geographical pattern of distribution of PCBs in the species studied.

Frank et al. (1975) collected birds' eggs from the Niagara peninsula in 1971. Eggs from carnivorous species of birds at the top of the aquatic food chain contained the highest levels of PCBs (3.5–74 mg/kg). Terrestrial carnivores contained lower, but still relatively high, residues (0.2–1 mg/kg). Eggs from herbivorous and insectivorous birds contained much lower residues of PCBs. Again, eggs from terrestrial birds tended to contain lower levels (0.05–2 mg/kg) than those feeding on aquatic prey (0.14–4 mg/kg). Focardi et al. (1988) compared the PCB residues in the eggs of 8 species of water bird. The residues were found to be higher in fish-eating birds than in invertebrate feeders. The invertebrate feeders tended to contain higher percentages of the lower chlorinated congeners. Bird species that fed on other birds or fish had higher liver residues of PCBs than those feeding on mammals (Cooke et al., 1982). Peregrine falcons, herons, sparrowhawks, kingfishers, and great crested grebes had relatively high residues of PCBs. By contrast, golden eagles were only very lightly contaminated with PCBs.

Bowes & Jonkel (1975) found a similar pattern in Arctic and subarctic food chains with PCB levels following the pattern: Arctic charfish < seals < adult polar bears < polar bear cubs.

Mean PCB concentrations of 0.0018 mg/kg were found by Tanabe et al. (1984) in zooplankton, 0.048 mg/kg in myctophid, 0.068 mg/kg in squid, and 3.7 mg/kg in striped dolphin (all based on a whole-body, wet weight basis) sampled from the western North Pacific. The

authors concluded that the bioaccumulation of chlorinated hydrocarbons was dependent on physical and chemical factors, such as water solubility and lipophilicity, in the lower trophic levels, whereas, in higher trophic levels, accumulation was affected by biochemical factors, such as the biodegradability of pollutants and the metabolizing capability of the organism.

5.1.4.4 *Effects of age, sex, and reproductive status on uptake and elimination*

Bache et al. (1972) found that the burden of PCBs increased with age in lake trout from Cayuga lake, Ithaca, New York, sampled in 1970 (residues ranged from 0.6 to 30.4 mg PCBs/kg). An age- and length-related increase in PCBs was found in striped bass from the Hudson River and Long Island Sound; the author (Connell, 1987) stated that this observed relationship was due to the slow rate of bioaccumulation of the PCBs, particularly the higher chlorinated congeners.

PCBs have been shown to accumulate with age in marine mammals, such as pinnipeds (Addison et al., 1973; Frank et al., 1973; Helle et al., 1983) and cetaceans (Gaskin et al., 1983; Aguilar & Borrell 1988; Subramanian et al., 1988). Helle et al. (1983) found mean levels of 5.1 mg PCBs/kg (in extractable fat of blubber) in newly-born ringed seal pups, 17.3 mg/kg in seals of 2–4 months of age, and 65.3 mg/kg in sexually mature adults (4–12 years). However, lower levels of PCBs have been found in females compared with males (Martineau et al., 1987) and the age-related increase has often not been found in females (Addison & Smith, 1974). In many studies, while levels of PCBs in males have increased with age, those measured in females have fallen (Born et al., 1981; Gaskin et al., 1983; Aguilar & Borrell, 1988). Gaskin et al. (1983) found that PCB levels in the blubber of male harbour porpoises increased from 48.4 mg/kg at birth to 161 mg/kg after 8 years, whereas, in females, levels fell from 51 to 14.7 mg/kg. A significant decrease in the PCB levels was found by Subramanian et al. (1988) in female Dall's porpoises from 2 years of age onwards; 2 years is required for the animals to reach sexual maturity. Excretion of PCBs during reproduction is known, from the laboratory, to be an important means of females losing residues. This PCB loss has been shown to be because of the transfer of PCBs to

offspring via milk during lactation (Addison & Brodie, 1977). Addison & Brodie (1977) calculated that female grey seals excreted about 15% of their body burden of PCBs via lactation. In striped dolphins, females transferred between 72 and 98% of their body burden to the offspring (Fukushima & Kawai, 1981; Tanabe et al., 1982). It was suggested by Tanabe (1988) that such large transfer was because of the very high lipid content of the milk. Relocation of the PCB burden during pregnancy is generally thought not to be as important; in grey seals, the mother transfers only about 1% of her body burden to her offspring (Donkin et al., 1981) and in striped dolphins, only 4–9% (Fukushima & Kawai, 1981; Tanabe et al., 1982). However, Duinker & Hillebrand (1979) suggested that a much bigger percentage of female body burden (up to 15%) could be transferred to the fetus across the placenta of Harbour porpoise.

Clark & Lamont (1976) calculated that female big brown bats transferred between 17 and 32% of their body burden of PCBs to their young, during gestation. The concentration of PCBs in adult females plus their litters declined with increasing age of the female. PCB levels were 0.83–3.6 mg Aroclor 1260/kg (wet weight) in adults and 0.22–3.3 mg/kg in litters.

When Passino & Kramer (1980) measured PCBs in deepwater ciscoes from Lake Superior, male fish contained significantly higher levels of PCBs (2.3 mg/kg wet weight) than females (1.2 mg/kg), eggs containing 0.51 mg/kg. Lemmetyinen et al. (1982) found annual rates of elimination via egg production of 45% in the female Arctic tern and 24% in the herring gull. Adelie penguins eliminated only 4% of their PCB body burden after laying their annual clutch of 2 eggs (Tanabe et al., 1986b). Elimination was thought to be dependent on the relative weights of the egg and mother.

5.1.4.5 *Time trends in residues*

Buckley (1983) analysed various species of terrestrial plants from New York state. Total decreases of 42% in PCB residues were found between 1978 and 1980.

PCB levels in fish in the Hudson River, New York declined between 1977 and 1981. The PCB levels were much higher in the Upper

Hudson River (4217–1431 mg/kg of lipid), near to a major discharge of PCBs, than in the Lower Hudson River (1604–319 mg/kg) (Sloan et al., 1983).

Frank et al. (1978) measured PCB levels in various fish species from Lakes Huron and Superior during the period 1968-76. PCB residues declined in lake trout and lake whitefish in Lake Superior between 1971 and 1975, but increased slightly over the same period in bloaters and white sucker. In Lake Huron, PCB levels decreased between 1968 and 1971, and, in alewife, rainbow smelt, and walleye, between 1975 and 1976. In some of the study areas, residues increased in cisco, yellow perch, coho salmon, and splake but, at most locations, and, for other species analysed, no trends in PCB levels were found. St Amant et al. (1984) analysed fish from Lake Michigan between 1971 and 1981. An overall decrease in PCB levels was found for all species monitored except the walleye. Levels decreased from a maximum of 22.4 mg/kg at the beginning of the study to 3.8 mg/kg or less in 1981.

Fish from all over the USA were analysed in 1980-81 by Schmitt et al. (1985) who found a significant downward trend (0.88–0.53 mg/kg PCB; wet weight) when mean residues were compared with fish collected between 1976 and 1977 (Schmitt et al., 1983). A similar downward pattern in residues was found in the Baltic when Moilanen et al. (1982) compared residues found in pike and herring caught between 1978 and 1982 with those in fish sampled between 1972 and 1978 (Paasivirta & Linko, 1980). Haahti & Perttila (1988) found a continued decline in PCB residues between 1979 and 1986, when residues in herring muscle tissue decreased from 2.7–3.7 mg/kg to 0.3–1.1 mg/kg.

An overall fall in PCB levels was found by Newton & Bogan (1978) in sparrowhawk eggs during the period 1971-74. Cooke et al. (1982) analysed liver samples from grey herons, kestrels, and barn owls for PCB residues during the period 1967-77. They found a significant decline in PCB residues over the sampling period in all 3 species. The mean residues in heron, kestrel, and barn owl for the period 1967-71 were 5.77, 1.57, and 0.44 mg/kg, respectively, and for 1977, 0.56, 0.6, and 0.15 mg/kg, respectively. However, Newton et al. (1986), when analysing sparrowhawk eggs from 1971-80, found

that, although levels had fallen in the early 1970s, they had risen again in the late 1970s (mean PCB residues in eggs ranged from 16 to 293 mg/kg in lipid). Data on PCB residues in the livers of kestrel, sparrowhawk, heron, kingfisher, and the great crested grebe, collected from the late 1960s up to 1987, were analysed statistically by Newton & Haas (1989). For the great crested grebe, a significant overall decline in PCB residues was found when comparing data from 1987 with that from the 1960s. For the other species, there was no significant difference. Spitzer et al. (1978) reported that there was no significant change in PCB levels in osprey eggs collected from the Connecticut-New York area during the period 1969-76. Similarly, Wiemeyer et al. (1987) did not find any change in the carcase levels of PCBs in ospreys from the Eastern United States when comparing the 1971-73 and 1975-82 periods. They did find that adults contained significantly higher concentrations of PCBs than immature ospreys.

Blus et al. (1979) analysed brown pelican eggs from South Carolina and Florida between 1969 and 1976. The highest levels of PCBs were found in South Carolina (means ranged from 5.25 to 7.63 mg/kg wet weight), but no significant trend was found during the study period. In Florida, the authors did not find any significant change in eggs collected from colonies in Florida Bay and on the Gulf Coast over the study period (means ranged from 0.62 to 1.18 mg/kg), but the Atlantic coastal colony showed a significant increase in PCB residues (from a mean of 2.68 to 6.12 mg/kg) between 1969 and 1976.

In analysing herring gull eggs from the Great Lakes between 1974 and 1978, Weseloh et al. (1979) found a significant decline in PCB residues from colonies on all the lakes. Lake Ontario, the most contaminated, showed the biggest decline from 170 to 75 mg PCBs/kg at one of the colonies, with other less contaminated Lakes, Huron, Superior, and Erie, showing levels in the range of 50–86 mg/kg in 1974 and 32–46 mg/kg in 1978.

Moksnes & Norheim (1986) analysed herring gull eggs collected from the Norwegian Coast between 1979 and 1981 and found that the PCB levels were not significantly different from those in eggs collected in 1969; mean PCB residues ranged from 1.2 to 6.7 mg/kg wet weight.

They found a small but significant increase in the most persistent congeners and a significant decrease in DDE and the DDE/PCB ratio, but not in total PCB levels.

An analysis of the eggs of double-crested cormorant (an inshore-subsurface feeder), Leach's storm petrel (an offshore-surface feeder) and Atlantic puffin (an offshore-subsurface feeder) was carried by Pearce et al. (1989), every 4 years, between 1968 and 1984. In the Bay of Fundy, Canada, PCB levels declined significantly during this period in all 3 species. PCB levels in the cormorant were consistently higher throughout than those in the other 2 species, ranging from 4 to 29.5 mg/kg (wet weight). Petrel and puffin eggs collected from the Atlantic Coast of Newfoundland showed lower levels than those in eggs from both the Bay of Fundy and the St Lawrence River estuary; as in the St Lawrence River, no significant trend in PCB levels was observed. A significant decline in PCB residues was found in gannet eggs collected during the same period from the gulf of St Lawrence (Elliott et al., 1988).

The frequency of occurrence of measurable PCB residues has increased in large-scale sampling exercises; PCBs in mallard wings increased from 39% in 1976-77 (White, 1979) to 95% in 1979-80 (Cain, 1981). Cain & Bunck (1983) found that, in 1976, 21% of European starlings collected in the USA contained PCBs compared with 83% in 1979.

Addison et al. (1986) analysed the blubber of Arctic ringed seals (*Phoca hispida*) from Holman Island, NWT, Canada, in 1981. They found mean PCB levels of 0.58 mg/kg (wet weight) in the females and 1.28 mg/kg in the males. These concentrations were significantly lower than those detected in the same species from this area in 1972. Over this same period, *pp'*-DDE levels, although at lower levels, also fell significantly, but it should be noted that total DDT levels in blubber are much lower than PCB levels and have not changed significantly.

5.1.4.6 Seasonal patterns in residues

Jensen et al. (1969) observed that there was considerable seasonal variation in the fat content of herring caught in the Baltic Sea, ranging from 1% in the spring to 10% in the autumn and that this seasonal

change in fat content led to seasonal changes in the tissue levels of PCBs.

Cooke et al. (1982) found a seasonal pattern of PCB levels in European kestrels. Residues in both fat and liver were low in the autumn, but increased from about January, with a peak almost invariably occurring during the second quarter of the year (April, May, or June). Seasonal patterns were based on samples collected over a 10-year period. Similar trends were found in sparrowhawks and barn owls, but fewer samples were available.

5.1.5 Appraisal

PCB contamination is widespread and has been measured in a wide variety of biota between the 1960s and the present day. They are present throughout the world and, although initially concentrated in areas of high industrial activity, are now found in organisms living in remote areas, such as the oceans and the polar regions. In the past, PCB levels were positively correlated with areas of heavy industry and consequent discharge but, with the implementation of PCB controls, in some countries, these geographical differences are becoming less clear. Generally, levels of PCBs are declining in areas previously high in PCBs. However, time-trend analysis for the general environment shows little change in total PCBs since the late 1960s. The ratio of congeners is, as would be expected, changing, with lower chlorinated isomers disappearing and the more highly chlorinated ones becoming more dominant in environmental samples.

PCBs are persistent and bioaccumulate in many organisms, because of their high lipid solubility and low biodegradability, and usually enter food-chains from water containing industrial discharge and by precipitation.

Because of their hydrophobic nature, PCBs are associated with both oildrop-like aggregates in the surface microlayer of water and with sediment on the bottom.

They are accumulated by micro- and macroplankton organisms that live in the surface microlayer and by bottom-living organisms.

5.2 Levels in animal feed

The effects of pollution are seen in the use of fish-meal in poultry and fish farming. Kolbye (1972) stated that this may contain PCB levels of 0.6–4.5 mg/kg.

Hansen et al. (1981) studied the transfer of PCBs in swine foraging on sewage sludge amended soils in 1975-76. Sixteen Berkshire sows were overwintered for 2 seasons on 4 experimental plots that had been treated with 0, 126, 252, or 504 tonnes/hectare (on a dry solids basis) of Chicage sewage sludge for the 8 preceding years. The estimated PCB residues in the soils of the 4 plots (average of 3–4 samples) were 1.62, 1.88, 2.13, and 2.81 mg/kg dry weight (mean values of 3–4 samples/plot). The mean concentrations in fat of 3–4 sows per plot were 36 ± 9, 106 ± 64, 191 ± 97 and 389 ± 118 μg/kg fat basis. Of the 12 individual congeners that were present in the fat, 3 accounted for more than 50% of the congeners, e.g., 2,3,4,2',4',5'-, 2,4,5,2',4',5'-hexachlorobiphenyl and 2,3,4,5,2',4',5'-heptachlorobiphenyl.

In vegetable animal feed (155 samples) originating from 5 areas of the world, samples, collected in 1984/85, contained PCB levels of 0.0009 (Africa) up to 0.0093 mg/kg dry weight (Europe). In feed from North and South America and the Far-East, the levels were between 0.0024 and 0.0066 mg/kg. Different types of feed originating from agriculture in the Federal Republic in Germany, collected in 1985, contained PCB levels of the order of 0.02 mg/kg dry weight. In feed (301 samples) originating from animals (exclusive fish meals), collected in 1985, 0.021–0.036 mg/kg dry weight was found (DFG, 1988).

Levels of 10–100 μg/kg are given for groats, soybeans, and cotton seed, and a mean value of 18 μg/kg is given for mixed feedstuffs. Fish meal contained levels of 110–330 μg/kg (Klein, 1983).

Samples of fish meal from different areas of the world, collected in 1985, were analysed for the presence of PCBs. In 323 samples, the PCB contents varied between 0.006 and 0.055 mg/kg dry weight. The PCB congeners numbers 28, 138, and 153 were present in the highest quantities (DFG, 1988).

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5.3 Levels in human food

5.3.1 General

Two general reviews of PCB residues in food, animal feed, human milk, plants, soils, and packaging materials have been published by Khan et al. (1976) and Sawhney & Hankin (1985).

The PCB contents of a variety of foods on the Swedish market has been measured by Westöö & Norén (1970a) and Westöö et al. (1971). Less than 0.1 mg/kg was found in samples of butter, margarine, vegetable oils, eggs, beef, lamb, chicken, bread, biscuits, and baby food; one sample of pork out of more than 100 had a PCB content of <0.5 mg/kg.

In the period 1980-81, 5270 food samples were drawn at wholesale or production levels or at the site of importation including: butter, cheese, eggs, kidneys from pigs and cattle, and fat of poultry. Levels in Danish butter (99.4% of the samples) were below 0.05 mg/kg and those in imported butter (100%), below 0.125 mg/kg; Danish cheese (100% of the samples) levels were below 0.05 mg/kg and, in imported cheese, 82.4% of samples had levels below 0.125 mg/kg and the other 17.6%, below 0.2 mg/kg; 100% of eggs had levels below 0.05 mg/kg, and 100% of kidneys of pigs and cattle were below 0.15 mg/kg; 96% of poultry fat samples had levels below 0.15, and 4%, below 0.20 mg/kg, on a fat basis (not stated) (Statens Levnedsmiddelinstitut, Danmark, undated).

Mes et al. (1989b) studied the presence of specific isomers of PCB congeners in fatty foods of the Canadian diet. A total of 93 food composites from the cities of Ottawa and Halifax were analysed for 34 PCB isomers, as part of a revised total diet programme. Each market basket comprised approximately 200 different food types collected from each of 4 major supermarkets in Ottawa during September 1985 and January 1986, and, in Halifax, in September

1986. Foods were used *per se*, or prepared and cooked in a manner ready for consumption, then composited to give 112 composites from each market basket. Thirty-one selected composites, representing the fatty foods were analysed from each market basket.

PCB isomers 118, 138, 153, and 180 were found in all dairy products, except skimmed milk. Cheese and butter contained the highest levels of PCB residues. The residue level of isomer 118 (2,4,5,3',4'-pentachlorobiphenyl) in butter was the highest e.g., 0.7 μg/kg, of all PCB isomers found in dairy products. Almost all meat, fish, and poultry contained PCB isomers 183 and 187. Occasionally, isomers 49, 87, 185, and 189 were also present, but isomer 105 (2,3,4,3',4'-pentachlorobiphenyl), present in most dairy products, was only found in some beef samples. Fresh water fish contained most PCB isomers (28 out of 34 selected PCB isomers), at levels considerably higher than those in any other meat, fish, or poultry samples. The level of isomer 110 in fresh water fish was 3.05 μg/kg. PCB isomers 138, 153, 180, and 187 were present in almost all samples of meat and fish products, fats, oils, and soups. Cooking fats, salad oils, and margarine contained relatively low levels of PCB residues. PCB isomers 37, 49, 87, 105, and 185 were not detected in meat and fish products, fats, oils, or soups.

The calculated sum of all PCB isomer residues found in selected food commodities (except fish) ranged from 0.03 to 1.98 μg/kg on a wet basis, and from 0.07 to 10.71 μg/kg on a lipid basis, with mean values of 0.60 and 3.91 μg/kg, respectively. However, the mean residue levels of fish and fish products were considerably higher, i.e., 10 and 194 μg/kg on a wet and lipid basis, respectively.

The major PCB isomers in fatty foods were isomers 37, 52, 99, 110, 118, 138, 153, 180, and 187.

The PCB levels obtained in an extensive study by the US Food and Drug Administration are shown in Table 15. These values are considerably higher than those reported from Sweden, but they are probably biased, as they include samples originating from areas previously suspected of having been subject to local pollution.

In a Canadian survey, PCB levels of less than 0.01 mg/kg were found in eggs (Mes et al., 1974) and a mean of 0.042 mg/kg was found in

domestic and imported cheese with a maximum of 0.27 mg/kg (Villeneuve et al., 1973b).

Table 15. PCB levels in food in the USA[a]

Food	% Positive (0.1 mg/kg)	Level in positive samples (mg/kg)	
		Mean	Maximum
Cheese	6	0.25	1.0
Milk	7	2.3	27.8
Eggs	29	0.55	3.7
Fish	54	1.87	35.3

[a] From: Kolbye (1972).

A preliminary study was carried out to estimate the dietary intake of PCBs in fresh food composites grown in Ontario in 1985. The following 5 food composites: fresh meat and eggs, root vegetables (including potatoes), fresh fruit, leafy and other above-ground vegetables, and cow's milk were analysed. The concentrations in the different food composites were below 0.0005 mg/kg. The annual dietary intake of PCBs was estimated to be 32.6 μg (Davies, 1988).

In Japan, a similar range of PCB contents has been reported for most foods; however, some high levels have been reported for rice and vegetables harvested in fields polluted with PCBs (Environmental Sanitation Bureau, 1973). The PCB content of most fish on the market was less than 3 mg/kg.

Cantoni et al.(1988) analysed different food items, in 1985-87, in Italy, taking 20–60 samples per item. Different types of meat were analysed and the median concentrations were 0.25–0.50 mg/kg, on a fat basis. Twenty to 50% of the samples were positive. Poultry contained 0.028 mg/kg, cow's milk 0.05 mg/kg, cream 0.027 mg/kg, butter 0.065 mg/kg and fish 1.105 mg/kg, on a fat basis; 71% of fish samples contained PCBs.

When the fat of poultry (42 samples) and 44 eggs was analysed, PCB values were below 0.3 mg/kg (Dutch Agricultural Advisory Commission, 1983).

In the Federal Republic of Germany, wheat was analysed during the period 1972-82. The mean concentrations for 1972-78 ranged from 10 to 30 μg/kg; in the period 1980-82, the range was <2.0–18 μg/kg (Klein, 1983). In wheat and rye (total 850 samples), median levels of 0.4–1 μg/kg product were found in 1984 (Codex Alimentarius, 1986). The concentrations found in other food items are summarized in Table 16.

Table 16. PCBs in food (1982) in the Federal Republic of Germany[a]

Food	Total no. of samples	Number of samples below detection limit[a]	Variation min-max (μg/kg)	Mean (μg/kg)
Milk	854	234	<2-3000	126.7 (FB)
Beef	76	43	<10-687	72.4 (FB)
Pork	58	36	<10-458	58.1 (FB)
Poultry	64	61	<10-85	7.3 (FB)[c]
Meat products	185	86	<4-2700	114.2 (FB)
Eggs	82	67	<5-230	9.1 (FW)
Fish (only cod, herring, plaice)	70	-	40-87	41.1 (FW)
Food of plant origin				
Oil	167	139	<5-65	7.1 (FB)
Cereals	345	44	<2-30	6.7 (FW)
Potatoes	106	106	<2	-

[a] From: Klein (1983).
[b] Not stated.
[c] Only 3 samples.
FB = fat basis.
FW = fresh weight.

Samples of canned ham exported from Czechoslovakia to the USA in 1983 contained PCBs levels of up to 4.8 mg/kg (Anon., 1983a,b).

In the FAO/WHO collaborating centres for the food contamination monitoring programme, the median levels were:

Cereals	below 10 μg/kg
Vegetable fat/oils	below 5 μg/kg
Fresh fruit and vegetables	0.5–5 μg/kg
Animal fat (depending on type of animal and origin)	20–240 μg/kg
Whole fluid cow's milk (depending non country)	10–200 μg/kg (on fat basis)
Butter	30–80 μg/kg
Whole dried cow's milk	20–50 μg/kg
Hen eggs	< 10 μg/kg
Fresh finfish	10–200 μg/kg

(WHO, 1985b).

5.3.2 *Drinking-water*

Ruoff et al. (1988) examined 83 drinking-water samples from the Federal Republic of Germany and from 5 other European countries for their contents of the PCB congeners 28, 52, 101, 138, 153, and 180. The average total content of the 6 congeners was 0.002 μg/litre water. The average concentrations of the above-mentioned PCB congeners in the drinking-water of 6 countries were 0.0001, 0.001, 0.00018, 0.00035, 0.00037, and 0.00042 μg/litre. The variation between the 6 countries was quite small.

The highest concentration of PCBs reported in domestic tap water was 0.1 μg/litre in the Kyoto area of Japan (Panel on Hazardous Trace Substances, 1972 cf. WHO/EURO, 1988), but, levels, more likely to be encountered, should not exceed 0.001 μg/litre.

The contamination of a drinking-water system in Pickens County, South Carolina by PCBs discharged from a manufacturing facility was described by Billings et al. (1978). They observed that PCBs discharged by a capacitor manufacturing plant resulted in levels as high as 0.818 μg/litre in finished potable water.

5.3.3 Dairy products

A number of data on food-producing animals have recently become available within the framework of the Joint FAO/WHO Food Contamination Monitoring Programme (JFCMP, 1985). All reported median values of PCBs in animal fat (excluding milk fat) were below the respective limits of detection, which varied from 0.001 mg/kg in the United Kingdom to a high of 0.5 mg/kg in Thailand and the USA. Data on PCB levels in cow's milk fat were supplied by the Federal Republic of Germany, Japan, the Netherlands, the United Kingdom, and the USA. The United Kingdom and the USA reported that median concentrations in cow's milk were below the detection limits of 0.5 μg/kg and 0.5 mg/kg, respectively.

The available data are summarized in Table 17.

From the end of 1982 to the beginning of 1983, high levels of PCBs were detected in milk from several dairy farms in Switzerland. The investigations showed that the silo coatings and consequently the silage from the silos were the origin of the contamination of the milk. The PCB levels were between 0.80 and 3.80 mg/kg fat. PCB dissolution in acid juice, mechanical erosion of the coatings, and volatilization of the coating surface seemed to be the principal mechanisms explaining the migration of PCBs into the silage (Alencastro et al., 1984).

Forty-two samples of cow's milk (14 samples in 1976, 14 in 1983, and 14 in 1986) and 41 samples of market milk (10 in 1976, 16 in 1983, and 15 in 1986) were analysed for PCBs, in Israel. During this period, a change was observed in the PCB distribution in the milk samples. The percentage of hexachlorobiphenyl decreased with time and the pentachlorobiphenyl increased (Pines et al., 1988).

The monitoring data for dairy products from all over the world for 1980-83 have been summarized by the Joint FAO/WHO Food Contamination Monitoring Programme (WHO, 1986a,b).

Table 17. Occurrence of PCBs in dairy products

Country	Year	Product	Number of samples	Mean concentrations in mg/kg on fat basis (range)	Reference
North America					
USA	1973-1974	milk (bulk)	198 (9 positive)	1.91 (0.32-4.99)	Willett (1980)
Europe					
Germany	1982-1986	milk	3279	0.09-0.14[a]	DFG (1988)
(3 areas)	1983-1986	butter/cheese	2088	0.05-0.11	
Westphalian area	1972-1974	butter	-	0.38 (0.25-0.54)	Claus & Acker (1975)
Northern part	1978-1980	milk	-	0.17-0.20	Codex Alimentarius (1986)
	1984	milk	3510	0.013	
Northern part	-	butter	1836	0.0077[c]	Codex Alimentarius (1986)
	-	meat and fat	957 (about 3/4 positive)	0.01[b]	DFG (1988)
		cows entrails	51	0.149[b]	
Sweden	1972-1977	beef, pork and meat products (domestic and imported)	232 (217 negative)	< 0.001-0.01 (whole product)	Vaz et al. (1982)
Denmark	1981-1982	milk	-	0.10-0.13	Jensen (1983b)

Table 17 (continued)

Netherlands	1975-1977	milk	315	0.16 (0.06-0.33)	Gezondheidsraad (1985)
	1980-1983	milk	-	0.07-0.13	
	1978-1984	milk	2319	< 0.1-0.2	Olling (1984)
	1977-1981	cattle fat	-	0.11[b] (< 0.05-0.55)	Greve & Wegman (1983)
		pork	-	0.07 (< 0.05-0.66)	
	1983	fat of cattle, pork, calves	40-45	< 0.03[b]	Dutch Agric. Adv. Comm. (1983)
		sheep	22	< 0.03[b]	
Switzerland (6 locations)	-	milk	6	0.034-0.144	Rappe et al. (1987)

[a] Major congeners were Nos. 138 and 153.
[b] Median value.
[c] Arithmetic mean.

5.3.4 Fish and shellfish

A summary of the monitoring data on fish from all over the world for 1980-83 has been published by the Joint FAO/WHO Food Contamination Monitoring Programme (WHO, 1986a,b).

As might be expected, the PCB values found in fish depended on the fat content and the pollution of the fishing area (Westöö & Norén, 1970a; Berglund, 1972).

In a collaborative study by 7 national laboratories (International Council for the Exploration of the Sea, 1974), the PCB contents in the muscle tissue of fish taken from the North Sea were measured. A mean of 0.01 mg/kg was found in cod, while herring contained up to 0.48 mg/kg, with most samples in the range of 0.1–0.2 mg/kg; plaice contained 0.1 mg/kg or less. Similar values were reported by Zitko (1974) for fish taken from the North Atlantic.

Risebrough & de Lappe (1972) reported levels higher than 3 mg/kg in fish from New York Sound and Tokyo Bay, both very polluted areas. Even higher levels of PCBs were found in fish from polluted lakes and inland waterways, a level of 20 mg/kg being found in fish from Lake Ontario, and levels over 200 mg/kg in fish from the Hudson River (Stalling & Mayer, 1972). Similar correlations between pollution and PCB levels have been reported from the United Kingdom in fish (Portmann, 1970), and in mussels (Holdgate, 1971).

Jensen et al. (1969) found PCB levels of 0.27 mg/kg and 0.33 mg/kg, respectively, in the muscle tissue of herring and cod from the same area of the Baltic, though the cod is at a higher trophic stage. The 2 species had 4.4 and 0.32% of extractable fat, respectively, and, when the PCB level was calculated on the fat content, values of 6.8 mg/kg for the herring and 11 mg/kg for the cod were obtained. Cod liver has a much higher fat content than cod muscle, and Jensen (1973) reported the ratio of PCB concentrations in cod liver and muscle to be over 100, the maximum in liver being 59 mg/kg. Jensen et al. (1969) remarked that the considerable seasonal variation in the fat content of the herring, rising from 1% in spring to 10% in autumn, influenced the tissue level of PCBs.

There are many examples of different PCB levels in similar species collected from areas of high and low pollution. Jensen et al. (1972b)

found 5 times as much PCBs in herrings caught in waters off industrialized areas near Stockholm, as in herrings from the cleaner waters of the west coast of Sweden.

Different freshwater and seawater fish were analysed for PCB contents, during the period 1981-83, in the Netherlands. Eel from different places over the period 1971-81 contained 0.2–13 mg/kg on a product basis (in the edible part). The median value was between 1 and 2 mg/kg. Seafish from the North Sea, such as herring and mackerel, contained 0.1–0.2 mg/kg, on a fat basis. The same level was found in shrimps and mussels (Freudenthal & Greve, 1973; Greve & Wegman, 1983; van der Kolk, personal communication, 1984a).

The mean PCB contents in the liver of cod from the North Sea, North Atlantic, and Baltic Sea, were 2.1–5.7, 0.48, and 10.4–12.8 mg/kg, respectively (Klein, 1983).

When fish from the North Atlantic, North Sea, and Baltic Sea, were collected in 1985, PCB concentrations of 0.098–0.123 mg/kg fillet weight were found in fish from the North Atlantic and North Sea and 0.338 mg/kg fillet weight in fish from the Baltic Sea. In total, 60 samples were analysed. The PCBs 101, 138, and 153 were the major congeners (DFG, 1988).

The PCB concentration in freshwater fish of the River Rhine was found to be more than 2 mg/kg. The mean PCBs levels decreased, however, over the period 1976-81 from 1.92 to 0.38 mg/kg (fresh weight) (Klein, 1983).

In 1984, PCB concentrations in freshwater fish (59 samples) collected in the River Rhine ranged from 0.742 to 1.017 mg/kg fillet weight. In this case, the major congeners were 138 and 153, but numbers 28, 52, 101, 180 were also present. In total, 199 samples of eel were collected in a number of surface waters and analysed for the presence of PCBs. The levels ranged from 1.42 to 6.51 mg/kg fresh weight. In studies reported by DFG (1988), the highest levels of PCBs were found in the River Rhine.

In the United Kingdom, fish and shellfish were analysed for PCBs during the period 1982-84 (HMSO, 1986). The results are summarized in Table 18.

Table 18. PCB levels in marine fish and shellfish[a]

Year	Product	Tissue	No. of samples	Range (mg/kg)
1982	Marine fish (from England) (7 types of fish)	liver	381	0.3-4.1
1982	Marine fish (from England) (7 types of fish)	muscle	326	0.03-0.13
1983	Marine fish (imported) (5 types of fish)	muscle	102	nd-0.06
1983	Shellfish (imported) (4 types of shellfish)	muscle	53	nd-0.06
1984	Fish oils		16	0.11-2.3

[a] From: HMSO (1986).

Different types of marine fish and shellfish from different areas in the United Kingdom were analysed during the period 1977-84. Those from the North Sea coast contained concentrations in the range of 0.04–5.7 and <0.001–0.058 mg/kg, respectively, while those from the English channel contained <0.05–6.9 and <0.006–0.1 mg/kg, respectively, and those from the West coast, <0.002-8.4 and <0.001–0.25 mg/kg wet weight. PCB concentrations in fish livers of 0.2 up to 12.9 mg/kg wet weight were found during this period (Franklin, 1987).

When samples of fish of different species, collected from major USA watersheds in 1976, were analysed, PCBs were found in 93% of the samples. Fifty-eight of the samples had levels exceeding 5 mg/kg, on a whole fish basis. The PCB concentrations ranged from less than 0.3 to 140 mg/kg, on a whole fish basis (Veith et al., 1979).

Maack & Sonzogni (1988) analysed 98 fish (14 species) of different sizes from Wisconsin waters, for the presence of PCB congeners. Among the most prominent congeners were numbers 153/132, 138, 66/95, 110, 180, 70/76, 146, 28/31, 149, 118, and 105. The total PCBs (determined by adding individual congener concentrations)

ranged from 0.070 to 7.0 mg/kg. The mean concentration was 1.3 mg/kg.

Blue crabs (*Callinectes sapidus*, an important member of the estuarine food web), collected from Campbell Creek and surroundings in South Carolina, were analysed for PCBs in 1985. The highest mean total concentration was 0.861 mg/kg muscle tissue. In 1986, the mean concentrations in blue crab collected by 8 stations in the same area ranged from 0.026 to 0.361 mg/kg muscle tissue. Blue crab (15 samples) collected from the coast of South Carolina, contained concentrations of <0.020–0.372 mg/kg tissue (Marcus & Mathews, 1987).

PCBs concentrations in sea fish were determined in 1971-77 in Japan. In-shore fish (90 samples) showed concentrations of 0.2–0.72 mg/kg fresh weight and pelagic fish (112 samples), 0.005–0.265 mg/kg fresh weight (Watanabe et al., 1979).

Data on individual species of fish, submitted by Japan, showed the following median levels: barracuda, 70 μg/kg; conger eel, 290 μg/kg; croaker, 200 μg/kg; flounder (yellow-tail), 90 μg/kg; hair-tail, 100 μg/kg; mullet, 84 μg/kg; and seabass, 110 μg/kg. Median levels for other species of fish, such as cod, mackerel, pacific saury, rockfish, salmon, and sardines, were below 100 μg/kg (WHO, 1986b).

Using a very sensitive analytical method, Tanabe et al. (1987) found the toxic non-*ortho*-substituted coplanar 3,4,3',4'-tetrachloro-, 3,4,5,3',4'-pentachloro-, and 3,4,5,3',4',5'-hexachlorobiphenyl in finless porpoise, at concentrations of 13.5, 0.89, and 0.64 μg/kg, respectively.

Blue mussel (*Mytilus edulis*) was collected from coastal areas near Osaka and Hokkaido, Japan, in 1984-86. Depending on the site of collection, the average PCB concentrations (11–13 samples) ranged from 0.56 to 65.0 μg/kg (Miyata et al., 1987).

5.3.5 Influence of food processing

Fifty striped bass (*Morone saxatilis*) were analysed for the presence of PCBs in the fish fillets before, and after, boiling, steaming, baking, frying, microwaving, or poaching, to study the possible reduction of the PCB residues by these cooking procedures. PCB contents were

reduced by approximately 10%, by all 6 methods of cooking. No significant reductions were observed with the other cooking methods (Armbruster et al., 1987).

5.3.6 Food contamination by packaging materials

When Villeneuve et al. (1973a) analysed packaged food in Canada, they found that 66.7% of the samples contained PCB levels of less than 0.01 mg/kg, 30.7% contained between 0.01 and 1 mg/kg, and 2.6% contained more than 1 mg/kg. The highest PCB levels were in a rice sample (2.1 mg/kg), where the packaging material contained 31 mg/kg, and in a dried fruit sample (4.5 mg/kg), in a container containing 76 mg/kg. In a survey of packaging containers, approximately 80% were found to contain PCB levels of less than 1 mg/kg, while about 4% contained levels higher than 10 mg/kg. The most likely source of PCBs in packaging materials was the recycling of waste paper containing pressure-sensitive duplicating paper (carbonless copying paper) (Masuda et al., 1972).

Relatively high PCB levels in some packaged foods in Sweden, mainly of imported origin, could be attributed to migration from the packaging material (Westöö et al., 1971). The highest level encountered was 11 mg/kg in a childrens' breakfast cereal; PCB levels of 70 mg/kg and 700 mg/kg were found in the material of the inner bag containing this product and in the outer cardboard container, respectively. Up to 2000 mg/kg was found in cartons of other samples.

In the United Kingdom, levels in imported waste-paper, which could be contaminated with PCBs from carbonless copying paper and subsequently used to manufacture food contact paper and board materials, were found to be low, compared with the 10 mg/kg limit for PCBs recommended by the British Paper and Board Industry Federation for food contact materials (HMSO, 1989).

5.3.7 Appraisal

Foods have become contaminated with PCBs by 3 main routes:

- accumulation of PCBs in the different food-chains in the environment and consumption of fish, birds, or other animals and crops;
- direct contamination of food or animal feed by an industrial accident;
- migration from packaging materials into food.

During the past years, many thousands of samples of different foodstuffs have been analysed for PCB contamination. The most common foodstuffs analysed have been fish, meat, and milk. Many fish samples have been taken in an effort to monitor aquatic pollution. In addition, samples have been taken, for regulatory or similar purposes, from sources suspected of being relatively highly contaminated. The fact that most samples have not been taken at random, jeopardizes the proper assessment of the exposure of the general population.

5.4 General population exposure

5.4.1 Air

Relatively high levels of PCBs have been detected in indoor air, especially in kitchens and offices with electric installations (Jensen, 1983a) (section 3.2.4 and 5.1.1).

Results from the US EPA indicate PCB concentrations in the air ranging from 1 up to 50 ng/m^3; similar results have been reported from Japan (WHO, 1976). Assuming a level of 5 ng PCBs/m^3 in urban air, a breathing rate of 22 m^3/day, retention and absorption of inhaled particles/vapour of 50%, and a mean residence time of PCBs in the body of 3 years, air would contribute 0.8 μg/kg to the PCB concentration in the body. Higher concentrations of PCBs in indoor air could increase this estimate (WHO/EURO, 1988).

Van der Kolk (1985) calculated air intake through inhalation for the Dutch population of about 36 ng/day, a quantity approximately 1000 times lower than the intake with food.

During the manufacture, formulation, or use of PCBs, where levels in the workroom air correspond to exposure limit values, varying

between 0.1 mg/m^3 and 1 mg/m^3, the calculated mean intakes would range between 1 and 10 mg during an 8-h workshift. In some occupational situations, much higher concentrations have been measured and the estimates of intakes would be higher (WHO/EURO, 1987).

5.4.2 Drinking-water

Levels reported in drinking-water are typically between 0.1 and 0.5 ng/litre. Even assuming a PCB level of 2 ng/litre in drinking-water, consumption of 2 litre/day contributes 0.04 μg/kg body weight to the PCB concentration in the body. This additional quantity is negligible in comparison with the intake via food (WHO/EURO, 1988).

5.4.3 Intake by infants through mother's milk

The daily intake of PCBs was calculated in breast-fed infants in the countries participating in a monitoring study by Slorach & Vaz (1983, 1985) (Table 19).

The intakes in EEC countries were calculated to range from 3 to 11 μg/kg body weight per day, compared with 0.12–0.3 μg/kg body weight for bottle-fed infants in Denmark (WHO/EURO, 1985).

In Yusho infants with clinical symptoms of poisoning, the daily intake of PCBs with breast milk was calculated to be 70 μg/kg body weight (Jensen, 1983b) (see section 9.1.2.2).

5.4.4 Infant and toddler total diet

Johnson et al. (1979) analysed the average diet of 6-month-old infants and 2-year-old toddlers for the presence of PCBs. Ten market baskets were collected in 10 cities in the USA. The foods were prepared in the manner in which they would be prepared and served in the home. Trace amounts of PCBs were detected in only one infant and one toddler diet.

In the USA, Gartrell et al. (1986b) found a daily intake of 0.011 μg PCBs/kg body weight in infants consuming infant diets in 1978. In the years 1979, 1980, and 1981/82, the intake was below the detection

Table 19. Calculated daily intakes of PCBs by breast-fed infants (μg/kg body weight) [a]

Country/area	Year(s)	Calculation according to US FDA method [b]		Calculation according to national method [c]	
		median	maximum	median	maximum
Belgium, Brussels	1982	3.6	10.4	NR	NR
China, Beijing	1982	NR	NR	0.45[d]	0.45[d]
Israel, Jerusalem	1981/82	2.0	9.5	NR	NR
Germany, Hanau	1981	NR	NR	9.5	45
Japan, Osaka	1980/81	1.6	4.4	2.3	6.3
Sweden, Uppsala	1981	4.4	8.1	5.9	11
USA 22 states	1979	4.5[e]	13.5	4.5[e]	22.5
Yugoslavia, Zagreb	1981/82	2.8	7.2	2.8	7.7

[a] Assuming a milk consumption of ca 130 g/kg body weight and a milk fat content of 3.5% (w/w). Calculations based on data for all mothers studied. Results for different methods of PCB analysis shown separately. From: Slorach & Vaz (1983, 1985); Van der Kolk (1984b).

[b] Sawyer method.

[c] "Own method".

[d] PCB level below limit of detection (0.1 mg/kg fat) in milk samples.

[e] PCB level below limit of detection (1 mg/kg fat) in milk samples.

NR = No data on levels in milk reported.

level. The intake by toddlers was 0.099 μg/kg body weight in 1978 and not detectable in the following 3 years.

Tuinstra et al. (1985a) analysed samples of infant food from the Dutch market and found average PCB levels of 0.1–0.2 μg/kg food (the maximum level found was 1.1 μg/kg).

5.4.5 Total intake by adults via food

The oral consumption of contaminated products is presumed to be the main route of exposure to the PCBs.

It has been stated that the major part of the human dietary intake of PCBs is from fish (Berglund, 1972; Hammond, 1972). This may well be true in areas such as Japan or certain localities near the North American Great Lakes, where fish from polluted waters may form a relatively large part of the diet. Several investigators from Japan have measured the daily intake of PCBs in food; the highest mean value recorded was 48 μg/day, of which 90% was from fish (Kobayashi, 1972); the lowest was 8 μg/day (Ushio et al., 1974).

In much of Europe and North America, however, the daily intake of fish is in the region of 30–40 g, and most of the fish is taken from waters of low pollution with PCB levels in the fish not exceeding 0.1 mg/kg. Berglund (1972) has estimated that the daily intake of PCBs from fish in Sweden is in the region of 1 μg, though if the fish consumed were solely Baltic herring, the intake would be about 10 μg/person. It is difficult to make an assessment of the PCB intake from foods other than fish. Westöö et al. (1971) in their extensive study of the Swedish diet, reported that most foods contained PCB levels of less than 0.1 mg/kg; and concluded that this corresponds to a daily intake of less than 100 μg.

Weekly intakes in the range of 23–889 μg/person have been reported from the USA (OTA, 1979). The higher range concerns people consuming more than 12 kg/year of Lake Michigan fish.

The intake of total PCBs by the general adult population depends greatly on the geographical area and food habits.

5.4.6 Total diet/market-basket studies

Data on total-diet studies of PCBs have been reported from a few countries. These reported intakes show a wide variation, which can partially be explained by methodological factors, such as the ways in which samples below the limits of determination are considered, especially when noting the different limits of determination. Considering the available data, an average intake of 5–15 μg/day for the non-occupationally exposed population in industrialized countries may be the best available estimation.

These estimates apply to the average diet of an average adult citizen. In practice, few people are really "average" in their consumption pattern. Given the widespread nature of the contamination, however, a higher intake in one food group is more or less balanced by a lower intake in another food group with an equal calorie intake. Total intake will certainly be higher for diets with a more than average calorie content (van der Kolk, 1985).

Gartrell et al. (1985) determined the total intake of PCBs by 16- to 19-year-old males in the USA. The samples represent a typical 14-day diet. Approximately 120 individual food items (of 12 food groups), including drinking-water, were collected for each market-basket sample in 20 cities in the period 1979-80. Only 2 samples of meat, fish, and poultry contained PCBs with an average concentration of 0.002 mg/kg.

Gartrell et al. (1985, 1986a) reported a daily intake in the USA of 0.016, 0.027, 0.014, 0.008, and 0.003 μg PCBs/kg body weight during the years 1977, 1978, 1979, 1980, and 1981/82, respectively.

Manske & Johnson (1975) collected 35 market baskets in 32 cities over the period 1971-72. PCB residues were found in the range of 0.035–0.15 mg/kg in 51 composites. Fish and oils, fats, and shortenings contained the highest levels. The same authors (Manske & Johnson, 1977) carried out a market-basket study representing the basic 2-week diet of a 16- to 19-year-old male. The various foods were prepared in the manner in which they would normally be served and eaten. Thirty market-baskets, containing 12 classes of foods (in total 360 composites) were collected in 30 cities in the period

1973-74. A trace of PCB was found once in whole milk, ground beef, and fish fillet.

The FDA revised the concept of the Total Diet Study in 1982. As discussed by Gunderson (1988b), the Total Diet Study conducted before 1982 was based on a "composite sample approach", regardless of the diet involved. The revised study is based on updated dietary survey information and allows the "total diet" of the US population to be represented by a relatively small number of food items for a greater number of age/sex groups. The daily intake expressed in ng/kg body weight per day for PCBs (Aroclor 1221, 1242, and 1254) in 1982-84 for the age groups 6–11 months, 2 years, 14–16-year females, 14–16-year males, 25–30-year females, 25–30-year males, 60–65-year females and 60–65-year males were: 0.8, 1.2, 0.4, 0.5, 0.5, 0.6, 0.4, and 0.5 ng/kg body weight per day, respectively (Gunderson, 1988b).

Foods, representative of Canadian eating habits, as determined by a national nutritional survey, were prepared for eating, categorized, and blended into 11 different composites representing the dietary intake for 5 cities over the period 1976-78. It concerned 194 samples, collected in winter and in summer. The average dietary intake was 0.001 μg PCB/kg body weight (McLeod et al., 1980).

Over a period of 2 years, 126 different food items of a market-basket of 16- to 18-year-old males were purchased every 2 months in the period 1976-78, in the Netherlands. The foodstuffs were prepared for eating and were combined in 12 commodity groups. The mean concentration and range of PCBs in 5 food classes was:

Class	Mean concentration (mg/kg on fat basis)	Range
Meat, poultry, and eggs	-	0.13–0.17 (2)[a]
Fish	0.07	0.04–0.24 (7)
Dairy products	-	0.04–0.06 (2)
Sugar and sweets	-	0.08 (1)
Drinks, drinking-water	-	0.035 (1)

[a] In parentheses: number of positive composites.

The authors calculated a daily intake of PCBs of 15 μg/person (a maximum level was 90 μg/person (de Vos et al., 1984). In the period May-July 1976, 100 total diets (summer meals) were collected and besides organochlorine pesticides, PCBs were determined as decachlorobiphenyl, after perchloration, and calculated as Aroclor 1260. The mean intake of PCBs/person per day was 11.6 μg with a range of 3–71 μg (Greve & van Hulst, 1977; Greve & Wegman, 1983; van der Kolk, 1985).

In 1978, another survey was carried out with 100 total diets during the winter (winter meals). It was estimated that the daily intake was 6 μg/person (range 1–19 μg).

Zimmerli & Marek (1973) studied the total human intake of PCBs from prepared meals in 1971-72 in Bern, Switzerland. Five typical total diets were composed and analysed. The intake of PCBs, especially with daily diets containing cheese, meat, fish, or fat, ranged from 6 to 84 μg.

According to a calculation by Sümmerman et al. (1978), the average weekly intake of PCBs in the Federal Republic of Germany was about 215 and 268 μg/week for females and males, respectively. Much lower figures, 36–44 μg/week, were calculated by Klein (1983).

A survey of the daily PCB intake from the total diet of Japanese women (number of samples varied from 18 to 60) was performed for the years 1972-76. The daily intake of PCBs averaged approximately 10 μg/person (range 2.8–21.2 μg). The main source of PCBs in the diet of Japan was in-shore fish. There was no clear change in daily intake over the 5-year period studied (Watanabe et al., 1979).

Ushio & Doguchi (1977) studied the dietary intake of PCBs in Tokyo. They found an average daily intake of PCBs of 6.3 μg/person (range, trace–17 μg/person). It was concluded that the dietary daily intake of PCBs for the majority of the population of Tokyo rarely exceeded 20 μg/person, when no heavily contaminated fish were consumed.

Yakushiji et al. (1977) found that the PCB daily intake through meals of unexposed adults living in Osaka prefecture, was 3–20 μg/day.

Data for PCBs in the diets of Canada, Guatamala, Japan, the United Kingdom, and the USA over the period 1972-83 were summarized by Gorchev & Jelinek (1985). The mean dietary intake reported was

at, or below, 0.06 μg/kg body weight, the mean intake per person ranged from <0.01 to 0.12 μg/kg body weight (Slorach et al., 1982; WHO, 1986b).

5.4.7 Total intake of major congeners by adults via food

In the Federal Republic of Germany, the daily intake of the 3 PCB congeners numbers 138, 153, and 180, together with the different food items, was calculated. The intake (μg/day) with meat and meat products was 0.30; with fish and fish products 0.36; eggs and egg products 0.008; milk and milk products 0.40; cheese 0.11; butter 0.39; fats and oil 0.098; bread and pastries 0.17; potatoes 0.081; vegetables 0.11 and fruits 0.082 (DFG, 1988).

5.4.8 Time trends in different matrices

Although many countries introduced severe restrictions on the manufacture, use, and disposal of PCBs many years ago, it is difficult to discern any marked decline in the levels in human milk fat, from the published data.

Levels of PCBs were estimated in 1085 samples of different cereals, collected in the Federal Republic of Germany over the period 1972/74-1984. The levels, which were the highest in 1972/74 0.04 mg/kg (0.005–0.12 mg/kg), decreased during the years to 0.004–0.005 mg/kg dry weight in 1984 (DFG, 1988).

Data from the Federal Republic of Germany showed no clear trend in PCB levels in human milk during 1975-79 (Slorach et al., 1982). The same was found in the Netherlands over the period 1974-83 (Greve & Wegman, 1984).

Japanese data showed a decline in PCB levels in the fat of whole cow's milk during the period 1972-79. A decline was also found in PCB levels in finfish from coastal waters and in total marine fish (Slorach et al., 1982).

A downward trend was found in human milk from Japan over the period 1972-80. Each year, a large number of samples (361–877 samples/year) were analysed. In 1972, the median level was about 0.8 mg/kg and, in 1980, 0.5 mg/kg, on a fat basis. A gradual decline was observed (Slorach & Vaz, 1983).

In Canada, human milk and adipose tissue from Ontario residents were analysed over the period 1969-74. The values found did not indicate a trend in this period.

The mean total PCB intakes determined in the FDA Total Diet Study, for the period 1971-87, for a typical "adult" diet, represented in Fig. 4, reflect that of a 14- to 16-year-old male during 1982-87. A clear decline was shown from approximately 7 μg/person per day to less than 0.1 μg/person per day (Gunderson, 1988a).

The daily intake of PCBs, expressed as ng/kg body weight per day, by 6-month-old and 2-year-old children in the years 1980, 1981/82, and 1982/84 did not show a trend, while, in adults, a decrease from 8 to 0.5 ng/kg body weight per day was observed over the same years (Gunderson, 1988b).

5.5 Concentrations in the body tissues of the general population

The PCB levels in body tissues are a good indication of the overall and total exposure of the body to PCBs.

Several factors may influence the concentrations of PCBs in body tissues, including duration and level of exposure, the route and pattern of exposure, the chemical structure of the PCB (degree and position of chlorination in the molecule), the amount of adipose tissue, other simultaneous exposures, as well as other biological parameters.

5.5.1 Adipose tissue

In general, while highly chlorinated congeners accumulate more easily, a lower degree of substitution provides more possibilities for hydroxylation and facilitates excretion. Factors other than the degree of substitution also affect accumulation, particularly the position and pattern of substitution (WHO/EURO, 1987).

The available information on the occurrence of PCBs in the body fat of the general population is summarized in Table 20.

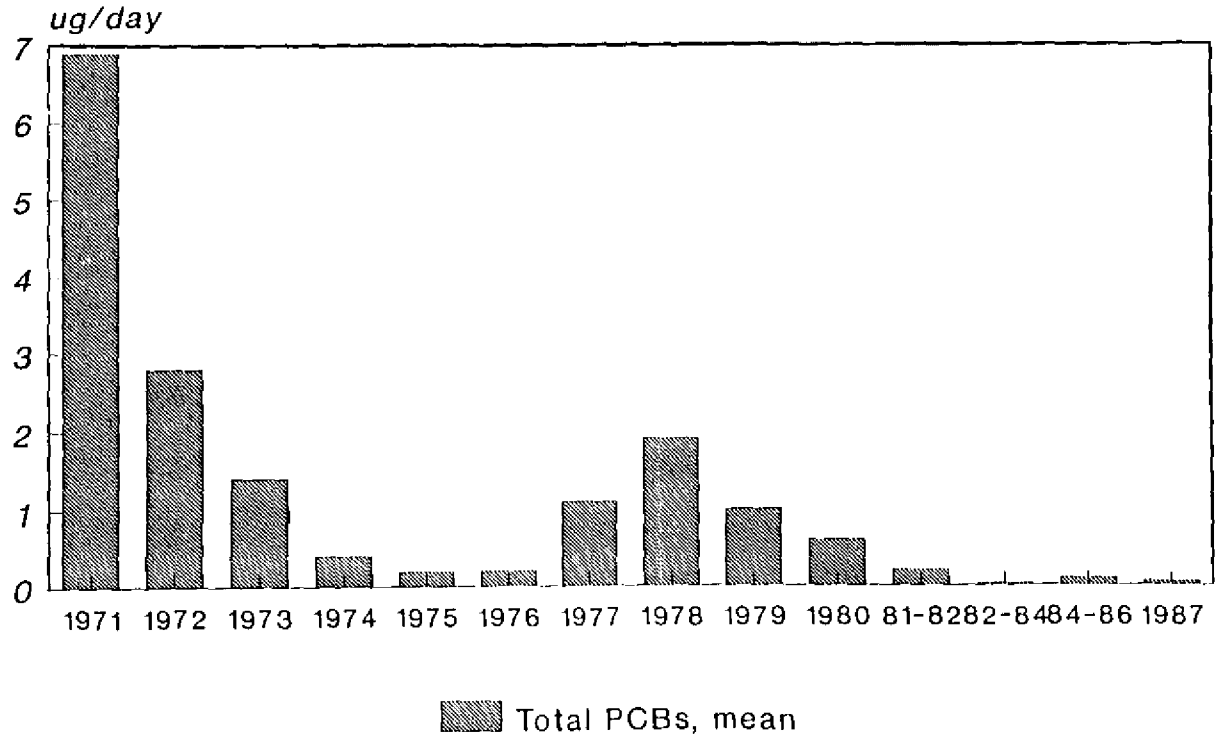


Fig. 4. FDA Total Diet Study. Total PCB intakes. "Adult" intakes = 14-to 16-year-old males since 1982. From: Gunderson (1988a).

Table 20. Concentrations of PCBs in the body fat of the general population

Country	Year	Number of samples	Mean concentration in mg/kg on fat basis (range)	Reference
North America				
USA (18 states)	-	637	< 1 (68.9%)[e] < 1-2 (25.9%)[e] > 2 (5.2%)[f]	Yobs (1972) Price & Welch (1972)
Northeast Louisiana	1980 1984	8 10	1.04 (0.38-2.33) 1.23 (0.65-1.44)	Holt et al. (1986)
Texas	1969-1972	88 (15 positive)	1.7 (0.6-9.9)	Burns (1974)
New York (urban and rural vicinity)	-	101 (women)	3.4 ± 1.1	Bush et al. (1984)
Canada	-	99	0.94 (0.04-6.8)[a]	Mes et al. (1982)
Ontario	1976 and 1984	570	2.1-2.2	Frank et al. (1988)

Table 20 (continued)

Country	Year	Number of samples	Mean concentration in mg/kg on fat basis (range)	Reference
Asia				
Japan (Kochi ara)	-	-	2.86 (maximum 7.5)	Nishimoto et al. (1972a,b)
Japan	1971-1982	-	0.5-6.0[a]	Katsunuma et al. (1985)
Tokyo	1974	30	1.04 (0.38-2.5)	Fukano & Doguchi (1977)
Japan	-	241	0.30-1.48	Curley et al. (1973b)
New Zealand	-	51	0.82	Solly & Shanks (1974)
Africa				
South Africa	1982	63	0.15-5.18	van Dijk et al. (1987)
Europe				
Austria (Vienna area)	-	32	0.3-7.3	Pesendorfer et al. (1973)
Finland	-	105	0.2	Mussalo-Rauhamaa et al. (1984)
Germany, Federal Republic of	-	20	5.7	Acker & Schulte (1970)
	-	282	8.3	Acker & Schulte (1974)
	1982-1983	50[b]	0.5-1.5	Niessen et al. (1984)
Italy (Siena)	1983-1984	26	1.75[c] (dry weight)	Focardi et al. (1986)

Table 20 (continued)

Country	Year	Number of samples	Mean concentration in mg/kg on fat basis (range)	Reference
Netherlands	1973-1983	24-78 per year	1.6-2.5[d]	Greve & van Harten (1983a); Greve & Wegman (1983, 1984)
Norway (Oslo)	-	40	1.6	Bjerk (1972)
Spain	1985-1987	14	1.68	Camps et al. (1989)
United Kingdom	-	201	< 1.0	Abbott et al. (1972)
	1976-1977	236	0.7 (nd-10)	HMSO (1986)
	1982-1983	187	0.9 (0.1-6.9)	

[a] Wet weight.
[b] 34 infants, 14 children, and 2 older children.
[c] About 60% included only five congeners: Nos. 118, 138, 153, 170, 180.
[d] Median.
[e] Percentage of samples.

5.5.1.1 PCBs in the fetus

PCBs are also present in serum and all organs of the body in proportion to their fat content. PCBs pass more, or less (depending on structure and chlorination), through the placenta into the fetus. Since the fetus has little adipose tissue until 7 months of age, PCB concentrations may be higher in vital organs, such as the adrenal gland, but available data suggest somewhat lower levels in the brain (Masuda et al., 1978a; Kodama & Ota, 1980).

Masuda et al. (1978a) found PCB levels of 270–960 μg/kg fat in adipose tissue samples of fetuses beyond 7 months of gestation. Levels in the adipose tissue of adult females from the same geographical area ranged from 270 to 1360 μg/kg fat. The mean concentrations were 470 μg/kg for fetuses and 780 μg/kg for adult females. However, since the ranges showed an overlap and the number of samples was small, it is not clear whether this represents a true difference.

5.5.1.2 Congeners in adipose tissue

Wegman & Berkhoff (1986) investigated the presence of the different congeners in 24 human fat samples, collected in 1984. The following congeners were present at the highest levels: 2,4,4'-trichloro-, 2,4,5,2',5'-pentachloro-, 2,4,5,3',4'-pentachloro-, 2,3,4,2',3',4'-hexachloro, 2,3,4,2',4',5'-hexachloro-, 2,4,5,2',4',5'-hexachloro-, 2,3,4,5,2',4',5'-heptachloro, 2,3,4,5,2',3',4',5'-octachloro, and 2,3,5,6,2',3',5',6'-octachlorobiphenyl.

Focardi & Romei (1987) analysed 30 samples of adipose tissue, obtained from patients in Siena, Italy, in 1986, for the presence of 19 PCB congeners. The results indicate that the mean PCB (as sum of the congeners) concentration was 1063 μg/kg dry weight (range 391–1918 mg/kg). The major constituents of the PCBs (about 60%) were the isomers 99, 138, 153, 170, and 180.

Human adipose tissue was analysed for 3 non-*ortho* chlorine substituted coplanar congeners: 3,4,3',4'-tetrachloro-, 3,4,5,3',4'-pentachloro- and 3,4,5,3',4',5'-hexachlorobiphenyl (Kannan et al., 1988). Twelve samples, from 7 male and 5 female persons were obtained from hospitals. The average total PCB concentrations were

1.22 and 1.02 mg/kg (wet weight basis), respectively. The concentrations of the 3 congeners were 94–860, 120–730, and 36–200 ng/kg, on a wet weight basis, respectively.

5.5.2 Blood of the general population

Finklea et al. (1972) studied human plasma of different races of the population (723 volunteers with ages ranging up to 60 years) of urban and rural areas of South Carolina. The average concentration was 5 μg/litre (range 0–29 μg/litre). No age effect was found, but ethnic differences and ethnic residence interactions were significant. Kreiss (1985) found mean serum concentrations in the non-occupationally exposed population in the USA, of between 4 and 8 μg/litre, with 95% of the individuals having serum PCB concentrations of less than 20 μg/litre. More data are sunumarized in Table 21.

Maternal blood and fetal cord blood were collected from volunteers from an urban and rural vicinity in upstate New York. Whole blood samples were taken from 101 women (26 ± 4 years) entering maternity facilities. Maternal blood contained 3.4 ± 1.1 μg PCBs/ kg and fetal cord blood contained 2.4 ± 1.0 μg/kg whole blood. The PCB congeners making up these totals were surprisingly few; 38% of the total residue in the maternal blood and 21% of the fetal cord blood comprised only 4 components, 2,4,4'-trichlorobiphenyl, 2,4,5,2',4',5'-hexachloro-, 2,3,4,2',4',5'-hexachloro-, and 2,3,5,6,2',3',6'-heptachlorobiphenyl. The congener 2,5,2',5'-tetrachlorobiphenyl crossed the placenta preferentially (Bush et al., 1984).

The concentrations of PCBs were determined in blood samples from 120 women hospitalized for miscarriages and 120 full-term pregnancy controls. The average PCB level was higher in women with miscarriages than in control women (8.65 μg/litre and 6.89 μg/litre, respectively, as Fenclor 54 and 14.81 and 14.90 μg/litre, respectively, as decachlorobiphenyl). The reproductive history of each woman was assessed together with confounding variables and with environmental exposure and food intake. Food consumption did not indicate diet as the main source of PCB intake (Leoni et al., 1989).

A cross section of the population of Michigan was studied following an accidental exposure in 1978. Five years after the accident, PCB

Table 21. Concentrations of PCBs in whole blood of the general population

Country	Year	Number of samples	Mean concentration in μg/litre (range)	Reference
Canada				
Ontario area (patients suspected of being exposed dermally)	1975-1976 1980-1981 1984	118	18	Frank et al. (1988)
Japan				
	-	-	3.2	Doguchi & Fukano (1975)
	-	28 (women)	2.6	Kuwabara et al. (1978)
(Osaka area)	1976 1972-1977	16 (women) -	2.8 (1.7-4.6) 3-4	Kuwabara et al. (1979) Yakushiji et al. (1977)
farmers	1978-1983	-	trace-21.4[b]	Katsunuma et al. (1985)
Tokyo	1973 1975	27 10	3.19 (2.2-5.1) 2.59 (1.8-3.8)	Fukano & Doguchi (1977)

Table 21 (continued)

Country	Year	Number of samples	Mean concentration in μg/litre (range)	Reference
Finland	-	-	3.1-12	Karppanen & Kolho (1973)
Netherlands	-	34 (women) 31 (men)	4.5 (nd-11.6) 4.8 (1.0-17.1)	Blok et al. (1984)
	1978 1980 1981 1982	48-127 samples/year	3.1[e] 3.5 4.4 4.4	Greve & Wegman (1983, 1984)
North America				
South Carolina (urban and rural area)	1968	723	5 (4.2-5.5)[a]	Finklea et al. (1972)
Michigan (areas of Lake Michigan)	1973 1979-1981	1100	56[c] 17.2-23.6[c]	Kreiss (1985)
Lake Michigan (high fish consumption)	1985	196	5.5 ± 3.7	Schwartz et al. (1983)

Table 21 (continued)

Country	Year	Number of samples	Mean concentration in μg/litre (range)	Reference
Yugoslavia (residents around River Krupa; contamination by a plant using PCBs)	1984-1986	10[f] 19[g] 4[h]	155 (35-480)[d] 11 (6-18) 5 (2-7)	Jan & Tratnik (1988a)

[a] Plasma.
[b] Serum.
[c] Geometric mean.
[d] Arithmetic mean.
[e] Median concentration.
[f] Living close to plant.
[g] Living 1-3 km from plant.
[h] Non-exposed other areas.

and PBB residues were measured in adipose tissue and serum. Serum levels of PCB were measured in 1681 adults and 1462 children. Children (430) were found to have uniform levels throughout the state (mean concentration 4 ± 2 μg/litre). In adults, the serum PCB levels were higher in the area with highest PBB levels. The mean serum PCB level was 21 μg/litre, compared with control levels for the rest of the state of 9 μg/litre. No sex difference was found (Wolff et al., 1982a).

Specific PCB isomer levels in the blood of 30 children, ages 2–5 years, residing in an area of PCB-contaminated soil in Canada, were compared with those of 25 children in a non-contaminated area. The sum of individual PCB isomer levels in the exposed and non-exposed group were not significantly different, e.g., 0.54 μg/litre (range 0.22–0.99 μg/litre) and 0.88 μg/litre (range 0.28–2.30 μg/litre). The major component in both groups was 2,4,5,2',4',5'-hexachlorobiphenyl (Mes, 1987).

High levels of PCBs were found in the blood (up to 100 μg/litre) in patients with severe weight loss (Hesselberg & Scherr, 1974). This was attributed to the release of PCBs from the mobilization of fat.

Greve & van Harten (1983b) studied the relationship between the levels of PCBs in the adipose tissue and in the blood of the same persons. A total of 48 persons were involved in this study. A concentration factor (concentration in adipose tissue divided by concentration in blood) of 660 was found.

5.5.3 *Human milk*

Human milk is the major source of exposure for breast-fed infants. The amount of human milk secreted varies widely. The composition of the milk is related to the amount secreted, the stage of lactation, the timing of withdrawal (early or late in feeding) and to individual variations among lactating women. The individual variations depend on maternal age, health, social class, and diet. The concentration of PCBs depends primarily on the lipid concentration in milk. Wide variations in published results are caused by inaccuracies inherent in the analytical methods used for the quantification of lipids, and whether the milk sample is collected early or late during the feeding period. The fat content increases during emptying, and the fat content

of milk from the 2 breasts may differ. According to a recent determination, the fat level in human milk averages 2.6–4.5% (WHO/EURO, 1988).

Whether the differences in concentration in various countries are merely a function of the analytical methods used and the type of samples collected or whether true differences in body burden exist, is not clear at present. For instance, some countries have reported levels of PCBs in human milk fat ranging from nondetectable to 14 mg/kg, while, in other countries, the highest levels found have been around 3 mg/kg. Because of these variations, calculating an average dose for nursing infants is difficult. The same difficulties exist when attempts are made to investigate trends over time (WHO/EURO, 1988).

The results of the older studies have been obtained with a less sophisticated method using packed column GC. With this method only a dozen peaks can be separated. The quantitative results are reported as "total PCB values", though different techniques of quantification and different types of calculations were used.

In contrast with the situation with many organochlorine insecticides, the levels of PCBs in human milk fat are higher in European countries, Japan, and the USA than in China (Slorach & Vaz, 1983, 1985), and are significant, particularly in the highly industrialized countries. Results from a large number of countries have been summarized by Jensen (1983a, 1985, 1987), Acker et al., (1984), Katsunuma et al. (1985) (especially Japanese data; period 1972-83); and WHO/EURO, (1987,1988). The countries concerned are: Argentina, Austria, Belgium, Canada, Finland, France, Federal Republic of Germany (Klein, 1983), German Democratic Republic, Israel, Japan, the Netherlands, Norway, Poland, Romania, South Africa, Sweden, Switzerland, Turkey, United Kingdom, USA, USSR, and Yugoslavia. The average levels of PCBs in human milk do not appear to differ very much between the industrialized countries and range between 0.5 and 2 mg/kg milk fat, except in Czechoslovakia, the Federal Republic of Germany, India, Denmark and Italy, where levels up to 3 mg/kg milk fat were found (Jensen, 1983b; Acker et al., 1984) (Table 22).

Table 22. Concentrations of PCBs in breast milk of the general population

Region Country	Year	Number of samples	Mean concentration in mg/kg on fat basis (range)	Reference
North America				
USA (Michigan)	1977-1978	1057	1.5 (maximum 5.1)	Wickizer et al. (1981); Wickizer & Brilliant (1981)
Canada (Quebec)	-	154	0.84 (nd-4.34)	Dillon et al. (1981)
Ontario	1971-1974 1978	- 215	1.2 (0.1-3.0) 0.6 ±0.3	Atkinson (1979)
Ontario	1975-1985	348	0.023 (0.016-0.033)[a]	Frank et al. (1988)
Five regions across Canada	1982	210	0.697	Mes et al. (1986)
Regina, Saskatchewan	1979	80	0.0052 (0.001-0.019)[a]	Qureshi & Robertson (1987)

Table 22 (continued)

Region Country	Year	Number of samples	Mean concentration in mg/kg on fat basis (range)	Reference
Asia				
Japan (Osaka)	1972-1977	-	0.030-0.040[a]	Yakushiji et al. (1977)
	1969-1976	19-52 each year	1-2	Yakushiji et al. (1979)
India (Ahmedabad	1981-1982	50	not present	Jani et al. (1988)
Hawaii (different islands)	1979-1980	54	0.80 ±0.43 (0.13-2.2)	Takei et al. (1983)
Europe				
Germany, Federal Republic of	since 1970	several thousands	1.0-2.5 (98% of samples between 0.001-7.2)	Acker et al. (1984); Cetinkaya et al. (1984); Heeschen et al. (1986); Lorenz & Neumeier (1983)
	-	2709	1.77	Fooken & Butte (1987)
Netherlands (11 centres country-wide)	1983	278	0.72 (0.27-2.20)[b]	Greve et al.(1985); Greve & Wegman (1984)
	1977-1979, 1981	2649	2.1	Olling (1984)
United Kingdom (Scotland)	1979-1980	30	0.01 (nd-0.04)	HMSO (1986)
	1983-1984	30	< 0.01 (nd-0.02)	

Table 22 (continued)

Region Country	Year	Number of samples	Mean concentration in mg/kg on fat basis (range)	Reference
Italy (Rome)	1983-1985	65	0.070 (0.007-0.176)[a,c]	Dommarco et al. (1987)
Finland (different parts)	1984-1985	183 (165 of women)	0.57 (0.05-10.7)	Mussalo-Rauhamaa et al. (1988)
Sweden (5 regions)	-	300[e]	1.06-1.18 (four regions) 1.44 (one region)	Noren (1983)
	1972	227[d]	1.05	Noren (1988)
	1976	245	0.99	
	1980	340	0.78	
	1984-1985	102	0.60	
Austria (Vienna)	-	22	1.54 (0.58-3.78)	Pesendorfer (1975)
Other regions		9	1.29 (0.95-1.57)	Pesendorfer (1975)

[a] Whole milk.
[b] Median concentration.
[c] Arithmetic mean.
[d] Number of mothers that provided 4-7 samples each (samples were pooled).
[e] In each region, 300 mothers gave breast milk 3-5 days after parturition.

The variation in residue levels in human milk during lactation was investigated in 5 women in the Federal Republic of Germany. Month-mix samples, composed of breast milk samples collected weekly, were analysed over a lactation period of between 5 and 9 months. The ages of the women ranged from 23 to 36 years. The PCB concentrations were between 0.61 and 2.20 mg/kg, on a fat basis. While the concentrations remained relatively constant, some fluctuations were seen but no trend was observed over the lactation period investigated (Fooken & Butte, 1987).

Breast milk samples from 16 women in Canada were analysed for PCBs at 8 intervals (7, 14, 28, 42, 56, 70, 84, and 98 days) during the lactation period. The average PCB concentrations in breast milk varied between 22.8 and 29.7 μg/kg whole milk. No clear decrease or increase was observed. The average milk/blood ratio for PCBs was 23 and remained relatively constant during lactation (Mes et al., 1984).

Wolff (1983) reported the half-life of PCBs (percentage chlorine not specified) in breast milk to be 5–8 months and found that the concentration of PCBs in breast milk was 4–10 times that in the maternal blood. Similar results were reported by Jacobson et al. (1984b).

In a study by Kuwabara et al. (1978), the relationship was investigated between breast-feeding and PCB residues in the blood of children whose mothers were occupationally exposed to PCBs. The children ingested their mother's milk for periods of < 1 to 3 years. The age of the children at the time of the study ranged up to 13 years. The data provide evidence that PCBs are retained in the children's body for many years and that longer intake of mother's milk tends to increase PCB levels in the blood of the children. The PCB levels in the blood of the 20 occupationally-exposed women and their 39 children ranged from 8.3 to 84.5 and 0.8 to 93.2 μg/litre, respectively.

The results suggest that the PCB levels in the blood of children are much more influenced by the transportation of PCBs through the mother's milk than through the placenta. Furthermore, it was found that the gas chromatographic patterns of the blood PCBs of the children, breast fed for a long time, were different from those of their

mothers. Blood from 16 non-occupationally exposed mothers and their children (17), showed that, as the length of the breast-feeding period increased, there was an increase in the PCB levels in the blood of the children. The mean blood PCB level in mothers was 2.8 ± 0.8 μg/litre; in children, it was 3.8 ± 3.6 μg/litre. In this study, no clear change in blood PCBs patterns between mothers and children was observed (Kuwabara et al., 1979).

Samples of maternal blood, milk, and umbilical cord blood were collected from 43 mothers giving birth to their first or second child; all the mothers had lived in Oslo during the previous 2 years. Blood samples were collected immediately after delivery, either by Caesarean section (16 Norwegians) or normally (20 Norwegians and 7 immigrants). Subcutaneous fat samples were obtained during the operation. Samples of colostrum and milk were obtained 3 and 5 days postpartum. PCBs were found in 135 of the total 168 samples. In the Norwegian women and infants, PCBs were the major contaminants, whereas only traces of PCBs were found in the samples of immigrants. The average concentrations in the maternal serum, cord serum, colostrum, and breast milk of Norwegian women (Caesarean and normally delivered taken together) were : 10, 3–5, 18–21, 20–23 μg/kg wet weight (Skaare et al., 1988).

5.5.3.1 *Major PCB congeners in human milk*

Commercial PCB preparations consist of complex mixtures of environmentally stable compounds with a wide range of chlorine contents. PCBs are transferred to breast-fed infants with the fat of the mother's milk. Thus, infants nurtured on maternal milk are exposed to relatively high concentrations of the higher chlorinated PCBs in the short period preceding the full functioning of certain organs, e.g., the liver (Jensen, 1983b; Slorach & Vaz, 1983; Gezondheidsraad, 1985).

Three major congeners were present in breast milk, e.g., PCB congener numbers 138, 153, and 180 (DFG, 1988).

Slorach & Vaz (1983) reported that the GC patterns of PCBs in breast milk samples from different countries were similar. The peaks denoted 146, 174, and 180 were dominant in the gas chromatograms.

The total levels of PCBs and the concentrations of certain congeners in Swedish human milk, sampled in 1972-89, were studied by Noren et al. (1990). Minor changes in the distribution of the congeners were found over the period of study. The most abundant of the non-*ortho* coplanar PCBs in Swedish human milk was 3,4,5,3',4'-pentachlorobiphenyl (126), with levels decreasing from 0.35 μg/kg milk fat (1972) to about 0.10 μg/kg (1989).

Safe et al. (1985a) analysed a sample of breast milk using the congener-specific PCB method and found the following major components: 2,4,4'-trichloro-; 2,4,5,4'-tetrachloro-; 2,4,5,2',4'-pentachloro-; 2,4,5,3',4'-pentachloro-; 2,3,4,5,2',5'-hexachloro-; 2,4,5,2',4',5'-hexachloro; 2,3,4,5,2',3',4'-heptachloro-; and 2,3,4,5,2',4',5'-heptachlorobiphenyls.

The major PCB congeners in the breast milk of Japanese women from the general population were: 2,4,4'-trichloro-; 2,4,3',4'-tetrachloro-; 2,4,5,3',4'-pentachloro-; 2,3,4,2',3',4'-hexachloro-; 2,3,4,5,2',4'-hexachloro-; and 2,3,4,5,2',4',5'-heptachlorobiphenyls. The congeners were present in 5% or more samples; a few other congeners were present in only 1–3% (Gyorkos et al., 1985; Jensen, 1983b).

Sixty-eight breast milk samples collected in the Netherlands were used to determine the congener distribution. The indicator congeners, present in the highest concentrations, were: 2,4,4'-trichloro-, 2,4,5,2',5'-pentachloro-, 2,4,5,3',4'-pentachloro-, 2,3,4,2',4',5'-hexachloro-, 2,4,5,2',4',5'-hexachloro-, 2,3,4,5,2',4',5'-heptachlorobiphenyl (Wegman & Berkhoff, 1986).

Schecter et al. (1989a) analysed a total of 17 samples of human milk from Thailand and Vietnam, for the presence of PCB congeners. The main congeners that were present were 138, 153, and 180 (each in the range of 8–31 μg/litre). The other congeners, normally present, were all below the detection limit of 2 μg/litre.

In a study on pooled human milk samples from a 1982 nation-wide survey in Canada, Mes & Marchand (1987) compared the relative amounts of 29 selected PCB isomers with amounts in milk samples of unexposed Rhesus monkeys. In the pooled milk sample, 397 μg PCBs/litre, on a fat basis, were found and the PCB isomer numbers 74, 99, 118, 138, 153, and 180 were the main contributors. Most of the predominant PCB isomers in human milk were also observed in

monkey's milk, but monkey's milk had relatively low levels of PCB isomers numbers 74 and 99.

In another study, Davies & Mes (1987) analysed breast milk samples from Canadian, Indian, and Inuit (Eskimo) mothers in Canada. The 18 samples were received from 5 Indian and Inuit nursing zones. The combined total PCB isomer level (on a whole-milk basis) of the native population was comparable with that of the national population. Even the levels of the 5 largest PCB congeners (Nos. 74, 118, 138, 153, and 180) were comparable.

Individual congeners in the blood of Yusho- and Yu-Cheng patients are discussed in section 5.6.

5.5.3.2 *Factors that influence the intake of PCBs with milk*

Present data suggest that the PCB content of human milk varies considerably from individual to individual.

Many factors affect the level of PCBs and other organochlorine compounds in breast milk including the fat content of the milk; time from start of lactation; mother's age; mother's body weight; parity; number of children previously breast-fed; origin and residence; eating habits; season; smoking; use of household products; amount of milk; and exposure at work (WHO/EURO, 1985, 1988).

In a given woman's milk, there are fluctuation in the PCB levels in whole milk and in milk fat during one nursing session and during the day (Jensen, 1983b). A decrease of PCB levels in both milk and milk fat has been found during the lactation period. Furthermore, the PCB concentration in human whole milk and milk fat increases with the age of donor. Another confounding factor is that the PCB levels decrease with increasing numbers of deliveries and lactations (Greve et al. 1985); lactation serves as a period for the biological elimination of PCBs (Jensen, 1983b). The PCB levels in human milk are higher in heavily populated and industrialized areas than in rural areas. Furthermore, in general, the PCB levels in the breast milk of women from developing countries are lower (Jensen, 1983b).

Cetinkaya et al. (1984) studied the PCB levels in human milk samples from all over the Federal Republic of Germany. At the same time, data were collected by means of a detailed questionnaire on residency,

workplace, smoking, drinking and eating habits, and the age of participating individuals.

The breast milk of 45 women consuming lacto-vegetarian food was compared with that of 41 women consuming conventional food in the Federal Republic of Germany in the period 1979-81. The PCB concentration was comparable, e.g., 2.2 and 2.5 mg/kg, on a fat basis, respectively (Acker et al., 1984).

Fish consumption was positively correlated with PCB levels in maternal serum and breast milk. PCB levels in serum increased with age, but were unrelated to social class, parity, or body weight (Schwartz et al., 1983).

Eight hundred and one Wisconsin anglers were surveyed for fishing and consumption habits in 1985. The mean annual number of sport-caught fish meals was 18 (range 7.1 to 33.3). The mean number of non-sport-caught fish meals was 24. The median PCB serum congener sum level for 192 anglers was 1.3 μg/litre (range, nd to 27.1 μg/litre). Statistically significant positive Spearman correlations were observed between sport-caught fish meals and PCB levels in serum and between kg of fish caught and PCB levels in serum (Fiore et al., 1989).

PCBs were measured in maternal serum, cord blood, placenta, and serial samples of breast milk and colostrum, from 868 women in North Carolina (USA). Forty-three per cent of the women were primiparous. Breast milk was collected at 6 weeks, 3 months, and 6 months, and, in a few cases, up to 18 months postpartum. The median PCB concentration in breast milk decreased during the sampling period from 1.77 to 1.02 mg/kg, on a fat basis. The PCB concentration dropped by about 20% over 6 months and 40% over 18 months. This implies that excretion in milk is a major factor in lessening the mother's body burden; however, it also implies substantial exposure of the child. Colostrum contained a median value of 1.74 mg/kg. PCBs concentrations were higher in milk than in serum and higher in maternal serum than in the placenta. The levels in cord blood were almost always below the limit of quantification. Older women and women who regularly drank alcohol had higher PCB levels in their milk; blacks had higher levels than whites. In general, women had higher levels in their first lactation and in the

earlier samples of a given lactation, and levels declined both with time spent breast-feeding and with number of children nursed (Rogan et al., 1986a).

Two hundred and forty-two newborn infants of mothers who consumed moderate quantities of contaminated lake fish and 71 infants whose mothers did not eat such fish were examined during the immediate post partum period. PCB exposure was correlated with lower birth weight and smaller head circumference, and the authors claimed that these effects were not attributable to any of 37 potential confounding variables, including socioeconomic status, maternal age, smoking, etc. (Fein et al., 1984).

The mother's diet may be an important determinant of the PCB levels in her milk. In some areas of the world, the intake of PCBs from eating contaminated fish has been claimed to be the most important source of PCBs in human milk. Dairy products and meat may be contaminated via natural food or feedstuffs (WHO/EURO, 1988).

In a pilot study on the course of the PCB concentration in human milk during 6 months of lactation, some PCB determinants were studied in 23 women and their infants. The average PCB concentration in the milk of 14 mothers during a 6-month period amounted to 0.66 $\pm$ 0.12 mg/kg, on a fat basis. In univariate analyses, the PCB concentration on a fat basis was strongly associated with pre- versus post-pregnancy weight gain, age, and occupation. After multiple regression analysis, the PCB concentration on a fat basis remained significantly associated with changes in weight gain. The pre-pregnancy Quetelet Index of the mother (height/weight) and the estimated PCB content of the diet (fish) were correlated with the PCB concentration, on a milk basis (Drijver et al., 1988).

5.5.4 Other tissues

Schecter et al. (1989b) analysed the tissues of 3 patients from the North American continent, with no known history of chemical exposure, for the presence of PCB isomers. The total PCB concentrations in the 9 tissues studied were different. The highest levels were found in adipose tissue, subcutaneous fat (range 86–423 μg/kg), adrenals (25–103 μg/kg), liver (3–149 μg/kg), bone marrow (26 μg/kg), kidneys (2–31 μg/kg); levels in the spleen, lung,

and testes were below 12 μg/kg. Congeners present in the highest concentrations were numbers 28, 74, 118, 153, 105, 138, 183, and 180.

5.6 Accidental exposures (Yusho- and Yu-Cheng)

In 1968, a large number of persons in Japan were accidentally poisoned by the consumption of a batch of rice oil contaminated with Kanechlor 400. A similar accident happened in the Province of Taiwan in 1979, where the affected persons had also consumed rice-bran oil contaminated with PCBs. The 2 cases of poisoning were called Yusho and Yu-Cheng accidents, respectively (see section 9.1.2.1).

The average PCB concentration in the plasma of Yusho children was 6 μg/litre, compared with 3.7 μg/litre in controls. Breast-fed Yusho children had higher levels than children not breast-fed (Abe et al., 1975).

The concentrations of PCBs in the adipose tissue, liver, and blood of Yusho patients, about 5 years after the outbreak, were 1.9 ± 1.4 mg/kg, 0.08±0.06 mg/kg, and 6.7±.3 μg/litre, respectively. These values were only about twice those of controls. The mean blood PCB level of 278 persons involved in the Yu-Cheng accident was 89.1 μg/litre (range 3–1156 μg/litre). Six months after the exposure, the concentrations of PCBs in the blood had decreased to 12–50 μg/litre. The mean blood concentration of 165 patients, 9–18 months after the onset of poisoning, was 38 μg/litre (range 10–720 μg/litre) (see section 9.1.2.1). The blood PCB level of some Yu-Cheng patients (99±163 μg/litre), was much higher than that of the Taiwanese population (1.2±0.7 μg/litre), one year after the outbreak of the intoxication.

Chen et al. (1985) analysed the blood of 165 Yu-Cheng patients, 9–18 months after the onset of poisoning, and found 10–720 μg PCBs/litre with a mean value of 38 μg/litre. The blood of 10 patients, 9–27 months after poisoning, contained 0.02–0.2 μg PCDFs/litre. The PCDF-congeners found in tissues were the same as those found by Masuda et al. (1985).

Seven PCB congeners including: 2,4,5,3',4'-pentachloro-; 2,3,4,3',4'-pentachloro-; 2,4,5,2',4',5'-hexachloro-; 2,3,4,2',4',5'-hexachloro-; 2,3,4,5,3',4'-hexachloro-; 2,3,4,5,2',4',5'-heptachloro-; and 2,3,4,5,2',3',4'-heptachlorobiphenyls, were identified in the blood and tissues of Yusho, Yu-Cheng patients and controls.

Major PCDF congeners identified in the tissues and blood of Yusho and Yu-Cheng patients were 2,3,6,8-tetrachloro-; 2,3,7,8-tetrachloro-; 1,2,4,7,8-pentachloro-; 2,3,4,7,8-pentachloro-; and 1,2,3,4,7,8-hexachlorodibenzofurans. The 2,3,4,7,8-pentachloro-compound was predominant. The concentrations of PCDFs in the adipose tissue and liver of Yusho patients were 6–13 μg and 3–25 μg/kg tissue, respectively. No PCDFs could be detected in the controls. Besides PCBs and PCDFs, 4-methylthio-2,5,2',5'-tetrachlorobiphenyl (concentrations ranging from 0.1 to 1.4 μg/kg tissue) and 4-methylsulfone-2,5,2',5'-tetrachlorobiphenyl (range 0.3–2.5 μg/kg tissue) were also found (Masuda et al., 1985).

5.7 Occupational exposure

5.7.1 Accidental exposure

Though the volatility of the PCBs is low, they are found in rather high concentrations in the workroom air in both the long-term open use of PCBs and in temporary or acute events where evaporation into the air is possible. The measured air concentrations of PCBs in long-term exposure situations, such as the manufacturing of transformers or capacitors, varied from 30 to 1000 $\mu g/m^3$, depending on the year of measurement and the factory concerned (Silbergeld, 1983).

In discontinuous work, such as the inspection and repair of transformers and capacitors, levels of between 0.1 and 60 $\mu g/m^3$ have been observed (Wolff, 1985). PCB concentrations in the breathing zone of workers in transformer repair and maintenance work varied between 0.01 and 24.0 $\mu g/m^3$ (Moseley et al., 1982).

In the atmosphere of an electroindustrial plant in Bela Krajina, levels in the manufacturing room, where the autoclave was emptied, averaged 2000 $\mu g/m^3$ (range, 1400–3200 $\mu g/m^3$); an average of

80 $\mu g/m^3$ (range 40–120 $\mu g/m^3$) was found in the working environment in capacitor manufacture (Jan et al., 1988b).

Digernes & Astrup (1982) determined the concentrations of PCBs in the atmosphere of the workplace of data screen operators, because skin rashes and eczema had been reported among the workers. The PCB concentrations in the working atmosphere (3 samples: concentrations ranging from 0.056 to 0.081 $\mu g/m^3$) were about 50–80 times higher than the maximum level of PCBs in 3 samples collected outside the building (0.0005–0.001 $\mu g/m^3$). The indoor and outdoor samples also differed qualitively. The indoor samples contained only Aroclor 1242, while outdoor samples contained a mixture of Aroclor 1242 and 1254.

Acute emergency events may cause extremely high concentrations of PCBs in the air, particularly in cases when PCBs are burnt or heated (fire, short circuit with electric arcing, burning in welding, etc.). Levels of up to 10 000–16 000 $\mu g/m^3$ have been measured. In the case of extensive leaks of unheated PCBs from capacitors, concentrations of 1900 $\mu g/m^3$ have been measured in workroom air (Elo et al., 1985; WHO/EURO, 1987).

In connection with fires and electrical explosions, due to short circuits, PCBs may be decomposed at elevated temperatures varying from a few hundred to 2000 °C. Soot may be produced in large amounts, consisting of particles that may contain PCB concentrations up to 5000–8000 mg/kg of soot (Elo et al., 1985; O'Keefe et al., 1985; WHO/EURO, 1987).

When evaluating PCB exposure, it is important to take into account skin absorption from surfaces and tools, in addition to exposure via inhalation. Surface concentrations of PCBs in capacitor factories have varied between 4 and 60 $\mu g/m^2$, and, where PCB leaks have occurred, levels of up to 30 mg/m^2 have been measured. Where PCBs have been used long-term, contamination levels of 1–2 $\mu g/cm^2$ have been found on tools and tables.

A transformer was found to have overheated and released an oily mist containing PCBs and their pyrolysis by-products, in a Department building in New Mexico. The transformer contained Askarel (87% Aroclor 1260 and 13% of a mixture of tri- and tetrachlorinated

benzenes). The 3-storey building was extensively contaminated via the following ways:

- mist entered 2 rooms, adjacent to the basement in which the transformer was located;
- direct spread of mist and fumes through stairways;
- air drafts created by open windows and exhaust fans, spreading fumes throughout the building;
- foot traffic by employees and other persons;
- the exhaust vent of the transformer room, located near the intake vents for the building's air-conditioning system.

Air samples obtained up to 14 h after the incident showed levels of 48 $\mu g/m^3$ in the transformer vault and 20 $\mu g/m^3$ in the room above the vault. Wipe samples of surfaces showed PCB levels ranging from 30 million $\mu g/m^2$ for grossly contaminated surfaces to 4700 $\mu g/m^2$ for surfaces without visible contamination.

Five to 7 days later, air and surface samples were analysed for 2,3,7,8-tetrachlorodibenzofuran (TCDF), which was found to be present in the air at an average level of 48 pg/m^3 in most contaminated areas. In wipe samples, the levels ranged from 5 ng/m^2 to 41.224 ng/m^2. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) was not detectable in either air samples (detection limit, 0.5–5.0 pg/m^3 air) or wipe samples (detection limit 180 ng/m^2) (Anon., 1985).

Very high concentrations of these toxic chemicals may be found in soot emitted in connection with fires and explosions in capacitors.

Thus, skin contamination, and the ingestion and inhalation of soot particles, may result in serious exposure in PCB accidents and emergencies.

A short-term, follow-up study was performed on 55 workers in a gear plant, whose work did not involve the use of PCBs. Exposure was to the total residual PCB left behind by a capacitor company that had formerly (3 years before) used the site. Air samples contained < 10 $\mu g/m^3$ and mean concentrations in wipe samples ranged from 23 to 161 $\mu g/100\ cm^2$. The 38 workers had a mean PCB concen- tration in serum of 14.4 and the 17 office workers, 4.8 μg/litre. When the

PCB determinations were repeated in the 2 following years, no clear decrease was observed (Christiani et al., 1986).

5.7.2 Occupational exposure during manufacture and use

Occupational exposure occurs during the manufacture of PCBs as well as during their use by the electrical industry. It may also be widespread among mechanics in contact with lubricating oils and hydraulic fluids, among workers exposed to varnishes and paints, and among office workers who have contact with pressure-sensitive duplicating paper (carbonless copying paper), some brands of which readily transferred PCBs to skin (Kuratsune & Masuda, 1972).

5.7.2.1 Adipose tissue

Levels of PCBs in the adipose tissue of occupationally exposed workers have been found to vary between 26 and 50 mg/kg (range, 2.2–290 mg/kg). There is a strong correlation between the blood PCB concentration and PCB levels in adipose tissue, but the distribution of the various congeners between plasma and adipose tissue is not the same, as described above.

Emmett (1985) found the following congeners in the adipose tissue of present and past transformer workers exposed to Aroclor 1242 and 1254: 2,4,3',4',5'-pentachloro-, 2,3,4,3',4'-pentachloro-, 2,3,4,5,2',4'-hexachloro-, 2,3,4,6,3',4'-hexachloro-, 2,4,5,3',4',5'-hexachloro-, 2,3,4,5,2',3',4'-heptachloro-, and 2,3,4,5,6,3',4'-heptachlorobiphenyl.

5.7.2.2 Blood

Karppanen & Kolho (1973) analysed the blood of 26 persons, 9 non-exposed, 6 persons handling PCBs, and 11 persons employed for 4 years in a capacitor-manufacturing plant in Finland. In the latter case, Aroclor 1242 was used. The average concentrations in the blood of the 3 groups were 7.1 μg/kg (3.1–12 μg/kg), 49.5 μg/kg (36–63 μg/kg), and 440 μg/kg (70–1900 μg/kg), on a wet weight basis.

More recent results of a Finnish control group of workers indicated serum PCB levels of 1.2 ± 0.6 μg/litre in an industrial area (Luotamo

et al., 1985; WHO/EURO, 1987). With acute exposure to high concentrations of PCBs in air (8000–16 000 $\mu g/m^3$), for a short period, blood PCB concentrations rose to levels of 30 μg/litre; a return to the normal level of 3 μg/litre was achieved, 4 weeks after termination of exposure (Elo et al., 1985; WHO/EURO, 1987).

Similar plasma values were found in workers from Japanese capacitor factories, but, here, skin lesions were noted (Hasegawa et al., 1972a). In this same study, it was reported that air levels of PCBs of 10–50 $\mu g/m^3$ were measured in a factory where KC-300 was used in the manufacture of electric condensers. PCB levels in the serum of workers ranged from 100 to 650 μg/litre. One month after the use of PCBs had been suspended, serum levels remained unchanged (90–740 μg/litre). However, in another factory making electric condensers, serum levels decreased from an average of 800 to 300 μg/litre, within 3 months of the use of PCBs being discontinued (Kitamura et al., 1973). According to Hara et al. (1974), the half-time of PCBs in the blood of workers, engaged in the manufacture of electric condensers for less than 5 years, was several months, while that of workers employed for more than 10 years was 2–3 years.

Kuwabara et al. (1978) reported mean PCB levels of 36.8 μg/litre (range 8.3–84.5 μ/litre) blood in 20 PCB-workers, 39 children had blood levels of 14.3 μg/litre (0.8–93.2 μg/litre), and 12 Yusho patients, 4.2 μg/litre (1.8–8.6 μg/litre).

Fact-finding surveys of 63 workers, who were occupationally exposed to PCBs (Kanechlor 500) in the production of silk thread or of paint, were carried out in Japan in 1974-75; some of them and their families were also surveyed again in 1975-82. Nineteen per cent of them showed PCB levels higher than 50 μg/litre plasma. These persons did not show the typical clinical findings of Yusho patients. During 7 years, no clear decline was observed (Takamatsu et al., 1984).

There is clear evidence that relatively high PCB levels persist in the blood of workers whose "external" exposure ceased several months or years previously. The blood PCB concentrations in capacitor manufacturing workers, who had been exposed for 1–24 years, varied

between 24.4 and 192 μg/litre; this was higher than levels in the blood of a reference population (0.5–33 μg/litre) (Maroni et al., 1981a).

In Japan, Yakushiji et al. (1984a) studied the rate of decrease and the half-life of PCBs in the blood of children (aged 1–13 years) and their mothers, who were occupationally exposed to PCBs, over a 5-year period (1975-79). The mean concentration of 121 blood samples from 50 children was 17.4±22.9 μg/litre and that in 65 samples from 29 mothers was 32.3±20.6 μg/litre. The concentrations of PCBs in the blood of the children varied over a wide range, because of differences in the duration of breast-feeding. The rate of decrease of the PCB concentration in the blood in both 18 children and 8 mothers was relatively constant and independent of the PCB concentrations. A one-compartment model equation was sufficient to represent the decrease in the concentration of PCBs in the blood. The mean rate constant of the decrease for the children was 24.2% per year, approximately 2.6 times higher than that of the mothers (9.2%), equivalent to half-lives of 2.8±1.1 and 7.1±2.7 years, respectively. The dilution effect due to the increase in body weight was the most important factor that affected the reduction of the PCB concentrations in the children.

A total of 118 blood samples, mainly from employees in industries using PCBs, were collected in the period 1975-85. In 64 blood samples, an average level of 17 μg/litre (range nd–110 μg/litre) was found (Frank et al., 1988).

Brown & Lawton (1984) studied the partitioning of PCBs between adipose tissue and serum in a population of 173 capacitor workers, who were occupationally exposed to Aroclors 1254, 1242, and 1016 for various periods of time. The serum levels of PCBs were significantly dependent on the level of lipids in the serum, but not on that in the albumin. The apparent contribution of cholesterol and its esters to PCB transport is nearly equal to their contribution to the total serum neutral lipids. The level of serum lipids PCBs must be equal to the adipose fat PCBs level.

Yakushiji et al. (1984b) studied the relationship between breast-feeding and the PCB levels in the blood. The blood samples of 50 children (121 samples) and of 29 occupationally exposed mothers (65 samples) were analysed during the period 1975-79. The PCB levels

in the blood of the children were greatly influenced by the duration of breast-feeding, but showed little relationship to the PCBs levels in maternal blood.

6. KINETICS AND METABOLISM

6.1 Absorption

6.1.1 Inhalation

Studies on rats (6 per group) showed that an aerosol containing a PCB mixture (Pydraul A200: 42% chlorine), particle size 0.5–3.0 μm, at a concentration of 30.4 ± 3.4 g/m^3 for 30 min, was readily absorbed through the lungs. The PCB concentration in the liver, 15 min after cessation of exposure, was 50% of the maximum concentration attained after 2 h (70 mg/kg tissue) (Benthe et al., 1972).

6.1.2 Dermal

Vos & Beems (1971) and Vos & Notenboom-Ram (1972) applied Aroclor 1260 to the shaved backs of rabbits and found systemic effects in the kidneys, indicating that PCBs can penetrate the skin (see section 8.2.5).

Nishizumi (1976), using tritium-labelled PCBs (40% chlorine), found evidence for the dermal absorption of PCBs in rats.

In a study of the occupational exposure of electrical workers to PCBs (Pyralen 3010 and Apirolio, 42% chlorine content), Maroni et al. (1981a) concluded that absorption of PCBs occurred through the human skin. Quantitative data were not available.

6.1.3 Oral

When polychlorobiphenyl isomers were administered orally, by gavage, to rats, at levels of 5, 50, or 100 mg/kg body weight for the lower chlorinated compounds and up to 5 mg/kg for the higher chlorinated compounds, 90% of the compounds were rapidly absorbed by the gastrointestinal tract (Albro & Fishbein, 1972; Berlin et al., 1973; Melvås & Brandt, 1973).

Using Rhesus monkeys, Allen et al. (1974a,b) determined that >90% of a single oral dose of 1.5 or 3.0 g Aroclor 1248/kg body weight

was absorbed over a period of 2 weeks. Drill et al. (1981) and US EPA (1985) reviewed a number of studies indicating that PCBs are readily absorbed from the gastrointestinal tract following oral administration.

Bleavins et al. (1984) found that, over a period of 5 weeks, European ferrets absorbed 85.4% of a single dose of ^{14}C-labelled Aroclor 1254 (0.05 mg) given in food.

In contrast to the above studies, Norback et al. (1978) claimed that 59.3–87% of a single oral dose of 2,4,5,2',4',5'-hexachlorobiphenyl passed unabsorbed through the intestines of monkeys, the first week after dosing.

6.2 Distribution

6.2.1 Inhalation (rat)

Maximum PCB concentrations in the liver and brain of rats occurred 2 and 24 h, respectively, after a single, 30-min exposure to 30.4 ± 3.4 g/m^3 of Pydraul A200 aerosol (42% chlorine content). The concentrations in these tissues declined, while concentrations in adipose tissues reached a maximum after 48 h (Benthe et al., 1972).

6.2.2 Oral (rat)

As in the case of other lipophilic substances, the absorption and distribution of PCBs will, in all probability, take place via the lymphatic system (by the chylomicrones) (DFG, 1988).

Following absorption, the clearance of PCBs from the blood and tissues follows a biphasic pattern. The compounds rapidly clear from the blood and accumulate in the liver and adipose tissue or are metabolized in the liver to metabolites that are excreted in the urine and/or bile (Drill et al., 1981).

Kurachi & Mio (1983) exposed mice to Kaneclor 400 at 100 mg/kg diet, for 5–20 days. High levels were found in the gonads, skin, adipose tissue, adrenals, and kidneys.

In a study by Grant et al. (1971a), 4 days after an oral dose of Aroclor 1254 was given to rats at 500 mg/kg, the concentrations of PCBs in

the fat, liver, and brain were 996, 116, and 40 mg/kg, respectively. Similar results showing that the highest concentration was in the fat, were obtained in rats given Aroclor 1254 in the diet (Curley et al., 1971), in boars (Platonow et al., 1972), cows (Platonow & Chen, 1973), and in pigeons and quail (Bailey & Bunyan, 1972). In the studies of Curley et al. (1971), the tissue concentrations initially showed a rapid rise and then a slow increase while the PCB diet was being administered; Grant et al. (1974) fed diets containing Aroclor 1254 at 0.2, 20, and 100 mg/kg to rats for 8 months, during which period the tissue concentrations reached a steady state that was dose-dependent (Table 23). Similar tissue distribution data for Aroclors 1016 and 1242 have been reported by Burse et al. (1974) and for Kanechlor-400 by Yoshimura et al. (1971).

Table 23. Tissue distribution of PCBs (mg/kg wet weight) in rats fed Aroclor 1254, Aroclor 1242, or Aroclor 1016 at 100 mg/kg for about 6 months

Tissue	Aroclor 1254[a]	Aroclor 1242[b]	Aroclor 1016[b]
Blood	0.40	0.53 (plasma)	0.38 (plasma)
Liver	16	4.21	7.86
Brain	3.4	1.69	2.98
Kidneys		1.89	3.21
Heart	7.3		
Fat	32.0	110	236
Urine		0.03	0.28

[a] From: Grant et al. (1974).
[b] From: Burse et al. (1974).

The study by Burse et al. (1974) showed that, with continuous feeding of 3 types of Aroclor (see Table 23) at 100 mg/kg diet, a steady state was not reached for 6–8 months and that the decline of stored PCBs in adipose tissue (when the animals were kept on a PCB-free diet) was slow and did not reach zero during a recovery period of 5–6 months. This is surprising because the Aroclor sample used should not have contained appreciable amounts of hexachlorobiphenyls and higher isomers. Mizutani et al. (1977), discussing this aspect, came to the conclusion that mobilization from storage sites

rather than metabolism constitutes the rate-limiting step in the depletion of the body burden of PCBs.

It was demonstrated that, as the number of chlorine atoms on the biphenyl rings increased from 1 to 6, the tissue/blood ratio tended to increase. This increase was also proportional to the amount of lipid in the tissues with, consequently, a higher degree of bioaccumulation (Matthews, 1983, cf. WHO/EURO, 1988).

The fat-plasma partition-coefficients for the different PCB congeners range from 50 up to 310 (DFG, 1988).

6.2.3 Oral (monkey)

Feeding studies were carried out on female, rhesus monkeys given doses of 0, 5, 20, 40, or 80 μg Aroclor 1254/kg body weight per day, for a period of 37 months (Arnold et al., 1984). Eighty monkeys were divided into 5 groups, each of 16 animals. The mean body weight of the monkeys at the start of the study was 6.44 kg. The Aroclor 1254 was dissolved in corn oil with glycerol as sweetener and fed to the monkeys in gelatin capsules. Samples of blood, adipose tissue, and faeces were collected every month and the presence of PCBs, determined. After 27 weeks, levels of 1, 2–3, 9, 18, and 37 mg PCBs/kg fat were found in the 5 groups; after 47 weeks, blood levels were 1–3, 12, 35, 73, and 129 μg/litre respectively. PCB concentrations in whole blood increased more rapidly during the first 10 months of the study than in the remaining 27 months, in all groups. Concentrations in adipose tissue (fat) increased continuously during the 37 months. The ratio profiles of PCB levels in blood/adipose tissue, remained relatively static between the second and twenty-seventh month of feeding. The data in terms of relative concentrations (concentration/dose) suggest that the bioaccumulation or retention of PCBs may be dose-dependent, particularly for adipose tissue. The data available from PCBs in faeces indicate a dose-dependent PCB absorption.

6.2.4 Oral (humans)

According to the study by Nishimura et al. (1976) cf. Katsunuma et al. (1985), the PCBs within a human fetus are not evenly distributed. The concentrations of PCBs were highest in the skin and lowest in

the brain among the 5 major organs (cerebrum, heart, liver, kidneys, and skin). That the highest level was found in the skin might have been because of the high solubility of the compounds in adipose tissue. In other words, PCBs accumulate increasingly as the body fat of a fetus increases. The authors stated that the low residue levels in the brain were likely to be because PCBs have a poor affinity for the brain lipids.

6.2.5 *Individual congeners of PCBs*

More detailed information on the tissue distribution of PCBs and their metabolites has been obtained by the administration of pure ^{14}C-labelled compounds, using both whole-body autoradiography and scintillation counting of tissue samples. Berlin et al. (1975) demonstrated that, after a single oral dose of ^{14}C-labelled 2,5,2',4',5'-pentachlorobiphenyl, radioactivity rapidly entered the circulation of mice and was distributed in the tissues, particularly in the liver, kidneys, lungs, and adrenals. Subsequently, the radioactivity in the body fat increased, rising to a maximum within 4–24 h. In most other tissues, the radioactivity decreased rapidly after dosing, but the authors noted a special affinity for the skin, the bronchiolar epithelium of the lungs, and certain glandular secreting tissues. Soon after administration of the dose, radioactivity appeared in the bile and was eliminated in the faeces. Similar results were obtained by Melvås & Brandt (1973) in mice treated with 2,4,2',4'-tetrachlorobiphenyl, which possessed a high affinity for the adrenal cortex, the corpora lutea, and glandular secreting tissue. In quail treated with 2,4,2',3'- and 2,4,3',4'-tetrachlorobiphenyl, the radioactivity in the egg yolk was high, exceeding that in the fat. Gage & Holm (1976) determined concentrations in the abdominal fat of mice, 7 and 21 days after they were administered a single dose (13–165 μg/mouse) of one of 14 PCB congeners, by gavage. Relatively low levels (< 10 ng/g per μg dose) were found at 7 days for 4,4'-dichloro-; 3,2',4',6'-tetrachloro, and 2,3,4,2',4',6'-hexachlorobiphenyl with relatively high levels ($\geq$ 100 ng/g per μg dose) for 2,4,5,2',4',5'-hexachloro-, and the 4,2',4',6'-, and 2,4,2',4'- tetrachlorobiphenyls.

Muehleback & Bickel (1981) treated rats, by gavage, with a single dose of ^{14}C-2,4,5,2',4',5'-hexachlorobiphenyl at 0.6 or 3.6 mg/kg body weight. The rats were examined 1 h, 24 h, 6 weeks, 20 weeks,

or 40 weeks after dosing. The highest levels of PCBs were found in the muscle, liver, adipose tissue, and skin, early in the study. By the end of the study, the highest PCB levels were found in the adipose tissue followed by the skin, muscle, and liver. During the 40-week study period, only 16% of the total dose was excreted.

The pharmacokinetics of individual monochloro-, dichloro-, tetrachloro-, pentachloro-, and hexachlorobiphenyls were studied by Matthews & Anderson (1975a,b), Lutz et al. (1977), and Tuey & Matthews (1977). The mono- and dichlorobiphenyls were largely removed from adipose tissue within 4–7 days, the 3 higher chlorinated biphenyls were eliminated much more slowly. The half-life for the tetrachlorobiphenyl from adipose tissue was 15 days. Skin effects were more or less comparable.

Beran et al. (1983) studied the distribution of ^{14}C-labelled 2,5,4'-tri-, 2,4,5,2',4',5'-hexa-, and 2,3,4,5,2',3',4',6'-octachlorobiphenyl in the haematopoietic tissues of squirrel monkeys (*Saimiri scureus*) and C67Bl mice using whole-body autoradiography. An accumulation of radioactivity was observed in the bone marrow of one monkey after iv injection (substances dissolved in DMSO) of the tri- or hexachlorobiphenyl. The same was found in 3 normal mice treated with the octachlorobiphenyl. A study using whole-body autoradiography and spleen-colony assay in supralethally irradiated mice, implanted with syngenic bone-marrow cells, indicated that the major part of the radioactivity was localized outside the bone-marrow haemic compartment, probably in the fat. Nevertheless, the trichloro- and octachlorobiphenyls were found to inhibit the *in vitro* formation of granulocytic colonies from mouse progenitor cells. Very low uptake of labelled chlorobiphenyls was observed in the thymus, spleen, and lymph nodes.

^{14}C-labelled-2,4,2',4'-tetrachloro- and 3,4,3',4'-tetrachlorobiphenyl were each administered orally to male Sprague-Dawley rats in a single dose at 0.54 mg/kg and 0.51 mg/kg, body weight, respectively. Distribution and covalent binding were studied. The accumulation of 2,4,2',4'-tetrachlorobiphenyl in adipose tissue was much higher than that of 3,4,3',4'-tetrachlorobiphenyl, though the level in the blood was consistently higher in the 3,4,3',4'-tetrachlorobiphenyl-treated rats. The radioactivity bound in covalent linkages

with cellular macromolecules in several tissues was determined. The data indicated that covalent binding was higher in 3,4,3',4'-tetrachlorobiphenyl-treated rats than in those treated with 2,4,2',4'-tetrachlorobiphenyl, particularly in the liver and blood components. These results suggest that the 2 tetrachlorobiphenyl isomers have different pharmacokinetic properties in rats and that the association of covalent binding with 3,4,3',4'-tetrachlorobiphenyl induced toxicities might be important. The microsomal enzyme system is likely to play an important role in the *in vivo* covalent binding of tetrachlorobiphenyls (Shimada & Sawabe, 1984).

In pharmacokinetic studies, 11 groups of 3 male ICR mice/group were administered daily doses of 100 mg 2,5,2',5'-tetrachlorobiphenyl/kg body weight dissolved in corn-oil/acetone (9:1), by gavage, for 8 consecutive days. Thirteen groups of 3 mice were administered (by gavage) 8 mg 3,4,3',4'-tetrachlorobiphenyl/kg in the same vehicle every other day for 10 doses. One group was sacrificed just before each of the last 3 doses, the other groups were sacrificed at intervals of 0.5–336 h after dosing. After dosing to an apparent steady-state, 2,5,2',5'-tetrachlorobiphenyl was found to have a tissue elimination half-life of between 39.5 and 70 h. The half-life of 3,4,3',4'-tetrachlorobiphenyl was 26–62.5 h. The 3,4,3',4'-tetrachlorobiphenyl had a substantially greater partitioning from serum into adipose tissue, liver, and thymic tissues. Studies were undertaken to compare the toxic potency of these 2 tetrachlorobiphenyls, when similar tissue concentrations of the 2 isomers were achieved in target and storage tissues. The studies demonstrated that thymic atrophy occurs at lower doses and tissue concentrations of 3,4,3'4'-tetrachlorobiphenyl than those required to produce hepatotoxicity. These two organ toxicities were produced only by 3,4,3'4'-tetrachlorobiphenyl, despite the fact that equivalent or higher tissue concentrations of 2,5,2',5'-tetrachlorobiphenyl were achieved *in vivo*, in all tissues. The conclusion was that the *in vivo* difference in the toxic potency of these tetrachlorobiphenyl isomers does not result from the differences in their tissue disposition, elimination, and ultimate bioaccumulation (Clevenger et al., 1989).

6.2.6 Appraisal

Matthews & Dedrick (1984), in a review, concluded that the pharmacokinetics of PCBs are complicated by numerous factors, not least of which is the existence of 209 different chlorinated biphenyls. While all PCB congeners are highly lipophilic and most are readily absorbed and rapidly distributed to all tissues, PCBs are cleared from the tissues at very different rates, and the same congeners may be cleared at different rates by different species. With the exception of special situations in which PCBs may be passively eliminated in lipid sinks, e.g., milk or eggs, clearance is minimal prior to metabolism to more polar compounds. Rates of PCB metabolism vary greatly with species and with the degree and positions of chlorination. Mammals metabolize these compounds most rapidly, but, even among mammalian species, the rates of metabolism vary greatly. In all species studied, the more readily metabolized chlorinated biphenyls have adjacent unsubstituted carbon atoms in the 3–4 positions. Congeners that do not have adjacent unsubstituted carbon atoms may be metabolized very slowly and therefore cleared very slowly. PCBs that are not readily cleared concentrate in adipose tissue.

6.3 Placental transport

6.3.1 Laboratory animals

The results of a number of animal studies have demonstrated that PCBs and specific congeners can cross the placental barrier and accumulate in the tissues of fetuses (US EPA, 1987). In studies in which monkeys were exposed prior to, and during, gestation, signs of PCB intoxication were observed in nursing, but not in newborn offspring (Allen & Barsotti, 1976; Iatropoulos et al., 1978). Results such as these have led to the conclusion that transfer through nursing may account for higher exposure of the young than placental transfer.

Groups of pregnant ddN mice were fed diets containing Kanechlor 500 (mainly comprising pentachloro- and hexachlorobiphenyls) at 0.01 (controls), 0.94, or 86 mg/kg diet from day 1 to 18 of pregnancy. Regardless of the dietary level of PCBs, whole-body levels in the fetuses were only 0.1–0.2% of the total maternal intake, indicating

limited transplacental transfer (Masuda et al., 1978a). Two groups of ddN mice were fed Kanechlor 500 (mainly containing pentachloro- and hexachlorobiphenyls at 0 or 0.94 mg/kg diet) from the day of insemination throughout gestation and for 5 weeks after delivery of offspring. Total PCBs were 100 times greater in the suckling animal than in the fetuses at term, from dams fed the same amount, indicating a considerable transfer of PCBs during lactation (Masuda et al., 1978a).

Masuda et al. (1979) fed female ddN-mice diets containing polychlorinated biphenyls: 2,4,4'-trichloro-; 2,5,3',4'-tetrachloro-; 2,4,5,2',5'-pentachloro-; 2,3,4,2',4',5'-hexachloro-; 2,4,5,2',4',5'-hexachloro-; 2,3,4,5,6,2',5'-heptachloro-; and 2,3,4,5,2',3',4',5'-octachlorobiphenyl at levels of 0.32, 0.42, 0.42, 0.44, 0.44, 0.16, and 0.23 mg/kg diet, respectively, for 18 days prior to, or after, mating. Animals were either sacrificed on day 18 of gestation or allowed to deliver and the offspring maintained for 5 weeks on a normal diet. All the PCBs were qualitatively transferred across the placenta and through the milk. The amount transferred during lactation was greater than that transferred transplacentally.

The transfer of 2,4,5,2',4',5'-hexachlorobi[^{14}C-]phenyl across the placenta during the course of pregnancy in Sprague-Dawley mice was studied by Vodicnik & Lech (1980). The PCB was injected intraperitoneally at 100 mg/kg body weight, in corn oil, 2 weeks prior to mating. The concentrations of ^{14}C-PCB in the fetuses from 12- and 18-day pregnant animals were 0.71 and 2.45 mg/kg tissue, respectively. At birth, the total carcass concentration for all newborn animals was less than 3 mg/kg tissue, which represents less than 3% of the dose present in the mothers at birth.

Placental transfer of polychlorinated biphenyls has also been reported in the mouse by Berlin et al. (1975) and Melvås & Brandt (1973).

Curley et al. (1973a) found some placental transport of Aroclor 1254 in the rat.

Groups of pregnant and non-pregnant Wistar rats received a dose of ^{14}C-2,4,5,2',4',5'-hexachlorobiphenyl (2.1 μC/kg), intraperitoneally. The amount of radioactivity transferred through the placenta was 2.7% of the administered dose, whereas 39.2% of the original dose was transferred through the milk (Ando et al., 1978).

Aroclors 1221 and 1254 were found to cross the placenta of rabbits, when administered orally to does during gestation. The concentration in fetal tissues was dose-dependent and much lower with Aroclor 1221 than with Aroclor 1254; the concentration of the latter in the fetal liver was greater than that in the maternal liver (Grant et al., 1971b).

Bleavins et al. (1984) fed female European ferrets a single dose of ^{14}C-labelled Aroclor 1254 in the diet (0.05 mg), early (day 14) or late (day 35) in gestation, and determined the placental transfer of PCBs. Placental transfer to the kits was 0.01% (per kit) of the maternal dose, when the dams were exposed early in gestation, and, 0.04%, when the dams were exposed late in gestation. Placental transfer of PCBs was considerably less than mammary transfer, with a ratio at 1 week of lactation of 1:15 and 1:7 for offspring of dams dosed early or late in gestation, respectively.

Groups of lactating mother Rhesus monkeys, between 1 and 3 months post partum, received 16 mg Clophen A-30/kg per day for 30 days. One mother/infant pair served as a control. Clophen A-30 concentrations in the serum of both mother and infant and the milk were determined on days -14, -7, 0, 1, 2, 4, 8 and at weekly intervals thereafter. One mother and all infants were killed and tissues taken for PCB analysis. The concentration of Clophen A-30 in milk was 20 times higher than maternal serum levels. Infant serum levels were 2–5 times higher than their mothers. Tissue levels were generally higher in the infants. Clophen A-30 tended to concentrate in the infant fat, bone marrow, and adrenals (Bailey et al., 1980).

Groups of 24 Rhesus monkeys were maintained on diets that provided Aroclor 1016 at doses of 0, 4.5, or 18.1 mg/kg body weight per day throughout gestation and a 4-month nursing period. At birth, the concentrations of PCBs in the skin of infants were similar to concentrations in the subcutaneous fat of the mothers. At weaning, the PCB content in the mesenteric fat of the infants was 4–7 times greater than that in the subcutaneous fat of the mothers. Gas chromatographic patterns showed that the adult adipose tissue did not include the total spectrum of peaks observed in the Aroclor 1016 standard, and that all of the peaks in the mesenteric fat of the infants at weaning and 4 months after weaning were qualitatively similar to

those in the adult adipose tissue. According to the authors, these data suggested an inability of the fetus to metabolize and excrete certain congeners that are more readily metabolized and eliminated by adults and older infants (Barsotti & Van Miller, 1984).

6.3.2 Wildlife

A 6 1/2-year-old desert bighorn (*Ovis canadensis cremnobates*) ewe and her term ram fetus were used to study the distribution and concentrations of PCBs in different organs and tissues. Fourteen maternal and 13 fetal tissues were analysed for their presence of organochlorine hydrocarbons. PCBs averaged 85 and 88% of the total residue loads for maternal and fetal tissues, respectively. It is remarkable that the "natural" PCB levels in the different organs and tissues were nearly the same, i.e., in maternal organs and tissues between 0.37 and 0.44 mg/kg, and, in fetal organs and tissues, between 0.30 and 0.35 mg/kg, on a fat basis (Turner, 1979).

6.3.3 Humans

Four studies of placental passage in humans, based on small samples drawn from the general Japanese population, have yielded inconsistent results (Yoshimura, 1974; Akiyama et al., 1975; Kodama & Ota, 1977; Masuda et al., 1978a).

PCBs were detected in the umbilical tissues, umbilical blood, amniotic fluid, and baby's blood from a woman who was occupationally exposed to Kanechlors 300 and 500 in a capacitor factory (Yakushiji et al., 1978). PCB levels in these tissues and fluids were considerably lower than that in the mother's blood.

Jacobson et al. (1984b) examined maternal and cord serum (196 or 198 samples each) for the presence of PCBs, in women who resided in the Michigan area (USA), where, in 1973, a PBB-incident occurred. Mean concentrations of maternal and cord serum were 4.7 μg/litre (1.1–14.3 μg/litre) and 2.0 μg/litre (0.1–7.2 μg/litre), respectively. Placental passage was indicated by a significant maternal to cord serum correlation for PCBs. The fact that cord serum levels were lower than those in maternal serum is consistent with the notion that the placenta may function as a partial barrier. The transfer rate of PCBs in maternal blood through the placenta to cord blood

may vary, depending on the chemical nature of each PCB isomer (Ando et al., 1984). Ando et al. (1985) examined the PCB concentrations in the maternal blood, breast milk, and the placenta of 6 Japanese women. They found that the congeners present were more typical of Kanechlor 500 than Kanechlor 300, 400, or 600. The results indicated that, as the chlorine content of the PCB congeners increased, the correlation between the placental content of congeners and those in the maternal blood and breast milk also increased. The same was found in laboratory animals (Allen & Barsotti, 1976; Masuda et al., 1978b).

A study on the transfer of PCBs to infants from their mothers was carried out in Japan from 1974 to 1976 by Kodama & Ota (1977). When the cord blood was considered as the infant blood at birth, the level of PCBs in the blood of breast-fed infants rose gradually with ingestion of breast milk, exceeded the level in the blood of their mothers after 3 months, continued to increase up to the age of 1 year and then significantly decreased, 2 years after birth. The PCB concentrations in the blood of non-breast-fed infants remained low (Table 24).

Table 24. Level of PCBs in mothers' and babies' blood (average over 3 years in μg/litre)[a]

Maternal blood	4.5	(0.8-15.5)
Cord blood	1.1	(nd-5.6)
Mother's blood (breast-feeding)	2.5	(nd-10.8)
Babies' blood (3 months old)	3.6	(0.2-10.9)
Babies' blood (1 year old)	4.7	(0.8-17.7)
Mother's blood (bottle feeding)	2.7	(0.6-8.7)
Babies' blood (3 months old)	1.6	(nd-7.6)
Babies' blood (1 year old)	0.7	(nd-2.1)

[a] From: Kodama & Ota (1977).

6.4 Excretion and elimination

6.4.1 Following oral dosing

The excretion of PCBs is, to a large extent, dependent on the metabolism of PCBs to form more polar compounds (US EPA, 1987). At equilibrium, the elimination of PCBs from all tissues will be dependent on the structure-dependent metabolism rates of the individual PCB congeners. For example, the biological half-lives in the rat range from 1.15 days for 2,2'-dichlorobiphenyl to approximately 460 days for 2,4,5,2',4',5',-hexachlorobiphenyl (Tanabe et al., 1981; Wyss et al., 1986). Metabolites of the more highly chlorinated congeners are eliminated primarily via the faeces (Goto et al., 1974; WHO/EURO, 1987).

When the analysis of faeces is limited to the determination of unchanged PCBs, the recovery of the dose administered is incomplete; in boars receiving single or repeated doses of Aroclor 1254, not more than 16% of the dose was recovered from the faeces and less than 1% in the urine (Platonow et al., 1972). Better recoveries have been obtained with PCB labelled with radioactive isotopes. Yoshimura et al. (1971) found 70% of the activity from a dose of tritium-labelled Kanechlor 400 in the faeces and 2% in the urine, over a 4-week period. Berlin et al. (1973, 1975) found over 75% of the activity from ^{14}C-labelled pentachloro- and hexachlorobiphenyls in the faeces and less than 2% in the urine; most of the faecal elimination consisted of PCB metabolites. Similar results were obtained by Melvås & Brandt (1973) with tetrachlorobiphenyls.

Hashimoto et al. (1976) examined the excretion of ^{14}C-PCB compounds given to rats by gavage, at a total dose of 6.35–7.85 mg/kg body weight, over a period of 5–50 days. The PCBs studied were predominantly tetra- and hexachlorinated isomers. The results indicated that 1.9–4.9% of the dose of tetrachlorobiphenyls was excreted in the urine, with higher amounts excreted in rats treated for longer periods. In rats treated with hexachlorobiphenyls, only 0.3% of the dose was excreted in urine. About 47–68% of the dose of both tetrachloro- and hexachloro-isomers was eliminated in the faeces.

Bleavins et al. (1984) found 22.1% and 1.8% in the faeces and urine, respectively, during the first week following dosing of 0.05 mg ^{14}C-labelled Aroclor 1254 to female European ferrets.

A biological half-life of about 200 days was recorded in the fat of rats after feeding with Aroclor 1254 (Grant et al., 1974). Berlin et al. (1975) noted that, in mice dosed with a pentachlorobiphenyl, there was an initial rapid elimination from the liver while liver PCB levels were high, followed by a slower elimination when most of the PCB was located in the fat. The author suggested that the mobilization of PCBs from fat, and, therefore, their half-life in the body, depends upon their rates of metabolism. Berlin et al. (1973) investigated the hypothesis that the ability of a PCB to be readily degraded with a half-life of a few days depended on the presence of 2 adjacent unsubstituted carbon atoms in the molecule, rather than on the number of chlorine atoms, though the presence of such unsubstituted pairs depends to a large extent on the degree of chlorination. They came to the conclusion that this hypothesis probably applied to unsubstituted pairs in the 3,4-position, but that in the 2,3-position, their susceptibility to metabolic degradation was influenced more by the presence of chlorines in the *o*-position of the ring bridge.

Sprague-Dawley rats, white Swiss mice, and Rhesus monkeys were administered a single dose of ^{14}C-2,2'-dichlorobiphenyl, by gavage. Within 6 days, mice eliminated a total of approximately 46% of the PCB (urine, 20%; faeces, 26%). There was no clear difference between male and female mice. In the rat, the total elimination was 51–56% after 9 days, mainly via the biliary/faecal route. The monkeys had the highest elimination rate, a total of 68.6% (urine, 54%; faeces, 14.6%), within 10 days (Milling et al., 1979).

Male and female Wistar rats were administered a daily dose of ^{14}C-2,5,4'-trichlorobiphenyl for 14 days. The animals were killed 5 days after receiving the last dose. The compound was rapidly eliminated primarily with the faeces. Most of the trichlorobiphenyl was metabolized (78.5%) and the major metabolites excreted were identified as hydroxy-, dichloro-, and conjugated derivatives (Lay et al., 1979).

The elimination of tetrachlorobiphenyl isomers in mice fed diets containing a single isomer, at 10 mg/kg diet for 20 days, was studied

by Mizutani et al. (1977). Biological half-lives for the isomers 2,3,2',3'-tetrachloro-, 2,4,2',4'-tetrachloro-, 2,5,2',5'-tetrachloro-, 3,4,3',4'-tetrachloro-, and 3,5,3',5'-tetrachlorobiphenyl, were 0.9, 9.2, 3.4, 0.9, and 2.1 days, respectively.

Gage & Holm (1976) studied the influence of molecular structure on the excretion of 14 PCB congeners in mice. They found that the 4,4'-dichloro-; 3,3',4',6'-tetrachloro-; 2,3,2',4',6'-pentachloro-; and 2,3,4,2',4',5'-hexachloro-isomers were eliminated most rapidly. These compounds had at least one pair of unsubstituted *ortho-meta*, vicinal carbon atoms, a configuration thought to be important for rapid metabolism and excretion. The most slowly eliminated compounds were 2,4,5,2',4',5'- and 2,3,4,2',4'5'-hexachlorobiphenyl.

2,4,5,2',4',5'-Hexachlorobiphenyl was the PCB congener found in the highest concentration in human adipose tissue, while 2,4,6,2',4',6'-hexachlorobiphenyl was not detected (Jensen & Sundström, 1974a). As both of these compounds are found in commercial PCB mixtures and in the environment, the presence of the 2,4,5,2',4',5'-hexachlorobiphenyl in adipose tissue appears to be related to resistance to metabolism (US EPA, 1987). That this congener is not, or is only minimally, metabolized is also indicated by the finding that the blood concentration of this congener decreased only 10% over 300–500 days (Chen et al., 1982) and by the results of *in vitro* metabolism studies with human liver microsomes (Schnellman et al., 1984a,b).

Felt et al. (1977) examined the elimination of ^{14}C-2,5,4'-trichlorobiphenyl in rhesus monkeys. The monkeys were fed 550 mg of the compound in fruit, daily, for 84 days. On the basis of total excretion and recovered radioactivity, the half-life was found to be 4.5–4.8 days.

Male and female Sprague-Dawley rats were administered ^{14}C-labelled 2,4,6,2',4'-pentachlorobiphenyl by gavage and the urine and faeces were collected. After 8 days, the animals were killed. The elimination of the PCBs followed a bi-exponential rate expression with a-phase half-lives of 0.90 and 0.95 days and b-phase half-lives of 4.2 and 3.8 days, for males and females, respectively (Felt et al., 1979).

6.4.2 Following parenteral dosing

The results of injection studies indicate that PCBs can be excreted unmetabolized into the gastrointestinal tract. Yoshimura & Yamamoto (1975) recovered unchanged tetrachlorobiphenyl from the duodenal contents of rats injected intravenously with tetrachlorobiphenyl. Daily excretion for 4 days ranged from 0.5 to 0.8% of the total dose/day. Goto et al. (1974) found that 4.7–23.2% of injected PCBs were excreted unchanged into the gastrointestinal tract by day 10 after dosing, with the excretion of a penta-isomer greater than the excretion of di-, tri-, or tetra-isomers.

Adult male Sprague-Dawley rats received doses of 4 symmetrical hexachlorobiphenyl ^{14}C-isomers, i.e., 2,3,5,2',3',5'-hexachloro-, 2,3,6,2',3',6'-hexachloro-, 2,4,5,2',4',5'-hexachloro-, and 2,4,6,2',4',6'-hexachlorobiphenyl, by intravenous injection. Most of the radioactivity was eliminated in the faeces with less than 1% found in the urine. The metabolites showed evidence of dechlorination, chlorine shifts, and possible metabolism by direct insertion of a hydroxyl group. There was also evidence supporting the intermediate step of an arene-oxide as a predominant mechanism of PCB metabolism (Kato et al., 1980).

The disposition of 2 symmetrical ^{14}C-labelled 2,3,6,2',3',6'-hexachloro- and 2,4,5,2',4',5'-hexachlorobiphenyl was studied in 24-month-old, male, Sprague-Dawley rats, after iv treatment. More than 50% of the 2,3,6,2',3',6'-hexachlorobiphenyl was metabolized and excreted via the bile into the faeces within 2 days, and only 2% was excreted in urine. More than 90% was eliminated as metabolites. In contrast, 2,4,5,2',4',5'-hexachlorobiphenyl was redistributed from the liver, muscle, and skin to the adipose tissue, where it accumulated without being metabolized. Only 2% of the total dose was eliminated, primarily in the faeces, within 21 days. In 2- to 3-month-old rats, the general pattern of disposition of these hexachlorobiphenyls did not change with age; however, there were differences in the rates of elimination and in the tissue levels. There was enhanced metabolic retention in the muscle, skin, and adipose tissue of older rats, which suggested an age-related decrease in tissue clearance. The larger volume of adipose tissue could not explain this observation. In general, there were few changes in decay rates from

tissues or in biliary excretion, so age had a greater effect on the disposition of the "persistent" 2,4,5,2',4',5'-hexachlorobiphenyl than on the metabolizable 2,3,6,2',3',6'-hexachlorobiphenyl (Birnbaum, 1983).

Ethane exhalation was increased in male Sprague-Dawley rats, 30 days after a single ip injection of Aroclor 1254 (500 mg/kg body weight). Before day 30, there was no increase in ethane production. Parallel increases in hepatic malondialdehyde levels were found. A single ip injection of 3,4,3',4'-tetrachloro-, 2,3,4,5,4'-pentachloro, and 2,4,5,2',4',5'-hexachlorobiphenyl (300 μmol/kg) also increased (after 30 days) the production of malondialdehyde and ethane, indicators of *in vivo* lipid peroxidation. These effects were not reflected in increased diene conjugation (Dogra et al., 1988).

Sipes et al. (1980, 1982a,b) studied the distribution, metabolism, and excretion of ^{14}C-labelled 4,4-dichloro-, 2,4,5,2'4'5'-hexachloro-, or 2,3,6,2'3',6'-hexachlorobiphenyl in beagle dogs and cynomolgus monkeys, after a single intravenous dose. The elimination of the test substances from the blood of both species was shown to be biphasic. The results for dichlorobiphenyl showed that the dog eliminated 50% of the dose (urine, 7%; faeces, 43%) within 24 h, while the remainder was found mainly in the adipose tissue. By 5 days, 90% had been eliminated. The monkey eliminated less than 15% of the dose within 24 h, with less than 1% in the faeces. The remainder was found in the adipose tissue. Within 28 days, 59% of the dose had been eliminated, chiefly in the urine. Biliary excretion after 24 h was shown to be 33% in the dog and only 0.4% in the monkey.

The data for 2,4,5,2',4',5'-hexachlorobiphenyl showed that the dog eliminated 66% (urine, 3%; faeces, 63%) within 3 days; the monkey eliminated 18% of the dose (of which 17% was in the faeces), 90 days following administration. The remainder was found in the adipose tissue. In the studies with 2,3,6,2',3',6'-hexachlorobiphenyl, the dog eliminated 52% of the dose within 24 h (urine, 11%; faeces, 41%) and 70% in 3 days. The monkey eliminated 19% during the first 24 h, divided equally between urine and faeces. By 15 days, 61% had been eliminated, primarily in the faeces. The 24-h biliary excretion was 26% and 2.4% in the dog and the monkey, respectively.

6.4.3 Humans

Chen et al. (1982, 1985) studied the presence of PCBs in the blood of human beings, in the Province of Taiwan, after they had consumed rice-bran oil contaminated with Kanechlor 500 and PCDFs. Blood samples from 17 patients were examined, with 2–3 samples taken from each patient, 2–17 months apart. The results indicated that the tetrachloro- and some pentachloro- isomers tended to be eliminated more rapidly than the other pentachloro- and the hexachloro- and heptachloro- isomers. Half-lives for the 2,4,5,2',4'- and 2,3,4,3',4'-pentachloro- isomers in the blood were 9.8 and 8.7 months, respectively. Two adjacent unsubstituted carbon atoms at the *meta, para* positions facilitated metabolism and the subsequent elimination from the blood. PCBs containing adjacent unsubstituted carbon atoms at the *ortho and meta* positions of the biphenyl ring are eliminated very slowly and will accumulate.

Bühler et al. (1988) administered a uniformly ^{13}C-labelled PCB mixture similar to Aroclor 1254 to a volunteer. A single dose of 329 μg/kg body weight was ingested; blood samples taken over a period of 260 days were analysed for ^{13}C- and ^{12}C-PCBs using GC/MS and GC/ECD. Elimination of the isomers followed a first order kinetics. The half-lives for the isomers 2,3,4,2',4',5'-hexachlorobiphenyl, 2,4,5,2',4',5'-hexachlorobiphenyl, and 2,3,4,5,2',4',5'-heptachlorobiphenyl were 321, 338, and 124 days, respectively.

6.4.4 Elimination via milk (animals)

Vodicnik (1986) studied the disposition of ^{14}C-2,4,2',4'-tetrachlorobiphenyl (150 mg/kg body weight administered intraperitoneally) as a function of non-pregnant body weight in virgin, late pregnant, and early post partum ICR mice and their offspring. The highest concentrations were observed in adipose tissue and the mammary glands, regardless of reproductive state. The concentrations of the tetrachlorobiphenyl equivalents in the tissues differed among the 3 groups, possibly because of the alterations in lipid deposition/mobilization associated with pregnancy and lactation. Approximately 20% of ^{14}C-activity was eliminated from the carcass of virgin mice, 4 days after administration, but no decrease was seen in late-pregnant animals. Minimal transplacental transfer of

^{14}C-activity occurred (approximately 1%), but the tetrachlorobiphenyl was rapidly eliminated in breast milk to nursing offspring. Ninety per cent of the total-carcass ^{14}C-activity was eliminated from lactating mice over a 4-day period, approximately 75% of which could be accounted for in neonatal carcasses.

Saschenbrecker et al. (1972) found that, after oral administration of doses of Aroclor 1254 of 10 or 100 mg/kg to cows, 6.27 and 74.5 mg/litre, respectively, appeared in the milk after 24 h. These levels were reduced to less than one-half within 3 days, but traces still remained at 50 days. Cows receiving 200 mg/day of Aroclor 1254 reached a steady state concentration of 61 mg/kg in the milk fat and 42 mg/kg in the body fat, after 10 days (Fries et al., 1973).

The "carry-over factor" from animal feed into the cow's milk showed that the lower (tri-, tetra-, and penta-) chlorinated biphenyls have a lower carry-over factor than the higher (hexa- and hepta-) chlorinated biphenyls. Thus, it is the latter that are particularly concentrated in cow's milk fat. From studies in the Federal Republic of Germany, it was found that the major congeners in cow's milk were numbers 138, 153, and 180 (DFG, 1988).

6.4.4.1 *Elimination via breast milk*

The composition of common commercial PCB mixtures clearly differs from the composition of the PCB contents of human fat or human breast milk, because of the preferential elimination of certain PCB congeners containing 3 or 4 *ortho* substituents and the retention of PCBs with 1 or 2 *ortho* substituents (Kuroki & Masuda, 1977; Watanabe et al., 1979; Yakushiji et al., 1979).

The major PCB components (and average relative concentrations) that have been identified in breast milk in the Osaka area in Japan include: 2,4,4'-trichlorobiphenyl (8.4%); 2,5,2',5'-tetrachlorobiphenyl (2.0%); 2,4,5,4'-tetrachlorobiphenyl (19%); 2,4,5,2',5'-pentachlorobiphenyl (2.8%); 2,4,5,3',4'- pentachlorobiphenyl (11.8%); 2,4,5,2',4',5'-hexachlorobiphenyl (15.5%); 2,3,4,2',4',5'-hexachlorobiphenyl (15.8%); 2,3,4,3',4',5'-hexachlorobiphenyl (2.3%); 2,3,4,6,2',4',5'-heptachlorobiphenyl (1.6%); 2,3,5,6,2',4',5'-heptachlorobiphenyl (3.2%). These

PCB-congeners constituted at least 95% of the PCBs in the breast milk of the women examined in Osaka.

In recent studies, the contents of PCBs in human milk and maternal blood were compared for US citizens (Bush et al., 1984, 1985). Eight individual PCB congeners comprised 52% of the total PCB residues in the milk and 48.5% in the blood. The mean concentrations for total PCBs were 26.5 μg/kg for whole milk and 3.5 μg/kg for blood. The percentages of the different congeners are given in Table 25.

6.5 Metabolic transformation

6.5.1 PCBs

The metabolism of PCBs has been investigated in numerous studies on animals and reviewed by Drill et al. (1981) and the US EPA (1987). The PCBs were usually administered by the oral or parenteral route.

Phenolic products are the major PCB metabolites, though sulfur-containing metabolites, trans-dihydrodiols, polyhydroxylated PCBs, and methyl ether derivatives have also been identified. Although the effects of the chlorine substitution pattern on sites of oxidation have not been studied systematically, US EPA (1987) suggested the following:

- hydroxylation is favoured at the *para* position in the least chlorinated phenyl ring, unless this site is sterically hindered (i.e., 3,5-dichloro-substitution);
- in the lower chlorinated biphenyls the *para* position of both biphenyl rings and carbon atoms that are *para* to the chloro substituent are all readily hydroxylated (Sparling et al., 1980);
- the availability of 2 vicinal unsubstituted carbon atoms (particularly C5 and C4 in the biphenyl nucleus) also facilitates the oxidative metabolism of the PCB substrate, but is not a necessary requirement for metabolism;
- as the rate of chlorination increases on both phenyl rings, the rate of metabolism decreases;

Table 25. Concentrations of most abundant PCB congeners present in whole breast milk and maternal blood[a]

Congener	Milk (40 samples)		Maternal blood (101 samples)		Ratio milk/blood
	μg/litre	% of total PCBs	μg/litre	% of total PCBs	
2,4,5,2′,4′,5′-hexachlorobiphenyl	3.2	12	0.31	8.8	10
2,3,5,6,2′,3′,6-heptachlorobiphenyl	2.5	9.4	0.27	8.0	9.2
2,4,5,2′,3′,4′-hexachlorobiphenyl	2.1	7.8	0.58	17	3.5
2,5,3′4′-tetrachlorobiphenyl	1.7	6.6	0.01	-	500
2,3,4,5,2′4′5′-heptachlorobiphenyl	1.2	4.5	0.03	3.7	9.4
2,3,4,5,3′,4′-hexachlorobiphenyl	1.0	4.0	0.01	-	125
2,4,5,2′,4′-pentachlorobiphenyl	1.1	4.0	0.12	3.4	8.9
2,3,4,3′,4′-pentachlorobiphenyl	0.97	3.7	0.25	7.6	3.8
Total PCBs	26.5	-	3.5	-	7.5

[a] Modified from: Bush et al. (1985).

- the metabolism of specific PCB isomers by different species can result in considerable variations in metabolic pattern.

Kannan et al. (1989) studied the possible involvement of frontier (*pi*) electrons in the metabolism of polychlorinated biphenyls. The electron density, at each carbon atom, of the highest occupied *pi* orbital of 13 PCB molecules was calculated and the result was compared with their *in vitro* and/or *in vivo* metabolism. It was found that:

- the carbon position at which the frontier electron density was the highest was most readily hydroxylated or sulfonated;
- if the carbon with the highest frontier (*pi*) electrons was occupied by chlorine, either a replacement occurred or the carbon with the next highest electron density was activated for metabolism;
- because of steric hindrance, "*ortho*" carbons were least preferred for such reactions, in spite of possessing favourable electron density;
- this was applicable to both phenobarbital (PB)-type and 3-methylcholanthrene (3-MC)-type PCB inducers.

The authors suggested that frontier (*pi*) electron density could be an easy guide for understanding the metabolic products of persistent and toxic environmental pollutants *in vitro* and *in vivo*, and for understanding their environmental fate.

There appears to be little metabolism of PCBs with 6 or more chlorine substituents (Matthews & Anderson, 1975b). When between 2 and 5 chlorine substituent PCBs are metabolized, the metabolic products are primarily hydroxylated compounds, frequently found as glucuronide conjugates (hydroxymethoxy derivatives) and partially dechlorinated metabolites. In some cases, smaller amounts of dihydrohydroxy compounds and related substances are also found.

The parent compound is also eliminated in various quantities in faeces, hair, and maternal milk, but very little unmetabolized compound is excreted in the urine. This pattern is not unusual for lipophilic xenobiotics.

PCB metabolism has been examined in primates (monkeys) by Greb et al. (1975), Hsu et al. (1975a,b), and Allen & Norback (1976); in ungulates (cows, pigs, and goats) by Platanow & Chen (1973), Safe et al. (1975), and Gardner et al. (1976); in rats by Grant et al. (1971a), Hutzinger et al. (1972), Yoshimura et al. (1973), Goto et al. (1973, 1974, 1975), Safe et al. (1974), Matthews & Anderson (1975b), van Miller et al. (1975), Sundström & Jansson (1975), Sundström et al. (1976a), Lay et al. (1975, 1979), Chen et al. (1976), Kamal et al. (1976), and Norback et al. (1976); in mice by Berlin et al. (1973), Yamamoto & Yoshimura (1973), and Sundström & Jansson (1975); in rabbits by Grant et al. (1971b), Hutzinger et al. (1974), Sundström & Wachmeister (1975), and Sundström et al. (1976b); in pigeons, and quails by Koeman et al. (1969), Hutzinger et al. (1972), Bailey & Bunyan (1972), and Sundström & Jansson (1975); and in trout by Hutzinger et al. (1972).

The different metabolic products formed from pure isomers in these various species have been catalogued in an NAS report (1979) and in a review by Sundström et al. (1976a). Neither of these reports is complete, but, together, they cover most of the studies up to 1979.

In the rat, monochloro-, dichloro-, trichloro-, tetrachloro-, pentachloro-, and at least one hexachlorobiphenyl, yielded at least one hydroxylated metabolite. Some isomers produced as many as 5 different hydroxylated metabolites including both mono- and dihydroxy- derivatives. Most of the hexachloro-, octachloro-, and decachlorobiphenyls did not yield detectable levels of hydroxylated products.

Similar hydroxylated derivatives were also produced in other species, but the ability to metabolize PCBs is not absolutely uniform in all species. In the rabbit, dichloro-, tetrachloro-, and hexachlorobiphenyls were metabolized, while further down the phylogenetic scale, the pigeon only metabolized monochloro- and dichlorobiphenyls and the trout failed to metabolize any of the chlorinated biphenyls tested. Table 26 shows the PCBs tested in different species and indicates whether or not the organism was able to metabolize the compound. Although different species may metabolize a given isomer, the metabolic products are not necessarily identical. An example of this is found in the simple 4,4'-dichlorobiphenyl which

is metabolized by the rat, rabbit, and goat, but does not give identical products in these species; all 3 species produce 4,4'-dichloro-3-hydroxybiphenyl as a metabolite, but, in addition, the rat produces 4,4'-dichloro-, 2,3-dihydroxybiphenyl, and the goat produces 3,4'-dichloro- 4-hydroxybiphenyl as a metabolite.

Table 26. Metabolism of various PCBs in different organisms

Compound	Species					
Chlorobiphenyl	Trout	Pigeon	Mouse	Rat	Rabbit	Monkey
4-mono-	-	+		+	+	
4,4'-di-	-	+		+	+	
2,2'				+		
2,4'				+		+
2,5,2'-tri						+
2,4,2',4'-tetra-				+		
2,5,2',5'	-	-		+	+	+
3,4,3',4'				-		
2,3,4,5,6,-penta-				+		
2,4,5,2',5'			+	+		
2,4,6,2',4'				+		
2,4,6,2',6'				+		
2,4,6,3',5'				+		
2,3,4,6,4',				+		
2,3,4,3',4'				-		
2,4,5,2',4',5',-hexa-	-	-		(±)[a]	+	
2,4,6,2',4',6'				(±)[a]		
2,3,5,6,2',3',5',6'-octa-			-			
2,3,4,5,6,2',3',4',5',6'-deca			-			

[a] These compounds were reported by Sundström et al. (1976a) as failing to produce hydroxylated derivatives, but were positive in an IARC report referred to in an NAS report (NAS, 1979).

+ = Compound is metabolized; - = Compound not metabolized; (blank) not tested.

However, a product such as the 3,4'-dichloro-4-hydroxybiphenyl found in the goat involves a chlorine shift, which may be indicative of a more toxic intermediate.

Many different pathways of metabolism have been described as summarized in Fig. 5 (Safe, 1984; WHO/EURO, 1987).

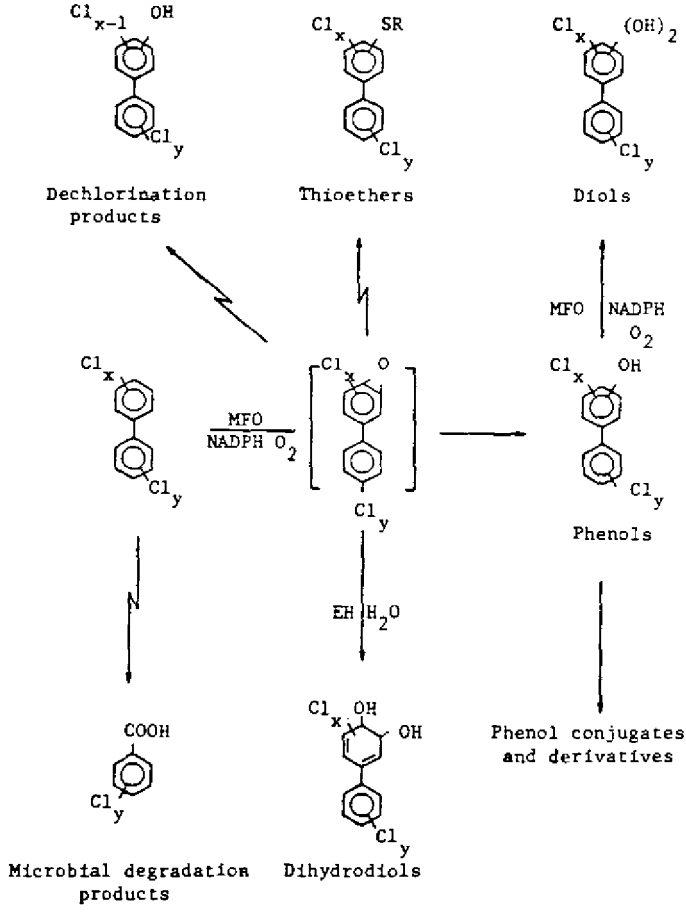


Fig 5. Metabolic pathways of PCBs.
From: Safe (1984); WHO/EURO (1987).

These pathways include hydroxylation, and conjugation with thiols and other water-soluble derivatives. The most important pathway seems to be through hydroxylation and subsequent conjugation. Rats and mice that were exposed to dichloro-, tetrachloro-, or pentachlorobiphenyls by intraperitoneal injection or diet, eliminated metabolites as glutathione conjugates and other sulfur-containing compounds (Kurachi, 1983; Kurachi & Mio, 1983). Mammalian metabolism of many individual PCBs may proceed via oxide intermediates, which have not been isolated, but are presumed to be precursors of some of the major metabolites identified. One type of metabolite is the methylsulfone PCB metabolite that has been identified in environmental samples by Jansson et al. (1975) and WHO/EURO (1987), and in human milk by Yoshida & Nakamura (1979).

The formation of xenobiotic thioether derivatives, including glutathione, cysteinylglycine, cysteine, and *N*-acetylcysteine (mercapturic acid) conjugates, is generally considered a pathway for the detoxification of reactive intermediates. Mio & Sumino (1985) detected methylsulfonyl metabolites, by using GC/MS/COM, from the adipose tissues of mice treated with Kanechlor 300, 400, 500, or 2,5,2',5'-tetrachlorobiphenyl. Metabolites were detected in the faeces of mice treated with 2,5,2',5'-tetrachlorobiphenyl, e.g., 6 sulfur-containing and 5 non-sulfur-containing metabolites. The elimination rates for one week were 1.7% and 43%, respectively. The methylsulfonyl metabolites accumulated in the liver, adipose tissue, and lungs. Mio & Sumino (1985) proposed the methylsulfonyl metabolic pathway of 2,5,2',5'-tetrachlorobiphenyl.

Klasson-Wehler et al. (1987) administered a single dose of 2,3,6,4'-tetrachlorobiphenyl to 3 groups of 5 female C57B1 mice at 0, 10, or 100 mg/kg body weight. ^{35}S-cysteine was administered by ip injections 4 times at 12-h intervals. The animals were sacrificed and the organs analysed on day 12. Methyl [^{35}S]sulfonyl-tetrachlorobiphenyl was found in the lungs, kidneys, and fat of the treated mice, as well as minor amounts of tetrachlorobiphenyl and traces of methylthiotetrachlorobiphenyl.

The formation of serial methylsulfonyl metabolites can be summarized as follows: the glutathione conjugate is converted, by cleavage, to a cysteine or thiol conjugate and translocated into the

liver. The thiol conjugate from the cysteine moiety is transmethylated by thiol-*S*-methyltransferase and is oxygenated by cytochromes P-450 and P-448 oxidase or is glucuronidated by UDP-glucuronyl-transferase in the liver, resulting in methylsulfonyl derivatives.

The occurrence of *trans*-dihydrodiol metabolites suggests that the metabolism of PCBs proceeds through the formation of arene oxide intermediates (US EPA, 1987). Arene oxides are potential electrophiles that have been implicated in cellular necrosis, mutagenicity, and carcinogenicity (Safe et al., 1975; Sundström et al., 1976a).

While the arene oxide pathway is important in carcinogenic considerations, it may not be the primary pathway for the metabolism of PCBs, in most cases. So far, most discussions about the metabolism of PCB isomers have focused on the position and number of the chlorine substituents.

The metabolic products of dichloro-, trichloro-, tetrachloro-, pentachloro-, and hexachlorobiphenyl appear to reflect direct hydroxylation at the *meta* and/or *para* positions, relative to the position of the phenyl-phenyl bond. In a few instances, a methoxy group is found instead of a second hydroxyl. This direct mechanism appears to operate, therefore, irrespective of the degree of chlorination, and, for the most part, irrespective of the position of the chlorine substituents. In the rabbit, some exceptions have been found that involve: a chlorine shift and the removal of a chlorine, in the case of the 4,4'-dichlorobiphenyl, the formation of a dihydrodiol at the *meta* and *para* positions, in the case of 2,5,2',5'-tetrachlorobiphenyl, and the removal of a chlorine from one of the rings, in the case of 2,4,5,2',4',5'-hexachlorobiphenyl (Sundström et al., 1976a).

Studies carried out by Matthew & Anderson (1975b) and Tuey & Matthews (1977) showed that monochloro- and dichlorobiphenyls were rapidly metabolized and excreted and that pentachloro- and hexachlorobiphenyls were poorly metabolized and retained longer in the adipose tissue and skin. The situation for the tetrachlorobiphenyls is more complicated.

The following analysis is based on the data on metabolites identified and reported in the review by Sundström et al. (1976a).

6.5.2 Dichlorobiphenyls

Consideration of the various dichloro- isomers shows that, when chlorines are only on one ring, hydroxylation occurs on the non-chlorinated ring. Single hydroxylation occurs *para* to the phenyl-phenyl bond; if another hydroxylation occurs, it is always *meta* to the phenyl-phenyl bond. This holds true for the 3 different isomers tested: 2,3-; 2,4-; and 3,4-dichlorobiphenyls. When the dichloro-compounds are symmetrically chlorinated on each ring, as in 2,2'-; 3,3'-; and 4,4'-dichloro compounds, the same pattern applies generally, but with a variation on the theme and an exception in the case of 4,4'-dichlorobiphenyl. In the case of 2,2'- and 3,3'-dichloro compounds, monohydroxylation occurs *meta* and *para* to the phenyl-phenyl ring, respectively. In both cases, double hydroxylation involves both *meta* and *para* positions on the same ring, (that is, *meta* and *para* to the phenyl-phenyl bond). In the case of 4,4'-dichloro-biphenyl, there appears to be a difference in the rat. The mono-hydroxy- derivative is *meta*, but the dihydroxy derivative is *ortho* and *meta* to the phenyl-phenyl bond. Not only is the rat metabolism of the 4,4'-compound an exception, but the rabbit also shows an unusual response to this compound. In the rabbit, the monohydroxy-derivative is the same *meta* hydroxy found in the rat, but, instead of a dihydroxy- compound, the rabbit produces a chlorine shift and a single hydroxy group in the *para* position as well as dechlorination and hydroxylation in the *para* position. These latter products have been considered as characteristic of the arene oxide intermediate pathway. Nevertheless, among the 6 different dichloro- isomers examined, all produced a monohydroxy- derivative, either *meta* or *para* to the phenyl-phenyl bond, and all but the 4,4' produced dihydroxy- derivatives were *meta* and *para* on the same ring to the phenyl-phenyl bond.

The absence of a substitution at 4,4'- with vicinal unsubstituted positions cannot be correlated with rapid metabolism, since this property is also shared by both a rapid and slowly metabolized isomer. This is in direct contradiction to the often repeated statement "the presence of at least two adjacent unsubstituted carbons, particularly in positions 3,4-, or 5- or 3',4'- or 5'- is required for rapid metabolism of chloro-biphenyl" (Jensen & Sundström, 1974b; Berlin et al., 1975;

Safe et al., 1975; Matthews & Anderson, 1976; NIOSH, 1977; Matthews & Tuey, 1980).

6.5.3 Tetrachlorobiphenyls

Examination of the 2 different tetrachloro- isomers, 2,3,5,6,-tetrachloro- and 2,5,2',5',-tetrachlorobiphenyl, showed that, in the case of the molecule with all 4 chlorines on one ring, the products were monohydroxy- derivatives *meta* or *para*, dihydroxy- derivatives *meta* and *para*, and a *para* hydroxy- plus a *meta* methoxy- group or a *meta* hydroxy- and a *para* methoxy- group, all on the unsubstituted ring. The symmetrical 2,5,2',5'-tetrachlorobiphenyl in the rat gave the *meta* hydroxy-, but in the rabbit a *para* hydroxy-, and also in the rabbit a dihydro-dihydroxy-, on the *meta* and *para* positions. The asymmetric 2,4,3',4'-tetrachlorobiphenyl gave monohydroxy-derivatives, both in the *meta* position, either in the three or five position. It seems that an alternative enzyme pathway is available in the rabbit.

The level of retention was highest for 2,4,2'4'-tetrachlorobiphenyl descending in the following order; 2,5,2',5'-, 3,5,3',5'-, 3,4,3',4'-, 2,3,2',3'-, and 2,6,2',6'-tetrachlorobiphenyl. Since no PCBs were detected in the liver, and only small amounts of 2,3,2',3'- and 3,4,3',4'-tetrachlorobiphenyls in the carcass, it can be concluded that these 2 isomers were readily metabolized and excreted. Both compounds have unsubstituted vicinal positions. However, the compounds slowest to be metabolized were 2,4,2',4'- and 2,5,2',5'-tetrachlorobiphenyls, which also have unsubstituted vicinal positions. Metabolic restriction cannot be entirely attributed to substitution at the 4,4'- positions (Kato et al., 1980), since this also occurred in 3,4,3',4'-tetrachlorobiphenyl, which was removed relatively rapidly.

The excretion of the monohydroxy metabolites of 3,4,3',4'-tetrachlorobiphenyl and 2,4,3',4'-tetrachlorobiphenyl (orally administered) in rats has been demonstrated by Yoshimura et al. (1973); Yamamoto & Yoshimura (1973); Yoshimura & Yamamoto (1975); and Yoshimura et al. (1974). They demonstrated that the metabolites of the first isomer were 2-hydroxy- or 5-hydroxy- compounds, while the metabolites of the second isomer were 5-hydroxy- and 3-hydroxy- compounds. All hydroxy metabolites were excreted

non-conjugated via the bile and no parent isomers were found in the bile. Yoshimura & Yamamoto (1975) found that unchanged 2,4,3',4'-tetrachlorobiphenyl was excreted through the intestine, when it was intravenously injected in rats with the bile duct ligated, while no metabolite of this isomer was excreted by this route.

The results with the 2,5,2',5'- molecule are probably related to an arene oxide pathway. Direct evidence for this was reported by Forgue et al. (1980), who showed that 3,3,3,-trichloropropene-1,2-oxide, which is an inhibitor of epoxide hydrase, blocked the formation of the suspected arene oxide metabolites. The arene oxide mechanism supposedly operates in rabbits and monkeys for 2,5,2',5'-tetrachlorobiphenyl and, possibly, also in rats for 2,4,5,2',4',5'-hexachlorobiphenyl. Isomers that may utilize the arene oxide pathway, to some extent, are: 4,4'-dichloro-; 2,5,2',5'-tetrachloro-; and 2,4,5,2',4',5'-hexachlorobiphenyl.

6.5.4 Hexachlorobiphenyls and higher chlorinated compounds

The symmetrical hexachlorobiphenyls were used in a study by Matthews & Tuey (1980), in which Sprague-Dawley rats were injected intravenously with the PCBs and killed at increasing time intervals from 15 min to 42 days. The 2,3,6,2',3',6'- isomer was rapidly metabolized and excreted compared with the other isomers, which were slowly metabolized and excreted with much longer half-lives. The results indicated that the metabolism of hexachlorobiphenyls is slow, when the position of the chlorine atoms is such that arene oxide formation is inhibited.

2,3,6,2',3',6'-Hexachlorobiphenyl produces only one metabolite in the rat: 2,3,6,2',3',6'-hexachloro-4'-hydroxybiphenyl, which is believed to be the result of arene oxide formation. All commercial mixtures of PCBs will contain congeners that could be metabolized via the arene oxide pathway. However, it does not seem to be the major pathway of metabolism for most of the components of the commercial products, since most of the higher congeners will not have vicinal unsubstituted carbons.

The metabolic data on individual isomers shows that, at least up to hexachloro- compounds, ordinary hydroxylation can take place. It is reasonable to consider that it is not only as a consequence of poor

metabolism that pentachloro- and hexachloro- compounds are persistent in the tissues, but rather that they are not metabolized as readily, because they are sequestered from tissues in which the bulk of the metabolism takes place. In support of this position, it has been shown by Matthews & Anderson (1975b) that, when animals are caused to lose a substantial portion of body weight, the stored higher chlorinated compounds can, indeed, be metabolized. Octachloro- and decachlorobiphenyls would not be expected to be easily metabolized, simply because there are few or no sites for hydroxylation to take place. It was found (Vodicnick & Lech, 1980; Vodicnick et al., 1980) that almost the entire body burden of 2,4,5,2',4',5'-hexachlorobiphenyl was removed from mothers given this PCB and that it was transferred to their offspring via the nursing mother's milk. In mice, the preferential distribution of this PCB in milk reflects the high fat content of mouse milk.

Virgin, female, Sprague-Dawley mice, injected ip with 50 or 100 mg [^{14}C] 2,4,5,2',4',5'-hexachlorobiphenyl/kg body weight in corn oil for 2 weeks, prior to mating, eliminated virtually their entire body burden of the compound through milk during one lactation cycle (Gallenberg & Vodicnick, 1987).

Storage is caused by lack of metabolism and also implies that the availability of adjacent unsubstituted carbons is the determinant for metabolism. Direct hydroxylation reactions do not require unsubstituted adjacent carbons. Rapid storage in fat is the rate-limiting factor in the removal of most PCBs, with the exception of isomers that might be very rapidly metabolized by arene oxide formation, such as 2,3,6,2',3',6'-hexachlorobiphenyl.

Matthews & Anderson (1975b) extended their study to include a fasting period to reduce the weight of the test rats and showed that severe fasting mobilized stored PCBs and brought them into the metabolic pool.

6.5.5 Retention and turnover

Mizutani et al. (1977) studied the pharmacokinetic behaviour of 6 different tetrachlorobiphenyls. They administered mice the 6 isomers, at 10 mg/kg body weight, for 20 days. The isomer concentrations in the liver and the remainder of the carcass were determined

at various times during the recovery period. They found that the accumulated body burden was a function of both storage ratio and biological half-life.

The results of Mizutani et al. (1977) suggest that the correlations claimed between the position of the chlorine substituents and storage or metabolic activity (Kato et al., 1980; Matthews & Tuey, 1980) are not simply explained.

The hypothesis that the position of the chlorine atoms alone determines the rates of metabolism, accumulation, and excretion does not appear to be entirely supported. This idea has been used to support the notion that PCBs with unsubstituted vicinal carbon atoms favour metabolism by arene oxide formation.

6.5.6 Appraisal

The results of most studies suggest that PCBs are absorbed by the organ systems (gastrointestinal tract, lung, and liver), representing the likely routes of entry into the body. This is particularly true for the gastrointestinal tract where absorption is rapid. PCBs, once absorbed, are usually distributed in a biphasic manner and are rapidly cleared from the blood and accumulated in the liver and adipose tissue, or they can be metabolized in the liver, to form metabolites that are excreted in the urine and bile. In some studies on humans, the skin, an organ rich in adipose tissue, had a high PCB content, whereas the brain content was low. This distribution can also include the fetus and human milk, an extension of the adipose tissue system in the body. Mobilization of PCBs from fat appears to depend on their rates of metabolism. Metabolic pathways include hydroxylation, and conjugation with thiols and other water-soluble derivatives, some of which can involve reactive intermediates, such as the arene oxides. The most important pathway seems to be hydroxylation and subsequent conjugation. This pathway is facilitated by the presence of at least one pair of unoccupied vicinal carbon atoms in the PCB structure. Persistence in tissue is not correlated with high toxicity. Differences in toxicities among PCBs may be associated with specific metabolites and/or their associated intermediates.

7. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

7.1 Toxicity for microorganisms

7.1.1 Freshwater microorganisms

Zullei & Benecke (1978) used the motility of filamentous blue-green algae (Cyanophyceae) of the genus *Phormium* as a bioassay for the rapid determination of the toxicity of various compounds. They tested the relative toxicity of purified, specific chlorobiphenyls and of PCB commercial mixtures (Clophen). Inhibition of motility was greatest in the presence of chlorobiphenyls of low chlorination. All mono- and dichlorinated isomers were inhibitory at the test concentration of 100 μg per test spot of algae. Tetra- and hexachlorobiphenyls did not have any effects; the effects of trichlorobiphenyl isomers varied, the 2,5,2' isomer not producing any effects and the 2,4,4' and 3,4,4' isomers being inhibitory. Tests using the commercial mixtures confirmed the greater toxicity of low chlorination levels; Clophen A30 was more toxic than Clophen A60, though the presence of more than expected, low-chlorinated compounds in the Clophen A60 reduced the difference in toxicity.

Cultures of the green alga *Chlorella pyrenoidosa* were incubated with 1 mg/litre of Aroclors 1242, 1254, and 1268 (Hawes et al., 1976a). The initial culture was 5 days old with a cell density of 27×10^6 cells/ml. After 8 h of incubation with the PCBs, cell densities in the cultures were 64% lower than controls for Aroclor 1242, 45% lower for Aroclor 1254, and 36% lower for Aroclor 1268. As the study progressed, the cell densities in the cultures improved relative to the controls; cell density in the Aroclor 1254 culture was equal to that in the control by 129 h and the density in the Aroclor 1268 culture was equal to the control by 59 h. Although the density in the Aroclor 1242 culture remained much lower than that in the control throughout the culture period, there was evidence of recovery with this compound. The toxicity of the Aroclors was inversely proportional to their degree of chlorination. A concurrent

investigation of the primary productivity of the alga (Hawes et al., 1976b), suggested that the productivity of individual cells was stimulated by the Aroclors, with a positive relationship between the level of chlorination and the effect. However, this did not, take into account the differences in density between cultures (PCBs reduce growth through cell division) and the authors pointed out that the response of the alga to the PCBs was not simple. They stated that the density, culture age, and Aroclor type were all factors that influenced response.

Larsson & Tillberg (1975) cultured the green alga *Scenedesmus obtusiusculus*,in a liquid medium, in concentrations of Aroclor 1242 ranging between 10 and 1000 μg/litre. Growth was reduced at concentrations of 300 μg Aroclor/litre or more; viability was only affected at the highest concentration of 1000 μg/litre. Reduced phosphate uptake, which was nearly identical in light or in darkness, was reduced from 300 μg/litre upwards. The authors regarded this as a result of an effect on the plasmalemma. At 800 μg PCBs/litre, the results of some studies suggested an effect of the uncoupling of oxidative phosphorylation; at 1000 μg/litre, both respiration and oxygen evolution were inhibited.

The effects of various Aroclors on the respiration and photosynthesis of the green alga *Chlorella vulgaris* were examined by Sinclair et al. (1977). Aroclor 1221, at a final concentration in the medium at 10^{-4} mol/litre (= 192 mg/litre based on an average relative molecular mass for the Aroclor at 192), produced a rate of oxygen production in the light of 43% of control levels and a rate of oxygen uptake in the dark of 59% of control levels. The Aroclors were dissolved using dimethylformamide (DMF) as a solubilising agent; whilst this had some effects on the parameters measured, they were very little compared with the effects of the Aroclors (94% of control levels). A dose-response curve of the effect of Aroclor 1221 on the respiratory uptake of oxygen in the dark, in the presence of glucose, showed that there was already a marked effect at a concentration of 10^{-7} mol/litre and that a maximum (at 50% inhibition) was reached at a concentration of 10^{-6} mol/litre (= 1.92 mg/litre).

A further series of studies was performed to investigate the individual processes of oxygen exchange in the alga. Respiration in the dark

was investigated in the absence of added glucose, to monitor "endogenous" respiration, which was found to be stimulated by Aroclor 1221 at concentrations of 10^{-4} mol/litre or more. Net oxygen production in the light (photosynthetic oxygen production minus respiratory oxygen usage) was reduced at a concentration of 10^{-4} mol/litre. At this concentration of Aroclor 1221, there was approximately 50% stimulation of endogenous respiration and approximately 50% inhibition of net oxygen production. Calculated photosynthetic rate was unaffected by the Aroclor. Increasing light intensity reduced the effect of Aroclor 1221 on net oxygen production; intensities of 8.2×10^4 ergs /cm^2 virtually eliminated the effect. Other measures directly or indirectly associated with photosynthesis (fluorescence, oxygen evolution in flashing light, the Emerson enhancement phenomenon) were not affected by the Aroclor. The authors suggested that the photosynthetic apparatus of *Chlorella* was unaffected by Aroclor 1221; the major, and probably the only, effect of the PCBs being a stimulation of endogenous respiration rate. Results with Aroclors 1242 and 1268 were consistent with those for Aroclor 1221; both inhibited net oxygen production in the light and glucose-driven respiration in the dark, but stimulated endogenous respiration in the dark (Sinclair et al., 1977).

Luard (1973) reported inhibition of ^{14}C uptake by the green alga *Scenedesmus quadricauda* at concentrations of Aroclor 1254 as low as 0.1 µg/litre. At this concentration, the Arocl or caused a 20% inhibition of ^{14}C uptake, which rose to 65% inhibition at 1 mg/litre.

A marked effect of the initial number of cells in the incubation tube on the toxicity of Aroclor 1254 for the green alga *Chlorella pyrenoidosa* was demonstrated by Cole & Plapp (1974). At a constant concentration of 1 mg Aroclor 1254/litre, the numbers of algal cells in the initial incubation medium were as varied as 1, 10, 100, or 1000 µg alga/ml of medium. At the highest inoculation rate, the growth of the alga was unaffected by the Aroclor. At lower initial inoculation, the rate of growth was reduced to between 11 and 55% of control levels. A comparable effect was found using ^{14}C fixation as the parameter; with inoculation rates of 1000 µg alga/ml medium, the Aroclor did not have any effects, whereas lower inoculation rates reduced carbon fixation to between 6 and 13% of control levels.

Mosser et al. (1972) showed that 2 species of freshwater algae (*Euglena gracilis* and *Chlamydomonas reinhardtii*) were unaffected by 100 μg PCBs/litre (type unspecified). Ewald et al. (1976) determined the 48-h EC_{50} on the growth of *Euglena gracilis* to be 4.4 mg/litre for Aroclor 1221 and 55 mg/litre for Aroclor 1232. Aroclor 1242 showed no inhibition at 100 mg/litre. Aroclor 1221, at the EC_{50} concentration of 4.4 mg/litre, significantly depressed carbon fixation and chlorophyll levels, but did not affect oxygen consumption. Uptake of L-leucine was increased 2-fold, but incorporation was not affected. Uridine uptake was significantly decreased, but thymidine uptake and incorporation were not affected.

In studies by Glooschenko & Glooschenko (1975), 3 algal species from the Great Lakes were cultured with Aroclor at concentrations of 1, 5, 10, 20, or 50 μg/litre. Cell numbers of the diatom *Synedra acus* were reduced in culture from day 3 of treatment with Aroclor 1242, at 10, 20, or 50 μg/litre, and from day 7, with 1 or 5 μg/litre. The green alga *Scenedesmus quadricauda* showed a lag phase of 3 days in all concentrations of Aroclor 1242. After 3 days, exponential growth occurred in all treatments, except for the highest dose levels (20 and 50 μg/litre) which showed little or no cell division. A second green alga (*Ankistrodesmus falcatus*) was more sensitive, showing significantly reduced cell numbers at all dose levels of Aroclor 1242. *Ankistrodesmus* was used to examine the relative toxicities of different Aroclors. Cell numbers were 57, 66, 36, and 53% of control levels for Aroclors 1016, 1221, 1242, and 1248, respectively, after 2 days of culture. Carbon fixation, estimated as uptake of ^{14}C from solution, was 73, 98, 51, and 59% of control levels for the 4 Aroclors, respectively.

Dive et al. (1976) cultured the ciliate protozoan *Colpidium campylum* with purified chlorobiphenyls and with a commercial mixture (Pyralene 3010). None of the 16 isomers affected the ciliate's growth and reproduction at concentrations of 0.01 or 0.1 mg/litre; similarly, Pyralene 3010 was not toxic at these concentrations. 2-Monochlorobiphenyl showed little toxicity for the organism at 1 mg/litre and little or no toxicity was demonstrated by the tetrachloro-, pentachloro-, and hexachlorobiphenyls at this concentration or at 10 mg/litre (with the exception of 2,5,2',5'-tetrachlorobiphenyl, which inhibited growth considerably, limiting it to about 10% of

controls at 10 mg/litre). 4,4'-Dichlorobiphenyl was not toxic at any concentration tested (up to 10 mg/litre) but both 2,3- and 2,5-dichlorobiphenyls were toxic, killing all organisms at both 1 and 10 mg/litre. These results are comparable with other reports that the lower chlorinated biphenyls are the most toxic for microorganisms; differences in toxicity could not be explained by the differential uptake of the different isomers.

It was reported by French (1976) that the EC_{50} for growth inhibition of Aroclor 1254 on the flagellated protozoan *Crithidia fasciculata* was 10.5 mg/litre. The PCBs slightly inhibited (after 6 h) and then increased (after 24 h) the carbon dioxide evolution of cultures utilizing D-glucose. After 6 h exposure, the uptake and incorporation of thymidine and uridine (but not L-leucine) were inhibited; inhibition was transient and returned to normal after 12 or 24 h. Fine structural changes were noted after exposure to PCBs including: deterioration of the kinetoplast, mitochondrial or cellular swelling, and the presence of concentric membrane arrays. It was concluded that cell population growth inhibition was due to disruption of uptake, incorporation of nucleic acids, and loss of cell regulatory capacity.

7.1.2 Marine and estuarine microorganisms

Bourquin & Cassidy (1975) and Bourquin & Kiefer (1975) investigated the effects of Aroclors 1016 and 1242 on 85 bacterial isolates from various estuarine environments near Pensacola, Florida. Twenty six of the 85 isolates were inhibited to various extents by 0.5 mg of either of the PCBs, applied to a disc placed on the surface of an agar plate on which the bacteria were growing. Zones of inhibition ranged from 14 to 20 mm in diameter. Cultures that showed sensitivity to Aroclor 1242 were also inhibited by Aroclor 1016. Sixty five percent of isolates inhibited by 0.5 mg of Aroclor 1242 were still sensitive at 0.1 mg, and 58% of those sensitive to Aroclor 1016 at 0.5 mg were still sensitive to 0.1 mg. Four isolates were examined in a liquid medium. Inhibition of the cultures was characterized by a greatly extended lag phase (extended from 2 h to at least 14 h); when growth occurred, growth curves were parallel with those of the controls. The physiological activity of sensitive and insensitive isolates were investigated to try to explain the reasons behind sensitivity. More of the sensitive isolates were amylase and

gelatinase producers (76 and 86%, respectively, compared with 33 and 42%, respectively, for the whole range of isolates). The significance of this observation is unclear. Because of the method of exposure in this screening exercise, it is difficult to relate the results to exposure in natural waters and to draw conclusions about likely hazards for aquatic bacteria.

Kleppel & McLaughlin (1980) determined the toxic threshold of Aroclor 1254 for the estuarine diatom *Skeletonema costatum* to be between 3×10^{-9} and 3×10^{-8} µg/cell. When the effect of cell density on the toxicity of the Aroclor for the organism was examined, maximum inhibition occurred with the lowest inoculum rates.

Michaels et al. (1982) estimated the effects of Aroclor 1254 on photosynthesis in the marine diatom *Thalassiosira pseudonana* (= *Cyclotella nana*) by monitoring the uptake of ^{14}C-carbon dioxide. The numbers of viable cells in the culture were also estimated. Total cell numbers were estimated at regular intervals during the 48 h of the experiment and the minimum number of viable cells required to produce the increase in numbers between periods calculated. This gave an estimate of the viable numbers, retrospectively, for each period. Inhibition of ^{14}C-uptake per culture, per cell, and per viable cell was evident within 1 h of the start of the incubation. By 48 h, the ^{14}C uptake per culture was reduced to 0.2% of control levels, per cell, to 13% of control levels, and per viable cell, to 34% of control levels. The authors concluded that the effect of Aroclor 1254 on the diatom is a combination of inhibition of carbon assimilation by individual cells and inhibition of cell division.

In an earlier study, Fisher & Wurster (1973) exposed 2 estuarine diatoms (*Thalassiosira pseudonana* and *Rhizosolenia setigera*) and an estuarine green alga (*Dunaliella tertiolecta*) to Aroclor 1254 at 0.1 or 10 µg/litre, cultured over 100 h. There was no effect on the growth of the alga. *T. pseudonana* was unaffected by the PCB at 0.1 µg/litre. The effect of the Aroclor on *T. pseudonana* at 10 µg/litre was dependent on temperature; there was a 17% reduction in growth rate at 25 °C, a 44% reduction in growth rate at 18 °C, and a 58% reduction in growth rate at 12 °C. The growth of control cultures was greatest at the highest temperature. The growth of *R. setigera* was completely stopped by all concentrations of PCB tested, for the

first 48 h of culture. When growth resumed, the degree of inhibition was greater at 10 °C than at 15 °C. Fisher et al. (1976) exposed the marine diatom *Thalassiosira pseudonana* to 1 μg Aroclor 1254/litre in cultures containing various levels of nitrate nutrient. The toxic effects of the PCBs on the growth of the diatom were greatest at low nitrogen levels. Analysis of variance showed the diatom to be significantly dependent for growth on nitrogen concentration and on PCB concentration, and that the PCB effect was significantly nitrogen dependent. The authors pointed out that marine phytoplankton are often nitrogen-limited in nature and suggested that the effects of pollutants, such as PCBs, may, therefore, vary with season. The greatest effects are likely to occur during bloom conditions, when competition for nutrients is greatest. Fisher (1975) considered that the presence of PCBs, even at concentrations far above the maximum recorded level in sea water, would not affect the overall carbon fixation by phytoplankton. Although the cell division of some organisms was adversely affected, enough insensitive species existed to compensate for the sensitive species. Species diversity and community structure were likely to be affected.

In a study by Craigie & Hutzinger (1975), 6 marine algae were cultured for 6 days in the presence of commercial mixtures of PCBs (Aroclors 1221 to 1262; Phenoclors DP3 to DP6), PCTs (Aroclor 5460), and specific chlorobiphenyls. Each compound or mixture was applied to the culture medium at 2 concentrations (1 and 100 mg/litre). The algae were representatives of 6 different classes: Bacillariophyceae - *Skeletonema costatum*, *Thalassiosira fluviatilis*; Chlorophyceae - *Dunaliella tertiolecta*; Chrysophyceae - *Monochrysis lutheri*; Prainophyceae - *Platymonas* sp.; Rhodophyceae - *Porphyridium* sp.; Xanthophyceae - *Olisthodiscus* sp. All were cultured at 20 °C. Growth was estimated by turbidity. The response to particular Aroclors was species dependent; the least sensitive species was *Dunaliella* and the most sensitive was *Olisthodiscus*. At 1 mg/litre of the PCB mixtures, there was relatively little inhibition of *Dunaliella*, *Platymonas*, *Skeletonema*, or *Thalassiosira*. *Olisthodiscus* was completely inhibited by Aroclors 1248, 1254, 1260, and Phenoclor DP4. The Phenoclor series was more toxic for *Olisthodiscus* than the Aroclors. *Porphyridium* and *Monochrysis* showed intermediate sensitivity. Generally, the Aroclors with higher

chlorination levels were less toxic for all species than the Aroclors with lower chlorination levels. Results with pure, specific chlorinated biphenyls confirmed that highly chlorinated compounds are less toxic than those with only 1–4 chlorine atoms per molecule. Experiments with biphenyls containing identical percentages of chlorine showed that biological response was highly dependent on the structure of the molecule. The 2,4,2',4'-tetrachlorobiphenyl was more toxic for both *Dunaliella* and *Olisthodiscus* than the 2,5,2',5'-isomer, and both were more toxic than either the 2,3,4,5- or the 3,4,3',4'- isomers. The last was not toxic for any of the algae, even when added at 100 mg/litre.

Luard (1973) reported a significant reduction in ^{14}C uptake by the estuarine green alga *Dunaliella tertiolecta* in the presence of Aroclor 1254, at 100 μg/litre. The culture showed ^{14}C uptake at 65% of control levels. At 1000 μg/litre, uptake was further reduced to 59% of controls. The ^{14}C uptake was unaffected at 10 μg/litre.

7.1.3 Soil microorganisms

When Murado et al. (1976) added Aroclors to a liquid or solid medium on which the soil microfungus *Aspergillus flavus* was cultured, mycelial growth was reduced progressively as the dose of Aroclor 1254 increased from 5 to 50 mg/litre in liquid culture. At 25 mg/litre, the dry weight of the mycelium was reduced to 1.4, 3.4, 3.9, 3.3, and 54.6% of control levels by Aroclors 1232, 1242, 1248, 1254, and 1260, respectively. At the same time, the relative RNA content of the mycelium increased, rising from a control level of 5.9 μg RNA/mg dry weight to between 13.2 and 18.6 μg RNA/mg dry weight for Aroclors 1232 to 1254. Aroclor 1260 had no marked effect on RNA. The DNA content was not affected by any treatment. Cultures on solid medium showed a delay in sporulation and a decrease in the diameter of colonies at doses up to 20 $\mu g/cm^2$.

Glooschenko & Glooschenko (1975) cultured the soil alga *Navicula pelliculosa* with Aroclors 1016, 1221, 1242, and 1248 at a concentration of 20 μg/litre. The numbers of cells in the culture, after 2 days, were reduced to 66, 53, 46, and 56% of control levels for the 4 Aroclors, respectively.

7.1.4 Plankton communities

Phytoplankton communities from 2 lakes, one oligotrophic and one eutrophic, were exposed to PCBs, as Clophen A50, at 26 μg/litre (Södergren & Gelin, 1983). In the community from the eutrophic lake with a greater biomass of phytoplankton, measurement of ^{14}C uptake, monitored immediately after the addition of the PCBs, showed a reduction of 34% compared with the controls. Monitoring carbon fixation 16 h later showed the phytoplankton recovering from the effect of the PCBs, with only 21% inhibition relative to the controls. The results differed in the community from the oligotrophic lake. ^{14}C uptake immediately after the addition of the Clophen was 70% less than that in the controls; 16 h later, the effect was greater, at 84% inhibition. The authors pointed out that these results parallel findings in pure culture showing that a high density of organisms reduces the effects of PCBs.

Mosser et al. (1972) first demonstrated the effects of PCBs on both single and mixed cultures of marine phytoplankton. Two organisms, a marine diatom (*Thalassiosira pseudonana*) and a marine green alga (*Dunaliella tertiolecta*) were used. The diatom is sensitive and the alga insensitive to PCBs. The application of PCBs (not specified) to mixed cultures changed the usual dominance of the diatom into dominance of the alga, even at concentrations of the PCBs (1 and 10 μg/litre) that had no discernible effects on the diatom in pure culture.

The effect of Aroclor 1254 on the relative biomass of 2 species of marine diatoms *Phaeodactylum tricornutum* and *Cyclotella cryptica* was examined by Lundy et al. (1984). The diatoms were cultured together in either 10 or 20 μg PCBs/litre for 6 days. At both concentrations of Aroclor, the ratio between the species was shifted in favour of *Phaeodactylum*. After 6 days, the ratio of *Phaeodactylum* : *Cyclotella* was 0.8 in the controls and 2.63 in the treated cultures (10 μg Aroclor 1254/litre).

Biggs et al. (1979) exposed a mixed culture of 2 marine algae to PCBs (Aroclor 1254) at 50 μg/litre. In the control culture, *Thalassiosira pseudonana* became the dominant organism over *Dunaliella tertiolecta*. After exposure to the PCBs, the *Thalassiosira* was affected, but the *Dunaliella* was not. By day 2 of Aroclor 1254

exposure, *Dunaliella* was the dominant species. Fisher et al. (1974) showed a similar effect with the greater effects of PCBs on the sensitive diatom *Thalassiosira pseudonana* when the organism was in competition with other organisms. The effect was also demonstrated using natural communities of phytoplankton, when *Thalassiosira* was also selectively affected.

Biggs et al. (1978) exposed a natural community of marine phytoplankton (from which large detritus and zooplankton had been filtered) to Aroclor 1254 at either 5 or 10 μg/litre. Cell division, chlorophyll-a synthesis, and ^{14}C uptake were monitored, as well as particle size. Treatment with the Aroclor reduced community growth rates by 20–50%, compared with controls. Growth had not fully recovered after 10 days. The ^{14}C uptake was reduced for 6 days. The control cultures became dominated by algae larger than 8 μm in diameter. The PCB-treated cultures showed strong inhibition of these larger algal cells and the culture became dominated by small cells.

In a study by Iseki et al. (1981), a natural community of plankton was exposed, *in situ*, in a marine environment, to Aroclor 1254 in large bags holding 68 m^3 of seawater. The Aroclor was added to the bag giving an initial concentration in the upper layers of about 40 μg/litre (15 μg/litre at 10 m depth). Over time, the levels of PCB fell in the upper layer and increased in the lower layer in the bag. Six days after addition, the concentrations at all depths were less than 15 μg/litre. Immediately after addition of the PCBs, the rate of sedimentation of the particles increased; these particles were thought to be dead or senescent large cells, such as diatoms, and this sedimentation was assumed to be responsible for the major part of the loss of the PCBs from the water. Zooplankters were eliminated from the bags by this level of Aroclor; no recovery was seen over the 21 days of the experiment. Large diatoms were selectively eliminated from the bags and replaced by small flagellates as the dominant organism.

Moore & Harriss (1972, 1974) exposed a natural community of plankton to PCBs (as Aroclor 1242) at 10 or 25 μg/litre. The population was collected from natural water, placed in glass bottles suspended *in situ*, and monitored for uptake of ^{14}C, added to the bottles as bicarbonate. After incubation, the community was

separated into small "nannoplankton" and larger "net-plankton" by filtration at a mesh size of 53 μm. Nannoplankton radiocarbon uptake accounted for 72.6% of the total community carbon uptake and was not affected by either of the concentrations of Aroclor 1242. The net-plankton uptake of ^{14}C was reduced by 56% at 10 μg Aroclor/litre and by 58% at 25 μg/litre. The authors suggested that PCBs at levels found in natural waters would alter the species diversity or community structure of microorganisms and that this might affect higher levels of the food chain with specialist feeders utilizing one type of prey. O'Connors et al. (1978) exposed natural communities of phytoplankton, *in situ*, in dialysis bags in a salt marsh. Large zooplankton herbivores were removed by filtration through a mesh. Aroclor 1254 was added to the bags to give water concentrations of 1–10 μg/litre. Larger diatoms were selectively inhibited by the Aroclor, even at the lower dose (1 μg/litre). The authors suggested that, not only would phytoplankton communities be affected by PCBs in natural waters, but that the effect would be carried forward through the food chain. Gelatinous predators, such as jellyfish, could be selected at the expense of fish, since fish tend to depend directly, or indirectly, on the larger phytoplankton.

Natural communities of phytoplankton from a stream and a reservoir were cultured with Aroclors 1232 and 1254 by Kricher et al. (1979). Although the algal communities were different in composition, both Aroclors exerted similar effects on both communities; primary productivity was reduced in a dose-dependent manner. Aroclor 1232 was more toxic than Aroclor 1254 at 1 mg/litre. Algal species within the populations were differentially affected by the Aroclors; diatoms were particularly susceptible and treatment produced disproportionate numbers of blue-green algae, such as *Anacystis*. The authors pointed out that the insensitive species still accumulated PCBs and, therefore, formed the basis for the accumulation of the Aroclors in aquatic food chains.

7.1.5 Interactions with other chemicals

Mosser et al. (1974) investigated the interactions between Aroclor 1254, DDT, and DDE in a marine diatom *Thalassiosira pseudonana*. The diatom was cultured for 4 days with either 10 or 50 μg Aroclor 1254/litre, 100 μg DDE/litre or 500 μg DDT/litre (with each

chemical alone or in combination). The PCBs alone (at 10 μg/litre) and the DDE alone had little effect on the growth of the diatom; when combined these treatments were synergistic, growth being less than half that of the control culture. Higher concentrations of either compound increased the inhibitory effect. In contrast, DDT reduced the toxic effects of PCBs at higher concentrations (50 μg/litre). Treatment with the Aroclor alone at 50 μg/litre almost stopped the growth of the diatom. Simultaneous treatment with DDT at 500 μg/litre restored growth to 60–70% of control levels. Lower concentrations of DDT had a comparable, but reduced, effect. Addition of the DDT to the medium, 12 or 24 h after culture had begun in the presence of PCBs, also reversed the inhibitory effect.

7.1.6 Tolerance

Fisher et al. (1973) showed that strains of diatoms, isolated from the Sargasso Sea, were more sensitive to the effects of PCBs than isolates of the same species, obtained from estuaries or the continental shelf. It was suggested by the authors that the difference in sensitivity was derived from the variable environment of the estuarine strains; these strains are able to cope with wide variations in their living conditions, not experienced in the open ocean of the Sargasso, and, therefore, were better able to cope with stress from chemical pollutants.

When Cosper et al. (1984) compared the sensitivity of clones of 2 species of diatom (*Asterionella japonica* and *Ditylum brightwelii*) from polluted and unpolluted sites, *Asterionella* was less sensitive than *Ditylum* to the action of PCBs (Aroclor 1254); some strains of the former were tolerant of 25 μg Aroclor/litre whereas no strains of the latter could tolerate this concentration. There was evidence that strains of *Asterionella* from the polluted site were more tolerant than the same species from unpolluted sites. One strain, from the polluted site, was tolerant to Aroclor 1254 at 50 μg/litre.

7.2 Toxicity for aquatic organisms

7.2.1 Aquatic plants

Mahanty (1975) grew the aquatic angiosperm *Spirodela oligorhiza* in a sterile culture solution, to which had been added Aroclor 1242, at

concentrations of 5-100 mg/litre. The numbers of colonies were counted throughout the 14-day exposure. The highest dose (100 mg/litre) was found to be lethal. At both 25 and 50 mg/litre, though there was some growth, the colonies were small and showed morphological differences from control colonies including: smaller fronds, in larger numbers than usual, and a characteristic striped pattern of chlorosis on the fronds. Even at 5 mg/litre, growth was reduced by 50% (as recorded by the number of colonies and the fresh weight). Mahanty & McWha (1976), using only the 5 mg/litre dose, found reduced growth, an unusual striped pattern of chlorosis, and a reduction in the levels of chlorophyll and total RNA, but no change in the levels of DNA. When Mahanty & Fineran (1976) studied treated (5 mg/litre) and untreated fronds of *Spirodela* by electron microscopy, they found almost complete disorganization of the internal structure of the chloroplasts in chlorotic tissue. Organization of other cell components was largely unaffected.

7.2.2 Aquatic invertebrates

The acute toxicity of PCBs for aquatic invertebrates is summarized in Tables 27 and 28. Toxicity is very variable between species, even closely-related species. For most aquatic invertebrates, there is an effect of degree of chlorination of the PCBs, but this is not a direct correlation, either negative or positive, the most toxic PCBs often being in the mid range of chlorination. Under flow-through conditions, the toxicity of PCBs appears to be much higher. Over 96 h, under static conditions, LC_{50} values ranged between 12 μg/litre and > 10 mg/litre for different organisms and different PCBs.

MATC (maximum acceptable toxicant concentrations) were set for various PCBs by the US EPA (1980). These are expressed as a range between no-observed-effect values and lowest concentration tested that produced a measurable effect. For *Daphnia magna*, these values were 1.2 and 3.5 μg/litre for Aroclor 1248 , and 2.5 and 7.5 μg/litre for Aroclor 1254. For the scud (*Gammarus pseudolimnaeus*) values for Aroclor 1242 were 2.8 and 8.7 μg/litre and values for Aroclor 1248 were 2.5 and 5.1 μg/litre. Aquatic larvae of the midge (*Tanytarsus dissimilis*) had a no-observed-effect level of 0.5 μg/litre and a lowest effective concentration at 1.2 μg/litre.

Table 27. Acute toxicity of PCB mixtures for freshwater invertebrates

Organism	Size/age	Stat/flow[a]	Temperature (°C)	Hardness (mg/litre)[b]	pH	PCB type (Aroclor)	Parameter	Concentration (mg/litre)	Reference
Scud *(Gammarus pseudolimnaeus)*	mature	flow	15	272	7.4	1242	96 h - LC_{50}	0.01	Mayer & Ellersieck (1986)
	juvenile	flow	18			1248	96 h - LC_{50}	0.029	Nebeker & Puglisi (1974)
	juvenile	flow	18			1242	96 h - LC_{50}	0.073	
Scud *(Gammarus fasciatus)*	mature	stat	21	44	7.1	1248	96 h - LC_{50}	0.052	Mayer & Ellersieck (1986)
	mature	stat	21	44	7.1	1254	96 h - LC_{50}	2.4	
Glass shrimp *(Palaemonetes kadiakensis)*	mature	flow	15	272	7.4	1254	168 h - LC_{50}	0.003	Mayer & Ellersieck (1986)
Crayfish *(Orconectes nais)*	early instar	stat	21	44	7.1	1242	168 h - LC_{50}	0.03	Mayer & Ellersieck (1986)
Crayfish *(Procambarus* sp.*)*	early instar	stat	21	44	7.1	1254	168 h - LC_{50}	0.1	Mayer & Ellersieck (1986)
	immature	stat	12	44	7.5	1254	96 h - LC_{50}	> 0.55	

Table 27 (continued)

Organism	Size/age	Stat/ flow[a]	Temper- ature (°C)	Hardness (mg/litre)[b]	pH	PCB type (Aroclor)	Parameter	Concen- tration (mg/litre)	Reference
Stonefly *(Pteronarcella badia)*	first year	stat	10	170	7.2	1016	96 h - LC_{50}	0.61 (0.42-0.88)	Mayer & Ellersieck (1986)
Damselfly *(Ischnura verticalis)*	late instar	flow	15	272	7.4	1242	96 h - LC_{50}	0.4	Mayer & Ellersieck (1986)
		flow	15	272	7.4	1254	96 h - LC_{50}	0.2	
Dragonfly *(Macromia* sp.*)*	late instar	stat	21	44	7.1	1242	168 h - LC_{50}	0.8	Mayer & Ellersieck (1986)
		stat	21	44	7.1	1254	168 h - LC_{50}	0.8	

[a] Stat = static conditions: water not changed during the exposure; flow = flow-through conditions; concentration of toxicant continuously maintained.

[b] Hardness expressed as mg $CaCO_3$/litre, unless otherwise stated.

Table 28. Acute toxicity of PCB mixtures for marine invertebrates

Organism	Size/age	Stat/ flow[a]	Temper- ature (°C)	Salinity ($^{O}/_{oo}$)	PCB type	Parameter	Concentration (mg/litre)	Reference
Cockle	adult	stat	15		Aroclor 1248	48 h - LC_{50}	> 10	Portmann &
(Cardium	adult	stat	15		Aroclor 1254	48 h - LC_{50}	> 10	Wilson (1971)
edule)	adult	stat	15		Aroclor 1260	48 h - LC_{50}	> 10	
	adult	stat	15		Aroclor 1262	48 h - LC_{50}	> 10	
	adult	stat	15		Clophen A30	48 h - LC_{50}	3.0	
	adult	stat	15		Clophen A60	48 h - LC_{50}	> 10	
Eastern oyster *(Crassostrea virginica)*	adult	flow	28	28	Aroclor 1016	96 h - EC_{50}	0.01	Mayer (1987)
Brown shrimp *(Penaeus aztecus)*	adult	flow	30	29	Aroclor 1016	96 h - LC_{50}	0.01	Mayer (1987)

Table 28 (continued)

Organism	Size/age	Stat/ flow[a]	Temperature (°C)	Salinity (‰)	PCB type	Parameter	Concentration (mg/litre)	Reference
Brown shrimp *(Crangon crangon)*	adult	stat	15		Clophen A60	48 h - EC_{50}	> 10	Portmann & Wilson (1971)
	adult	stat	15		Aroclor 1242	48 h - LC_{50}	1.0	
	adult	stat	15		Aroclor 1248	48 h - LC_{50}	0.3-1.0	
	adult	stat	15		Aroclor 1254	48 h - LC_{50}	3.0-10.0	
	adult	stat	15		Aroclor 1260	48 h - LC_{50}	> 10	
	adult	stat	15		Aroclor 1262	48 h - LC_{50}	> 10	
	adult	stat	15		Clophen A40	48 h - LC_{50}	0.3-1.0	
	adult	stat	15		Clophen A30	48 h - LC_{50}	1.0-3.3	
	adult	stat	15		Clophen A50	48 h - LC_{50}	3.3-10.0	

Table 28 (continued)

Grass shrimp	1 day	stat	25	25	Aroclor 1016	96 h - LC_{50}	0.15	Mayer (1987)
(Palaemonets	3 days	stat	25	25	Aroclor 1016	96 h - LC_{50}	0.021	
pugio)	6 days	stat	25	25	Aroclor 1016	96 h - LC_{50}	0.017	
	9 days	stat	25	25	Aroclor 1016	96 h - LC_{50}	0.019	
	12 days	stat	25	25	Aroclor 1016	96 h - LC_{50}	0.021	
	15 days	stat	25	25	Aroclor 1016	96 h - LC_{50}	0.024	
	18 days	stat	25	25	Aroclor 1016	96 h - LC_{50}	0.037	
	30 days	stat	25	25	Aroclor 1016	96 h - LC_{50}	0.044	
	adult	stat	25	25	Aroclor 1016	96 h - LC_{50}	0.052 (0.046-0.057)	
	adult	flow	30	28	Aroclor 1016	96 h - LC_{50}	0.012	
	1 day	stat	25	25	Aroclor 1242	96 h - LC_{50}	0.015	
	3 days	stat	25	25	Aroclor 1242	96 h - LC_{50}	0.019	
	6 days	stat	25	25	Aroclor 1242	96 h - LC_{50}	0.015	
	9 days	stat	25	25	Aroclor 1242	96 h - LC_{50}	0.017	
	12 days	stat	25	25	Aroclor 1242	96 h - LC_{50}	0.016	
	15 days	stat	25	25	Aroclor 1242	96 h - LC_{50}	0.024	
	18 days	stat	25	25	Aroclor 1242	96 h - LC_{50}	0.034	
	30 days	stat	25	25	Aroclor 1242	96 h - LC_{50}	0.041	
	adult	stat	25	25	Aroclor 1242	96 h - LC_{50}	0.057 (0.048-0.062)	

[a] stat = static conditions: water not changed during the exposure; flow = flow-through conditions; concentration of toxicant continuously maintained.

7.2.2.1 Short- and long-term toxicity

Roberts (1975) exposed the common mussel (*Mytilus edulis*) to Aroclors 1242 and 1254 and studied byssus formation. The 24- and 48-h EC_{50}s for a reduction in the number of mussels byssally-attaching were 2.2 and 3.0 mg/litre, respectively, for Aroclor 1254. EC_{50}s after exposure to Aroclor 1242 were 0.9 mg/litre for 24 h and 1.0 mg/litre for 48 h. Duke et al. (1970) maintained oysters (*Crassostrea virginica*) at concentrations of 1, 10, and 100 µg Aroclor 1254/litre and monitored shell growth over a period of 96 h; the rates of shell growth were decreased by 19, 41, and 100%, respectively. Lowe et al. (1972) found the growth rate (height and wet weight) of young oysters (*Crassostrea virginica*) to be significantly reduced after exposure, in flowing sea water, to 5 µg Aroclor 1254/litre, for 24 weeks. No effects on growth were observed at 1 µg/litre over a period of 30 weeks. Oysters exposed to 5 µg/litre showed atrophy of the digestive diverticular epithelium and degeneration of the vesicular connective tissues of the hepatopancreas together with leukocytic infiltration. There was complete tissue recovery after 12 weeks in clean water.

After exposing *Daphnia magna* to Aroclor 1254, over a period of 14 days under static renewal procedures, Maki & Johnson (1975) calculated an LC_{50} of 24 µg/litre.

Nebeker & Puglisi (1974) calculated 3-week LC_{50} values, under static conditions, for a range of Aroclors on *Daphnia magna*. Aroclors were dissolved in acetone and triton X100 to maintain the PCBs in solution. Tests were performed in raw Lake Superior water. Results are presented in Table 29. The Aroclors most toxic for *Daphnia* had between 48 and 62% chlorination; the most toxic Aroclor was 1248. Under flow-through conditions, renewing the original test concentration of the Aroclor continuously, the Aroclors were much more toxic. Two-week LC_{50} values for Aroclors 1248 and 1254 were 2.6 and 1.8 µg/litre, respectively, while the 3-week LC_{50} for Aroclor 1254 was 1.3 µg/litre. Groups of 40 scud (*Gammarus pseudolimnaeus*) were exposed to various concentrations of Aroclor 1242 under flow-through conditions. No animals survived exposure for 2 months, at Aroclor concentrations of 26 µg/litre or more.

Table 29. Toxicity of various Aroclors for *Daphnia magna* in static tests[a]

Aroclor	3-week LC_{50} (μg/litre)	Confidence limits (95%)
1221	180	(158.0-205.0)
1232	72	(62.6-82.8)
1242	67	(55.4-81.0)
1248	25	(21.4-29.2)
1254	31	(25.8-37.2)
1260	36	(27.7-46.8)
1262	43	(37.0-49.9)
1268	253	(222.0-288.0)

[a] From: Nebeker & Puglisi (1974).

Survival at lower exposures was 52% at 8.7 μg/litre and 77% at 2.8 μg/litre (control survival was low at 48%).

Duke et al. (1970) conducted acute, flowing-water bioassays on pink shrimp (*Penaeus duorarum*). At 0.1 mg/litre, 100% of the shrimps were killed within 48 h of exposure to Aroclor 1254. There was no mortality after 48 h of exposure to 0.01 mg/litre Aroclor. In long-term flowing-water bioassays, Nimmo et al. (1971a) found that Aroclor 1254, at a concentration of 0.94 μg/litre killed 51% of juvenile pink shrimps within 15 days. Juveniles were found to be more sensitive than adults; 50% of adults were killed after exposure to 3.5 μg/litre over 35 days. There were no apparent symptoms of poisoning prior to death.

Striped hermit crabs (*Clibanarius vittatus*) were kept in static sea-water solutions containing 3, 5, 10, 15, 20, 25, or 30 μg/litre of Aroclor 1254 for 96 h (Stahl, 1979). No deaths were reported, though the crabs exposed to the higher concentrations (20, 25, and 30 μg/litre) were less active. Six crabs already exposed to 30 μg PCBs/litre were then placed in solutions containing 300 μg/litre for a further 96 h; there were still no deaths.

Vernberg et al. (1977) exposed fiddler crab (*Uca pugilator*) larvae to concentrations of 0.1, 1.0, 5, 10, 50, or 500 μg Aroclor 1254/litre, for 96 h. They did not find any effects on survival at 0.1 or 1.0 μg/litre; Aroclor 1254 at 5 μg/litre increased deaths by 20%, but

the increase was not statistically significant. Exposure to 10 μg PCBs/litre resulted in a 57% reduction in survival of larvae. Increasing the PCB concentration to 50 μg/litre did not greatly increase the effect. The 500 μg/litre concentration killed all larvae. Increasing exposure time, at 5 μg/litre, produced a significant reduction in survival after 14 days. Exposure of larvae to Aroclors 1016 or 1254 at 0.1, 1, or 5 μg/litre for periods of up to 168 h, was then investigated. No significant effects were found on survival with any concentration of Aroclor 1016, for up to 120 h of exposure. After 168 h, survival rates of larvae exposed to 1 and 5 μg/litre were reduced to 61 and 66%, respectively. There was no effect at 0.1 μg/litre. Aroclor 1254 did not have any effects on survival at concentrations of 0.1 or 1 μg/litre. Survival was reduced after exposure to 5 μg Aroclor 1254/litre for more than 96 h, increasing from 60–81% up to 168 h. Exposure to 10 μg Aroclor 1254/litre caused 55% deaths after 120 h; there were no further deaths after 168 h. Fifty per cent of adult male crabs, exposed to Aroclor 1254 or Aroclor 1016 at 50 μg/litre, died after 2 days and after 4–6 days, respectively. Females (50%) exposed to 50 μg/litre survived for 7 days after exposure to Aroclor 1016 but for only 4 days after exposure to Aroclor 1254.

Neff & Giam (1977) exposed juvenile horseshoe crabs (*Limulus polyphemus*) to concentrations of Aroclor 1016 of 10, 20, 40, or 80 μg/litre, for up to 96 days. The crabs were divided into 2 groups: group A consisted of juveniles at the late first tailed stage and group B, of juveniles at the early second tailed stage. The authors calculated LT_{50}s (LT_{50}: median survival time for a given exposure concentration) of 20.8 days at 40 μg/litre and 20.3 days at 80 μg/litre for group A juveniles. The LT_{50} for group B crabs at 80 μg/litre was 61 days, but less than 50% had died within 96 days at 40 μg/litre.

7.2.2.2 Response to temperature and salinity

In a study by Vernberg et al. (1977), larval fiddler crabs (*Uca pugilator*) were exposed to "sub-lethal" concentrations of Aroclor 1254 and 1016 and the conditions of temperature (15–30 °C) and salinity (15–36°/oo) varied. Exposure to 0.01 μg Aroclor/litre showed no consistent effects of temperature or salinity, though the organisms exposed under conditions furthest from the optimum

(25 °C and 30°/oo) were more likely to differ significantly from the controls. At the optimum temperature and salinity, no deaths were recorded in adult crabs exposed to 0.1, 1, 10, or 100 μg Aroclor 1254/litre for up to 3 weeks. Lowering the salinity or increasing the temperature did not have any effects on survival with Aroclor 1254 or 1016 at 5 μg/litre. Lowering both salinity and temperature (to 5°/oo and 10 °C) caused 50% of crabs to die between 21 and 28 days of exposure to Aroclor 1016 at 5 μg/litre, but there were no lethal effects of Aroclor 1254 at the same concentration. Lowering the temperature further (7 °C and 5°/oo) reduced the 50% survival time to between 5 and 8 days for both Aroclors.

Nimmo & Bahner (1974) reported some deaths in adult brown shrimp (*Penaeus aztecus*) exposed to a "sub-lethal" concentration of Aroclor 1254 (3 μg/litre), for 7 days, after subjection to salinity shock. The shrimp normally adapts readily to the wide range of salinity found in its natural estuarine habitat. Roesijadi et al. (1976a) exposed the adult grass shrimp (*Palaemonetes pugio*) to sub-lethal (6.3–8.8 μg/litre) and lethal (57.6–76.4 μg/litre) concentrations of Aroclor 1254 for 96 h, at various salinities. They found little effect on haemolymph chloride concentration or osmolarity, chloride space (the apparent volume of distribution of chloride ions), or chloride exchange kinetics. The shrimp showed an adaptive altered permeability to chloride ions at a salinity of 17°/oo, the isotonic point. PCBs did not affect this permeability change in adult shrimp. In the juvenile grass shrimp, there was a reduction in haemolymph chloride levels at low salinities in non-steady state exposures; the PCBs delayed the permeability change. This disruption of haemolymph chloride was associated with high numbers of deaths, even at the "sub-lethal" exposure concentration. It was concluded that juveniles died from salinity shock, because of delayed adaptive response. In another study (Roesijadi et al., 1976b), grass shrimp were exposed to Aroclor 1254 at 29.4 μg/litre for 96 h at various salinities. No appreciable effect was observed on total free amino acid levels in abdominal muscle, indicating that intracellular osmoregulation was not a major consequence of PCB toxicity, though changes in individual amino acid concentrations suggested an altered metabolic state. The authors found that blood glycine levels showed large decreases after the

transfer of the shrimps to clean water, a delayed response to the Aroclor exposure.

7.2.2.3 Reproduction

Sea urchin (*Arbacia punctulata*) eggs were exposed to concentrations of Aroclor 1254 of 0.5, 1.0, 5.0, and 10.0 mg/litre (Adams, 1983). There was no effect on percentage fertilization, percentage pluteus development, or percentage mortality when eggs were exposed at fertilization. However, when eggs were exposed 1 h prior to fertilization, there was a significant reduction in fertilization efficiency at all doses. At all but the lowest dose, there was a significant increase in mortality and a significant depression in successful pluteus development.

Maki & Johnson (1975) calculated EC_{50}s for total young produced, average brood size, and percentage of days reproducing, during a 14-day exposure of *Daphnia magna* to Aroclor 1254; the results were 19, 23, and 25 µg/litre, respectively. *Daphnia magna* were exposed to a range of Aroclors, by Nebeker & Puglisi (1974) who estimated reproductive impairment, measured as a percentage of surviving young relative to controls. The study was conducted over 3 weeks under static conditions. Results are presented in Table 30. Reproductive impairment matches lethality of the Aroclors (see Table 29);

Table 30. Reproductive impairment of *Daphnia magna* exposed to Aroclors under static conditions[a]

Aroclor	Concentration (µg/litre) producing reproductive impairment	
	50%	16%
1221	125	89
1232	66	53
1242	63	48
1248	24	16
1254	28	18
1260	33	22
1262	41	24
1268	206	162

[a] From: Nebeker & Puglisi (1974).

there was no indication of reproductive effects of the Aroclors at concentrations below those leading to the death of adults or young. No young were produced by scud (*Gammarus pseudolimnaeus*) exposed to 8.7 μg Aroclor 1242/litre. Scud exposed at 2.8 μg/litre produced fewer young per surviving adult (4.2), compared with controls (6.8).

7.2.2.4 Moulting

Several authors have suggested that crustaceans may be more susceptible to the toxic effects of PCBs during moult (Duke et al., 1970; Wildish, 1970; Nimmo et al., 1971a,b). Fingerman & Fingerman (1979) exposed 2 groups of fiddler crabs (*Uca pugilator*) at 8 mg Aroclor 1242/litre, one group for 40 days, and the other for only the first 14 of the 40 days. Eye-stalks were removed on day 15 to increase moulting activity. Controls underwent rapid ecdysis, with more than 50% of the population completing moult within 40 days. Crabs exposed to the Aroclor for the full 40 days showed less moulting, with no more than 10% of the population completing moult. Crabs exposed for 14 days showed 20% of the population successfully moulting. Removal of eye-stalks on day 1 of the study produced similar results, in terms of numbers of crabs moulting in each treatment, but speeded-up moult in the controls. No more Aroclor-exposed crabs moulted after eye-stalk removal. In an earlier study, Fingerman & Fingerman (1977) exposed fiddler crabs to Aroclor 1242 at 8 mg/litre for 38 days. Either eye-stalks or 4 walking legs were removed to stimulate moulting. Both control groups underwent ecdysis rapidly. Treated crabs without eye-stalks did not undergo any moult. Moulting in those with legs removed was much slower than in the controls. The authors also exposed crabs to dibenzofuran (1,2,3,4,5,6,7,8-octachlorodibenzofuran) at 16 ng/litre. This is equivalent to the maximum reported dibenzofuran contamination of the Aroclor with the dose equivalent to (in terms of the dibenzofuran) the same concentration (8 mg/litre) in the PCB mixture. There was only a slight inhibition of moulting caused by the dibenzofuran.

Neff & Giam (1977) exposed juvenile horseshoe crabs (*Limulus polyphemus*) to concentrations of Aroclor 1016 of 10, 20, 40, or 80 μg/litre, for up to 96 days. The crabs were divided into 2 groups: group A consisted of juveniles at the late first tailed stage and group B

of juveniles at the early second tailed stage. ET_{50}s (median time for moulting to begin) were calculated between the start of the study and the first moult (ET_{50}-1) and between subsequent moults (ET_{50}-2 to -n). No moult occurred within 96 days at concentrations of Aroclor of 40 or 80 μg/litre in either group of crabs. The ET_{50}-1, in group A at 10 and 20 μg/litre, was not different from controls; the ET_{50}-2 was slightly decreased. In group B, 10 and 20 μg/litre did not affect the ET_{50}-1; 40 and 80 μg/litre delayed the onset of the first moult by 7 and 9 days, respectively. The ET_{50}-3 were substantially decreased at 10, 20, and 40 μg Aroclor/litre.

7.2.2.5 Behaviour

Hansen et al. (1974a) studied the avoidance response of the pink shrimp (*Penaeus duorarum*) and the grass shrimp (*Palaemonetes pugio*) given a choice between clean water and water containing Aroclor 1254, at concentrations of between 0.001 and 10 mg/litre. Pink shrimp did not avoid any of the concentrations used; grass shrimp only significantly avoided the highest dose.

7.2.2.6 Population structure

The composition of communities of estuarine animals, in aquaria, were studied under different exposures to Aroclor 1254 (0.1, 1.0, and 10.0 μg/litre) for 4 months (Hansen, 1974). The author found that, in control groups and the group at the lowest concentration, the community was mainly comprised (>75%) of arthropods, mostly the amphipod *Corophium volutator*. At 1 and 10 μg Aroclor 1254/litre, the numbers of arthropods decreased and the numbers of chordates increased; at 10 μg/litre, over 75% of the animals were tunicates. The highest concentration of Aroclor decreased the numbers of phyla, species, and individuals represented (particularly of amphipods, bryozoans, crabs, and molluscs), whereas the numbers of annelids, brachypods, coelenterates, echinoderms, and nemertines were unaffected.

7.2.2.7 Interactions with other chemicals

Maki & Johnson (1975) exposed *Daphnia magna* to various combinations of DDT (0.2–0.75 μg/litre) and Aroclor 1254 (2–24 μg/litre).

They studied adult mortality, total young produced, average brood size, and percentage days reproducing, during a 14-day exposure period. The effects of one toxicant significantly enhanced the action of the other for all test parameters. In the presence of a no-observed-effect level of PCB (12 μg/litre), the susceptibility of *Daphnia* to DDT increased by one third. When combined with 0.5 μg DDT/litre, the toxicity of Aroclor 1254 was doubled.

In a study by Nimmo & Bahner (1976), the pink shrimp (*Penaeus duorarum*) was exposed to various combinations of Aroclor 1254 (0.7–1.1 μg/litre), cadmium (640–829 μg/litre), and methoxychlor (0.9–1.0 μg/litre) and numbers of shrimps dying were monitored. The results showed no evidence of synergism or potentiation in any combination.

7.2.3 Fish

The acute toxicity of PCBs for fish is summarized in Table 31. Values for 96-h LC_{50}s vary between 0.008 mg/litre, for the fry of the fathead minnow, to > 100 mg/litre for channel catfish. This considerable variation is dependent on species and on the PCB mixture but appears to depend little on test conditions, such as temperature and water hardness. The toxicity of PCBs appears much greater in flow-through tests, where the water concentration of the PCBs is constantly maintained.

MATC (maximum acceptable toxicant concentrations) were set by the US EPA (1980) and are expressed as a range between the no-observed-effect level (based on the results of long-term studies and the sub-lethal as well as the lethal effect) and the lowest concentration showing a measurable effect. These values, for the fathead minnow, were 5.4 and 15.0 μg/litre for Aroclor 1242; 0.1 and 0.4 μg/litre for Aroclor 1248; 1.8 and 4.6 μg/litre for Aroclor 1254, and 1.3 and 4.0 μg/litre for Aroclor 1260. The early life stage of the estuarine sheepshead minnow gave values of 3.4 and 15.0 μg/litre for Aroclor 1016 and 0.06 and 0.16 μg/litre for Aroclor 1254.

Table 31. Acute toxicity of PCB and PCT mixtures for fish

Organism/ reference	Size/ age	Stat/ flow[a]	Tem- perature	Alkali- nity[b] (°C)	Hard- ness[b]	pH	PCB type	Parameter	Concentration (mg/litre)
Channel catfish	0.60 g	stat	20		40	7.4	Aroclor 1016	96-h LC_{50}	>100
(*Ictalurus*	yolk-sac	stat	25		272	7.4	Aroclor 1016	96-h LC_{50}	0.44 (0.34-0.56)
punctatus)	2.80 g	flow	17		272	7.4	Aroclor 1242	96-h LC_{50}	>0.10
Mayer &	2.80 g	flow	22		272	7.4	Aroclor 1248	96-h LC_{50}	>0.1
Ellersieck	2.80 g	flow	22		272	7.4	Aroclor 1254	96-h LC_{50}	>0.20
(1986)	2.80 g	flow	22		272	7.4	Aroclor 1260	96-h LC_{50}	>0.40
Atlantic salmon (*Salmo salar*) Mayer & Ellersieck (1986)	5.60 g	flow	17		314	7.6	Aroclor 1016	96-h LC_{50}	0.13 (0.11-0.16)
Brook trout (*Salvelinus fontinalis*) Mayer & Ellersieck (1986)	3.0 g	flow	12		314	7.6	Aroclor 1016	96-h LC_{50}	>0.80
Brown trout	4.60 g	flow	12		314	7.6	Aroclor 1016	96-h LC_{50}	0.14 (0.11-0.18)
(*Salmo trutta*)	1.10 g	stat	13		44	7.4	Aroclor 1260	96-h LC_{50}	> 24.0
Mayer & Ellersieck (1986)									

Table 31 (*continued*)

Organism/ reference	Size/ age	Stat/ flow[a]	Tem- perature	Alkali- nity[b] (°C)	Hard- ness[b]	pH	PCB type	Parameter	Concentration (mg/litre)
Cutthroat trout	2.70 g	stat	9	159	162	7.4	Aroclor 1221	96-h LC_{50}	1.17 (0.96-1.43)
(*Salmo clarki*)	2.20 g	stat	9	159	162	7.4	Aroclor 1232	96-h LC_{50}	2.5 (1.72-3.08)
Mayer &	2.40 g	stat	9	159	162	7.4	Aroclor 1242	96-h LC_{50}	5.42 (3.82-7.68)
Ellersieck	2.50 g	stat	9	159	162	7.4	Aroclor 1248	96-h LC_{50}	5.75 (5.1-6.5)
(1986)	2.50 g	stat	9	159	162	7.4	Aroclor 1254	96-h LC_{50}	42.5 (38.7-46.7)
	2.70 g	stat	9	159	162	7.4	Aroclor 1260	96-h LC_{50}	60.9 (55.4-67.0)
	2.40 g	stat	9	159	162	7.4	Aroclor 1262	96-h LC_{50}	> 50
	2.20 g	stat	9	159	162	7.4	Aroclor 1268	96-h LC_{50}	> 50
	2.70 g	stat	9		162	7.4	Aroclor 4465	96-h LC_{50}	> 65
	2.10 g	stat	9		162	7.4	Aroclor 5442	96-h LC_{50}	> 50
	2.90 g	stat	9		162	7.4	Aroclor 5460	96-h LC_{50}	> 50
Lake trout	fry	stat	10		170	7.2	Aroclor 1016	96-h LC_{50}	0.48 (0.39-0.60)
(*Salvelinus namaycush*)	yolk-sac	stat	10		170	7.2	Aroclor 1016	96-h LC_{50}	0.89 (0.69-1.15)
Mayer & Ellersieck (1986)									

Table 31 (*continued*)

Organism/ reference	Size/ age	Stat/ flow[a]	Tem- perature	Alkali- nity[b] (°C)	Hard- ness[b]	pH	PCB type	Parameter	Concentration (mg/litre)
Rainbow trout	0.50 g	stat	12		44	7.4	Aroclor 1016	96-h LC_{50}	0.14 (0.11-0.16)
(*Salmo gairdneri*)	2.50 g	flow	10		272	7.4	Aroclor 1016	96-h LC_{50}	0.62 (0.42-0.90)
Mayer &	fry	flow	12		314	7.6	Aroclor 1016	96-h LC_{50}	0.44 (0.37-0.53)
Ellersieck	1.80 g	flow	17		272	7.4	Aroclor 1242	120-h LC_{50}	0.07
(1986)	1.80 g	flow	17		272	7.4	Aroclor 1248	120-h LC_{50}	0.05
	1.80 g	flow	17		272	7.4	Aroclor 1254	120-h LC_{50}	0.14
	1.80 g	flow	17		272	7.4	Aroclor 1260	96-h LC_{50}	>0.23
Harlequin fish	10-30 mm		flow	20	20	8.1	Aroclor 1221	96-h LC_{50}	1.05
(*Rasbora*	10-30 mm		flow	20	20	8.1	Aroclor 1232	96-h LC_{50}	0.32
heteromorpha)	10-30 mm		flow	20	20	8.1	Aroclor 1242	96-h LC_{50}	0.37
Tooby et al.	10-30 mm		flow	20	20	8.1	Aroclor 1254	96-h LC_{50}	1.1
(1975)	10-30 mm		flow	20	20	8.1	Aroclor 1262	96-h LC_{50}	>100
Bluegill sunfish	0.90 g	stat	12		44	7.4	Aroclor 1016	96-h LC_{50}	0.60
(*Lepomis*	1.80 g	flow	20		272	7.4	Aroclor 1016	96-h LC_{50}	0.46 (0.39-0.54)
macrochirus)	2.20 g	flow	17		272	7.4	Aroclor 1242	120-h LC_{50}	0.13
Mayer &	0.80 g	stat	18		44	7.1	Aroclor 1248	96-h LC_{50}	0.69 (0.48-0.99)
Ellersieck	2.20 g	flow	22		272	7.4	Aroclor 1248	120-h LC_{50}	0.14
(1986)	0.80 g	stat	18		44	7.1	Aroclor 1254	96-h LC_{50}	2.74 (1.29-5.81)
	2.20 g	flow	22		272	7.4	Aroclor 1254	96-h LC_{50}	0.20
	2.20 g	flow	22		272	7.4	Aroclor 1260	96-h LC_{50}	0.40

Table 31 (*continued*)

Organism/ reference	Size/ age	Stat/ flow[a]	Tem- perature	Alkali- nity[b] (°C)	Hard- ness[b]	pH	PCB type	Parameter	Concentration (mg/litre)
Longnose sucker (*Catostomus catostomus*) Mayer & Ellersieck (1986)	finger	flow	12		314	7.5	Aroclor 1016	96-h LC_{50}	0.33 (0.22-0.49)
Yellow perch	1.20 g	flow	17		314	7.6	Aroclor 1242	96-h LC_{50}	>0.15
(*Perca flavescens*)	1.10 g	flow	17		314	7.6	Aroclor 1248	96-h LC_{50}	>0.1
Mayer &	1.00 g	flow	17		314	7.6	Aroclor 1254	96-h LC_{50}	>0.15
Ellersieck	1.20 g	flow	17		314	7.6	Aroclor 1260	96-h LC_{50}	>0.20
(1986)									
Fathead minnow	fry	flow	24				Aroclor 1254	96-h LC_{50}	0.008
(*Pimephales*	fry	flow	24				Aroclor 1242	96-h LC_{50}	0.015
promelas)	3 months	flow	24				Aroclor 1242	96-h LC_{50}	0.30
Nebeker et al. (1974)									
Cisco (chub)	22 days	flow	7	30-35	40-48		Aroclor 1254	96-h LC_{50}	>10
(*Coregonus* sp.)	22 days	flow	7	30-35	40-48		Aroclor 1254	120-h - LC_{50}	3.2 (1.9-5.5)
Passino & Kramer (1980)									

Table 31 (*continued*)

Organism/ reference	Size/ age	Stat/ flow[a]	Tem- perature (°C)	Alkali- nity[b]	Hard- ness[b]	pH	PCB type	Parameter	Concentration (mg/litre)
Carp (*Cyprinus carpio*) Kimura et al. (1974)	fry	stat	23-25				Kanechlor 300	96-h LC_{50}	1.45
Guppy (*Lebistes reticulatus*) Kimura et al. (1974)	fry	stat	24-25				Kanechlor 300	96-h LC_{50}	0.9
	0.35 g	stat	24-25				Kanechlor 300	96-h LC_{50}	3.2

[a] stat = static conditions: water not changed during the exposure;
flow = flow-through conditions; concentration of toxicant continuously maintained.
[b] Alkalinity and hardness expressed as mg/litre $CaCO_3$, unless otherwise stated.

7.2.3.1 Short- and long-term toxicity

The toxicity of Aroclors for 3 species of freshwater fish, over exposure periods of up to 30 days, was systematically investigated by Mayer et al. (1977) under flow-through conditions. Results are presented in Table 32. Short-term tests consistently underestimate the toxicity of PCBs.

Table 32. Toxicity of Aroclors for fish (LC_{50}s in μg/litre) at 17 °C[a]

Aroclor	Exposure (days)					
	5	10	15	20	25	30
Rainbow trout						
1242	67	48	18	10	12	-
1248	54	38	16	6.4	3.4	-
1254	-	160	64	39	27	-
1260	-	326	143	78	49	51
Bluegill sunfish						
1242	-	-	164	125	120	84
1248	136	115	111	106	100	78
1254	-	-	303	260	239	177
1260	-	-	-	-	-	400
Channel catfish						
1242	-	-	219	150	132	87
1248	-	121	121	115	104	75
1254	-	303	286	293	181	139
1260	-	535	482	512	465	433

[a] From: Mayer et al. (1977)

Duke et al. (1970) kept juvenile pinfish (*Lagodon rhomboides*) in seawater containing 1, 10, or 100 μg Aroclor 1254/litre for up to 48 h. There were no deaths at any concentration. It was suggested by Nimmo et al. (1975) that acute toxicity tests underestimated the true sensitivity of marine species; in bioassays lasting 1 week or more, Aroclor proved to be 100 times more toxic than acute exposure

suggested. In tests lasting 2 weeks or longer, Aroclor 1254 was lethal for longnose killifish (*Fundulus similis*) at 1 μg/litre and for pinfish and spot (*Leiostomus xanthurus*) at 5 μg/litre. Hansen et al. (1974b) did not find any significant lethal effects in pinfish exposed to 100 μg Aroclor 1016/litre for 96 h but significant mortality (50%) was observed after 33 days at 32 μg/litre, and, after 18 days, at 100 μg/litre. Nebeker et al. (1974) exposed the flagfish (*Jordanella floridae*) to Aroclor 1248 for 40 days. No fish survived at a concentration of 18 μg/litre and only 35% survived at 5.1 μg/litre. The fish at these two concentrations almost completely lost their fins and tails. Fish survival was not affected at concentrations of 2.2 μg/litre or less. In a study by Defoe et al. (1978), fathead minnow (*Pimephales promelas*) larvae were exposed, in flow-through bioassays, to Aroclors 1248 and 1260 for 30 days; the LC_{50}s were calculated to be 4.7 and 3.3 μg/litre, respectively.

Hansen et al. (1976a) fed fingerling channel catfish (*Ictalurus punctatus*) a diet containing 20 mg Aroclor 1242/kg for 20 weeks. The fish showed a reduced weight gain and hypertrophy of the liver. When the treated fish were transferred to a control diet for 8 weeks and then back to the dosed diet for a further 8 weeks, weight gain and liver weights returned to normal levels. No histopathological lesions were observed in any of the fish fed PCBs.

Rainbow trout (*Salmo gairdneri*) were fed a diet containing 1, 10, or 100 mg Aroclor 1254/kg over a period of 330 days (Nestel & Budd, 1975). No effects on growth rates were seen, but renal lesions were observed at all doses; however, they were not dose-related. Foci of renal necrosis, with cellular or granular cast formation were seen. A significant increase in the number of hepatocytes per unit area in the liver was observed at all doses and appeared to be dose-related. A reduction of 'white pulp' (lymphatic elements) in the spleen was observed at 10 and 100 mg/kg diet. Fish with renal necrosis also had reduced splenic white pulp and a reduced white cell count.

7.2.3.2 Carcinogenicity

Hendricks et al. (1977) studied the combined effects of Aroclor 1254 (100 mg/kg diet) and aflatoxin B_1 (6 mg/kg diet) in rainbow trout. A significantly reduced incidence of liver tumours was observed in

the combination. There was no retardation of growth in the treated animals, but they showed glycogen depletion in hepatocytes, hyperaemia, and white pulp depletion in the spleen.

PCB administration prior to aflatoxin B_1 treatment also decreased the liver tumour incidence, whereas when Aroclor 1254 was fed after exposure of trout embryo to aflatoxin B_1, there was no effect on the formation of liver tumours (Shelton et al., 1984b).

When rainbow trout were fed 0, 1, 4, or 8 mg aflatoxin B_1/kg diet or aflatoxin B_1 at these dose levels plus 50 mg Aroclor 1254/kg diet, the incidence of hepatic tumours was lower in the groups receiving aflatoxin combined with PCBs (Shelton et al., 1984a). The inhibition of aflatoxin B_1-mediated carcinogenicity was also correlated with the decreased bacterial mutagenicity of this compound in the presence of an Aroclor 1254-induced drug metabolizing enzyme fraction from fish. The potential mechanisms of this interaction were further investigated by Shelton et al. (1986) by studying the effects of Aroclor 1254 on aflatoxin B_1 distribution, metabolism, and adduct formation. The results from the *in vivo* studies showed that PCB treatment resulted in a marked increase in the metabolism of aflatoxin B_1 to aflatoxin M_1 and their glucuronide conjugates. The DNA-adduct levels in the PCB-treated fish were 48–96% lower than those in the controls. The results in the fish model using aflatoxin B_1 as the carcinogen were associated with the activity of Aroclor as an inducer of cytochrome P-450-dependent monooxygenases (Halverson et al., 1985; Shelton et al., 1986).

7.2.3.3 Effects on developmental stages and reproduction

Birge et al. (1978) determined LC_{50}s and LC_1s for 4 species of fish from the fertilization of the eggs to 4 days after hatching. Exposure times varied with species dependent on the time taken to hatching of the eggs; hatching took 22 days for rainbow trout and 3–4 days for the other species. In most species, eggs were considerably less sensitive to the toxic effects of Aroclors than larvae. The major exception was the rainbow trout for which the duration of exposure of the eggs until hatching was considerably longer than for other species. LC_{50}s ranged from 0.32 to 11.16 μg/litre for the 4 species (up to 4 days after hatching) and 4 different PCB mixtures; LC_1s

ranged from 0.009 to 0.26 μg/litre. Results are presented in Table 33. The rainbow trout was the most sensitive species tested.

Adult minnows (*Phoxinus phoxinus*) were fed Clophen A50 at 20, 200, or 2000 mg/kg diet (on a dry weight basis), for 40 days (Bengtsson, 1980). Growth was monitored from day 46 to day 79; a significant increase in growth (relative to controls) was seen in fish fed the highest dose. Other doses caused increases in growth, but these were not significant. Stimulated growth had been observed in previous studies with minnows fed Clophen A50 at 0.88–78 mg/kg diet (Bengtsson, 1979). Between days 127 and 166, the swimming performance of the fish was tested using a rotary flow technique. Although the PCBs impaired swimming performance, this was not statistically significant. Reproduction was monitored from day 235 (first day of spawning) to day 300. Spawning was delayed in the treated groups by 1 day, 1 week, and 3 weeks for the 3 treatments (20, 200, and 2000 mg/kg diet), respectively. Only the highest dose affected hatchability of eggs, which was reduced by approximately 80%.

Snarski & Puglisi (1976) did not find any adverse effects on survival, growth, or reproduction of brook trout (*Salvelinus fontinalis*) exposed to concentrations of Aroclor 1254 of up to 0.94 μg/litre, for 71 weeks. Survival and growth of alevin-juveniles from exposed parents were unaffected for up to 90 days.

Continuous-flow bioassays were conducted over 8 months on fathead minnow (*Pimephales promelas*), exposing the fish to either Aroclor 1242 or 1254 (Nebeker et al., 1974). Reproduction occurred at, and below, 5.4 μg Aroclor 1242/litre, but spawning and egg production were very variable. With Aroclor 1254, reproduction occurred at, and below, 1.8 μg/litre. Spawning occurred at 1.8 μg/litre, but was significantly less than spawning at the lower concentrations of 0.23 and 0.52 μg/litre. Egg hatchability and fry survival were good at 1.8 μg/litre. Eggs were more resistant than fry at 15 and 51 μg Aroclor 1242/litre; with Aroclor 1254 at a concentration of 15 μg/litre, eggs hatched readily, but all fry were dead within 96 h.

Halter & Johnson (1974) kept coho salmon (*Oncorhynchus kisutch*) eggs in solutions containing 4.4–56.4 μg Aroclor 1254/litre. Exposure continued for 2 weeks before, and 4 weeks after hatching,

Table 33. Toxicity of PCBs for the embryolarval stages of fish[a,b]

Organism	Aroclor 1016		Aroclor 1242		Aroclor 1254	
	LC_1 (μg/litre)	LC_{50} (μg/litre)	LC_1 (μg/litre)	LC_{50} (μg/litre)	LC_1 (μg/litre)	LC_{50} (μg/litre)
Channel catfish (*Ictalurus punctatus*)	0.08	11.16 (9.93-12.97)	0.14 (0.07-0.23)	4.24 (3.32-5.34)	0.05 (0.02-0.09)	1.76 (1.36-2.24)
Goldfish (*Carassius auratus*)	0.10	13.21 (10.63-16.43)	0.04 (0.01-0.08)	2.64 (1.89-3.61)	0.02 (0.01-0.04)	1.18 (0.84-1.61)
Rainbow trout (*Salmo gairdneri*)	0.011 (0.003-0.027)	1.08 (0.7-1.56)	0.01 (0.002-0.025)	1.03 (0.67-1.51)	0.009 (0.003-0.02)	0.32 (0.22-0.45)
Redear sunfish (*Lepomis microlophus*)	0.26 (0.1-0.51)	7.82 (5.74-10.35)	0.19 (0.08-0.35)	3.56 (0.65-4.66)	0.02 (0.01-0.04)	0.53 (0.39-0.7)

[a] From: Birge et al. (1978).

[b] Exposure under static conditions, but with water renewed every 12 h. Exposure was initiated 2–6 h after spawning (except for rainbow trout where exposure was initiated 15 min after fertilization) and continued to 4 days post-hatching. Hatching times varied: 22 days for rainbow trout (13.5–14.3 °C); 3 days for catfish (29–31 °C); 3–4 days for goldfish and sunfish (20–24 °C); hardness 90–115 mg/litre; pH 7.6–8.1.

until the young were alevins. Hatchability was reduced by 30% at the highest concentration of 56.4 μg/litre. Survival of alevins was markedly higher when eggs were transferred to clean water prior to hatching, but there was still 58% mortality in alevins hatched from eggs at the highest dose. When the alevins were exposed to the PCBs for 4 weeks after hatching, survival was inversely related to exposure concentration. No group survived as well as the controls (for example, 18% died at 4.4 μg/litre and 90% at 26 μg/litre, or more).

In a study by Defoe et al. (1978), fathead minnow (*Pimephales promelas*) were maintained in flow-through bioassays in solutions of Aroclors 1248 or 1260, for 240 days (a full life-cycle test). Reproduction occurred at all concentrations tested (up to 3 μg/litre for Aroclor 1248 and up to 2.1 μg/litre for Aroclor 1260). The authors concluded that PCBs did not produce major effects on reproduction at concentrations up to the 30-day LC_{50} and that reduced populations after long-term exposure are largely due to larval mortality.

Weis & Weis (1982) exposed eggs of the mummichog (*Fundulus heteroclitus*) to concentrations of Aroclor 1254 of 0.01–10 mg/litre (after cleavage had begun). No effect was found on embryonic development or hatching and embryonic mortality was negligible. Seven-day larval tests also showed no effect on mortality up to the highest concentration. However, the authors found approximately 20% larval mortality, when larvae were exposed to 5 mg/litre for 72 h, after hatching from eggs at the highest exposure concentration. In a second group of studies, eggs were exposed to 10 mg Aroclor 1242/litre; no malformations were found, though there was a consistent retardation of hatching. There was a positive correlation between hatching rate and female length (length being related to age). Larvae exposed to 5 mg/litre showed an average of 45% mortality within 72 h. Pre-exposure as eggs to 10 mg/litre greatly increased larval mortality; pre-exposure to 1 mg/litre resulted in an intermediate response. There was no mortality in control larvae, even when they had been pre-exposed as eggs.

Eggs of brook trout (*Salvelinus fontinalis*) were exposed to Aroclor 1254 (0.043–13 μg/litre) for 10 days before hatching, and the fry for 118 days after hatching (Mauck et al., 1978). Median hatching time, egg hatchability, and sac-fry survival were not affected by the PCBs.

Significantly decreased survival (32% survived) was seen after 48 days at 3 μg/litre. There was significant mortality of fry after 118 days with exposure to concentrations of 3.1 μg/litre and above. Growth of the trout, as measured by weight, was significantly decreased after 48 days at concentrations of 1.5 μg/litre or more. By the end of the study (118 days), no significant differences in weight were seen between surviving fry on different treatments. Analysis of the backbone composition at this time showed that hydroxyproline and phosphorus were significantly decreased by concentrations of 0.43 μg/litre or more and that, at 0.69 μg or more/litre, calcium levels were significantly increased. Although collagen was significantly decreased at 0.69, 3.1, and 6.2 μg/litre, it was unaffected at 1.5 μg/litre; no explanation for the anomaly was suggested.

Schimmel et al. (1974) exposed sheepshead minnow (*Cyprinodon variegatus*) eggs, immediately after fertilization, to Aroclor 1254 at concentrations of between 0.1 and 10 μg/litre. The fertility of eggs was unaffected. Hatching was significantly reduced (by 30%) only at the highest exposure. Survival of fry to 2 weeks was significantly reduced at concentrations of 0.32 μg/litre or above (30% survival at 0.32 μg/litre and 9% survival at 10 μg/litre). The 3-week LC_{50} for embryo-fry was calculated to be 0.93 μg/litre for Aroclor 1254. Many of the dying fish exhibited fin rot. Exposure of juveniles and adults to the same concentrations of the Aroclor produced 24% mortality in juveniles at the highest exposure rate and no mortality in adults. Some fin rot was seen in adults.

In another study, Hansen et al. (1975) exposed embryos, fry, juveniles, and adults of sheepshead minnow (*Cyprinodon variegatus*) to concentrations of Aroclor 1016 of 0.1–10 μg/litre, for 28 days, in intermittent flow bioassays. No effects on survival were observed during this period. When exposed to concentrations of 32 or 100 μg/litre, there was high mortality in eggs, juveniles, and adults; all were killed at 100 μg/litre. The authors calculated that the 28-day LC_{50}s for juveniles and adults were 20 and 19 μg/litre, respectively.

Freeman et al. (1982) fed Atlantic cod (*Gadus morrhua*) diets containing 1–50 mg Aroclor 1254/kg for 5.5 months. Altered steroid biosynthetic patterns *in vitro* were observed in the testes and head kidneys (adrenal equivalent) of dosed fish. Histological examination

revealed abnormalities in the testes, gills, and livers. Testicular abnormalities included derangement of lobules, hyperplasia of lobule walls, and disintegration and/or fatty necrosis of spermatogenic elements. In fish fed at dietary rates of 5–50 mg/kg, hyperplasia of the epithelial layer of the secondary lamellae of the gills was noted. Fatty degeneration of the liver was observed in all treated fish. Similar testicular abnormalities were observed by Sangalang et al. (1981), but only in sexually mature individuals or at a stage of rapid spermatogenic proliferation.

7.2.3.4 Physiological and biochemical effects

Coho salmon (*Oncorhynchus kisutch*) were fed diets containing a mixture of PCBs (1:4, Aroclor 1242:1254) at a concentration of 50 or 500 mg/kg dry feed (Leatherland & Sonstegard, 1978). Serum triiodothyronine (T3) levels were significantly reduced after 3 months, in fish fed the highest dose. Thyroxine (T4) levels were not affected. After 3 months, the T3:T4 ratio was significantly higher in fish fed the highest dose than in control and low-dose fish. Fish on 500 mg/kg had significantly lower body weights than controls by the end of the study. A mixture of 50 mg PCBs/kg and 5 mg mirex/kg significantly reduced serum triiodothyronine and thyroxine levels over a period of 3 months, but did not affect the T3:T4 ratio. Leatherland & Sonstegard (1979) fed rainbow trout (*Salmo gairdneri*) diets containing Aroclor 1254 at 500 mg/kg dry feed, for up to 2 months. The PCBs did not have any significant effects on thyroid histology or on serum thyroid hormone levels. Liver weights, total liver lipid content, and carcase lipid content were significantly greater in treated fish. Mayer et al. (1977) fed fingerling coho salmon (*Oncorhynchus kisutch*) 1.45–14 500 μg Aroclor 1254/kg body weight per day, for 260 days. Channel catfish (*Ictalurus punctatus*) were fed the same Aroclor at rates of 48 and 480 μg/kg body weight per day for 193 days. Thyroid activity (as measured by ^{125}I uptake) was significantly stimulated at dose rates of 14.5 μg/kg per day, and above, in coho salmon. Stimulation ranged from 52%, at 14.5 μg/kg per day, to 119%, at 14 500 μg/kg per day, compared with controls. In catfish, both dose rates of Aroclor 1254 caused significant increases in thyroid activity, whereas other Aroclors (1232, 1248, and 1260) did not have any significant effects on the thyroid at the

same dose rates. Folmar et al. (1982) injected yearling coho salmon (*Oncorhynchus kisutch*) intraperitoneally with a total of 150 μg Aroclor 1254/kg body weight (2 injections, 10 days apart), prior to smoltification. Over a 6-week period, the authors did not find any significant effects on gill Na-K ATPase activity. However, the PCBs did alter the normal developmental patterns of thyroxine; there was a delay in the normal increase in circulating thyroxine levels. Triiodothyronine levels were significantly elevated after approximately 3 weeks, but then fell to well below control levels after 6 weeks. Fish were transferred to seawater; there was no significant effect on the gill Na-K ATPase activity in the treated group, but there was a significant increase in mortality (6%). Ten per cent of fish, dosed with PCBs and placed in sea water containing No 2 fuel oil at 700 μg/litre, died; this was an additive effect.

Fingerman (1980) kept Gulf killifish (*Fundulus grandis*) in a seawater solution containing Aroclor 1242, 1254, or 1268 at 8 mg/litre, for up to 28 days. The author removed the lower half of the caudal fin to study fin regeneration. No significant effects were observed with either Aroclor 1242 or 1254. With Aroclor 1268, a significant decrease in regeneration rate was observed after 28 days, when the study was conducted in the spring, and after 7 days, in the autumn. No differences were found at other sampling times.

Rainbow trout (*Salmo gairdneri*) were administered capsules containing 0.173 g Aroclor 1254 every second day over a 6-day period (Kiessling et al., 1983). Two to 4 weeks after the last capsule, isolated gills were perfused. There was no significant difference in adrenergic response in the gill vascular bed and no significant difference in the "oxygen transfer factor" (% changes in oxygen in saline from dorsal aorta before, and after, addition of adrenaline). Similarly, there was no effect on muscle glycogen content.

Johansson et al. (1972) dosed brown trout (*Salmo trutta*) twice, 4 days apart, with 5 mg Clophen A50/kg body weight, either by capsule or by intramuscular injection. The fish were fed for 43 days, starved for 116 days, and fed again for another 87 days. Metabolic analysis of the fish was undertaken on day 43 and at the end of the study. A significant increase in body weight was noted at the end of the study, but not after 43 days. Blood glucose, muscle glycogen, and the

liver-somatic index (liver weight as a ratio of body weight), which had all increased significantly after 43 days, decreased significantly by the end of the study (compared with controls). Both haematocrit and haemoglobin levels had significantly decreased after 43 days but, by the end of the study, were not significantly different from those of the controls.

In a study by Camp et al. (1974), fingerling catfish (*Ictalurus punctatus*) were kept in water containing Aroclor 1254 at 8 mg/litre. There was a significant increase in the serum transaminase activity of the fish after 4 h. The cortisol content of the serum was depressed, but not significantly so. The sodium:potassium ratio was constant.

Merkins & Kinter (1971) exposed the killifish (*Fundulus heteroclitus*) to concentrations of Aroclor 1221 of 7.5, 25, or 75 mg/litre. No fish died, at the lowest concentration, over a period of 4 days; 50% died at 25 mg/litre within 24 h and 88% at 75 mg/litre, within the same period. Serum osmolality, and serum ion levels (Na and K) were then measured. Within 6 h at 75 mg/litre, blood osmolality significantly increased, but sodium and potassium ions in the blood were not affected. After 24 h at 75 mg/litre, there was also a significant increase in sodium ions, but no effects on potassium ions. None of these parameters were affected by exposure at 25 mg/litre for 24 h.

7.2.3.5 Behavioural effects

Fingerman & Russell (1980) exposed male Gulf killifish (*Fundulus grandis*) to Aroclor 1242 at 4 mg/litre for 24 h. A significant reduction in whole-brain levels of both noradrenalin and dopamine were reported over this period. The swimming activity of the fish was monitored by counting the number of times they crossed lines marked on the bottom of the tank within a 10-min period, after exposure to the Aroclor for 24 h. Activity was significantly increased and remained so for a further 2 days.

The avoidance response was studied by Hansen et al. (1974a) in the sheepshead minnow (*Cyprinodon variegatus*), the pinfish (*Lagodon rhomboides*), and the mosquitofish (*Gambusia affinis*), when given a choice between clean water and water containing Aroclor 1254 at 0.001, 0.01, 0.1, 1.0, or 10 µg/litre. Sheepshead minnow did not avoid any concentration; pinfish avoided only the highest

concentration of the Aroclor. Mosquitofish significantly avoided concentrations of 0.1, 1.0, and 10 μg/litre.

Peterson (1973) did not find any effect on temperature selection in Atlantic salmon (*Salmo salar*) exposed to 2 mg Aroclor 1254/litre, for 24 h prior to a horizontal temperature gradient test. Similarly, Miller & Ogilvie (1975) did not find any effect of Aroclor 1254 on temperature selection when brook trout (*Salvelinus fontinalis*) were exposed to a water concentration of 25–100 mg/litre, for 24 h, prior to temperature gradient tests. Even at a concentration of 100 mg/litre for 48 h, which was sufficient to cause some mortality, temperature selection was still unaffected.

7.2.3.6 Interactions with other chemicals

Halter & Johnson (1974) found that the median survival time for coho salmon (*Oncorhynchus kisutch*) fry, exposed to Aroclor 1254 at 32.2 μg/litre, was greater than 336 h. When fry were exposed to mixtures of Aroclor and DDT, for 2 weeks, the survival times were always similar to the more rapid reaction time found for DDT alone. The authors suggested that this indicated the lack of an additive effect.

7.2.4 Amphibians

Tadpoles (*Rana chensinensis*) were maintained in water containing PCBs (as Kanechlor 300) at 0.5, 5.0, 50, or 500 μg/litre. At the 2 highest doses, all individuals died rapidly. The time of onset of lethality was related to dose level; at 5 μg/litre, death occurred between 15 and 21 days, and, at 0.5 μg/litre, on the thirty-second day after first exposure. Growth at 0.5 and 5.0 μg/litre did not differ from that of controls. Tail abnormalities were found, but there was no correlation with PCB concentrations and a NOEL could not be established. The mechanism by which PCBs caused tail malformation was not known (Hasegawa, 1973).

Birge et al. (1978) conducted embryo-larval bioassays on 3 species of amphibia. Exposure to various PCBs was maintained from 2–6 h after spawning to 4 days after hatching, using static renewal procedures (Table 34). Toxicity increased with increasing chlorination, the leopard frog being the most sensitive species with an LC_{50} of 1.03 μg/litre after exposure to Aroclor 1254. The authors also

Table 34. Toxicity of PCBs for the tadpoles of amphibians[a,b]

Organism	Aroclor 1016		Aroclor 1242		Aroclor 1254		Capacitor 21	
	LC_1 (μg/litre)	LC_{50} (μg/litre)	LC_1 (μg/litre)	LC_{50} (μg/litre)	LC_1 (μg/litre)	LC_{50} (μg/litre)	LC_1 (μg/litre)	LC_{50} (μg/litre)
American toad (*Bufo americanus*)	0.35 (0.15-0.64)	7.16 (5.39-9.34)	0.03 (0.01-0.06)	2.71 (1.91-3.75)	0.02 (0.01-0.05)	2.02 (1.44-2.77)	0.21 (0.08-0.42)	9.97 (7.21-13.53)
Fowler's toad (*Bufo fowleri*)	0.18 (0.09-0.33)	27.72 (21.77-35.08)	0.22 (0.12-0.36)	12.09 (9.74-14.91)	0.07 (0.04-0.11)	3.74 (2.98-4.64)	0.55 (0.3-0.91)	28.02 (22.59-34.47)
Leopard frog (*Rana pipiens*)	0.1 (0.05-0.16)	6.19 (4.95-7.69)	0.04 (0.02-0.06)	2.13 (1.72-2.63)	0.02 (0.01-0.03)	1.03 (0.83-1.27)	0.03 (0.02-0.06)	2.87 (2.29-3.57)

[a] From: Birge et al. (1978).

[b] Exposure under static conditions, but with water renewed every 12 h. Exposure was initiated 2–6 h after spawning and continued to 4 days post-hatching. Hatching times varied between 3 and 4 days, therefore, exposure varied between 7 and 8 days. Temperature 20–24 °C; hardness 90–115 mg/litre; pH 7.6–8.1.

calculated an LC_1 value from the same study; the leopard frog and American toad were equally sensitive at 0.02 μg/litre. The eggs were much less sensitive to the PCBs than the hatched larvae, with LC_{50}s ranging from 3.5 to 250 μg/litre, for 3 different Aroclors and Capacitor 21, and 3 species of tadpole.

7.2.5 Aquatic mammals

Following-up on field reports of the reproductive effects of PCBs on seal reproduction (see section 7.4.4), Reijnders (1986) conducted a study on captive common seals (*Phoca vitulina*) fed fish contaminated with PCBs. The contaminated diet produced an average daily intake of PCBs of 1.5 mg compared with the control level of 0.22 mg/day. Twelve female seals were used as controls and 12 as the treated group. Blood samples were taken regularly and assayed for circulating steroid hormones progesterone and estradiol. Females were mated with undosed males. Of the 12 females in the control group, 10 became pregnant; all 12 ovulated. Only 4 females became pregnant out of the 12 fed the PCB-contaminated diet; again all 12 ovulated. Throughout the breeding cycle, no significant differences were found between the hormonal profiles of pregnant animals in the treated and control groups. No significant differences were observed in progesterone levels in the treated and control groups, despite the fact that many fewer treated females became pregnant. However, a rise in estradiol levels in non-pregnant females in the control group was not found in non-pregnant females in the treated group, suggesting a difference in non-pregnancy in treated females. The effects of PCBs occurred only late in the breeding cycle at the time of implantation of the embryo. Seals, like mink, show delayed implantation of the embryo as a normal component of the annual reproductive cycle. No conclusions about the mechanism of action could be drawn.

Brouwer et al. (1989) fed common seals (*Phoca vitulina*) on a diet of polychlorinated biphenyl-contaminated fish (average daily intake 1.5 mg PCBs) for almost 2 years. Significant reductions in levels of plasma total and free thyroxine, triiodothyronin, and retinol were found compared with those in seals maintained on a "low" contaminated diet (average daily intake 0.22 mg PCBs). It should be noted that the diet consisted of fish contaminated in the environment and not dosed. No attempt was made to analyse levels of retinol in the

different fish diets. The "high" contamination group were caught in the Wadden sea and the "low" contamination group in the north-east Atlantic. When the fish were analysed for other likely contaminants, it was found that *pp*'-DDE also showed higher levels in the "high" contamination group than the "low" contamination group; average daily intakes of *pp*'-DDE were estimated to be 0.4 mg and 0.13 mg, respectively.

7.3 Toxicity for terrestrial organisms

7.3.1 Plants

Aroclor 1254 was applied to soil at rates of 10, 100, or 1000 mg/kg (Weber & Mrozek, 1979). Both soybean (*Glycine max*) and fescue (*Fescue arundinacea*) were grown in the soil, from seed, for up to 26 and 42 days, respectively. The height of the soybean plants and the fresh top weights of both plants were measured. PCBs applied to the soil significantly reduced height and fresh top weight of soybean plants, only at the highest rate of application. Low rates were inhibitory, but not significantly so. Aroclor applied to the soil also reduced the fresh top weight of fescue at the highest rate of application (1000 mg/kg); lower application rates of the Aroclor did not have any effects. The addition of activated carbon to the soil (3.7 tonnes/ha; approximately 3333 mg/kg) annulled the inhibitory effect of PCBs. The Aroclor also inhibited the uptake of water by the soybean in proportion to the dose applied to the soil; water uptake was monitored between 21 and 25 days after sowing of the seed. The reduction in water uptake over this 5-day period was 12%, with the application of 1 mg Aroclor 1254/kg soil, rising to 52% at 1000 mg/kg soil. Again, the effect on water uptake was eliminated by the addition of carbon to the soil (1% rising to 4% inhibition over the dose range).

Continuation of the experiment through a second and third crop of soybeans on the same soil, without further addition of Aroclor 1254 (Strek et al., 1981), showed similar effects on the height, top fresh weight, and water uptake of the plants, reflecting the persistence of the Aroclor. However, there were no significant effects at doses lower than 1000 mg/kg, with the exception of reduced height in the third crop, seen at all dose levels. All effects were eliminated by the addition of activated carbon to the soil. The same authors found that

beet (*Beta vulgaris*) was significantly affected by 1000 mg Aroclor 1254/kg, using the same parameters of water uptake, height, and fresh top weight between 14 and 56 days after sowing. Doses of 100 mg/kg or less did not have any significant effects. Effects at the highest dose were again eliminated by the addition of activated carbon to the soil. Growth parameters, taken at harvest, showed no apparent inhibition of corn (*Zea mays*) or sorghum (*Sorghum bicolor*) by Aroclor 1254 over the same dose range. There was, however, a reduction of plant height over the first 5 days of growth at 100 and 1000 mg/kg in corn, but the plants recovered.

Mrozek et al. (1983) grew *Spartina alterniflora* plants in mud or sandy soils in the presence of 2.2 μg PCBs/kg (54% chlorine similar to Aroclor 1254), admixed with the soil, over a 6-week period. Plants grown in sand showed significantly reduced values for cumulative change in height (−30%) and the number of live leaves per stem (−25%), and increased values for the number of stems per plant (−300%), whereas plants grown in mud showed a significantly reduced value for cumulative change in the number of stems per plant (−75%). Mud-grown plants also exhibited an altered biomass distribution, as indicated by the aerial:below ground biomass ratio, which increased from 1.2 to 1.5, on a dry weight basis.

7.3.2 Terrestrial invertebrates

Hatch & Allen (1979) observed the behaviour of the snail (*Cepeae (=Helix) nemoralis*), with regard to the rasping of conspecifics' shells to obtain calcium. On a low calcium diet (0.53 mg calcium/kg), snails showed an increased tendency to rasp the shells of other snails, in order to obtain calcium. The best indicator of this behaviour was found to be the counting of holes bored completely through the shell. This behaviour was not seen with a high calcium diet (250 mg calcium/kg). The addition of PCBs, as a mixture of Aroclors 1016 and 1254, to the high calcium diet at a rate of 0.5, 1.0, or 5.0 mg/kg increased the number of snail shells penetrated by other snails. Penetration increased in a dose-dependent manner with 2, 5, and 7% penetration for the 3 dose rates, respectively. Damage to shells, without actual penetration, also increased with PCB treatment from the low level found on the control diet to between 16 and 21% on the PCB diet. No clear dose-dependent effect was seen using this method

of assessing damage. Fourth instar nymphs of the grasshopper (*Chorthippus brunneus*), were dosed topically with the PCB mixture Aroclor 1254 (Moriarty, 1969). A single dose of either 12.5, 50, or 200 μg/insect was applied in a volume of 1 μl of 1,4-dioxan. No sublethal effects were detected on either development or reproductive potential. At the highest dose, there appeared to be a latent toxicity that could be correlated with the mobilization of lipids at moult; more moulted males died than unmoulted males over the test period. Females took longer to moult than males and showed a distinctly bimodal distribution in time to death, with a similar correlation between toxicity and moult. Males showed 46% mortality and females, 41%, after treatment with 200 μg Aroclor 1254. Fungal infection affected insects on the lower doses and mortality figures are, therefore, unreliable.

Lichtenstein et al. (1969) exposed *Drosophila melanogaster* to the dry residue of various PCBs. They exposed flies to Aroclors 1221, 1232, 1242, and 1248 at 200 or 800 μg. No mortality was observed after 48 h at 200 μg. At 800 μg, there was an increase in mortality with decreasing chlorination (after a 48-h exposure to Aroclor 1221, 92% had died; only 45% died after exposure to Aroclor 1248 over the same length of time). No mortality was observed after a 48-h exposure to 2000 μg of Aroclors 1254, 1260, 1262, or 1268. In a separate study, the authors treated houseflies (*Musca domestica*) topically with either 10 or 20 μg (in 2 μl of acetone); mortality was assessed after 24 h. Results were comparable with those from the study on *Drosophila*; deaths were dose related and occurred with Aroclors up to 1254, where mortality was 10% at the higher dose. Aroclors of higher chlorination than 1254 had no effect. Lower chlorinated Aroclors had the greatest effect with more deaths at the highest dose (20 μg) and lowest chlorination (Aroclor 1221) than with any other treatment (43% killed). Plapp (1972) found that the 24-h LC_{50} for Aroclor 1254 in the housefly (*Musca domestica*) was >3000 μg/jar where the Aroclor was added to a container in acetone, which was dried before the addition of the flies. This was true for both DDT-susceptible and DDT-tolerant strains. The same author reported a powerful synergistic effect between carbaryl and Aroclor 1254; the LC_{50} with carbaryl alone was calculated to be 1386 μg/jar

and that for carbaryl:PCB in the ratio of 1:5, 96 μg/jar. The Aroclor was as powerful a synergizing agent as piperonyl butoxide.

Youssef et al. (1974) hatched eggs of the housefly (*Musca domestica*) on a medium of paper tissue dosed with 0.808 g of Aroclor 1254 per 200 g of tissue. The adult flies hatching from the eggs were examined using the electron microscope for effects on the male reproductive tissue. The PCBs induced nuclear and flagellar abnormalities in developing spermatids. Spermatid nuclei failed to elongate and membranes originating from the nuclear envelope formed invaginations into the nucleus. These resulted in the appearance of cytoplasmic inclusions in the nucleus. Spermatid flagellae contained an abnormal number of axonemes and mitochondrial derivatives; abnormal spermatids did not coil and degenerated.

In a study by Wasilewska et al. (1975), female nematodes (*Acrobeloides nanus*) were exposed to Aroclor 1254. Initially, 60 μg of the Aroclor were added to a petri dish (on the surface of agar) in which there were 20 nematode worms. The nematodes fed on a culture of bacteria introduced to the agar at the same time as the worms. After 5 days of exposure, eggs and adult nematodes were counted and adult weights determined. No significant effects were found. In a second study, over a longer period (10 days), nematodes were exposed to 15, 30, or 60 μg of the Aroclor. Adverse effects increased with dose, and even at the lowest dose, the number of adults was reduced from 123 to 76, the number of eggs from 539 to 288, and the weight of adults from 18.9 to 9.4 μg. At the highest dose of 60 μg per dish, the number of adults was 32, the number of eggs, 37, and the weight of adults, 4.9 μg.

7.3.3 Birds

Five-day dietary LC_{50}s for PCBs in birds ranged from 604 to >6000 mg/kg diet (Table 35). Generally, the oral single dose LD_{50} and the dietary LC_{50} data are similar to those for mammals. PCBs are less toxic for birds than other organochlorines, such as DDT and its metabolites and the chlorinated cyclodienes.

The toxicity of Aroclors in birds increases with the percentage chlorination (generally reflected in the final 2 digits of the Aroclor number), according to the data of Hill et al. (1975) and Hill &

Table 35. Toxicity of PCBs for birds

Species	Sex	Age	Route[a]	PCB type	Parameter	Dose/concentration (mg/kg)	Reference
Bobwhite quail (*Colinus virginianus*)		10 days	diet	Aroclor 1221	5-d LC_{50}	>6000	Hill et al. (1975)
		10 days	diet	Aroclor 1232	5-d LC_{50}	3002 (2577-3501)	Hill et al. (1975)
		10 days	diet	Aroclor 1242	5-d LC_{50}	2098 (1706-2610)	Hill et al. (1975)
		10 days	diet	Aroclor 1248	5-d LC_{50}	1175 (966-1440)	Hill et al. (1975)
		10 days	diet	Aroclor 1254	5-d LC_{50}	604 (410-840)	Hill et al. (1975)
		10 days	diet	Aroclor 1260	5-d LC_{50}	747 (577-937)	Hill et al. (1975)
		10 days	diet	Aroclor 1262	5-d LC_{50}	871 (702-1069)	Hill et al. (1975)
	male	1 year	oral	Aroclor 1268	acute LD_{50}	>2000	Hudson et al. (1984)
Japanese quail (*Coturnix coturnix japonica*)		14 days	diet	Aroclor 1221	5-d LC_{50}	>5000	Hill & Camardese (1986)
		14 days	diet	Aroclor 1232	5-d LC_{50}	>5000	Hill & Camardese (1986)
		14 days	diet	Aroclor 1242	5-d LC_{50}	>6000	Hill & Camardese (1986)
		14 days	diet	Aroclor 1248	5-d LC_{50}	4819 (4267-5443)	Hill & Camardese (1986)
		14 days	diet	Aroclor 1254	5-d LC_{50}	2929 (2516-3409)	Hill & Camardese (1986)
		14 days	diet	Aroclor 1260	5-d LC_{50}	2195 (1861-2589)	Hill & Camardese (1986)
		14 days	diet	Aroclor 1262	5-d LC_{50}	2304 (1978-2684)	Hill & Camardese (1986)

Table 35 (*continued*)

Species	Sex	Age	Route[a]	PCB type	Parameter	Dose/concentration (mg/kg)	Reference
Mallard (*Anas platyrhynchos*)		10 days	diet	Aroclor 1221	5-d LC_{50}	>5000	Hill et al. (1975)
		10 days	diet	Aroclor 1232	5-d LC_{50}	>6000	Hill et al. (1975)
		10 days	diet	Aroclor 1242	5-d LC_{50}	3182 (2613-3879)	Hill et al. (1975)
		10 days	diet	Aroclor 1248	5-d LC_{50}	2798 (2264-3422)	Hill et al. (1975)
		10 days	diet	Aroclor 1254	5-d LC_{50}	2699 (2159-3309)	Hill et al. (1975)
		10 days	diet	Aroclor 1260	5-d LC_{50}	1975 (1363-2749)	Hill et al. (1975)
		10 days	diet	Aroclor 1262	5-d LC_{50}	3008 (2461-3634)	Hill et al. (1975)
	male	8-9 months	oral	Aroclor 1242	acute LD_{50}	>2000	Hudson et al. (1984)
	male	8-9 months	oral	Aroclor 1254	acute LD_{50}	>2000	Hudson et al. (1984)
	male	8-9 months	oral	Aroclor 1260	acute LD_{50}	>2000	Hudson et al. (1984)
	male	8-9 months	oral	Aroclor 1268	acute LD_{50}	>2000	Hudson et al. (1984)
Red-winged blackbird (*Agelaius phoeniceus*)			diet	Aroclor 1254	6-d LC_{50}	1500	Stickel et al. (1984)
Ring-necked pheasant (*Phasianus colchicus*)		10 days	diet	Aroclor 1221	5-d LC_{50}	>5000	Hill et al. (1975)
		10 days	diet	Aroclor 1232	5-d LC_{50}	3146 (2626-3948)	Hill et al. (1975)
		10 days	diet	Aroclor 1242	5-d LC_{50}	2078 (1843-3879)	Hill et al. (1975)
		10 days	diet	Aroclor 1248	5-d LC_{50}	1312 (1166-1477)	Hill et al. (1975)
		10 days	diet	Aroclor 1254	5-d LC_{50}	1091 (968-1228)	Hill et al. (1975)
		10 days	diet	Aroclor 1260	5-d LC_{50}	1260 (1106-1433)	Hill et al. (1975)
		10 days	diet	Aroclor 1262	5-d LC_{50}	1234 (1086-1402)	Hill et al. (1975)

Table 35 (*continued*)

Species	Sex	Age	Route[a]	PCB type	Parameter	Dose/concentration (mg/kg)	Reference
Starling (*Sturnus vulgaris*)			diet	Aroclor 1254	4-d LC_{50}	1500	Stickel et al. (1984)
Brown-headed cowbird (*Molothrus ater*)			diet	Aroclor 1254	7-d LC_{50}	1500	Stickel et al. (1984)
Grackle (*Quiscalus quiscula*)			diet	Aroclor 1254	8-d LC_{50}	1500	Stickel et al. (1984)

[a] oral = acute oral test (result expressed as mg/kg body weight); diet = dietary test (result expressed as mg/kg diet).

Camardese (1986). Hill et al. (1974) noted that the toxicity of Aroclors is not simply a reflection of the chlorine content of the different Aroclors. They adjusted the dietary content of the Aroclors to a constant dietary chlorine level and found the same increased toxicity with higher Aroclor numbers.

Dahlgren et al. (1972) reported some mortality in sub-adult pheasants after regular oral doses of Aroclor 1254 ranging from 10 to 210 mg. Mortality was related to both dose and body weight; heavier birds lived longer, though they lost a greater proportion of body weight. A sudden heavy intake of PCBs led to high brain residues. Brain residues were best correlated with death; residues in the brain of about 300–400 mg/kg were considered by the authors to be diagnostic of acute poisoning and death (Dahlgren et al., 1972). Stickel et al. (1984) concluded that similar levels in the brain killed red-winged blackbirds, starlings, brown-headed cowbirds, and grackles. Intake of lower doses of PCBs over long periods does not lead to such high brain residues; the cause of death after long-term exposure appears to be oedema and related symptoms.

7.3.3.1 *Short-term toxicity*

Hurst et al. (1973) observed differential toxicity of PCBs between bobwhite quail hens and cocks. This differential was eliminated when the tests were conducted on birds not in the breeding condition and with short daylengths. Females survived better than males, only when they were laying eggs, and survival was well correlated with the numbers of eggs produced. The authors concluded that females reduce their exposure to PCBs by eliminating the compound in the eggs.

When Koeman et al. (1969) fed Japanese quail a diet containing 2000 mg Phenochlor DP6/kg, all the dosed birds died between 6 and 55 days of dosing. The quail developed hydropericardia at this dose level. Vos & Koeman (1970) fed one-day-old cockerels a diet containing PCBs at 400 mg/kg, for 60 days; the PCBs were in one of the following forms, Phenochlor DP6, Clophen A60, or Aroclor 1260 (all 3 are 60% chlorinated). The mean survival time was calculated to be 24.3 days for Phenochlor and 20.5 days for Clophen, only 3 out of 20 birds died on the diet containing the Aroclor.

Microscopically, centrolobular liver necrosis was found in chicks fed the first 2 compounds. Atrophy of the spleen and porphyria were observed in all dosed groups.

Miranda et al. (1987) studied the effects of acute oral exposure of Japanese quail to Aroclor 1242 (100, 250, or 500 mg/kg), or 2,4,2',4'-tetrachlorobiphenyl and 3,4,3',4'-tetrachlorobiphenyl (both 87.6 mg/kg) in corn oil. Control birds received only the corn oil. The birds were killed after 48 h. All the PCB compounds caused a significant increase in porphyrin content and delta- aminolevulinic acid synthetase (ALA-S) activity in the small intestine and liver. All the compounds increased the cytochrome P-450 content of the liver. In the intestine, the P-450 content was only increased by Aroclor 1242 and 2,4,2',4'-tetrachlorobiphenyl. The activity of 7-ethoxy-resorufin *O*-deethylase was increased by all compounds in both the intestines and liver. In the liver, 7-ethoxycoumarin *O*-deethylase (ECOD) activity was unchanged or decreased, but, in the intestines, ECOD activity increased with dose. No tissue differences in ECOD activity were found after treatment with 2,4,2',4'-tetrachlorobiphenyl and 3,4,3',4'- tetrachlorobiphenyl. It was concluded that the small intestine was more responsive than the liver to the porphyrinogenic effect of a single oral dose of PCBs, and, that the induction of drug metabolizing enzymes in the quail was tissue-specific, depending on the PCB preparation used.

Day-old chicks were fed on a diet containing 500 mg PCBs/kg. All the birds died between the third and the tenth week of dosing; a reduction in the dosage to 250 mg/kg delayed the onset of death until the thirteenth week (Platonow & Funnell, 1971). Mortality did not occur in chickens dosed at 200 mg/kg over a period of 3 weeks (Flick et al., 1965). Harris & Rose (1972) fed one-day-old broiler chicks diets containing 100, 200, or 400 mg PCBs/kg (Aroclors 1242, 1254, and 1260). No mortality occurred at doses of up to 100 mg/kg, over a period of 4 weeks. Over the same period, all the birds on Aroclor 1242, 60% of the birds on Aroclor 1254, and none of the birds on Aroclor 1260, died, all at a dosage of 400 mg/kg. Holleman et al. (1976) fed day-old broiler chicks and turkey poults on diets containing Aroclor 1242 at 38, 75, or 150 mg/kg for 4 weeks. The authors found increased mortality at 75 mg/kg (21% mortality) with the chicks, but this was not significantly different from controls;

however, there was a significant increase in deaths at 150 mg/kg (75% mortality). Significantly increased mortality was not found in the turkeys at any dose level, but the mortality rate in the controls was 33%. Both the 75 and 150 mg/kg diets produced oedema and other lesions attributed to PCB toxicity. Prestt et al. (1970) maintained Bengalese finches on a diet containing various concentrations of Aroclor 1254. The estimated dose rate for 50% mortality, over 56 days, was 254 mg/kg per day.

7.3.3.2 Egg production

Most studies demonstrating the lowering of egg production by PCBs were conducted on chickens. The most severe effects came from dosing with Aroclors in the middle of the range of chlorination (Aroclors 1232–1254). The literature has been reviewed by Stendall (1976).

Platonow & Reinhart (1973) fed chickens with Aroclor 1254 at either 5 or 50 mg/kg diet over 39 weeks. Egg production was erratically reduced with the lower doses and sharply reduced on 50 mg/kg diet. A dietary dose of 2 mg/kg did not have any reproductive effects on chickens over 9 weeks (Lillie et al., 1974) or after 39 weeks (Platonow & Reinhart, 1973). Scott et al. (1975) showed a 10% reduction in egg production in chickens related to egg residues of PCBs (Aroclor 1248) of 3 mg/kg. When egg residues reached 4.5 mg/kg, the production rate was further reduced. A significant reduction in egg production was demonstrated by Call & Harrell (1974) after dosing Japanese quail with 3 different Aroclors at 62.5–5000 mg/kg, over 33–264 days.

7.3.3.3 Hatchability and embryotoxicity

Aroclors reduced the hatchability of chicken eggs. In 2 studies, Lillie et al. (1974) examined the effects on hatchability of Aroclors 1221, 1232, 1242, 1248, and 1268, all fed at 2 or 20 mg/kg diet, over 9 weeks. Aroclors 1221 and 1268, with low and high chlorination, respectively, showed no effects at 20 mg/kg diet. Aroclor 1248 produced some adult mortality at 20 mg/kg diet and nearly eliminated hatching of the eggs produced. Aroclor 1242 showed similar, but slightly less severe, effects; there was even less effect with Aroclor

1232. Cecil et al. (1974) tested a similar range of PCBs at the same dosages (2 and 20 mg/kg diet). They also reported no effects for Aroclors 1221 and 1268. Aroclors 1254, 1232, 1242, and 1248 reduced hatchability, as in the previous study. PCBs that reduced hatchability also produced abnormalities in the chicks. The fertility of eggs was not affected by any of the treatments. Females were artificially inseminated with semen collected from males fed a similar diet of PCBs. Scott (1977) dosed chickens with 0.5, 1, 10, or 20 mg PCBs/kg diet and found no effect at the 2 lowest doses. Hatchability was reduced at 10–20 mg Aroclor 1248/kg diet. Kosutzky et al. (1979) dosed chickens with 2 other PCBs (Delor 103 and 105) (42 and 54% chlorination, respectively), at 5 mg/kg diet, for 6 weeks; there was little effect on hatchability, which returned to control levels soon after a return to a clean diet. Solomon et al. (1973) studied the effects of PCBs (Aroclor 1254) on pheasants. The birds were dosed at weekly intervals, for 17 weeks, with gelatin capsules con- taining 50 mg/bird for the hens or 25 mg/bird for the cock birds. No effects were observed on fertility and there was no increase in the numbers of abnormal embryos. In another study, Ax & Hansen (1975) maintained white leghorn pullets on a diet containing Aroclor 1242 or 1254 at 20 mg/kg, or 2,4,5,3',4'-pentachlorobiphenyl, for a period of 10 weeks. Average embryonic mortality was found to be significantly increased, i.e., 54.7, 59.2, and 74% for the 3 compounds, respectively. In the same study, the authors found that average embryonic mortality in eggs laid by birds dosed with 2,5,2'-trichloro-, 2,5,2',5'-tetrachloro-, or 2,4,5,2',4',5'-hexachlorobiphenyl was not significantly different from that in the controls. When both broiler breeder hens and leghorn hens were fed diets containing either 20 or 50 mg Aroclor 1242/kg, for 1 week, the hatchability of the eggs laid was reduced by 67.3 and 26.8%, respectively, of control levels, on the 50 mg/kg diet (Briggs & Harris, 1973). Hatchability also was reduced at 20 mg/kg diet, but the time required to achieve the same depression as that found with the higher dose was doubled. Even after dosing had finished, embryotoxicity continued and, in fact, increased until, after 6 weeks, hatchability was between 0 and 10% of controls for both birds at both doses.

Chickens given Aroclor 1254 at 50 mg/litre in the drinking-water, for 6 weeks, showed progressive reduction in egg hatchability. This

fell to zero after 3 weeks (Bush et al., 1974). Hatchability remained at almost zero for the first 8 weeks of the chickens receiving control water following dosing, but returned to normal after a further 8 weeks.

Platonow & Reinhart (1973) fed chickens on a diet containing 50 mg Aroclor 1254/kg for 39 weeks. There was some adult mortality; egg production and hatchability fell almost to zero. Residues of Aroclor in the last eggs produced ranged between 25 and 50 mg/kg. After 6 weeks of uncontaminated food, egg residues dropped and hatchability improved. The authors reported that egg residues of less than 5 mg/kg had no effect on hatchability, whereas residues greater than 10–15 mg/kg led to embryotoxic effects. Scott et al. (1975) related hatchability to egg residues. At residue levels of 3 mg/kg, hatchability was reduced by 44%, and, at residue levels of 4.5 mg/kg, it was reduced to almost zero.

The yolk-sacs of eggs from pheasant, mallard, goldeneye duck, and black-headed gull were injected with 3,4,3',4'-tetrachlorobiphenyl at 0.1 mg/kg (pheasant and mallard) or 1.0 mg/kg (pheasant, goldeneye duck and black-headed gull) after 4 or 5 days of incubation (Brunström & Reutergardh, 1986). A significant decrease in the hatching rate was seen only in pheasants, at the highest dose. At a dose of 1 mg/kg, all the embryos died before hatching, but, at 0.1 mg/kg, no effect on hatching was observed. No gross abnormalities were noted in either hatched chicks or dead embryos. A great difference was noted by the authors between the avian embryos in this study and chicken embryos, with regard to sensitivity towards tetrachlorobiphenyl. In chicken embryos, a dose of 0.004 mg/kg, administered on day 4 of incubation, gave a significant reduction in hatching. At 0.02 mg/kg, no embryos survived to hatching (Brunström & Darnerud, 1983). Carlson & Duby (1973) injected Aroclors directly into chicken eggs on the first day of incubation, or 9 days later. Aroclor 1242 severely limited hatchability at levels of more than 2.5 mg/kg. Aroclors 1254 and 1260 had no effect at 10 mg/kg. Delaying the injection until day 9 of incubation reduced the effect of Aroclor 1242. With 5 mg/kg injected at day zero, hatchability was 8.3%; when the same dose was given at day 9, 82% of eggs hatched. These results are not compatible with those of Scott et al. (1971) who reported that most embryonic deaths occurred late

in incubation. However, these authors were not dosing the eggs directly, but measuring the residues in eggs from dosed females. PCBs administered directly into the eggs may not produce effects comparable with those produced by the same material received from the mother hen, because of different distribution in the egg. Platonow & Reinhart (1973) dosed hens at 50 mg/kg diet. Early in the study, the majority of embryo deaths occurred late in incubation. As the study progressed, the time of embryo death moved to earlier in the incubation period. Bush et al. (1974) showed that there was greater mortality for any given egg residue as the period of dosing the mother hen progressed. Their experimental chickens were dosed for 6 weeks at 50 mg/litre drinking-water and then kept for a further 20 weeks on clean water. On day 11 of the study, an egg yolk residue of 50 mg/kg was associated with 50% mortality in the embryos. On day 131, 50% mortality was associated with an egg residue of only 10 mg/kg. The greatest toxicity of PCBs for chicken embryos occurred after 11 weeks of clean water, that is 17 weeks into the study. At this stage, the eggs would be receiving doses of PCBs from material stored within the hen. Late in the study, residues of between 6 and 8 mg/kg in egg yolks (equivalent to 3.6 mg/kg whole egg) were correlated with between 14 and 36% mortality. Platonow & Reinhart (1973) reported that egg residues greater than 10–15 mg/kg caused embryotoxic effects whereas low residues of less than 5 mg/kg did not produce any effects. Abnormalities were reported by Cecil et al. (1974) in 34% of 843 embryos that died during their study. The most common abnormality was oedema, which was seen in 50% of all chicks showing any abnormality. Tumasonis et al. (1973) also reported deformities in chicks.

7.3.3.4 *Eggshell thinning*

Since the 1950s, thin eggshells have been characteristic of many wild bird populations, though the effect was not noticed until some time afterwards. Thin shells has been a contributory factor to reduced reproductive capacity, particularly in birds of prey. The main chemical causing thin shells appears to be DDE, a metabolite of DDT. It has been shown to cause thin eggshells in laboratory experiments, as well as through the correlation of field data. Literature on thin eggshells has been reviewed by Cooke (1973). Most experimental

studies using PCBs have shown no effect on shell thickness. Peakall (1971), in the first controlled study, dosed ring doves at 10 mg PCBs (Aroclor 1254)/kg diet or at 25 mg (equivalent to 160 mg/kg body weight) injected ip. Shells were ashed and weighed. Two separate studies on dietary dosing showed no effect on shell weight. In the first study, 2 groups of birds were compared, in the the second the same birds were used, comparing their eggs before and after dosing. Injection of PCBs, 1–4 days prior to egg laying, also had no effect. Studies on mallard dosed with Aroclor 1254 at 25 mg/kg diet and bobwhite quail dosed at 50 mg/kg diet over 2 years and also on mallard dosed at up to 500 mg/kg diet for 5 weeks (Heath et al., 1972) showed no effects on shell thickness. There was an apparent shell thickening of about 6% at the highest dose, which could not be statistically confirmed. The same authors outlined results from a study on white leghorn chickens. Aroclor 1242 at 10 or 100 mg/kg diet or Aroclor 1254 at 100 mg/kg diet did significantly reduce shell thickness. There were no measurable effects of: Aroclor 1242 at 1 mg/kg diet, Aroclor 1254 at 10 mg/kg, or Aroclor 1260 at 100 mg/kg diet (Heath et al., 1972). Experimental details and detailed results were not given for the work on chickens. Lillie et al. (1974) dosed chickens with a range of Aroclors, at 2 or 25 mg/kg diet, for 9 weeks. Aroclors 1248 and 1242 greatly reduced the hatchability of eggs and caused some adult mortality, but failed to cause thinning of the eggshells. When Britton & Huston (1972) fed single comb White Leghorns Aroclor 1242 at 80 mg/kg diet, for 6 weeks, no effects on shell thickness were observed. Dahlgren & Linder (1971) failed to demonstrate any deleterious effects on the eggshells of pheasants, dosed by gelatin capsule, once a week for 17 weeks, with doses of Aroclor 1254 up to 50 mg. Call & Harrell (1974) fed various Aroclors in the diet to Japanese quail for 21 days. Very significant shell thinning was found with Aroclors 1254 and 1260 at doses of 1250 and 1000 mg/kg diet, respectively. At these high doses, egg production was severely diminished and shell dimensions were based on very few eggs. Adult mortality might have occurred at these doses; the paper does not make it clear whether this actually happened. At lower doses of 78.1 and 62.5 mg/kg diet of Aroclors 1254 and 1260, respectively, there was also significant egg-shell thinning and reduced egg production. Aroclor 1242 was tested at 312.5 and 5000 mg/kg diet and both doses caused shell

thinning, though this was to a lesser degree than with other Aroclors at similar doses. Risebrough & Anderson (1975) showed that eggshells thinned by dietary DDE were not further affected by adding PCB (Aroclor 1254) to the experimental DDE diet. Results on shell thinning are, therefore, not completely clear. It is generally agreed that PCBs do not affect birds in this way and the few results suggesting shell effects are regarded as anomalous or difficult to interpret, because of experimental design. Shell thinning can occur because of several different direct and indirect factors. DDE and sulfanilamide have direct effects on the deposition of calcium in the shell or on its mobilization from the skeleton, which acts as a calcium store. PCBs are more likely to affect shells indirectly by reducing food consumption; none of the studies cited above reported whether individual birds took less food because of the dosing with Aroclors. Haseltine & Prouty (1980) fed 24 pairs of mallard with Aroclor 1242 at 0 or 150 mg/kg diet for 12 weeks and reported a reduction in shell thickness of 8.9%. They pointed out that all females laying thin-shelled eggs showed a significant depression in body weight. This, they regarded as sufficient explanation for the shell thinning. Much of the shell thinning found in Japanese quail eggs, laid by females given a single oral dose of Aroclor 1254 of 500 mg/kg body weight, was thought to be due to reduced food consumption (Haegele & Tucker, 1974).

Biessmann (1982) did not find any effects on eggshell thickness on dosing Japanese quail with Clophen A60 at levels of up to 150 mg/kg diet. However, the breaking strength of the eggs was reduced.

Hill et al. (1976) fed 6-month-old laying Japanese quail hens a diet containing 10 mg Aroclor 1242/kg, for 40 days. Eggs were collected and measured and, after 40 days, were found to have significantly thinner shells (5.2%) than the controls. The authors stated that the handling of the birds and the diet had no effect on food consumption or hen weights during the test. This is the only study showing shell thinning at moderate dose levels without an effect on food consumption. The question of whether PCBs can cause shell thinning, therefore, remains open.

7.3.3.5 Effects on the male

Platonow & Funnell (1971) kept day-old, white leghorn cockerels on a diet containing 250 mg Aroclor 1254/kg, for up to 13 weeks. They found a significant reduction in the weight of both combs and testes after 9 and 13 weeks and, a reduction in comb weight, only, after 6 weeks of dosing. In a later study, Platonow & Funnell (1972) found a more severe effect at 500 mg/kg; the comb was significantly reduced in weight after just one week of dosing and the testicular weight significantly reduced after 4 weeks, relative to the controls. The control combs and testes increased in weight during the course of the study; treated birds failed to develop either comb or testes.

Lillie et al. (1974) did not find any effects on weight gain, food intake, or semen characteristics in leghorn cockerels fed Aroclor 1248 at 10 or 20 mg/kg diet for 8 weeks. They also did not find any effects on fertility or hatchability of fertile eggs laid by similarly dosed females. Liver weights were significantly increased at both dose levels, and heart weights were significantly decreased at the highest dose.

7.3.3.6 The effects of stress

Stress, imposed in various ways, increases the sensitivity of birds to PCBs. Stress seems to have its effect by increasing the mobilization of fat. Lower fat storage decreases the attenuation of PCB toxicity seen when fat uptake of the material acts as an effective temporary detoxification mechanism. Dahlgren et al. (1972) showed that brain residues were higher in pheasants subject to starvation stress than in unstressed birds dosed at the same rate. deFreitas et al. (1972) obtained similar results using cold stress or starvation in pigeons. As a corollary, biochemical adaptation to stress is inhibited by exposure to PCBs. This is presumed to be due to residues in non-lipid tissues (Dieter, 1974).

7.3.3.7 Physiological, biochemical, and behavioural effects

Jefferies & Parslow (1972) dosed young lesser blackbacked gulls (*Larus fuscus*) with daily gelatin capsules containing Aroclor 1254 at 50, 100, 200, or 400 mg/kg body weight, for 8 weeks. Mean individual thyroid weights were significantly increased by 32% (taking all dosed birds as a single group). There was also an increase

in the mean cross-sectional area of the thyroid. There was, however, no dose-related effect of PCBs on thyroid weight. The same authors (Jefferies & Parslow, 1976) showed a similar effect of increased thyroid weight when they dosed guillemots (*Uria aalge*) for 45 days with Aroclor 1254 at 12 or 25 mg/kg body weight. Hurst et al. (1974) also found a significant stimulation of thyroid growth after feeding bobwhite quail a diet containing 5, 50, or 500 mg Aroclor 1260/kg for 4 months. Spear & Moon (1985) raised ring doves on either a low iodine or normal diet. Insufficient iodine caused thyroid hyperplasia. This hyperplasia was reversed within 7 days by a single dose of 3,4,3',4'-tetrachlorobiphenyl at 60 mg/kg body weight. The PCB treatment also caused a significant decrease in core body temperature and serum total thyroxine (T4) and triiodothyronine (T3). No effect, other than decreased serum T3 and T4, was caused by dosing doves with PCBs on a diet containing normal iodine levels.

Behavioural effects of PCBs have been noted by several authors. Peakall & Peakall (1973) reported decreased parental attentiveness in ring doves dosed at 10 mg Aroclor 1254/kg diet. Kreitzer & Heinz (1974) measured the avoidance response (from a moving silhouette) in Japanese quail chicks, for 14 days before, and 8 days after, dosing with Aroclor 1254 at 200 mg/kg diet. After dosing, the avoidance response was significantly reduced. Normal responsiveness to the silhouette was not recovered after 6 days on a clean diet. Two examples of hyperactivity in birds were also noted. European robins fed one mealworm/day containing 5 μg Clophen A50, for 11–13 days, showed increased migratory restlessness (Ulfstrand et al., 1971). There were similar tendencies in redstart fed one mealworm/day, containing 11 μg Clophen A50, for 12 days, it was estimated that the birds had ingested 132 μg of PCB overall (Karlsson et al., 1974).

A reduction was reported by Dobson (1981) in the nest-building activity of pigeons (*Columba livia*), dosed orally, by gelatin capsule, with 15 mg Aroclor 1254/day, throughout a courtship cycle. The birds produced a nest but the number of twigs used was reduced compared with the controls. Reproductive and thyroid hormones were measured in blood plasma samples, taken each day during the courtship cycle. While the patterns of hormone secretion remained the same in both control and treated birds (rises and falls of hormone

levels occurred at comparable times in the 2 groups) the absolute circulating levels of the hormones were changed by the treatment. Both thyroxine and luteinising hormone levels in the treated birds were elevated relative to the controls. The levels were significantly higher, except at the beginning and the end of the cycle. It was concluded that hormone levels were unaffected, except when they would naturally be changing, suggesting an interference with the feedback control of hormone secretion and a central nervous site of action. Tori & Peterle (1983) kept mourning doves (*Zenaida macroura carolinensis*) on a diet containing Aroclor 1254 at 10 or 40 mg/kg for 42 days. The doves were then paired and observed each day for 30 days. Both treatments significantly increased the mean number of days in the courtship phase; only 4 out of 8 pairs on 10 mg PCBs/kg completed this phase and moved onto the nesting phase; none of the birds on 40 mg/kg had completed the courtship phase within 30 days. Behaviour was scored to measure intensity and, at both doses, this was significantly reduced overall. Although dosed birds formed pair-bonds approximately 4 days sooner than controls, there was no significant difference in the length of the pair-bond formation period or in behaviour scores during this period in doves fed 10 mg/kg. The length of time spent in the courtship period was extended significantly (by 8.5 days) by PCBs at 10 mg/kg. Behaviour scores were not significantly affected, but dosed birds averaged 32% lower scores. Of the birds reaching the nesting phase, there was no significant difference between controls and dosed birds with regard to length of time spent nesting or behaviour scores in the nesting phase. PCBs, however, significantly delayed the onset of nest initiation (by approximately 7 days) and, therefore, egg laying.

Japanese quail were dosed with Clophen A60 in the feed at 150 mg/kg, from the first week of life up to 42 days of age, while the birds were developing sexually and becoming reproductively mature (Biessmann, 1982). In females, progesterone levels were not greatly affected by the PCBs, but estradiol levels in blood plasma were lower before sexual maturity and were less stable during egg laying. In males, levels of testosterone and dihydrotestosterone (the primary metabolite) were not affected. Quail fed up to 150 mg Clophen A60/kg diet during the time of sexual maturation (second to fourth weeks of age) showed delayed onset of egglaying and a

diminished capacity to lay eggs. Hormone levels in both males and females were not significantly different from those in the controls.

A possible mechanism for central nervous effects was provided from studies on neurotransmitters. Dopamine and noradrenalin were depleted in the brain of the ring dove in a dose-related manner with increasing brain residues of PCBs (Heinz et al., 1980).

7.3.3.8 Interactive effects with other chemicals

The only information on the interaction between PCBs and other chemicals in birds has shown PCBs to be additive and not synergistic. Kreitzer & Spann (1973) carried out tests on several pairs of chemicals to study pesticidal synergism in young pheasants and Japanese quail. Two PCBs were used in the study. Aroclor 1262 and malathion showed additive results, when fed in the diet to 16-day-old Japanese quail. Aroclor 1254 and DDE were also additive, when given in the diet to 9-day-old quail. Another study on the possible interactive effects of PCBs was conducted by Heath et al. (1972), who found that feeding Aroclor 1254 and DDE in the diet to 14-day-old Japanese quail gave additive results. There was no evidence of mutual potentiation or antagonism.

7.3.4 Terrestrial mammals

Acute oral LD_{50} values reported for PCBs in mink ranged from >750 to 4000 mg/kg body weight. Acute LD_{50} values for 3 Aroclors in mink were determined by Aulerich & Ringer (1977) after administration orally, by gavage, or by intraperitoneal injection. Mortality was assessed 4 days after i.p. administration and 14 days after oral administration. The lethality of the Aroclors was found to be inversely related to the chlorine content; Aroclor 1221 was most toxic and Aroclor 1254 least toxic (Table 36). This is in marked contrast to the situation in birds, where toxicity was correlated positively with chlorine content of the PCBs (see section 7.3.3).

Table 36. Acute toxicity of Aroclors for mink[a]

Aroclor	LD_{50} (mg/kg body weight)	
	Intraperitoneal	Oral
Aroclor 1221	>500–<750	>750–<1000
Aroclor 1242	1000	>3000
Aroclor 1254	>1250–<2250	4000

[a] From: Aulerich & Ringer (1977).

7.3.4.1 Short-term toxicity

Ferrets (*Mustela putorius furo*), fed a diet containing 20 mg of Aroclor 1242/kg, for 8 months, developed enlarged, thickened, and deformed toe-nails with hyperkeratosis at the junction of the skin and sponchium, and dysplasia of the root of the nail and the matrix. The same diet containing Aroclor 1016 did not produce these effects (Bleavins et al., 1982).

Bleavins et al. (1980) showed the ferret to be less sensitive to PCBs than the mink, though LD_{50} values were not determined. Aroclor 1242 at 20 mg/kg diet killed all mink (3 males and 12 females) to which it was fed. The same diet did not kill any ferrets, though it did cause reproductive failure.

No mortality occurred in mink fed a diet containing 1 mg PCBs/kg over 183 days (Wren et al., 1987a).

Hornshaw et al. (1986) conducted 28-day LC_{50} tests on mink, using Aroclor 1254, in a study to investigate the effects of age, season, and diet on the toxicity of PCBs; no effects were noted on any of these parameters. In replicate tests, the calculated LC_{50} values varied between 79 and 84 mg/kg diet (48–132, range of confidence limits). The authors noted that the period of observation after dosing was critical in assessing the results, since mortality continued after dosing had stopped and the PCBs were persistent in the body. Taking total mortality over 28 days of dosing and a further 7 days of observation, the LC_{50} values fell to between 47 and 58 mg/kg diet.

A consistent finding among various studies is an effect of PCBs on food consumption and, therefore, on body weight. The most detailed analysis of food consumption during the feeding of Aroclor 1254 to mink is presented by Hornshaw et al. (1986). Young mink fed the Aroclor over 28 days showed a dose-dependent decrease in the amount of food consumed. The cumulative weight of food consumed over 5 weeks (1 week predosing and 4 weeks dosing) for controls was 7574 g. This was reduced progressively with increasing dose of Aroclor 1254 at 10, 18, 32.4, 58.3, and 105 mg/kg diet to 6447, 6153, 4816, 3556, and 2723 g, respectively. This led to loss of original body weight over the study period rising to more than 40% at the highest dose. Similar effects were seen in adults of both sexes; females, with a smaller initial body weight, were more severely affected than males. This effect has implications for the interpretation of results of dietary toxicity tests. The effects seen are a combination of the direct toxic effects of the compound and the indirect effects of progressive starvation. The doses of PCBs to which the animals are exposed must also be calculated with reduced food intake in mind; apparent doses are higher than real exposure as dose rates increase.

Organ weights (expressed as a percentage of brain weight) were unaffected by Aroclor 1254 at doses up to 105 mg/kg diet, with the exception of the heart and the adrenal glands. Heart weight was reduced in both adult and young mink fed Aroclor 1254 at 58 mg/kg diet or more; adrenal weights were increased by doses of 13 mg/kg diet or more (Hornshaw et al., 1986).

Female minks received 0.1 or 0.5 mg of 3,4,5,3',4',5'-hexachlorobiphenyl/kg diet, or 2.5 or 5.0 mg of 2,4,6,2',4',6'- and 2,3,6,2',3',6'-hexachlorobiphenyl/kg diet for 12.5–14.5 weeks. In both studies, 3,4,5,3',4',5'-hexachlorobiphenyl was the most toxic isomer, causing high mortality and reduced body weights (Aulerich et al., 1985).

Clark & Prouty (1977) fed female big brown bats (*Eptesicus fuscus*) on a diet of meal-worms containing 10 mg Aroclor 1254/kg. After the feeding period of 54 days, the bats were starved to simulate loss of body fat during the period of migration (when the animals do not feed). Two out of 12 bats died. The brain residues of 20 mg PCBs/kg

at the end of the study were considered to be sub-lethal, since no neurotoxic symptoms were observed before death.

7.3.4.2 Reproductive effects

Experimental investigations of mink reproduction in relation to environmental pollution were carried out as a result of the reduced reproductive success seen after feeding farm mink with fish from the Great Lakes. Early studies, therefore, involved the analysis of fish for pollutants and the experimental feeding of both the fish and of mixtures of chemicals contained in various fish in the Great Lakes.

Aulerich & Ringer (1977) performed a comprehensive series of feeding studies using coho salmon from 2 of the Great Lakes (Michigan and Erie), other fish species from the same source, salmon from the west coast of the USA, and various combinations of organochlorine contaminants.

In their first study, ocean fish (perch or whiting) were used as control diets and the reproductive performances were compared of dosed and undosed female mink mated with undosed males. Lake Michigan coho salmon, as 30% of the diet, had the most severe effect on reproduction, i.e., total reproductive failure, as measured by numbers of live kits surviving 4 weeks after parturition. Coho salmon from Lake Erie also reduced reproductive success; 12 females produced only 7 kits still alive 4 weeks after birth. Two other species of fish from Lake Michigan produced less severe effects, 5 kits being produced on a diet of 30% bloater chub and 15 kits, on a diet of yellow perch. Controls produced more than 40 kits over the same period. Kits produced on Lake Michigan or Lake Erie fish, other than salmon, and surviving to 4 weeks of age showed significantly lower body weights than the controls. The small numbers of surviving kits from mothers fed Lake Erie salmon also showed reduced body weight at 4 weeks of age. No kits were produced after feeding Lake Michigan salmon diets to females (Aulerich & Ringer, 1977).

In a long-term, low-level feeding study, 4 different Aroclors (1016, 1221, 1242, and 1254) were included in the diet of mink at a rate of 2 mg/kg. Groups of 8 female and 2 male animals were given this, or a control, diet for 11 months, from August to June. The reproductive performance of the animals on different diets is summarized,

together with mortality, in Table 37. Body weight, haemoglobin levels, and haematocrit were monitored at monthly intervals during the study and no significant effects of PCBs were noted. Only one of the test diets (containing Aroclor 1254) adversely affected reproduction, with only 1 live birth in the study period. This single kit was considerably lighter at birth than the controls and failed to survive 4 weeks after birth (Aulerich & Ringer, 1977).

The reproductive effects of either Lake Michigan coho salmon or Aroclor 1254 were reversible, when animals were transferred to a control diet. Eleven females fed salmon as 30% of the diet for a year, and then given control food for a further year, produced young with an average litter size of 3.5 kits per mated female, in the second year of the study. No young had been produced in the first year of the study, during dosing. Similarly, 3 females given a year of control food following a year on a diet containing 5 mg Aroclor 1254/kg, produced an average of 4.3 young per mated female in the second year of observation (Aulerich & Ringer, 1977).

In a later study, Bleavins et al. (1980) fed 2 different Aroclors at various dose levels to mink and ferrets. Aroclor 1242 was fed to mink at doses ranging from 5 to 40 mg/kg diet; Aroclor 1016 was given at only 20 mg/kg diet. Results for mortality and reproductive effects are summarized in Table 38, together with some data for Aroclor 1254 taken from Aulerich & Ringer (1977).

There was a clear reproductive effect of Aroclor 1242 at a dose of 5 mg/kg diet, but no significant mortality. Aroclor 1242 caused 66% mortality at 10 mg/kg diet and 100% mortality at 20 mg/kg diet. Aroclor 1016, at 20 mg/kg diet, caused some deaths of adults and reduced birth-weight and survival of kits, but the reproductive effects were considerably less severe than those caused by Aroclor 1242 at 5 mg/kg diet. The authors (Bleavins et al., 1980) calculated dietary LC_{50} values for Aroclors 1242 and 1254, using their own data and data from Aulerich & Ringer (1977), to be 8.6 and 6.7 mg/kg diet, respectively. It is clear that reproductive effects are less marked at lower levels of chlorination of Aroclors.

Reproductive effects on mink were reported by Jensen et al. (1977), who fed groups of 10 females at 0.05, 3.3, or 11 mg PCBs/kg diet (type unspecified), for 66 days. The highest dose eliminated

Table 37. Effects of Aroclors on mortality and reproduction in mink[a]

Aroclor[b]	Adult females			Kits				
	Number died (%)	Number mated	Number whelped	Number born		Whelped/ female mated	Alive at 4 weeks	Average weight (g ± SE) at birth
				live	dead			
Control	0	8	8	28	5	4.1	18	9.9 ± 0.32
1016	0	8	8	28	8	4.5	16	9.2 ± 0.33
1221	12	7	7	43	1	6.3	37	9.6 ± 0.22
1242	12	7	7	35	4	5.6	32	9.3 ± 0.27
1254	12	7	2	1	1	0.3	0	5.4

[a] From: Aulerich & Ringer (1977).
[b] Aroclors all fed at 2 mg/kg diet.

successful reproduction, whereas 3.3 mg/kg severely reduced the number of kits born per female.

Table 38. Summary of mortality and reproduction in mink fed various dietary levels of Aroclors

Treatment level (mg/kg diet)	Period fed (days)	Number dead/ total number	Number of kits/ female
Aroclor 1254[a]			
0	280	1 / 7	5.0
0	297	0 / 8	4.1
2	297	1 / 8	0.3
5	280	2 / 7	0.0
10	280	5 / 7	0.0
Aroclor 1242[b]			
0	247	3 / 30	4.9
2	297	1 / 8	5.6
5	247	1 / 15	0.0
10	247	10 / 15	0.0
20	192[c]	15 / 15	0.0
40	138[d]	15 / 15	0.0
Aroclor 1016[b]			
0	247	3 / 30	4.9
2	297	0 / 8	4.5
20	247	3 / 15	6.3

[a] From Aulerich & Ringer (1977).
[b] From: Bleavins et al. (1980).
[c] All mink died within 192 days on diet.
[d] All mink died within 138 days on diet: no females survived to whelping.

Wren et al. (1987b) did not find any significant effects on numbers of kits produced or surviving to weaning age (5 weeks) after feeding mink with Aroclor 1254 at 1.0 mg/kg diet, over 183 days. The dosing period covered the seasonal period when the animals came into breeding condition as well as a period of giving birth to the young. Although the weights of kits born to dosed females were not significantly different at 1 week postpartum, the weight gain of kits was then affected and weights were significantly different from those of the controls at ages 3 and 5 weeks. At age 5 weeks, when the kits were weaned, the mean body weight of kits of the controls was

227.8 g, while the mean body weight of kits fed by dosed mothers was 161.2 g.

Similar effects on the reproduction of female mink fed PCBs (type unspecified) were observed by Jensen et al. (1977), i.e., a reduction in the numbers of whelps born per pregnant female. The authors killed the females after they had given birth and examined the numbers of implantation sites in the uterus. This did not differ statistically between groups (on average, 6.6 in control females, 6.1, in females fed 5 mg/kg diet, and 4.5, in females fed 15 mg/kg diet PCBs). However, the number of kits born to the same females showed a marked effect of the PCBs: 5.1 (on average) born to control mothers; 2.9, to mothers fed 5 mg/kg diet PCBs, and 0, to mothers fed 15 mg PCBs/kg diet. The authors concluded that the effects of PCBs occur at the time of implantation or later, causing resorption of implanted embryos.

Male mink seemed unaffected by doses of Aroclor that caused reproductive effects in females. Males, dosed and mated with undosed females, fathered normal numbers of kits (Aulerich & Ringer, 1977). Wren et al. (1987b) did not note any effects of Aroclor 1254, fed to male mink over 183 days at a rate of 1 mg/kg diet. Testicular size and testicular histology were unaffected by the PCBs at any stage of the reproductive cycle.

Treatment of adult, male, white-footed and white mice with Aroclor 1254 in the diet at a level of 400 or 200 mg/kg (equivalent to 57 or 29 mg/kg body weight), for 2 weeks resulted in a reduced testicular spermatozoan concentration and, in the white-footed mice, a reduced absolute weight of the seminal vesicles. In both strains, the absolute weights of the testes and the final body weights were unchanged (Sanders & Kirkpatrick, 1975; Sanders et al., 1977).

The reproductive performance of 27 pairs of white-footed mice (44–222 days of age), was compared with that of 26 control pairs, within 60 days of exposure to Aroclor 1254 at a dietary level of 200 mg/kg. One-third of the exposed pairs did not survive the exposure but produced at least one litter. The number of pairs producing at least one litter was reduced by 65% and the number producing 2 or more litters was reduced by 91%. Litter size was not

affected. No offspring survived to weaning in the 7 first litters of PCB-fed pairs (Merson & Kirkpatrick, 1976).

A group of 10 pairs of wild-caught, white-footed, mice and groups of 18 (12 weeks of age) and 19 (16 weeks of age) pairs of laboratory-raised, white-footed mice received Aroclor 1254 in the diet at 10 mg/kg. Control groups comprised 10, 15, and 20 pairs, respectively. The reproductive performance of the first group was recorded for 18 months. The duration of the other studies varied from 7 to 15 months. The number of young per litter, 28 days after birth, was lower in all treated groups. In laboratory-raised mice paired at 12 weeks of age, the birth interval was increased and the number of young per litter at birth reduced (Linzey, 1987a). The second generation of mice, maintained on the same diet as their parents, did not differ in weight at birth, but were significantly smaller at 4, 8, and 12 weeks of age. A similar trend was observed in the few young of the third generation. The uterus, ovaries, and accessory glands, but not the testes, weighed less in exposed groups than in the controls (Linzey, 1987b). Linzey (1987a) reported similar reproductive effects of Aroclor 1254 at a much lower dose.

The author suggested that the major consistent effect on the survival of the young being fed milk was the result of much higher levels of PCBs being transported via lactation than via the placenta.

Cottontail rabbits (*Sylvilagus floridanus*) were fed Aroclor 1254 at 10 mg/kg diet for 12 weeks, and then transferred to a clean diet and allowed to breed. No effects were observed on any reproductive parameters, and reduction in food availability did not change this lack of effect (Zepp & Kirkpatrick, 1976).

7.3.4.3 Physiological effects

Wren et al. (1987a) examined histologically various organs in male and female mink, dosed for 183 days with Aroclor 1254 in the diet. At autopsy, no effects were seen on the histology of the pituitary and adrenal glands. Brain histology also appeared normal. Thyroid follicles gave the general appearance of minimal activity but did not differ between treatments. Measurement of plasma thyroid hormones (T3 -triiodothyronine; T4 -thyroxine) did not show any significant differences between treatments in male mink. Females showed

reduced circulating T3 in a single sample, in January, but no other differences were seen at other stages of the study. Thyroxine levels were not affected at any time.

7.4 Effects on organisms in the field

The acute toxicity of PCBs is relatively low for most species and will not, therefore, kill enough individuals to affect populations. However, because of the high potential for bioaccumulation sufficient residues of PCBs may build up to cause direct lethal effects over time. Although PCBs are almost universally present in the tissues of organisms in the environment, there are relatively few examples of proved effects of these residues on populations of the organisms. Sublethal effects, affecting populations by reducing reproduction or growth, are possible, but difficult to prove, because PCBs are always present with other environmental contaminants. Many possible effects of PCBs in the environment have been suggested in the literature, but few have actually been investigated in the field. It has proved difficult, if not impossible, to relate residues of PCBs in tissues to possible sublethal toxic effects; residues found after laboratory dosing cannot be directly related to the field situation.

7.4.1 Plants

Klekowski (1982) studied the ostrich fern (*Matreuccia struthiopteris*) growing in the flood plain of the Housatonic River, Massachusetts, USA. This area of the river is contaminated with PCBs from land-fill sites containing waste materials from the manufacture of transformers in the nearby city of Pittsfield. Contamination with PCBs (principally Aroclor 1254) had been a regular feature of the river area for a period of more than 40 years. The frequency of somatic mutations in the fern population was compared to a control population from an uncontaminated area. The levels of PCBs in river sediments ranged from 1.4 to 139 mg/kg dry weight; at the site where the majority of fern spores were collected, the level of PCBs was 26.3 mg/kg. The somatic mutation frequency for the contaminated population was 5.2–6.2 times higher than that for the controls. It is not known whether similar genetic damage had occurred in other inhabitants of this contaminated habitat. No other studies seem to have been

conducted on the possible effects of PCBs, from land-fill sites, on plants.

7.4.2 Fish

There have been many suggestions in the literature that PCBs might affect populations of fish in the wild. Studies attempting to demonstrate such an effect are few and, generally, inconclusive or negative.

Olofsson & Lindahl (1979) used the ability of the cod (*Gadus morrhua*) to react to different velocities of water under rotary flow, to examine the effects of water pollution. Cod sampled from polluted waters off the Swedish Coast were compared with cod sampled from unpolluted areas. The ability of the fish to react to rotary flow was significantly reduced in animals from polluted areas. However, the authors were unable to relate the reduced reaction of the fish to levels of various pollutants measured in muscle tissue. Experimental studies showed that PCBs affected the reactions of the fish; the residue level in muscle that was associated with this effect was 1.8 mg/kg. This was 30 times greater than the actual residues of PCBs measured in the cod from the polluted area. While the authors stated that the distribution of the PCBs in experimental fish and fish taken from the wild would almost certainly have been different, that PCBs exert the above effect in the field must be regarded as not proved.

Zitko & Saunders (1979) collected eggs of Atlantic salmon (*Salmo salar*) from various areas and measured the PCB contents of the eggs that proved infertile. The hatchability of different batches of eggs was tested in the laboratory. No correlation was found between residues of PCBs and the hatchability of the eggs; in fact the batch of eggs showing the lowest hatchability also showed very low residues of PCBs. However, it should be stated that hatchability was seldom affected by PCBs in laboratory experiments ; effects were more usually seen on the developing young. Hogan & Brauhn (1975) related the survival of fry hatched from rainbow trout (*Salmo gairdneri*) eggs to the contamination of the eggs with PCBs. Five batches of eggs hatched in 1971 had shown percentage mortalities, 30 days after hatching, ranging from 10 to 28%. The eggs contained total organochlorine residues of between 0.31 and 1.30 mg/kg, the majority of which was PCBs. A batch of eggs collected in 1972

showed 75% mortality, 30 days after hatching. Many of the fish hatched with such deformities as scoliosis, lordosis, kyphosis, absence of caudal vertebrae, cranial deformities, and projecting mandibles. This batch of eggs contained 2.7 mg PCBs/kg and 0.09 mg total DDT/kg (metabolites present not stated).

Westin et al. (1983) investigated the effects of PCBs, passed on to the eggs of striped bass (*Morone saxatilis*) by the female fish, and of PCBs in food organisms fed to the hatched larvae. The hatchlings were fed on brine shrimp (*Artemia* sp.) from 2 sources, one contaminated with PCBs and the other not. No effects of either maternal PCBs or PCBs from the food were found. Residues of PCBs in young fish decreased consistently throughout the study, which was conducted in water free of PCBs. The authors suggested that PCBs from the mother and from food are unlikely to affect the offspring in the wild. A similar conclusion was drawn about the survival of lake trout (*Salvelinus namaycush*) fry, hatched from eggs contaminated with PCBs in the wild (Willford, 1980). Eggs taken from the wild and hatched in clean water showed good survival of the offspring (suggesting that residues of PCBs in the eggs were not responsible for the failure of the species in Lake Michigan). However, experimental exposure of eggs, and hatched larvae/fry to levels of PCBs in water and food, similar to those found in the lake, led to high mortality and the increased occurrence of deformities in fry. The author concluded that the levels of PCBs in lake water and food items would be sufficient to lead to the population decline seen in the lake. It should, however, be pointed out that other factors in Lake Michigan could also have contributed to the failure of the lake trout. Sea lampreys had increased in number in the lake and could have caused population decline by predation.

The relationships between the occurrence of hepatic diseases and specific chemicals present in sediment were studied by Malins et al. (1987). The concentrations of PCBs in the sediments from 4 urban and 2 non-urban areas in Puget Sound USA, were determined. In 3 of the sites, the concentrations were < 0.01 and, in the other 3, the concentrations ranged from 0.11 to 0.53 mg/kg. Over 900 individual organic compounds were found. To study the fish diseases, English sole (*Parophrys vetulus*), rock sole (*Lepidopsetta bilineata*), and Pacific staghorn sculpin (*Leptocottus armatus*) were collected. The

organs of fish containing the greatest number of lesions were the liver, kidneys, and gills. Liver cell adenoma, hepatocellular carcinoma, cholangiocellular carcinoma, haemangioma, and fibroma constituted major types of liver lesions. Statistically significant correlations between levels of chemicals in sediment and hepatic neoplasms in the bottom-dwelling fish suggest a general cause-and-effect relationship, but there is little firm evidence about the actual cause of these neoplasms, in particular, in this case, whether PCBs were involved.

7.4.3 Birds

In studies on chickens and different PCB-mixtures, Vos et al. (1970) and Vos & Koeman (1970) found that the induction of subcutaneous and abdominal oedema, centrilobular liver necrosis, hydropericardium, and higher mortality was more or less related to the presence of tetrachloro- and pentachlorodibenzofurans, as impurities in the PCB samples.

From the middle of February to the end of March 1968, an epizootic disease closely resembling chicken oedema disease occurred in Japan. Two million chickens were involved, of which 400 000 (20%) died. The clinical signs were laboured breathing, droopiness, ruffled feathers, high mortality, and decreased egg production. Autopsy revealed marked subcutaneous oedema, hydropericardium, ascites, pulmonary oedema, muscular ecchymosis in the thorax or inside of the thigh, and yellowish mottled appearance of the liver. The cause of the disease was found to be Kanechlor 400 contamination of the feed. Experimental reproduction of these symptoms with Kanechlor 400 was successful. The remaining sample chicken feed contained 1300 mg of Kanechlor 400/kg feed (Kuratsune et al., 1972).

Administration of PCBs leads to an atrophy of lymphoid tissue in chickens (Flick et al., 1965; Vos & Koeman, 1970), and in pheasants (Dahlgren et al., 1972). Vos & de Roij (1972) and Vos & van Driel-Grootenhuis (1972) came to the conclusion that these effects could be attributed to an immunosuppressive effect of PCBs. Vos & de Roij (1972) suggested that the ability of PCBs to increase the susceptibility of ducklings to duck hepatitis virus (Friend & Trainer, 1970) and of fish to fungal disease (Hansen et al., 1971) could be attributed to this immunosuppressive effect.

Koeman et al. (1973) analysed 6 adult cormorants (*Phalacrocorax carbo sinensis*), found dead in the wild, for PCB residues. Three additional birds were shot and 6 fully grown nestlings were also taken. The authors also carried out a study on 5 cormorants that were dosed with the PCB, Clophen A60 (a 60% chlorinated PCB mixture that seemed to correspond most closely with the PCBs profile of material found in dead birds taken from the wild). The birds were initially dosed with the PCBs in the diet, but, subsequently, the PCBs were administered orally in gelatin capsules, until they died. PCB levels in the brains and livers of the dead birds found in the wild were higher, overall, than the levels obtained by dosing. The authors thought it highly probable that this was indicative of PCB poisoning of the birds in the wild. Without further detailed studies, this conclusion can only be implied. The higher residues in dead birds from the wild suggest that a large body burden was taken up, relatively safely in fat, and released quickly on starvation, prior to death.

A field study, to show the effects of a sub-lethal dose of PCBs on puffin (*Fratercula arctica*) breeding success and survival, was conducted by Harris & Osborn (1981). A total of 150 puffins, trapped on the Isle-of-May National Nature Reserve, Fife, Scotland, were implanted, 108 with between 30 and 35 mg of PCBs (Aroclor 1254) and 42 with sucrose as controls. The test chemicals were implanted in open-ended silastic tubes into the peritoneum. All birds were then marked and released back into the wild. The same birds returned in successive years to breed on the island. Breeding and survival of the implanted birds were monitored through the breeding seasons of 1977, 1978, and 1979. Observations on survival were also made in 1980. Some implanted birds were killed on recapture, and analysed for PCBs, in each of the years of observation. No effects on survival or breeding were seen. PCB levels in fat increased by a factor of between 10 and 14 compared with levels in birds that had not been implanted with the Aroclor.

Herring gull (*Larus argentatus*) reproductive success in the area of the Great Lakes declined with increasing residues of organochlorines in the birds. Breeding success improved as these residues fell in the 1970s (Weseloh et al., 1979). The species was chosen as an indicator of environmental pollution in the area and has been extensively studied. Poor nesting success in the species is related to high

embryonic mortality (Gilbertson & Hale, 1974). Abnormal chicks have been reported for herring gulls and also for other fish-eating species from the area including: night herons, ring-billed gulls, common terns, and Caspian terns (Gilbertson et al., 1976). Eggs from these species contained residues of PCBs, but it was not possible to directly relate these residues to chick abnormalities. Gilbertson & Fox (1977) found a correlation between total organochlorine content and the hatchability of herring gull eggs. While it cannot be shown that PCBs were directly responsible for the overall effect, PCB residues in the livers of hatched chicks, were the only contaminant that was significantly correlated with the presence of pericardial oedema. Weseloh et al. (1979) concluded that the reproductive success of the herring gull can only safely be correlated with total organochlorine residues and that the possible effects of PCBs cannot be isolated. Shell thinning usually attributed to DDE alone, does not occur significantly in these gulls. Hays & Risebrough (1972) suggested that PCB residues in terns were responsible for the high percentage of abnormal young in a colony from Long Island Sound.

Twenty-four black-crowned night heron (*Nycticorax nycticorax*) eggs were collected at the San Francisco Bay National Wildlife Refuge in 1983. Twelve of these were collected from separate nests, when late-stage embryos were pipping and an additional egg was randomly collected from each nest for organochlorine analysis. Other anomalies and skeletal defects were not apparent. Embryonic weights (with partially absorbed yolk sacs removed) were 15% lower in comparison with controls collected at Patuxent Wildlife Research Center. Crown-rump length and femur length were shorter in the San Francisco Bay embryos. The geometric mean PCB concentration was 4.1 mg/kg wet weight with a range of 0.8–52.0 mg/kg. A negative correlation existed between embryonic weight and log-transformed PCB residues in whole eggs, suggesting a possible impact of PCBs on embryonic growth. DDE did not show such a correlation (Hoffman et al., 1986).

Klaas & Swineford (1976) found low PCB residues (0.26–3.4 mg/kg wet weight) in 35 screech owl (*Otus asio*) eggs (16 of which were known to be addled) taken from the wild; there was no relationship between the presence of residues and hatching failure. Dosing captive screech owls with 3 mg Aroclor 1248/kg (McLane & Hughes,

1980) showed no effects on eggshell thickness, number of eggs produced, young hatched, or young fledged. Residues of PCBs measured in the eggs ranged between 3.9 and 17.8 mg/kg. This range covers the egg residue levels that were clearly associated with effects in experimental chickens and pheasants.

Eggs from 315 clutches of sparrowhawks (*Accipiter nisus*) from 9 sites in Scotland were examined by Newton & Bogan (1978) and Newton (1979). Eggs that failed to hatch were collected and analysed for PCBs, DDE, and for aldrin and dieldrin. Statistical analysis showed little variation in residues within a single clutch, but wide variation between clutches, even clutches from the same female in the same area in different years. On this basis, analysis of single eggs was taken as representative of the complete clutch. Analysis of variance and multiple regression were used to try to relate particular effects, such as shell thinning, addling of eggs, and late-embryo mortality, with particular organochlorines. Results showed that addling of eggs was significantly correlated with levels of both DDE and PCBs. Because of the close correlation between residues of DDE and PCBs in eggs of sparrowhawks, it is not possible to tell whether only one, or both, organochlorines were involved in egg addling. PCBs showed the strongest relationship with addling. Shell thinning was more directly linked with DDE. Newton et al. (1982) concluded that the level of PCB residues in merlin (*Falco columbarius*) was not sufficiently high to have exerted any effect on the breeding success of this species in Britain. Hodson (1975) did not find any effects of PCB residues in Richardson's merlin in Canada and attributed all effects to DDE. A relationship between DDE residues and shell thinning and the breeding success of the bald eagle (*Haliaetus leucocephalus*) was demonstrated by Wiemeyer et al. (1984). PCB residues were correlated with DDE residues. The authors concluded that contaminants other than DDE contributed no more than a minor role in reproductive effects on this species in the field. It was considered that PCBs might have contributed to reproductive problems, but that the evidence was unclear. Newton et al. (1986) presented a statistical analysis of residues in sparrowhawks related to reproductive success. Study populations from many sites throughout the British Isles showed different reproductive success. Some of this variation could be related to levels of organochlorine compounds in

eggs. When shell thickness index was related to PCBs alone, a significant negative correlation was detected. However, once DDE residues were included, PCBs did not improve the model. It was concluded that DDE alone could account for all of the reproductive effects recorded and that PCBs, at the levels of contamination found, probably did not play a role in reduced breeding performance. Newton et al. (1988) examined new data on residues of organochlorine compounds in the eggs of the peregrine falcon (*Falco peregrinus*) and also reassessed older data. Total information considered included information on residues and breeding success covering the period 1963-86. The PCB residues found were not considered to have had a significant effect on breeding success in this species. In earlier studies, Wiemeyer et al. (1975, 1987) could not isolate any single organochlorine compound as responsible for the reduced breeding success of the fish-eating osprey (*Pandion haliaetus*).

Heinz et al. (1983) examined the breeding success of groups of red-breasted mergansers (*Mergus serrator*) on islands in northwestern Lake Michigan. This is a fish-eating species and, since eating fish from the Great Lakes had been shown to affect captive mink, the authors investigated the possible effects of contaminants (measured in blood samples taken from the birds) on reproduction. Other, non-contaminant effects were also examined. Many organochlorine contaminants of the environment were found in eggs including 14 different organochlorine compounds; there was a correlation between the levels of many of these compounds. No relationship could be established between levels of PCBs, or any other contaminant, and the breeding success of the birds. The hatching success of dabbling ducks also seemed to be largely unaffected by feeding in Lake Michigan, despite the presence of residues of PCBs and other contaminants in the eggs (Haseltine et al., 1981).

Appraisal

Effects of PCBs have been shown in laboratory studies on many domestic species of birds, but few wild species. However, there are many studies showing measurable residues of PCBs in wild birds. PCBs have been implicated in population decline in several bird species in different parts of the world, but it is seldom easy to

demonstrate directly the effects of PCBs on populations of birds in the field. This is largely because PCB residues invariably occur together with other organochlorine compounds, such as DDE and dieldrin. Separating out individual effects can only be done completely satisfactorily when laboratory data are available for the same species and each individual pollutant. Some idea of likely effects can be obtained from statistical manipulation of data from the field, though, in this case, correlation is the best that can be achieved. In practice, few field studies give the results that have been predicted from laboratory studies on other species; that is direct extrapolation from laboratory to field and species to species is not straightforward.

7.4.4 Mammals

Laboratory studies involving the dosing of non-laboratory mammals with PCBs are limited to a few species. Field studies have been conducted on a wider range of species.

Norström et al. (1988) studied liver and adipose tissue specimens of polar bears (121 samples) obtained by Inuit hunters from 12 zones in the Canadian Arctic Archipelago in 1982-84 (see section 5.1.4). Six PCB congeners (Nos 99, 153, 138, 180, 170, and 194) constituted approximately 93% of total PCBs. The major PCBs accumulated belong to the group formed by combinations of 2,4-dichloro-, 2,4,5-, 2,3,4-trichloro-, and 2,3,4,5-tetrachloro- substitution on each ring.

Congeners with 2,4-, 3,4-dichloro-, 2,3,4-, 2,3,5-trichloro-, 2,3,4,6-, 2,3,5,6-tetrachloro- or 2,3,4,5,6-pentachloro- substitution on one ring, such as PCB Nos 118, 138, 187, 183 and 196, which usually bioaccumulate readily in mammals, were all at lower levels compared with congeners with only 2,4,5-trichloro- and 2,3,4,5-tetrachloro- substitution in ringed seals, such as PCB Nos 153, 180, and 170. The last 3 congeners accounted for 71% of total PCBs in polar bears. Thus, it appears that the polar bear is able to metabolize PCB congeners in which there are nonchlorinated *para* positions, adjacent nonchlorinated *ortho-meta* positions, or both *ortho* positions chlorinated in one ring.

DeLong et al. (1973) measured various organochlorine pollutants (DDT, DDD, DDE, dieldrin, and PCBs) in sea lions from the Channel Islands off the Californian coast. Previous observations had

recorded a high incidence of premature births in the population and organochlorine residues from females showing premature or normally-timed parturition were compared. Both DDT and PCB residues (measured against a standard of Aroclor 1254) were significantly higher in the females producing premature pups. Residues were estimated in the blubber, liver, and brain, and, for the first 2 tissues, the ranges of values, for the 2 groups of females, did not overlap. Previous studies on both substances indicated possible reproductive effects in mammals, corresponding to some extent with those observed in the sea lions. Cause and effect could not, therefore, be directly established for each of the pollutants alone. Helle et al. (1976a) collected ringed seals from Simo, on the northern Bothnian Bay area of the Baltic Sea, in October/November. This population of seals shows reduced reproductive capacity and the sampled population showed only 27% of females pregnant, compared with other reports of 62.5% and 85–90% for the same species elsewhere. Residues of DDT and PCBs were compared with those in seals from other areas of the Baltic and found to be lower (Table 39). The seals sampled from Simo were divided into pregnant and non-pregnant groups (n= 15 and 26, respectively).

Table 39. Levels of DDT and PCBs (mean mg/kg±S.E.) in extractable fat of blubber from ringed seal from the Baltic Sea[a]

Area	Number	DDT	PCBs
Northern most part of the Bothnian Bay	40	110±10[b]	69±4.4[b]
Gulf of Bothnia	33	200±28	110±15

[a] Data from: Helle et al. (1976a).
[b] Value significantly different from those in the Gulf of Bothnia ($P<0.05$).

DDT and PCBs levels were both significantly higher in non-pregnant animals (Table 40). All females from both groups showed a corpus luteum in one ovary, indicating that all had ovulated. About half of the non-pregnant females showed indications of an embryo having been implanted, which had subsequently aborted or resorbed. Again

cause and effect could not be established directly. The authors pointed out that normally breeding Californian sea lions had DDT levels as high as those in Baltic seals showing reproductive failure and proposed this as an indication that PCBs were the causative agent.

Table 40. Levels of DDT and PCBs (mean mg/kg ± S.E.) in extractable fat of blubber in non-pregnant and pregnant ringed seal of reproductive age[a]

	Number	DDT	PCBs
Non-pregnant	26	130±13[b]	77±5.2[b]
Pregnant	15	75±11	56±6

a Data from: Helle et al. (1976a).
b Values for non-pregnant females significantly higher than those of pregnant females. DDT $P<0.01$; PCBs $P<0.05$.

It was further pointed out that the group of non-pregnant females would include some animals that were not pregnant for reasons other than the presence of organochlorine compounds. In a later paper (Helle et al., 1976b), the same authors reported that some of the non-pregnant females showed abnormal uteri with stenosis or occlusion of the uterine horns. They, therefore, subdivided the non-pregnant females in their second sample into those showing the anatomical abnormality and those not. Both DDT and PCBs were significantly higher in the occluded group than in pregnant animals. Non-pregnant females, without occlusions, showed residues of DDT and PCBs not significantly different from those in pregnant animals, and significantly lower than those females with occlusions. Residues in males were comparable with the highest residues found in females (Table 41).

There is some indication of a positive correlation between PCB residues and age in male seals but not in females (Addison et al., 1973; Addison & Smith, 1974). These observations are presumed to indicate that females excrete some of their body burden of PCBs in the milk.

These field observations have been confirmed in a study in which captive seals were fed on fish from the Wadden Sea (where reproductive problems had been found in the wild seal population) and

compared with controls fed fish from the Atlantic Ocean. Seals eating the contaminated fish, which differed from the control fish only in the PCB content, showed the same failure to carry the fetus successfully to term seen in the wild (Reijnders, 1986; see section 7.2.5).

Table 41. Levels of DDT and PCBs (mean mg/kg±S.E.) in extractable fat from blubber of ringed seal from Simo, Bothnian Bay[a]

Group	Sample description	Number	DDT	PCBs
I	pregnant females	24	88±9.7	73±6.6
II	non-pregnant females with stenoses and occlusions	29	130±10	110±7.8
III	non-pregnant females with normal uteri	8	100±15	89±11
IV	fetuses	24	62±4.3	49±3.0
V	males	24	130±18	100±13
probability of similarity between test groups (t-test)				
I-II			$P<0.01$[b]	$P<0.01$[b]
I-III			$P>0.05$	$P>0.05$
I-IV			$P<0.05$[c]	$P<0.01$[b]

[a] Data from: Helle et al. (1976b).
[b] Groups significantly different at the 99% level.
[c] Groups significantly different at the 95% level.

Subramanian et al. (1987) collected samples of blubber from male Dall's porpoise (*Phocoenoides dalli*) in the northwestern Pacific Ocean and analysed the samples for organochlorine content. Blood samples taken from the same animals were analysed for testosterone, a male sex steroid, and for aldosterone, another steroid hormone, responsible for blood electrolyte balance. Testosterone levels in blood were correlated with blubber levels of DDT and PCBs; as the organochlorine content increased, testosterone levels decreased. There was no relationship between blubber organochlorine levels and blood levels of aldosterone. The number of samples was small (n=12) and, though the relationship between DDT and testosterone was significant, the apparent relationship with PCBs was not. The

animals were sampled outside the breeding season, when testosterone levels would be expected to be low.

In a study by Clark & Lamont (1976), 26 pregnant big brown bats (*Eptesicus fuscus*) were collected from the field and maintained on a control diet, in captivity, until they gave birth to young. Levels of PCBs were measured in both the adults and the offspring. The concentrations of PCBs in litters with dead young were significantly greater than in litters where both young were born alive (mean for litters with dead young was 2.44 mg/kg; mean for all other litters was 0.34 mg/kg). The contents of PCBs ranged between 1.07 and 1.96 mg/kg wet weight in adults and between 0.28 and 1.69 mg/kg in the young.

7.4.4.1 *Appraisal*

PCBs have been implicated in population declines of seals and sea lions. Population decreases and reproductive failure have been observed in seals from the Baltic Sea, the Wadden Sea (southeastern North Sea), and the Gulf of St. Lawrence and in sea lions off the Californian coast. Poor reproduction has been correlated with residues of PCBs in the affected animals. A major problem in such studies is the occurrence of more than one chemical pollutant in the animals. PCBs are found together with other organochlorine compounds and heavy metals. Conclusions, therefore, have often relied on making the best correlation between observed effects and residues and checking cause and effect relationships on animals more amenable to laboratory study. A study on captive seals confirmed field observations on the effects of PCBs on these marine mammals (see section 7.2.5).

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

Evaluation of the toxicity of Aroclors and other commercial PCB mixtures is complicated by numerous factors, including isomer and congener composition, differences in species susceptibility, quantitatively inconsistent data, and various degrees of contamination with toxic compounds, such as chlorinated dibenzofurans. Because of these factors and a lack of data for some of the Aroclors (most studies have been conducted on the higher chlorinated Aroclors), it is assumed that effects resulting from exposure to a specific Aroclor are representative of effects that may be produced by the other Aroclors. Many of the literature sources do not give details of the composition of the PCB mixture used in the studies.

Reviews on the literature concerning the toxicity of PCBs are given by ATSDR (1989), Kimbrough (1980, 1987), Safe (1984), NIH (1985), and Lorenz & Neumeier (1983).

8.1 Single exposures

8.1.1 Oral

(*a*) *Aroclors*

The acute oral LD_{50} values for a number of Aroclors are presented in Table 42. The lowest oral LD_{50} in the rat was 1.0 g/kg body weight for Aroclor 1254 (Garthoff et al., 1981).

In Sherman rats, lethal doses of Aroclor 1254 and 1260 in peanut oil caused ulceration in the duodenum and glandular stomach (Kimbrough et al., 1972). Osborne-Mendel rats, receiving a single oral dose of 50 mg/kg body weight of Aroclor 1254 in corn oil, showed an increased relative liver weight together with the induction of microsomal enzymes, within 12 h (Litterst et al., 1974).

Monkeys, sacrificed 4 days after gastric intubation of Aroclor 1248 at 1.5 or 3.0 g/kg body weight (no vehicle reported), exhibited enlarged livers with proliferation of the endoplasmic reticulum and

Table 42. Acute oral LD_{50}s of Aroclors[a]

Aroclor	Species/strain	Sex/age[b]	LD_{50} (g/kg body weight)	References
1254	rat/Wistar	male/30 days	1.3	Grant & Phillips (1974)
		female/30 days	1.4	
		male/60 days	1.4	
		female/60 days	1.4	
		male/120 days	2.0	
		female/120 days	2.5	
	rat/Sherman	male/weanling	1.295	Linder et al. (1974);
		NR/adult	4-10	Kimbrough et al. (1972);
	rat/Osborne-Mendel	male/adult	1.01 (single dose)	Garthoff et al. (1981)
			1.53 (5 doses over 2 1/2 weeks)	
			1.99 (5 doses, 1 day/week)	
1221	rat/Sherman	female/NR	4.0	Nelson et al. (1972)
1260	rat/Sherman	NR/adult	4-10	Linder et al. (1974)
		M/weanling	1.315	
1242	rat/Sprague-Dawley	male/adult	4.25	Bruckner et al. (1973)
1262	rat	NR	11.3	Panel on Hazardous Trace Substances (1972)

[a] References: ATSDR (1989); WHO (1976).

[b] NR = not reported.

Information on solvents used was not available.

hypertrophy and hyperplasia of the gastric mucosa (Allen et al., 1974a).

(*b*) *Individual congeners*

Estimated oral LD_{50} values in 30 days for individual congeners in corn oil in Hartley guinea-pigs (probably single application) were 0.5 mg/kg body weight for 3,4,5,3',4',5'-hexachlorobiphenyl, less than 1 mg/kg body weight for 3,4,3',4',-tetrachlorobiphenyl, more than 3 mg/kg body weight for 2,3,4,5,3',4',5'-heptachlorobiphenyl, and more than 10 mg/kg body weight for 2,4,5,2',4',5'-hexachlorobiphenyl (McKinney et al., 1985).

8.1.2 Inhalation

No acute data were available.

8.1.3 Dermal

Median lethal doses for a single application of Aroclors to the skin of rabbits ranged from >0.79 to <1.27 g/kg body weight for Aroclors 1242 and 1248 in 50% corn oil, to >1.0 to <3.17 g/kg body weight for undiluted Aroclor 1221, and >1.26 to <2.0 g/kg body weight for Aroclor 1260 (Fishbein, 1974).

8.1.4 Other routes

(*a*) *Aroclors*

With a single intravenous dose of Aroclor 1254 in a 1% lecithin-saline suspension, the LD_{50} for adult female Sherman rats was 0.4 g/kg body weight (Linder et al., 1974). The LD_{50}s for Aroclor 1254 in DMSO for various mouse strains, following a single intraperitoneal injection, varied between 0.9 and 1.2 g/kg body weight (Lewin et al., 1972).

(*b*) *Individual congeners*

The intraperitoneal LD_{50} for 2,4,3',4'-tetrachlorobiphenyl in CF-1 mice was 2.15 g/kg body weight, while that of its main metabolite, (5-hydroxy-2,4,3',4'-tetrachlorobiphenyl) was 0.43 g/kg body weight, which suggests that the acute toxicity of

2,4,3',4'-tetrachlorobiphenyl might be attributable to this phenolic metabolite (Yamamoto & Yoshimura, 1973).

In male Wistar and Charles-River CD rats, a single intraperitoneal dose of 1 mg 3,4,5,3',4',-pentachlorobiphenyl/kg body weight or a single oral dose of 50 mg 3,4,5,3',4',5'-hexachlorobiphenyl/kg body weight caused significant liver enlargement accompanied by fatty changes, atrophy of the thymus, and decreased relative spleen weights. Mono-*ortho* substituted biphenyls, such as 2,3,4,5,3',4'-hexachlorobiphenyl and 2,4,5,3',4'-pentachlorobiphenyl, induced these effects in the liver and thymus to a minor degree following an intraperitoneal dose of 50 mg/kg body weight, while di-*ortho* substituted hexachloro- and heptachlorobiphenyls did not cause adverse effects at this dose level (Kohli et al., 1979; Yoshihara et al., 1979).

8.2 Short-term exposures

8.2.1 Oral

8.2.1.1 Aroclors

(*a*) *Mouse*

While oral intoxications by PCB mixtures in monkeys are easily recognizable by their effects on the skin, skin lesions in female ddN mice were only observed after 2–3 months of daily oral exposure to 1.6 mg of a technical PCB mixture (48% chlorine) per mouse (80 mg/kg body weight per day) in olive oil. The lesions included alopecia, erosions, ulcerations, and eczematous changes around the eyelids. No increase in mortality and only slight growth retardation were seen after 26 weeks of exposure (Nishizumi, 1970).

Koller (1977) found histological changes in the liver of mice exposed to 37.5 mg Aroclor 1254/kg diet for 6 months. A dose level of 3.75 mg/kg diet was without effect.

The oral toxicities of Kanechlor 400, 500, and 600 were compared by feeding male mice diets containing 300 mg PCBs/kg for 14 weeks (Kawanishi et al., 1975). Fatty degeneration and accumulation of pigment in the liver were observed in the mice fed Kanechlor 600.

(b) Rat

At lethal, oral doses of undiluted Aroclor 1242 (100 mg/kg body weight, every 2 days, for 3 weeks), Sprague-Dawley rats showed reduced body weight, thymus atrophy, chromodacryorrhea, progressive dehydration, and central nervous system depression with terminal ataxia and coma. Fatty changes were observed in the liver and kidneys (Bruckner et al., 1973).

Male and female Sherman rats (10 animals of each sex) were fed diets containing 0, 20, 100, 500, or 1000 mg of Aroclor 1260 or Aroclor 1254/kg (equivalent to 0, 1.5, 7, 36, or 72 mg/kg body weight, respectively) for 8 months. The animals receiving the 2 highest dose levels showed reduced growth. Female rats fed Aroclor 1260 at 500 and 1000 mg/kg diet showed a high mortality rate. However, only 3 rats fed Aroclor 1254 at 500 mg/kg diet died. Significant increases in relative liver/body weight ratios were found for both Aroclors at all doses tested. Microscopically enlarged hepatocytes, cytoplasmic inclusions, increased lipid levels, and foamy cytoplasm were all found consistently. Adenofibrosis was found at higher doses (500 and 1000 mg/kg diet) and corresponded to the glistering white areas seen on gross inspection. These areas also showed cholangiofibrosis (according to Kimbrough, synonymous for bile duct proliferation, bile duct adenomatosis, and fibroadenoma) (Kimbrough et al., 1972).

Growth and mortality rates were unaffected in male Sprague-Dawley rats exposed for 1 year to a diet containing Aroclors 1248, 1254, or 1262 at 100 mg/kg diet (equivalent to 5 mg/kg body weight) compared with controls (Allen et al., 1976).

Female Charles-River CD rats were fed for 20 weeks on a diet containing 0, 10, 30, or 100 mg Aroclor 1254/kg (equivalent to 0, 0.5, 1.5, and 5 mg/kg body weight, respectively). No increase in mortality rates occurred but growth inhibition was seen at 30 mg/kg from month 2 onwards and at 100 mg/kg diet from week 2 onwards. Skin lesions, initially on the ears, were found after 10–20 weeks of exposure to Aroclor 1254 at all dose levels. The lesions, including alopecia and reddened and thickened skin with hyperkeratosis, subcutaneous oedema, and infiltration by polymorphonuclear leukocytes, also involved the nose, tail, and feet at the highest exposure level (Zinkl, 1977).

Effects on the liver following exposure to PCB mixtures have mainly been investigated in rats (see section 8.6.1.1).

(*c*) *Rabbit*

Four groups of 5 male and 5 female New Zealand White rabbits were administered 300 mg Aroclor 1221, 1242, or 1254 in corn oil, via a stomach tube, once a week, for 14 weeks. The fourth group received only the vehicle.

The mortality rate was increased and the body weight gain was reduced after 14 weeks of oral exposure to Aroclor 1254, but not after exposure to Aroclor 1221 or 1242. Liver/body weight ratio and SGOT and SGPT activities were increased in the animals treated with Aroclor 1242 or 1254, but not in those treated with Aroclor 1221. In the animals treated with Aroclor 1254, the smooth endoplasmic reticulum was condensed in the liver cell and formed hyalin inclusions which might have been accompanied by a loss of enzyme activity. Lipid accumulation, pigment deposition, nuclear changes, and necrosis were also found (Koller & Zinkl, 1973).

(*d*) *Pig*

Pigs, fed Aroclor 1242 or 1254 at a dietary level of 20 mg/kg (equivalent to 0.8 mg/kg body weight) for 91 days, showed gastric lesions, consisting of erosions and necrosis. Two pigs fed a high-dose regimen of 100 mg of Aroclor 1254/kg body weight for 11 days, also showed hypertrophy and hyperplasia of the gastric mucosa; this was also found in monkeys at low exposure levels (Hansen et al., 1976b).

(*e*) *Cow*

Holstein cows were studied throughout a complete lactation period, a non-lactating period, and 42 days of a subsequent lactation period for overt responses to Aroclor 1254. Four cows received daily doses of 0, 10, 100, or 1000 mg/cow (1000 mg/cow is equivalent to 1.67 mg/kg body weight) over 60 days. The mean daily milk production and net energy of a complete lactation period did not differ between control and PCB-treated animals. At the end of the study, the concentrations of PCBs were 0.005, 0.021, 0.14 in blood plasma; 1.9, 10.9, 91.3 in milk fat, and 1.4, 6.9, 70.0 μg/kg in adipose tissue for the 10, 100, and 1000 mg PCB groups, respectively. No signs

of impaired health, productivity, or changes in blood and urine chemistry were observed (Willett et al., 1987).

(f) Monkey

Rhesus monkey

(i) Aroclor 1242

Becker et al. (1979) exposed 6, 7-8-month-old, male Rhesus monkeys to Aroclor 1242 at levels of 0, 3, 10, 10, 30, or 100 mg/kg diet (equivalent to 0, 0.12, 0.4, 0.4, 1.2, or 4.0 mg/kg body weight, respectively) to study changes in the stomach mucosa. At 3, 10, 30, and 100 mg/kg diet, 4 monkeys died after 245, 146, 92, and 137 days of exposure, respectively. All exposed monkeys showed a decreased body weight gain. At all dose levels, changes were observed in the folds of the suborbital facial skin, and eyelids became swollen and red. From day 71 at 3 mg/kg diet, days 69 and 77 at 10 mg/kg diet, and day 12 at the higher exposure levels, stomach biopsies revealed an apparent arrest of the differentiation of generative cells of the isthmus and neck regions into parietal and zymogenic cells. Mature parietal and zymogenic cells, which were found only in the bases of the glands, showed signs of injury, such as dilatation of the rough endoplasmic reticulum on the zymogenic cells, irregularity of the mitochondria in parietal cells, and irregular luminal membranes and an increase in the number of autophagic vesicles in both type of cells. The severity of the lesions was directly correlated with both duration and level exposure. A no-effect level was not obtained in this study.

A group of 5 Rhesus monkeys, 1–2.5 years old, was exposed to a diet containing 1 mg of Aroclor 1242/kg (equivalent to 0.04 mg/kg body weight) for 133 days. A control group contained 4 monkeys. No adverse effects were found (McNulty et al., 1980).

Characteristic lesions, metaplasia in epithelial structures, such as sebaceous glands, nail beds, gastric mucosa, and ameloblast surrounding unerupted teeth were reported to have developed in Rhesus monkeys, 13 months after a 40-day diet containing 400 mg Aroclor 1242/kg (equivalent to 16 mg/kg body weight) (McNulty, 1985).

(ii) Aroclor 1248

A group of 5 (4 males and 1 female), 1-month-old Rhesus monkeys, without previous exposure, were administered 30 daily doses of 35 mg of Aroclor 1248/kg body weight, by gavage, in corn oil. Four animals received only corn oil. No mortality or clinical signs were observed, except for a decrease in body weight gain, slightly reduced food consumption, and anaemia. Mild microscopic changes were observed in the thymus, bone marrow, eye, skin, stomach mucosa, and liver (Abrahamson & Allen, 1973).

Six male Rhesus monkeys, aged 1 1/2–2 years were fed a diet containing 300 mg Aroclor 1248/kg for 3 months. Three animals served as controls. A decrease in body weight was observed. Within one month, all the animals fed PCBs had alopecia, subcutaneous oedema, particularly of the face, which manifested as swollen eyelids, erythema, and acneiform lesions involving the areas devoid of hair (Allen & Norback, 1972 cf. Hayes (1987)).

Six adult, female Rhesus monkeys were fed 25 mg Aroclor 1248/kg diet for 2 months. Facial oedema, alopecia, and acneiform changes developed within 1 month and 1 animal died 2 months after removal from the experimental diet. In addition to the above changes, this animal showed anaemia, hypoproteinaemia, hypertrophy, and hyperplasia with invasion through the muscularis mucosa, focal haemorrhages and ulcerations of the gastric mucosa, and bone marrow hypoplasia. Eight months later, the 5 surviving animals continued to show clinical signs of intoxication. The PCB concentration in body fat, which, after 2 months of treatment, averaged 127 mg/kg, had decreased 8 months later to 34 mg/kg (Allen et al., 1974a).

Groups of 9 adult, female Rhesus monkeys (weight approximately 5.6 kg), were fed a diet containing 0, 2.5, or 5.0 mg Aroclor 1248/kg (equivalent to 0, 0.1, or 0.2 mg/kg body weight, respectively) for an average period of 18.2 months. An additional group of 4 males was fed 5.0 mg/kg diet. Control groups contained 12 female and 6 male monkeys. The Aroclor 1248 contained 4.4–8.7 ng polychlorinated dibenzofurans/kg diet. The female monkeys were mated with control males after 6 months of exposure (the reproductive effects are discussed in section 8.4.1.3). Levels of Aroclor 1248 in adipose

tissue reached a plateau after 1 year at 2.5 mg/kg diet and after 6 months at 5 mg/kg diet. Exposed males showed slight to moderate periorbital oedema and congestion of the eyes. Females showed an average 15% loss in body weight over the first 5 months of both exposures, while food consumption was normal. At 6 months, they all showed loss of hair, acne of the face and neck, and erythema and swelling of the eyelids. Skin biopsies revealed keratinization of the affected hair follicles. One female monkey died after 173 days of exposure to 2.5 mg/kg diet and one female died after 310 days of exposure to 5.0 mg/kg diet. Both animals developed terminal enteritis due to Shigellosis, which was resistant to treatment. At autopsy, the animals showed generalized alopecia, subcutaneous oedema, and acne. Microscopically, follicular epithelial hyperplasia with inflammation of the surrounding tissue, and keratinization of the hair follicles were observed. The livers showed focal areas of necrosis, enlarged hepatocytes, and fatty changes (Barsotti et al., 1976).

The surviving females in the former study, 8 per dose level, were placed on a control diet for approximately 1 year after an average total intake of 270 and 498 mg Aroclor 1248, respectively. There was a gradual improvement in their physical condition and, within one year, their gross appearance was no longer different from that of the controls. However, their breeding performance was still affected, as outlined in section 8.4.1.3 (Allen et al., 1980).

(iii) Aroclor 1254

Several pilot studies were carried out before this major study to characterize the toxicity of Aroclor 1254 and to compare the toxic findings in the Rhesus and Cynomolgus monkey (Tryphonas et al., 1984, 1986b; see section 8.2.1.6). In these pilot studies, Mes & Marchand (1987) and Mes et al. (1989a) measured the concentrations of PCBs in the blood, adipose tissue, and faeces.

A preliminary report describes the results of an ongoing study after 54 weeks of daily oral administration of gelatin capsules containing 0, 5, 20, 40, or 80 μg Aroclor 1254/kg body weight, in corn oil-glycerol, to groups of 16 adult, female Rhesus monkeys (*Macaca mulatta*). At this stage, a slight decrease in body weight gain was observed in the exposed monkeys together with a decrease in water consumption, but not in food consumption. In week 52, the

incidences of prominent nail beds, of nails separated from the beds, and of prominent tarsal glands increased in the animals exposed at 80 μg/kg body weight (Arnold et al., 1984).

Aroclor 1254, at a dose level equivalent to 280 μg/kg body weight was given for 5 days per week to Rhesus monkeys (*Macaca mulatta*) over a period of 27–28 months. Four animals were treated as described and 4 animals served as controls. The Aroclor 1254 was administered in apple-juice-gelatin-corn oil emulsion. The weight of the monkeys at the beginning of the study was approximately 4 kg. Terminal clinical signs of varying severity included finger nail detachment, exuberant nail beds, weight loss, stomatitis, and normocytic anaemia. At necropsy, the bone marrow was hypocellular with cytoplasmic vacuoles in erythroid precursor cells. Histopathological lesions included dilatation of the tarsal gland ducts, atrophy, or absence of, splenic and lymphonodal germinal centres, bone marrow depletion, gingival erosion and ulceration, moderate mucinous hypertrophic gastropathy with cystic dilatation of occasional gastric glands, hepatocellular enlargement and necrosis, hypertrophy of biliary duct epithelium, hyperplasia of biliary ducts, hypertrophy of the gall bladder epithelium, and an equivocal increase in the number of lysosomes in the thyroid follicular epithelial cells. The terminal PCBs concentrations in a number of organs were as follows: adipose tissue 106.7–2073.2 mg/kg (in control animals 0.26–0.65 mg/kg); brain, 31.2–252.0 mg/kg; kidneys, 85.4–964.1 mg/kg; and liver, 255.1–828.1 mg/kg tissue. The PCB concentrations were expressed on a mg/kg fat basis. It was concluded that skin appendicular lesions are good clinical indices of PCB exposure in monkeys and that lymphoreticular lesions (atrophy and absence of lymphoid follicular centres) are good indicators of impending or active immunological crisis (Tryphonas et al., 1986a).

(iv) Miscellaneous studies

Accidental exposure of a colony of 256 Rhesus monkeys to PCBs in a concrete sealant produced a disease characterized by high mortality, gradual weight loss, behavioural changes, alopecia, acne, facial oedema, swollen eyelids, diarrhoea, anaemia, poor breeding performance, and high incidences of abortions and still births. Samples of the concrete slabs within several buildings were obtained and

analysed. Significant levels of PCBs (5280 mg PCB/kg sample) were found (Altman et al., 1979; McConnell et al., 1979).

The effects of exposure to PCBs on the eyes were investigated by Ohnishi & Kohno (1979), who administered a banana injected with 0.5 mg of PCBs/kg body weight, daily, to 8 adult Rhesus monkeys of both sexes for 1–5 months. Two out of this group were fed PCBs with polychlorinated dibenzofurans (2.5 μg/kg body weight). Four untreated animals were used as controls. One month after the onset of the exposures there was a reduction in body weight. When pressure was applied to the eyelids of treated monkeys, white secretions extruded. Within 3 months alopecia, swelling of the eyelids, and acne-form eruptions developed. The retina and choroid were normal. The histopathological changes in the eyelids were comparable in both groups of exposed monkeys and included the appearance of keratinous cysts and atrophy of the Meibomian glands with hyperkeratosis and hyperplasia of the ductal epithelium.

Cynomolgus monkey

Groups of 5 or 6 adult, female Cynomolgus monkeys (*Macaca fascicularis*) were exposed to 3, weekly doses of 4.7 mg of Aroclor 1248/kg body weight (equivalent to 2 mg/kg per day) or to 3-weekly doses of 11.7 mg of Aroclor 1254/kg body weight (equivalent to 5 mg/kg per day) in an apple juice-corn oil emulsion. The monkeys were exposed until necropsy at day 30–164 in dead or moribund condition. A control group contained 5 monkeys. In both exposed groups, body weight loss, emaciation, facial oedema, finger-nail loss, and lacrimation were observed. Common histopathological lesions were: dilated Meibomian gland ducts, mucinous hyperplasia and hypertrophy of the gastric mucosa, enlargement, fatty degeneration, and necrosis of hepatocytes, bile duct and gall bladder epithelial cell hypertrophy and hyperplasia, and thyroid changes in follicular cell size and the number of intracytoplasmic lysozomes.

The onset of the signs and lesions of toxicity was not as rapid and uniform as that in Rhesus monkeys. Aroclor 1248 appeared more toxic than Aroclor 1254 (Tryphonas et al., 1984).

Groups of 4 adult, Rhesus and 4 adult, Cynomolgus female monkeys, weighing 3.2–4.5 and 3.2–5.2 kg, respectively, received doses of Aroclor 1254 at 0 or 280 μg/kg body weight for 5 days/week

(equivalent to 200 μg/kg per day) in an apple-juice-gelatin-corn oil emulsion for 27–28 and 12–13 months, respectively. This study showed that the Rhesus monkey is more susceptible to PCB toxicity than the Cynomolgus monkey (Tryphonas et al., 1986b).

Hori et al. (1982) exposed 1 female, Cynomolgus monkey to daily doses of Kanechlor 400 (without detectable quantities of polychlorinated dibenzofurans) at 2 mg/kg body weight, in olive oil. They also exposed 3 monkeys to a PCB mixture with a chromatographic pattern similar to that of the Yusho mixture (2 or 4 mg/kg body weight), and 1 monkey to 2 mg/kg body weight of the same mixture, without detectable quantities of polychlorinated dibenzofurans (detection limit not given). The doses were administered 6 times per week in a piece of banana. Two controls received only the vehicle. The 2 monkeys receiving the Yusho mixture at 4 mg/kg body weight died within 4 and 8 weeks, respectively. The other monkeys were kept for 20 weeks. In all monkeys exposed to the Yusho mixture, toxic effects were similar to those already described above. In addition, there was cytoplasmic vacuolation and dilatation of the convoluted tubules with cytoplasmic casts in the kidneys. The other 2 mixtures induced less severe reductions in body weight gain, immunosuppression and histopathological alterations in liver, kidneys, and periorbital skin. The effects in the animals fed a diet with dibenzofurans yielded enhanced decreases in body weight, immunosuppression, fatty liver and histological changes, in addition to hair loss, acne-form eruptions, oedema of the eyelids and cornification of the skin, compared with the other test substances.

8.2..1.2 *Individual congeners*

(*a*) *Monkey*

Rhesus monkeys have been exposed to various congeners, as outlined in Table 43.

No toxicity could be demonstrated either by clinical appearance or by histopathological examination for isomers with 2 or 4 chlorine atoms *ortho* to the biphenyl bridge. The clinical signs observed in monkeys exposed to 3,4,3',4'-tetrachlorobiphenyl (up to 3 mg/kg diet) and 3,4,5,3',4',5'-hexachlorobiphenyl (at 1 mg/kg diet) were

Table 43. Toxicity of PCB-congeners in Rhesus monkeys[a]

Congener[b]	No. of animals/ group	Exposure		Time clinical toxicity first noted (day)	Deaths
		mg/kg diet	period (days)		
2,5,4'-TriCB	4	5	84	-	0
3,4,3',4'-TCB	3	3⇒1[c]	215	14-21	3
	5	1	38	27	1
2,5,2',5'-TCB	3	3⇒1[c]	215	-	0
	5	1⇒5[d]	200	-	0
3,4,5,3',4',5'-HCB	1	0.1	127	117	1
	4	0.5	63	28-30	4
	1	1	57	20	1
2,4,5,2',4',5'-HCB	4	15	122	-	0
	1	65	63	-	0
2,4,6,2',4',6'-HCB	4	15	122	-	0
	1	65	64	-	0
2,3,6,2',3',6'-HCB	4	15	122	-	0

[a] From: McNulty et al. (1980); McNulty (1985); Iatropoulos et al. (1977).
[b] TriCB = trichlorobiphenyl; TCB = tetrachlorobiphenyl; HCB = hexachlorobiphenyl.
[c] Dietary level reduced after 23 days.
[d] Dietary level raised after 133 days.

similar in character and severity to those produced by Aroclor 1242 (at 100 mg/kg diet) and Aroclor 1248 (at 25 mg/kg diet) in monkeys (Allen et al., 1974a). The same histopathological lesions were found. The lesions of the skin and eyes were described as an expression of squamous atrophy or squamous cyst formation of the sebaceous glands. The epithelial changes in the skin and nails were found to be reversible. In this study, 2,5,2',5'-tetrachlorobiphenyl did not produce any clinical or pathological lesions at 3 mg/kg diet. Aroclor 1242 and 1248 were reported to contain about 0.24 and 0.34% of 3,4,3',4'-tetrachlorobiphenyl, and it was concluded that this

congener could account for some of the toxicity of the commercial mixtures (McNulty et al., 1980; McNulty, 1985).

Rhesus monkeys exposed to 2,5,4'-trichlorobiphenyl showed a reversible primary injury of the arterioles, capillaries, and venules in the adrenal glands, kidneys, liver, brain, and lungs (Iatropoulos et al., 1977).

(*b*) *Other animal species*

In studies on rats and mice, individual PCB-congeners caused adverse effects on the liver, spleen, and thymus. The most toxic compounds were the planar congeners 3,4,3',4'-tetrachlorobiphenyl, 3,4,5,3',4'-pentachlorobiphenyl and 3,4,5,3',4',5'-hexachlorobiphenyl.

Biocca et al. (1981) and Aulerich et al. (1985) compared the toxicities of various hexachlorobiphenyl isomers in mice. Male C57 BL/6 mice were exposed via the diet to 0.3, 1, 3, 10, 30, 100, or 300 mg 3,4,5,3',4',5'-hexachlorobiphenyl; 10, 30, 100, or 300 mg 2,4,5,2',4',5'-hexachlorobiphenyl, 2,3,6,2',3',6'-hexachlorobiphenyl, or 2,4,6,2',4',6'-hexachlorobiphenyl/kg diet for 28 days. There were marked differences in dose response and in the severity of the pathological effects among the isomers. 3,4,5,3',4',5'-Hexachlorobiphenyl was the most toxic isomer causing mortality, and body and organ weight effects at all dose levels and was the only isomer that produced excess porphyrin accumulation. It was also the isomer that occurred in the highest concentration in the fat and the liver. 3,4,5,3',4',5'-Hexachlorobiphenyl caused subcutaneous oedema, enlargement of the liver with accentuated hepatic lobular markings, fatty infiltration, hepatocellular swelling and necrosis, and atrophy of the thymus. The other 2 isomers caused the same lesions, but to a lesser extent.

In the mice, the overall order of toxicity was 3,4,5,3',4',5'-hexachlorobiphenyl >2,4,6,2',4',6'-hexachlorobiphenyl >2,4,5,2',4',5'-hexachlorobiphenyl >2,3,6,2',3',6'-hexachlorobiphenyl, based on the effects on mortality and growth, and on histopathology.

8.2.2 Intraperitoneal: reconstituted PCB mixtures

Bandiera et al. (1984) administered reconstituted mixtures of PCDFs and reconstituted mixtures of PCBs, by intraperitoneal injection, to immature Wistar rats, to determine the effects on weight loss, thymic atrophy, and the induction of P-448 dependent monooxygenases. The mixtures consisted of compounds that persisted in the blood and liver of Yusho patients. From the results, it was clear that the PCDFs were 600 to 2100 times more toxic than the PCBs.

A group of 4, one-month-old, male Wistar rats received intraperitoneally a reconstituted PCB mixture containing 13 of the major congeners that have been identified in human milk, at the corresponding relative concentrations. The mixture was injected on days 1 and 3 in corn oil at dose-levels of 0, 0.45, 0.90, 4.5, or 45 mg/kg body weight. The rats were killed on day 6 for histopathological studies. At the highest exposure level, increased relative liver weights and enlarged and vacuolated hepatocytes were observed together with changes in nuclei. In the thyroid, a mild reduction in follicular size, focal collapse, and changes in nuclei were found. No changes were seen with 0.9 mg/kg body weight (Gyorkos et al., 1985) (see section 8.8.1.1).

8.2.3 Dermal exposure

(*a*) *Aroclors*

Solutions of Phenoclor DP6, Clophen A60, or Aroclor 1260 in isopropanol were applied in doses of 118 mg on 50 cm^2 of the shaved back skin of groups of 4 New Zealand rabbits, 5 times per week, for 38 days. A group of 4 rabbits received the vehicle only. After initial reddening, transverse wrinkling and thickening of the skin developed with hyperplasia and hyperkeratosis of the epidermal and follicular epithelium. These effects were more marked with Clophen and Phenoclor than with Aroclors. During the study, deaths occurred in the Clophen- and Phenoclor-treated groups. Body weights and relative kidney weights were decreased in the Aroclor-treated rabbits. Histological liver changes were least marked in the Aroclor-treated rabbits. Treated rabbits had fluorescing livers and bone under UV radiation and also showed other evidence of porphyria. In the kidneys, hydropic degeneration of the convoluted tubuli, and tubular

dilatation were found. There was atrophy of the thymic cortex and a reduction of germinal centres of the lymph nodes, as well as leukopenia, and some animals in all groups showed oedema of the abdominal and thoracic cavities, subcutaneous tissue, and pericardium. Faecal elimination of copro- and protoporphyrine was increased by all 3 PCBs, but was lowest with Aroclor 1260 (Vos & Beems, 1971).

Puhvel et al. (1982) exposed groups of 3 female, hairless mice of 2 strains, (Skh:HR-1 and HRS/J), topically to Aroclor 1254 (4 doses of 1 or 8 mg/week, for 6 weeks) or Phenoclor 54 (5 doses of 0.2 mg/week, for 10 weeks) in acetone or an acetone-mineral oil-Tween 80 emulsion, or to the vehicle only. Punch biopsies of the skin were taken regularly. The skin of treated mice appeared grossly normal after the exposures, but examination of microscopic skin samples of Phenoclor-treated mice showed hyperkeratosis of the stratum corneum, epidermal hyperplasia, disappearance of sebaceous glands, and the presence of numerous keratinous cysts. No histological changes were observed in the internal organs.

(*b*) *Individual congeners*

In the study of Puhvel et al. (1982), described above, groups of 3 hairless mice of both strains were also exposed topically to 5 doses of 0.2 mg 3,4,3',4'-tetrachlorobiphenyl/week, for 10 weeks. Grossly there were no visible changes. The histological changes induced in HRS/J mice were similar to those found after Phenoclor treatment. However, identical changes induced in Skh:HR-1 mice were already observed by 4 weeks. After 8 weeks, these lesions were more marked and also included hyperkeratosis of the sebaceous follicles and hyperkeratinization of intradermal pilar cysts. Often these cysts ruptured into the dermis leading to dense infiltrates of polymorphonuclear leukocytes. The treated mice showed weight gain, primarily because of large intra-abdominal fat deposits.

In a dermal toxicity study on rabbits, with a protocol identical to that of the study of Vos & Beems (1971), skin lesions on animals treated with 2,4,5,2',4',5'-hexachlorobiphenyl were less severe than those on Aroclor 1260-treated animals. The liver damage observed histologically was essentially the same after treatment with either Aroclor 1260 or 2,4,5,2',4',5'-hexachlorobiphenyl, but the individual

congener was more porphyrogenic (Vos & Nootenboom-Ram, 1972). In another study, 4 applications of a 25% solution of 3,4,3',4'-tetrachlorobiphenyl in olive oil to the inner surface of the ears of rabbits resulted in the same lesions that were found after 2 applications of undiluted Kanechlor 400 or 500. The lesions included hyperkeratosis, dilatation of hair follicles, and the formation of keratinous cysts (Komatsu & Kikuchi, 1972).

8.2.4 Appraisal

Rhesus monkey is the most sensitive test species with regard to the general toxicity of PCBs, both as a mixture and as individual congeners. The toxicity of mixtures may be confounded by the presence of impurities, such as PCDFs, which are, or may have been, present in the mixtures tested. PCBs induce some of the biological and toxicological effects qualitatively similar to those induced by PCDFs. Another confounding variable in these studies is the difference in the composition of the mixtures (Aroclor 1242, 1248, 1254) used.

Bearing the above in mind, the available data show that Aroclor 1248, containing 4.4–8.7 ng of PCDFs/kg, still showed adverse general toxic effects in Rhesus monkeys at a dose of 0.1 mg/kg diet per day (0.09 mg/kg body weight per day) administered for an average of 18.2 months (Bowman et al., 1981). A NOEL for general toxicity was not established for Aroclor 1248. The NOEL for the general toxicity of Aroclor 1242 was 0.04 mg/kg body weight per day, as established after dietary exposure for 133 days. The main effects induced by Aroclor 1248 at 0.09 mg/kg body weight per day were an increased mortality rate, growth retardation, alopecia, acne, swelling of the Meibomian glands, and, possibly, immunotoxicity. Microscopically, enlarged hepatocytes, fatty liver with focal necrosis, and epithelial hyperplasia and keratinization of hair follicles were found. These effects appeared reversible. Aroclor 1254 at a dose level of 0.200 mg/kg body weight per day showed several effects, not reported for 1248 (lymforeticular lesions, finger-nail detachment, gingival effects) and vice-versa (acne, alopecia), which could be related to the confounding variables noted above. Several effects observed in the monkeys exposed to Aroclor 1254 (hypertrophic gastropathy, bone marrow hyperplasia) were also

observed in monkeys exposed to Aroclor 1248, but at a higher dose (4 mg/kg body weight per day). In contrast with the severe effects observed in adult Rhesus monkeys at low doses, relatively mild effects were shown by suckling Rhesus monkeys exposed to much higher doses.

8.3 Skin and eye irritation, sensitization

The injury to skin and eyelids following oral and/or dermal exposure to PCBs has been discussed in sections 8.2.1 and 8.2.3.

8.4 Reproduction, embryotoxicity, and teratogenicity

8.4.1 Reproduction and embryotoxicity

8.4.1.1 Oral

(*a*) *Mouse*

In castrated, mature, male NMRI mice (10–13 per group) that received 28 daily doses of 0.25 mg Aroclor 1254/mouse, in peanut oil, the weight of the seminal vesicles was decreased, but this was not seen in intact mice (Örberg & Lundberg, 1974).

When 23 adult female NMRI mice were mated with 22 control males and orally intubated with 0.025 mg Clophen A60/day, in peanut oil, for 62 days prior to mating and up to days 8–10 of gestation, blastocytes failed to implant. Twenty-five (14 experimental and 11 control animals) out of the 45 animals were used to study the effects of PCBs on the estrous cycle. Effects, such as prolonged estrous cycle and less frequent periods of sexual receptivity and a decline in the number of implanted ova, were found (Örberg & Kihlström, 1973).

In order to study the effects of PCBs on the development of sexual functions in the early postnatal period, these authors also mated mice that had been suckled by mothers dosed with Clophen A60 during the lactation period. A decrease in the frequency of implanted ova was noted, when both parents of the couple had been suckled with milk containing PCBs. When adult female NMRI mice received 50 mg of Clophen A60/kg body weight once per week, subcutaneously,

during lactation, the same effect was observed in the offspring after mating with similarly exposed males (Kihlström et al., 1975).

(b) Rat

In a 2-generation reproduction study, groups of 10 male and 20 female Sherman weanling rats were fed diets containing 1, 5, 20, or 100 mg of Aroclor 1254/kg (equivalent to 0.06, 0.32, 1.5, and 7.6 mg/kg body weight, respectively), or diets containing 5, 20, or 100 mg/kg of Aroclor 1260 (equivalent to 0.39, 1.5, and 7.5 mg/kg body weight, respectively). Control groups comprised 20 male and 40 female rats. The F0 rats were started on the diet at 3–4 weeks of age and the F1 rats, at weaning. The F0 rats were pair-mated when 3 and 7 months old to produce the F1a and F1b generations, respectively. Breeding-stock F1b rats were selected at weaning and pair-mated when 3 months old to produce the F2a, and, when 8 months old, the F2b generation. Rats exposed to Aroclor 1254 at 20 mg/kg diet or more showed a reduced litter size at birth, but not when exposed at weaning, in the F1b and F2 generations. At 100 mg/kg diet, the number of litters in the F2 generation was decreased. In 2 F2a and 2 F2b litters no live offspring were found at birth, while pup survival at weaning was reduced in the F2a generation. At weaning, exposed F1a pups weighed less than their controls. Increased relative liver weights were found in male F1a weanlings at 1 mg Aroclor 1254/kg diet and in all weanlings at 5 mg/kg diet or more. Adult rats showed increased relative liver weights at levels of 20 mg/kg diet or more. No reproductive effects were found with 5 mg Aroclor 1254/kg diet. In groups treated with Aroclor 1260, increased liver weights were found in all weanlings at 5 mg/kg diet or more, but no effects on reproduction were seen, even at 100 mg/kg diet (Linder et al., 1974).

The only effect observed in Holtzman rats fed Aroclor 1254 at a level of 500 mg/kg diet, for 3 weeks, was an increase in relative testes weights (Garthoff et al., 1977). Increased absolute testes weights and unchanged body weights were found in 6-month-old offspring of Sprague-Dawley dams exposed to daily doses of 30 mg Aroclor 1260/kg body weight in ethanol-sesame oil on days 14–20 of gestation. No effects on testes weight were found in animals treated with Aroclor 1221 or Aroclor 1242 (Gellert & Wilson, 1979).

Sager (1983) evaluated the effects on the reproductive function of adult male Holtzman rats following exposure of their mothers to doses of 8, 32, or 64 mg Aroclor 1254/kg body weight in peanut oil, on days 1–3, 5, 7, or 9 of lactation. At all dose levels, 165-day-old males showed a decreased relative ventral prostate weight, and, at the 2 higher doses, a decreased relative weight of seminal vesicles and testes as well as decreased body weight. In the ventral prostate, alveoli were decreased in number and showed folding of the mucosa and flattened epithelial cells. At 130 days of age, the male offspring at all 3 dose levels showed a reluctance to mate with control breeders, leading to a decreased number of pregnancies. Moreover, at the 2 higher dose-levels, the females showed a reduced number of implantations and an increased resorption rate. The litters showed a reduced weight gain up to 11 days of age.

This study was repeated with an evaluation of the reproductive performance of the second generation male rats from 130 days of age, following mating with normal females. In the first study, autopsy on pregnant females was carried out on day 11 or 12 of gestation. The females had fewer implants, fewer embryos, and a reduced proportion of ovulated eggs that implanted, compared with controls. The effects were dose-related. In a second study, females mated to the same males were autopsied on day 2 or 4 after mating. Sperm counts were not affected. At the 2 highest doses, fewer females had eggs in the expected state of development, the average number of blastocytes found in one uterine horn on day 4 was reduced, and an increased incidence of abnormally developed embryos was observed (Sager et al., 1987).

Female Wistar rats exposed to daily doses of 10 mg Aroclor 1254/kg body weight, for at least one month, showed a prolonged estrous cycle, decrease in sexual receptivity, delay in timing of copulation, vaginal bleeding during gestation, decrease in litter size, and delay in the time of parturition. After mating of the rats to control males, the female offspring, exposed *in utero* and during lactation, showed a slower rate of body weight gain, higher mortality, earlier vaginal opening, and a delay in the appearance of the first estrous cycle (Brezner et al., 1984).

(c) *Monkey*

Groups of 9 adult female Rhesus monkeys were exposed to a diet containing Aroclor 1248 (containing polychlorinated dibenzofurans) at levels of 2.5 or 5.0 mg/kg (Barsotti et al., 1976; Allen et al., 1979, 1980). The study and the maternal toxicity data have already been described in section 8.2.1.6. Within 4 months, menstrual bleeding and the duration of the menstrual cycle were increased. Flattening and prolongation of the serum progesterone peak during the menstrual cycle was observed. After 6 months of exposure, the females were mated with control males. Reproductive dysfunction was obvious as shown in Table 44. Following the total exposure period of 18.2 months, the mothers were put on a control diet. Their menstrual cycles and serum progesterone levels returned to pre-exposure values. One year after exposure ceased, the females were again mated with control males and showed a recovery of their reproductive status (Table 44; Allen et al., 1980).

Other groups of adult, female Rhesus monkeys were continuously fed diets with 0, 0.25, and 1.0 mg Aroclor 1016/kg (equivalent to 0, 0.01 and 0.04 mg/kg body weight, respectively), in which no polychlorinated dibenzofurans were detected (no details). No maternal toxicity was noted at these levels. In this study, the females were mated with control males after 7 months of exposure. Reproductive dysfunction was not observed. Decreased birth weights were found in the offspring of mothers exposed to Aroclor 1016 at 1.0 mg/kg diet. Skin hyper-pigmentation occurred in both exposure groups (Barsotti & Van Miller, 1984). Preliminary reports have indicated possible effects on learning and behavioural tasks. The milk contained an average of 1.45 and 3.92 mg/kg fat at 0.25 and 1.0 mg/kg, respectively, whereas the serum of the mothers contained 0.012 and 0.027 mg/litre, respectively (Heironimus et al., 1981; Levin & Bowman, 1983).

In these studies, the monkeys were maintained on the diets during the gestation and lactation of the first generation. PCBs are known to cross the placenta and to be excreted via breast milk (see section 6.3). The 6 infants born to monkeys during exposure at 2.5 or 5.0 mg Aroclor 1248/kg diet showed decreased birth weights, a small stature, and a decreased body weight gain during nursing. Within 2 months,

Table 44. Reproductive status of Rhesus monkeys exposed to dietary levels of Aroclor 1016 or 1248

PCB mixture (Aroclor)	Exposure level		Total intake at conception (mg/kg)	Conceptions	Abortions and resorptions	Stillborn	Live births	Reference
	Diet (mg/kg)	Body weight (mg/kg)						
1016	0	0	0	8/8	0/8	0/8	8/8	Barsotti &
	0.25	0.01	8[c]	8/8	0/8	0/8	8/8	van Miller
	1.0	0.04	30[c]	8/8	0/8	0/8	8/8	(1984)
1248	0	0	0	12/12	0/12	0/12	12/12	Barsotti et al.
	2.5	0.09[a]	105	8/8	3/8	0/8	5/8	(1976)
	5.0	0.2	210	6/8	4/8	1/8	1/8	
1248	0	0	0	8/8	0/8	0/8	8/8	Allen et al.
	2.5	0.09[a]	270	8/8[b]	1/8	0/8	7/8	(1980)
	5.0	0.2	498	7/7[b]	1/7	2/7	4/7	

[a] From: Bowman et al. (1981) amended.

[b] Breeding 1 year after exposure.

[c] Calculated assuming a body weight of 5 kg.

signs of intoxication appeared including acne, increased skin pigmentation, swelling of the eyelids, and loss of eyelashes. In 3 milk samples, values ranging from 0.154 to 0.397 mg PCBs/kg milk were measured, and, 1 milk sample contained 16.44 mg PCBs/kg fat. Three infants died. Necropsy and histopathology revealed atrophy of the thymus and lymph nodes, hypocellular bone marrow, moderate fatty infiltration of the liver, hypertrophic Meibomian glands, and keratinization of hair follicles. One dead infant showed hyperplasia of the gastric mucosa. The 3 surviving infants were weaned and subsequently showed marked improvements in their physical status (Allen & Barsotti, 1976; Allen et al., 1979, 1980). At 6 and 12 months of age, they were found to be hyperactive in a locomotor activity test and, between 7 and 24 months of age, they did not learn reversal tasks as readily as the controls. The PCB body burdens of these infants ranged between 11 and 27 mg/kg body fat, at the age of 8 months, and dropped to 0–1.6 mg/kg, at the age of 23 months. However, using the same apparatus, these infants showed hypolocomotor activity at 44 months of age in comparison with the same controls (Bowman et al., 1978; Bowman & Heironimus, 1981; Bowman et al., 1982; Levin & Bowman, 1983).

The infants delivered by the same adult females, after 1 year on a control diet, showed a reduced body weight and signs of intoxication similar to those observed in their siblings of the first breed. Two infants in each exposed group died. Milk samples contained 0.02–0.19 mg PCBs/kg milk (Allen et al., 1980). At 12 months of age, when the PCB body burdens were only slightly higher than those of the controls, the infants showed hyperlocomotor activity (Bowman et al., 1982).

Groups of 4 or 6 Rhesus monkeys, which had been exposed to 0 or 2.5 mg Aroclor 1248/kg diet *in utero* and during nursing until 4 months after birth, were tested at 4–6 years of age on delayed spatial alternation (DSA), a spatial learning and memory task. Deficits in performance accuracy were detected in 2 cohorts of monkeys, whose mothers had been fed 2.5 mg Aroclor 1248/kg diet for an 18-month period ending at least 12 months prior to pregnancy. The deficit was most apparent at the shorter delays, suggesting impairments in association or attention processes were involved rather than memory impairment. Such a deficit was also found in monkeys fed 1.0 mg

Aroclor 1016/kg diet, but the effect was less pronounced. The appearance of a PCB-induced cognitive deficit more than 3 years after the end of exposure indicated the existence of long-term adverse consequences of perinatal PCB exposure (Levin et al., 1988).

Clophen A30, which did not contain detectable levels of polychlorinated dibenzofurans (limit of detection < 1 mg/kg), was given by gavage in a 1% solution of methylcellulose in water, once daily for 30 days, to 3 lactating Rhesus monkeys and their offspring at a level of 16 mg/kg body weight. PCB concentrations were measured in the serum of both mothers and infants and in the milk, on days -14, -7, 0, 1, 2, 4, 8, and then at weekly intervals until the end of the study. The mean PCB concentrations in the serum of mothers and infants were between 0.13 and 1.16 mg/litre and 0.07 and 2.67 mg/litre, respectively (before treatment days -14 and -7). The mean PCB levels in milk ranged from 0.63 mg/kg on day 1 of exposure to 18.90 mg/kg. On days -14 and -7, the concentrations in milk were 0.14 and 0.34 mg/kg (wet weight). Five control pairs were used. One dam and her offsping were sacrificed on day 22, exhibiting symptoms of anorexia, depression, lethargy, and ataxia. Two of 3 infants showed a decreased body weight gain. At autopsy of the infants, after the exposure period, slight degenerative changes were seen in the liver and the kidneys, together with slight demyelination of the central nervous system, slight to moderate gliosis of the cerebrum, and slight granular cell layer thinning of the cerebellum. On the basis of earlier work with adults in which the degenerative changes described above were considerable, the authors concluded that the nursing infants seemed to be less susceptible than the adults under the conditions of the studies (Iatropoulos et al., 1978; Bailey et al., 1980).

8.4.2 Teratogenicity

8.4.2.1 Aroclors (oral)

(*a*) *Mouse*

Haake et al. (1987) reported that treatment of pregnant C57Bl/6 mice with Aroclor 1254, by gavage, at 224 mg/kg body weight, on day 9

of gestation, did not result in any fetuses with cleft palate (see section 8.6.6).

(*b*) *Rat*

Wistar rats were exposed to dietary levels of Kanechlor 400 of up to 250 mg/kg from day 1 to day 21 of gestation (Mizunoya et al., 1974). Fetuses showed decreased body weights from 10 mg/kg diet onward (equivalent to 0.67 mg/kg body weight), but did not show any increased incidence of malformations. Maternal toxicity was not observed and litter size and the number of litters were unaffected. Decreased pup survival was noted at dietary levels from 50 mg/kg (equivalent to 3.5 mg/kg body weight) upwards. The 28-day-old offspring showed decreased body weight and increased relative liver weight from 10 mg/kg.

Commercial Kanechlor 300 or 500 was mixed with food and administered to pregnant Sprague-Dawley rats, throughout gestation, at levels of 20, 100, or 500 mg/kg diet. On day 21, about three- quarters of the pregnant females were sacrificed; the remainder were allowed to litter naturally and the postnatal development of the pups was observed.

Kanechlor 500 at a concentration of 500 mg/kg resulted in decreased maternal weight gain and decreased food consumption. At 20 and 500 mg Kanechlor 300/kg, and 500 mg Kanechlor 500/kg, the fetal weight decreased significantly. Resorption and malformations were not increased by treatment with Kanechlors. The Kanechlors did not show a teratogenic potential in this study (Shiota, 1976a).

Offspring of Sprague-Dawley rats that received 20 mg of Kanechlor 500/kg body weight on days 15–21 of gestation were slower than controls in achieving the water maze test at the age of 12–13 weeks, but did not perform worse in the open field test and in the swimming test (Shiota, 1976b). Behavioural effects were also observed in the offspring of ICR dams, 23–27 days of age, exposed to Aroclor 1254 in the diet at levels of 11 or 82 mg/kg (equivalent to 1.7 and 12 mg/kg body weight) from 3 days befor mating up to weaning. The offspring were maintained on the same diet. PCB exposure did not have any effects on the ability to learn an avoidance response, but increased the latency to make such a response. Moreover, the young mice exhibited slower habituation to an open field (Storm et al., 1981).

The effects of Fenchlor 42 (trichloro- 63%, tetrachloro- 33%, and small amounts of dichlorobiphenyl; purity 97.5%) exposure of Fischer 344 male and female rats were studied through assessment of the behavioural development of their F1 progeny. Female rats were administered 5 daily ip injections of corn oil or 5–10 mg Fenchlor 42/kg body weight per day, 2 weeks prior to mating. Another group received 2–4 mg/kg per day during gestation (days 6–15 of pregnancy) and a third group of 8 previously treated lactating females received corn oil or 1–2 mg/kg per day on postnatal days 1–21. The total doses in the 3 groups were 25–50, 20–40 and 20–40 mg/kg body weight. Dose-dependent differences in behaviour were found in the offspring of the PCB-treated animals. Differences in the development of cliff avoidance reflexive behaviour, swimming ability, and open field activity were evident. The PCB exposure of female animals during gestation and lactation resulted in impaired acquisition of the active avoidance behaviour, while preconception PCB exposure affected active avoidance performance, as reflected in an increased number of avoidance responses to reach criterion for extinction (Pantaleoni et al., 1988).

Doses of 0, 6.25, 12.5, 25, 50, or 100 mg/kg body weight per day of Aroclor 1254 were administered to rats, by gavage, on days 6–15 of gestation. Average pup weights were reduced at 100 mg/kg, though total litter weight (average weight times number of fetuses) did not differ from controls. There were no skeletal or visceral abnormalities or effects on conception, resorptions, litter size or number, or average litter weight in any of the treated groups (Villeneuve et al., 1971b).

Spencer (1982) exposed Holtzman rats to a diet containing Aroclor 1254 at levels of 25 up to 900 mg/kg diet from day 6 to day 15 of gestation and found reduced maternal body weight gain and decreased fetal survival at birth from 300 mg/kg diet (equivalent to 18 mg/kg body weight) upwards, and decreased fetal weights at birth from 100 mg/kg (equivalent to 8 mg/kg body weight) upwards. No visceral or skeletal data were available.

When Sherman rats were exposed to doses of Aroclor 1254 of up to 100 mg/kg body weight, in peanut oil, from day 7 to day 15 of gestation, a decrease in the survival of the pups was found. At

weaning, the survival and body weight of the grossly normal pups were reduced at the 100 mg/kg dose level, but not at 50 mg/kg body weight. No effects were observed at 100 mg Aroclor 1260/kg body weight (Linder et al., 1974).

(*c*) *Monkey*

Two pregnant Cynomolgus monkeys (*Macaca fascicularis*) were dosed with Aroclor 1254 at 100 mg/kg body weight per day and 1 monkey, at 400 mg/kg body weight per day, from day 60 of gestation. One control animal received the vehicle, corn oil. The 2 monkeys fed 100 mg/kg delivered dead male infants after 105 and 108 days of dosing, and the female fed 400 mg/kg delivered a female infant (with no overt clinical signs of toxicity) that died at 139 days of age with an acute bronchopneumonia. The breast milk of the monkey fed 400 mg/kg contained, over a period of 5–75 days after parturition, concentrations of 73.7 up to 139.4 mg/kg, on a fat basis. No overt signs of toxicity were observed in the adult animals, with exception of finger nail loss. All 3 treated monkeys showed impaired immunological capacity, assessed at approximately 50 days postpartum (148 days of treatment) (Truelove et al., 1982).

(*d*) *Rabbit*

Rabbits were exposed to 0, 1.0, or 10.0 mg Aroclor 1254/kg body weight and in another study to 0, 12.5, 25.0, or 50 mg/kg body weight (purity not reported), by gavage, on days 1–28 of pregnancy. Abortions, still births, and maternal deaths occurred at 12.5 mg/kg body weight or more, but no teratogenic effects were found (Villeneuve et al., 1971a,b).

8.4.2.2 Aroclors (subcutaneous)

(*a*) *Mouse*

A possible teratogenic effect was observed in ddY mice subcutaneously exposed to doses of 1–5 mg Kanechlor 500/mouse (equivalent to 40–200 mg/kg body weight) in 95% ethanol from day 6 to day 15 of gestation. A dose-related increase in maternal mortality was observed from a dose of 3 mg/mouse onwards. Some dams showed skin lesions, alopecia, or swelling of the liver, but no effects on body weight gain. A slight increase was noted in the incidence of

dead and resorbed fetuses. The incidence of cleft palate was increased in a dose-related manner from the lowest dose (Watanabe & Sugahara, 1981).

8.4.2.3 Individual congeners (oral)

(a) Mouse

Örberg (1978) fed groups of 20–56 pregnant female NMRI-mice 0, 0.05, or 0.5 mg 2,5,4'-trichloro- or 2,4,5,2',4',5'-hexachlorobiphenyl, dissolved in peanut oil, per animal, from days 1 to 6 of gestation. A significant decrease in the pregnancy of implanted ova was found with the 0.5 mg treatment. No effects on percentage of pregnancies and mean number of corpora lutea were found. There were no effects at the lower dose level.

A dose-related increase in embryotoxicity and the incidence of malformed fetuses, mainly showing cleft palate and hydronephrosis, was found in pregnant CD-1 mice after exposure to daily doses of 2, 4, 8, or 16 mg 3,4,5,3',4',5'-hexachlorobiphenyl/kg body weight, in cotton-seed oil, on days 6–15 of gestation. Lower dose levels, e.g., 0.1 and 1 mg/kg body weight were without effects. No dibenzofurans were detectable (no details) in the test compound. The dams showed a decreased body weight gain at 8 mg/kg body weight. The authors reported that 3,4,3',4'-tetrachlorobiphenyl and 2,3,4,2',3',4'-hexachlorobiphenyl also produced the same teratogenic effects, though they were less potent than those of 3,4,5,3',4',5'-hexachlorobiphenyl (Marks et al., 1981).

A neurobehavioural "spinning" syndrome (a syndrome characterized by the fact that the mice rotate or spin in a circular motion when held by the tail) and hydronephrosis developed in CD-1 mouse weanlings, whose dams received, by gavage, 32 mg 3,4,3',4'-tetrachlorobiphenyl/kg body weight, in corn oil, on days 10–16 of gestation. Maternal neurotoxicity was not observed. Histological and ultrastructural examination of the CNS of affected mice revealed longitudinal projections of the cylindrical CNS in the ventral and dorsal roots and, to a lesser extent, in cranial nerve roots. The effect was possibly related to an observed altered development of striatal synapses (Chou et al., 1979; Tilson et al., 1979; Agrawal et al., 1981).

(*b*) *Rat*

The congener 3,4,3',4'-tetrachlorobiphenyl was found to be embyrotoxic and caused accumulation of blood in the aminotic fluid and the gastrointestinal tract of fetuses from Sprague-Dawley rats treated on days 6–18 of gestation with doses of 3 or 10 mg/kg body weight in corn oil. Decreased fetal growth was also observed (Wardell et al., 1982). When the rats were allowed to deliver, high perinatal mortality was observed, which appeared to be related to an increase in gestational length and to be independent of the smaller total litter size. In addition, pup weights were found to be lower than those of controls (Rands et al., 1982; White et al., 1983).

(*c*) *Guinea-pig, mouse*

Neither embryotoxicity nor teratogenicity were found in Dunkin Hartley guinea-pigs, and CBA mice exposed *in utero* to 2,4,5,2',4',5'-hexachlorobiphenyl during gestation (Mattsson et al., 1981; Brunström et al., 1982; Aulerich et al., 1985) and in C57BL/6N mice similarly exposed to 2,4,5,2',4',5'- or 2,3,4,5,3',4'-hexachlorobiphenyl (Birnbaum et al., 1985).

Pregnant guinea-pigs received a total dose of 100 mg technical grade Clophen A50 orally, in peanut oil, from day 16 to day 60 of gestation, 25 mg 2,4,5,2',4',5'-hexachlorobiphenyl from day 16 to day 60 of gestation, or 100 mg from day 22 to day 60 of gestation. The administration of Clophen A50 resulted in fetal deaths, but no maternal deaths. In contrast, 2,4,5,2',4',5'-hexachlorobiphenyl did not cause fetal deaths. Prenatal weight of live fetuses was increased by a dose of 25 mg, but not by 100 mg of 2,4,5,2',4',5'-hexachlorobiphenyl (Brunström et al., 1982).

(*d*) *Monkey*

In a briefly reported study, 6 female Rhesus monkeys received 9 doses of 70 or 350 μg 3,4,3',4'-tetrachlorobiphenyl/kg body weight by gavage, in corn oil, from day 20 to day 40 of gestation. A control group comprised 12 animals. Maternal toxicity (not specified) but no mortality, was reported in all exposed monkeys from day 31 following exposure. Between days 17 and 35 following exposure all exposed fetuses and 3 out of 12 control fetuses aborted (McNulty, 1985).

8.4.3 Appraisal

The Rhesus monkey is the most sensitive species with regard to general toxicity (see section 8.2) and particularly with regard to reproductive toxicity. The presence of PCDFs and the variation in PCB composition may be confounding factors in determining the reproductive toxicity of PCB mixtures. Aroclor 1248, containing 4.4–8.7 μg PCDFs/kg, adversely affected the reproductive performance of female Rhesus monkeys, mated with control males after 6 months of dietary exposure to a toxic dose of 0.09 mg/kg body weight per day and continuation of the exposure for an average of up to 10 months. This effect was reversible after an exposure-free period of 1 year. No effect on reproduction was found in female Rhesus monkeys exposed to a non-toxic dose of 0.01 or 0.03 mg Aroclor 1016 (reported not to contain PCDFs)/kg body weight per day and mated after 7 months with control males.

Neonates of the nursing mothers exposed to Aroclor 1248 showed adverse effects similar to those seen in their mothers and, in addition, persistent behavioural disturbances, atrophy of the thymus and lymph nodes, bone marrow hypoplasia, and hyperplasia of the gastric mucosa. Neonates of the mothers after the recovery period still showed adverse effects, as well as the neonates of the mothers exposed to Aroclor 1016. These effects were caused by PCBs, with or claimed to be without, PCDFs, transmitted via the placenta during gestation and later via the breast milk. Neonates have much greater susceptibility to PCB toxicity when exposed via the mothers compared with suckling monkeys orally exposed. Reproductive toxicity has also been observed in the mink, rabbit, and rat. The changes seemed to be related to alterations in the serum levels of gonadal steroid hormones, as a result of enzyme induction. PCBs may also bind to the cytoplasmic estrogen receptor. Effects have also been observed on the estrus cycle of female rats, minks, and monkeys, on the sex organs of male rats, and on the implantation rate of fertilized ova following exposure of female mice or male rats.

Comprehensive teratological examinations have not been conducted; however, the available studies indicated that the Aroclors were not teratogenic in rats and nonhuman primates, when tested via the oral route during the critical periods of organogenesis at doses that

produced fetotoxicity and/or maternal toxicity. Although the fetotoxicity of Aroclors is documented in several species of animals, the possibility that contaminants (e.g., PCDFs) might be (partly) responsible for the effects should be recognized.

The results of the reproduction and teratogenicity studies are summarized in Tables 45, 46, and 47.

8.4.4 Mutagenicity and related end-points

8.4.4.1 DNA damage

PCBs have been shown to interact with the proteins, RNA and DNA, after metabolic activation. The potential of readily metabolizable PCB-congeners to cause primary DNA damage was indicated by the activity of 2,5,2',5'-tetrachlorobiphenyl and its metabolites in causing DNA, single-strand breaks in an alkaline elution assay with L-929 cells *in vitro* (Stadnicki et al., 1979). Furthermore, unscheduled DNA synthesis was elicited by 4-chlorobiphenyl *in vitro* in Chinese hamster ovary cells (Wong et al., 1979). No unscheduled DNA synthesis was elicited by Aroclor 1254 in rat hepatocytes *in vitro* (Probst et al., 1981).

DNA-breaking activity was found in an alkaline elution assay with hepatocytes of intact rats treated *in vivo* with a single, high dose (500 mg Aroclor 1254/kg body weight, intraperitoneally, or 1295 mg/kg body weight, orally) with complete repair of the damage within 48 h (Robbiano & Pino, 1981). Aroclor 1254 was also shown to be a DNA-breaking agent in an alkaline elution assay *in vitro* with rat hepatocytes (Sina et al., 1983). An alkaline sedimentation assay showed the DNA-breaking activity of Aroclor 1254 in rats treated *in vivo* with a single intraperitoneal dose of 500 mg/kg body weight. In this assay, the same Aroclor 1254 pretreatment of the rats *in vivo* elevated the DNA-breaking activity of the direct-acting, alkylating *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine and the carcinogens, dimethylnitrosamine and benzo(*a*)pyrene, *in vitro* (Mendoza-Figueroa et al., 1985).

Table 45. PCBs: reproduction and embryo toxicity

Animal (strain, sex)	PCB mixture	Exposure period (oral)	NOAEL (mg/kg body weight)	LOAEL (mg/kg body weight)	Parameters, effects	Reference
Rat (Sherman, 10 male, 20 female)	Aroclor 1254 Aroclor 1260	continuous up to weaning		0.06 (1254)	increased relative liver weights in male F_1A weanlings	Linder et al. (1974)
				0.32 (1254)	former effect in all weanlings	
			0.32 (1254)		reproduction parameters	
			7.5 (1260)		reproduction parameters	
Rhesus monkey (female)	Aroclor 1016	7 months	0.03 (0.04)		reproduction parameters [0.03(0.04): decreased birth weight] [0.01: skin hyperpigmentation]	Barsotti & van Miller (1984)
Rhesus monkey (female)	Aroclor 1248	6 months		0.09	abortions, resorptions, live births	Barsotti et al. (1976)
		1 year after exposure	0.09	0.2	stillborn, live births	Allen et al. (1980)

Table 46. PCBs: teratogenicity

Animal (strain)	PCB-mixture	Exposure period (oral)	NOAEL (mg/kg body weight)	LOAEL (mg/kg body weight)	Parameters, effects	Reference
Rat	Aroclor 1254	days 6 to 15 of gestation	50	100	reduced average pup weight	Villeneuve et al. (1971b)
Rat (Holtzman)	Aroclor 1254	days 6 to 15 of gestation	< 8	8	decreased fetal weight at birth	Spencer (1982)
Rat (Sherman)	Aroclor 1254	days 7 to 15 of gestation	100		reproduction effects	Spencer (1982)
Rabbit	Aroclor 1254	days 1 to 28 of gestation	10	12.5	abortions, still births, maternal deaths	Villeneuve et al. (1971a,b)
	Aroclor 1221	days 1 to 28 of gestation	25		fetotoxicity	

Table 47. PCBs: teratogenicity of individual congeners

Animal (strain)	PCB-mixture	Exposure period (oral)	NOAEL (mg/kg body weight)	LOAEL (mg/kg body weight)	Parameters, effects	Reference
Mice (NMRI)	2,5,4′-TCB 2,4,5,2′,4′, 5′-HCB	day 1 to 6 of gestation	0.05/animal	0.5/animal	decrease in the number ofimplant/dams	Örberg (1978)
Mice (CD-1)	3,4,5,3′,4′, 5′-HCB	day 6 to 15 of gestation		2	embryotoxicity, malformations (cleft palate, hydronephrosis)	Marks et al. (1981)
	3,4,3′,4′-TCB 2,3,4,2′, 3′4′-HCB			8	maternal toxicity, less potent than that of 3,4,5,3′,4′,5′-HCB	
Rat (Sprague-Dawley)	3,4,3′,4′-TCB	day 6 to 18 of gestation		3	embryotoxicity	Wardell et al. (1982)
Rhesus monkey	3,4,3′,4′-TCB	day 20 to 40 of gestation		0.07	maternal toxicity, total abortions	McNulty (1985)

8.4.4.2 Mutagenicity tests

Many mutagenicity tests have been carried out over the years, with different PCB mixtures. Most of these were commercial mixtures the composition of which was not described. Only a few studies are available on specific congeners. Besides studies on microorganisms, mammalian cell point mutation, dominant lethal assays, micronucleus tests, chromosome and cytogenicity studies, and DNA repair studies were carried out. With a few exceptions the results of most of the studies with PCB mixtures were negative (see Table 48).

Aroclor mixtures and the congener 2,5,2',5'-tetrachlorobiphenyl and its metabolites did not induce point mutations in *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, and TA 1538 with, and without, metabolic activation (Wyndham et al., 1976; Hsia et al., 1978; Bruce & Heddle, 1979; Schoeny et al., 1979; Shahin et al., 1979), neither did 2,4,2',4'- and 3,4,3',4'-tetrachlorobiphenyl and 2,4,6,2',4',6'-hexachlorobiphenyl in the strains TA 98 and TA 100 (Schoeny, 1982).

However, Wyndham et al. (1976) found a dose-related mutagenic activity of 4-chlorobiphenyl and, to a lesser extent, of Aroclor 1221 in the strain TA 1538, after metabolic activation by the S9 liver fraction of uninduced rabbits. The study was repeated 3 times in the same laboratory, but the results of Wyndham et al. (1976) could not be confirmed (Safe, 1980). Schoeny (1982) could not detect any mutagenic activity of 4-chlorobiphenyl in the same dose range in the strains TA 98, TA 100, TA 1535, and TA 1537, with, or without, the S9 liver fraction of induced rats.

Dose-related chromosome breakage was found in human lymphocytes exposed to the planar PCB congener, 3,4,3',4'-tetrachlorobiphenyl, at $0.1–10^{-4}$ μg/ml (Sargent et al. (1989). In contrast, the non-planar 2,5,2',5'-tetrachlorobiphenyl did not cause chromosome damage in a comparable test, even at concentrations as high as 1 μg/ml. However, a combination of 3,4,3',4'-tetrachlorobiphenyl at a concentration of 10^{-5} μg/ml with 2,5,2',5'-tetrachlorobiphenyl caused chromosomal damage that was far in excess of what might be expected from higher doses of 3,4,3',4'-tetrachlorobiphenyl alone. The results suggest that some PCB congeners may interact to cause synergistic effects.

Table 48. Results of mutagenicity, and related, tests

Chemical substance	Test system	Strain	Dose	Metabolic activation	Result	Reference
2,5,2',5'-tetrachloro biphenyl	*Salmonella typhimurium*	TA 1538	200 µg/plate 100 µg/plate 50 µg/plate 10 µg/plate	modified microsomal fraction from rabbits	- - - -	Wyndham et al. (1976)
Aroclor 1268	*Salmonella typhimurium*	TA 1538	200 µg/plate 100 µg/plate 50 µg/plate 10 µg/plate	modified microsomal fraction from rabbits	- - - -	Wyndham et al. (1976)
Aroclor 1254	*Salmonella typhimurium*	TA 1535 TA 1537 TA 98 TA 100	4 different concentrations, figures not given	both with, and without, S-9 in all cases	- - - -	Heddle & Bruce (1977)
Aroclor 1254	*Salmonella typhimurium*	TA 1535 TA 1537 TA 98 TA 100	8 different concentrations from 0.5 to 500 µg/plate	both with, and without, S-9	- - - -	Schoeny et al. (1979)
Aroclor 1254	*Salmonella typhimurium*	TA 1535 TA 1537 TA 98 TA 100	0.05, 0.5, 5, 50, and 500 µg/plate	both with, and without, S-9	- - - -	Bruce & Heddle (1979)

Table 48 (continued)

Chemical substance	Test system	Strain	Dose	Metabolic activation	Result	Reference
Aroclor 1254	*Salmonella typhimurium*	TA 1538 TA 98	50, 100, 500, 1000, 2000, 5000 µg/plate	both with, and without, S-9	- -	Shahin et al. (1979)
Aroclor 1242 Clophen A60	V79 hamster cells co-cultivated with lethally irridatiated hepatocytes		50, 100, and 150 µg/ml	without metabolizing cells	- -	Hattula (1985)
Aroclor 1254	Micronucleus test (erythrocytes)		4 different concentrations, figures not given		-	Heddle & Bruce (1977)
Aroclor 1254	Micronucleus test	(C57B1/6 x C3H/He) F_1 mice	(approximately) LD_{50}, 1/2, 1/4, and 1/8 of the highest dose (5 consecutive days, ip)		- (at all doses)	Bruce & Heddle (1979)

Table 48 (continued)

Chemical substance	Test system	Strain	Dose	Metabolic activation	Result	Reference
Kanechlor 500	Micronucleus test with polychromatic erythrocytes	ddY-mice	100 mg/kg in corn oil orally and 100 mg/kg 95% ethanol subcutaneously	-	-	Watanabe et al. (1982)
Aroclor 1254	Chromosomal aberrations	(embryonic Ring Doves)	0 or 10 mg/kg diet		inconclusive	Peakall et al. (1972)
Aroclor 1254	Chromosomal aberrations	(human lymphocytes)	100 mg/litre culture medium		-	Hoopingarner et al. (1972)
Aroclor 1254	Chromosomal abnormalities in bone marrow and spermatogonial cells	male Holtzmann rats	5, 50, 500 mg/kg diet		negative at all doses	Garthoff et al. (1977)
Aroclor 1242	Chromosomal abnormalities in bone marrow cells and spermatoonial cells	Osborne-Mendel rats	5000 mg/kg × 1[a] 2500 mg/kg × 1 1250 mg/kg × 1 500 mg/kg × 4		- - - -	Green et al. (1975a)

Table 48 (continued)

Chemical substance	Test system	Strain	Dose	Metabolic activation	Result	Reference
Clophen A30	*Drosophila melanogaster* (adults or larvae)		62.5, 125, 250, and 500 mg/litre substrate	-	-[b]	Nilsson & Ramel (1974)
Clophen A50	*Drosophila melanogaster* (adults or larvae)		25, 50, 100, and 200 mg/litre substrate	-	-[b]	Nilsson & Ramel (1974)
Aroclor 1242	Dominant Lethal test	Osborne-Mendel rats	2500 mg/kg × 1[a] 1250 mg/kg × 1 625 mg/kg × 1 250 mg/kg × 5 125 mg/kg × 5		- - - - -	Green et al. (1975b)
Aroclor 1254	Dominant Lethal test	Osborne-Mendel rats	150 mg/kg × 5[a] 75 mg/kg × 5		- -	Green et al. (1975b)
Aroclor 1254	Dominant Lethal test	Osborne-Mendel rats	25, 100 mg/kg diet for 70 days		- -	Green et al. (1975b)

Table 48 (continued)

Chemical substance	Test system	Strain	Dose	Metabolic activation	Result	Reference
Aroclor 1254	Sperm Abnormality	(C57 B1/6 x C3H/He)F_1 mice	(approximately)LD_{50}, 1/2, 1/4, 1/8 top dose on 5 consecutive days, ip		negative at all doses	Bruce & Heddle (1979)
Aroclor 1254	mitotic index	human lymphocytes	100 mg/litre culture medium		mitotic index equivocal	Hoopingarner et al. (1972)
4-chloro-biphenyl and metabolites	DNA repair and unscheduled synthesis (hydroxyurea addition suppress DNA synthesis)	Chinese hamster ovary cells	10^{-5}mmol/litre ^{3}H-4-chloro-biphenyl, 24 h		covalent-binding to protein, RNA, and DNA Increase specific activity with DNA	Wong et al. (1979)

[a] Means single dose (× 1) or 5 doses in 5 days (× 5).

[b] No loss or non-disjunction of sex-chromosomes.

SD = Significant decrease.

Peakall et al. (1972) carried out cytogenic studies on Ring dove embryos (*Streptopelia risoria*); 6 embryos were from dove pairs not fed PCBs (controls) and 17 embryos were from PCB-fed (10 mg/kg diet) pairs. The frequencies of chromosome aberrations were recorded for chromosome pairs occurring in metaphase cells of allantoic sac and limb bud origin. Mean aberration rates were as follows: control 0.8% (range 0–2.0%) and PCB-treated 1.8% (range 0–9.4%). It was concluded by the authors that these results were indicative of a possible clastogenic action of PCBs.

A DNA repair assay was carried out by Wong et al. (1979) using CHO cells and measuring the effects of 4-chlorobiphenyl (10 mol/litre) on the unscheduled DNA synthesis (UDS) in the presence of hydroxyurea (HU), a chemical agent that suppresses normal replicative DNA synthesis. The quantification of DNA synthesis was determined by the uptake of [H^3]-thymidine into the cellular DNA. A significant (1.6-fold) enhancement of UDS was found when the cells were incubated for 2.5 h in the presence of HU, 4-chlorobiphenyl, and thymidine.

8.4.4.3 Cell transformation

Aroclor 1254 did not cause an increase in benzo(*a*)pyrene-induced transformation in a test using C3H10 T1/2 CL8 mouse embryo fibroblasts (Nesnow et al., 1981).

Aroclor 1254 also failed to transform Golden Syrian hamster cells 76–582 in culture at 50 µl/ml (Pienta, 1980).

8.4.4.4 Cell to cell communication

The congener 2,4,5,2',4',5'-hexachlorobiphenyl inhibited one form of intercellular communication in V79 Chinese hamster cells, i.e., metabolic cooperation by mutant rescue at non-cytotoxic levels, while 3,4,5,3',4',5'-hexachlorobiphenyl was inactive (Tsushimoto et al., 1983).

8.4.4.5 Interaction

Grolier et al. (1989) studied the effects of Vitamin A dietary intake (2 and 20 IU/g of food) on the mutagenicity of benzo(*a*)pyrene

(B(*a*)P) towards *Salmonella typhymurium* TA 98, either in control rats or in animals treated with 2,4,5,2',4',5'- hexachlorobiphenyl and 3,4,3',4'-tetrachlorobiphenyl. The planar tetrachlorobiphenyl strongly increased B(*a*)P-monooxygenase activity and glutathione transferase, while the non planar hexachlorobiphenyl was a strong inducer of epoxide hydrolase and a weak inducer of B(*a*)P-monooxygenase. Enzyme induction was not modified by changes in Vitamin A intake. A greater mutagenic effect was observed in the tetrachlorobiphenyl group than in the hexachlorobiphenyl group. This could be related to the specific form of cytochrome P-450 induced by the tetrachlorobiphenyl congener. In PCB-treated rats, the mutagenic activity of B(*a*)P was higher in the 20-IU group than in the 2-IU group.

8.4.4.6 Cell division parameters

Tests on Osborne-Mendel rats gave various results, but may provide the most important clue to the mechanism of action of PCBs in carcinogenesis. At high doses (5000 mg Aroclor 1242/kg given once, and 500 mg/kg, given in a series of 4 daily doses), there were significant decreases in the numbers of spermatogonial cells in mitosis. Single dose levels of 1250 or 2500 mg/kg gave negative results (Green et al., 1975a). Garthoff et al. (1977) also found negative results in male Holtzmann rats treated with 0, 5, 50, or 500 mg Aroclor 1254/kg diet for 5 weeks with regard to the mitotic indices of bone marrow and spermatogonial cells. The data of Hoopingarner et al. (1972) showed an increase in mitotic index in human lymphocytes exposed to Aroclor 1254.

The above-mentioned studies provide evidence that Aroclors can enhance cell proliferation, and this is of special interest because it suggests that the Aroclors may act to promote carcinogenesis to a greater extent than to initiate it. The effect on cell proliferation requires further examination in a variety of systems.

8.5 Carcinogenicity

Hayes (1987) critically reviewed the available evidence for, and against, the view that environmental PCBs present a significant potential carcinogenic hazard for humans.

8.5.1 Long-term toxicity/carcinogenicity

(*a*) *Mouse*

Nagasaki et al. (1974) exposed 10 groups of dd mice (6–12 of each sex) to Kanechlor 300, 400, or 500 in the diet at levels of 0, 100, 250, or 500 mg/kg (equivalent to 0, 5, 12.5, and 25 mg/kg body weight, respectively) for 32 weeks. Nine nodular hyperplasia and 7 hepatocellular carcinomas were found in 17 male mice, and 4 cases of liver hypertrophy in 17 female mice, after exposure to 500 mg Kanechlor 500/kg diet. No neoplasms were found in the other groups.

In another mouse study, groups of male BALB/cJ mice were fed 0 or 300 mg Aroclor 1254/kg diet (equivalent to 50 mg/kg body weight) for 6 or 11 months. Adenofibrosis was observed in the livers of all 22 mice fed Aroclor 1254 for 11 months, but not in those of the 24 mice exposed for 6 months. Hepatomas were noted in 9/22 mice exposed for 11 months and in 1/24 mice exposed for 6 months. No tumours were found in the controls (Kimbrough & Linder, 1974).

(*b*) *Rat*

In a preliminary study, liver tumours (multiple adenomatous nodules) were induced by Kanechlor 400 (containing 2,4,3',4'-; 2,5,3,3'-; 2,3,4,4'-; and 3,4,3',4'-tetrachlorobiphenyls) in 6/10 females, but not in male Donryu rats, in 400 days. The dietary exposure was periodically adjusted according to animal weights and ranged from 38.5 to 616 mg/kg diet. The latter dose level was administered for 275 days. The number of animals used was small (10 treated and 5 control rats of each sex). Increased incidences of pneumonia, and lung and intracranial abscesses were found in rats on a diet containing Kanechlor 400, possibly because of lowered resistance to infection (Kimura & Baba, 1973).

Ito et al. (1974) fed 10 groups of 29 male Wistar rats with Kanechlor 300, 400, or 500 at dose levels of 100, 500, or 1000 mg/kg diet (equivalent to 5, 25, and 50 mg/kg body weight, respectively) for 28–52 weeks. Another group received the control diet. A number of animals died in all groups (4 up to 21 animals); within the treated groups, deaths were more or less dose related. Adenofibrosis was observed in the livers of rats fed 1000 mg/kg diet of all 3 mixtures.

Kanechlor 500 produced nodular hyperplasia at all dose-levels and at a higher incidence than the mixtures with a lower chlorine content. No neoplastic nodules were observed in the controls. Kanechlor 300 and 500 (100 mg/kg diet) did not show significant growth inhibition or increases in liver weight. No fibrosis or cholangiofibrosis, bile duct proliferations, fatty changes, or cellular hypertrophy in the liver were found. The liver nodular hyperplasia, designated as pre-neoplastic by the investigators, was found in 3/25 of the Kanechlor 500 (100 mg/kg diet) treated animals, 1/22 of the Kanechlor 300 (100 mg/kg diet) treated animals, and 0/18 controls. The 1/22 (4.5% incidence in the Kanechlor 300, 100 mg/kg diet) is not significant and the 2 higher dose levels of this product did not induce such changes. It can be concluded that Kanechlor 300 did not induce neoplasia at dietary levels of up to 1000 mg/kg over a 52-week period, in this study. At the 1000 mg/kg level, Kanechlor 300 did produce other evidence of chronic liver toxicity including oval cell and bile-duct proliferation, fatty changes, and cellular hypertrophy and, possibly, cholangiofibrosis (2/15). In the case of Kanechlor 500 (100 mg/kg diet), essentially the same picture was obtained. In this group, 3/25 cases of nodular hyperplasia were found. In the case of Kanechlor 400 with the dietary levels of 100 and 1000 mg/kg, 2/16 and 3/10 of the animals had nodular hyperplasia in the liver, respectively.

In a preliminary study on Sherman rats (10 animals of each sex/dose), Aroclor 1254 at dietary levels of 0, 20, 100, or 500 mg/kg, and Aroclor 1260 at levels of 0, 20, 100, 500, or 1000 mg/kg, for 8 months, did not give neoplastic nodules or hepatocellular carcinoma. At 500 mg/kg, Aroclor 1254 produced adenofibrosis in 10/10 male animals and at 100 and 500 mg/kg, in 7/10 and 9/10 females, respectively. This change was only seen in 2/10 male and 4/10 female animals with Aroclor 1260. The authors stated that hepatocellular adenofibrosis is a persistent progressive lesion that consists of a marked proliferation of fibrous tissue and epithelial glandular cells that are well differentiated in mice, but appear atypical in rats (Kimbrough et al., 1972).

A group of 200 female Sherman rats was given Aroclor 1260 at an average dietary level of 100 mg/kg (range, 70–107 mg/kg), for 21 months. The PCB intake declined from 11.6 mg/kg per day during

the first week to 6.1 mg/kg at 3 months and to 4.3 mg/kg body weight per day, later on. The control group also comprised 200 rats. The survival rate and the food intake were not affected and no treatment-related signs of toxicity were observed. Body weight gain was decreased from 3 months after the onset of the exposures. Hepatocellular carcinomas were present in the liver of 26/184 (14%) exposed rats and 1/173 (0.58%) control rats. The livers of most of the remaining exposed rats (144/184) showed hyperplastic nodules, while none were found in control rats. A total of 182 exposed rats and 28 control rats had livers with foci or areas of cytoplasmic alteration. A few livers of exposed rats showed adenofibrosis. No induction of tumours in other organs and no metastases from the liver tumours were found (Kimbrough et al., 1975).

Calandra (1976) reported the findings from several long-term studies, performed by a commercial laboratory for Monsanto. (These studies have never been published). In these studies, 1000 rats were divided into 10 groups of 100 animals (50 of each sex) and 9 of the groups were exposed to Aroclors 1242, 1254, or 1260 at dietary levels of 1, 10, or 100 mg/kg diet. Apparently, 5 animals of each sex were sacrificed at 3, 6, and 12 months with about 35 animals killed at the end of the 2-year studies. In the animals sacrificed early, only one nodular hyperplasia was observed and it was in the group fed 100 mg Aroclor 1260/kg for 12 months. Mortality in these studies was high and approximately one-third of the 105 animals anticipated to be exposed for 2 years at each dietary level died. Hepatomas were observed in 7/25 livers from animals fed 100 mg Aroclor 1260/kg, in 4/26 fed Aroclor 1254, 3/19 fed Aroclor 1242, and only in 1/168 animals receiving the 1–10 mg/kg diets. Nodular hyperplasia was twice as prevalent as hepatomas in the high-dose animals, particularly in the Aroclor 1254 group (Harbison et al., 1987).

In a limited study, groups of 24 Fischer 344 rats of each sex received a diet containing Aroclor 1254 at 0, 25, 50, or 100 mg/kg diet (equivalent to 0, 1.2, 2.5, and 5 mg/kg body weight, respectively) for 104–105 weeks. The survival rate decreased with a dose-related trend in male, but not in female rats (92, 83, 58, and 46%, respectively). From 10 weeks of exposure onwards, the body weight gain of all rats, except that of the low-dose males, decreased. In the groups receiving the 2 highest dose levels, alopecia, facial oedema,

exophthalmos, and cyanosis were observed. Foci of hepatocellular alterations, which were dose-related, were found at all dose levels, but not in the controls. The incidence of non-neoplastic hyperplastic nodules in male rats with 25, 50, or 100 mg/kg diet was 5/24, 8/24, and 12/24 and in female rats 6/24, 9/22, and 17/24, respectively (US EPA, 1980). None was found in the controls. Hepatocellular adenoma and carcinomas were found in 1/24 males and 1/24 females on the 50 mg/kg diet and in 3/24 males and in 2/24 females on the 100 mg/kg diet. Non-neoplastic liver lesions included degenerative changes and aggregates of macrophages with crystalline cytoplasmic structures and pigment granules. An apparently dose-related increase in the incidence of intestinal metaplasia was observed in both sexes and 0, 1, 3, and 2 adenocarcinomas located in the pyloric region of the glandular stomach were found at 0, 25, 50, and 100 mg/kg diet, respectively. Morgan et al. (1981) and Ward (1985) reexamined the NCI (1978) data with respect to gastric adenocarcinomas, hepatocellular adenomas, and carcinomas. Morgan et al. (1981) found incidences of focal stomach lesions, mostly metaplasia, of 6, 10, 17, and 35% in rats receiving 0, 25, 50, or 100 mg Aroclor 1254/kg diet, respectively. Adenomas were found in 6 treated rats. When compared with the incidences of stomach adenocarcinomas in historical controls (1/3548), the incidence of 6/144 was statistically significantly increased (NCI, 1978; Morgan et al., 1981; Ward, 1985).

Groups of 70 Sprague-Dawley rats of each sex received a diet containing Aroclor 1260 in corn oil at a concentration of 100 mg/kg diet (equivalent to 5 mg/kg body weight) for 16 months and 50 mg/kg diet (equivalent to 2.5 mg/kg body weight) for an additional 8 months. All surviving rats received a basal diet from month 25 to month 29. The control group comprising 63 rats of each sex, received the basal diet with corn oil for 18 months and the basal diet alone for an additional 5 months. All surviving rats received the basal diet from the 25th month to the 29th month. Data on growth were not available. Groups of 2 control or 3 PCB-treated rats of each sex were partially hepatectomized at 1, 3, 6, 9, 12, 15, and 18 months. At 24 months, a similar group was sacrificed; after 29 months all remaining animals were sacrificed. The mortality rate was not affected by the exposure. In the livers of exposed rats, centrolobular hypertrophy was apparent at 1 month, foci at 3 months, and areas of

cellular alteration after 6 months, neoplastic nodules after 12 months, trabecular carcinomas after 15 months, and adenocarcinomas after 24 months. Metastases in the lung were not found. In exposed rats that survived 18 months or longer, hepatocellular carcinomas were present in 43/47 females and in 2/46 males, but were absent in 81 controls. Simple and cystic cholangioma at 18 and 23 months, respectively, and adenofibrosis at 22 months were present in the treated rats (Norback & Weltman, 1985).

Rao & Banerji (1988b) fed 3 groups of 32 weanling Wistar rats a protein diet containing 0 (coconut oil), 50, or 100 mg Aroclor 1260/kg diet, for 120 days. The incidence of neoplastic nodules in the liver was 0/32, 24/32 and 16/32, respectively. Adenofibrosis was also observed in the treated animals.

In order to exclude possible effects of dibenzofurans and to investigate the effect of the degree of biphenyl-chlorination, groups of 152 and 144 male Wistar rats were exposed to Clophen A30 and Clophen A60, respectively, not containing detectable quantities (detection limit not stated) of dibenzofurans, for 800 days at a dose of 100 mg/kg diet. A group of 139 rats received a control diet. After 800 days, randomly selected rats were killed daily, until all survivors had been examined by day 832. The survival rate of the remaining exposed rats was increased by day 800. In rats autopsied by day 800 and in rats autopsied later, the incidence of hepatocellular carcinoma was increased by exposure to Clophen A60 (9/129 and 52/85, respectively) relative to controls (0/131 and 1/53, respectively), but not by exposure to Clophen A30 (1/138 and 3/87, respectively). There was a marked trend from foci of hepatocellular alteration to neoplastic nodule to carcinoma with increasing time and degree of biphenyl chlorination. Controls mainly showed foci. Non-neoplastic liver lesions with increased incidences of bile duct hyperplasia were found in rats receiving Clophen A30 and A60, and cysts in rats receiving Clophen A60. The incidence of adenofibrosis in the liver was decreased, compared with that in the controls, in all exposed rats that were killed after exposure (Schaeffer et al., 1984).

8.5.2 Tumour promotion/anticarcinogenic effects

(a) Mice

Tatematsu et al. (1979) studied the effects of inducers of liver microsomal enzymes on the induction of hyperplastic liver nodules by *N*-2-fluorenylacetamide (2-FAA) in male F344 rats. The rats were fed a diet containing 200 mg 2-FAA/kg diet for 2 weeks and then given 500 or 1000 mg Kanechlor 500/kg diet for the following 8 weeks. Partial hepatectomies were performed at the end of the third week of the study. Kanechlor 500 in the dose levels applied showed a promoting effect.

Ito et al. (1973) and Nagasaki et al. (1974, 1975) exposed groups of 20–38 male dd mice to diets containing Kanechlor 400 or 500 at 100 or 250 mg/kg for 24 weeks. Control groups consisted of 20 mice. Combined exposure to Kanechlor 500 at 100 and 250 mg and either 50, 100, or 250 mg α- or β-BHC (hexachlorocyclohexane)/kg diet enhanced the development of nodular hyperplasia and hepatocellular carcinomas. A combination of Kanechlor 500 and γ-hexachlorocyclohexane did not produce tumours. Dosing with Kanechlor 500 alone at a dietary level of 100 and 250 mg/kg, and β- or γ-hexachlorocyclohexane at dietary levels of up to 500 mg/kg did not produce tumours. However, α-hexachlorocyclohexane (250 mg/kg diet) produced 10/38 hepatocellular carcinomas and 30/38 hyperplastic nodules.

In another study, both inhibition and promotion were observed following transplacental and transmammary exposure of mice to PCBs prior to, or simultaneously with, exposure to dimethylnitrosamine (DMNA). In this study, Aroclor 1254 was administered intraperitoneally to female Swiss CD-1 mice on the 19th day of gestation, at a dose of 500 mg/kg body weight. Groups of 17–31 sucklings of these mice and of controls were then treated intraperitoneally with DMNA on postnatal day 4 or 14, or remained untreated. The progeny were killed at 28 weeks or at 18 months of age. Aroclor 1254 exposure decreased the incidence of tumours in the liver and lung, induced by DMNA administered at postnatal day 14. The average numbers of lung tumours per mouse were also decreased. However, Aroclor 1254 increased the liver tumour-bearing mice with extensive DMNA-initiated liver tumours

at 18 months of age, especially when DMNA was administered on postnatal day 4. Mice exposed only to Aroclor 1254 did not show tumour incidences higher than those of controls (Anderson et al., 1983). The authors also reported that 2 higher chlorinated biphenyls, 2,4,5,2',4',5'-hexachlorobiphenyl and 2,3,5,2',3',5'-hexachlorobiphenyl, were the dominant congeners persisting in the tissues of the PCB-treated mice. It should be noted that only the more highly chlorinated PCBs (>50% by weight) were reported as promoters of hepatocarcinogenesis in rodents. The promoting activities of the lower chlorinated PCBs have not been determined so far.

(*b*) *Rat*

As shown in Table 49, administration of PCBs to rats after exposure to several initiating agents promoted the development of neoplastic lesions of the liver. In these studies, treatment of the rats with a control diet of PCBs alone did not usually lead to neoplastic changes in the liver. Preston et al. (1981) compared the promoting effect of exposure of rats to Aroclor 1254 with that of exposure to Aroclor 1254 from which the polychlorinated dibenzofuran moieties had been removed, and did not find any significant differences. The results of this study suggested that the promoting effect of commercial PCBs cannot be ascribed entirely to the presence of chlorinated dibenzofurans. Tatematsu et al. (1979) showed a dose-effect relationship in the observed promoting effect of Kanechlor 500.

Inhibition, rather than promotion, of liver neoplasms was observed when female Donryu rats were exposed to Kanechlor 400 preceding, or simultaneously with, exposure to 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) (Kimura et al., 1976). Simultaneous dietary exposure of groups of 16–24 male Sprague-Dawley rats to Kanechlor 500, at a dose-level of 500 mg/kg (25 mg/kg body weight per day), and to 3'-Me-DAB, or *N*-2-fluorenylacetamide (2-FAA), or diethylnitrosamine (DENA), or combinations of these carcinogens, for 20 weeks, showed almost complete inhibition of neoplastic nodules and hepatocarcinomas (Makiura et al., 1974). It should be noted that the results of this study may be influenced by the extreme toxicity, as shown by the weight records, especially when the substances were combined.

Table 49. Promotion of liver neoplasms in rats exposed to PCBs after treatment with carcinogenic substances

Strain	Sex	Group size	Carcinogenic substances[a]	PCBs	Dose[b] (mg/kg diet)	Exposure period (weeks)	Neoplasms promoted by PCBs	Reference
Donryu	female	25	3'-Me-DAB	Kanechlor 400	400	26	carcinoma	Kimura et al. (1976)
Wistar	male	20-24	DENA	Kanechlor 500	2 x 15 mg/week	4	nodules carcinoma	Nishizumi (1976)
F 344	male	15-16	2-FAA	Kanechlor 500	500 and 1000	8	hyperplasia nodules	Tatematsu et al. (1979)
F 344	male	20	EHEN	Kanechlor	500	32	carcinoma	Hirose et al. (1981)
Sprague-Dawley	male	40	DENA	Aroclor 1254[c]	100	18	carcinoma	Preston et al. (1981)

[a] 3'-Me-DAB = 3'-methyl-4-dimethylaminoazobenzene; DENA = diethylnitrosamine; 2-FAA = *N*-2-fluorenylacetamide; EHEN = *N*-ethyl-*N*-hydroxyethylnitrosamine.

[b] Unless otherwise specified.

[c] With and without PCDFs.

The antitumour activity of Aroclor 1254 was demonstrated in male Sprague-Dawley rats, inoculated with Walker 256 tumour cells. Groups of 16 rats received PCB doses of 50, 100, or 200 mg/kg body weight for 2 weeks, once in 2 days, starting on the day of tumour cell injection. A group of 16 rats did not receive PCBs. The inhibition of tumour growth and transplantability were dose-related (Kerkvliet & Kimeldorf, 1977). The antitumour activity of Phenoclor DP5 was observed in groups of 20 female Swiss mice inoculated with Ehrlich's tumoral ascites liquid, after receiving PCBs in the diet at levels of 0, 10, 50, or 250 mg/kg, for 120 days (Keck, 1982).

Nishizumi (1980) showed that placentally transferred PCBs inhibited diethylnitrosamine (DENA)-induced liver tumours. Groups of ten, 10-week-old female Wistar rats were treated with 40 or 200 mg Kanechlor 500/kg body weight, by gavage, on days 5, 10, and 15 of gestation. One F1 offspring from each litter was killed for quantification of liver PCBs. The remaining F1 offspring were exposed to 50 mg DENA/litre drinking-water, continuously for 5 weeks. At 16, 20, and 24 weeks after the beginning of the DENA exposure, 6–8 rats of each sex from each treatment group were killed and examined histologically. A significant reduction in tumour incidence occurred only in male offspring in the 200-mg group. The liver-PCB values in 28-day-old F1 mice were < 1, 18 ± 7, and 360 ± 30 mg/kg tissue for the controls, 40, and 200 mg/kg groups, respectively. It was suggested that placental transfer of PCBs protected the treated rats from DENA-induced liver tumours.

The inhibitory effect of PCBs on tumour initiators following simultaneous exposure has been explained by an enhanced metabolism of the initiator by PCB-induced mixed function oxygenase.

Tests for putatively preneoplastic enzyme-altered foci in the liver of rats have shown a dose-related increase in the promotion of such foci by intraperitoneal exposure to Aroclor 1254 in tricaprylin or by oral exposure to Clophen A50 in olive oil, following oral administration of diethylnitrosamine (Deml & Oesterle, 1982; Pereira et al., 1982; Oesterle & Deml, 1983).

The highest oral dose of Clophen A50 not enhancing the number and area of enzyme-altered foci in female Sprague-Dawley rats, treated for 11 weeks with doses of 0, 0.1, 0.5, 1, 5, or 10 mg/kg body weight

after initiation by a single dose of 8 mg/kg body weight of diethylnitrosamine, was 0.5 mg/kg body weight (Deml & Oesterle, 1987).

8.5.3 Initiation, promotion, and other special studies on individual congeners

2,5,2',5'-Tetrachlorobiphenyl and its metabolite 2,5,2',5'-tetrachlorobiphenyl-3,4-oxide were tested in a pulmonary tumour induction assay with intraperitoneally injected A/T mice of both sexes, and in a two-stage skin carcinogenicity assay with dermally-exposed female SENCAR mice. Pulmonary adenomas and skin papillomas were not induced (Preston et al., 1985).

Female Harlan-Sprague-Dawley rats received 2,4,2',4'- tetrachlorobiphenyl or 2,5,2',5'-tetrachlorobiphenyl at 100 mg/kg diet for 28 weeks, 1 week after oral exposure to diethylnitrosamine (DENA). Both congeners showed a promoting effect on the development of foci of hepatocellular alteration. The effect was approximately 10-fold greater in rats receiving 2,4,2',4'-tetrachlorobiphenyl (Preston et al., 1985).

The effects of PCB mixtures and selected congeners have also been investigated by Hayes et al. (1985, 1986) using the resistant hepatocyte model developed by Farber and coworkers (Solt & Farber, 1976; Tsuda et al., 1980; Farber, 1984a,b, 1986). The ability of 2,4,2',4'- and 2,5,2',5'-tetrachlorobiphenyl, 2,4,5,2',4',5'- hexachlorobiphenyl, and a mixture of PCB-congeners (the composition of which resembled that ascertained in human breast milk) to initiate enzyme-altered hepatocellular nodules was investigated in proliferating hepatocytes of neonatal or partially hepatectomized adult rats (the PCB-congeners did not contain detectable levels of dibenzonfurans or dioxins). Neonatal rats were exposed 3 times in 3 weeks and adult rats once. After several weeks, the rats received a selection regimen of 2-acetylaminofluorene followed by partial hepatectomy (neonates) or necrotizing carbon tetrachloride (adults). None of the PCB exposures generated nodules in contrast to known initiators (Hayes et al., 1985).

Subsequent studies by Hayes et al. (1986) using the afore-mentioned compounds and 3,4,3',4'-tetrachlorobiphenyl (a typical MC-type inducer of cytochrome P-450-dependent monooxygenases) showed

that these PCBs (50 μmol/kg body weight), given 10 days after a dose of the initiator, DENA, and 7 days before 2-AAF, all reduced the size of the 2-AAF-selected gamma-glutamyltranspeptidase-positive nodules. These results show that, in contrast to the previous studies, PCBs also exhibit "anti-promoting" activities in this Farber-model, which utilizes 2-AAF as a mito-inhibitory toxin.

8.5.4 Skin carcinogenicity

Aroclor 1254 (100 μg/mouse) administered 18 h prior to the initiator, 7,12-dimethylbenz(*a*)anthracene (DMBA), significantly decreased the incidence of papilloma formation in female Charles-River CD-1 mice. 2,4,5,2',4',5'-Hexachlorobiphenyl (625 μg/mouse), a PCB congener that resembles phenobarbital in its mode of induction of drug-metabolizing enzymes, did not act as an anticarcinogen, whereas 3,4,3',4'-tetrachlorobiphenyl was more active than Aroclor 1254 as an inhibitor. 3,4,3',4'-Tetrachlorobiphenyl resembled methylcholanthrene in their mode of cytochrome P-450 induction (Parkinson et al., 1983) and decreased the number of DMBA-initiated papillomas/mouse. Although the PCB treatment did not modulate the incidence of papillomas caused by benzo(*a*)pyrene, it was suggested that the anticarcinogenic effects of PCBs on mouse skin tumours initiated by DMBA were due to altered metabolism and DNA binding of the carcinogen by the PCB-induced skin monooxygenases (DiGiovanni et al., 1979).

Berry et al. (1978, 1979) studied the tumour-promoting activity of Aroclor 1254 in groups of 30 female CD-1 mice initiated with 0.2 mmol/litre (equivalent to 51 μg) DMBA. One week later, a positive control group received 2 μg tetradecanoylphorbolacetate (TPA) and an experimental group received 100 μg Aroclor 1254 in acetone. The TPA and Aroclor applications were made twice weekly for 30 weeks. The TPA promotion resulted in 92% of the animals developing papillomas, while none developed in the Aroclor-treated animals. It was concluded that Aroclor 1254 was not a skin tumour promoter at the dose used in this study. Inhibition of skin papilloma was observed when Aroclor 1254 was administered 18 to 72 h prior to DMBA treatment and promotion by TPA.

Poland et al. (1982) used HRS/J hairless mice to study the tumour promotion activity of Aroclor 1254 in combination with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG). Twenty female mice per group received a single administration of MNNG (5 micromol in acetone) or acetone alone applied on the skin, and were then treated topically, twice weekly, with 1 mg Aroclor/mouse, dissolved in acetone, for 20 weeks. No tumours were induced in the control group; in the MNNG-treated mice, 4/19 had papillomas. It was concluded that Aroclor had a weak promoting effect.

8.5.5 Appraisal

In summarizing the potential carcinogenic activity of PCBs, it is perhaps more informative to express it in terms of what is known about the mechanisms of chemical carcinogenicity (Hayes, 1987). In other words, what the evidence is to support the carcinogenicity of PCBs through genotoxic/initiating, cocarcinogenic, promotional/antipromotional, and progressional activities. There is no evidence to support genotoxic activity for PCBs and, in *in vitro* studies, evidence for initiating activity through direct interactions with DNA is weak. Poor initiating activity is consistent with the demonstrated lack of mutagenic activity in various short-term tests. There is evidence to suggest that PCBs can potentiate the activity of known carcinogens (or act as cocarcinogens) in *in vitro* systems, but the opposite result is often seen in *in vivo* studies, suggesting that certain protecting enzyme systems present in the intact systems are absent in the *in vitro* systems. There is a substantial body of evidence to support the promotional activity of PCBs, particularly the more highly chlorinated ones, in rodent liver, and this activity may depend on the sequence in which the chemicals are administered in experimental animal studies. In addition, promotional activity is correlated closely, but not consistently, with the induction of MFO activity. The hyperplastic effect (stimulation of cell proliferation) of PCB inducers could promote preneoplastic growth. This type of activity may possibly involve a threshold, suggesting that it may not be a factor in low-level exposures to PCBs. The anticarcinogenic activity of PCBs may also depend on the sequence of events in experimental animal studies, and it may be related more to the antipromotional properties of PCBs, possibly functioning as protectants of mito-inhibitory

toxicity. The interpretation of the available animal data involving the commercial PCB mixtures is often complicated by lack of information concerning the presence and contribution of chlorinated dibenzofuran impurities, as well as variations in congener composition to toxicity. In structure-activity terms, a key factor in determining promotional activity appears to be the degree of chlorination, which may reflect increased resistance to metabolism and elimination and possibly also higher degrees of *ortho*-substitution among the congeners present. *Ortho*-substituted PCBs (possibly acting as persistent PB type inducers) have been shown to be effective tumour promoters, and, at least in the case of the closely related PBBs, it has been shown that a non-toxic and non-promoting dose of a non-*ortho*-substituted congener in combination with a promoting dose of a highly *ortho*-substituted congener has a synergistic effect. This result may explain why the mixtures can have greater promoting ability than the individual congeners involved. This result might also suggest multiple pathways for promoting activity, possibly involving the Ah receptor as well as the putative receptor for phenobarbital. The possibility that PCBs might promote carcinogenesis in tissues, other than liver, in animals exposed to various tissue-specific, initiating agents, needs to be addressed. Nevertheless, the potential for human liver cancer from exposure to PCBs cannot be reliably predicted from animal studies. Overall, there is reason to exercise caution in extrapolating the available animal data on the carcinogenic potential of PCBs for humans.

8.6 Special studies: target-organ effects

The lesions commonly introduced in animals after acute, short-term, or long-term administration/application of PCB mixtures and/or individual congeners concern the liver, skin, immune system, reproductive system, oedema at various sites, as well as disturbances of the gastrointestinal tract and the thyroid gland.

8.6.1 Liver

8.6.1.1 PCB mixtures

The toxic effects of PCBs result both directly and indirectly from their presence in certain organs, such as the liver, where they induce, in various degrees, a variety of liver enzymes. Some of these enzymes are active in the metabolism of the PCBs themselves, while others involve activation, deactivation, detoxication, etc., of other compounds.

In itself, induction of enzymes by xenobiotics does not represent a toxic manifestation, rather it is the ordinary response to such foreign chemicals, which results generally in their detoxication and ultimate modification, enabling them to be excreted from the organism. In this sense, the response of the liver to such compounds is a biological protective mechanism. Since some compounds, including PCBs, are capable of inducing not only enzymes that result in their own detoxication, but others as well, and the level of enzyme induction may be high enough to cause liver pathology, a line cannot be drawn that clearly separates a normal biological function from a toxic manifestation. Superimposed on this situation is the direct toxic action of the compounds on liver tissue, because of the properties of the parent compound or its metabolites.

An enlarged liver and increased absolute and relative liver weights are commonly reported as gross effects of PCB administration. The lowest-observed-effect levels, in studies on different rat strains, exposed to a diet containing Aroclor 1254, for a (dose-related) increase in relative liver weights, vary between 20 and 100 mg/kg diet (equivalent to 1 and 5 mg/kg body weight, respectively) (Kimbrough et al., 1972; Bruckner et al., 1974; Burse et al., 1974; Grant et al., 1974; Allen et al., 1976; Zinkl, 1977; Hinton et al., 1978; Kasza et al., 1978b; Jonsson et al., 1981; Baumann et al., 1983).

The liver hypertrophy is microscopically visible as enlarged, pleiomorphic hepatocytes, sometimes multinucleated or with enlarged nuclei. A liver alteration observed by many investigators after exposure of rats to various PCB-mixtures is fatty degeneration, characterized by fat vacuolation and/or a foamy appearance of the

cytoplasm. Ultrastructurally, an increase in the number and size of cytoplasmic lipid droplets and liposomes (membrane-associated lipid droplets) can be observed. Fatty degeneration of the liver was already observed after exposure of male Sprague-Dawley rats to a diet containing 5 mg Aroclor 1242/kg diet (equivalent to 0.25 mg/kg body weight) for 2–6 months (Bruckner et al., 1974) and after exposure of male Holtzman rats to a diet containing 5 mg Aroclor 1254/kg for 5 weeks (Kasza et al., 1978b). Chu et al. (1977) found a comparable effect on the liver with ≥20 mg Aroclor 1254 or 1260/kg diet for 28 days. Another characteristic change is the appearance of eosinophilic, lamellar, cytoplasmic inclusions (Kimbrough et al., 1972; Kasza et al., 1978b) or "hyaline-like material" (Grant et al., 1974). Electron microscopy revealed that these changes corresponded to concentric laminated membranes of smooth endoplasmic reticulum ("whorls"; "myelin figures") (Vos & Beems, 1971; Kimbrough et al., 1972; Allen et al., 1976; Kasza et al., 1978b; Jonsson et al., 1981). Proliferation of the smooth endoplasmic reticulum and a decrease in rough endoplasmic reticulum are commonly observed in rats exposed to dietary levels of PCB mixtures that also induce fatty degeneration. Kasza et al. (1978b) further observed a marked proliferation of Golgi condensing vesicles containing lipoprotein in the livers of male Holtzman rats fed Aroclor 1254, for 5 weeks, at 5 mg/kg diet. A decreased number of these vesicles was seen at 50 and 500 mg/kg diet (equivalent to 2.5 and 25 mg/kg body weight, respectively), together with a marked increase in the smooth endoplasmic reticulum and lysosomes. The above decrease in Golgi vesicles was also observed in Sprague-Dawley rats by Hinton et al. (1978). The proliferative changes of the endoplasmic reticulum are closely related to the observed induction of microsomal enzymes, as discussed in section 8.6.1.2. Atypical mitochondria (Burse et al., 1974; Kasza et al., 1978a,b), and single cell and focal necrosis (Grant et al., 1974; Allen et al., 1976; Jonsson et al., 1981; Baumann et al., 1983) have also been described.

Hypobilirubinaemia was produced in rats by Bastomsky et al. (1975), who investigated the mechanism by administering daily intraperitoneal injections of Aroclor 1254 (25 mg/kg body weight, in corn oil) to female rats for 4 days, before measuring bilirubin glucuronide formation by hepatic microsomes *in vitro*. PCB treatment was not

effective in increasing UDP-glucuronosyltransferase (EC 2.4.1.7) activity. Serum bilirubin levels in Gunn rats were also significantly decreased by PCB treatment; the rats are genetically deficient in UDP-glucuronosyltransferase (2.4.1.7) activity.

The fluorescing of livers on exposure to UV radiation, consistent with the presence of porphyrin, and accumulation of brown pigment, positive for iron, especially in Kupffer cells and perivascular macrophages have also been reported (Kimbrough et al., 1972; Burse et al., 1974; Zinkl, 1977; Jonsson et al., 1981). The changes described in the livers of mice (Nishizumi, 1970) and rabbits (Koller & Zinkl, 1973), following exposure to PCB mixtures, are comparable with those in rats.

8.6.1.2 Individual congeners

The effects of chlorination and the chemical composition of PCBs, with regard to the dose-effects relations in liver toxicity after short-term exposure, are indicated by the data of Biocca et al. (1981). In this study, hepatotoxic effects were observed in mice after 5 weeks of maintenance on diets containing 0.3 mg of 3,4,5,3',4',5'-hexachlorobiphenyl, while similar effects were observed only after 30 mg of 2,4,5,2',4',5'-hexachlorobiphenyl and 100 mg of 2,4,6,2',4',6'-hexachlorobiphenyl/kg diet. No effects were found with 300 mg of 2,3,6,2',3',6'-hexachlorobiphenyl/kg diet. Similar dependence of liver toxicity on the chemical composition of the PCB mixture would be anticipated following long-term exposure in mice and other species.

8.6.2 Enzyme induction

8.6.2.1 Effects on liver enzymes of PCBs

Proliferation of the smooth endoplasmic reticulum is a common observation in the liver cells of experimental animals following exposure to PCB mixtures. This effect is accompanied by an increase in microsomal protein and the induction of cytochrome P-450, cytochrome P-448, and drug-metabolizing enzymes, including the microsomal monooxygenases (EC 1.14.14.1), epoxide hydrolases (EC 3.3.2.3), UDP-glucuronosyltransferases (EC 2.4.1.17),

NADPH-cytochrome c reductase (EC 1.6.2.4) and esterases (EC 3.1.1.1), and the cytosolic glutathione *S*-transferase (EC 2.5.1.18). The subject has been reviewed by Safe (1984).

The spectral, enzymatic, and electrophoretic properties of the microsomal enzymes, induced by Aroclor 1248, 1254, 1260, and Kanechlor 400, are consistent with the inducing properties of both the phenobarbital (PB) and 3-methylcholanthrene (MC) classes of inducers. They induce both cytochromes P-450 and P-448 and associated enzymes (Alvares & Kappas, 1977; Goldstein et al., 1977; Yoshimura et al., 1978; Iverson et al., 1982; Lashneva & Tutelyan, 1984; Khan et al., 1985; Tutelyan et al., 1986). Aroclor 1016, administered to Sprague-Dawley rats at 50 mg/kg per day for 4 days, intraperitoneally, elicited a barbiturate type of inducing effect on the hepatic microsomal oxidative enzyme system. Aroclor 1016 caused increases in liver cytochrome P-450 content, microsomal protein, and its ethylmorphine *N*-demethylase activity. It did not induce cytochrome P-448 in liver microsomes.

A dose-related induction of hepatic and, in some cases, extrahepatic microsomal enzymes was observed in several animal species including the rat, rabbit, mouse, ferret, guinea-pig, hamster (Safe, 1984), mink (Shull et al., 1982; Aulerich et al., 1985) and monkey (Iverson et al., 1982). Distinct interspecies variations have been demonstrated. For example, while 6 daily intraperitoneal doses of 25 mg of Aroclor 1254/kg body weight caused a potent induction of benzo(*a*)pyrene hydroxylase in adult, male Sprague-Dawley rats, no, or a minimal, induction of this monooxygenase was observed in adult, male Swiss mice after 4 daily intraperitoneal doses of 50 mg/kg body weight and in male New Zealand rabbits after 2 intraperitoneal doses of 100 mg/kg body weight on days 1 and 4 (Alvares et al., 1982). Furthermore, when comparing the inducing potency of Aroclor 1242 in the mink and the genetically related ferret, Shull et al. (1982) measured a greater induction of cytochrome P-448 and MC-type monooxygenases and no toxic effects in the ferret at a dosing regime that resulted in toxic effects in the mink (100 mg/kg body weight on day 1, 200 mg/kg body weight on day 5, sacrifice on day 10). The authors considered the observed induction moderate in both species compared with that observed in the rat. Earlier, it had been found that male Sprague-Dawley rats were indeed more sensitive than

ferrets with respect to the inducing effect of Aroclor 1254 following a single intraperitoneal dose of 500 mg/kg body weight, though the responses of both species were comparable qualitatively (Lake et al., 1979). Moreover, pretreatment of rats with Aroclor 1254 resulted in the induction of microsomal cytochromes P-450 c, P-450 d (MC-inducible), P-450 b and P-450 e (PB-inducible) (Ryan et al., 1979a,b, 1982). In general, the extent of induction of microsomal enzymes by PCB-mixtures increased with increasing chlorine content up to 54%. The effect has also been demonstrated with single pure PCBs administered orally (Ecobichon & Comeau, 1975). The results are summarized in Table 50 and show a greater degree of enzyme induction with the higher chlorinated compounds (see section 8.6.1.2).

Table 50. Stimulation of microsomal enzyme activity by single chlorinated biphenyls[a]

Chlorine substituents	Hepatic microsomal enzyme activity			
	O-Demethylation	*N*-Demethylation	Aniline hydroxylation	Nitroreduction
4	0	0	0	0
2,2′	0	+	+	0
2,4′	0	0	+	0
4,4′	+ +	+ +	+ +	+
2,5,2′,5′	0	+	+ +	+
2,4,2′,4′	+ +	+ +	+ +	0
2,4,5,2′,4′,5′	+ +	+ +	+ +	+ +
2,3,5,2′,3′,5′	+ +	+ +	+ +	+ +
2,4,6,2′,4′,6′	+ +	+ +	+ +	+ +
2,3,4,5,2′,3′,4′,5′	+ +	+ +	+ +	+ +

[a] From: Johnstone et al. (1974).
0 = No activity.
+ = Slight activity.
+ + = Marked activity.

Litterst et al. (1972) exposed groups of 6 male Osborn-Mendel rats to Aroclors 1242, 1248, 1254, or 1260 in the diet, at concentrations of 0, 0.5, 5.0, 50, or 500 mg/kg diet, for 4 weeks. Increased

microsomal nitroreductase and demethylase activities occurred at 0.5 mg/kg or more, increased pentobarbital hydroxy- lation and increased relative liver weight occurred at 5.0 mg/kg or more, and increased liver triglycerides occurred at 50 mg/kg diet. An inducing activity similar to, or lower than, that of Aroclor 1254 has often been found for more chlorinated mixtures (Villeneuve et al., 1971a, 1972; Bickers et al., 1972; Chen & Dubois, 1973; Ecobichon & Comeau, 1974; Schmoldt et al., 1974; Sawyer et al., 1984). Aroclor 1016 and 1242, both containing 42% chlorine but differing in congener composition, showed qualitative and quantitative differences in inducing effects. For example, Aroclor 1254 enhanced ethylmorphine *N*-demethylase activity 3-fold, while the maximum increase produced by Aroclor 1016 was only 40%. The 2 Aroclors also differed in their induction of the various forms of cytochrome P-450 (Alvares et al., 1982). Adult, male Sprague- Dawley rats were administered, intraperitoneally, a dosage of 0 or 50 mg Aroclor 1016 in corn oil/kg body weight, for 4 days. Aroclor 1016 was a potent inducer of *N*-methylase but a poor inducer of benzo(*a*)pyrene hydroxylase. Administration of 100 mg Aroclor 1016 in corn oil/kg body weight per day to adult male New Zealand White rabbits, for 4 days, resulted in an increase in liver cytochrome P-450 activity and decreases in benzphetamine-*N*-demethylase and benzo(*a*)pyrene hydroxylase activities compared with the controls. 7-Ethoxycoumarine-*O*-deethylase and 7-ethoxyresorufin-*O*-deethylase activities were comparable with those in the controls (Ueng & Alvares, 1985). Therefore, it can be concluded that the degree and type of induction not only depends on the chlorine content of the mixture, but is also a function of the congener composition, as will be discussed further in the next section.

Not only species specificity, but also marked tissue specificity has been observed. While Aroclor 1254 was found to be a potent inducer of cytochrome P-450 content and benzo(*a*)pyrene hydroxylase activity in the rat lung and liver (Alvares & Kappas, 1977), it caused a 46% decrease in cytochrome P-450 content, a 31% decrease in benzo(*a*)pyrene hydroxylase activity, and a 61% decrease in ethylmorphine *N*-demethylase activity in the rabbit lung. Aroclor 1254 caused induction of cytochrome P-450 and both enzymes in the

kidneys of these rabbits, but benzo(*a*)pyrene hydroxylase was not induced in the liver (Alvares et al., 1982).

The inducing effect of PCB mixtures on the monooxygenase system has been observed in the livers of both male and female rats (Chen & Dubois, 1973; Grant & Phillips, 1974), minks and ferrets (Lake et al., 1979; Shull et al., 1982), in the livers of pregnant rats (Alvares, 1977) and rabbits (Villeneuve et al., 1971a), in the placenta of rats (Alvares & Kappas, 1975), in fetal and neonatal rat livers (Alvares & Kappas, 1975; Baker et al., 1977; Inoue et al., 1981; Jannetti & Anderson, 1981; Lashneva et al., 1987), in immature rat livers (Chen & Du Bois, 1973; Narbonne, 1980), and in mature and senescent rat livers (Birnbaum & Baird, 1978).

The lowest-observed-adverse-effect levels and the no-observed-effect levels for enzyme induction, found in short-term diet studies on rats, are presented in Table 51.

Bruckner et al. (1977) showed that when Aroclor 1254 was administered in the diet, at a level equivalent to 0.25 mg/kg body weight, microsomal enzyme activity was induced after 1 day of exposure. Narbonne (1980) found a significant induction with 0.1 mg Phenoclor DP6/kg body weight, given in the diet, after 3–5 days.

After a few weeks of exposure to Aroclor 1254 or 1260, at low dietary levels of between 0.25 and 1.25 mg/kg body weight, a plateau in microsomal enzyme activity was reached that was maintained over several months of exposure (Chen & Du Bois, 1973; Grant et al., 1974; Bruckner et al., 1977). Following short-term exposure, dietary levels of between 5 and 25 mg/kg may stimulate microsomal enzymes for up to 4 months (Grant et al., 1974; Bruckner et al., 1977). Levels of 0.05 or 0.1 mg/kg body weight failed to produce any effects or the periods of induction at these levels were long (Grant et al., 1974; Chen & Du Bois, 1973).

A marked induction of the liver monooxygenase system was observed in the offspring of female rats given a single oral dose of a mixture of PCBs (Sovol) (500 mg/kg body weight) on the 14th day of pregnancy. In one-day-old rats, an increase in cytochrome P-450 content associated with an increase in the cytochrome b 5 level, an increase in NADPH-cytochrome c reductase activity, an increased

Table 51. Microsomal enzyme induction by PCB-mixtures in rats

PCB-mixture	Rat strain	Sex male/female	Exposure period	No-effect-level mg/kg body weight	Lowest-observed-adverse effect level, mg/kg body weight	Reference
Aroclor 1016	Sprague-Dawley	male	3 weeks[a]	0.1	1	Iverson et al. (1975)
Aroclor 1242	Sprague-Dawley	male	3 weeks[a]	0.1	1	Iverson et al. (1975)
	Osborne-Mendel	male	4 weeks	< 0.025	0.025	Litterst et al. (1972)
	Sprague-Dawley	male	2-6 months	< 0.25	0.25	Bruckner et al. (1974, 1977)
Aroclor 1248	Osborne-Mendel	male	4 weeks	< 0.025	0.025	Litterst et al. (1972)

Table 51 (continued)

Aroclor 1254	Osborne-Mendel	male	4 weeks	< 0.025	0.025	Litterst et al. (1972)
	Wistar	male	2-8 months	< 0.1	0.1[c]	Grant et al. (1974)
	Wistar	male	2 weeks	0.25	0.5	Den Tonkelaar & van Esch (1974)
	Wistar	male	12 weeks	0.05	0.5	
	Sprague-Dawley	male	0-20 weeks	0.05	0.25	Turner & Green (1974)
	Holtzman	male	3 weeks	< 0.25	0.25	Bruckner et al. (1977)
						Garthoff et al. (1977)
Aroclor 1260	Osborne-Mendel	male	4 weeks	< 0.025	0.025	Litterst et al. (1972)
	Holtzman	male	1-13 weeks	< 0.05	0.05	Chen & DuBois (1973)
		female	1-13 weeks	0.05	0.25	
Phenoclor DP6	Sprague-Dawley[b]	male	3 days	< 0.1	0.1	Narbonne (1979, 1980)

[a] Daily dosing by gavage; the other studies are all diet studies.
[b] Immature rats (60-65 g).
[c] Significant effect after months 4 and 6, but not after months 2 and 8.

rate of aminopyrine-*N*-demethylation activity in microsomes and also increased 3,4-benzo(*a*)pyrene hydroxylation, 7-ethoxycoumarin *O*-deethylation, and NADPH-dependent lipid peroxidation were found. The activity of the cytochrome P-450 system in the young rats remained elevated during the early postnatal period (Lashneva et al., 1987).

8.6.2.2 Effects on liver enzymes of "biologically filtered" PCB mixtures

Young Sprague-Dawley rats were administered a total of 38 oral doses of a PCB mixture in olive oil at 0, 0.25, 1.0, 4.0, 16.0, 64.0, 256, or 1025 μg/kg body weight, twice a day, over 1 month; the mixture contained 55% chlorine and had a gas-chromatographic profile very similar to that of the congeners found in the breast milk of Japanese women. A dose-related induction of liver aminopyrine demethylase and benzo(*a*)pyrene hydroxylase (EC 1.14.14.1) was found with doses of 1.0 μg/kg body weight or more. PCB-binding to liver microsomes was increased at doses of 4.0 μg/kg body weight or more (Shimada & Ugawa, 1978). In another study, 1-month-old, male Wistar rats received (intraperitoneally) doses of 0, 1, 10, 25, 50, or 100 mg/kg body weight of a reconstituted PCB-mixture in corn oil, containing average levels of 13 of the major congeners found in the breast milk of Japanese women (purity >98.5%). Each dose was administered in 2 portions on days 1 and 3. The same dose regimen of Kanechlor 500 was also tested. The rats were killed on day 6. The reconstituted PCB mixture and Kanechlor 500 caused dose-related increases in liver benzo(*a*)pyrene hydroxylase activity that were 3.5 and 2.2 times the control value, respectively, at 1 mg/kg body weight. The ED_{50} of the reconstituted breast milk PCB mixture for the induction of rat hepatic microsomal aryl hydroxylase (AHH) was 7 times lower than that of Kanechlor 500. The authors concluded that the increased potency of the breast milk-PCB mixture reflected the preferential bioconcentration of the relatively toxic congeners 2,4,5,3',4'-penta-, 2,3,4,3',4'-penta-, and 2,3,4,5,3',4'-hexachlorobiphenyl (Parkinson, et al., 1980b). When Gyorkos et al. (1985) repeated the studies, the reconstituted mixture was inactive at the lowest dose level but exhibited mixed-type microsomal enzyme induction characteristics at the higher dose levels. Increases in the

activities of several hepatic microsomal monooxygenases, including dimethylaminoantipyrine *N*-demethylase, aldrin epoxidase, benzo(*a*)pyrene hydroxylase and ethoxyresorufin-*O*-deethylase were found.

8.6.2.3 Effects of individual congeners on liver enzymes

The enzyme-inducing potencies of individual PCB congeners have been studied extensively and reviews have been published (Goldstein, 1980; Safe, 1984; Safe et al., 1985b), in which the following structure-activity relationships are proposed. The most active congeners with respect to the induction of aryl hydrocarbon hydroxylase (and toxicity), 3,4,5,4'-tetrachloro-, 3,4,3',4'-tetrachloro-, 3,4,5,3',4'-pentachloro-, and 3,4,5,3',4',5'-hexachlorobiphenyl, are substituted at both *para* positions, at 2 or more *meta* positons, but not at *ortho* positions. These congeners can assume coplanar conformations and are approximate stereoisomers of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin. They resemble 3-methylcholanthrene and 2,3,7,8-tetrachlorodibenzo-*para*-dioxin in their mode of hepatic enzyme induction, inducing hepatic microsomal benzo(*a*)pyrene hydroxylase, ethoxyresorufin-*O*-deethylase, and the cytochromes P-450 a, P-450 c, and P-450 d.

These congeners are only present as trace compounds in commercial PCB mixtures, but appear in significant quantities in breast milk (Noren et al., 1990).

The least active of these 4 coplanar congeners, 3,4,5,4'-tetrachlorobiphenyl, also shows a phenobarbital type of hepatic microsomal enzyme induction, inducing dimethylaminoantipyrine, ethylmorphine and related *N*-dealkylases, biphenyl-4-hydroxylase, aldrin epoxidase, several *O*-dealkylases, and the cytochromes P-450 a, P-450 b, and P-450 e. This "mixed-type" induction pattern is also shown by 3,4,4'-trichlorobiphenyl, and by all the mono-*ortho*, and at least 7 di-*ortho*, substituted analogues of the coplanar PCB congeners. Several of these congeners, e.g., 2,4,5,3',4'-penta, 2,3,3',4,4'-penta, 2,3,4,5,3',4'-hexa-, and 2,3,4,5,2',4'-hexachlorobiphenyl are components of commercial PCB mixtures and have been identified in breast milk.

Studies have revealed that 4,4'-dichlorobiphenyl, with no *meta* substituents exhibits a PB-type induction pattern in rats. Adding *meta* substituents as in 3,4,4'-tri-, and 3,4,5,4'-tetrachlorobiphenyl will give a mixed PB- and 3-MC-type induction pattern. While 3,4,3',4'-tetrachlorobiphenyl is a potent inducer of microsomal hepatic aryl hydrocarbon hydroxylase(AHH), it did not significantly increase the activities of benzo(*a*)pyrene-hydroxylase, [^{3}H]-4-chlorobiphenyl-hydroxylase, and ethoxyresofurin-*O*-deethylase (EROD) at a dose level of 10 μmol/kg (Andres et al., 1983).

Most other PCB congeners are phenobarbital-type inducers or are inactive. In general, the more highly chlorinated of these congeners are more active inducers than the lower chlorinated ones, probably reflecting the relative half-lives of these compounds. The non-availability of 2 adjacent unhalogenated carbon atoms and *para*-substitution are 2 factors that decrease the degradability of the congeners and increase their inducing activity.

Various congeners were tested for their inducing activity in responsive C57BL/6J mice, i.e., mice containing the Ah receptor protein, and in non-responsive DBA/2J mice, lacking this receptor, after single intraperitoneal (Robertson et al., 1984; Silkworth et al., 1984) or oral (Kohli et al., 1980) doses in corn oil and cottonseed oil, respectively. The coplanar PCBs and their mono-*ortho* substituted analogues all induced benzo(*a*)pyrene hydroxylase or ethoxyresorufin deethylase in responsive mice, but not, or only to a minor degree, in non-responsive mice. Most tested mono-*ortho* substituted analogues of coplanar PCBs slightly induced aminopyrine *N*-demethylase in both strains, while the coplanar congeners did not induce this enzyme.

The above structure-activity relationships were confirmed in a few limited studies on monkeys. Hepatic aryl hydrocarbon hydroxylase was induced in 3 young, male Rhesus monkeys after a single oral dose of 1 mg of 3,4,3',4'-tetrachlorobiphenyl/kg body weight and in 3 young male monkeys during continued feeding of a diet containing 0.5 mg of 3,4,5,3',4',5'-hexachlorobiphenyl/kg (McNulty, 1985). A single oral dose of 18 mg of 2,5,2',5',-tetrachlorobiphenyl/kg body weight, administered to male Rhesus monkeys, in corn oil, elevated hepatic cytochrome P-450 levels, while no change was noted in the

activities of several microsomal enzymes (Allen et al., 1975b). Mono-*ortho* or di-*ortho* substituted analogues of coplanar PCB congeners have not been tested in monkeys.

Vodicnik et al. (1980) studied the effect of 2,4,5,2',4',5'-hexachlorobiphenyl on hepatic microsomal monooxygenase activity in virgin or pregnant and lactating Sprague-Dawley mice and their offspring. A single intraperitoneal dose of 100 mg/kg body weight, was administered 14 days before mating. Prior to, and during early pregnancy, hepatic monooxygenase activity in pretreated mice was greater than that in the controls. No differences were found between pregnant and virgin mice. Mothers, pretreated with the hexachlorobiphenyl and sacrificed on the day of birth, had lower microsomal monooxygenase activity and cytochrome P-450 content than PCB-pretreated virgins sacrificed concurrently. No differences were noted between these groups of animals during lactation. Hepatic enzyme activities and cytochrome P-450 content were not different between newborn offspring of corn oil- and PCB-pretreated mothers. However, these parameters were elevated in 5- to 20-day postpartum nursing offspring from pretreated mothers, compared with those from corn oil-pretreated mothers suggesting the transfer of hexachlorobiphenyl through the breast milk in quantities sufficient to affect hepatic microsomal monooxygenase activity.

In a study on ICR mice, Vodicnik (1986) administered 150 mg ^{14}C-2,4,2',4'-tetrachlorobiphenyl intraperitoneally, and compared hepatic microsomal ethoxycoumarin-*O*-deethylase activity and liver concentrations of ^{14}C-activity. It was shown that pregnant mice were less responsive to the inducing effects of the tetrachlorobiphenyl than virgin or postpartum mice. This diminution in response may be, in part, responsible for the lack of elimination of the tetrachlorobiphenyl equivalents from the late pregnant animal during the 4-day experimental period (see section 6.4.3).

Hardwick et al (1985) studied both the time course and dose-response for the induction of the 2 isoenzymes and their respective mRNAs after administration of 3,4,5,3',4',5'-hexachlorobiphenyl to rats. It was concluded that the congener under study induced 2 major 3-MC-inducible isoenzymes of cytochrome P-450 and their mRNAs in a coordinated manner, probably via a common mechanism. The data

are consistent with the hypothesis that both genes are probably regulated by a single receptor in the rat. The magnitude of the increase in the isoenzymes was greater than the increase in the amount of translationally active mRNA in polysomes, suggesting that other factors may also influence the relative induction of these P-450 isoenzymes.

In this study, the BP-type inducers, 2,4,6,2',4',6'- and 2,4,5,2',4',5'-hexachlorobiphenyl, both of which have been reported to increase the hepatic cytosolic receptor level and consequently enhance enzyme induction *in vivo*, were not able to enhance EROD or AHH induction by 3,4,5,3',4'-pentachlorobiphenyl *in vitro*.

The mixed-type inducer 2,3,4,2',4',5'-hexachlorobiphenyl inhibited enzyme induction by 3,4,5,3',4'-pentachlorobiphenyl *in vitro*, when used in concentrations of at least 400 times higher than that of the 3,4,5,3',4'-pentachlorobiphenyl. Enzyme induction by 3,4,3',4'-tetrachlorobiphenyl was inhibited by 2,3,4,2',4',5'-hexachlorobiphenyl at concentrations at least 40 times higher, and enzyme induction by 3,4,5,3',4',5'-hexachlorobiphenyl was inhibited by 2,3,4,2',4',5'-hexachlorobiphenyl at concentrations at least 8 times higher. Since the concentration of 2,3,4,2',4',5'-hexachlorobiphenyl found in human adipose tissue is about 300 times higher than those of the 3 coplanar PCBs, this inhibition of enzyme induction probably occurs after natural exposure to PCB mixtures. If enzyme induction by 3,4,3',4'-tetrachlorobiphenyl and 3,4,5,3',4',5'-hexachlorobiphenyl is also inhibited by various concentrations of 2,3,4,2',3',4'-hexachlorobiphenyl, inhibition of enzyme induction after natural exposure to a mixture of PCBs is to be expected.

It was concluded that the *in vitro* enzyme induction by mixtures of PCBs cannot be determined by the simple addition of the induction by the individual PCBs. Possibly, *in vivo* enzyme induction seems additive, because some compounds increase the receptor level, while other compounds inhibit enzyme induction (van Vliet, 1990).

8.6.2.4 Appraisal

The liver is the organ most often implicated in the toxicity of PCBs in animals. Hepatotoxicity has been observed in numerous studies with exposed mice, rats, guinea-pigs, rabbits, dogs, and monkeys.

The effects, which appear to be reversible at low doses, are similar among the species and include enzyme induction, liver enlargement, fat deposition, and necrosis. Enzyme induction is the most sensitive indicator of hepatic effects, but few studies have been designed to define the minimum effective doses of PCB mixtures. The liver enlargement is associated with hepatocyte enlargement and an increase in smooth endoplasmic reticulum and/or increased enzymatic activity. Proliferative lesions in the liver have been attributed to Aroclor treatment. The hepatic effects of Aroclors in animals appear to be typical of chlorinated hydrocarbons. Histologically-documented liver damage is a consistent finding among PCB-exposed animals.

8.6.3 Effects on vitamins and mineral metabolism

8.6.3.1 Effects of PCB mixtures

PCB mixtures have been found to decrease levels of retinol (Vitamin A) in the liver of rats (Innami et al., 1976; Kato et al., 1978; Hudecova et al., 1979), rabbits (Villeneuve et al., 1971a), and in the plasma of pigs (Guoth et al., 1984). Levels of thiamine (Vitamin B1) were decreased in the blood, liver, and sciatic nerve of rats (Yagi et al., 1979) and levels of pyridoxal phosphate (Vitamin B6) were decreased in several tissues of rats, while riboflavin (Vitamin B2) levels remained unaffected (Fujiwara & Kuriyama, 1977). The changes in the levels of retinol and thiamine were thought to be secondary to the induction of metabolizing enzymes (Yagi et al., 1979; Saito et al., 1982). The induction of these enzymes was also found to be responsible for the increased *de novo* synthesis of L-ascorbic acid that was observed in the plasma, tissues, and urine of PCB-treated rats (Fujiwara & Kuriyama, 1977; Chakraborty et al., 1978; Chow et al., 1979; Saito et al., 1983). Lipid peroxidation was increased in the liver of PCB-treated rats and Saito et al. (1983) suggested that ascorbic acid may have initiated the peroxidation.

It was shown that induction of NADP-cytochrome c reductase (EC 1.6.2.4) and insufficiency of lipid peroxide scavengers, such as alpha-tocopherol (Vitamin E) and glutathione peroxidase (EC 1.11.1.9), could also be involved in the enhancement of lipid

peroxidation by PCBs (Saito et al., 1982, 1983; Kamohara et al., 1984).

PCB mixtures decreased the activity of both sodium/potassium- and magnesium-dependent adenosinetriphosphatase (EC 3.6.1.3) in the tissues of rats (Narbonne et al., 1978; La Rocca & Carlson, 1979). The results of *in vitro* studies on isolated rat mitochondria showed that PCB mixtures may act as inhibitors of respiration and uncouplers of oxidative phosphorylation (Sivalingan et al., 1973; Nishihara, 1983, 1985). However, contradictory results have been obtained *in vivo* with respect to the NAD/NADH ratio, the ADP/O ratio, and state 3 and state 4 respiration rates (Mehlman et al., 1974; Chesney & Allen, 1974; Garthoff et al., 1977).

Byrne & Sepkovic (1987) studied the *in vitro* incorporation of monovalent cations into rat erythrocytes as a model for evaluating the impairment of electrogenic transport by PCBs. Female, Sprague-Dawley rats were fed 50 mg Aroclor 1242 or 1254/kg diet for 7 months. The uptake of ^{86}Rb by erythrocytes in the Aroclor 1254 group was depressed compared with that in the control group in K^+- depleted culture media. No changes were observed with Aroclor 1242. A reduction in ^{86}Rb incorporation was also seen in erythrocytes from the Aroclor 1254 group in a Na^+-depleted medium. Ouabain did not have any effect in the Aroclor 1254 group, because Aroclor 1254 suppressed the cationic transport maximally. This study provides evidence that PCBs (Aroclor 1254) can damage the cell sufficiently to decrease the active transport of monovalent cations.

Male Fischer 344 rats were dosed daily, intragastrically, for 5, 10, or 15 weeks with 0, 0.1, 1, 10, or 25 mg Aroclor 1254/kg body weight in corn oil, to investigate the effects on calcium metabolism, femur morphometry, and nephrotoxicity. The relative liver weights were increased significantly with doses of 1.0 mg/kg or more after 5 weeks treatment. The relative kidney weights were increased after 15 weeks treatment in the 10 and 25 mg/kg groups. Hypercalcaemia was present in the 25 mg/kg group after 5 and 10 weeks treatment, but not after 15 weeks. Serum triglyceride levels were elevated after 5 weeks treatment, but decreased after 10 and 15 weeks. Serum cholesterol levels were increased at the 2 higher dose levels with all

3 lengths of treatment. Urinary alkaline phosphatase and lactate dehydrogenase activities were elevated at 5, 10, and 15 weeks of treatment. Femur density was increased at the 10 mg/kg dose level after 5 weeks, and at all dose levels after 10 and 15 weeks. Cross-sectional, medullary, and cortical areas of the midpoint of the femur were significantly decreased at the higher dose levels after 10 and 15 weeks of exposure. The per cent medullary area was decreased after 10 and 15 weeks treatment indicating a decrease in medullary size and also a decrease relative to the cortical bone area. The result was weaker bones after 15 weeks at the highest dose level. Thus, PCB exposure affects calcium metabolism and bone morphometry (Andrews, 1989).

8.6.3.2 *Effects of individual congeners*

3,4,3',4'-Tetrachlorobiphenyl induced a decrease in serum and liver retinol and retinyl palmitate in C57BL/Rij mice. In "non-responsive" DBA/2 mice, only serum retinol was decreased. The time and dose-responses observed suggested that the difference in aryl hydrocarbon hydroxylase responsiveness was not directly involved in the effects on retinoid levels (Brouwer et al., 1985).

Powers et al. (1987) administered female, Sprague-Dawley rats single, intraperitoneal injections of 1, 5, or 15 mg 3,4,3',4'-tetrachlorobiphenyl/kg body weight and found a dose-related depression of plasma retinol levels, 24 h after treatment. The loss of plasma retinol appeared to be a function of depressed levels of the retinol-binding protein (RBP)-transthyretin ternary complex. No free retinol was observed in the plasma. Hepatic retinyl palmitate hydrolase (RPH) activity was depressed and highly and positively correlated with the plasma retinol levels. Doses of either 2,4,5,2',4',5'- and 3,4,5,3',4',5'-hexachlorobiphenyl, equimolar to the 15 mg/kg tetrachlorobiphenyl dose, failed to cause a similar depression in plasma retinol in treated female rats.

A study was carried out to investigate the effects of PCBs on retinoid homeostasis in Sprague-Dawley rats. Female Sprague-Dawley/Rij rats were fed a Vitamin A-deficient diet for 12–16 weeks. Serum retinol concentrations at the end of this period were decreased to approximately 10% of the normal retinol level. The rats were

repleted with radiolabelled [3H]retinol by feeding a diet containing 18.5 MBq (8000 IU) of retinol/kg diet for 14 days. Saturation in the blood was reached after 6 days [3H]retinol repletion. On day 7, the rats were either treated with an intraperitoneal dose of 3,4,3',4'-tetrachlorobiphenyl (15 mg/kg) in corn oil, or corn oil alone. Exposure to tetrachlorobiphenyl resulted in significant reductions in both retinol and retinyl ester concentrations in the liver and lung to 25% and 44% of the controls, respectively, and a reduction of retinol in the heart of 35% of the controls. No changes in concentrations were observed in the skin and kidneys (Brouwer et al., 1988).

Female WAG/Rij rats received a single ip injection of corn oil, or 15 or 200 mg 3,4,3',4'-tetrachlorobiphenyl/kg body weight and were killed on days 1,3,7, or 14 to study the effects on serum and hepatic retinoid contents and liver morphology. There was a significant increase in liver weight at the highest dose level after 3, 7, and 14 days. There was a rapid increase in the 3H-tetrachlorobiphenyl levels present after 7 days, after which a rapid decline occurred. Tetrachlorobiphenyl induced a significant decrease in serum retinol content in the 200 mg tetrachlorobiphenyl group on days 3 and 7. The same was found for the retinol and retinyl palmitate contents of the liver. Ultrastructural alterations in the hepatocytes, such as proliferation and vesiculation of the endoplasmic reticulum and mitochondrial enlargement with inclusions, were found (Durham & Brouwer, 1989).

2,2',5,5'-Tetrachlorobiphenyl caused inhibition of Ca/Mg- and Mg-dependent adenosinetriphosphatase in the liver of rats (Lin et al., 1979). *In vitro*, several PCB congeners inhibited Na/K- and Mg-dependent adenosinetriphosphatase. Although a general trend towards increased inhibition, paralleling increased chlorination, was observed, no correlation was evident between chlorine substitution patterns and inhibitory activity (La Rocca & Carlson, 1979).

8.6.4 Effects on the gastrointestinal tract

Effects on the stomach have been studied or observed by Allen & Norback (1973); Allen et al. (1974a); Allen (1975); Becker et al. (1979) and Tryphonas et al. (1986a) in monkeys. Oral administration

of Aroclor 1242, 1248, or 1254 to monkeys produced gastritis, which progressed to hypertrophy and hyperplasia of the gastric mucosa. Related effects included mucous-filled cysts that penetrated the muscularis mucosa. These effects were initiated by exposure as low and/or short as a single gavage dose of 1.5 g Aroclor 1248/kg body weight, 25 mg Aroclor 1248/kg diet for up to 1 year, 3 mg of Aroclor 1242/kg diet, for 71 days, or 280 μg/kg body weight for 28 months.

In studies on monkeys, Becker et al. (1979) carried out stomach biopsies and found microscopically apparent arrest of the differentiation of generative cells of the isthmus and neck into parietal and zymogenic cells. Mature parietal and zymogenic cells, which were found only in the bases of the glands, showed signs of injury, such as dilatation of the rough endoplasmic reticulum on the zymogenic cells, irregularity of the mitochondria and irregular luminal membranes in parietal cells, and an increase in the number of autophagic vesicles on both types of cell (see 8.2.1.6).

The Aroclor-induced gastric lesions, which occurred mainly along the greater curvature of the stomach (not in the cardiac or pyloric regions) and did not occur in other sections of the gastrointestinal tract, have only been observed in pigs and monkeys (Hansen et al., 1976b; Becker et al., 1979; Drill et al., 1981). The gastric effects may therefore be species specific. Aroclor 1254 induced metaplasia and adenocarcinoma in the glandular stomach of F344 rats (see section 8.7.1.2).

8.6.5 Effects on lipid metabolism

8.6.5.1 Effects of PCB mixtures

Consistent with the histopathological observation of fatty degeneration in the liver (see section 8.2.1), short-term exposure to commercial mixtures of PCBs induced increases in the contents and concentrations of total lipids, triglycerides, cholesterol, and/or phospholipids in this organ of the rat and rabbit (Litterst et al., 1972; Bruckner et al., 1974; Itokawa et al., 1976; Garthoff et al., 1977; Hinton et al., 1978; Ishidate et al., 1978; Dzogbefia et al., 1978; Yagi, 1980; Kato & Yoshida, 1980, 1981; Kato et al., 1982).

Litterst et al. (1972) exposed male Osborne-Mendel rats, for 4 weeks, to diets containing Aroclor 1242, 1248, 1254, or 1260 at levels of, or between, 0.5, 5.0, 50, and 500 mg/kg (equivalent to 0.025, 0.25, 2.5, and 25 mg/kg body weight). Aroclor 1248 caused the highest dose-related increase in the triglyceride concentration in the liver, which was significant at 500 mg/kg diet (equivalent to 25 mg/kg body weight). The lowest-observed-effect level was reported by Bruckner et al. (1974), who exposed male Sprague-Dawley rats to 0, 5, or 25 mg of Aroclor 1242/kg diet (equivalent to 0, 0.3, and 1.5 mg/kg body weight, respectively), for 2, 4, or 6 months and found a slight increase in the concentrations of total lipids in the liver at both exposure levels.

Levels of total lipids, triglycerides, and/or cholesterol in the serum of rats and rabbits, exposed to PCB mixtures, were found to be increased (Koller & Zinkl, 1973; Allen et al., 1976; Itokawa et al., 1976; Garthoff et al., 1977; Zinkl, 1977; Kato & Yoshida, 1980, 1981; Yagi, 1980; Kato et al., 1982; Baumann et al., 1983; Hladkà et al., 1983; Carter, 1985). Wistar rats received Clophen A50, twice weekly, by gavage, at levels of 2, 10, 50, 150, or 250 mg/kg body weight, for 6 weeks. Serum triglyceride and cholesterol levels were increased in a dose-related manner at 50 and 2 mg/kg body weight, respectively (Baumann et al., 1983). Decreased serum triglyceride levels were reported by Kato et al. (1982). Fischer rats exposed for 8 days to Aroclor 1254 in the diet at levels of 8 mg/kg (0.4 mg/kg body weight) or more showed a dose-related increase in serum total cholesterol concentrations. Hypercholesterolaemia was not found at 4 mg/kg diet (Carter, 1985). Studies on monkeys exposed to Aroclors 1248 or 1254 for 1–2 years revealed lowered serum levels of total lipids, triglycerides, and cholesterol (Barsotti et al., 1976; Arnold et al., 1984). The cause of these changes may be an altered synthesis and/or lipoprotein transport in the liver. No increase in the rate of synthesis of liver triglycerides was found following intraperitoneal exposure of rats to 3–8 daily doses of 50 mg of Aroclor 1254/kg body weight (Hinton et al., 1978; Sandberg & Glaumann, 1980). The observed increases in the half-lives of liver triglycerides and phospholipids (Hinton et al., 1978) and the observed increase in the number of Very Low Density Lipoproteins (VLDL) in the liver, without a change in lipid composition (Sandberg & Glaumann, 1980),

seems to be indicative of impaired transport of these lipids from the liver to the blood. This was also demonstrated by the repression in serum VLDL and in the incorporation of tritiated water in serum total lipids following tritiated water injection, found in rats exposed for 24 days to a low-protein diet containing 1000 mg of Aroclor 1248/kg (50 mg/kg body weight) (Kato et al., 1982). Sandberg & Glaumann (1980) observed an impaired transport of VLDL from the endoplasmic reticulum to the Golgi apparatus. This compares well with the observed flattening of the Golgi apparatus, which also lacks secretory vesicles with lipoprotein particles (Hinton et al., 1978). No explanation was found in the available literature for the observed increase in serum triglyceride levels in rats.

Ishidate et al. (1978) measured a decreased rate of synthesis of phospholipids, especially of phosphatidyl choline, in the liver of rats that had received 2 daily doses of a PCB mixture at 100 mg/kg body weight, composed mainly of tetrachlorobiphenyl isomers. Decreased phospholipid synthesis was also observed by Hinton et al. (1978). The accumulation of phospholipids in the proliferated endoplasmic reticulum was ascribed to the observed depression of the secretion of lipoproteins into blood (Hinton et al., 1978; Ishidate et al., 1978; Sandberg & Glaumann, 1980) and to a depressed catabolism of liver phospholipids (Ishidate et al., 1978).

The synthesis of cholesterol in the rat liver may be increased by PCB mixtures considering the increased concentration of labelled cholesterol in the liver following $^{3}H_2O$-injection (Kato et al., 1982) or ^{14}C-glucose or ^{14}C-acetate administration (Yagi, 1980) in rats that had been exposed for 3–5 weeks to diets containing 1000 mg of Aroclor 1248/kg diet or 500 mg Kanechlor 500/kg diet, respectively. It was also shown that the activity of 3-hydroxy-3-methylglutaryl Coenzyme A reductase (EC 1.1.1.34) was increased in rats following a 6-day exposure to a diet containing 1000 mg Aroclor 1248/kg diet (equivalent to 50 mg/kg body weight) (Kato & Yoshida, 1980). The enhanced synthesis of cholesterol has to compete with an enhanced degradation, as Aroclor 1248 has been shown to induce cholesterol 7-alpha-hydroxylase (EC 1.14.14.1) in rats (Quazi et al., 1984). Decreased biosynthesis of liver cholesterol was found in rats exposed for 30 days to Aroclor 1254 at a dietary level of 500 mg/kg (Kling & Gamble, 1982). Hypercholesterolaemia in PCB-exposed rats can

be explained partly by an increased synthesis of cholesterol and/or an increase in serum high density lipoprotein cholesterol, which was observed in several studies (Ishikawa et al., 1978; Yagi, 1980; Kato & Yoshida, 1981; Carter, 1985).

Isolated hepatocytes were capable of secreting protein and triacylglycerol in the form of VLDL into serum-free media. Eighty per cent of 2,4,5,2',4',5'-hexachlorobiphenyl released from hepatocytes was in association with VLDL, the remainder being in association with protein (Gallenberg & Vodicnik, 1987).

8.6.5.2 *Effects of individual congeners*

Charles-River CD rats received a single oral dose of 3,4,5,3',4',5'-, 2,4,5,2',4',5'-, or 2,3,5,2',3',5'-hexachlorobiphenyl in cotton-seed oil. After 72 h, all isomers had increased the levels of total lipids in the liver. 3,4,5,3',4',5'-Hexachlorobiphenyl had the most pronounced effect. This isomer was the only one that increased the levels of total cholesterol, cholesterol esters, and triglycerides in the liver, while the other 2 isomers slightly increased the content of liver phospholipids (Kohli et al., 1979).

Shireman (1988) studied the lipoprotein-mediated transfer of 2,4,5,2',4',5'-hexachlorobiphenyl into cultured human fibroblasts, and found that the plasma lipoproteins may play a role in the distribution of this hexachlorobiphenyl to peripheral cells. Using normal skin fibroblasts incubated with medium containing serum LDL or high density lipoproteins (HDL) labelled with the ^{14}C-hexachlorobiphenyl, the author characterized the cellular incorporation, and efflux from cells, of this congener and concluded that HDL might be involved in the delivery of hexachlorobiphenyl to cells and not, as generally thought, in the transport from cells.

2,4,5,2',4',5'-Hexachlorobiphenyl was shown to be distributed among rat and human plasma lipoproteins and protein *in vitro*. It was readily transferred among plasma constituents and its distribution was related to the triacylglycerol:protein ratio in the plasma. One h following intravenous administration of 70 μg labelled hexachlorobiphenyl to virgin, female Sprague-Dawley rats, the hexachlorobiphenyl was primarily distributed to low density lipoprotein (LDL) with the hypertriglyceridemia of late pregnancy; more than

70% of circulating hexachlorobiphenyl was associated with very low density lipoproteins (VLDL). VLDL is a major substrate for mammary gland lipoprotein lipase, which is elevated during lactation. When hexachlorobiphenyl was complexed with human VLDL and injected intravenously into late pregnant mice, mammary gland concentrations of the compound exceeded those in the adipose tissue at all sacrifice times between 5 min and 6 h (Gallenberg & Vodicnik, 1987; Gallenberg et al., 1987).

8.6.6 Effects on porphyrin metabolism

8.6.6.1 Effects of PCB mixtures

Hepatic porphyria has been induced by a number of commercial PCB mixtures (Clophen A60; Phenochlor DP6; Aroclor 1016, 1232, 1242, 1254, and 1260; Kanechlor 400, 500, and 600) in mice, rats, rabbits, chickens, and Japanese quail. Young rats, guinea-pigs, and minks seem to be less sensitive (Strik, 1973). The porphyria was characterized by the presence of pigment in the liver which fluoresced red under UV radiation (Vos & Beems, 1971; Kimbrough et al., 1972; Vos & Nootenboom-Ram, 1972; Zinkl, 1977; Honda et al., 1983), an increase in the concentration of porphyrins in the liver (Goldstein et al., 1974, 1975; Grote et al., 1975; Iverson et al., 1975; Kawanishi et al., 1975) and an increase in the concentrations of δ-aminolevulinic acid, porphobilinogen, and porphyrins in the urine or faeces (Vos & Beems, 1971; Vos & Notenboom-Ram, 1972; Goldstein et al., 1974, 1975; Baumann et al., 1983; Honda et al., 1983). Vos & Beems (1971) found increased faecal elimination of coproporphyrin and protoporphyrin in rabbits dermally treated with 118 mg Aroclor 1260/day (free of PCDFs), 5 days/week, for 36 days and Vos & Notenboom-Ram (1972) found the same results when female, New Zealand rabbits received a 120 mg application of Aroclor 1260 on the shaved skin, 5 days/week, for 4 weeks.

When Sherman rats were exposed for up to 13 months to a diet containing 100 mg Aroclor 1254/kg or for up to 26 weeks to Aroclor 1242 at 100 or 500 mg/kg diet (equivalent to 5 and 25 mg/kg body weight, respectively) a delayed onset of porphyria was noted after 2–7 months of exposure. The porphyria was mainly characterized by the excretion and hepatic storage of uroporphyrin and

heptacarboxyporphyrin, resembling human porphyria cutanea tarda (Goldstein et al., 1974, 1975). A dose-dependent increase in the concentration of liver porphyrins was observed in female, Sprague-Dawley rats receiving 21 daily doses of Aroclor 1242 (by gavage) in corn oil at 10 or 100 mg/kg body weight, but not at 1 mg/kg body weight. Female rats were more sensitive than male rats and Aroclor 1016 at the same dietary level had less effect than Aroclor 1242 (Iverson et al., 1975). Others also noted the greater effect of higher chlorinated PCB mixtures on liver and urinary levels of porphyrins (Goldstein et al., 1974, 1975; Kawanishi et al., 1975). Kawanishi et al. (1973, 1974) showed that administration, in the diet, of Kanechlors KC-300 and KC-500 to rats at 500 mg/kg produced a marked increase in urinary excretion of copro- and uroporphyrins, and in faecal elimination of protoporphyrin, but no increases were observed with Kanechlor KC-400.

Increased urinary coproporphyrin levels were found in male Sprague-Dawley rats exposed for 2, 4, or 6 months to a diet containing Aroclor 1242 at 5 or 25 mg/kg (equivalent to 0.25 and 1.25 mg/kg body weight) (Bruckner et al., 1974).

Porphyria in rats and rabbits has been associated with the observed stimulation of delta-aminolevulinate synthase (EC 2.3.1.37), the rate-limiting enzyme in the haem synthesis of porphyrins (Goldstein et al., 1974, 1975; Grote et al., 1975; Drill et al., 1981; Hill, 1985), and with the inhibition of uroporphyrin decarboxylase (EC 4.1.1.37), as measured in chick embryo cells and chicken erythrocytes *in vitro* (Kawanishi et al., 1983; Sano et al., 1985). Seki et al. (1987) observed 80% inhibition of liver uroporphyrin decarboxylase together with a 15-fold increase in the activity of liver δ-amino-levulinate synthase and accumulation in the liver of a large amount of uroporphyrin in C57BL/6 mice exposed for 3 weeks to Kanechlor 500 at a dietary dose of 500 mg/kg. Liver microsomal cytochrome P-450 was increased and induction of microsomal enzymes was observed. The effects were less outstanding in ddY mice whereas liver cytosol levels of the PCBs were comparable in both strains. The authors postulated that the development of porphyria is causally related to the inhibition of uroporphyrin decarboxylase rather than the induction of drug metabolizing function. Porphyria would

develop only when the ratio of hepatic uroporphyrin decarboxylase and δ-aminolevulinate synthase decreased to less than 1.0.

8.6.6.2 Effects of individual congeners

The levels of coproporphyrin and protoporphyrin found in the faeces of rabbits, dermally exposed to 5 doses/week of 120 mg of 2,4,5,2',4',5'-hexachlorobiphenyl (no dibenzofurans detected) in isopropanol, for 4 weeks, were more elevated than those in the faeces of rabbits exposed similarly to Aroclor 1260 (Vos & Notenboom-Ram, 1972). Koss et al. (1980) also found 2,4,5,2',4',5'-hexachlorobiphenyl highly effective in inducing porphyria in female rats receiving, orally, 64 mg of this PCB-congener/kg body weight in oil, once every 2 days, for 10 weeks. In mice receiving a diet containing 300 mg of one of various tetrachlorobiphenyls, hexachlorobiphenyls, or Kanechlors/kg, for 14 weeks, the most pronounced increases in the levels of coproporphyrin and protoporphyrin in the liver were found in animals fed 3,4,5,3',4',5'- and 2,4,6,2',4',6'-hexachlorobiphenyl, and Kanechlor 600, followed by animals fed 3,5,3',5'- and 2,5,2',5'-tetrachlorobiphenyls and Kanechlor 500. No porphyrinogenic action was found in mice fed 3,4,3',4'-, 2,4,2',4'-, 2,3,2',3'-, or 2,6,2',6'-tetrachlorobiphenyl, 2,3,4,2',3',4'-hexachlorobiphenyl, or Kanechlor 400 (Kawanishi et al., 1975). Accumulation of uroporphyrins was observed in the livers of "responsive" C57BL/6 mice treated with 3,4,5,3',4',5'-hexachlorobiphenyl, but not in the livers of "non-responsive" ddY mice. It was suggested that induction of apocytochrome P-450 may take part in inducing porphyrin synthesis (Sano et al., 1985).

Sano et al. (1985) studied the mechanism of the porphyrinogenic activity of PCBs using cultured chick embryo liver cells to examine the relationship between the induction of delta-aminolaevulinic acid (ALA) syntbetase and the inhibition of uroporphyrinogen dicarboxylase. The porphyrinogenic effect of PCBs exhibited a defined structure-activity relationship in that only 3,4,3',4'-tetrachloro- and 3,4,5,3',4',5'-hexachlorobiphenyl out of 9 biphenyls produced a marked accumulation of uroporphyrin in the liver cells. In ALA-supplemented cultures. these 2 congeners led to the accumulation of a large amount of uroporphyrin III, whereas with the other PCBs (which were weak inducers of porphyrin synthesis) the accumulated

porphyrin was mostly protoporphyrin. These results suggested that the active inducers of porphyrin synthesis also inhibit uroporphyrinogen decarboxylase, in 2 steps, i.e., first, in the formation of hexacarboxylic porphyrinogen III from heptacarboxylic porphyrinogen III, and, second, in the formation of heptacarboxylic porphyrinogen III from uroporphyrinogen III. The inhibition of uroporphyrinogen decarboxylase leads to a depletion of haem. In addition, induction of apocytochrome P-450 by PCBs may contribute to a decrease of haem. As a result, synthesis of ALA synthetase increases, leading to an accumulation of uroporphyrin in liver.

8.6.7 Effects on the endocrine system

8.6.7.1 Effects of PCB mixtures

The underlying cause of the reproductive toxicity of PCBs, described in section 8.4, may be alterations in hormonal receptor binding and/or alterations in the steroid hormone balance through effects on metabolism and excretion.

Precocious vaginal opening was observed in neonatal Sprague-Dawley rats receiving a subcutaneous dose of 10 mg of Aroclor 1221 (2000 mg/kg body weight) in sesame oil on days 2 and 3 of life. At 6 months of age, these females showed persistent vaginal estrus and anovulation, despite no further exposure to Aroclor 1221. Doses of Aroclor 1221, 1242, 1254, or 1260 at 1 mg/kg were without effect. Groups of 22-day-old Sprague-Dawley rats were injected subcutaneously with Aroclor 1221 or 1242 at 1, 10, 100, or 1000 mg/kg body weight or Aroclor 1254 or 1260 mixed in sesame oil at 1, 10, or 100 mg/kg body weight. Uteri were weighed. New-born female pups were injected subcutaneously on the second and third day postpartum with Aroclor 1221 at 1 or 10 mg/day or Aroclor 1242, 1254, or 1260 in sesame oil or dimethylsulfoxide at 1 mg/day. Pups were weaned at 21 days and examined daily from the 25th day of puberty. Animals were sacrificed at 7 or 8 months, at which time organs were examined. A significant uterotrophic response was noted with 1000 mg Aroclor 1221/kg, but not with the other PCBs (Gellert, 1978).

Indirect evidence for a weak estrogenic activity of PCBs was found for various Aroclors by the glycogen response of immature rat uterus (Bitman & Cecil, 1970; Bitman et al., 1972; Ecobichon & Mackenzie, 1974) or the less sensitive uterotropic response, observed in immature rats exposed to Aroclor 1221, 1232, or 1248, but not in immature rats exposed to Aroclor 1254 or 1260 (Ecobichon & Mackenzie, 1974; Gellert, 1978). More direct evidence is the inhibition *in vitro* of the binding of labelled 17-beta-estradiol to the rat uterine receptor by Aroclors 1221 and 1254 (Nelson, 1974).

Pregnant mares' serum was administered to immature female outbred rats on day 29 postpartum, and, 60 h later, rats were injected with human chorionic gonadotrophin. On day 34, the animals were divided into groups and treated orally with sesame oil (control), or 20 mg PCBs/kg (Clophen A30). Two days later they were killed and the ovaries removed and analysed for *in vitro* synthesis of progesteron (unincubated, incubated, and incubated with luteinizing hormone). The addition of luteinizing hormone resulted in an approximately 100% increase in progesterone synthesis above basal level with tissue exposed to PCBs. With control tissue there was a 31% increase with luteinizing hormone (Fuller et al., 1980).

PCBs induced a decrease in gonadal steroid hormone levels in rats, minks, seals, and monkeys. When, after confirmed ovulation, mature female Rhesus monkeys were exposed during the following cycle to daily gavage doses of 4, 16, or 64 mg of Clophen A30/kg body weight, for 28 days, ovulation was blocked in 2 out of 4 treated monkeys. One out of 16 controls was anovulatory. The levels of luteinizing hormone and follicle-stimulating hormone were not changed by the treatment (Müller et al., 1978).

Plasma progesterone levels were decreased in female rats exposed for 36 weeks to a dietary level of Aroclor 1242 of 75 mg/kg (equivalent to 3.7 mg/kg body weight) (Jonsson et al., 1976), and in female minks exposed for 12.5–14.5 months to a dietary level of 2.5 mg Aroclor 1254/kg (equivalent to 0.25 mg/kg body weight) (Aulerich et al., 1985). The decreased levels of gonadal hormones can be explained by enhanced metabolism of steroids, which are normal substrates for microsomal enzymes. Increases in the formation of the metabolites of progesterone and/or testosterone were

measured in rats intraperitoneally exposed 1–5 times to Aroclor 1260, Aroclor 1254, or Kanechlor 400 (Krogh Derr, 1978; Lin et al., 1982; Yoshihara et al., 1982). In contrast with these findings, increased testosterone levels were found in male piglets exposed for 6–12 weeks to Aroclor 1232, 1242, or 1254 at 250 mg/diet. This increased production of testosterone was related to increased relative testes weights (Platonow et al., 1976).

Female rhesus monkeys (*Macaca mulatta*) were administered gelatin capsules containing daily doses of 0, 5, 20, 40, or 80 μg Aroclor 1254/kg body weight, dissolved in corn oil plus glycerol. After approximately 2 years of dosing, when the monkeys were considered to be in a state approaching adipose-tissue PCBs equilibrium, each dose group of 16 animals was divided into 2 test groups. Daily blood samples from both test groups were acquired for estrogen and progesteron analysis during one menstrual cycle. Serum estrogen and progesteron concentrations in PCB-dosed monkeys were comparable with those in the controls, except the luteal phase progesterone levels in monkeys dosed with 20 and 80 μg/kg. There were no apparent treatment-related differences in the incidence of anovulatory cycles or in the temporal relationship between the estrogen peak and mensus onset, mensus end, or the progesterone peak. Mean PCB concentrations in the blood and adipose tissue for the different dose levels administered were as follows: blood, 1, 11, 37, 74, and 125 μg/litre and for adipose tissue 0.79, 7.88, 22.62, 47.6 and 85.3 mg/kg tissue, respectively (Truelove et al., 1987).

Effects on plasma corticosteroid levels have also been observed. The levels were decreased in female mice exposed to a diet containing 25 mg Aroclor 1254/kg (equivalent to 3.7 mg/kg body weight) for 3 weeks, and in male mice exposed to a diet containing 400 mg Aroclor 1254/kg (equivalent to 57 mg/kg body weight) for 2 weeks. No effects were found on adrenal weight (Sanders & Kirkpatrick, 1975). However, increased levels of plasma corticosterone and enlarged adrenal glands were observed in male mice of another strain exposed to a diet containing 200 mg Aroclor 1254/kg, for 2 weeks (Sanders et al., 1977). Wasserman et al. (1973) reported increased plasma corticosterone levels in rats receiving Aroclor 1221 in the drinking-water, at a concentration of 250 mg/litre, for 10 weeks. This finding complies with morphological features of hyperfunction

of the adrenal zona fasciculata found in rats that had received 200 mg Aroclor 1221/litre drinking-water, for 6 weeks.

When female rats were exposed to Aroclor 1254, in their diet at doses of 0, 1, 5, 10, or 50 mg/kg (equivalent to 0, 0.05, 0.25, 0.5, and 2.5 mg/kg body weight/day, respectively) for 5–7 months, relative adrenal weights as well as serum levels of corticosterone, dehydro-epiandrosterone, and dehydro-epiandrosterone sulfate were decreased in a dose- and time-related manner. In the same studies, the effects with less chlorinated Aroclors were less pronounced (Byrne et al., 1988).

In addition, the ultrastructure of beta-cells of the pancreas of rats was found to be changed after 13 months of exposure to 200 mg Aroclor 1254/litre drinking-water. These changes included marked dilatation and vesiculation of the rough endoplasmic reticulum, hyperplastic Golgi complexes with a reduction in the number of secretory granules, and an increase in the number of beta-acinar and acinar-beta cells. The changes in the pancreas were suggested to be secondary to the increase in the level of glucocorticoids (Wasserman et al., 1975). An increased relative adrenal weight was observed in pigs fed Aroclor 1242 or 1254/kg at 20 mg/kg diet (equivalent to 0.8 mg/kg body weight) for 91 days (Hansen et al., 1976b).

Thyroid hormone levels were decreased in rats exposed to Aroclor 1254 at levels of 50 mg/kg diet or more for 4–12 weeks (Collins et al., 1977; Collins & Capen, 1980a). Two explanations were offered. One was the observed increase in biliary excretion of thyroxine and triiodothyroxine (Bastomsky, 1974; Collins & Capen, 1980b) and the larger proportion of biliary thyroxine present as glucuronide (Bastomsky, 1974), most likely as a result of induction of microsomal uridine diphosphate-glucuronosyltransferase (EC 2.4.1.17) (Bastomsky & Murthy, 1976). The other explanation was a direct effect of PCBs on thyroid follicular cells. When male Holtzman or Osborne-Mendel rats were fed a diet containing Aroclor 1254 at a level of 0, 5, 50, or 500 mg/kg (equivalent to 0, 0.25, 2.5, and 25 mg/kg body weight), thyroid follicular cells exhibited a dose-dependent hypertrophy and hyperplasia. An abnormal accumulation of large colloid droplets and irregular lysosomes in the follicular cells were observed at 5 mg/kg diet or more and reduced serum thyroxine

occurred at 50 mg/kg diet or more. A no-observed-effect level could not be established. Microvilli were decreased in number, shortened, and irregularly branched (Collins et al., 1977; Kasza et al., 1978a,b; Collins & Capen, 1980a, 1980b). The hypothalamus-pituitary axis seems not to be affected in view of the observed increase in the serum level of thyroid-stimulating hormone and in the iodine uptake by the thyroid following PCB exposure (Bastomsky, 1974, 1977; Collins & Capen, 1980a).

Collins & Capen (1980a) suggested that the well-documented PCBs-related disturbances in reproduction, growth, and development may be related to alterations in thyroid structure and function in the dam, fetus, or neonate. The lowering of serum thyroxine appears to be the combined result of a direct effect on thyroid follicular cells with an interference in hormone secretion plus an enhanced peripheral metabolism of thyroxine.

8.6.7.2 Effects of individual congeners

Exposure of rats to various congeners produced different responses in steroid metabolism. The most marked effects were observed after exposure to 2,4,5,2',4',5'-hexachlorobiphenyl, which was found to decrease the half-life of progesterone (Örberg & Ingvast, 1977), to increase hydroxylation of progesterone, testosterone, and androstenedione, and to decrease the 5-alpha-reduction of progesterone and testosterone (Dieringer et al., 1979; Yoshihara et al., 1982). 3,4,5,3',4'-Pentachlorobiphenyl was found to depress the total microsomal metabolism of progesterone and testosterone, though the 7-α-hydroxylation of these steroids was markedly stimulated (Yoshihara et al., 1982). No, or very slight, effects on steroid metabolism were found in rats exposed to chlorobiphenyls with 4 chlorine atoms or less (Örberg & Ingvast, 1977; Dieringer et al., 1979).

Yoshimura et al. (1985) described a marked induction of liver microsomal cytochrome P-450 and cytosolic DT-diaphorase as a cause of a possible disorder of steroid homeostasis and promotion of carcinogenicity of 4-nitroquinoline *N*-oxide (4-NQO) in rats pretreated with 3,4,5,3',4'-pentachlorobiphenyl. The animals were sacrificed 5 days after pretreatment. The results of the studies

showed that 7-α-hydroxylation of both progesterone and testosterone in liver microsomes was increased, but hydroxylation at the 2-α-, 6 α-, and 16 α-positions were depressed, together with 5 α-reduction. The induced isoenzyme P-452 was most responsible for the 7-α-hydroxylation of testosterone.

The major component (32 mol %) of the Aroclor 1221 mixture is 2-chlorobiphenyl. The major metabolite (4,4'-dihydroxy-2-chlorobiphenyl) of 2-chlorobiphenyl has been shown to have a significant binding activity with the soluble uterine estrogen receptor protein in the rat, suggesting a possible explanation for the unique estrogenic activity of Aroclor 1221 in the rat (Korach et al., 1987).

8.6.8 Immunotoxicity

Some of the studies described below are summarized in Table 52.

8.6.8.1 Effects of PCB mixtures

(*a*) *Mouse*

Relative thymus and spleen weights of C57BL/6 mice were unaffected by exposure to Aroclor 1016, for 3–41 weeks, at a dietary level of 167 mg/kg (Silkworth & Loose, 1979). Dietary exposure of outbred mice (*Mus musculus*) to Aroclor 1248 at 50, 100, 500, or 1000 mg/kg diet (equivalent to 7.1 up to 143 mg/kg body weight), for 3 or 5 weeks, did not elicit gross signs of immunotoxicity (Thomas & Hinsdill, 1978).

BALB/c mice fed Aroclor 1242 at a dose-level of 0 or 167 mg/kg diet (equivalent to 0 and 29 mg/kg body weight) for 3–9 weeks, did not show adverse effects on the thymus, spleen, and lymph nodes (Loose et al., 1977, 1978).

In addition, Carter & Clancy (1980) observed an increased graft versus host response in a decreased number of spleen cells in 4BALB/c mice, which were exposed to a single intraperitoneal dose of 1000 mg Aroclor 1242/kg body weight in corn oil. Spleen enlargement and lymphocyte depletion were observed.

Offspring of Swiss-Webster mice, exposed via the dams which were fed Aroclor 1254 at dietary levels of 10, 100, or 250 mg/kg, did not exhibit an altered hypersensitivity reaction to oxazoline, an altered

Table 52. The humoral and cell-mediated immunotoxicity of PCBs administered via the diet in short-term studies

Strain	PCB-mixture	Exposure period (weeks)[a]	Parameter tested[b]	Result[c]	LOEL[d] (mg/kg)	NOEL[d] (mg/kg)	Reference
Monkey							
Rhesus	Aroclor 1248	44	anti-SRBC antibody titre	D	5.0 (d)	2.5 (d)	Thomas & Hinsdill (1978)
			anti-tetanus toxicoid antibody titre	NE	-	5.0 (d)	
			serum gamma-globulin fraction	D	5.0 (d)	2.5 (d)	
Cynomolgus	Kanechlor 400 (purified)	20	anti-SRBC antibody titre	D	2 (bw)		Hori et al. (1982)
			serum gamma-globulin fraction	D	2 (bw)		
Cynomolgus	Aroclor 1254	21	anti-SRBC antibody titre	D	2.5 (d)		Truelove et al. (1982)
			anti-tetanus toxicoid antibody titre	NE		10 (d)	

Table 52 (continued)

Rabbit							
New Zealand	Aroclor 1254	5	anti-SRBC antibody titre	NE		6.54 (bw)	Street & Sharma (1975)
			serum gamma-globulin levels	NE		6.54 (bw)	
			delayed hypersensitivity reaction to tuberculin	NE		6.54 (bw)	
			popliteal lymph node antibody-forming cells	D	0.92(bw)	0.18 (bw)	
Guinea-pig							
	Clophen A60 and Aroclor 1260	4-7	anti-tetanus toxicoid antibody titre	D	50 (d)	10 (d)	Vos & van Driel-Grootenhuis (1972)
			delayed hypersensitivity reaction to tuberculin	D	50 (d)	10 (d)	
			anti-tetanus toxicoid producing cells in popliteal lymph nodes	D	50 (d)	10 (d)	
Rat							
Sprague-Dawley	Aroclor 1254	1	mitogen response to phytohaemagglutinin	I	250 (d)		Bonnyns & Bastomsky (1978)
			response to poke-weed mitogen	NE		250 (d)	
			serum gamma-globulin fraction	D	250 (d)		

Table 52 (continued)

Strain	PCB-mixture	Exposure period (weeks)[a]	Parameter tested[b]	Result[c]	LOEL[d] (mg/kg)	NOEL[d] (mg/kg)	Reference
Sprague-Dawley	Aroclor 1254	10	interleukin 2 production induction by KLH	D	50 (d)		Exon et al. (1985)
			natural killer cell cytotoxicity	D	50 (d)		
			anti-KLH antibody titer	D	50 (d)		
Mouse							
ICR	Kanechlor 500	3	host-resistance to herpes simplex virus	D	33 (bw)	18 (bw)	Imanishi et al. (1980)
			host-resistance to ectomelia virus	D	33 (bw)	18 (bw)	
ICR	Kanechlor 500	3	host-resistance to influenza virus	D	400 (d)	200 (d)	Imanishi et al. (1984)
			host-resistance to Staphylococcus aureus	D	100 (d)		
ICR/JCL	Kanechlor 500	4	sensitivity to *E. coli* endotoxin	NE (bw)	-	100 µg/kg	Oishi & Hiraga (1980)
Swiss-Webster	Aroclor 1254	12	hypersensitivity reaction to oxazoline, anti-bovine serum albumine antibody titre and phagocytosis of SRBC by macrophages	NE	-	> 250 (d)	Talcott & Koller (1983)

Table 52 (continued)

BALB/c	Aroclor 1242	3-6	host-resistance to endotoxin	D	167 (d)		Loose et al. (1978)
			host-resistance to malaria	D	167 (d)		
BALB/c	Aroclor 1242	6	spleen cellularity	NE		167 (d)	Loose et al. (1977)
			spleen PFC	D	167 (d)		
			serum immunoglobulins G1, A, M	D	167 (d)		
C57BL/6	Aroclor 1016	3-41	graft versus host response mixed lymphocyte response	NE		167 (d)	Silkworth & Loose (1979)
				I	167 (d)		
			mitogen response to lipopolysaccharide	I	167 (d)		
			mitogen response to concanavalin A	I	167 (d)		
Mus musculus	Aroclor 1248	5	host-resistance to *Salmonella typhimurium*	D	1000 (d)		Thomas & Hinsdill (1978)
			host-resistance to endotoxin	D	1000 (d)		

[a] Up to day of primary immunization.
[b] SRBC = Sheep red blood cells; KLH = Keyhole limpet haemocyanin; PFC = Plaque forming cells.
[c] I = Increased; D = Decreased; NE = No effect found.
[d] LOEL = Lowest-observed-effect-level; NOEL = No-observed-effect level: in mg/kg diet (d) or mg/kg body weight per day (bw).

anti-bovine serum albumin antibody titre or an altered degree of phagocytosis of sheep red blood cells by peritoneal macrophages, compared with controls (Talcott & Koller, 1983).

Pathogen-free ICR/JCL mice (aged 4 weeks) were intubated orally, once a week, for 4 weeks, with 0, 10, or 100 μg Kanechlor 500/kg body weight. Two days after the final treatment, half of the animals of each group were injected intraperitoneally with 0, 50, 250, or 500 μg *E.coli* endotoxin/mouse. Sensitivity to endotoxin was determined by 24-h mortality rate. The oral administration of Kanechlor 500 up to a dose level of 100 μg/kg body weight did not have any effect on the sensitivity to the endotoxin (Oishi & Hiraga, 1980).

The relative potencies of PCB mixtures Aroclors 1260, 1254, 1248, 1242, 1016, and 1232 to inhibit the murine, splenic, plaque-forming cell response to sheep red blood cells was determined for C57Bl/6 mice. The ED_{50} values for the reduction in the splenic, plaque-forming cells were 104, 118, 190, 391, 408, and 464 mg/kg body weight, respectively. It was apparent that the higher PCBs (Aroclors 1260, 1254, and 1248) were more potent than the lower chlorinated mixtures.

Previous studies have shown that a subeffective dose of Aroclor 1254 (25 mg/kg), interacted with an immunotoxic dose of TCDD (3.7 nmol/kg), resulting in, a significant antagonism of the toxicity of the latter compound. Co-treatment of mice with a dose of all these PCB mixtures at 25 mg/kg and a reconstituted PCB mixture, as occurs in breast milk, in combination with TCDD (3.7 nmol/kg) showed that all (except Aroclor 1232) significantly antagonized the TCDD-mediated inhibition of the splenic, plaque-forming cell response in C56Bl/6 mice (Davis & Safe, 1989).

A single administration of 500 mg Aroclor 1254/kg, intraperitoneally, inhibited the plaque-forming (PFC) response to subsequent challenge with sheep erythrocytes in Ah locus positive (C57Bl/6N or B6C3F1N) mice. However, Aroclor 1254 did not give induction in the Ah locus negative DBA/2N mice. When B6C3F1 mice were challenged with sheep red blood cells, 6 or 16 weeks after Aroclor 1524 treatment, substantial recovery of a PFC response was

observed. In older (76-week-old) B6C3F1 mice severe depression of the PFC response was observed.

In contrast with its profound depression of a PFC response, Aroclor 1254 (up to 1250 mg/kg) caused a slight increase in lymphocyte proliferation induced by either T or B cell mitogens. A single 500 mg/kg dose of this Aroclor also suppressed the ability of recipient B6C3F1 animals to reject a challenge with either the syngenic fibrosarcoma (PYB6) or the gram negative pathogen *Listeria monocytogenes* (Lubet et al., 1986).

Heinzow et al. (1988) studied the effect of 2,4,5,2',4',5'-hexachlorobiphenyl in the E rosette formation with sheep red blood cells (SRBC) as one of the characteristics of human T-lymphocytes. The minimal concentration eliciting a significant monoclonal CD2 receptor antibody sparing effect was 1.5×10^{-10} mol/litre.

C3H/HeN mice were treated, twice a week, for 2 or 3 weeks prior to mating, with olive oil or with Kanechlor 500 at an oral dose of 50 mg/kg body weight. The offspring, some of which were nursed by unexposed dams, were tested for immunocompetence, 4–15 weeks after birth. The dams did not show any adverse effects on body weight, absolute spleen weight, and spleen cellularity. The B-cell activity of the offspring was comparable with that of controls. The helper T-cell activity was reduced up to 7–11 weeks after birth: the effect was more pronounced in prenatally-exposed groups (Takagi et al., 1989).

(*b*) *Rabbit*

Rabbits appear most sensitive with respect to the immunotoxicity of PCBs. Street & Sharma (1975) exposed groups of 5–7 New Zealand rabbits to Aroclor 1254 at dietary levels of 0, 3.7, 20, 45.8, or 170 mg/kg (equivalent to 0, 0.18, 0.92, 2.1, or 6.54 mg/kg body weight) for 44–57 days. When compared with control animals, an increased degree of thymus atrophy was observed at all dose levels except for 20.0 mg/kg. At the 2 higher dose-levels, relative spleen weights were decreased and the number of germinal centres reduced. When 8 female New Zealand rabbits received 118 mg of Phenochlor DP6, Clophen A60, or Aroclor 1260 (free of PCDFs), on the back skin, 5 times per week, for 38 weeks they showed leukopenia, thymus atrophy, and loss of germinal centres in the spleen and lymph nodes.

No such changes were observed in the 4 controls (Vos & Beems, 1971). Vos & Notenboom-Ram (1972) found the same effects in rabbits administered 120 mg Aroclor 1260 (free of PCDFs)/day, 5 days/week, for 4 weeks. No adverse gross immunotoxic effects were observed in groups of 10 New Zealand rabbits fed various Aroclors at dose levels of 150 mg/kg body weight, once a week, for 12–14 weeks (Koller & Thigpen, 1973).

When New Zealand rabbits were exposed orally, via intubation, to Aroclor 1242 at a dose of 150 mg/kg body weight, once a week, for 11 weeks, the anti-pseudo rabies virus antibody titre and serum gamma-globulin levels were decreased (Koller & Thigpen, 1973). The overall picture is one of immunosuppression, though in 2 diet studies an increased activation of the cell-mediated immune response was observed (Bonnyns & Bastomsky, 1976; Silkworth & Loose, 1979).

New Zealand rabbit offspring, exposed via the dams fed 0, 10, 100, or 250 mg of Aroclor 1248/kg diet, showed a decrease in the delayed hypersensitivity reaction to dinitrofluorobenzene in the highest dose group. No effects were observed on the splenic, plaque- forming cell response, the antibody titre against sheep red blood cells, and the mitogen responses to Concanavalin A and Phytohaemagglutinin (Thomas & Hinsdill, 1980).

(*c*) *Guinea-pig*

Atrophy of the thymus has been reported in female guinea-pigs exposed to Clophen A60 or Aroclor 1260 for 4–7 weeks at a dietary level of 50 mg/kg (equivalent to 2 mg/kg body weight). Following stimulation with tetanus toxoid, the authors found a lower antitoxin titre and a lower count of antitoxin-producing cells in comparison with control guinea-pigs, resulting in a significant reduction in immunoglobulins. The skin reaction after tuberculination in animals immunized with Freund's complete adjuvant (as a parameter of cell-mediated immunity) was also depressed at the 50 mg/kg dose level (Vos & van Driel-Grootenhuis, 1972).

Female guinea-pigs fed diets containing 50 mg Aroclor 1260/kg for 6 weeks had significantly lowered tetanus antitoxin titres, circulating leukocytes and lymphocytes, and thymus atrophy (Vos & van Genderen, 1973). Also treatment with 10 mg Aroclor 1260/kg diet

for 8 weeks produced splenic atrophy (Vos & de Roij, 1972). The Aroclor 1260 was free from PCDFs (no details).

(*d*) *Monkey*

Offspring of Rhesus monkeys appeared very sensitive to the toxic effects of PCB exposure during gestation and nursing, as already discussed in section 8.4.1. Thymic atrophy, loss of germinal centres and of lymph nodules of the spleen, and bone marrow hypocellularity were found in 3 out of 6 offspring that died during their first year of life due to exposure to PCBs via their mothers. The mothers, 9–12 per group, were fed diets containing 0, 2.5, or 5.0 mg of Aroclor 1248/kg (equivalent to 0, 0.09, and 0.2 mg/kg body weight), for 18 months and were bred after 6 months of exposure. One mother in each exposed group died during exposure, showing an increased susceptibility to *Shigella flexneri*. At autopsy, no lesions were observed in lymphoid organs and tissues (Allen & Barsotti, 1976; Barsotti et al., 1976). When the surviving mothers were placed on a control diet for approximately 1 year after exposure and then rebred, there was a decided improvement in their health, but their infants were still severely affected by PCBs. In the 2 offspring in each exposed group that died after weaning at the age of 4 months, the effects on the thymus, spleen, and bone marrow were similar to those described for the first generation (Allen et al., 1980).

Groups of mature, female Rhesus monkeys received diets containing 0, 2.5, or 5.0 mg Aroclor 1248/kg. After 11 months, all monkeys received intravenous injections of sheep red blood cells (SRBC) as well as an intramuscular injection of tetatus toxin (TT). Booster injections and a second TT injection were given after a number of weeks. Blood samples were taken over a period of 20 weeks after immunization.

The anti-sheep red blood cells (SRBC) antibody titres, and antibody response to TT were not clearly affected. The γ-globulin-levels were lower in the PCB-treated animals. After 6 months, the PCB-treated monkeys developed chloracne, alopecia, and facial oedema (Thomas & Hinsdill, 1978).

Hori et al. (1982) also found immunosuppression in monkeys exposed to PCB mixtures (without detectable quantities of PCDFs), compared with 2 control monkeys. A more severe immunosuppression was

observed in another monkey exposed to a comparable PCB mixture with PCDFs.

In a pilot study, one infant Cynomolgus monkey, the mother of which had been exposed to Aroclor 1254 at a dose-level of 400 μg/kg body weight, showed a decreased anti-sheep erythrocyte antibody titre following primary immunization in comparison with one control infant (Truelove et al., 1982).

Atrophy and loss of germinal centres in the spleen and other lymphoid tissues were observed in groups of 5–6 female Cynomolgus monkeys following exposure to Aroclor 1254 or 1248, in an apple juice-corn oil emulsion, 3 times per week, at dose levels of 5 and 2 mg/kg body weight, respectively, until death at day 29–164. The monkeys exposed to Aroclor 1254 showed bone marrow hypocellularity and leukopenia. Lesions seen in control monkeys were similar to those described as spontaneous (Tryphonas et al., 1984; see also section 8.2.1).

Limited data exist on the humoral or cell-mediated responses in infants, exposed to PCBs via their mothers.

8.6.8.2 *Effects of individual congeners*

Thymus atrophy was observed in monkeys exposed for 1–6 months to 3,4,3',4'-tetrachlorobiphenyl, but not in monkeys exposed to 2,5,2',5'-tetrachlorobiphenyl (McNulty et al., 1980).

Decreased relative weights of the thymus and increased or decreased relative weights of the spleen were induced by single intraperitoneal doses of the planar congeners 3,4,3',4'-tetrachlorobiphenyl (at 10 mg/kg body weight) and 3,4,5,3',4'-pentachlorobiphenyl (at 245 mg/kg body weight) in "responsive" C57BL/6 mice, i.e., mice possessing the cytosolic Ah receptor protein, but not, or only to a minor degree, in "non-responsive" DBA/2 mice (lacking this receptor). The tetrachlorobiphenyl further decreased the number of cells per spleen and the number of splenic, plaque-forming cells at 10 and 100 mg/kg body weight, respectively. Further chlorination at the *ortho*-position decreased the toxicity of these congeners. No adverse effects were induced by 2,4,5,3',4'- and 3,4,5,2',4'-pentachlorobiphenyl (at 490 mg/kg body weight), 2,3,4,5,3',4',5'-hepta-

chlorobiphenyl (at 593 mg/kg body weight) and the di-*ortho* substituted tetrachlorobiphenyls (at 100 mg/kg body weight) (Silkworth & Grabstein, 1982; Robertson et al., 1984; Silkworth et al., 1984).

Similar trends were observed in Wistar rats with respect to the induction of decreased relative thymus and spleen weights (see section 8.2.1.1). Biocca et al. (1981) exposed C57BL/6J mice to various hexachlorobiphenyl isomers in the feed for 28 days. The most toxic isomer tested was 3,4,5,3',4',5'- hexachlorobiphenyl which, among others, caused a marked thymus atrophy and a moderate depletion of lymphocytes in the spleen. 2,4,6,2',4',6'-Hexachlorobiphenyl caused the same lesions, albeit at much higher dose-levels, while the 2,4,5,2',4',5'- and 2,3,6,2',3',6'-hexachlorobiphenyls were virtually inactive.

The *in vivo* generation of cytotoxic T-lymphocytes (CTL) in response to allogeneic tumour challenge is sensitive to suppression by 3,4,5,3',4',5'-hexachlorobiphenyl, a poorly metabolized, Ah receptor-binding PCB isomer. Groups of 5–8 C57Bl/5 mice treated with a single oral dose of 0, 10, or 100 mg 3,4,5,3',4',5'-hexachlorobiphenyl/kg body weight, 2 days prior to the intraperitoneal injection of allogeneic P815 tumour cells, exhibited a dose-dependent reduction in peak CTL activity in the spleen. When examined on a kinetic basis, the TCL response was reduced in magnitude with no evidence for a shift in the kinetics of the response induced by 3,4,5,3',4',5'-hexachlorobiphenyl.

3,4,5,3',4',5'-Hexachlorobiphenyl exposure, prior to antigen challenge (day -14, -7, or -1 relative to P815 injection on day 0), produced significant suppression of the CTL response. 3,4,5,3',4',5'-Hexachlorobiphenyl treatment (10 mg/kg body weight), 6 weeks prior to such a challenge, was still significantly suppressive, though the reduced degree of suppression suggested that recovery was in progress. When 3,4,5,3',4',5'-hexachlorobiphenyl exposure occurred after antigen challenge, significant suppression was produced only when exposure occurred within the first 3 days of the response, suggesting that, as the CTL matured, their sensitivity to 3,4,5,3',4',5'-hexachlorobiphenyl diminished. Clearance of the allogeneic tumour cells from the peritoneal cavity was delayed in 3,4,5,3',4',5'-hexachlorobiphenyl-treated mice and was associated

with an altered composition of the white blood cell infiltrate in this cavity. Symptoms of overt toxicity, as well as immunotoxicity, were apparent at lower doses of 3,4,5,3',4',5'-hexachlorobiphenyl in male compared with female mice. In addition, interactive effects of 3,4,5,3',4',5'-hexachlorobiphenyl exposure and P815 antigen challenge on body weight and thymic involution were observed in both male and female mice (Kerkvliet & Baecher-Steppan, 1988a).

A modest dose-dependent suppression of the proliferative response to alloantigen in mixed lymphocyte culture (MLC) was observed with lymphocytes from C57Bl/6 mice (groups of 5–6 mice) exposed to 10 or 100 mg 3,4,5,3',4',5'-hexachlorobiphenyl, while the cytotoxic T-lymphocytes CTL response generated in MLC was significantly suppressed only with 100 mg/kg. The amount of time between treatment with 3,4,5,3',4',5'-hexachlorobiphenyl and sacrifice, which ranged from 2 to 23 days, did not appear to influence the degree of immunosuppression produced by 3,4,5,3',4',5'-hexachlorobiphenyl exposure. Mitomycin C-treated lymphocytes from C57Bl/6 mice treated with 10 or 100 mg 3,4,5,3',4',5'-hexachlorobiphenyl/kg body weight, were not suppressive when added as third party cells to an independent MLC. However, if the mice were alloimmune, lymphocyte-mediated suppression of the MLC response was observed and directly correlated with the magnitude of the CTL response present in the same population. Thus, 3,4,5,3',4',5'-hexachlorobiphenyl-treated mice that had less CTL activity compared with vehicle-treated mice also had less suppressor activity. Avoidance of stimulator cells lysis by using H-2 incompatible MLC stimulator cells revealed the existence of antigen-nonspecific suppressor activity that was greater with lymphocytes from vehicle-treated mice than from 3,4,5,3',4',5'- hexachlorobiphenyl-treated mice, suggesting that both CTL and suppressor cell activities were suppressed by 3,4,5,3',4',5'-hexachlorobiphenyl exposure. Direct addition of 3,4,5,3',4',5'-hexachlorobiphenyl to lymphocyte cultures *in vitro* indicated a lack of direct toxicity of 3,4,5,3',4',5'-hexachlorobiphenyl on lymphoproliferative responses to mitogen or alloantigen at concentrations equal to or less than 1×10^{-6} mol/litre. Thus, the *in vitro* functional integrity of lymphocytes obtained from 3,4,5,3',4',5'-hexachlorobiphenyl-treated mice coupled with the lack of a direct lymphocytic effect *in vitro* suggest an indirect mechanism

of action for the 3,4,5,3',4',5'-hexachlorobiphenyl-mediated suppression of CTL activity *in vivo*. Previous reports implicating suppressor cell induction and/or activation by Ah-receptor-binding, halogenated, aromatic hydrocarbons that mediate the inhibition of CTL generation were not confirmed (Kerkvliet & Baecher-Steppan, 1988b).

8.6.8.3 Appraisal

The alterations in gross measures of immunological function (spleen and thymus weights, lymphocyte counts, histology of lymphoid organs and tissues) in mammals are highly suggestive of an immunosuppressive effect of PCB mixtures and some higher chlorinated congeners. More direct evidence of an immunodepressive effect has been obtained by methods that detect functional alterations in the humoral and cell-mediated immunity in mammals. One study on monkeys demonstrated a more severe immunosuppression by a PCDF-contaminated PCB mixture compared with a non-contaminated PCB mixture. Rabbits and monkeys are the most sensitive species. No-observed-effect levels are 100 μg Aroclor 1248/kg body weight per day and < 100 μg of Aroclor 1254/kg body weight per day for monkeys and 180 μg of Aroclor 1254/kg body weight per day for rabbits.

8.6.9 Neurotoxic effects

Depressed spontaneous motor activity was shown by male CD-mice exposed to a single oral dose of 500 mg Aroclor 1254/kg body weight in Emulphor:saline. No effects were found in motor coordination tests and on pentenylene-tetrazol-induced seizures. Neurochemical tests with isolated mouse brain synaptosomes showed inhibition of the uptake of neurotransmitters and precursors, and stimulation of the release of neurotransmitters (Rosin & Martin, 1981).

Male Wistar rats exposed to doses of 500 or 1000 mg Aroclor 1254 and 1260/kg body weight, in corn oil, showed a reduced norepinephrine concentration in the frontal cortex and hippocampus. No changes were measured in the hypothalamus and brainstem. The neurochemical effects appeared to be associated with the actual presence of PCBs in the tissues (Seegal et al., 1985).

8.6.10 Skin effects

Cutaneous effects occurred in Rhesus monkeys fed diets that contained Aroclors, for short periods (Allen & Norback, 1973; Allen et al., 1974a; Allen, 1975; Barsotti et al., 1976; Thomas & Hinsdill, 1978; Allen et al., 1979; Altman et al., 1979; Becker et al., 1979; McConnell et al., 1979; McNulty et al., 1980). The effects included facial (particularly periorbital) oedema, purulent discharge from the eyes, chloracne, and alopecia. The effects, which appeared to be reversible, were produced by doses as low as 2.5 mg Aroclor 1248/kg for 1–6 months, and 1 mg Aroclor 1242/kg (equivalent to 0.04 mg/kg body weight) for 6 months. Rats exposed to Aroclor 1254 in the diet developed alopecia and facial oedema after 104 weeks at 50 mg/kg, and exophthalamos after 72 weeks at 50 mg/kg. These effects did not occur after 104 weeks at 25 mg/kg (equivalent to 1.25 mg/kg body weight) (NCI, 1978).

8.6.11 Effects on the lung

Many PCBs are metabolized to methylthio derivatives in mice (Mio et al., 1976), seals (Jensen & Jansson, 1976) and humans (Yoshida & Nakamura, 1979). The metabolic pathways leading to the generation of these metabolites have been shown to involve glutathione conjugation of an arenoxide intermediate (Preston et al., 1984). Lund et al. (1986) studied the interactions of these metabolites with the lung. It was found that the PCB metabolite, 4,4'-bis-(methylsulfonyl)-2,5,2',5'-tetrachlorobiphenyl ($(MeSO_2)$2TCB), selectively accumulates in the Clara cells of the bronchiolar epithelium and in the secretory contents of the bronchiolar lumen. *In vitro* characterization of this interaction of tritiated ($MeSO_2$)2TCB with lung suggests that this selective accumulation is due to the presence of a secreted ($MeSO_2$)2TCB-binding protein in the respiratory tract of rats, mice, and humans. The protein appears to be an almost globular, low-relative-molecular-mass acidic protein that binds with methylsulfonyl-PCBs (Lund et al., 1986).

In a study on 3 groups of C57Bl mice, administered orally 0, 10, or 100 mg 2,3,6,4'-tetrachlorobiphenyl/kg body weight with repeated administration of ^{35}S-cysteine, Klasson-Wehler et al. (1987) found that the major compound present in the lung was 4-methylsulfonyl-

tetrachlorobiphenyl, indicating the presence of specific binding sites for this metabolite in lung tissue, mainly in the tracheo-bronchial mucosa.

Groups of 20 male SD rats were given (gastric intubation) 0 or 25 mg Kanechlor 400 in edible oil once, and, in 2 other groups, the same doses 4 times per week. Groups of 5 animals were killed 2, 7, 14, and 28 days after the last ingestion, and tissues were studied with light and electron microscopy. The lungs of the rats particularly showed peribronchiolar cell infiltrations, and electron microscopy revealed lipid vacuoles and altered lamellar bodies or lysosomes in type II alveolar cells and alveolar macrophages. These changes were most marked 7 days after the last ingestion and were more severe in the short-term application (Shigematsu et al., 1978).

8.6.12 Miscellaneous

Haake et al. (1987) used mature, male C57Bl/6J mice and virgin, female C57Bl/6N mice to study the influence of Aroclor 1254 on the 2,3,7,8,-TCDD induction of teratogenic abnormalities. Dams were treated by oral gavage with either corn oil, Aroclor 1254 (244 mg/kg), or TCDD (20 μg/kg) or Aroclor followed by TCDD or Aroclor followed by dexamethasone (90 mg/kg). Aroclor 1254 alone was administered on day 9, corn oil and TCDD on day 10, and dexamethasone on day 13. In the combinations, the Aroclor was given the day before the TCDD or dexamethasone. TCDD induced 61.8± 23.1% cleft palate per litter; Aroclor with TCDD, 8.2±1.5%; Aroclor alone, 0%; dexamethasone alone, 69.9±18.2%, and Aroclor followed by dexamethasone, 85.8±29.1%. Previous studies have shown that Aroclor 1254 can act as a partial antagonist of the microsomal enzyme induction and immunotoxic effects of TCDD in the mice strain used and, in this study, it was shown that Aroclor 1254 also antagonizes TCDD-mediated teratogenicity. It did not have any effect on the effects mediated by dexamethasone.

Wölfle et al. (1988) found that treatment of male Wistar rats with 200 mg 3,4,3',4'-tetrachlorobiphenyl/kg body weight, injected intraperitoneally, markedly stimulated growth of enzyme-altered liver foci and [3H]-thymidine incorporation into nuclear DNA. In the liver, enlarged hepatocytes, due to hypertrophy, and fine-to-medium fatty-

droplet deposition in hepatocytes were found, but no liver necrosis. Hence, it was concluded, that post-necrotic regenerative growth as the cause of the tetrachlorobiphenyl-mediated stimulation of hepatocytes proliferation, could be excluded. The treatment with tetrachlorobiphenyl *in vivo*, markedly increased EGF-stimulated autophosphorylation of the EGF-receptor (a plasma membrane protein) in liver plasma membranes. These results suggest that altered growth control is due to a direct effect of tetrachlorobiphenyl on hepatocytes.

8.7 Factors modifying toxicity; mode of action

8.7.1 Factors modifying toxicity

As PCBs can stimulate microsomal enzyme activity, it can be expected that they may potentiate the action of other chemicals that undergo microsomal activation, and antagonize the action of those that are detoxified. Antagonism was for example observed in studies on rodents with drugs like pentobarbital (Villeneuve et al., 1972; Sanders et al., 1974; Sanders & Kirkpatrick, 1975; Rosin & Martin, 1983), hexobarbital (Bickers et al., 1972; Tanaka & Komatsu, 1972), and zoxazolamine (Bickers et al., 1972).

Lashneva et al. (1985) and Khan et al. (1985) found potentiation of the rate of microsomal enzyme induction in rats with a combination of 50 mg Sovol (mixture of PCBs)/kg body weight and 500 mg 2,6-ditert-butyl-4-methylphenol (ionol)/kg body weight.

Villeneuve et al. (1972) demonstrated the antagonistic effect by the reduction of phenobarbital sleeping time in rats receiving Aroclors 1242, 1254, and 1260 in their diet, but not in those receiving Aroclor 1221. This was confirmed by Johnstone et al. (1974) with a series of single PCBs. Tanaka & Komatsu (1972) found that the hexobarbital-induced sleeping time in female rats was reduced to 49% of the control value by daily oral doses of Kanechlor 500 of 2 mg/kg for 3 days (total 6 mg/kg). When a daily dose of 0.4 mg/kg was given for 15 days (total 6 mg/kg), no reduction in sleeping time was observed. When this small dose was continued for 45 and 53 days, the reduction remained at 12–13%. Phillips et al. (1972) did not find any potentiation of the cholinesterase-inhibitory action of

parathion in rats dosed with Aroclors 1221 and 1254; this does not necessarily imply that there was no enhanced activation of parathion, as a stimulation of detoxication may have occurred concurrently. A stimulation of parathion detoxication, but not of activation, has been demonstrated in rabbit microsomes (Villeneuve et al., 1971a). Lichtenstein (1972) reported a potentiation by PCBs of the toxicity of parathion for flies.

Aroclor 1254 at 160 mg/kg diet fed to 5-week-old male and female Fischer-344 rats, for 8 weeks, reduced mortality due to feeding hexachlorophene at a concentration of 600 mg/kg diet, from 77% to 7% and completely prevented the paralysis that was observed in all animals on the hexachlorophene diet alone. However, histological changes in the brain characteristic of hexachlorophene exposure were still apparent in the animals on the combined treatment, and the possibility of delayed toxicity beyond the 8 weeks of the study could not be eliminated. The protective effect of Aroclor 1254 was explained by its capacity to enhance detoxication by means of hepatic microsomal enzyme induction (Jones et al., 1974).

Coté et al. (1985) studied a mixture of 15 "persistent" chemicals, including Aroclor 1254, in Sprague-Dawley rats at dose levels of 0, 1, 10, 100, and 1000 times the Canadian water quality objectives (WQO) of each chemical. The PCB (Aroclor 1254) treatments were 0, 0.001, 0.01, 0.1, or 1.0 μg/kg diet for 90 days. No influence on food intake, body weight, organ weights, clinical chemistry, haematology, or histopathology were observed.

As these polychlorinated hydrocarbons seem to have the same mechanism of action, questions arise on the possible interactions between these compounds. In one reported teratogenicity study, groups of 18–21 pregnant C57BL/6N mice received (by gavage) the vehicle corn oil, or daily doses of 3 μg 2,3,7,8-TCDD/kg body weight, 10 or 20 mg 2,3,4,5,3',4'-hexachlorobiphenyl/kg body weight, 25 or 50 mg 2,4,5,2',4',5'-hexachlorobiphenyl/kg body weight, or combinations of TCDD and hexachlorobiphenyl at these dose-levels in corn oil, from day 10 to day 13 of gestation. All chemicals were more than 98.9% pure and the hexachlorobiphenyls did not contain detectable levels of dibenzofurans or TCDD. TCDD alone caused a low incidence of cleft palate and moderate

hydronephrosis, 2,3,4,5,3',4'-hexachlorobiphenyl only caused mild hydronephrosis, and 2,4,5,2',4',5'-hexachlorobiphenyl did not produce any effects. However, treatment of pregnant mice with a combination of TCDD and 2,3,4,5,3',4'-hexachlorobiphenyl caused 5- and 10-fold increases in the incidence of cleft palate at 10 and 20 mg of hexachlorobiphenyl/kg body weight, respectively. No enhancement of TCDD-induced hydronephrosis was observed, and the incidence of TCDD-induced cleft palate was not affected by simultaneous 2,4,5,2',4',5'-HCB treatment (Birnbaum et al., 1985).

Male Sprague-Dawley rats were given a regimen consisting of PCBs, 1 mg/day; polychlorinated quaterphenyls (PCQs), 1 mg/day; PCDFs, 10 μg/day or a mixture of PCBs, PCQs, and PCDFs (1 mg + 1 mg + 10 μg/day) in olive oil, orally, for 22 days. The congeners and ratios in the PCBs, PCQs, and PCDFs were the same as those in Japanese Yusho oil (see section 9.1.2.1). The PCB-treated rats showed hepatic hypertrophy, immunosuppression, and increased drug-metabolizing enzyme activities in hepatic microsomes. PCQ treatment did not produce any significant effects. PCDF and the mixture PCBs + PCDFs caused hypertrophy of the liver, immuno-suppression, increased and drug-metabolizing enzyme activity to a much greater extent than that found for PCBs (more than 100 times more) and weight loss and thymic atrophy (Kunita et al., 1985).

Female Cynomolgus monkeys were administered PCBs (5 mg), PCQs (5 mg), or a mixture containing 5 mg PCBs + 20 μg PCDFs in olive oil injected in a piece of banana, daily, for 20 weeks. The PCBs and PCDFs comprised the same congeners as those in Japanese Yusho oil. The PCB-treated monkeys showed hepatic hypertrophy, immunosuppression, and increased drug-metabolizing enzyme activities in hepatic microsomes, but were devoid of the dermal symptoms characteristic of Yusho. PCQs caused an increase in drug-metabolizing enzyme activities in hepatic microsomes and immunosuppression, but these effects were much less severe than those of PCBs. The mixture with PCDFs caused hypertrophy of the liver, immunosuppression, increase in drug-metabolizing enzyme activities (more than 100 times that of PCBs) and weight loss and thymic atrophy. Dermal symptoms characteristic of Yusho patients

were also found, but not with PCBs or PCQs alone (Kunita et al., 1985).

8.7.2 Mechanisms of toxicity

The analogous structure-activity relations of individual PCB congeners with respect to most of their toxic responses and to their potency in inducing cytochrome P-448-dependent aryl hydrocarbon hydroxylase, indicate that the most active PCB congeners (the coplanar congeners) are those that are approximate stereoisomers of 2,3,7,8,-tetrachlorodibenzo-*p*-dioxin (TCDD). These findings suggest a common mechanism of action.

As is proposed for 2,3,7,8-TCDD, this mechanism is based on the binding affinity of PCB congeners to the cytosolic Ah-receptor protein, a product of the regulator Ah gene (Poland & Glover, 1977; Parkinson & Safe, 1981; Bandiera et al., 1982). The induction is dependent on the position and number of chlorine atoms in the molecule and the congeners that bind most strongly to the Ah-receptor show the strongest induction of monooxygenases and the highest toxicity (effects on the liver including increase in liver weight, increase in liver enzyme activity and lipid content, porphyria, atrophy of the thymus, and effects on reproduction) (Ecobichon & Comeau, 1975; Goldstein, 1980). These very active congeners are the non *ortho*-substituted PCBs 3,4,3',4'- tetrachloro-, 3,4,5,3',4'-pentachloro-, and 3,4,5,3',4',5'-hexachlorobiphenyl, which are at least twice substituted in the *meta* and *para* positions.

In this model, the inducer-receptor complex is translocated into the nucleus, interacts with DNA, and eventually triggers the pleiotropic responses observed. The role of the receptor protein in the mechanism of action of PCBs is further substantiated by the differential effects of the congeners in non-responsive DBA/2J mice and responsive C57Bl/6J mice. Furthermore, there is a good relationship between the aryl hydrocarbon hydroxylase and ethoxyresorufin *O*-deethylase induction potencies in rat hepatoma H-4-II-E cells *in vitro* (Sawyer & Safe, 1982) and their relative binding affinities for the male Wistar rat hepatic cytosol receptor protein (Bandiera et al., 1982; Safe et al., 1985b).

Thus, the coplanar PCBs have mechanisms of action similar to those of the polychlorinated dioxins (PCDDs) and dibenzofurans (PCDFs) (see also WHO, 1989).

On the basis of the comparative toxic and biochemical potencies of coplanar and mono *ortho* coplanar PCBs, Safe (1990) suggested toxic equivalent factors TEFs (relating to 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin, TCDD, see WHO/EURO, 1987) for these compounds. See Table 53. Although there are certain limitations and uncertainties associated with the use of TEFs (WHO/EURO, 1987), they may be useful for an attempt to assess the risk of the combined exposure to coplanar PCBs and PCDDs/PCDFs.

Table 53. Proposed Toxic Equivalent Factor (TEF) values for the coplanar and mono *ortho* coplanar PCB congeners[a]

Congener	TEF value	Relative potency range
1. Coplanar PCBs		
3,4,5,3',4'-PeCB	0.1	0.3-0.0006
3,4,5,3',4',5'-HxCB	0.05	0.1-0.0012
3,4,3',4',-TCB	0.01	0.009-0.00008
2. Mono *ortho* coplanar		
2,4,5,3',4'-PeCB	0.001	0.0004-0.000006
2,3,4,3',4'-PeCB	0.001	0.0008-0.00006
3,4,5,2',4'-PeCB	0.001	0.00013-0.000018
2,3,4,5,4'-PeCB	0.001	0.00045-0.000074
2,3,4,3',4',5'-HxCB	0.001	0.0005-0.0000014
2,3,4,5,3',4'-HxCB	0.001	0.0004-0.0000065
2,4,5,3',4',5'-HxCB	0.001	0.0000055
2,3,4,5,3',4',5'-HpCB	0.001	no data available

[a] From: Safe (1990).

The frequently occurring mixed type, the PB-type, and the weak/noninducing type congeners with some degree of *ortho* substitution may also exert other more subtle toxic effects, either directly via conversion to hydroxylated derivatives, or indirectly through environmental transformations involving regiospecific dechlorination followed by hydroxylation.

In addition, some PCBs, particularly the lower chlorinated ones, can be more readily metabolized through arene oxide intermediates that may be directly genotoxic/carcinogenic. Arene oxide intermediates are also involved in the formation of the methylsulfonyl metabolites of PCBs, which selectively accumulate in the Clara cells of the bronchiolar epithelium and in the secretory contents of the bronchiolar lumen of the lungs. This apparently also involves specific binding proteins that may be important in the expression of certain types of pulmonary toxicity.

Finally, there are other forms of toxicity associated with PCBs that appear to involve certain non-receptor, protein-binding interactions.

8.7.3 Toxicity of impurities in commercial PCBs

In many toxicological studies on the effects of commercial PCB mixtures, the quantitative contribution of impurities to the toxic responses found is largely unknown (WHO, 1989; WHO/EURO, 1987).

9. EFFECTS ON HUMANS

The toxicological evaluation of PCBs presents many problems. PCBs usually occur as mixtures of many congeners, and many of the data on the toxicity of the PCBs are based on the testing of these mixtures. Some components of the mixtures are more easily degraded in the environment than others. Thus, the general population may be exposed to mixtures that are different from those to which workers, working with PCBs, are exposed.

There are great difficulties in assessing human health effects separately for PCBs, since, quite frequently, PCDFs have been present in the PCB mixtures to which humans have been exposed. The presence of PCDDs has occasionally been seen in accidents with certain PCB/chlorobenzene mixtures. Commercial PCBs have been shown to be contaminated with PCDFs and, therefore, in many cases it is unclear whether effects were attributable to the PCBs themselves or to the much more toxic PCDFs.

Because PCBs are ubiquitous and very persistent in the environment, humans have been, and will continue to be, exposed to them, particularly in industrialized countries. PCBs may be inhaled in small amounts through the air or ingested through food. People are primarily exposed to PCBs by consuming fish from contaminated water, but they can be also exposed via other food.

Furthermore, exposures have occurred through accidents and occupational exposure; in the latter case, for example, during the repair of transformers, capacitors, or during the handling of toxic wastes.

Since PCBs are lipophilic, they are preferentially stored in adipose tissue. They are also present, to a smaller extent, in serum, organs and tissues, and human milk. The concentrations of PCBs in the different organs depend on the lipid content of such organs, with the exception of the brain, where the concentration is lower than the lipid content would indicate. PCBs pass, to a certain extent, (depending on chlorination and structure) through the placenta. They are primarily excreted through the bile and milk. In addition to the lipid content, the ratios between adipose tissue, blood, and organs are

influenced by exposure level, sex, age, duration of exposure, and also by whether exposure is current (see section 5).

Since human milk is relatively easy to obtain, it has been used to monitor human exposure. Results of the many monitoring studies carried out in many countries all over the world have shown that average levels of total PCBs are below 2 mg/kg milk fat, though women living in heavily industrialized urban areas or who consume large quantities of fish from heavily contaminated areas, may have higher levels.

9.1 General population exposure

The general population is exposed to PCBs primarily by the oral route, e.g., by consumption of fish from contaminated waters. The monitoring data on adipose tissues, blood, and breast milk indicate that PCBs are absorbed via the gastrointestinal tract, but do not provide information regarding the extent of the absorption.

9.1.1 Acute effects - poisoning incidents

No data available.

9.1.2 Effects of short- and long-term exposure

9.1.2.1 Yusho and Yu-Cheng accidents

(*a*) *Yusho accident*

In June 1968, patients appeared at the Dermatology Clinic of Kyushu University Hospital, Fukuoka, Japan, suffering from chloracne. A group at the University undertook intensive clinical, chemical, and epidemiological investigations and found that the disease originated from the consumption of a batch of rice oil supplied in February 1968; the disease was called Yusho (rice oil disease) (Katsuki, 1969). This batch of rice oil was found to be contaminated with Kanechlor 400, a 48% chlorinated biphenyl, at 2000–3000 mg/kg, which entered the oil through a leak in a heat exchanger (Tsukamoto, 1969). Chlorinated dibenzofurans at 5 mg/kg were found in 3 samples of the toxic rice oil that contained PCB levels of about 1000 mg/kg (Nagayama et al., 1976). The Japanese literature on this incident has been

summarized in English by Kuratsune et al. (1976). The average estimated intake was 633 mg PCBs, 3.4 mg PCDFs, and 596 mg PCQs, roughly equivalent to 157 μg PCBs/kg per day, 0.9 μg PCDFs/kg per day, and 148 μg PCQs/kg body weight per day (Chen et al., 1985; Masuda et al., 1985).

The symptoms and signs of Yusho were described by Goto & Higuchi (1969) and by Okumura & Katsuki (1969). The earliest signs were enlargement and hypersecretion of the Meibomian glands of the eyes, swelling of the eyelids, and pigmentation of the nails and mucous membranes, occasionally associated with fatigue, nausea, and vomiting. This was usually followed by hyperkeratosis and darkening of the skin with follicular enlargement and acneiform eruptions, frequently with a secondary staphyloccoccal infection. These skin changes were most often seen on the neck and upper chest, but, in severe cases, extended to the whole body. It was estimated that the mean length of the latency period between exposure and the onset of clinical illness was 71 days, with a range of from 20 to 190 days (Kuratsune et al., 1972).

Biopsy skin samples showed hyperkeratosis, dilation of the follicles, and an accumulation of melanin in the basal cells of the epidermis; melanin granules have also been observed in biopsy samples of the conjunctiva. Oedema of the arms and legs was also seen in some patients. There were no definite signs of liver enlargement or liver disorders (Okumura & Katsuki, 1969), but slight rises in serum transaminases and in alkaline phosphatase were detected, and a liver sample from a Yusho patient showed an increase in the smooth endoplasmic reticulum (Hirayama et al., 1969). The majority of the patients were found to have respiratory symptoms, and suffered from a chronic bronchitis-like disturbance that persisted for several years (Shigematsu et al., 1971, 1978).

Kikuchi (1984) described the autopsy findings, up to July 1982, of 12 patients with Yusho including 2 stillborn babies. Characteristic pathological changes were acne-like eruptions and cutaneous pigmentation with histological features of follicular hyperkeratosis, dilated hair follicles, and an increase of melanin pigment in the epidermis. In addition, multiplication of the duct epithelium of the oesophageal glands was found in 6 patients. Twenty-four Yusho

patients were observed clinically over the period 1968-78. During this decade, the various clinical symptoms of the Yusho patients gradually diminished. However, some of the symptoms and signs, such as pigmentation of the skin, conjunctiva, and gingiva, eye discharge, and various non-specific symptoms still remained in a number of severely ill patients (Okumura, 1984).

Nakanishi et al. (1985) carried out clinical and experimental studies on respiratory involvement and alterations in the immune status. PCBs were not taken up by the bronchi, but were evenly distributed throughout the lung parenchyma. However, specific dose dependence and structural requirements of PCBs were shown to exist for accumulation in bronchial mucosa. A large amount of expectoration at an early stage of the disease may be related to this. Pathophysiological findings in Yusho patients revealed that respiratory involvement was mainly small airways disease, which may be caused by involvement of the cellular component (Clara cells) in the bronchioles and/or associated with viral or bacterial infections.

Changes in the immune status in these Yusho patients were decreases in IgA and IgM in the serum at an early stage of the disease and then a return to normal and suppression of cellular immunity. The changes in immune status in these Japanese patients were comparable with the findings in the Taiwanese patients (see below).

Hirayama et al. (1974) also reported that the serum bilirubin levels of patients were significantly lower than the normal level and that it was negatively correlated with the blood level of PCBs and the serum triglyceride level.

A considerable number of patients had elevated serum triglyceride levels, up to 4 times the normal values, though this was not correlated with the severity of the symptoms; these high values were maintained for 3 years in many patients (Uzawa et al., 1972). There were no marked abnormalities in serum cholesterol and phospholipid levels (Okumura & Katsuki, 1969; Uzawa et al., 1969). Nagai et al. (1969) reported an increase in urinary 17-ketosteroids excretion. Kusuda (1971) also observed changes in the menstrual cycle in approximately 60% of 81 female Yusho patients, when compared with their cycles prior to exposure. A positive correlation was observed by Okumura

et al. (1974) between the blood levels of triglycerides and PCBs in 42 patients.

Shigematsu et al. (1971) examined serum immunoglobulin levels in 38 patients, 2 years after the onset of the disease, and observed a decrease in IgA and IgM and an increase in IgG. Lower IgM levels were reported in patients showing chloracne (Saito et al. ,1972) (see also section 9.2.4.2).

Yusho patients did not appear to suffer from central nervous effects, but some complained of numbness of the arms and legs. Murai & Kuroiwa (1971) found a decrease in the conduction velocity in peripheral sensory nerves.

Determinations of PCB concentrations in the tissues of Yusho patients were made several months after the ingestion of the oil, using an X-ray fluorescence method for organic chlorine (Goto & Higuchi, 1969). Abdominal fat contained 13.1 mg/kg, subcutaneous fat 75.5 mg/kg, and nails 59 mg/kg. The mesenteric adipose tissue in 6 Yusho patients, analysed by gas-liquid chromatography 1–3 years after the occurrence of intoxication, contained an average PCB level of 2.5 mg/kg, which was considerably higher than the normal value (Masuda et al., 1974a). The mean blood level of PCBs in patients was 6 or 7 μg/litre (3 μg/litre for the general population), 5 years after exposure (Masuda et al., 1974b; Takamatsu et al., 1974). These authors also noted a specific gas-liquid chromatographic pattern that was peculiar to Yusho patients.

Eleven years after exposure, a mean concentrations of 6 μg PCB/litre and 2 mg PCQs/litre, but no PCDFs, were found (Kashimoto et al., 1985).

Urabe (1974) reported that the total number of Yusho patients had reached 1200 by September 1973 and that 22 of them had died. At the end of 1982, the number of identified patients was 1788 (Urabe & Asahi, 1985). Mucocutaneous signs had decreased year by year, but neurological and respiratory signs and symptoms and various complaints, such as general fatigue, anorexia, abdominal pain, and headache, had become more prominent among the patients.

Over time, the severity and the extent of the skin lesions decreased considerably in the exposed population. Fifteen years after the accident, only a few patients still had extensive chloracne.

By 1979, 31 Yusho patients had died, 11 (35.4%) of these from malignant neoplasms. Only 21.1% of all deaths in this Japanese prefecture would be expected from malignant neoplasms, but no clear correlation between the occurrence of Yusho and increased deaths from malignant neoplasms could be made, because of the small number of deaths observed and the unknown latency period.

By the end of 1983, 120 Yusho patients had died, 41 of these from malignant neoplasms. These included 8 stomach cancers, 11 liver cancers, and 8 neoplasms of the lung. A statistically significant excess mortality was seen for malignant neoplasms, cancer of the liver and cancer of the lung, trachea, and bronchi in males, but no such excess was noted in females. The excess from liver cancer deaths was seen mainly in Fukuoka prefecture, while no excess was seen in the Nagasaki prefecture (Ikeda et al., 1987).

(*b*) *Yu-Cheng accident*

In 1979, a similar incident occurred in Taiwan, the number of persons involved, by the end of 1980, was 1843. In the course of 3.5 years, 2061 persons were determined to be victims of PCB poisoning. The incident has been referred to as Yu-Cheng (Chang et al. 1980a,b, 1981; Chen et al., 1980, 1981; Hsu et al., 1985). The affected persons had consumed rice-bran oil contaminated with PCBs that was used as a heat transfer medium in the manufacture of the oil. The PCB intake was estimated to be 0.7–1.84 g and the latent period from the time of intake to the onset of clinical manifestations was approximately 3–4 months. The average estimated PCDFs intake was 3.8 mg and 586 mg PCQs (Chen et al., 1985a). Blood PCB levels ranged from 3 to 1156 μg/litre: 44.3% of 613 patients had levels of 51–100 μg/litre, and 27.6%, blood levels over 100 μg/litre. Six months after the exposure, the concentrations of PCBs, PCDFs, and PCQs were 12–50, 0.062–0.24, and 1.7–11 μg/litre. These blood levels were much higher than in the Yusho incident.

The concentrations of PCBs, PCDFs, and PCQs in 6 samples of rice-bran oil were 53–99 mg/kg, 0.18–0.40 mg/kg, and 25–53 mg/kg oil, respectively (Chen et al., 1981; Hsu et al., 1985; Chen et al.,

1985a). Miyata et al. (1985) found averages of 62 mg PCB/kg, 140 μg PCDFs/kg, and 20 mg PCQs/kg in 5 samples of oil. The levels of toxic compounds in rice-oil samples collected from the factory and school cafeterias and the families of the intoxicated patients in Taiwan were in the range of 53–99 mg PCBs/litre (except for one sample with 405 mg/litre), 0.18–0.40 mg PCDFs/litre, and 25–53 mg PCQs/ litre, respectively. The most toxic PCB reported in commercial PCB preparations was 3,4,3',4'-tetrachlorobiphenyl (Chen et al., 1984).

One hundred and thirty patients (46 males and 84 females), exposed accidentally to PCBs in Taiwan, were examined for ocular manifestations in 1979-80. Eye discharge was present in 80.5%, swelling of the upper lids in 60.4%, pigmentation of conjunctiva in 67.6%, hypersecretion and cystic swelling of the Meibomian glands in 70.7%. Heavy pigmentation of conjunctiva, abnormal cystic formation and hypersecretion of the Meibomian glands occurred in patients whose blood PCBs concentration was above 40 μg/litre. There was a correlation of the ocular effects and the blood concentration of PCBs (Fu, 1984).

Wong et al. (1985), determined the enzyme activity in placental tissue, obtained from 4 women who were exposed to contaminated rice-oil in Yu-Cheng 3–4 years before conception. Placental homogenates showed increases in monooxygenase enzymes, including aryl hydrocarbon hydroxylase, 7-ethoxycoumarin *O*-deethylase, and diol, quinone and phenolic metabolites of benzo(*a*)pyrene.

Lu & Wong (1984) described, in detail, the dermatological, medical, and laboratory findings on 829 patients (half males and half females) in Taiwan, poisoned with PCBs and related compounds. The ages of the patients ranged from 7 days to 78 years. A grading of the clinical severity of these cases was tried, and a possible association with the PCB concentrations in their blood was examined, but could not be demonstrated. The mean PCB concentration in 278 patients was 89.1 ± 0.9 μg/litre (median value 55 μg/litre); the maximum level was 1156 μg/litre and the minimum, 3 μg/litre.

One hundred and ten patients were studied within one year of the exposure. The mean blood PCB level was 39.3 ± 16.6 μg/litre, and the mean blood PCDFs and PCQs levels were 0.076 ± 0.038 and

8.6±4.8 μg/litre, respectively. Both the sensory and motor nerve conduction velocities of the patients were significantly lower than those of the controls (cases studied in the past who did not have neurological diseases) (Chen et al., 1985b).

Thirty-five patients out of 2000 cases of PCB poisoning in Taiwan were examined neurologically 2 years after the accident. The neurological manifestations included clinical, peripheral sensory neuropathy, headache, and dizziness. There was no relationship between the blood PCB concentrations in patients with neurological manifestations and those without. Sensory nerve conduction velocity was reduced and motor nerve conduction was delayed in about one-third to one-half of the patients (Chia & Chu, 1984).

The blood samples of 165 patients, collected 9–18 months after the onset of poisoning, contained 10–720 μg PCBs/litre with a mean value of 38 μg/litre (Chen et al., 1984).

It is worth noting that the highly toxic 2,3,7,8-tetrachloro-, 2,3,4,7,8-pentachloro-, and 1,2,3,4,7,8-hexachlorodibenzofuran isomers were present in samples from both the Japanese (Yusho) and the Taiwanese (Yu-Cheng) incidents.

The most common symptoms noticed were acneiform eruptions and follicular accentuation, skin and nail pigmentation, swelling of the eyelids and increased discharge from the eyes; headache, nausea, and numbness of the limbs. The major blood disorders were decreased erythrocyte counts, haemoglobin concentration, and gamma-immunoglobin, and increased white blood cell counts, serum triglyceride levels, and SGOT, SGPT, and serum alkaline phosphatase activities. Decreased concentrations of δ- aminolaevulinic acid and uroporphyrin were also observed (Chang et al., 1980a,b).

9.1.2.2 Effects of PCBs on babies and infants

Yoshimura (1971) reported diminished growth in boys, but not in girls, who had consumed the oil. Babies born to Yusho mothers were smaller than normal. Newborn babies showed a dark brown skin pigmentation that disappeared after a few months (Taki et al., 1969; Yagamuchi et al., 1971). Funatsu et al. (1972) found spotted and sporadic ossification of the skull and facial oedema with exophthalmia

in 4 babies, but there was no evidence of any teratogenic action. Pregnant Yusho mothers delivered babies with a peculiar clinical manifestation, which was called Fetal PCB Syndrome (FPS). In total, 36 babies showed this syndrome. It consisted of dark brown pigmentation of the skin and mucous membranes, gingival hyperplasia, exophthalmic oedematous eye, dentition at birth, abnormal calcification of the skull (as demonstrated by X-ray), rocker bottom heel, and a high incidence of low birth weight babies. It was suggested by the authors that a possible alteration in calcium metabolism in FPS might be related to the action of PCBs (PCDFs) on female hormones. There was no evidence of hypoadrenocorticism which would explain dark pigmentation in FPS children (Yamashita & Hayashi, 1985).

Jensen (1983b) calculated that the daily intake of PCBs by Yusho infants with clinical symptoms of poisoning was of the order of 70 μg/kg body weight.

Kuratsune et al. (1972) investigated whether Yusho disturbed children's growth. The affected school children, 23 boys and 19 girls, were compared in 1967, 1968, and 1969, with 719 healthy classmates matched by sex. The gains of the affected boys in both height and weight decreased significantly after the poisoning, while the affected girls did not show any changes in these respects.

Studies were carried out by Fein et al. (1984), Fein (1984), and Jacobson et al. (1984a,b) on 242 newborn infants whose mothers had consumed moderate quantities of contaminated lake fish and 71 newborn infants whose mothers had not eaten such fish, during the immediate postpartum period. PCB exposure (measured by both contaminated fish consumption and cord serum PCB levels) predicted lower birth weight, shorter length of gestation, and smaller head circumference. Both maternal consumption of fish and levels of PCBs in cord serum were positively correlated with lower birth weight, shorter gestation and smaller head circumference, and with impaired autonomic maturity and increased numbers of abnormal reflexes.

In the studies by Schwartz et al. (1983), Fein et al. (1984), and Jacobson et al. (1984a), the influence of important variables, such as smoking and alcohol use, were not studied extensively enough. The Brazelton test (Brazelton, 1973) was used in these studies. However,

this test was never intended to be used to evaluate neurological conditions (Prechtl, 1982). The value of this test to predict behavioural abnormalities in infants is small. The Public Health Council of the Netherlands (1985) concluded, therefore, that the reported changes could not be interpreted by the Brazelton test. The important confounding factors "smoking" and "alcohol" were not studied or not well studied, while it is known that these factors can result in such changes. Furthermore, there was an indication that women consuming more fish also consumed more alcohol and coffee and used more medical drugs than those who were not fish eaters.

Jacobson et al. (1985) examined visual recognition memory in 7-month-old infants of women who had consumed contaminated Lake Michigan fish. The authors reported a statistically significant correlation between cord serum PCB levels and impairment of visual recognition memory. It should be mentioned, however, that interpretation of these test results is difficult. In view of the variability associated with the measurements of fixation time (no standard deviations were reported), it is unclear whether any of the group means are statistically different. Moreover, the clinical meaning of the differences noted is not known.

Neonatal effects of transplacental exposure to PCBs (and DDE) were examined in a study on 912 children born between 1978 and 1982 in North Carolina. When the infants were born, samples of placenta, maternal and cord serum, and milk/colostrum were collected. Physical examination of each infant was performed and the Brazelton test (Brazelton, 1973) was applied. Fifty-nine per cent of the examinations were carried out in the first week, 20% in the second week, and 16% in the third week. The PCB levels in milk fat at birth (866 samples) ranged from nd to 4.0 mg/kg. There was no association between PCB levels and birth weight, head circumference, and hyperbilirubinaemia (neonatal jaundice). For the Brazelton test, the only cluster scores to be significantly affected by PCBs were the tonicity and reflex scores, with higher PCB levels (above 3.5 mg/kg milk fat). The results showed that higher PCB levels were associated with hypotonicity and hyporeflexia while higher DDE levels (4 mg/kg milk fat) were associated with hyporeflexia (DDE concentrations in milk fat ranged from nd to >6 mg/kg milk fat) (Rogan et al., 1986a).

As a follow-up study, Rogan et al. (1987) followed 858 children in the USA, from birth to one year of age, to determine whether the presence of PCBs in breast milk affected their growth or health. The PCB concentrations in breast milk ranged from 0.49 to 15.80 mg/kg, on a fat basis, and the DDE concentrations from 0.31 to 23.8 mg/kg milk fat. The lactation period varied from 13 (mothers with 4.00–15.80 mg PCBs/kg in their milk) to 26 weeks. No adverse effects on body weight or the frequency of visits for various illnesses were observed. There was no difference between bottle-fed and breast-fed children. In 1985, about 6 years after the mass poisoning in Taiwan, 117 children born to affected women (*in utero* exposure during, or after, the period of oil contamination) and 108 unexposed controls were examined (Rogan et al., 1988). The exposed children were shorter and lighter than the controls; they had more frequent abnormalities of the gingiva, skin, nails, teeth, and lungs than control children. The exposed children showed delay in developmental milestones, deficits on formal development testing, and abnormalities in behavioural assessment.

A follow-up study was carried out to determine the relationship between PCBs in mother's serum and breast milk and the health and development of the born infants, in Sheboygan, Wisconsin, USA, in the period 1980-81. Seventy-three mothers gave birth to 62 infants that were breast-fed and 11 that were bottle-fed. The ages of the mothers ranged from 18 to 36 years. The mean serum PCB level for the study population was 5.76 μg/litre (range, 1.29–14.9 μg/litre). Breast milk contained a mean PCB level of 1.13 mg/kg (range, 0.29–4.02 mg/kg) on a fat basis. The mother's blood serum PCB level during pregnancy was positively associated with the number and type of infectious illnesses the infants suffered later, such as colds, earache, and influenza during the first 4 months of life. The development and growth of the infant up to the age of 4 months was normal and was not affected by PCB levels (Smith, 1984).

Lan et al. (1989) selected 18 exposed children (9 males and 9 females), and a reference group of 44 unexposed children (26 males and 18 females), to study the congenital absence of permanent teeth. Among 9 transplacental Yu-Cheng girls and 9 boys, the permanent teeth germ was missing due to congenital factors in 4 girls and one boy. In the control group, one boy showed this phenomenon.

Fukuyama et al. cf. Lan et al. (1989) had already reported this effect in 1979.

Gladen et al. (1988a) investigated whether PCBs, either transplacental or through breast feeding, affected the scores on the Bayley Scales of infant development at 6 or 12 months of age, in 802 infants. Higher transplacental exposure to PCBs was associated with lower psychomotor scores at both 6 and 12 months of age. Exposure to PCBs through breast-feeding was apparently unrelated to Bayley scores.

The urine of 75 children born to mothers exposed to contaminated rice oil in Taiwan (1979), 74 controls, and 12 siblings of the children exposed between 1978 and 1985, was analysed for the presence of porphyrins. Total prophyrin excretion was elevated in the exposed children in comparison with the other 2 groups (exposed group, 95.2 μg/litre, control group, 80.7 μg/litre, and siblings, 72.6 μg/litre. The exposed children did not appear to have symptoms directly attributable to their porphyria, but the authors concluded that a mild disturbance in their porphyria metabolism appeared to be related to their intrauterine exposure (Gladen et al. 1988b).

Thirty-nine babies showing hyperpigmentation were born to PCB-poisoned mothers. In the orally exposed population of the Yu-Cheng episode, 24 deaths were reported and as many as 12 cases of hepatic disease including hepatomas, which was more than expected (Hsu et al., 1985).

9.1.3 *Appraisal*

Several Japanese research groups have concluded that the main signs and symptoms involved in the Yusho intoxications were caused by contaminants in the PCB-mixture, i.e., mainly PCDFs (Masuda et al., 1985; Kunita et al., 1985). This conclusion has mainly been based on the following observations:

(*a*) Blood levels of PCBs in the victims were not very different from those in the general population and several occupationally- exposed groups had higher PCB blood levels in the absence of any recognizable adverse health effects.

(*b*) There was an unusually high level of PCDF-contamination in the PCBs that contaminated the rice oil.

(*c*) Signs and symptoms did agree with what could be expected from exposure to PCBs and/or PCDFs (PCDDs).

However, blood levels in the Yusho victims were determined 5 years after exposure. Consequently, at the time of the intoxication, blood levels might have been much higher.

Furthermore, later studies on the biological potency of the dioxin-like coplanar PCBs indicated that the occurrence of these might have added significantly to the overall toxicity of the PCDFs (Safe, 1990).

In the case of the Yu-Cheng intoxication, blood levels of PCBs were determined within 1 year of the accident and were found to be much higher (i.e., about 70 μg/litre) than in the Yusho intoxication.

However, even at this time, some elimination of PCBs, especially lower chlorinated PCB congeners, can be assumed to have taken place. Thus, blood levels in the Yu-Cheng intoxication might also have been higher initially.

In summary, it can be concluded that the main symptoms of the Yusho and Yu-Cheng intoxications might have been caused mainly by combined exposure to PCBs (mainly the coplanar ones) and PCDFs. However, some of the symptoms, especially the chronic respiratory effects, may have been caused specifically by the methylsulfone metabolites of certain PCB congeners.

9.2 Occupational exposure

9.2.1 Acute toxicity - poisoning incidents

9.2.1.1 Acute dermal effects

Skin rash has occurred within a few hours after acute exposure to PCBs. Furthermore, itching, burning sensations, smarting, and sweating have been reported. Irritation of the conjunctiva was a constant symptom in acute exposure to high concentrations (Elo et al., 1985; Schecter & Tiernan, 1985). A few weeks or months after acute exposure (lasting a few hours) to high concentrations of PCBs

(10–16 mg/m^3), several skin symptoms were observed in some of the accidentally exposed population, such as slight pigmentation, ridges on the nails, and the worsening of acne vulgaris (Elo et al., 1985). Skin wipe tests on PCB-exposed workers were carried out by Maroni et al. (1981a), Smith et al. (1982), and Wolff (1984) for capacitor manufacturers, electrical equipment manufacturers, and transformer inspectors. Concentrations varying between 2 and 28 000 μg/m^2 of skin were measured. Considerable concentrations of PCBs were also found on the surfaces of hand tools in the factories (Maroni et al., 1981a; WHO/EURO, 1987).

9.2.2 Effects of short- and long-term exposure

Exposure through ingestion is possible in the working environment through the direct ingestion of soot particles or through the contamination of cigarettes or food by hands. Maroni et al. (1981a) measured high concentrations of PCBs in the palmar skin of capacitor workers; this might lead to the oral ingestion of PCBs, in addition to exposure via the dermal route.

Skin exposure is important in the case of long-term exposure, even though the ambient concentrations may be low. According to calculations made by Wolff (1985), in long-term exposure situations, skin may be responsible for up to 20% of the total body uptake of PCBs in workers exposed in capacitor manufacturing (WHO/EURO, 1987).

Symptoms similar to those of Yusho have been observed in workers in a Japanese condenser factory, including pigmentation of the fingers and nails, and acneiform eruptions on the jaw, back, and thighs. It was thought that these effects arose from local contact with PCBs; when the use of PCBs ceased, the symptoms disappeared (Hasegawa et al., 1972b). Chloracne is one of the most prevalent findings among PCB-exposed workers and particularly among those exposed to highly chlorinated compounds. Hara (1985) found prevalences of comedones and acne of 40%, and skin irritation and erythema of 13% in workers exposed for 1–24 years to Kanechlor 300 and 500. The blood PCB levels were 21–117 μg/litre. The degree of skin pathology was correlated with the blood PCB concentrations. In the production of capacitors, (oculo-) dermatological abnormalities were found in

37% of the cases, but typical PCB-associated changes were less prevalent. Fischbein et al. (1979) suggested that these signs and symptoms were due to exposure to PCDFs and/or PCDDs.

Fischbein et al. (1982) evaluated the dermatological effects of long-term (<5–>20 years) occupational exposure to PCBs, in a cross-sectional clinical survey of 326 capacitor manufacturing workers. Air PCB levels varied in the plant from 0.007 to 11.0 mg/m^3. A high prevalence (37%) of a wide spectrum of dermatological abnormalities was found, such as rashes, burning sensation of the skin, and chloracne, in most cases associated with typical comedones (6%), but the occurrence was less than that observed in Yusho patients, even though the serum PCB levels in the workers were much higher.

Two persons were reported with dermatological abnormalities suggestive of, but not specific for, chloracne, after occupational exposure to PCBs (Fischbein & Wolff, 1987). They had raised serum PCB concentrations (of the order of 80–100 μg/litre). Their wives also had increased blood PCB levels, with the same PCB pattern as their husbands. It was suggested by the authors that it would seem prudent to take appropriate industrial hygiene measures, to prevent the transmission of PCBs from the occupational environment into the home.

A cross-sectional study on 120 male workers was conducted to determine the prevalence of increased PCB absorption, as well as the presence of potentially-related clinical and metabolic abnormalities. Three groups were used: an exposed group (86), a nominally exposed (15), and an unexposed group (19 subjects). The exposed group had direct contact with PCB-containing transformer fluids, while the nominally exposed group worked in the same facility, but without direct contact, and the unexposed group was employed elsewhere. The average length of employment was 17 years (range, few months–40 years), 3 years and 9 months, and 4 years and 3 months, for the 3 groups, respectively. The average plasma PCB levels were 33.4, 14.2, and 12.0 μg/litre, and the average concentrations in adipose tissue were 5.6, 1.4, and 1.3 mg/kg, respectively. There were no statistically significant differences among the groups in levels of triglycerides, cholesterol, high-density lipoproteins, and SGOT. A significant correlation was demonstrated between plasma PCBs and

triglycerides and SGOT values, but not SGPT and gamma-GTP values (Chase et al., 1982).

To investigate the prevalence of oculo-dermatological findings, such as hypersecretion of the Meibomian glands, swelling of the upper eyelids, and hyperpigmentation of the conjunctiva (typical Yusho symptoms), in a population with long-term occupational exposure to PCBs, a group of 246 workers employed in 2 capacitor manufacturing facilities were studied in 1976, and 181 of these workers, again in 1979. The median plasma values of lower chlorinated PCBs were 63 μg/litre in 1976 and 49 μg/litre in 1979. For the higher chlorinated PCBs, these values were 18 and 17.5 μg/litre, respectively. The prevalences of oculo-dermatological findings, potentially related to the effects of PCBs, were 9.4 and 13.3%, at the two examinations. There was no significant association between such abnormalities and blood plasma/serum concentrations of PCBs (Fischbein et al., 1985).

Lees et al. (1987) studied the hypothesis that the dermal route of PCB exposure is a major contributor to the total body burden of PCBs in workers. The investigation was conducted simultaneously with a clinical study on switchgear workers engaged in transformer maintenance and repair operations. The geometric means in the serum and adipose tissue of exposed workers, previously exposed workers, and comparison group were, respectively: (serum) 12.2, 5.9, and 4.6 μg/litre, (adipose tissue) 2.1, 0.83, and 0.6 mg/kg. The geometric mean 8-h TWA concentrations in the different work areas (55 samples) ranged from 0.5 to 6.1 $\mu g/m^3$. The geometric mean surface concentrations (102 samples) ranged from 0.007 to 1.075 $\mu g/m^2$. From the available data, it was calculated that exposure by the dermal route (i.e., skin absorption) was considerable in comparison with respiratory exposure. The daily calculated total dose through inhalation ranged from 4.0 to 48.8 μg in the different work areas and via the dermal route, from 1.2 to 215.0 μg. It was considered though not conclusively, that the dermal and dermal/oral routes of exposure are the predominant contributors to body burden.

Shalat et al. (1989) reported 3 cases of kidney adenocarcinomas among young male utility workers who were responsible for maintaining electrical transmission equipment, including transformers. The duration of exposure ranged from 5 to 35 years.

The occurrence of chloracne and abnormal hepatic function as a result of occupational exposure to PCBs had already been reported by Jones & Alden (1936), Schwartz (1943), and Meigs et al. (1954).

Effects, such as chloracne, skin rashes, and burning eyes and skin, have been associated with occupational exposure to Aroclors and Kanechlors (Ouw et al., 1976; NIOSH, 1977; Fischbein et al., 1979, 1982, 1985; Baker et al., 1980; Drill et al., 1981; Kimbrough, 1987; US EPA, 1987). In these studies, monitoring data did not adequately characterize exposure levels, consequently correlations between the occurrence of skin lesions and the duration of exposure, or blood concentrations of the PCBs, are poor or nonexistent. Furthermore, the contamination of the PCBs with PCDFs and PCQs may be partly the cause of these skin changes.

Other effects reported in human exposure have been considered in a criteria document for recommended standards for occupational exposure to PCBs (NIOSH, 1977) and include several instances of chloracne that resulted from exposure to PCB vapours in various work situations. Other symptoms noted were sore throat, gastrointestinal disorders, and eye disturbances.

Fischbein et al. (1979) examined 168 male and 158 female workers at a capacitor plant, where they were exposed for <5 up to 25 years to Aroclors 1254, 1242, 1016, and 1221. TWAs for 8 h with ranges of 0.07–0.40, 0.40–0.60, and 0.60–11.0 mg/m^3 were considered low, medium, and high, respectively. Among work-related symptoms they found upper respiratory irritation and decreased rectal capacity, gastrointestinal, neurological, and dermatological symptoms. The dermatological symptoms occurred among 45% of the males and 55% of the females and are comparable with the symptoms found in Yusho victims. There was a significant correlation between plasma PCB levels and SGOT levels, though changes in most liver tests were not prevalent.

Maroni et al. (1981b) reported blood PCB concentrations of 41–1319 μg/litre in 80 electrical workers (half males, half females) employed in electric capacitor manufacture and testing plants. Sixty-seven persons were exposed to Pyralone 3010 and 13, to Apirolio (both PCBs containing 42% of chlorine). The mean age of the workers was 37 ± 8 years, and the mean duration of employment was

12±6 years. There were 6 cases of chloracne among the 80 workers. Sixteen of the males had liver abnormalities, including hepatomegaly and increased serum enzymatic activities; for 20% of these, the PCB concentration in the blood was <200 μg/litre. The females included 2 cases of bleeding haemangioma, one of whom also had chronic myelocytic leukaemia, but none of the females had liver abnormalities.

Ouw et al. (1976) studied 34 electrical industry workers exposed to 0.32–2.22 mg Aroclor 1242 (free from impurities)/m^3 compared with 30 control workers. The electrical workers consisted of 15 males (6 months–23 years employment) and 19 females (1 month–7 years employment). No clear indications of liver changes were found. Major complaints were burning of the eyes, face, and skin. One worker had chloracne without systemic effects and 5 workers had eczematous hand and leg rashes. These dermatological effects occurred at an air concentration of <1 mg PCBs/m^3. There were no significant health effects in workers at, or below, a blood PCB level of 200 μg/litre. Drill et al. (1981) concluded that individuals with blood levels of ≥ 200 μg/litre have an increased risk of chloracne and that chloracne may occur more frequently in workers exposed to PCBs that have been heated (presence of PCDFs) and to PCBs that have a ≥ 54% of chlorine.

A study was conducted to determine whether exposure to fumes or oil at the transformer incident site at New Mexico had caused illness. Exposed persons of different disciplines and unexposed employees were asked to complete a questionnaire. Eighty of the 101 persons with known exposure completed the questionnaire. The most common symptoms were: nausea (27.5%), eye irritation (22.5%), sore throat (21.2%), nose irritation (18.8%), chest tightness (15.0%), and headache (15.0%). The symptoms were transient and usually resolved as soon as the person left the site. Fifty-six exposed persons submitted sera for PCB analysis as did 20 controls. All but 4 persons had levels below 10 μg/litre. The medium for exposed persons was 4.1 μg/litre (range, 1.2–41.8 μg/litre compared with 2.4 μg/litre (range 0.9–8.0 μg/litre) for the controls (Anon., 1985).

A follow-up study on capacitor-manufacturing workers, exposed to PCBs, and their children, was conducted over the period 1973-79.

The PCBs that were used were Kanechlor 300 and 500. PCB levels in the blood (up to 120 μg/litre), as well as in breast milk, were 10–100 times higher than those of non-exposed Japanese persons. The levels in 8 women ranged from less than 50 μg/litre to about 400 μg/litre in whole milk. Blood PCB levels were correlated with the duration of PCB handling and breast milk PCB levels. The blood PCB levels ranged from 18.7 to 117 μg/litre in this population, 1 year after the use of PCBs was discontinued. The rate of decline of blood PCB levels, as well as the changes in the gas chromatography of blood PCBs over 7 years varied with the kind of PCB handled. The blood PCB levels tended to be higher (< 3 up to > 10 μg/litre) in children fed PCB-contaminated breast milk for a long period. The great majority of the workers had dermatological complaints, but these symptoms gradually disappeared with discontinuation of contact with PCBs. The blood chemistry of the workers showed only a correlation between PCB blood levels and serum triglycerides. Several of the children fed breast milk for a long period, showed the same medical findings as in Yusho (itchy skin, eczema, red eye, fever, catching cold, carious teeth). However, they were not diagnosed as suffering from PCB-poisoning, because the findings were neither serious nor related to the blood PCB levels (Hara, 1985).

Workers occupationally exposed to Kanechlor 500 or 600 showed higher PCB levels in plasma (2–251 μg/litre) than Japanese Yusho patients. Gas chromatographic patterns of their PCBs corresponded to the patterns of PCBs to which they were exposed, but, with time, the PCB pattern in plasma is changing. PCQs could not be detected in the plasma of the workers (Takamatsu et al., 1985).

Lawton et al. (1985) studied a group of 194 workers in capacitor manufacturing, exposed to Aroclor 1016, 1242 and/or 1254 before (1976) and after (1979). The use of PCBs in the operations was discontinued in 1977. The geometric mean serum levels and 5–95% ranges were: lower chlorinated PCBs, 363 μg/litre (57–2270 μg/litre) and 68 μg/litre (12–392 μg/litre), higher chlorinated PCBs, 30 μg/litre (6–142 μg/litre) and 19 μg/litre (4–108 μg/litre), respectively. The statistical findings were a depression in serum bilirubin and elevations in serum γ-glutamyltranspeptidase (GGTP) and lymphocyte levels, at the time of the first examination, and only an elevation of monocytes at the second.

In 1982, a survey was conducted in an electrical capacitor factory in the USA, using Aroclor 1242 from 1941 to 1971, with a change to Aroclor 1016 from 1971 to 1977. Of approximately 500 current employees (with an average of 12.9 years of employment) 205 took part in the survey. The geometrical mean PCB value for serum was 18.2 μg/litre (range, nd–424 μg/litre). Only 39% of the workers ever worked in areas with potential PCB exposure. More than 70% had serum levels below 30 μg/litre. There were no indications of acute PCB-related clinical effects. The workers' serum PCB levels were a function of duration of employment, cumulative occupational exposure, cumulative fish consumption, and cholesterol level (Acquavella et al., 1986).

The blood of women occupationally exposed to PCBs (Kanechlor 300 and 500) was analysed over the period 1975-79. Sixty-five samples were taken from 29 mothers. The PCB concentrations varied between 6.4 and 52.6 μg/kg (mean concentration 32.3 μg/kg). Clinical symptoms observed during the use of PCBs were minor in comparison with those of Yusho patients (Yakushiji et al., 1984b).

Guo et al. (1987) studied the influence of serum cholesterol and albumin on the partitioning of PCB congeners between human serum and adipose tissue. Fifty-five repair workers, who were either currently or had been previously exposed, and 56 comparison workers without exposure to PCBs were used. Seven PCB congeners, which had been quantified in both serum and adipose tissue in at least one-third of the selected populations, were evaluated. The effects of serum cholesterol in modifying the serum PCB concentrations are likely to be apparent in groups exposed to PCBs containing higher chlorinated congeners, such as Aroclors 1254 and 1260, rather than those containing lower chlorinated congeners, such as Aroclors 1242 and 1221.

A selected group of 51 workers (25 males and 26 females) with a mean length of exposure of 10 years (range 1–30 years) were compared with 2 groups consisting of 74 subjects (37 males and 37 females) and the same reference group of 67 workers (30 males and 37 females) used in another study, residing in the same areas, but without exposure to PCBs. The PCB concentrations in the blood of 28 out of the 51 subjects ranged from 88 to 1359 μg/litre. A

statistically significant increase was found in serum GGT activity, urinary D-glucaric acid (GLA), and porphyrin excretion, when compared with the respective control groups. Although the PCB workers had an average urinary excretion of porphyrins almost twice as high as those of the control groups, no dose-response relationship was found between urinary porphyrin excretion and blood PCB concentrations (Maroni et al., 1984).

Steele et al. (1986) found a gradual decrease in the body burden of the more highly chlorinated PCBs, as well as a more rapid decrease of the less chlorinated congeners over the period 1977-84 in groups of 5 current and retired workers, in comparison with 6 subjects without current exposure. The authors calculated the half-life for the lower chlorinated PCBs to be 6–7 months, and, for the higher chlorinated PCBs, 33–34 months. The evidence of different half-life estimates for serum PCBs, depending on the degree of chlorination, is consistent with the present knowledge of the pharmacokinetics.

Hola & Reznicek (1985) carried out a cytogenetic analysis of the peripheral lymphocytes of 48 employees at a precoated gravel plant using Delor 103 (a mixture of mainly trichlorobiphenyls) in comparison with 24 workers not exposed and 13 workers exposed to PCBs during the impregnation of condensers. The frequency of aberrant cells, percentage of blastic transformation, mitotic index, and proliferation index in peripheral lymphocytes, and a number of biochemical parameters were determined. In the 48 workers at the precoated gravel plant, there were 2.87% aberrations (PCB concentrations in plasma, 107 ± 104 μg/litre); 3.14% in the 13 PCB-exposed workers (PCB concentration in plasma 308 ± 253 μg/litre), and 2.04% in 24 non-exposed workers; 1.50% of aberrations were found in 20 controls.

Emmett (1985) studied a total of 55 workers (currently exposed (38) and 17 past transformer repair workers) in comparison with 56 unexposed workers. PCB exposures occurred from the air and contaminated surfaces, predominantly to Aroclor 1260, but there was some exposure to Aroclor 1242. There was widespread PCB contamination of the workplace surfaces and the 8-h time-weighted average concentration was between 0.7 and 24.0 $\mu g/m^3$, depending on the task of the worker. The bulk oils and air from the transformer

were analysed revealing that PCDFs (13–116 μg/kg) were present as well as PCBs. In one of the samples, 2,3,7,8-TCDF was found at 31 μg/kg. Eye irritation and tearing were more prevalent in the exposed group, but the symptoms were mild and/or transient. Ocular symptoms were also found, possibly caused by 1,1,1-trichloroethane and/or trichlorobenzene. Chloracne was not found. Two exposed workers reported a history of melanoma; none were reported in the control group. However, the difference was not statistically significant. Adipose tissue and serum PCB geometrical mean concentrations in exposed workers were 2.1 mg and 12.2 μg/kg, respectively, those in unexposed workers were 0.6 mg and 4.6 μg/kg, and those in previously exposed workers, 0.83 mg and 5.9 μg/kg. No correlations were observed between liver function tests and either adipose tissue or serum PCB concentrations. A significant negative correlation was found, after adjustment for confounding variables, between adipose tissue PCB levels and 24-h urinary 17-hydroxycorticosteroid excretion and a positive correlation between serum PCB levels and serum-GGT. No correlation was found between adipose tissue PCB concentrations and any serum lipid component (Emmett et al., 1988a,b).

Bercovici et al. (1983) collected blood from 17 women with recent missed abortions, 7 women who had experienced one or more missed abortions in the past, and 7 women with normal, second trimester pregnancies, and estimated the serum levels of PCBs and other organochlorine pesticides. The range of serum PCB levels in recent missed abortions was 10.9–416.5 μg/litre, and that of the control group, 12.2–40.0 μg/litre. Forty-seven per cent of the recent missed abortion group had PCB levels of the same magnitude as the controls (range, 10.90–42.8 μg/litre) and 53% had higher levels. In the former missed abortion group, PCB levels in the range of 45.3–109.1 μg/litre were found. The number of women examined in the different groups was small. Furthermore, half of the women with missed abortions had PCB levels in serum comparable with those of the controls. The authors also did not control for many variables that could significantly influence the incidence of abortions. It seems, therefore, that missed abortions, either recent or in the past, may be associated with PCB exposure.

PCB concentrations were determined in the blood from 10 women with normal pregnancies (controls) and from 17 women with premature deliveries. A significant difference was seen in blood serum concentrations of PCBs between the women with normal and those with premature deliveries. When the premature delivery group was split into a high-serum- (8/17) and a low-serum-PCB group (9/17), the high-serum-PCB group had a significantly higher serum PCB concentration than the control group. The values were 128 mg/litre in the high group, 19.3 μg/litre in the control group, and 21.4 μg/litre in the low group. In the high-PCB, premature delivery group, the mean serum concentration of tetrachloro- isomers was lower than that of the control group (0.6 vs 1.86 μg/litre), while the mean serum concentrations of pentachloro and hexachloro-isomers were higher (78.2 vs 15.67 μg/litre and 48.9 vs 1.72 μg/litre, respectively) (Wassermann et al., 1982). The indications that higher serum PCB levels may be associated with an increase in incomplete abortions and premature deliveries (Bercovici et al., 1983; Wassermann et al., 1982) could not be established as a definitive causal relationship.

Taylor et al. (1984) studied the relation of Aroclor 1254, 1242, and/or 1016 exposure to birth weight and gestational age in the offspring of women working in 2 capacitor plants. Fifty-one infants, born to 39 women employed at the 2 capacitor manufacturing facilities, had a mean birth weight of 153 g less than 337 infants born to 280 women employed in areas of the facilities without direct exposure. Mean gestational age in the first group was reduced by 6.6 days compared with the latter group. It was concluded that the small decrease in mean birth weight seemed likely to have resulted from a shortening of the gestation period rather than a retardation of intrauterine growth. Smoking and alcohol consumption by the mothers were not considered, and whether the socio-economic status of this group of women was similar to that of the control group is not clear.

In an update of this study, 200 women with direct exposure and 205 women without direct exposure, were used to study the relation of PCBs to birth weight and gestational age in the offspring. The authors concluded that these data indicated that there was a significant relationship between an increased serum PCB level and decreased birth weight and gestational age, and that the decrease in birth weight

was, at least partially, related to shortened gestational age (Taylor et al., 1989).

9.2.3 Appraisal

A discussion on the occupational epidemiological data on the basis of dose-response considerations needs an acceptable indicator of the degree of exposure and, in the particular case of PCB mixtures, a discussion on the nature of the congeners present. For most epidemiological studies reported, there are some, albeit often limited, data on levels of total PCBs in blood, which could be used as indicators for PCB exposure. It is recognized that the analytical procedures used are different. The blood of continuously exposed workers will contain absolutely and relatively more of the lower chlorinated congeners than that of human beings with background exposure only, or with past exposures (e.g., Yusho and Yu-Cheng populations). Consequently, the toxicological profile for these 2 types of exposure will differ (see also the appraisal on Yusho/ Yu-Cheng).

In some cases, the epidemiology of the continuously exposed workers shows a possible association between elevated exposure to PCB mixtures and the occurrence of liver enzyme alterations, hepatomegaly, and dermatological abnormalities, such as rashes and acne. In many studies, no associations were found. In some of these studies, limited end-points were investigated. Within the positive studies, there is a poor or non-existent correlation between the incidence and degree of effects and blood concentrations. Among the positive studies, adverse effects are predominantly reported in the studies with the higher blood levels. Possible contamination of used PCBs and PCB mixtures (particularly in transformers), with PCDFs and PCQs, may contribute to, or even determine, the toxicity observed. The overall conclusion is that continuous exposure to high concentrations of PCBs and PCDFs may result in effects on the skin and liver.

9.2.4 Special studies (target organ effects)

9.2.4.1 Liver

The liver is considered to be one of the most important target organs for PCB toxicity. Acute exposures to PCBs cause alterations in liver enzyme activities. Smith et al. (1982) found a statistically significant correlation between elevated liver enzyme activities and blood PCB concentrations, in workers exposed to PCBs in electrical equipment manufacturing or maintenance. A negative correlation was found in relation to the HDL cholesterol concentration and serum PCBs. Positive correlations were found between the liver enzyme activities of serum alanine aminotransferase (S-ALAT), serum aspartate aminotransferase (S-ASAT), serum gamma-glutamyltranspeptidase (S-Gamma-GT) and SGOT, and blood PCB concentrations, among workers exposed in an Italian capacitor factory. Hepatomegaly was also detected in most of the cases studied by Maroni et al. (1981a,b).

Workers occupationally exposed to PCBs, but mostly also exposed to PCDDs and/or PCDFs, showed significantly increased S-ASAT, S-ALAT, and gamma-GT activities. Sometimes elevated serum triglyceride values were also found. Recovery of these disturbances in liver function and morphology requires several weeks or months (Elo et al., 1985; Schecter et al., 1985). Fischbein (1985) reported the results of liver function tests in a population engaged in the manufacture of capacitors and transformers. A low prevalence of abnormal liver function tests was found and mean values for all tests were within normal ranges in 5 workers occupationally exposed to Aroclor 1016. Plasma antipyrine half-life was significantly lower than in matched controls, suggesting induction of hepatic mixed-function oxidases (Alvares et al., 1977). At the initial examination (in 1976, when PCBs were still being used), statistically significant correlations were found between log LDH and plasma levels of log HPCB (higher PCB congeners) and log TPCB (total PCBs) among female workers, while log-gamma-GTP was significantly correlated only with log HPCB among male workers. A significant increase to abnormal levels of gamma-GTP was noted at the follow-up examination (1979, 2.5 years after the use of PCBs had been discontinued) in both male and female workers, and preliminary results indicated significant correlations between gamma-GTP and

serum levels of PCBs among male workers. In occupationally exposed individuals, the serum or plasma PCB levels were higher than those found in patients in the Yusho and Yu-Cheng incidents. An effect transmitted via liver activity was hyperlipaemia, in which triglycerides and, in some instances, also cholesterol levels in the blood were elevated (Smith et al., 1982).

Hepatotoxicity is suggested in occupationally-exposed humans (Drill et al., 1981; US EPA, 1987). Drill et al. (1981) concluded that SGOT and/or GGPT appear to be the most sensitive indicators of PCB exposure in humans, and that changes in liver enzymes occur at levels below those at which chloracne occurs.

9.2.4.2 *Immunotoxicity*

Reports on the immunological effects of long-term, occupational exposures are sparse. Fischbein et al. (1979) found a suggestive increase in the occurrence of trivial infections in exposed workers. Immunological responses were found to be affected in Yu-Cheng victims (Lu & Wu, 1985) and in Yusho patients (Nakanishi et al., 1985). Acute accidental exposures of workers to PCBs and PCDFs have been studied for immunological responses and immunosuppressive changes have been found. The most important alterations were decreased numbers of T-lymphocytes and lowered T-helper/T-suppressor cell ratios. Responses of lymphocytes to phytohaemagglutinin, concavalin A, and pokeweed mitogen were also lowered. The observed changes persisted for 6 months after the acute exposure. No quantitative changes were observed for immunoglobulins (Elo et al., 1985; WHO/EURO, 1987, 1988).

Lü & Wu (1985) found that PCB patients suffered from various kinds of infections. Most frequent were those of the respiratory tract and skin, including pyoderma, tinea versicolor, dermotophytosis and warts. The low resistance of the patients suggested some degree of immunosuppression. The function of the immune system was tested in 143 patients. Examination during the first year revealed: decreased concentrations of IgM and IgA, but not of IgG; decreased percentages of total T-cells, active T-cells, and helper T-cells, but normal percentages of B-cells and suppressor T-cells; suppression of delayed type response to recalling antigens; enhancement of lymphocyte

spontaneous proliferation; and enhancement of lymphocyte proliferation with phytohaemagglutinin, pokeweed mitogen, and tuberculin stimulation, but not with concanavalin A. After 3 years, the positive rate of the tuberculin test recovered somewhat with time. The total numbers of T-cells and B-cells were normal, the number of suppressor T-cells (OKT-8) increased, but the number of helper T-cells (OKT 4) was still lower, so the immuno-regulating index (OKT 4/OKT8) was still very low. The lymphocyte proliferation stimulated by various mitogens was also enhanced.

In patients with PCB poisoning, IgA and IgM levels in serum apparently decreased for 2 years after the onset of the disease, but returned to normal in most cases, in spite of the persistence of the respiratory symptoms (Shigesmatsu et al., 1978, see section 9.2.4.3).

9.2.4.3 Respiratory system

In long-term exposure, up to 0.3–10 mg of PCBs may be inhaled in an 8-h working day. The respiratory tract is certainly the most important route of exposure in the case of acute emergency situations, where unprotected personnel working in areas containing such PCB concentrations may, in theory, inhale a total dose of up to 10 mg/day. This may imply a considerable cumulation of PCBs during long-term exposure (WHO/EURO, 1987, 1988).

Transient irritation of the mucous membranes of the respiratory tract has been reported in emergency situations, as well as difficulty in breathing at high concentrations. It has not been confirmed that short-term exposure causes other important respiratory effects, though increased susceptibility and a high risk of contracting chronic bronchitis have been suggested (Kimbrough, 1980; Elo et al., 1985; WHO/EURO, 1987).

In the case of unheated commercial PCBs, the amount of PCDFs inhaled might be very low, if any at all. The situation is totally different in the case of acute exposures to heated or decomposed PCBs, in which the inhaled total concentrations might be several orders of magnitude higher than above, though the irritative effect may prevent breathing in such contaminated rooms. Since the soot often contains a considerable fraction of particles, a few microns in size, it is partly breathed in and, thus, may lead to alveolar retention

of both soot and adsorbed chemicals. Carbon particles can accumulate in the lung tissues and regional lymph nodes. Inhalation of soot particles containing high concentrations of both PCBs and PCDFs would, in practice, be the most important mechanism of exposure (Parkes, 1982; WHO/EURO, 1987).

Warshaw et al. (1979) and Smith et al. (1982) found a correlation between serum PCB concentration and respiratory tract symptoms among workers exposed long-term to PCBs. An increase in the occurrence of chronic bronchitis was possibly due to a decrease in the immunological defence mechanism. No increase in mortality from respiratory system diseases was found. An indication for acute and chronic irritation of the respiratory tract was found by Brown & Jones (1981).

Shigematsu et al. (1978) studied the clinical, laboratory, and pathological findings on respiratory involvement in PCB poisoning in 401 patients. Respiratory symptoms included expectoration in 40% of the 289 non-smoking patients with PCB poisoning and mild wheezing in 2%. The incidence and severity of the symptoms was well correlated with the concentrations of PCBs in blood and sputa. The clinical examinations revealed bronchiolitis and pneumonia or atelectasis in about one-tenth of the patients with reticulo-linear shadows. The PCB concentrations in the blood and sputa were 27 and 8 μg/litre, respectively. The presence of PCBs in sputum may have been associated with the excretion from bronchial cells and/or with lipid II cells of the lung, phagocytosed in alveolar macrophages and expectorated.

9.2.4.4 *Neurotoxicity*

Acute and long-term exposures to PCBs have been reported to cause neurological and unspecific psychological or psychosomatic effects, such as headache, dizziness, nausea, depression, sleep and memory disturbances, nervousness, fatigue, and impotence (Smith et al., 1982; Elo et al., 1985; Hara, 1985; Schecter et al., 1985; Takamatsu et al., 1985; WHO/EURO, 1987).

Fischbein et al. (1979) reported the occurrence of these symptoms in 39% of male and 58% of female capacitor-manufacturing workers, exposed to PCBs for long periods (over 5 years). To what extent

these symptons were the direct consequences of exposure to PCBs and related compounds and how much they were dependent on general conditions in an emergency situation remains unclear.

Seppalainen et al. (1985) examined 16 men who were exposed to fumes resulting from the explosion of capacitors containing Clophen A30. Air concentrations of PCBs, measured 5.5 h after the explosion, were 8–16 mg/m^3 air (PCDFs and other compounds, such as monochloropyrenes and dichloropyrenes, were also formed). Most of the men had a transient sensory neuropathy in their lower extremities (WHO/EURO, 1987, 1988).

9.2.4.5 Blood pressure

Kreiss et al. (1981) examined 458 volunteers (> 12 years of age) from Triana (Alabama) and correlated serum PCB levels (Aroclor 1260) with blood pressure. This population was excessively exposed to DDT residues through the consumption of contaminated fish. The residents of this small rural town also had elevated PCB body burdens that were positively correlated with fish consumption. The mean serum PCB level was 17.2 μg/litre. The incidence of borderline (systolic of 140–159 mm Hg and diastolic of 90–94 mm Hg) and definite hypertension (systolic of ≥ 160 mm Hg and diastolic of ≥ 95 mm Hg) was 30% more than would be expected for a general population of the same age, race, and sex composition. However, this study did not have a control group in its design, and there were more confounding factors that make the study inadequate to conclude an association between blood PCB levels and hypertension.

A study was carried out to test the association of serum PCB levels and elevated blood pressure in 840 residents of New Bedford, Acushnet, Dartmouth and Fairhaven, Canada, in the period 1984-87. The mean PCB levels (as Aroclor 1254) were 5.9 and 5.8 μg/litre in 391 males and 449 females, respectively. The range in serum PCB levels for the total group was 0.38–154.2 μg/litre. There was a relationship of serum PCB level to age among the 840 individuals. In the 5 age groups: 18–24, 25–34, 35–44, 45–54, and 55–64 years, the mean serum PCB levels were 2.59, 3.84, 5.30, 8.18, and 8.96 μg/litre, respectively. Blood pressure levels did not appear to be correlated with serum PCB levels. The mean systolic readings,

taken at 3 different times, for the 840 individuals were 115.26± 18.85, 113.69±17.62, and 114.28±11.41. The diastolic readings were 72.19±10.94, 73.19±10.95, and 73.17±19.94. There was no between the sexes difference (Massachusetts Dept Public Health, 1987).

Akagi & Okumura (1985) studied the correlation of blood PCBs levels or PCB patterns and blood pressure in 59 Yusho patients (more than 40 years old). In spite of the passage of 13 years from the onset of the disease, 52.5% of the patients still had PCB levels higher than those of the general population. The frequency of hypertension in these patients was 16.9%, a value similar to that found in the general population of the same age and sex. Blood pressure was not associated with blood PCB levels or PCB pattern, but was associated with the well known factors influencing blood pressure, such as age, obesity, and habitual alcohol intake.

9.2.5 *Mortality studies*

Davidorf & Knupp (1979) conducted an epidemiological study on ocular melanoma incidence in Ohio from 1967 to 1977, attempting to associate Ohio counties with known high concentrations of PCBs and those with industries that might use PCBs with an increased incidence of ocular melanoma. The authors concluded that there was no causal relationship between PCB exposure and an increased annual occurrence of ocular melanoma in Ohio counties in the period 1967-77. Bahn et al. (1976) reported on 31 research and development employees subjected to "heavy" Aroclor exposure (quantity not reported) in a US petrochemical plant. Two had malignant melanomas, and according to the standard of the Third National Cancer Survey, incidence rates of only 0.04 would be expected among 31 persons (NCI, 1975). The retrospective cohort mortality studies of Brown & Jones (1981) and Brown (1987) reported data on PCB-exposed individuals who had worked in 2 electrical capacitor plants, one in New York, and the other in Massachusetts. Both plants had produced this type of capacitor for more than 30 years. The PCBs used were Aroclor 1254, Aroclor 1242, and Aroclor 1916. A combined total of 2588 exposed workers from both factories, with 3 or more months of exposure, were studied. The overall mortality (295 deaths) was lower than expected (318) and the mortality for

cancer deaths (62 observed) was also lower than expected (80). A statistically significant excess in deaths was observed in the disease category that includes cancer of the liver (primary and unspecified), gall bladder, and biliary tract (5 observed vs 1.9 expected). Most of the excess was observed in women employed in one plant. According to the authors, because of the small number of deaths and the variability of specific causes of death within this category, it remains difficult to interpret these findings with regard to PCB exposure.

At the first plant, there were 2 different facilities, a power capacitor manufacturing facility, and a small capacitor manufacturing facility. At the power capacitor facility, the TWAs for personal air samples were between 24 and 393 $\mu g/m^3$ for various jobs: in the winding work area and soldering work area, they were as low as 3 $\mu g/m^3$ and as high as 476 $\mu g/m^3$, respectively. At the second plant, where a few cases of rectal and liver cancer were found (see above) the PCB levels were much higher. Degreasers and solderers, for example, had TWAs for personal air of 1.260 and 1.060 $\mu g/m^3$, respectively, and heat soak operators and tankers had TWAs of 630 and 850 $\mu g/m^3$, respectively. The work area air samples contained levels as high as a TWA of 810 $\mu g/m^3$. The duration of exposure, without information concerning the level of exposure, when the levels varied so widely, weakens the statement about lack of correlation between duration of exposure and cancer mortality. In fact, the observed cancer cases for both the liver and rectum were markedly increased in the factory that had, at the time of measurement, the higher PCB levels. Notwithstanding the absence of detailed information, the data presented are suggestive of a dose-related increased incidence of mortality from rectal cancer and possibly liver cancer.

Although there was no correlation between the latent period and cancer mortality or between the duration of employment and cancer mortality, most of the cancers occurred in the second plant, which had the higher levels of PCBs at the time that the measurements were made. PCB levels were monitored in 1977 for personal air and work area air. Since procedures and processes were somewhat different during the years in which most of the workers were exposed, the figures on PCB levels do not necessarily indicate the exposure levels of the subjects. Nevertheless, the figures given do indicate the wide variation in PCB levels in air, with a 15-fold difference between the

lowest and highest levels among the different jobs. Although the different levels of dust and particulate matter are not known, it would be anticipated that an equally wide variation would exist.

A medical surveillance programme has been established for 482 persons, who were potentially exposed to PCBs, PCDFs, and PCDDs from an electrical transformer fire in Binghamton in 1981. Mean serum PCB concentrations (98% of the samples) were below 20 μg/litre, a value typical of a population with no unusual exposure. Mortality, symptomatology, cancer incidence, and reproduction events were assessed through 1984. The numbers of deaths, cases of cancer, fetal deaths, and infants with low birth weight or congenital malformations, were similar to those expected on the basis of age and sex-specific rates for upstate New York and other comparison populations. One-third of the fire-fighters and a number of persons, who were in the building during the first 24 h (or longer) reported a rash or itching skin, but no chloracne (Fitzgerald et al., 1989).

Bertazzi et al. (1981) reported the results of a mortality study on PCB-exposed workers, who were employed in the manufacture of electrical capacitors in an industrial area near Milan. The PCBs used over the period from 1946 to 1970 were Aroclor 1254, Pyralene 1476 (54% chlorine), and Pyralene 3010 and 3011 (42% chlorine). In 1954, a few measurements in the air were performed and the values of Aroclor 1254 were 5200–6800 $\mu g/m^3$. In 1977, airborne concentrations of Pyralene 3010 ranged from 48 to 275 $\mu g/m^3$. The minimum and maximum values of PCBs recovered from workplace surfaces and worker's hands were, 0.2–159 and 0.3–9.2 $\mu g/cm^2$, in 1977, and, in 1982 (2 years after the ban on production), 0.003–6.3 and 0.09–1.5 $\mu g/cm^2$, respectively. The mortality study spanned the 25-year period from 1954 to 1978. The control mortality rates were for subjects from the city in which the plant was located. There were 1310 workers (1020 females and 290 males) and the vital status was obtained for 98% of both sexes.

The study was enlarged and extended to include 2100 workers and to cover the period 1946-82. Vital status was ascertained for over 99% of the subjects and death certificates were obtained for all deceased persons. Expected deaths were calculated using 2 sets of mortality rates, national and local. Among male workers, cancer

deaths (14 observed vs 7.6 expected) were significantly increased as were deaths owing to cancer of the gastrointestinal tract (6 observed vs 2.2 expected). Also, mortality from haematological neoplasms (3 observed), and lung cancer (3 observed) was higher than expected. However, the excess was not statistically significant. Female workers exhibited an overall mortality that was significantly increased above expectations. Cancer deaths (12 observed vs 5.3 expected) and haematological neoplasms (4 observed vs 1.1 expected) were significantly higher than expected when compared with the local population. Interpretation of the results is limited by the small number of deaths: however, it is of interest that the gastrointestinal tract and the lymphatic and haematopoietic tissue seem to be the most probable human target sites for PCB carcinogenic activity (Bertazzi et al., 1987).

A cohort study on 142 male Swedish capacitor-manufacturing workers was performed between 1960 and 1978. The PCB was 42% chlorinated and contained different PCDFs totalling about 1400 μg/kg. The mean exposure time of the workers was 6.5 years. In 1973, 0.1 mg PCBs/m^3 was found in the air. Mortality was investigated for the period 1965-82 and cancer incidence from 1965 to 1980. Twenty-one deaths and 7 cancers were observed, which was in agreement with the anticipated numbers calculated from national statistics (Gustavsson et al., 1986).

Zack & Musch (1979) examined a small cohort of workers (89) with occupational exposure to PCBs. No liver cancer was reported among the 30 deaths that occurred in this study. There were increases for all malignancies (8 observed vs 4.4 expected, SMR = 179) and elevated lung cancer (4 observed vs 1.44 expected). Adjustment for the confounding variables due to multiple exposure to other agents was not made. By 1979, 31 Yusho patients had died, 11 (35.4%) of these from malignant neoplasms. Only 21.1% of all deaths in this Japanese prefecture would be expected from malignant neoplasms, but no clear correlation between the occurrence of Yusho and increased deaths from malignant neoplasms could be made, because of the small number of deaths observed and the unknown latency period.

By the end of 1983, 120 Yusho patients had died, 41 of these from malignant neoplasms. These included 8 stomach cancers, 11 liver cancers, and 8 neoplasms of the lung. A statistically significant excess mortality was seen for malignant neoplasms, cancer of the liver, and cancer of the lung, trachea, and bronchus, in males, but no such excess was noted in females. The excess from liver cancer deaths was seen mainly in Fukuoka prefecture, while no excess was seen in Nagasaki prefecture (Ikeda et al., 1987).

9.2.6 Appraisal

Some epidemiological studies on occupationally exposed workers and Yusho patients indicate an association between PCB exposure and cancer, especially with regard to hepatobiliary tumours. However, no definite conclusions, can be drawn from available data, because of the small numbers of deaths in the population studies, the lack of clear dose-response relationships in the occupational studies, and the difficulty in evaluating the effects of other compounds present in PCBs.

10. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The PCBs were evaluated by IARC in 1978 and 1987 (IARC, 1978; 1987). In 1987, IARC concluded that, because the role of impurities in PCBs in the carcinogenicity could not be excluded, and, because of the lack of knowledge on dose-response relationships, the evidence from epidemiological studies is limited. However, the evidence of carcinogenicity in laboratory animals is sufficient. Taking the combined evidence from human and experimental animal studies, the IARC Group concluded that PCBs are probably carcinogenic for humans (IARC, 1987).

Many countries and intergovernmental organizations have banned or severely restricted the production, use, handling, transport, and disposal of PCBs and PCTs. For an overview of these measures and regulations we refer to the Health and Safety Guide on PCBs and PCTs (WHO, 1992; IRPTC, 1986b).

At the meeting of the Joint FAO/WHO Expert Committee on Food Additives (WHO, 1990), particular attention was paid to the possible health consequences of the intake of PCBs by the suckling infant. It was not anticipated that adverse health effects would occur as a result of consuming breast milk. It should also be kept in mind that the infant consumes breast milk for a short period (1-2% of its total life span). In addition, other factors need to be considered:

- the benefits of breast milk and breast-feeding, including the nutritional, immunological, and other properties of the milk, as well as the psychological advantages, should not be discounted;
- the disadvantages of breast milk substitutes, because of the potential contamination due to infective agents, incorrect preparation, inadequate hygiene, etc.

For these reasons, JECFA was of the opinion that the advantages to the infant of breast-feeding outweigh any potential hazards due to the PCB content of breast milk, and advises that there is absolutely no justification for discouraging this practice.

The monitoring data have indicated, up to now, that the occurrence of PCBs in human milk persists at about the same levels during the years, with slight decreases or increases in the PCB concentration in breast milk in certain countries. Since the PCB levels in human milk are still too high, every effort should be made to prevent the entry of PCBs into the environment and to control their occurrence in the food supply. The Committee was reassured by the observation that the production of PCBs has largely ceased. Thus, it is expected that the levels of PCBs in the environment and food, and consequently in breast milk, will decrease with time (WHO, 1986b).

On the basis of the evaluated background data, an average dietary intake of PCBs for adults was estimated to amount to a maximum of 100 μg/week, or approximately 14 μg/day. For a 70-kg person, this is an intake equivalent to a maximum quantity of 0.2 μg/kg body weight per day (WHO/EURO, 1988).

The above data suggest that the main exposure of the general population to PCBs occurs through food. The daily intake of these compounds by breast-fed infants is about 1–2 orders of magnitude higher than for the rest of the population, compared either on the basis of body weight or energy consumption. However, compared with lifetime intake, a 6-month, breast-feeding period contributes less than 5% of the total body burden from lifetime exposure (WHO/EURO, 1988).

POLYCHLORINATED TERPHENYLS

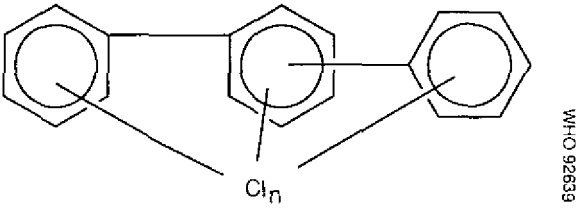
(Data relating specifically to polychlorinated terphenyls are scarce. Nevertheless, they are presented separately in this section.)

1. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

1.1 Identity

The chemical formula of the polychlorinated terphenyls (PCTs) can be given as $C_{18}H_{14-n}Cl_n$, in which n is the number of chlorine atoms, which can range from 1–14.

The chemical structure is:



The number of different PCTs theoretically possible is orders of magnitude higher than that for PCBs, but, in practice, as for PCBs, PCTs are not sold on a composition specification, but on their physical properties, which depend on the degree of chlorination.

Common name:	Polychlorinated terphenyls - PCTs
Major trade names:	The trade names are generally similar to those given for PCBs. In the Aroclor series, terphenyls are indicated by 54 in the first two places of the four digit code. In Japan, the PCTs are coded Kanechlor KC-C.

1.2 Physical and chemical properties

The physical and chemical properties of PCTs are very close to those of PCBs, and depend on the degree of chlorination.

1.3 Analytical methods

Extraction and clean-up procedures are similar to those used for PCBs (sections 2.3.1.1 and 2.3.1.2).

The gas-liquid chromatographic details are different from those of PCBs, because of the lower volatility of the PCTs. Zitko et al. (1972) used 3% OV 210 as the stationary phase with a column temperature of 200 °C. Thomas & Reynolds (1973) also used OV 210 with a column temperature of 250 °C and another system with 3% Dexsil as a stationary phase at 300 °C with a ^{63}Ni electron capture detector; this was also used by Addison et al. (1972). Sosa-Lucero et al. (1973) used OV 210 and SE 30 at 255 °C and Freudenthal & Greve (1973) used OV 17 with a temperature programmed from 200 °C to 285 °C. Thomas & Reynolds (1973) confirmed the identity by chlorination to tetradecachloroterphenyl with antimony pentachloride.

2. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

No specific information available. See PCBs.

3. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

Atmospheric input into the Great Lakes has been studied, because the lakes, as a whole, represent the largest surface area of any freshwater body in the world. Wingender & Williams (1984) found that atmospheric transport was a major pathway for the deposition of polychlorinated terphenyls into the Great Lakes (see section 4.1.1.1).

4. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

4.1 Residues in the environment

Relatively few studies have been carried out to determine polychlorinated terphenyls in biota. Freudenthal & Greve (1973) found levels of 0.12 mg/kg (wet weight) in oysters and 0.4 mg/kg (fat basis) in eels from the Netherlands. Levels of PCTs were generally lower than PCBs in the same samples. Renberg et al. (1981) analysed biota from the Baltic Sea and found levels of 2.8–17.2 mg/kg (wet weight) in white-tailed eagles, 0.5–1 mg/kg in grey seals, and 0.08 mg/kg in eels. In fish, Jan & Malnersic (1978) found PCT levels of 0.003–0.005 mg/kg in trout from the Soca River, Yugoslavia. Mean PCT levels of 0.0025 mg/kg (Doguchi, 1977) and 0.01 mg/kg (Takai et al., 1979) have been found in the freshwater and marine environment of Japan. Several bird species have been monitored for PCTs; levels of 0.03–2.2 mg/kg have been found in Japanese birds (Doguchi, 1977). Zitko et al. (1972) found levels of 1.4 mg/kg fat (wet weight) and 0.1 mg/kg in eggs of herring gulls from the Bay of Fundy, Canada. Hassell & Holmes (1977) analysed the livers of various birds of prey in the United Kingdom; residues ranged from <0.05 to 1.2 mg/kg. PCT levels of between 0.61 and 10.51 mg/kg were found in the fat of gulls from Italy, (Vannucchi et al., 1978) and black-headed gulls from the Baltic contained mean residues of 1.8 mg/kg in adipose tissue (Falandysz, 1980).

PCTs were also measured in the monitoring programme carried out all over Japan in the period 1974-81. In 1974, 1976, and 1978 no PCTs were found in 60, 156, and 75 samples of water (limit of determination 0.0001 mg/litre). No PCTs were found in sediment samples in 1974, but, in 1976 and 1978, 21/151 and 37/75 samples were positive, with PCT levels of 0.001–0.2 and 0.001–1.0 mg/kg, respectively. In fish in 1974, 1976, and 1978, PCTs were found in 3/11, 0/39, and 3/66 samples, in concentrations of 0.0002–0.2 mg/kg (Environment Agency Japan, 1983).

4.2 Residues in food

Ushio & Doguchi (1977) analysed cereal products, vegetable products including vegetable oils, seasonings, and seaweed, marine animal products, and terrestrial animal products including milk and eggs, for the presence of PCTs. Only the vegetable products contained average concentration of 0.05 μg/kg. Other authors referred to by Ushio & Doguchi failed to detect PCTs in edible oil, vegetables, meat, or fish.

No PCTs could be detected in a Canadian survey on eggs, domestic and imported cheese (Villeneuve et al., 1973b).

In Japan, the PCT contents of a number of foods were determined. The PCT contents of fish were lower than the PCB contents (Fukano et al., 1974). Villeneuve et al. (1973a) analysed packaged food in Canada and found that 94.5% of the samples contained less than 0.01 mg PCTs/kg and 5.5% contained 0.01–0.05 mg PCTs/kg.

4.3 Concentrations in adipose tissue

In Japan, Doguchi et al. (1974) found an average PCT level of 0.6 mg/kg in human fat, with a range of 0.1–2.1 mg/kg. In the same country, Takizawa & Minagawa (1974) found PCT levels of 0.02 mg/kg in the human liver ($n=6$), 0.01 mg/kg in the kidney ($n=2$), 0.02 mg/kg in the brain ($n=3$), and 0.04 mg/kg in the pancreas ($n=1$). Thirty samples of adipose tissue (from 18 males and 12 females), obtained in Tokyo in 1974, were analysed for PCTs. The average level of PCTs was 1.11 mg/kg (range 0.04–9.20 mg/kg), on a fat basis (Fukano & Doguchi, 1977). In the Netherlands, PCTs were found in human fat at levels of 0–1 mg/kg (Freudenthal & Greve, 1973).

4.4 Concentrations in blood

An average PCT level of 5.0 μg/litre was recorded in the blood of non-occupationally exposed volunteers in Japan (Doguchi & Fukano, 1975). Human blood samples were collected from 10 subjects in Tokyo in 1975 out of 27 subjects from whom blood had been obtained in 1973. The average concentration of PCTs in whole blood was

6.45 μg/litre (0.7–19.6 μg/litre) in 1973, and 5.32 μg/litre (1.1–9.4 μg/litre) in 1975 (Fukano & Doguchi, 1977).

5. KINETICS AND METABOLISM

5.1 Absorption

PCTs have been shown to be absorbed from the intestinal tract (Sosa-Lucero et al., 1973), but very little information is available on the rate of absorption.

5.2 Distribution

Diets containing Aroclor 5460 at levels of 10, 100, or 1000 mg/kg were administered to rats for 7 days. The greatest concentration (611 mg/kg at 1000 mg/kg diet) was in the liver, while the blood level was 5.85 mg/litre at 1000 mg/kg diet. PCT administration did not affect body weight, but a significant increase in liver weight occurred in the rats fed 1000 mg/kg diet (Sosa-Lucero et al., 1973). Table 54 shows the tissue distribution obtained in this study in rats fed with Aroclor 5460 and in another study using Aroclor 1254 (Curley et al., 1971).

Table 54. Tissue distribution (mg/kg wet weight) of PCTs (Aroclor 5460) in rats fed dietary levels of 100 mg/kg for 7 days and fed PCBs (Aroclor 1254) at 100 mg/kg for 9 days[a]

Tissue	Aroclor 5460	Aroclor 1254
Blood	1.32	0.1
Liver	47	6
Brain	5.1	4
Kidney	15.1	5
Heart	21.5	-
Fat	-	180

[a] From: Curley et al. (1971); Sosa-Lucero et al. (1973).

Addison et al. (1972) dosed cod *Gadus morhua* by gavage with the polychlorinated terphenyl (PCT) Aroclor 5460 (in herring oil) at 0.5 g/ml. After one week of starvation, the PCTs were present in

all the tissues analysed. Uptake efficiency appeared to be low with a total of 1–10 mg of Aroclor 5460 being distributed through all tissues out of 1 g administered. Liver was found to be the organ richest in PCTs, and probably contained most of the absorbed material. In a separate group of fish, analysed 70 days later (fish were fed during this period), PCT residues were not significantly lower.

5.3 Biotransformation

There is little information on the biotransformation of PCTs. Addison et al. (1972), using gas-liquid chromatography, noted a loss of PCTs with a shorter retention time in the excreta of a cod dosed orally with Aroclor 5460; the same loss was observed in rat faeces after the administration of a diet containing Aroclor 5460 (Sosa-Lucero et al., 1973).

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 Marine and estuarine organisms

PCTs, Aroclor 5460, did not show any toxic effects at either 1 or 100 mg/litre on *Dunaliella*, *Olisthodiscus*, or *Thalassiorsira*, the only 3 species tested with this mixture (Craigie & Hutzinger, 1975).

6.2 Terrestrial invertebrates

Lichtenstein et al. (1969) exposed *Drosophila melanogaster* to the dry residues of various PCTs. No mortality was observed after a 48-h exposure to 2999 μg of Aroclor 4465, 5442, or 5460.

6.3 Birds

A single study on the toxicity of Aroclor 5442, produced a 5-day LC_{50} of 4477 mg/kg (1301–15402 mg/kg) in Japanese quail (aged 14 days) (*Coturnix coturnix*) (Hill & Camardese, 1986).

Cecil et al. (1974) found that Aroclor 5442 at a dose level of 20 mg/kg diet did not change the hatchability of chicken eggs .

7. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

7.1 Single oral exposure

Early data, reported in abstract, indicated that the approximate oral LD_{50} values of the PCT-mixtures Aroclor 5442 and 5460, in corn oil, in rats were 10.6 and 19.2 g/kg body weight, respectively. For 3:1 mixtures of PCBs and PCTs, Aroclor 4465 and 2562, in corn oil, the LD_{50} values in rats were 16 and 6.3 g/kg body weight, respectively (US FDA, 1970).

7.2 Short-term oral exposure

7.2.1 Rat

Modifications in the liver were studied in groups of male Sprague-Dawley rats fed a diet containing Aroclor 5460 at a level of 0 or 10 000 mg/kg diet (equivalent to 0 or 400 mg/kg body weight). Body weights were slightly decreased after 3 weeks of exposure. The enlarged livers showed proliferation of the endoplasmic reticulum and formation of large concentric membrane arrays. Evidence of fatty degeneration was observed by Toftgard et al. (1980). Biochemical changes included an increase in microsomal protein and phospholipid, and a decrease in RNA and cholesterol. The specific esterase activities, *N*-demethylase and nitroreductase, were increased and those of glucose-6-phosphatase and aryl hydrocarbon hydroxylase decreased (Norback & Allen, 1972).

Sosa-Lucero et al. (1973) did not observe any signs of toxicity in groups of male Wistar rats exposed to a diet containing Aroclor 5460 at levels of up to 1000 mg/kg diet (equivalent to 50 mg/kg body weight) for 7 days. At 1000 mg/kg diet, relative liver weights were increased as well as microsomal protein, cytochrome P-450, and the specific activities of aniline hydroxylase and aminopyrine-*N*-demethylase. Mixed type induction of hepatic microsomal enzymes in rats exposed to PCTs has been observed by several

investigators (Ahotupa & Aitio, 1980; Toftgard et al., 1980; Nilsen & Toftgard, 1981).

Kiriyama et al. (1974) fed groups of male Wistar rats a control diet or diets with *ortho*-, *meta*-, or *para*-PCTs at a level of 2000 mg/kg diet (equivalent to 100 mg/kg body weight) for 2 weeks. *Ortho*- and *meta*-PCTs reduced growth and increased relative kidney weights, while only *meta*-PCTs decreased food intake and increased the relative liver weights. All mixtures increased plasma, but not liver, cholesterol levels. There was evidence of adrenal hypertrophy.

7.2.2 Monkey

A dietary level of Aroclor 5460 of 5000 mg/kg (equivalent to 200 mg/kg body weight) over 3 months caused growth retardation and increased relative liver weights in 6 Rhesus monkeys compared with 3 controls. 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 of Aroclor 1248/kg diet (equivalent to 12 mg/kg body weight), i.e., alopecia, facial oedema, swollen eyelids and lips, and purulent eye discharge. 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 (Allen & Norback, 1973).

7.3 Teratogenicity

Groups of 15 or 16 pregnant ddY mice were fed diets containing 0, 100, 500, or 2500 mg PCTs/kg (not specified) during gestation. The animals were sacrificed on day 18 and examined for embryonic effects. The fetuses of dams receiving the 500 and 2500 mg/kg diet showed a higher incidence of cleft palate in comparison with the controls. Pregnant ddY mice were administered 0, 50, or 100 mg PCTs/kg 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. Furthermore, when pregnant ddY mice were adrenalectomized on day 10, it did not suppress the development of cleft palate, but metapyrone, an inhibitor of corticosterone synthesis, significantly reduced the incidence of cleft palate in the fetuses. The results suggest that cleft

palate induced by PCTs is not due to a direct effect, but that an increase in the corticosterone level in the maternal plasma is involved in the mechanism of its development (Kaneko, 1988).

Pregnant Wistar rats were fed PCTs at levels of 0, 500, or 2500 mg/kg diet during gestation and the animals were sacrificed on day 20. Systemic oedema was observed in the fetuses of the animals fed 500 and 2500 mg PCTs/kg diet, but no cleft palate was found (Kaneko, 1988).

7.4 Carcinogenicity

Groups of 35 male ICR mice received a diet containing Kanechlor C (a mixture of 95% PCTs and 5% PCBs) at levels of 0, 250, or 500 mg/kg (equivalent to 0, 36, and 70 mg/kg body weight), for 24 weeks. The mice were sacrificed following 16 exposure-free weeks. Survivors numbering 28, 28, and 21 mice at 0, 250, and 500 mg/kg diet, respectively, were autopsied. A dose-related reduction in body weight gain and a dose-related increase in absolute liver weights were observed. Neoplastic nodules (nodular hyperplasia) were 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. The increases at the higher dose level were statistically significant (Shirai et al., 1978).

7.5 Miscellaneous effects

Evidence for the estrogenic activity of Aroclor 5442 was found using the glycogen response of the immature rat uterus. Aroclor 5460 was inactive in this test (Bitman & Cecil, 1970; Bitman et al., 1972).

The mixed type inducer, Aroclor 5460, increased the metabolism of 4-androstene-3,17-dione in male Sprague-Dawley rats intraperitoneally injected with 4 doses of 300 mg/kg body weight in 4 days (Nilsen & Toftgard, 1981). Reproductive effects have not been investigated. Groups of pregnant ddY mice received a control diet or diets containing PCTs (not specified) at levels of 50 or 500 mg/kg diet (equivalent to 7 or 70 mg/kg body weight). Increased incidence of cleft palate and other malformations was reported in the fetuses.

In neonates, reduced growth and survival as well as hyperactivity were observed (Kimura & Miyake, 1976). (No details available).

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ANNEX 1.
NUMBERING OF PCB CONGENERS

No.	Structure	No.	Structure	No.	Structure
Monochlorobiphenyls		Tetrachlorobiphenyls		**Pentachlorobiphenyls**	
1	2	47	2,2',4,4'	96	2,2',3,6,6'
2	3	48	2,2',4,5	97	2,2',3',4,5
3	4	49	2,2',4,5'	98	2,2',3',4,6
		50	2,2',4,6	99	2,2',4,4',5
Dichlorobiphenyls		51	2,2',4,6'	100	2,2',4,4',6
4	2,2'	52	2,2',5,5'	101	2,2',4,5,5'
5	2,3	53	2,2',5,6'	102	2,2',4,5,6'
6	2,3'	54	2,2',6,6'	103	2,2',4,5',6
7	2,4	55	2,3,3',4	104	2,2',4,6,6'
8	2,4'	56	2,3,3',4'	105	2,3,3',4,4'
9	2,5	57	2,3,3',5	106	2,3,3',4,5
10	2,6	58	2,3,3',5'	107	2,3,3',4',5
11	3,3'	59	2,3,3',6	108	2,3,3',4,5'
12	3'4	60	2,3,4,4'	109	2,3,3',4,6
13	3,4'	61	2,3,4,5	110	2,3,3',4',6
15	4,4'	62	2,3,4,6	111	2,3,3',5,5'
		63	2,3,4',5	112	2,3,3',5,6
Trichlorobiphenyls		64	2,3,4',6	113	2,3,3',5',6
16	2,2',3	65	2,3,5,6	114	2,3,4,4',5
17	2,2',4	66	2,3',4,4'	115	2,3,4,4',6
18	2,2',5	67	2,3',4,5	116	2,3,4,5,6
19	2,2',6	68	2,3',4,5'	117	2,3,4',5,6
20	2,3,3'	69	2,3',4,6	118	2,3',4,4',5
21	2,3,4	70	2,3',4',5	119	2,3',4,4',6
22	2,3,4'	71	2,3',4',6	120	2,3',4,5,5'
23	2,3,5	72	2,3',5,5'	121	2,3',4,5',6
24	2,3,6	73	2,3',5',6	122	2,3,3',4,5
25	2,3',4	74	2,4,4',5	123	2',3,4,4',5
26	2,3',5	75	2,4,4',6	124	2',3,4,5,5'
27	2,3',6	76	2',3,4,5	125	2',3,4,5,6'
28	2,4,4'	77	3,3',4,4'	126	3,3',4,4',5
29	2,4,5	78	3,3',4,5	127	3,3',4,5,5'
30	2,4,6	79	3,3',4,5'		
31	2,4',5	80	3,3',5,5'	**Hexachlorobiphenyls**	
32	2,4',6	81	3,4,4',5	128	2,2',3,3',4,4'
33	2',3,4			129	2,2',3,3',4,5
34	2',3,5	Pentachlorobiphenyls		130	2,2',3,3',4,5'
35	3,3',4	82	2,2',3,3',4	131	2,2',3,3',4,6
36	3,3',5	83	2,2',3,3',5	132	2,2',3,3',4,6'
37	3,4,4'	84	2,2',3,3',6	133	2,2',3,3',5,5'
38	3,4,5'	85	2,2',3,4,4'	134	2,2',3,3',5,6
39	3,4',5	86	2,2',3,4,5	135	2,2',3,3',5,6'
		87	2,2',3,4,5'	136	2,2',3,3',6,6'
Tetrachlorobiphenyls		88	2,2',3,4,6	137	2,2',3,4,4',5
40	2,2',3,3'	89	2,2',3,4,6'	138	2,2',3,4,4',5'
41	2,2',3,4	90	2,2',3,4',5	139	2,2',3,4,4',6
42	2,2',3,4'	91	2,2',3,4',6	140	2,2',3,4,4',6'
43	2,2',3,5	92	2,2',3,5,5'	141	2,2',3,4,5,5'
44	2,2',3,5'	93	2,2',3,5,6	142	2,2',3,4,5,6
45	2,2',3,6	94	2,2',3,5,6'	143	2,2',3,4,5,6'
46	2,2',3,6	95	2,2',3,5',6	144	2,2',3,4,5',6

No.	Structure
Hexachlorobiphenyls	
145	2,2',3,4,6,6'
146	2,2',3,4',5,5'
147	2,2',3,4',5,6
148	2,2',3,4',5,6'
149	2,2',3,4',5',6
150	2,2',3,4',6,6'
151	2,2',3,5,5',6
152	2,2',3,5,6,6'
153	2,2',4,4',5,5'
154	2,2',4,4',5,6'
155	2,2',4,4',6,6'
156	2,3,3',4,4',5
157	2,3,3',4,4',5'
158	2,3,3',4,4',6
159	2,3,3',4,5,5'
160	2,3,3',4,5,6
161	2,3,3',4,5',6
162	2,3,3',4',5,5'
163	2,3,3',4',5,6
164	2,3,3',4',5',6
165	2,3,3',5,5',6
166	2,3,4,4',5,6
167	2,3',4,4',5,5'
168	2,3',4,4',5',6
Hexachlorobiphenyls	
169	3,3',4,4',5,5'
Heptachlorobiphenyls	
170	2,2',3,3',4,4',5
171	2,2',3,3',4,4',6
172	2,2',3,3',4,5,5'
173	2,2',3,3',4,5,6
174	2,2',3,3',4,5,6'
175	2,2',3,3',4,5',6
176	2,2',3,3',4,6,6'
177	2,2',3,3',4',5,6
178	2,2',3,3',5,5',6
179	2,2',3,3',5,6,6'
180	2,2',3,4,4',5,5'
181	2,2',3,4,4',5,6
182	2,2',3,4,4',5,6'
183	2,2',3,4,4',5',6
184	2,2',3,4,4',6,6'
185	2,2',3,4,5,5',6
186	2,2',3,4,5,6,6'
187	2,2',3,4',5,5',6
188	2,2',3,4',5,6,6'
189	2,3,3',4,4',5,5'
190	2,3,3',4,4',5,6
191	2,3,3',4,4',5',6
192	2,3,3',4,5,5',6
193	2,3,3',4',5,5',6
Octachlorobiphenyls	
194	2,2',3,3',4,4',5,5'
195	2,2',3,3',4,4',5,6
196	2,2',3,3',4,4',5,6'
197	2,2',3,3',4,4',6,6'
198	2,2',3,3',4,5,5',6
199	2,2',3,3',4,5,6,6'
200	2,2',3,3',4,5',6,6'
201	2,2',3,3',4,5,5',6'
202	2,2',3,3',5,5',6,6'
203	2,2',3,4,4',5,5',6
204	2,2',3,4,4',5,6,6'
205	2,3,3',4,4',5,5',6
Nonachlorobiphenyls	
206	2,2',3,3',4,4',5,5',6
207	2,2',3,3',4,4',5,6,6'
208	2,2',3,3',4,5,5',6,6'
Decachlorobiphenyls	
209	2,2',3,3',4,4',5,5',6,6'

RESUME ET EVALUATION, CONCLUSIONS ET RECOMMANDATIONS

1 Résumé et évaluation

1.1 Introduction

Découverts vers la fin du siècle dernier, les biphényles polychlorés ou polychlorobiphényles (PCB) ont vu leur intérêt pour l'industrie rapidement reconnu en raison de leurs propriétés physiques. On les utilise dans le commerce depuis 1930 comme fluides diélectriques ou caloporteurs ainsi que pour diverses autres applications. Largement répartis dans l'environnement un peu par- tout dans le monde, ce sont des composés persistants qui s'accumulent dans les différentes chaînes alimentaires. L'exposition humaine aux PCB résulte en grande partie de la consommation d'aliments contaminés mais peut également résulter d'une inhalation ou d'une absorption percutanée sur les lieux de travail. Les PCB s'accumulent dans les tissus adipeux de l'homme et des animaux et peuvent déterminer des effets toxiques chez les uns et les autres, notamment en cas d'exposition répétée. Les effets pathologiques s'exercent principalement au niveau de la peau et du foie mais les voies digestives, le système immunitaire et le système nerveux peuvent également être atteints. Les polychlorodibenzofuranes (PCDF) qui constituent des contaminants des mélanges de PCB du commerce, ont une part importante dans la toxicité de ces composés. D'après les études effectuées sur des rongeurs, il semblerait que certains PCB soient cancérogènes et qu'ils puissent en outre agir comme promoteurs de la cancérogénicité d'autres produits chimiques.

Il est clair, d'après les données dont on dispose au sujet des polychlorobiphényles et des polychloroterphényles (PCT), qu'il vaudrait mieux que les denrées alimentaires soient totalement exemptes de ces composés. Il est cependant également clair que ramener à "zéro" ou presque l'exposition aux PCT ou aux PCB résultant de l'alimentation, conduirait à éliminer (par interdiction de la consommation) de grandes quantités d'aliments très importants comme

le poisson et plus encore, comme le lait maternel. C'est aux commissions scientifiques nationales et internationales qu'il appartient de décider du meilleur compromis entre une protection suffisante de la santé publique et la nécessité d'éviter de trop grandes pertes de denrées alimentaires.

Les données disponibles ne permettent pas de déterminer le niveau d'exposition à ces substances qui constituerait une garantie absolue de sécurité.

1.2 Identité et propiétés physiques et chimiques

Les PCB sont constitués de mélanges de dérivés aromatiques produits par chloration du biphényle en présence d'un catalyseur convenable. Ils répondent à la formule brute $C_{12}H_{10-n}Cl_n$, le nombre n d'atomes de carbone variant de 1 à 10.

Il y a théoriquement 209 homologues possibles mais seuls 130 d'entre eux sont probablement utilisés dans des produits commerciaux. En outre, les PCB peuvent contenir des impuretés consistant en polychlorodibenzofuranes (PCDF) et en quaterphényles chlorés. Ces impuretés sont assez stables et résistantes aux réactions chimiques dans les conditions normales. Tous les PCB sont lipophiles et très peu solubles dans l'eau. Il en résulte qu'ils pénètrent facilement dans la chaîne alimentaire et s'accumulent dans les tissus adipeux.

Les mélanges de PCB utilisés dans le commerce contiennent des polychlorodibenzofuranes à des concentrations qui vont de quelques mg/kg à 40 mg/kg. Il n'y a pas de dibenzo-*p*-dioxines polychlorées (PCDD) dans les PCB du commerce. Toutefois, en cas de mélange de PCB avec d'autres dérivés chlorés comme les chlorobenzènes utilisés dans les transformateurs, il arrive que l'on retrouve des PCDD à la suite d'incendies accidentels ou après incinération.

Les mélanges de PCB du commerce sont d'une couleur qui va du jaune clair au jaune foncé. Ils ne cristallisent pas, même à basse température, mais se transforment en résines solides. Dans la pratique les PCB sont plutôt ininflammables avec des points d'éclair assez élevés. Leur vapeur est plus lourde que l'air,avec lequel et ils ne forment pas de mélanges explosifs. Leur conductivité électrique est très faible mais leur conductivité thermique assez élevée et ils sont

extrêmement résistants à la décomposition thermique. Les PCB sont chimiquement très stables dans les conditions normales, toutefois, lorsqu'on les chauffe, ils peuvent donner naissance à d'autres composés toxiques comme les polychlorodibenzofuranes.

1.3 Méthodes d'analyse

Par suite de la découverte en 1966 de la présence de PCB dans des échantillons prélevés dans l'environnement, on s'est intéressé à leur analyse et à leur toxicité pour l'homme et son environnement.

En raison de la diversité des méthodes d'analyse utilisées, les données disponibles ne sont pas directement comparables; on peut néamoins les utiliser lorsqu'on se propose de prendre des mesures de contrôle et de prévention ainsi que pour une évaluation préliminaire des risques pour la santé et l'environnement imputables à ces produits.

Le dosage des PCB s'effectue par chromatographie en phase gazeuse avec détection par capture d'électrons, souvent sur colonne garnie, encore que l'on puisse recourir à des méthodes plus élaborées telles que la chromatographie sur colonne capillaire et la chromatographie en phase gazeuse couplée à la spectrométrie de masse, comme on l'a fait récemment pour identifier les différents homologues, améliorer la comparabilité des données analytiques issues de différentes sources et établir les bases d'une évaluation toxicologique.

Ces analyses nécessitent un programme important d'assurance de la qualité et, comme cela avait été recommandé, on a procédé à des étalonnages inter-laboratoires. La qualité et l'intérêt des données analytiques sont tributaires de la validité de l'échantillon et de la méthode d'échantillonnage. En outre, il est essentiel que le programme d'échantillonnage soit dûment planifié et documenté; on trouvera la description d'une technique détaillée d'échantillonnage dans le document WHO/EURO (1987).

1.4 Production et emplois

La production commerciale des PCB a commencé en 1930. Depuis, on les utilise largement dans le matériel électrique et également, en petites quantités, comme liquide ignifuge dans certains systèmes fonctionnant en circuit fermé.

A la fin de 1980, la production mondiale totale de PCB dépassait un million de tonnes et depuis, elle s'est poursuivie dans certains pays. Bien qu'on renonce de plus en plus à leur emploi et que la production soit soumise à des restrictions croissantes, de grandes quantités demeurent dans l'environnement, soit du fait de leur utilisation, soit sous la forme de déchets.

Ces dernières années, de nombreux pays industrialisés ont pris des mesures pour contrôler et limiter les rejets de PCB dans l'environnement. C'est probablement une recommandation émise par l'Organisation de Coopération et de Développement économiques (OCDE) en 1973 qui a joué un rôle prépondérant dans la promulgation de ces restrictions (OMS 1976; CIRC 1978; OCDE 1982). Depuis, les 24 pays membres de l'OCDE ont imposé des restrictions à la production, la vente, l'exportation et l'emploi des PCB et défini un système d'étiquetage de ces composés.

Actuellement, les émissions de PCB sont imputables à leur volatilisation à partir des décharges où sont enfouis des éléments de transformateurs, de condensateurs et autres déchets de ce genre, des boues d'égouts, des déversements accidentels ou non, des déchets de dragage et au rejet, dans des conditions défectueuses ou illégales, de ces produits sur des terrain à ciel ouvert. L'incinération des déchets industriels ou municipaux peut produire une pollution. La plupart des incinérateurs utilisés par les municipalités ne sont pas capables de détruire efficacement les PCB. L'explosion ou la surchauffe de transformateurs ou de condensateurs peut entraîner la libération de quantités importantes de PCB à proximité du lieu de l'incident.

Les PCB peuvent être transformés en polychlorodibenzofuranes par pyrolyse. Au laboratoire, c'est à des températures comprises entre 550 et 700 °C qu'on obtient le meilleur rendement en polychlorodibenzofuranes. Ainsi, l'incinération incontrôlée des PCB peut constituer une source importante de polychlorodibenzofuranes dangereux. Il est donc recommandé que la destruction des déchets contaminés par des PCB s'effectue dans des conditions soigneusement contrôlées, notamment en ce qui concerne la température d'incinération (supérieure à 1000 °C), le temps de séjour et la turbulence.

1.5 Transport, distribution et transformation dans l'environnement

Dans l'atmosphère, les PCB sont principalement présents en phase vapeur; la tendance a s'adsorber sur les particules augmente avec le degré de chloration. La présence quasi universelle des PCB donne à penser qu'ils sont transportés par l'atmosphère.

A l'heure actuelle, la principale source d'exposition aux PCB dans l'environnement général trouve son origine dans la redistribution de ces produits après leur passage dans le milieu. Cette redistribution s'effectue par volatilisation à partir du sol et de l'eau puis passage et transport dans l'atmosphère suivi d'un dépôt à sec ou en milieu humide (des PCB liés aux particules), les produits se revolatilisant ensuite pour continuer le cycle. Dans les précipitations, la concentration en PCB varie de 0,001 à 0,25 μg/litre. Comme la vitesse de volatilisation et de décomposition des PCB varient d'un homologue à l'autre, ce processus de redistribution entraîne une modification dans la composition des mélanges de PCB présents dans le milieu.

Dans l'eau, les PCB sont adsorbés sur les sédiments et autres matières organiques; les données d'expérience et de surveillance montrent que leur concentration dans les sédiments et les matières en suspension est plus élevée que dans la couche d'eau qui les surmonte. La forte adsorption des PCB sur les sédiments, notamment dans le cas des dérivés les plus chlorés, réduit leur vitesse de volatilisation. En se basant sur la solubilité dans l'eau et le coefficient de partage entre le *n*-octanol et l'eau, on peut estimer que les PCB les moins chlorés seront moins fortement sorbés que les homologues plus substitués. Bien que l'adsorption puisse immobiliser les PCB pendant des périodes relativement longues dans le milieu aquatique, on a montré de la désorption dans la couche d'eau environnante s'effectuait par voie abiotique ou biotique. Les sédiments aquatiques, qui contiennent de notables quantités de PCB, jouent donc le rôle à la fois de piège et de réservoir pour les organismes qui vivent dans ce milieu. On pense que l'essentiel de la charge en PCB du milieu est adsorbé sur les sédiments aquatiques.

La faible solubilité et la forte adsorption des PCB sur les particules de sol en limitent le lessivage; le lessivage est d'autant plus important que la substitution par le chlore est plus faible.

La décomposition des PCB dans l'environnement dépend de leur degré de substitution. En général, la persistance s'accroit parallèlement au degré de substitution. Dans l'atmosphère, la réaction en phase vapeur des PCB avec les radicaux hydroxyles (qui se forment par voie photochimique sous l'action du rayonnement solaire) pourrait constituer le principal processus de transformation. On estime que le temps de demi-réaction dans l'atmosphère varie de 10 jours pour un monochlorobiphényle à 1,5 année pour un heptachlorobiphényle.

Dans le milieu aquatique, l'hydrolyse et l'oxydation ne jouent pas un rôle important dans la décomposition des PCB. Dans le milieu, il semble que le seul processus viable de décomposition soit le photolyse. Cependant, les données expérimentales sont insuffisantes pour que l'on puisse en établir la vitesse et la degré dans l'environnement.

Les microorganismes décomposent assez rapidement le mono-, le di- et le trichlorobiphényle; cette dégradation étant plus grande dans le cas de tétrachlorobiphényles. Les biphényles plus substitués résistent à la biodégradation. La position des atomes de chlore sur le noyau biphényle influe de manière importante sur la vitesse de biodégradation. Les PCB qui contiennent des atomes de chlore en para sont plus facilement biodégradés. Les homologues les plus substitués subissent une biotransformation anaérobie par déchloration réductrice qui abaisse leur degré de substitution et les transforme en homologues plus facilement biodégradable par voie aérobie.

Le degré de bioaccumulation dans les tissus adipeux dépend de plusieurs facteurs : la durée et le niveau de l'exposition, la structure chimique du composé et notamment le nombre et la position des substituants. En général, ce sont les dérivés les plus substitués qui s'accumulent le plus facilement.

Les facteurs de bioconcentration des différents PCB qui ont été mesurés expérimentalement chez différentes espèces aquatiques (poisson, crevette, huitre) vont de 200 à 70 000 ou davantage. En haute mer, les PCB s'accumulent à des niveaux trophiques plus élevés

et l'on trouve davantage de biphényles fortement substitués chez les prédateurs qui se situent en fin de chaîne alimentaire.

Le passage des PCB du sol à la végétation se produit principalement par adsorption sur les surfaces externes des plantes terrestres; il n'y a guère de déplacement à l'intérieur de la plante.

1.6 Concentrations dans l'environnement et exposition humaine

Du fait de leur forte persistance et d'autres propriétés physiques et chimiques, les PCB sont présent dans tout l'environnement de la planète.

D'une façon générale, les concentrations dans l'air vont de 0,002 à 15 ng/m^3. Dans les zones industrielles, les valeurs sont plus élevées puisqu'elles peuvent être de l'ordre du μg/m^3. Dans les précipitations, elles vont de 1 ng à 250 ng/litre.

Dans les ambiances de travail, les concentrations dans l'air peuvent être beaucoup plus élevées. Dans certaines conditions, par exemple, dans le cas de la fabrication des transformateurs ou des condensateurs, on a pu observer des concentrations allant jusqu'à 1000 μg/m^3. En situation d'urgence, des concentrations atteignant même 16 mg/m^3 ont été mesurées. Après des incendies ou des explosions, la suie qui en résulte peut contenir de fortes concentrations de PCB. On en a ainsi trouvé jusqu'à 8000 mg/kg de suie. Dans ce cas d'ailleurs, ils s'accompagnent de polychlorodibenzofuranes. Dans les accidents impliquant des transformateurs contenant du chlorobenzène ainsi que des PCB, on trouve également des dioxines polychlorées.

Dans ces situations d'urgence, des particules de suie peuvent être ingérées ou inhalées ou encore contaminer la peau et entraîner une grave exposition du personnel. Quoiqu'il en soit, l'exposition de la population générale par la voie atmosphérique est très faible.

Les eaux de surface peuvent être contaminées par des PCB provenant de retombées atmosphériques, d'émissions directes à partir de sources ponctuelles ou de décharges. Dans certaines conditions, on a mesuré dans l'eau des concentrations allant jusqu'à 100-500 ng/litre. Dans les océans, on a observé des concentrations de 0,05 à 0,6 ng/litre.

Dans les régions non contaminées, l'eau de boisson contient moins de 0,01 ng de PCB/litre mais on a fait état de concentrations allant jusqu'à 5 ng/litre. Selon les régions et en fonction des conditions locales, le sol et les sédiments peuvent contenir des PCB à des concentrations allant de <0,01 à 2,0 mg/kg. Dans les régions polluées, les teneurs sont beaucoup plus fortes puisqu'elles peuvent atteindre 500 mg/kg.

Plusieurs milliers d'échantillons d'aliments divers ont été analysés au cours des années dans plusieurs pays à la recherche de contaminants et en particulier de PCB. La plupart des échantillons provenaient de produits déterminés, notamment du poisson ou d'autres aliments d'origine animale comme la viande et le lait. Il y a trois voies principales de contamination de la nourriture humaine :

a) passage de l'environnement aux poissons, oiseaux, bétail (par l'intermédiaire de la chaîne alimentaire) et récoltes;

b) migration dans les aliments à partir des matériaux de conditionnement (essentiellement au-dessous de 1 mg/kg, mais dans certains cas pouvant atteindre 10 mg/kg);

c) contamination directe des aliments destinés à l'homme ou aux animaux par suite d'un accident industriel.

La contamination des plus importantes denrées alimentaires par des PCB s'est située dans les limites suivantes: graisses animales 20-240 μg/kg; lait de vache 5-200 μg/kg; beurre 30-80 μg/kg; poisson 10-500 μg/kg - valeurs rapportées à la teneur en graisse. Certaines espèces de poissons (anguilles) ou produits tirés du poisson (foie de poisson ou huile de poisson) en contiennent des quantités beaucoup plus élevées, pouvant aller jusqu'à 10 mg/kg. Les concentrations relevées dans les légumes, les céréales, les fruits ainsi qu'un certain nombre d'autres produits sont inférieures à 10 μg/kg. Les principaux produits alimentaires dont il faut surveiller la contamination par les PCB sont le poisson, les fruits de mer, la viande, le lait et les produits laitiers. Les concentrations médianes dans le poisson observées dans divers pays sont de l'ordre de 100 μg/kg (par rapport aux graisses). Si l'on procède à des comparaisons, on constate que la teneur du poisson en PCB diminue lentement.

Les PCB s'accumulent dans les tissus adipeux et le lait maternel. Leur concentration dans les différents organes et tissus dépend de la teneur de ceux-ci en lipides, sauf dans le cas du cerveau. Les résidus de PCB présents dans les tissus adipeux de la population générale des pays industrialisés vont de - 1 à 5 mg/kg de graisses.

Dans les lipides du lait humain, la concentration moyenne en PCB totaux est de l'ordre de 0,5-1,5 mg/kg de lipides selon le lieu de résidence du sujet, son mode de vie et la méthode d'analyse utilisée. Les femmes qui habitent des zones urbaines fortement industrialisées et qui consomment beaucoup de poisson, surtout pêché dans des eaux très contaminées, peuvent avoir un lait contenant davantage de PCB.

Dans la plupart des cas, les extraits de PCB provenant d'échantillons prélevés dans l'environnement n'ont pas une composition analogue à celle des mélanges du commerce. On a également montré, en procédant par chromatographie en phase gazeuse à haute résolution, que la composition en homologues et la concentration relative des différents constituants présents dans les tissus adipeux et le lait maternel étaient très éloignées de celles des mélanges de PCB du commerce. L'analyse chromatographique des PCB présents dans les tissus adipeux humains et dans le lait maternel fait resortir une forte concentration de PCB fortement substitués tels que le 2,4,5,3',4'-pentachlorobiphényle, le 2,4,5,2',4',5'- hexachlorobiphényle, le 2,3,4,2',4',5'-hexochlorobiphényle, le 2,3,4,5,2',4',5'-heptachlorobiphényle et le 2,3,4,5,2',3',4'- heptachlorobiphényle. Quelques autres homologues sont présents en quantités beaucoup plus faibles; c'est le cas de la plupart des PCB coplanaires toxiques: le 3,4,3',4'-tétra-, le 3,4,5,3',4'-penta- et le 3,4,5,3',4,',5'-hexachlorobiphényle.

On a calculé que la dose quotidienne de PCB ingérée par les nourrissons à partir du lait maternel était de l'ordre de 4,2 μg/kg de poids corporel (5,2 μg/100 Kcal consommées) (WHO/EURO, 1988). La quantité moyenne totale de PCB ingérée avec le lait maternel au cours des six premiers mois de la vie est de 4,5 mg contre 357 mg pour le reste de l'existence (0,2 μg/kg et par jour ingéré avec la nourriture par une personne de 70 kg au cours d'une vie de 70 ans). La période d'allaitement correspond donc à 1,3 % de la dose totale ingérée au cours de l'existence, ce qui n'est pas très élevé compte

tenu de l'intérêt que présente l'allaitement au sein (WHO/EURO, 1988).

En s'appuyant sur les données de base ayant fait l'objet d'une évaluation, on peut calculer que l'apport de PCB par voie alimentaire ne dépasse pas 100 μg en moyenne par semaine, c'est-à-dire environ 14 μg/personne et par jour. Pour un individu de 70 kg, cela correspond à un apport quotidien maximum de l'ordre de de 0,2 μg/kg de poids corporel (WHO/EURO, 1988).

1.7 Cinétique et métabolisme

L'expérimentation animale rapportée dans la littérature comporte essentiellement l'exposition par voies orale, respiratoire et percutanée à des mélanges de PCB ou aux différents homologues. En général, les PCB sont rapidement absorbés, notamment pas la voie digestive après ingestion. Cette absorption se produit indiscutablement aussi chez l'homme mais les données concernant les taux d'absorption sont limitées.

D'après les résultats dont on dispose, il semble que la distribution des PCB dans l'organisme s'effectue selon un processus cinétique biphasé, les composés étant rapidement éliminés du sang et s'accumulant dans le foie et les tissus adipeux des divers organes. On est également fondé à penser que les PCB franchissent la barrière placentaire, s'accumulent dans le foetus et passent dans le lait maternel. Certaines études effectuées sur des sujets humains ont révélé une forte concentration de PCB dans l'épiderme mais la concentration dans l'encéphale était plus faible que ce que l'on aurait pu penser en s'appuyant sur la teneur en lipide de cet organe.

La mobilisation des PCB à partir des graisses dépend largement de la vitesse de métabolisation des différents homologues. L'excrétion est tributaire de la transformation des PCB en composés plus polaires: phénols, thiolo-conjugués et autres dérivés hydrosolubles. Les différentes voies métaboliques observées comportent une hydroxylation, une conjugaison avec des thiols et d'autres dérivés hydrosolubles avec parfois intervention d'intermédiaires réactifs comme les oxydes d'arène. On a montré que la vitesse de métabolisation dépendait de la structure des différents PCB et qu'elle était tributaire à la fois du degré de substitution et de la position de

substituants. Les métabolites polaires des PCB les plus chlorés sont éliminés principalement par la voie fécale mais l'excrétion urinaire n'est pas négligeable. Le lait maternel constitue une importante voie d'élimination. Certains PCB peuvent également être éliminés en passant dans le système pileux.

Les données cinétiques disponibles montrent que le demie-vie des divers PCB est très variable, ce qui peut s'expliquer par la variabilité du métabolisme en fonction de la structure, le tropisme tissulaire et d'autres facteurs qui influent sur la mobilisation à partir des sites d'accumulation.

Il n'y a pas toujours corrélation entre la persistance dans les tissus et une forte toxicité, et les différences de toxicité d'un homologue à l'autre peuvent être liées à des métabolites ou à des intermédiaires particuliers.

1.8 Effets sur les êtres vivants dans leur milieu naturel

Les PCB sont des contaminants universels du milieu et on les rencontre dans la plupart des compartiments de l'environnement—biotiques ou abiotiques—dans le monde entier. Etant donné que de nombreux pays en réglementent l'utilisation et la libération dans l'environnement, les décharges qui peuvent survenir sont beaucoup moins importantes que par le passé. Toutefois il semble, à la lumière des données disponibles, que le cycle des PCB dans le milieu entraîne une redistribution progressive de certains homologues en direction du milieu marin. Les dérivés les plus substitués sont ceux qui ont tendance à s'accumuler. Les PCB sont en grande partie adsorbés à la surface des particules de sédiments mais ils demeurent biodisponibles pour les divers organismes et leur accumulation se produit à des niveaux de plus en plus élevés de la chaîne alimentaire.

1.8.1 Etudes en laboratoire

Les mélanges de PCB exercent sur les microorganismes des effets qui varient énormément d'une espèce à l'autre puisque certaines sont affectées dès 0,1 mg/litre alors que d'autres supportent sans dommage des concentrations de 100 mg/litre; ces effets ne varient pas de façon régulière avec le degré de chloration des différents mélanges. La presque totalité des études consacrées aux effets des PCB sur les

organismes aquatiques portent sur des mélanges de type Aroclor. Les résultats en sont très variables et l'on ne peut pas établir de relation systématique entre le pourcentage de chloration ou les conditions écologiques et la toxicité, même dans le cas d'organismes très proches. Sur 96 heures dans des conditions statiques, les valeurs de CL_{50} varient de 12 µg/litre à > 10 mg/litre pour différentes espèces d'invertébrés aquatiques et divers mélanges de type Aroclor. Dans des conditions dynamiques, la toxicité des PCB augmente. En général, les mélanges les plus toxiques sont des Aroclors moyennement chlorés; en revanche, lorsque le degré de chloration est faible ou élevé, les mélanges sont moins toxiques. On le constate également dans le cas des effets sub-létaux, par example sur la reproduction de la daphnie. Les crustacés paraissent être plus sensibles aux PCB en période de mue. L'exposition de populations modèles à de l'Aroclor 1254 a permis d'observer une modification dans la structure de la communauté des espèces estuarielles, avec diminution du nombre d'amphipodes, de bryozoaires, de crabes et de mollusques, le nombre d'annélidés, de brachyopodes, de coelentérés, d'échinodermes et de némertiens restant inchangé. Les épreuves de toxicité aiguë portaient sur trop peu de ces groupes pour qu'on puisse en déduire si les résultats obtenus correspondent à des variations dans la sensibilité aux PCB ou à des différences dans les interactions entre espèces.

On constate des variations analogues dans la toxicité de ces mélanges chez les poissons pour lesquels la CL_{50} à 96 heures varie de 0,008 à 100 mg/litre. Des épreuves à long terme ont montré que, en cas d'exposition aiguë, notamment dans des conditions statiques, les données obtenues ne donnent qu'une valeur très sous-estimée de la toxicité des mélanges. La truite arc-en-ciel se révèle particulièrement sensible, les stades embryo-lavaires présentant une CL_{50} à 22 jours de 0,32 µg/litre dans le cas de l'Aroclor 1254, et la dose sans effet observable sur 22 jours étant de 0,01 µg/litre dans le cas des Aroclors 1016, 1242 et 1254.

Pour l'espèce *Pimephales promelas* on a obtenu pour la dose sans effet observable des valeurs respectivement égales à 5,4, 0,1, 1,8 et 1,3 µg/litre pour les Aroclors 1242, 1248, 1254 et 1260; dans le cas de *Pimelometopon pulcher,* on a obtenu une dose sans effet observable de 3,4 et 0,06 µg/litre respectivement pour les Aroclors 1016 et 1254.

On a pu confirmer expérimentalement des observations effectuées en milieu naturel et qui tendaient à montrer que des phoques se nourrissant de poissons ayant accumulé des PCB dans leur chair présentaient des troubles de la reproduction. Cet effet s'observe au cours des dernières phases du processus et se traduit par l'impossibilité pour l'embryon de s'implanter dans la paroi utérine.

Lors d'études à court terme, on a constaté que la toxicité de l'Aroclor pour les oiseaux augmentait avec le pourcentage de chloration; les CL_{50} par voie alimentaire à cinq jours allaient de 604 à >6000 mg/kg de nourriture. Les principaux effets sur la reproduction des oiseaux consistaient en une plus grande difficulté d'éclosion pour les oeufs et une certaine embryotoxicité. Ces effets ont continué malgré l'arrêt du traitement par les PCB, la concentration de PCB chez les poules diminuant par passage dans les oeufs. Rien n'indique que les Aroclors provoquent une amincissement de la coquille, tout du moins directement; toutefois l'effet qu'ils exercent sur la consommation de nourriture et le poids des poules agit indirectement sur l'épaisseur de la coquille des oeufs. des effets sub-létaux ont été signalés sur le comportement et les sécrétions hormonales.

Chez le vison, la toxicité aiguë de l'Aroclor diminue à mesure qu'augmente le pourcentage de chloration; la DL_{50} aiguë par voie orale se situant entre > 750 et 4000 mg/kg de poids corporel; le furet est moins sensible. L'Aroclor réduit la consommation de nourriture et par conséquent le taux de croissance des jeunes visons. L'administration d'Aroclor diminue et va même jusqu'à arrêter la reproduction des visons, qu'il soit administré directement ou par suite de l'ingestion de poisson contaminé dans la nature. Les Aroclors à forte teneur en chlore (notamment le 1254) ont un effet plus marqué. Lorsque cesse l'administration d'Aroclor par voie alimentaire, le taux de reproduction revient à la normale.

Les chauves-souris sont affectées par l'Aroclor libéré dans leur organisme à partir des graisses au cours de la migration.

Etant donné que la grande majorité des épreuves de laboratoire sur les organismes aquatiques et terrestres ont été effectuées avec des mélanges de PCB, il n'est pas possible d'attribuer à tel ou tel constituant en particulier tel ou tel type d'effets. De même, du fait que ces épreuves ont été exécutées dans des conditions qui ne

correspondent pas aux conditions écologiques réelles (c'est-à-dire à des concentrations supérieures à la solubilité des différents constituants et sans la présence de sédiment), il est difficile d'extrapoler les résultats de laboratoire à la situation réelle. Toutefois, on peut raisonnablement penser que tout effet sur les différentes populations d'organismes aquatiques ou terrestres qui pourrait s'observer à l'avenir, aura déjà été observé sur des populations locales antérieurement exposées à de fortes concentrations de PCB.

1.8.2 Etudes dans le milieu naturel

Les résultats qui tendraient à accréditer l'idée d'effets des PCB sur les populations de poissons dans leur milieu naturel ne sont pas concluants. L'interprétation des données recueillies sur les oiseaux au sein de leur milieu naturel est difficile, du fait de la présence de nombreux résidus provenant de divers organochlorés. La plupart des auteurs ont montré l'existence d'une corrélation entre les effets (embryotoxicité) observés et les résidus d'organochlorés totaux. Parmi tous les composés organochlorés présents ce sont les PCB qui offrent la meilleure corrélation avec les effets observés sur les embryons mais les résultats ne peuvent pas être considérés comme démontrant l'existence d'effets des PCB au sein du milieu naturel.

Un certain nombre de faits (confirmés en laboratoire) montrent que les PCB réduisent la capacité de reproduction des mammifères marins. Il s'agit d'une effet sur la nidation de l'embryon, mais qui peut également s'accompagner de modifications physiques au niveau des voies génitales des femelles.

Il n'est pas possible d'extrapoler les données obtenues en laboratoire lors d'études de toxicité aiguë et de toxicité à court terme, pour en tirer des conclusions relatives aux populations vivant dans le milieu naturel. L'incertitude qui règne quant aux effets attribués à tel ou tel constituant des mélanges de PCB, la méconnaissance de la nature exacte des homologues présents dans l'environnement et le caractère aléatoire de la biodisponibilité des PCB pour les divers organismes, sont autant de facteurs qui rendent difficile une estimation des l'exposition et des effets qui en découlent dans l'environnement. On peut considérer comme démontrés les effets observés sur les

populations de mammifères marins mais on ne sait pas encore à quels constituants des mélanges de PCB les attribuer.

Du fait de la tendance à la contamination croissante du milieu marin, il convient de rester très attentif aux effets exercés sur les organismes marins. Les observations effectuées en laboratoire ou dans le milieu naturel montrent clairement que la reproduction des populations de mammifères marins est affectée dans les zones fortement polluées. Dans les autres secteurs, il est probable que les résidus vont s'accroître, entraînant par voie de conséquence une augmentation des effets sur ces mammifères. On a moins de certitudes quant à la question de savoir si ces effets s'observeront chez d'autres organismes, notamment les oiseaux qui se nourrissent d'organismes marins.

A en juger par l'expérimentation en laboratoire, on pourrait s'attendre à des effets sur les populations et les communautés d'organismes inférieurs tel que le phytoplancton et le zooplancton. Il est difficile d'en apprécier l'ampleur et la portée. Selon les données actuellement disponibles, il ne semble pas que les poissons aient à souffrir des effets des PCB, encore qu'ils constituent une voie de contamination pour les mammifères et oiseaux piscivores.

Par exemple, les effets sur les espèces terrestres, les mammifères d'eau douce piscivores et chauves-souris migratrices qui avaient été signalés antérieurement, devraient être moins visibles à mesure que les résidus de PCB se redistribuent dans l'environnement. Les résidus présents dans les biotes terrestres ne semblent généralement guère être en recul à l'heure actuelle, mais on ne possède que peu ou pas de données sur les modifications affectant les différents homologues. La diminution des résidus de PCB fortement chlorés devrait être lente.

1.9 Effets sur les animaux d'expérience et les systèmes in vitro

1.9.1 Après une unique exposition

Après une unique exposition par voie orale, la toxicité aiguë des Aroclors est généralement faible chez le rat. Les jeunes animaux se révèlent plus sensibles (DL_{50}: 1,3-2,5 g/kg de poids corporel) que les adultes (DL_{50}: 4-11 g/kg de poids corporel). La DL_{50} la plus faible observées pour l'Aroclor 1254 chez le rat adulte a été de

1,0 g/kg de poids corporel. Aucune différence n'a été observée entre les sexes.

Chez les lapins, les valeurs de la DL_{50} dermique variaient de > 1,26 à < 2 g/kg de poids corporel en ce qui concerne l'Aroclor 1260 (dans l'huile de maïs) et de 0,79 à < 3,17 g/kg de poids corporel pour certains autres mélanges de PCB non dilués. Dans le cas d'une administration par voie intraveineuse, on a observé une DL_{50} de 0,4 g/kg de poids corporel pour l'Aroclor 1254 chez le rat; après injection intrapéritonéale, la DL_{50} chez la souris allait de 0,9 à 1,2 g/kg de poids corporel.

1.9.2 Après une exposition de brève durée

Après une exposition de brève durée par voie orale à des PCB purs ou en mélange, on a constaté que les principaux organes cibles chez les mammifères étaient le foie, la peau, le système immunitaire et le système reproducteur. Parmi les espèces étudiées c'est le singe Rhésus qui s'est révélé le plus sensible, les femelles l'étant davantage que les mâles. Des guenons adultes Rhésus exposées à un régime alimentaire contenant de l'Aroclor 1248 à raison de 2,5 mg/kg ou de 0,09 mg/kg d'Aroclor/kg de poids corporel et par jour, pendant six mois, ont présenté un accroissement du taux de mortalité, un retard de croissance, une alopécie, de l'acné, une hypertrophie des glandes de Meibom et peut-être une immunodépression. L'examen microscopique a révélé une infiltration graisseuse du foie avec des foyers de nécrose, une hyperplasie épithéliale et une kératinisation des follicules pileux. A plus fortes doses, des altérations histopathologiques ont également été observées dans d'autres tissus épithéliaux tels que les glandes sébacées et les glandes de Meibom, la muqueuse gastrique, la vésicule biliaire et le canal cholédoque, le lit inguéal et les améloblastes. Il y avait réduction des taux sériques de lipides totaux, de triglycérides et de cholestérol. L'exposition à des mélanges de PCB du commerce a entrainé l'augmentation de la concentration en lidipes totaux, en triglycérides et en cholestérol et/ou en phospholipides dans le foie. Parmi les différents PCB, ce sont le 3,4,3',4'-tétrachlorobiphényle, le 3,4,5,3',4',5'- ainsi que le 2,4,6,2',4',6'-hexachlorobiphényle qui se sont révélés les plus actifs. A la dose quotidienne de 0,2 mg/kg de poids corporel, l'Aroclor 1254 a également produit différents autres effets : lésions

lymphoréticulaires, chute de ongles, lésions gingivales, mais ni acné et ni alopécie. La dose sans effet observable en ce qui concerne la toxicité générale de l'Aroclor 1242 a été évaluée chez le singe Rhésus à 0,04 mg/kg de poids corporel par jour. Chez des singes Rhésus à la mamelle on a observé des effets relativement bénins après exposition à une dose beaucoup plus forte d'Aroclor 1248 (35 mg/kg de poids corporel par jour). C'est chez le rat qu'on a le mieux étudié les effets exercés au niveau du foie: il s'agit d'hypertrophie, de dégénérescence graisseuse, de prolifération du réticulum endoplasmique, de porphyrie, d'adénofibrose, d'hyperplasie des canaux biliaires, de kystes et des lésions précancéreuses et cancéreuses. Chez le rat et la souris, les effets des différents PCB ont été observés au niveau du foie, de la rate et du thymus, les homologues coplanaires étant les plus toxiques. Chez le singe, ces homologues ont produit, à des doses de 1-3 mg/kg de nourriture, des effets de nature et de gravité analogues à ceux que l'on avait observés après administration d'Aroclor 1242 à la dose de 100 mg/kg de nourriture et d'Aroclor 1248 à raison de 25 mg/kg de nourriture.

Après avoir été exposés par la voie dermique à certains PCB seuls ou en mélanges, des lapins et des souris ont présenté des effets au niveau de la peau et du foie, effets qui étaient analogues à ceux que l'on observe après administration par voie orale. Chez les lapins, on a également observé une atrophie du thymus, une réduction des centres germinaux des glanglions lymphatiques ainsi qu'une leucopénie.

1.10 Reproduction, embryotoxicité et tératogénicité

1.10.1 Reproduction et embryotoxicité

On n'a pas procédé à des études très complètes sur les effets génésiques ni sur la tératogénicité des PCB. Lors d'une étude de reproduction portant sur deux générations de rats, on a pu, en se basant sur des paramètres génésiques, établir dans le cas de l'Aroclor 1254 une dose sans effet observable de 0,32 mg/kg de poids corporel et de 7,5 mg/kg de poids corporel dans le cas de l'Aroclor 1260. Toutefois la dose la plus faible étudiée, qui était de 0,06 mg/kg de poids corporel, a entrainé une augmentation du poids relatif du foie chez les ratons juste sevrés.

Chez des singes Rhésus exposés à de l'Aroclor 1016, on a estimé à 0,03 mg/kg de poids corporel la dose sans effet observable en s'appuyant sur des paramètres génésiques. Toutefois, à cette dose, on constatait une réduction du poids de naissance et la dose la plus faible étudiée, soit 0,01 mg/kg de poids corporel, produisait une hyperpigmentation cutanée.

Pour l'Arcolor 1248 (contaminé par des polychlorodibenzofuranes), on a estimé à 0,09 mg/kg de poids corporel la dose sans effet observable chez le singe Rhésus, une année après l'arrêt de l'exposition.

1.10.2 Tératogénicité

Les études sur le rat et le singe dont on connaît les résultats ne font ressortir aucun effet tératogène après administration de PCB par voie orale aux animaux au cours de l'organogénèse. Chez le rat, on a estimé à 50 mg/kg de poids corporel la dose d'Aroclor 1254 sans effet observable relativement au poids des ratons, la dose la plus faible qui ait produit un effet étant de 2,5 mg/kg de poids corporel. L'effet retenu était la foetotoxicité (lésions au niveau des cellules folliculaires de la thyroïde).

Les épreuves de tératogénicité pratiquées sur des singes Rhésus, des souris et des rats au moyen de divers PCB n'ont pas permis de mettre en évidence une dose sans effet observable. Chez les singes Rhésus, une dose de 0,07 mg/k de poids corporel a entrainé des effets toxiques sur les mères (3,4,3',4'-tétrachlorobiphényle).

1.11 Mutagénicité

Les mélanges de PCB ne provoquent ni mutation ni lésion chromosomique dans divers systèmes d'épreuve. En revanche le 3,4,3',4'-tétrachlorobiphényle provoque des ruptures de chromosomes dans les lymphocytes humains *in vitro*. A fortes concentrations, les mélanges de PCB peuvent endommager la structure primaire de l'ADN, comme le montrent les ruptures constatées sur l'un des brin de l'ADN lors d'épreuves d'élution en milieu alcalin.

1.12

Cancérogénicité

L'interprétation des données relatives aux effets des mélanges de PCB du commerce sur l'animal est souvent compliquée du fait l'on manque de renseignements sur la présence ou la part relative des impuretés que constituent les chlorodibenzofuranes ainsi que sur la proportion des divers homologues dans le mélange.

Un certain nombre d'études de cancérogénicité à long terme ont été effectuées sur des rats et des souris à l'aide de mélanges tels que les Kanéchlors 300, 400 et 500, les Aroclors 1254 et 1260 ainsi que les Clophènes A30 et A60. Les Clophènes étaient exempts de chlorodibenzofuranes mais on ne possède aucune donnée sur la pureté des autres mélanges de PCB.

Chez des souris recevant une alimentation qui contenait du Kanéchlor 500 et de l'Aroclor 1254 à des doses d'environ 15 à 25 mg/kg de poids corporel, on a constaté une augmentation sensible des adénomes et/ou des carcinomes hépatocellulaires. Aucune tumeur maligne n'a pu être observée chez des souris traitées par du Kanéchlor 300 et du Kanéchlor 400.

Chez des rats exposés pendant plus d'une année à de l'Arcolor 1254 et 1260 ainsi qu'à du Clophène A30, on a observé une augmentation de la fréquence des adénomes et/ou des carcinomes hépatocellulaires. Le nombre plus élevé d'animaux porteurs de tumeurs observé dans ces études n'a pu cependant être considéré comme statistiquement significatif, à l'inverse de deux autres études. Ainsi, un accroissement de l'incidence des carcinomes hépatocellulaires (trabéculaires) et des adénocarcinomes a été mis en évidence après administration d'Arcolor 1260 et de Clophène A30 à la dose d'environ 5 mg/kg de poids corporel.

Les tumeurs hépatiques observées n'étaient pas de type invasif (il s'agissait de tumeurs bénignes ou de faible malignité, sans métastases) et elles n'abrégeaient pas la vie des animaux.

Dans certaines de ces études, on a observé une adénofibrose, des lésions prénéoplasiques et/ou des nodules néoplasiques dans le foie. Une épreuve portant sur l'Arcolor 1254 a permis de mettre en évidence un accroissement des lésions métaplasiques intestinales ainsi

que des adénocarcinomes dans la région glandulaire de l'estomac chez le rat.

L'hypothèse selon laquelle les PCB augmenteraient la cancérogénèse hépatique chez des rongeurs prétraités par des hépatocancérogènes est étayée par de nombreux faits. Toutefois l'activité initiatrice des mélanges de PCB chez les rongeurs n'est guère attestée. Sur la base des études de génotoxicité publiées, on peut conclure que les mélanges de PCB ne sont pas génotoxiques. Il s'ensuit que le lien entre la présence de tumeurs hépatiques et l'administration de PCB chez des rongeurs peut être attribué à des mécanismes épigénétiques entraînant une prolifération des cellules hépatiques et autres manifestations d'hépatotoxicité—autrement dit, il serait possible d'évaluer la toxicité des PCB en envisageant l'existence d'un seuil de toxicité. Il faut donc étudier la possibilité, pour les PCB, de favoriser la cancérogénèse dans des tissus autres que les tissus hépatiques, chez les animaux préexposés à divers cancérogènes spécifiques de tel ou tel tissu. Il est possible que l'activité anticancérogène des PCB, observée dans certaines études au cours desquelles on les avait administrés à des animaux pendant ou avant l'administration de cancérogènes, soit liée au fait que les PCB sont capables d'induire les enzymes microsomiques, d'où une stimulation du processus de détoxication.

Globalement, il est justifié d'être prudent dans l'extrapolation à l'homme des données obtenues sur l'animal en ce qui concerne le pouvoir cancérogène des PCB.

1.13 Etudes spéciales

Les lésions induites après exposition à divers PCB purs ou en mélange, s'observent au niveau du foie, de la peau, du système immunitaire, de l'appareil reproducteur, et elles s'accompagnent d'oedème et de troubles fonctionnels des voies digestives et de la glande thyroïde.

Les PCB sont capables d'induire diverses enzymes hépatiques. On a pu le mettre en évidence chez des rats, des souris, des cobayes, des lapins, des chiens et des singes en ce qui concerne les Aroclors 1248, 1254 et 1260 ainsi que le Kanéclor 400 (induction du cytochrome P450 et P448). Le pouvoir enzymo-inducteur des PCB augmente avec la teneur en chlore de la molécule. Il dépend également de la

composition du mélange, les PCB dans lesquels le chlore se trouve en *para-* et en *meta-* provoquant l'induction du P450. En ce qui concerne l'induction de l'AHH, la position des atomes de chlore semble plus importante que le degré de chloration. Les inducteurs les plus actifs de l'AHH sont les PCB dont les deux positions *para-* et au moins deux positions *meta-* sont substituées par du chlore. Des variations interspécifiques distinctes ont été mises en évidence. C'est avec l'Aroclor 1260 administré à des rats Osborn-Mendel que l'on a obtenu la dose sans effet observable la plus faible (0,025 mg/kg de poids corporel).

En ce qui concerne les effets sur le système endocrinien, il s'agit de modifications touchant la liaison aux récepteurs hormonaux et l'équilibre des hormones stéroïdiennes. On également des preuves directes et indirectes d'une faible activité oestrogénique exercée par les divers Arcolors. Chez des rats exposés pendant 36 semaines à une régime alimentaire contenant 75 mg d'Aroclor 1242/kg de nourriture, on a constaté une diminution du taux d'hormones gonadiques et une augmentation du poids relatif des testicules. Chez des souris femelles exposées pendant trois semaines à de l'Aroclor 1254 administré dans leur nourriture à raison de 25 mg/kg, on a observé une diminution des taux de corticostéroïdes plasmatiques sans augmentation concomitante du poids des surrénales. En revanche, chez une autre souche qui avait reçu pendant deux semaines une nourriture contenant 200 mg de ce mélange par kg, on a observé un accroissement du poids des surrénales.

On a constaté chez diverses espèces animales, que les mélanges de PCB exerçaient un effet immunodépresseur, les espèces les plus sensibles à cet égard étant les singes et les lapins. La dose sans effet observable la plus faible était de 0,1 mg/kg de poids corporel chez le singe et de 0,18 mg/kg de poids corporel chez le lapin.

Des souris ayant reçu une seule dose orale de 500 mg d'Aroclor 1254 par kg de poids corporel ont présenté une dépression de l'activité motrice. Cet effet s'explique probablement par une inhibition du captage et de la libération des neurotransmetteurs.

On a constaté que les mélanges de PCB diminuaient la concentration en vitamines A et B1 dans le sang et le foie de rats. Chez des rats et

des souris exposés à des mélanges de PCB on a observé une diminution des taux de vitamines A, B1, B2 et B6.

1.14 Facteurs qui modifient la toxicité et le mode d'action

Les PCB du commerce suscitent toute une série de réactions toxiques qui ressemblent en partie à celles qu'entraînent les polychlorodioxines et les polychlorodibenzofuranes. En outre, les relations structure-activité analogues observées parmi les divers PCB homologues, pour ce qui concerne les réactions toxiques qu'ils suscitent et leur aptitude à induire l'AHH dépendante du cytochrome P448, indiquent que les PCB ressemblent plus ou moins à des stéréoisomères de la 2,3,7,8,-TCDD sont les plus actifs. Ces observations laissent penser qu'il existe un mécanisme commun à la base de l'affinité de ces composés pour la protéine réceptrice de l'AH du cytosol. On a proposé des facteurs d'équivalence toxique pour la 2,3,7,8,-TCDD et ces PCB coplanaires. On n'a pas suffisamment étudier la nature des interactions probables entre les PCB et les polychlorodibenzofuranes ou les polychlorodibenzodioxines. Etant donné que les PCB sont capables de stimuler l'activité des enzymes microsomiques, ils peuvent avoir une influence sur l'action d'autres substances chimiques dont le métabolisme est sous la dépendance de ces enzymes. D'autres PCB, qualifiés de coplanaires, peuvent entraîner des manifestations toxiques plus subtiles. En outre certains PCB, en particulier ceux qui sont les moins substitué, peuvent être métabolisés sous forme d'intermédiaires de type oxyde d'arène et de métabolites méthylsulfonylés.

1.15 Effets sur l'homme

L'évaluation toxicologique des PCB pose de nombreux problèmes. Les PCB se présentent en général sous la forme de mélanges de nombreux composés et nombre des données relatives à la toxicité des PCB reposent sur l'étude de ces mélanges. Certains constituants des mélanges se décomposent plus facilement dans l'environnement que d'autres. Ainsi, la population générale peut-elle être exposée à des mélanges qui diffèrent de ceux auxquels sont exposés les travailleurs qui manipulent des PCB.

C'est principalement par contamination de la nourriture (organismes aquatiques, produits carnés et laitiers) que la population générale est exposée aux PCB. La dose journalière ingérée de PCB est de l'ordre de quelques microgrammes par personne dans la plupart des pays industrialisés. Ce type d'exposition n'entraîne pas de manifestations toxiques. Les nourrissons sont exposés aux PCB par l'intermédiaire du lait maternel. Par cette voie, la dose ingérée peut atteindre quelques microgrammes par kg de poids corporel et par jour.

On éprouve beaucoup de difficulté à évaluer les effets qu'exercent séparément sur la santé humaine les PCB, les polychlorodibenzofuranes et les polychlorodibenzodioxines étant donné que les polychlorodibenzofuranes sont de fréquents contaminants des mélanges de PCB et qu'occasionnellement, on a mis en cause la présence de polychlorodibenzodioxines dans les accidents survenus avec certains mélanges de PCB. On a montré que les PCB du commerce étaient contaminés par des polychlorodibenzofuranes et que, par conséquent, il était délicat dans bien des cas de savoir si les effets constatés sont attribuables aux PCB eux-mêmes ou aux polychlorodibenzofuranes qui sont beaucoup plus toxiques. Par conséquent, nombre de données tirés d'épisodes importants d'intoxication humaine, par exemple ceux de Yusho, de Yu-Cheng, etc. correspondent probablement à une exposition aux PCB et aux polychlorodibenzofuranes.

Les signes d'intoxication observés chez les malades de Yusho et de Yu-Cheng consistaient en hypersécrétion des glandes de Meibom au niveau des yeux, en oedèmes palpébraux et en pigmentation des ongles et des muqueuses, parfois associés à de la fatigue, des nausées et des vomissements. On observait généralement ensuite une hyperkeratose et un brunissement de la peau avec une hypertrophie folliculaire et des éruptions acnéiformes. Par ailleurs, on a également observé des oedèmes des bras et des jambes, une hypertrophie du foie avec troubles hépatiques, des troubles du système nerveux central et des troubles respiratoires évoquant la bronchite ainsi que des modifications dans l'état immunitaire des patients. Chez les enfants des malades de Yusho et de Yu-Cheng, on a observé une réduction de la croissance, une hyperpigmentation de la peau et des muqueuses, une hyperplasie gingivale, des paupières oedématiées avec xérophthalmie, la présence de dents dès la naissance, une calcification

anormale du crâne, des pieds bots en piolet et une forte incidence de faibles poids de naissance. Il n'a pas été possible de se prononcer de façon définitive quant à l'existence d'une corrélation entre l'exposition et l'apparition de tumeurs malignes chez ces malades car le nombre de décès était trop faible. Toutefois, on a observé une augmentation statistiquement significative, chez les hommes, de la mortalité par cancer et plus spécialement cancer du foie et du poumon.

En cas d'exposition sur les lieux de travail, on observe quelques heures plus tard des éruptions cutanées. En outre il est arrivé qu'après l'exposition à de fortes concentrations de PCB, se produisent des démangeaisons, des sensations de brûlure, une irritation de la conjonctive, une pigmentation des doigts et des ongles et une chloracné. La chloracné est une des manifestations qui reviennent le plus fréquemment chez les travailleurs exposés aux PCB. Outre ces signes cutanés d'intoxication, divers auteurs ont observé des troubles hépatiques, une immunodépression, une irritation passagère des muqueuses respiratoires, des effets neurologiques, psychologiques ou psychosomatiques aspécifiques tels que céphalées, vertiges, dépression, troubles du sommeil et de la mémoire, nervosité, fatigue et impuissance. Ce qu'on peut conclure de tout cela c'est qu'une exposition professionnelle permanente à de fortes concentrations de PCB et de polychlorodibenzofuranes peut entraîner des effets sur la peau et le foie.

Deux importantes études de mortalité ont été effectuées sur des cohortes de travailleurs. Après exposition à de l'Aroclor 1254, 1242 et 1016, on a observé une augmentation de la mortalité par cancer du foie et de la vésicule biliaire dans le cas d'une étude ou par cancer en général et plus particulièrement cancer des voies digestives dans le cas d'une autre étude. Aucune des études épidémiologiques disponibles ne donne de preuves concluantes d'une association entre l'exposition aux PCB et l'accroissement de la mortalité par cancer, du fait du trop petit nombre de décès dans la population exposée, de l'absence de relation dose-réponse et des impuretésprésents dans les mélanges de PCB.

2 Conclusions

2.1 Distribution

Du fait de leurs propriétés physiques et chimiques, les PCB sont dispersés dans tout l'environnement à l'échelle planétaire.

Les PCB sont presque universellement présents chez tous les êtres vivants dans leur milieu naturel et s'y accumulent facilement. On a également mis en évidence une bioconcentration le long de la chaîne alimentaire.

Les PCB les plus fortement chlorés sont ceux qui s'accumulent le plus.

2.2 Effets sur les animaux d'expérience

Les résultats tirés de l'expérimentation animale incitent à penser que les PCB ont un effet immunodépresseur comme le montre l'étude de leurs effets macroscopiques sur la fonction immunitaire (poids de la rate, poids du thymus et numération lymphocytaire). En ce qui concerne l'Aroclor 1248, la dose sans effet observable pour le singe a été évaluée à 100 μg/kg et à < 100 μg/kg de poids corporel dans le cas de l'Aroclor 1254. Il semble que l'effet immunosupresseur soit spécifique de tel ou tel PCB en particulier.

On n'observe en général d'effets toxiques sur la reproduction qu'aux doses qui produisent une intoxication de la mère. Les animaux nouveau-nés nourris avec le lait contaminé de leur mère (notamment chez le singe et les autres animaux utilisés comme modèles) semblent être particulièrement sensibles aux PCB et présentent, à côté d'autres symptômes toxiques, une réduction de la croissance. La dose d'Aroclor 1016 sans effet observable sur la reproduction est de 30 μg/kg de poids corporel chez le singe. Il n'a pas été possible d'en établir une dans le cas de l'Aroclor 1248.

Les PCB ne sont pas génotoxiques et rien n'indique qu'ils jouent le rôle d'initiateurs tumoraux. Ils n'ont pas non plus d'activité tumoro-promotrice. On peut en conclure que pour évaluer la toxicité des des mélanges de PCB, il est possible d'envisager l'existence d'un effet de seuil.

2.3 Effets sur l'homme

L'exposition de la population générale aux PCB s'effectue principalement par l'intermédiaire des aliments. Les nourrissons sont exposés par l'intermédiaire du lait maternel.

deux importants épisodes d'intoxication ont été observés au Japon (Yusho) et à Taïwan (Yu-Cheng). Les principaux symptômes observés ont été fréquemment attribués à la présence de contaminants dans les mélanges de PCB et notamment de polychlorodibenzofuranes. Le Groupe de travail en a conclu que ces symptômes pouvaient être dus à une exposition concomitante aux PCB et aux polychlorodibenzofuranes. Toutefois, certain, symptômes notamment des effets respiratoires chroniques, pourraient être dus plus particulièrement aux métabolites méthylsulfoniques de certains PCB.

2.4 Effets sur l'environnement

Si des effets ont été signalés sur des populations locales d'oiseaux, l'effet le plus important des PCB sur les êtres vivants dans leur milieu naturel consiste principalement en une réduction de la capacité de reproduction des mammifères marins. On a observé cet effet principalement dans des mers semi-fermées et constaté qu'il conduisait, localement du moins, à une réduction du nombre de ces mammifères. Comme on peut s'attendre à ce que les résidus de PCB présents dans l'environnement se redistribuent progressivement par l'intermédiaire du milieu marin, on peut penser qu'à l'avenir, les mammifères marins seront encore plus menacés.

3 Recommandations

- Il est recommandé de parvenir à un accord international sur les méthodes d'analyse afin d'améliorer la comparabilité des résultats des programmes de surveillance. Il faudrait continuer à mettre au point les méthodes d'analyse spécifiques de tel ou tel PCB, sans toutefois méconnaître la valeur des analyses basées sur les mélanges.
- Afin d'assurer la fiabilité des données d'analyse, il est fortement recommandé de procéder à un contrôle de qualité

interlaboratoires. Il est également recommandé de créer un réseau international d'encadrement et de soutien technique destiné à aider les pays en développement à participer aux activités de contrôle.

- Afin d'améliorer la précision dans l'évaluation du risque que représentent les PCB, il est recommandé d'effectuer des études à long terme sur des homologues déterminés ainsi que sur le mode d'action des divers constituants des mélanges, plus particulièrement en ce qui concerne leur activité tumoro-promotrice.

- Des études épidémiologiques visant à mieux évaluer le risque pour les nouveau-nés sont nécessaires, car ces derniers constituent le groupe le plus vulnérable de la population générale du fait qu'ils sont fortement exposés aux PCB par l'intermédiaire du lait maternel.

- Il conviendrait de mettre au point, pour les futures études épidémiologiques, des marqueurs biologiques sensibles et spécifiques concernant certaines des manifestations les plus subtiles de la toxicité des PCB (effets sur la reproduction, effets immunologiques et effets neurologiques).

- L'élimination des PCB doit s'effectuer par incinération dans des installations convenablement conçues et exploitées qui garantissent le maintien de températures élevées (plus de 1000 °C), du temps de séjour et de la turbulence nécessaires pour que la décomposition des molécules soit complète.

- Il faudrait étudier les moyen d'éliminer les PCB déjà présents dans les décharges contrôlées.

- Il convient d'inciter les responsables à assurer la surveillance des PCB dans l'environnement, la faune et la flore à l'échelle mondiale, afin de suivre la redistribution prévisible des résidus qui s'y trouvent.

- La contamination par les PCB peut réduire la capacité de reproduction des mammifères marins. Il faudrait inciter les responsables à entreprendre des études sur les effectifs de cétacés et leur capacité à se reproduire, tout en poursuivant les recherches

visant à établir quels sont les PCB qui sont responsables de ces effets.

RESUMEN Y EVALUACION, CONCLUSIONES Y RECOMENDACIONES

1. Resumen y evaluación

1.1 Introducción

Los bifenilos policlorados (BPCs) se descubrieron a finales del siglo pasado y se reconoció pronto su utilidad para la industria, debido a sus propiedades físicas. Se utilizan comercialmente desde 1930 como fluidos dieléctricos e intercambiadores de calor y en otras aplicaciones. Se encuentran ampliamente distribuidos en el medio ambiente de todo el mundo, son persistentes y se acumulan en la cadena alimentaria. La exposición humana a los BPCs se debe fundamentalmente al consumo de alimentos contaminados, pero también a la inhalación y a la absorción cutánea en los lugares de trabajo. Los BPCs se acumulan en el tejido adiposo de los seres humanos y de los animales, causando efectos tóxicos a ambos, particularmente en el caso de exposiciones repetidas. La patología se manifiesta sobre todo en la piel y el hígado, aunque también están expuestos el tracto gastrointestinal, el sistema inmunitario y el sistema nervioso. Los dibenzofuranos policlorados (BFPCs), que se encuentran como contaminantes en mezclas comerciales de BPCs, contribuyen de manera significativa a su toxicidad. Los resultados de los estudios realizados en roedores indican que algunos compuestos parecidos a los BPCs pueden ser carcinógenos y fomentar la carcinogenicidad de otros compuestos químicos.

De los datos disponibles de los bifenilos policlorados (BPCs) y los terfenilos policlorados (TPCs) es evidente que, en una situación ideal, sería preferible no tener en absoluto estos compuestos en los alimentos. Sin embargo, es igualmente claro que la reducción a cero o a un nivel próximo de la exposición a los BPCs o los TPCs en fuentes alimentarias significaría la eliminación (prohibición del consumo) de grandes cantidades de alimentos importantes, como el pescado, pero sobre todo la leche materna. Son los comités científicos nacionales e internacionales los que deben establecer el debido

equilibrio entre lo que se ha de hacer para conseguir un grado apropiado de protección de la salud pública y evitar pérdidas excesivas de alimentos.

A partir de los datos disponibles, no se pueden establecer niveles de exposición a los BPCs o los TPCs que puedan considerarse de garantía absoluta de inocuidad.

1.2 *Identidad y propiedades físicas y químicas*

Los BPCs son mezclas de productos químicos aromáticos, que se obtienen por cloración del bifenilo en presencia de un catalizador adecuado. La fórmula química de estos compuestos se representa como C_{12} H_{10-n} Cl_n, donde n es un número de átomos de cloro comprendido entre 1 y 10.

En teoría existen 209 compuestos análogos, pero sólo 130 tienen probabilidad de aparecer en productos comerciales. Además, los BPCs pueden contener dibenzofuranos policlorados (DFPCs) y cuarterfenilos clorados como impurezas. En condiciones normales, estas impurezas son relativamente estables y resistentes a las reacciones químicas. Todos los compuestos afines a los BPCs son lipófilos y tienen una solubilidad en agua muy baja. En consecuencia, se introducen fácilmente en la cadena alimentaria y se acumulan en el tejido adiposo.

Las mezclas comerciales de BPCs contienen DFPCs en concentraciones que oscilan entre unos pocos mg/kg y 40 mg/kg. En los BPCs comerciales no se encuentran dibenzo-*p*-dioxinas policloradas (DDPCs). Sin embargo, en casos de incendios accidentales y durante la incineración se pueden encontrar DDPCs cuando están mezcladas con otros compuestos clorados, como los clorobencenos utilizados en los transformadores.

Las mezclas comerciales de BPC tienen un color que va del amarillo claro al oscuro. No cristalizan, ni siquiera a baja temperatura, sino que se convierten en resinas sólidas. Los BPCs son prácticamente pirorresistentes, con una temperatura de inflamabilidad bastante elevada. Forman vapores más densos que el aire, pero no dan lugar a mezclas explosivas con éste. Su conductividad eléctrica es muy baja, la térmica es bastante alta y tienen una resistencia muy elevada

a la degradación térmica. En condiciones normales, los BPCs son químicamente muy estables, pero cuando se calientan pueden producir otros compuestos tóxicos, como los DFPCs.

1.3 Métodos analíticos

En 1966, a partir del descubrimiento de BPCs en muestras obtenidas del medio ambiente, aumentó el interés por el análisis de estos compuestos y por su toxicidad para la especie humana y su medio ambiente.

Los datos disponibles no son directamente comparables debido, a diferencias en la metodología analítica; no obstante, se pueden utilizar para establecer medidas de control y prevención y para la evaluación preliminar de los riesgos para la salud y el medio ambiente asociados a estos compuestos.

Los BPCs se han determinado mediante técnicas de cromatografía de gases con captura electrónica, a menudo utilizando columnas de relleno, aunque en estudios recientes se han empleado métodos más complejos, como la cromatografía en columna capilar y la de gases combinada con la espectrometría de masas, para identificar por separado los distintos compuestos análogos, mejorar la comparabilidad de los datos analíticos de fuentes diferentes y establecer una base para la evaluación de la toxicidad.

Para realizar estos análisis es necesario un amplio programa de garantía de la calidad, y se han realizado y recomendado estudios de intercalibración. La calidad y utilidad de los datos analíticos dependen decisivamente de la validez de la muestra y de que el muestreo sea adecuado. Por otra parte, es imprescindible contar con un programa de muestreo planificado y bien documentado. En la publicación WHO/EURO (1987) se describe con detalle un procedimiento de muestreo.

1.4 Producción y usos

La producción comercial de los BPCs comenzó en 1930. Se han utilizado ampliamente en equipo eléctrico, y en volúmenes más pequeños como líquido pirorresistente en sistemas de régimen cerrado.

Al final de 1980, la producción mundial total de BPCs era superior a un millón de toneladas y, desde entonces, la producción ha continuado en algunos países. A pesar de la creciente retirada del uso y de las restricciones sobre la producción, en el medio ambiente sigue habiendo cantidades muy elevadas de estos compuestos, bien en uso o como desecho.

En los últimos años, muchos países industrializados han adoptado medidas para controlar y limitar el flujo de BPCs hacia el medio ambiente. El factor decisivo que ha llevado a estas restricciones ha sido probablemente una recomendación de 1973 de la Organización de Cooperación y Desarrollo Económicos (OCDE) (OMS, 1976; CIIC, 1978; OCDE, 1982). Desde entonces, los 24 países miembros de la OCDE han limitado la fabricación, la venta, la importación, la exportación y el uso de BPCs, además de establecer un sistema de etiquetado de estos productos.

Entre las fuentes actuales de liberación de BPCs figuran la volatilización de vertederos que contienen transformadores, condensadores y otros residuos con BPCs, aguas residuales, fangos cloacales, derrames y desechos de dragado, y la eliminación inadecuada (o ilegal) en zonas abiertas. Se puede producir contaminación durante la incineración de desechos industriales y municipales. La mayoría de los incineradores municipales no son eficaces en la destrucción de los BPCs. La explosión o el sobrecalentamiento de transformadores y condensadores pueden liberar cantidades significativas de BPCs al entorno local.

Los BPCs se pueden convertir en DFPCs en condiciones pirolíticas. En las condiciones de laboratorio, la máxima producción de DFPCs se obtuvo a temperaturas entre 550 °C y 700 °C. Así pues, la combustión incontrolada de BPCs puede ser una importante fuente de los peligrosos DFPCs. Por lo tanto, se recomienda un cuidadoso control de la destrucción de desechos contaminados con BPCs, especialmente en relación con la temperatura de combustión (por encima de los 1000 °C), el tiempo de permanencia y la turbulencia.

1.5 *Transporte, distribución y transformación en el medio ambiente*

Los BPCs se encuentran en la atmósfera principalmente en fase de vapor; la tendencia a adsorberse sobre partículas aumenta con el grado de cloración. La distribución prácticamente universal de los BPCs parece indicar que los transporta el aire.

En la actualidad, la principal fuente de exposición en el medio ambiente general parece ser la redistribución de los BPCs que previamente se han introducido en él. Dicha redistribución se deriva de su volatilización del suelo y el agua para pasar a la atmósfera, con el posterior transporte por el aire y la eliminación de la atmósfera mediante sedimentación húmeda o seca (de los BPCs unidos a partículas), para luego volver a volatilizarse. Su concentración en las precipitaciones oscila entre 0,001 y 0,25 μg/litro. Dado que los ritmos de volatilización y degradación de los BPCs varían según los compuestos, esta redistribución produce una alteración en la composición de las mezclas de BPC presentes en el medio ambiente.

En el agua, los BPCs se adsorben en los sedimentos y otra materia orgánica; los datos experimentales y de supervisión han puesto de manifiesto que las concentraciones de BPCs en los sedimentos y en la materia en suspensión son más elevadas que en las masas de agua correspondientes. Una fuerte adsorción en el sedimento, especialmente en el caso de BPCs con un grado elevado de cloración, disminuye la tasa de volatilización. Sobre la base de su solubilidad en agua y los coeficientes de reparto *n*-octanol-agua, los compuestos del grupo del BPC menos clorados se adsorberán con menos fuerza que los isómeros con más átomos de cloro. Aunque la adsorción puede inmovilizar los BPCs en el medio acuático durante períodos relativamente largos, se ha demostrado que la liberación a la masa del agua se produce tanto por vía abiótica como biótica. Por consiguiente, las importantes cantidades de BPCs en los sedimentos acuáticos pueden actuar como sumideros del medio ambiente y como depósito de estos compuestos para los organismos. Se ha estimado que la mayor parte de los BPCs presentes en el medio ambiente está en el sedimento acuático.

La baja solubilidad y la fuerte adsorción de los BPCs en las partículas del suelo limitan la lixiviación; los compuestos con menor grado de

cloración tienen una tendencia mayor a la lixiviación que los más clorados.

La degradación de los BPCs en el medio ambiente depende del grado de cloración del bifenilo. En general, la persistencia de los isómeros de BPC aumenta con el grado de cloración. En la atmósfera, el proceso de transformación predominante puede ser la reacción en fase de vapor de los BPCs con radicales hidroxilos (formados fotoquímicamente por la luz solar). La semivida estimada de esta reacción en la atmósfera oscila entre unos 10 días para el monocloro-bifenilo y año y medio para el heptaclorobifenilo.

En el medio acuático, la hidrólisis y la oxidación no degradan de manera significativa los BPCs. La fotólisis parece ser el único proceso abiótico de degradación viable en el agua; sin embargo, los datos experimentales disponibles no son suficientes para establecer su proporción o importancia en el medio ambiente.

Los microorganismos degradan los bifenilos monoclorados, diclorados y triclorados de manera relativamente rápida, y más lentamente los bifenilos tetraclorados, mientras que los bifenilos con mayor grado de cloración son resistentes a la biodegradación. La posición de los átomos de cloro en el anillo bifenilo parece ser importante para determinar la tasa de biodegradación. Esta se da con preferencia en los compuestos que contienen átomos de cloro en posiciones -para. Los compuestos más clorados experimentan una transformación anaerobia, mediante un decloración reductora, para dar BPCs con menos átomos de cloro, que pueden luego continuar la biodegradación mediante procesos aerobios.

El grado de bioacumulación en el tejido adiposo depende de varios factores: la duración y el nivel de la exposición, la estructura química del compuesto y la posición y modelo de la sustitución. En general, se acumulan más fácilmente los compuestos con mayor número de sustituyentes de cloro.

Los factores de bioconcentración de distintos BPCs determinados experimentalmente en las especies acuáticas (peces, camarones, ostras) varía entre 200 y 70 000 o más. En mar abierto, hay bioacumulación de BPCs en los niveles tróficos más elevados, con una mayor proporción de los bifenilos más clorados en los depredadores que ocupan un lugar más alto en la escala.

La transferencia de los BPCs del suelo a la vegetación tiene lugar principalmente por adsorción en la superficie externa de las plantas terrestres; los desplazamientos que tienen lugar son escasos.

1.6 Niveles medioambientales y exposición humana

Debido a su elevada persistencia y sus demás propiedades físicas y químicas, los BPCs están presentes en el medio ambiente en todo el mundo.

En general, sus concentraciones en el aire son de 0,002 a 15 ng/m^3. En zonas industriales los niveles son más altos (hasta del orden de μg/m^3). En el agua de lluvia y la nieve alcanzan valores entre no detectables (1 ng) y 250 ng/litro.

En el medio de trabajo, los niveles en el aire pueden ser mucho más elevados. En ciertas condiciones, como por ejemplo en la fabricación de transformadores y condensadores, se han observado concentraciones de hasta 1000 μg/m^3. En casos de emergencia grave se han medido niveles de hasta 16 mg/m^3. En casos de incendios o explosiones se puede producir hollín que contiene niveles altos de BPCs. Se han encontrado niveles de 8000 mg de BPCs/kg de hollín. En este caso también hay DFPCs. En accidentes con transformadores que contienen bencenos clorados aparecen también dioxinas policloradas (DDPCs), además de BPCs.

En tales situaciones de emergencia se pueden producir ingestión, contaminación de la piel o inhalación de partículas de hollín, con una exposición grave del personal. Sin embargo, la exposición de la población general a través del aire es muy baja.

Las aguas superficiales se pueden contaminar con BPCs procedentes de la atmósfera, de emisiones directas de fuentes puntuales o de la eliminación de desechos. En ciertas condiciones se han medido concentraciones de 100-500 ng/litro de agua. En los océanos se han detectado niveles de 0,05 a 0,6 ng/litro.

En zonas no contaminadas, el agua potable contiene cantidades de BPCs inferiores a 1 ng/litro, pero se han notificado valores de hasta 5 ng/litro. El suelo y los sedimentos de diferentes zonas, dependiendo de las condiciones locales, contienen concentraciones que oscilan

entre <0,01 hasta 2,0 mg/kg. En las zonas contaminadas los niveles han sido mucho mayores, es decir, de hasta 500 mg/kg.

En los últimos años se han analizado muchos miles de muestras de productos alimenticios en varios países para detectar contaminantes, BPCs inclusive. La mayor parte de las muestras se tomaron de artículos alimenticios individuales, especialmente pescado y otros alimentos de origen animal, como carne y leche. Los alimentos humanos se contaminan con BPCs por tres vías principales:

a) absorción del medio ambiente por los peces, las aves, el ganado (a través de la cadena alimentaria) y los cultivos;

b) migración de los materiales de envasado a los alimentos (principalmente por debajo de 1 mg/kg, pero, en algunos casos, hasta 10 mg/kg);

c) contaminación directa del alimento o de los piensos por accidentes industriales.

Los niveles en los artículos alimenticios más importantes que contenían BPCs fueron: grasa animal, 20-240 μg/kg; leche de vaca, 5-200 μg/kg; mantequilla, 30-80 μg/kg; pescado, 10-500 μg/kg de grasa. Ciertas especies de peces (anguila) o productos derivados del pescado (hígado y aceites de pescado) contienen niveles mucho más altos, de hasta 10 mg/kg. En hortalizas, cereales, frutas y algunos otros productos la concentración observadas es de <10 μg/kg. Los principales alimentos cuya contaminación con BPCs requiere atención son el pescado, el marisco, la carne, la leche y otros productos lácteos. En diversos países se han notificado niveles medios en el pescado del orden de 100 μg/kg (de grasa). Las comparaciones realizadas parecen indicar que la concentración en el pescado está disminuyendo lentamente.

Los BPCs se acumulan en el tejido adiposo humano y en la leche materna. Su concentración en los distintos órganos y tejidos depende del contenido en lípidos, con la excepción del cerebro. Los residuos en el tejido adiposo de la población general de los países industrializados varía entre menos de 1 y 5 mg/kg de grasa, en función de la residencia del donante, su tipo de vida y el método analítico utilizado. Las mujeres que viven en zonas urbanas muy industrializadas, o que consumen una gran cantidad de pescado,

especialmente si procede de aguas con una contaminación intensa, pueden acumular en la leche concentraciones superiores de BPCs.

La composición de la mayoría de los extractos de BPCs procedentes de muestras del medio ambiente no se parecen a las mezclas comerciales. Utilizando el análisis de cromatografía de gases de alta resolución se ha demostrado también que la composición del conjunto de los productos afines y la concentración relativa de cada componente en el tejido adiposo y la leche materna son notablemente diferentes de las que se observan en los comerciales. Los BPCs detectados por cromatografía de gases en el tejido adiposo humano y la leche materna contienen sobre todo concentraciones relativamente altas de los compuestos más clorados, como: 2,4,5,3',4'-pentaclorobifenilo; 2,4,5,2',4',5'-hexaclorobifenilo y 2,3,4,2',4',5'-hexaclorobifenilo; 2,3,4,5,2',4',5'-heptaclorobifenilo; 2,3,4,5,2',3',4'-heptaclorobifenilo. Algunos otros compuestos del grupo de los BPCs están presentes en cantidades mucho más bajas, como los BPCs coplanares, muy tóxicos: 3,4,3',4'-tetraclorobifenilo, 3,4,5,3',4'-pentaclorobifenilo y 3,4,5,3',4',5'-hexaclorobifenilo.

Se ha calculado que la ingesta diaria de BPCs de los lactantes con la leche materna es del orden de 4,2 μg/kg de peso corporal (5,2 μg/100 kcal consumida) (OMS/EURO,1988). La cantidad media total de BPCs ingeridos con la leche materna durante los seis primeros meses de vida es de 4,5 mg, mientras que la calculada para el resto de su vida es de 357 mg (0,2 μg/kg por día, en la dieta de una persona de 70 kg durante 70 años de vida). Por consiguiente, el período de la lactancia aporta alrededor del 1,3 % a la ingesta de toda la vida, cantidad no muy grande si se tiene en cuenta los beneficios de la lactancia natural (OMS/EURO, 1988).

De acuerdo con los datos básicos evaluados, el promedio de BPCs en la ingesta alimentaria de los adultos alcanza un máximo de 100 g por semana, o alrededor de 14 μg/por persona al día. Para una persona de 70 kg, esto equivale a un máximo de 0,2 μg/kg de peso corporal al día (OMS/EURO, 1988).

1.7 Cinética y metabolismo

Se han descrito estudios en animales relativos fundamentalmente a las exposiciones oral, respiratoria y cutánea a mezclas de BPCs y a compuestos por separado. En general, los BPCs parece que se absorben con rapidez, particularmente en el tracto gastrointestinal tras la exposición oral. Es evidente que se produce absorción en los seres humanos, pero la información sobre las tasas de absorción de los BPCs en ellos es limitada.

Los datos de los estudios disponibles sobre su distribución parecen indicar un proceso cinético bifásico, con eliminación rápida de la sangre y acumulación en el hígado y en el tejido adiposo de diversos órganos. También hay pruebas de su transporte a través de la placenta, su acumulación fetal y su distribución en la leche. En algunos estudios realizados en la especie humana, la piel contenía una concentración elevada de BPCs, pero la concentración en el cerebro era inferior a la prevista en función de su contenido en lípidos.

La movilización de los BPCs de la grasa parece depender en gran medida de la tasa de metabolismo de cada uno de los BPCs. La excreción depende de su transformación en compuestos más polares, como fenoles, sistemas conjugados de compuestos de tiol y otros derivados solubles en agua. Entre las vías metabólicas están la hidroxilación y la conjugación con tioles y otros derivados solubles en agua, en algunos casos con la intervención de productos intermedios reactivos, como los óxidos de areno. Se ha demostrado que la tasa de metabolismo depende de la estructura del BPC y está en función del número de átomos de cloro y de su posición. Los metabolitos polares de los BPCs más clorados parece que se eliminan sobre todo por las heces, aunque también puede ser significativa la excreción en la orina. Una importante vía de eliminación es a través de la leche (materna). Algunos compuestos también se pueden eliminar por el pelo.

Los estudios cinéticos disponibles indican que hay una amplia divergencia en la semivida biológica entre los distintos compuestos del grupo, y esto puede ser debido a diferencias en el metabolismo dependientes de la estructura, las afinidades tisulares y otros factores que afectan a la movilización de los lugares de almacenamiento.

No siempre hay correlación entre la persistencia en los tejidos y una toxicidad elevada, y las diferencias de toxicidad entre los distintos compuestos pueden estar asociadas a metabolitos concretos o a sus productos intermedios.

1.8 Efectos sobre los seres vivos del medio ambiente

Los BPCs son contaminantes universales de la naturaleza, y están presentes en la mayoría de los compartimentos del medio ambiente, abióticos y bióticos, de todo el mundo. Desde que en numerosos países se comenzó a controlar el uso y la liberación, su incorporación al ambiente se ha reducido en comparación con la del pasado. Sin embargo, las pruebas obtenidas hasta ahora indican que el ciclo que siguen los BPCs está produciendo una redistribución gradual de algunos de los compuestos hacia el entorno marino. Existe una tendencia de los compuestos más clorados a una acumulación preferencial. Aunque gran parte de los BPCs se adsorben sobre las partículas del sedimento, mantienen la biodisponibilidad para los organismos, por lo que continuarán acumulándose en los niveles más altos de la cadena trófica.

1.8.1 Estudios de laboratorio

Los efectos de las mezclas de BPCs en los microorganismos son muy variables, y mientras que algunas especies presentan efectos adversos con concentraciones de 0,1 mg/litro, otras no se ven afectadas por concentraciones de 100 mg/litro; los efectos en las diferentes especies no dependen de manera sustancial del grado de cloración de las mezclas. Casi todos los estudios sobre los efectos de los BPCs en los organismos acuáticos se han realizado con mezclas de Aroclor. Los resultados obtenidos han sido enormemente variables, sin una relación clara entre el grado de cloración o las condiciones medio-ambientales y la toxicidad, incluso en organismos estrechamente relacionados. Los valores de la CL_{50} para un período de 96 h en condiciones fijas han variado entre 12 μg/litro y > 10 mg/litro para las distintas especies de invertebrados acuáticos y las diferentes mezclas de Aroclor. Las condiciones de flujo aumentaron la toxicidad de los BPCs. En general, la mezclas más tóxicas fueron las de Aroclor con un grado intermedio de cloración; las mezclas con un porcentaje de cloro bajo o alto resultaron menos tóxicas. Esto ocurrió también

en los efectos subletales, como los efectos sobre la reproducción en *Daphnia*. Los crustáceos parecen ser más sensibles a los BPCs durante la muda. En poblaciones utilizadas como modelo, la estructura comunitaria de las especies de estuario cambió tras la exposición a Aroclor 1254, y mientras que el número de anfípodos, briozoos, crustáceos y moluscos disminuyó, el de anélidos, braquiópodos, celentéreos, equinodermos y nemertinos se mantuvo inalterado. Se ha considerado un número excesivamente escaso de grupos en las pruebas de toxicidad aguda para determinar si los resultados reflejan cambios en la susceptibilidad a los BPCs o diferencias de interacción entre las especies.

La variación de la toxicidad de estos compuestos para los peces es similar, con una CL_{50} en 96 horas que oscila entre 0,008 y > 100 mg/litro. En las pruebas de larga duración se ha puesto de manifiesto que en la exposición aguda, particularmente en condiciones fijas, se subestima considerablemente la toxicidad de los BPCs. La trucha arco iris fue particularmente sensible, con CL_{50} de 0,32 µg/litro de Aroclor 1254 en 22 días durante las fases embrionario-larvarias, y un nivel sin efectos observados (NOEL) en 22 días de 0,001 µg/litro de Aroclor 1016, 1242 y 1254.

El pez de agua dulce *Pimephales promelas* mostró valores del NOEL de 5,4, 0,1, 1,8 y 1,3 µg/litro para los tipos de Aroclor 1242, 1248 1254 y 1260, respectivamente; el NOEL para el pez de estuario *Aplodinotus grunniens* fue de 3,4 y 0,06 µg/litro de Aroclor 1016 y 1254, respectivamente.

Las pruebas experimentales han confirmado las observaciones sobre el terreno que demostraban la presencia de trastornos de la reproducción en focas alimentadas con peces que contenían BPCs acumulados en el medio. El efecto se produce en una fase avanzada de la reproducción, impidiendo la implantación del embrión en la pared uterina.

En pruebas de corta duración, la toxicidad del Aroclor en las aves aumentó al hacerlo el porcentaje de cloración; las CL_{50} con cinco días de alimentación oscilaban entre 604 y 6000 mg/kg de alimentos. Los principales efectos de los BPCs sobre la reproducción de las aves fueron una reducción de la capacidad de eclosión de los huevos y embriotoxicidad. Estos efectos se mantuvieron tras finalizar la

administración, puesto que las gallinas reducían la cantidad de BPCs por medio de los huevos. No hay pruebas de que el Aroclor induzca directamente la formación de cáscaras de los huevos más finas; los efectos sobre el consumo de alimentos y el peso corporal de las gallinas influyen indirectamente en el espesor de la cáscara. Se han notificado efectos subletales en el comportamiento y en la secreción de hormonas.

La toxicidad aguda de los Aroclor en el visón disminuye al hacerlo el porcentaje de cloración, variando la DL_{50} de la toxicidad aguda varía entre >750 y 4000 mg/kg de peso corporal; el hurón es menos sensible. El Aroclor reduce el consumo de alimentos y, por consiguiente, el ritmo de crecimiento de los visones jóvenes. También reduce o impide la reproducción del visón, tanto si se le suministra directamente como si ingiere pescado contaminado. Cuanto mayor es el porcentaje de cloración de los Aroclor (sobre todo el 1254), mayores son sus efectos. El índice de reproducción vuelve a la normalidad tras el cese de la alimentación con Aroclor.

Los murciélagos son susceptibles al Aroclor que se libera de la grasa durante la migración.

La gran mayoría de las pruebas de laboratorio sobre animales acuáticos y terrestres se llevaron a cabo utilizando mezclas de BPCs, por lo que no es posible identificar qué componentes específicos de la mezclas fueron los causantes de los efectos. De manera análoga, las pruebas se realizaron en condiciones ambientales no reales (por ejemplo, sobrepasando la solubilidad y sin sedimento presente en las pruebas acuáticas), por lo que es difícil extrapolar los resultados del laboratorio al campo. Sin embargo, hay motivos para suponer que cualquier efecto sobre las poblaciones de organismos, que probablemente se podrán presentar de manera más generalizada en el futuro, ya se habrán observado en el pasado en poblaciones locales expuestas a altos niveles de BPCs.

1.8.2 Estudios sobre el terreno

Los resultados que indican efectos de los BPCs en poblaciones de peces sobre el terreno son poco concluyentes. La interpretación de los datos de campo en aves es difícil, puesto que también hay presentes residuos de muchos compuestos organoclorados diferentes.

La mayoría de los autores han señalado una correlación entre los efectos (embriotoxicidad) y la concentración total de residuos organoclorados. Del conjunto de los compuestos organoclorados presentes, los residuos de BPCs son los que tienen mayor correlación con la embriotoxicidad, pero los resultados no se pueden considerar como efectos de estos residuos demostrados sobre el terreno.

Hay pruebas (confirmadas en estudios de laboratorio) de que los BPCs reducen la capacidad reproductiva de los mamíferos acuáticos. Aunque ejercen su efecto en la implantación del embrión, también pueden ocasionar cambios físicos en el tracto reproductor de las hembras.

No es posible extrapolar las pruebas de laboratorio de toxicidad aguda durante un período corto a los efectos sobre el terreno en las poblaciones. La incertidumbre sobre qué componentes de las mezclas de BPCs causan los efectos, cuáles son los compuestos específicos presentes en el medio ambiente y cuál es la biodisponibilidad de los componentes de los BPCs para el organismo, en conjunto dificultan las estimaciones de las probables exposiciones en el medio ambiente y sus efectos. Los efectos sobre las poblaciones de mamíferos marinos se pueden considerar demostrados, pero todavía no se conoce qué componente o componentes de las mezclas de BPCs los producen.

Dada la tendencia hacia el aumento de contaminación del medio ambiente marino, se debería prestar más atención a los efectos sobre los organismos marinos. Hay pruebas claras de laboratorio y sobre el terreno de los efectos sobre la reproducción en poblaciones de mamíferos marinos de zonas intensamente contaminadas. Es probable que en el futuro aumenten los residuos y los efectos de los BPCs en otras poblaciones de mamíferos marinos. Es menos claro si se verán los efectos en otros organismos, como las aves que se alimentan de presas marinas.

Sería de esperar que, de acuerdo con los experimentos de laboratorio, se produjeran efectos en poblaciones y comunidades de organismos inferiores, como el fitoplancton y el zooplancton. Es difícil evaluar tanto la amplitud como la importancia de tales cambios. Con la información actualmente disponible, no cabe esperar efectos sobre

las poblaciones de peces, aunque éstos sean una vía de exposición para los mamíferos y las aves que se alimentan de peces.

Los efectos anteriormente descritos sobre especies terrestres, mamíferos de agua dulce que se alimentan de peces y murciélagos migratorios, por ejemplo, deberían ser menos evidentes a medida que se redistribuyan los residuos de BPCs. Los residuos en la biota terrestre muestran en la actualidad una pequeña disminución general, pero la información acerca de los cambios de los compuestos del grupo es escasa o nula. Se considera que la reducción de los compuestos más clorados será lenta.

1.9 Efectos en los animales de experimentación y en sistemas de prueba in vitro

1.9.1 Exposición única

La toxicidad aguda de los Aroclor, tras una exposición oral única, generalmente es baja en las ratas. Los animales jóvenes parecen ser más sensibles (DL_{50}: 1,3-2,5 g/kg de peso corporal) que los adultos (DL_{50}: 4-11 g/kg de peso corporal). La DL_{50} más baja de Aroclor 1254 de la que se tiene noticia en ratas adultas fue de 1,0 g/kg de peso corporal. No se observaron diferencias entre ambos sexos.

La DL_{50} cutánea en conejos osciló entre $> 1,26$ y < 2g/kg de peso corporal para el Aroclor 1260 (en aceite de maíz) y de 0,79 a $< 3,17$ g/kg de peso corporal para algunas otras mezclas no diluidas de BPC. Por vía intravenosa, las ratas mostraron para el Aroclor 1254 una DL_{50} de 0,4 g/kg de peso corporal; la DL_{50} en ratones tras la inyección intraperitoneal varió entre 0,9 y 1,2 g/kg de peso corporal.

1.9.2 Exposición de corta duración

Los principales objetivos a los que llegan las mezclas de BPCs o sus compuestos por separado en mamíferos con exposición oral de corta duración son el hígado, la piel y los sistemas inmunitario y reproductor. La especie más sensible de las probadas fue el mono Rhesus, siendo la hembra más susceptible que el macho. Las hembras adultas de mono Rhesus sometidas durante seis meses a una dieta con concentraciones de 2,5 mg/kg ó 0,09 mg/kg de peso corporal al día

de Aroclor 1248 mostraron un aumento de la tasa de mortalidad, retraso del crecimiento, alopecia, acné, inflamación de

las glándulas de Meibomio y posiblemente inmunosupresión. En el análisis microscópico, se encontró un hígado adiposo agrandado, con necrosis focal, hiperplasia epitelial y queratinización de los folículos pilosos. Con niveles de exposición más elevados, también se han observado cambios en otros tejidos epiteliales, como las glándulas sebáceas y de Meibomio, la mucosa gástrica, la vesícula biliar, el conducto biliar, los lechos de las uñas y el ameloblasto. Los niveles totales de lípidos, triglicéridos y colesterol en el suero disminuyeron. La exposición breve a mezclas comerciales de BPCs indujeron un aumento de la concentración de lípidos, triglicéridos, colesterol y fosfolípidos totales en el hígado, Entre los distintos compuestos de los BPCs, los más potentes fueron el 3,4,3',4'-tetraclorobifenilo, el 3,4,5,3',4',5'-hexaclorobifenilo y el 2,4,6,2',4',6'-hexacloro-bifenilo. Las concentraciones de 0,2 mg/kg de peso corporal al día de Aroclor 1254 mostraron también algunos otros efectos, como lesiones linforreticulares, desprendimiento de las uñas y efectos gingivales, pero no se produjeron ni acné ni alopecia. En los monos Rhesus se estableció un NOEL para la toxicidad general del Aroclor 1242 de 0,04 mg/kg de peso corporal al día. En monos Rhesus lactantes expuestos a dosis mucho más elevadas, de 35 mg/kg de peso corporal al día de Aroclor 1248, se observaron efectos relativamente ligeros. Donde mejor se han investigado los efectos sobre el hígado es en ratas, y entre ellos figuran hipertrofia, degeneración adiposa, proliferación del retículo endoplásmico, porfiria, adenofibrosis, hiperplasia del conducto biliar, quistes y cambios preneoplásicos y neoplásicos. En estudios sobre ratas y ratones, los distintos compuestos de los BPCs causaron efectos en el hígado, el bazo y el timo, siendo mayor la toxicidad de los compuestos planares. En los monos, dichos compuestos planares, en dosis de 1 a 3 mg/kg de dieta, indujeron efectos de carácter y gravedad análogos a los producidos por dosis de 100 mg/kg de dieta de Aroclor 1242 y dosis de 25 mg/kg de dieta de Aroclor 1248.

Las mezclas de BPCs y algunos de los compuestos causaron a conejos y ratones, tras una exposición cutánea, efectos en la piel y el hígado similares a los presentes después de la exposición oral. En los conejos

se observaron también atrofia del timo, reducción de los centros germinales de los nódulos linfáticos y leucopenia.

1.10 Reproducción, embriotoxicidad y teratogenicidad

1.10.1 Reproducción y embriotoxicidad

No se han realizado estudios completos de la reproducción y la teratogenicidad. En un estudio de reproducción de dos generaciones en ratas, se estableció un NOEL de 0,32 mg/kg de peso corporal, basado en parámetros de la reproducción (Aroclor 1254) y un NOEL de 7,5 mg/kg de peso corporal (Aroclor 1260). Sin embargo, la dosis más baja de las probadas, de 0,06 mg/kg de peso corporal, produjo en animales destetados un aumento del peso relativo del hígado.

En los monos Rhesus expuestos a Aroclor 1016, se estableció un NOEL de 0,03 mg/kg de peso corporal, utilizando como base los parámetros de la reproducción. Sin embargo, con esta concentración se observó una disminución del peso al nacer, y la dosis más baja de las probadas, de 0,01 mg/kg de peso corporal, produjo una hiperpigmentación de la piel.

Un año después de cesar la exposición, se detectó en los monos Rhesus un NOEL de 0,09 mg/kg de peso corporal para el Aroclor 1248 (con DFPCs).

1.10.2 Teratogenicidad

En los estudios disponibles en ratas y monos no hay indicación de ningún efecto teratogénico después de su exposición oral durante la organogénesis. En ratas, se apreció para el Aroclor 1254 un NOEL de 50 mg/kg de peso corporal en relación con el peso de las crías, y se podría suponer un NOEL de 2,5 mg/kg de peso corporal, tomando como base la fetotoxicidad (lesión en las células foliculares del tiroides).

En las pruebas de teratogenicidad con los compuestos por separado en ratones, ratas y monos Rhesus, no se estableció el NOEL. Una dosis de 0,07 mg/kg de peso corporal produjo en los monos Rhesus efectos tóxicos maternos (3,4,3',4'-tetraclorobifenilo).

1.11 Mutagenicidad

Las mezclas de BPCs no causaron mutaciones ni lesiones cromosómicas en distintos sistemas de prueba. El 3,4,3',4'-tetraclorobifenilo produjo fragmentación cromosómica de linfocitos humanos in vitro. Concentraciones elevadas de mezclas de BPCs pueden dar lugar a lesiones primarias en el ADN, como puso de manifiesto la rotura de cadenas sencillas de ADN en ensayos con soluciones alcalinas.

1.12 Carcinogenicidad

La interpretación de los datos disponibles sobre animales en relación con mezclas comerciales de BPCs se ve con frecuencia complicada por la escasez de información en cuanto a la presencia, o contribución, de las impurezas de dibenzofuranos clorados, así como a variaciones en la composición de los compuestos.

Se han llevado a cabo diversos estudios de carcinogenicidad de larga duración en ratones y ratas. Las mezclas que se utilizaron fueron: Kanechlor 300, 400 y 500, Aroclor 1254 y 1260 y Clophen A30 y A60. Se notificó que el Clophen no contenía DFPCs, pero no se aportaron datos sobre la pureza de los demás mezclas de BPCs.

En ratones alimentados con una dieta que contenía Kanechlor 500 y Aroclor 1254 en dosis de unos 15 a 25 mg/kg de peso corporal se observó un aumento significativo de adenomas hepatocelulares y/o carcinomas. En ratones tratados con Kanechlor 300 y 400 no se pudieron detectar neoplasmas.

En estudios de exposición de ratas a Aroclor 1254 y 1260 y Clophen A30 durante un período superior a un año se detectó un aumento de adenomas hepatocelulares y/o carcinomas. No se consideró estadísticamente significativo en estos estudios el aumento de la frecuencia de animales con cáncer, pero sí en otros dos estudios. Con Aroclor 1260 y Clophen A60 administrados a dosis de unos 5 mg/kg de peso corporal se observó un aumento de la frecuencia de carcinomas hepatocelulares (trabeculares) y adenocarcinomas.

Se consideró que los tumores hepáticos producidos no eran agresivos (benignos o de escasa malignidad, sin metástasis) y no acortaban la vida. En algunos estudios se notificaron casos de adenofibrosis, una

lesión preneoplásica, y/o nódulos neoplásicos. En una prueba en ratas con Aroclor 1254 se demostró un aumento relacionado con la dosis de metaplasia intestinal y adenocarcinomas de la parte glandular del estómago.

Hay pruebas claras que demuestran los efectos potenciadores de los BPCs en la carcinogénesis del hígado en roedores pretratados con hepatocarcinógenos. Existen algunos indicios de actividad iniciadora de las mezclas de BPCs en roedores. De los informes sobre estudios de genotoxicidad se puede concluir que las mezclas de estos compuestos carecen de genotoxicidad. De estos resultados se deduce que la asociación de los tumores hepáticos con la administración de BPCs a roedores se puede atribuir a algunos mecanismos epigenésicos que inducen la proliferación celular en el hígado y otras manifestaciones de hepatotoxicidad, por lo que en la evaluación de la toxicidad de los BPCs se puede seguir un método de determinación del umbral. Es necesario tener en cuenta la posibilidad de que los BPCs potencien la carcinogénesis en otros tejidos distintos del hígado en animales con exposición previa a diversos carcinógenos específicos de los tejidos. La actividad anticarcinógena que los BPCs han mostrado en algunos estudios, al tratar animales con estos compuestos durante la administración de carcinógenos y antes de ella, puede estar relacionada con las propiedades inductoras de enzimas microsomales de los BPCs, dando lugar a un aumento de la destoxificación.

En general, hay que ser prudentes a la hora de extrapolar a los seres humanos los datos disponibles sobre el potencial carcinógeno de los BPCs en animales.

1.13 Estudios especiales

Tras la exposición a mezclas de BPCs o a compuestos individuales, se observaron lesiones en el hígado, la piel, el sistema inmunitario, el sistema reproductor, edemas y alteraciones del tracto gastrointestinal y de la glándula tiroides.

Los BPCs pueden inducir la formación de diversas enzimas en el hígado. Esto se ha demostrado en ratas, ratones, cobayos, conejos, perros y monos utilizando Aroclor 1248, 1254 y 1260 y Kanechlor 400 (inducción del citocromo P450 y P448). La capacidad de

inducción aumenta con el contenido de cloro de la molécula. Depende también de la composición de congéneres: los que tienen el cloro en posición *para-* y *meta-* inducen la enzima P450. Para la inducción de la AHH, la posición del cloro parece ser más importante que el grado de cloración. Los inductores más potentes de la AHH son los compuestos con cloro en posición *para-* y por los menos dos en posición *meta-*. Se han observado diferencias claras entre especies. El NOEL más bajo (0,025 mg/kg de peso corporal) se encontró para el Aroclor 1260 en ratas Osborn-Mendel.

Se considera que los efectos sobre el sistema endocrino se manifiestan como alteraciones de la unión al receptor hormonal y del equilibrio hormonal esteroideo. Hay pruebas directas e indirectas de que diversos Aroclor producen una débil actividad estrógena. Se observó que en ratas expuestas a 75 mg de Aroclor 1242/kg de dieta durante 36 semanas se producía una disminución de los niveles de hormonas gonadales y un aumento del peso relativo de los testículos. En ratones hembra expuestos a Aroclor 1254 (25 mg/kg de dieta) durante tres semanas se detectó la reducción de los niveles de corticosteroides en el plasma, sin aumento del peso adrenal. En otra raza a la que se suministró una dieta con 200 mg/kg durante dos semanas se observó un aumento del peso adrenal.

Las mezclas de BPC han mostrado un efecto inmunosupresor en varias especies animales, siendo monos y conejos los más sensibles. Los NOEL más bajos fueron de 0,1 mg/kg de peso corporal en monos y de 0,18 mg/kg de peso corporal en conejos.

En ratones a los que se suministró una dosis oral única de 500 mg/kg de peso corporal de Aroclor 1254 se observó una disminución de la actividad motora. Esto probablemente se debió a una inhibición de la absorción y liberación de neurotransmisores.

Se ha encontrado que las mezclas de BPCs hacen disminuir en las ratas el nivel sanguíneo y hepático de las vitaminas A y B_1. En ratas y ratones expuestos a mezclas de BPCs se produjo una reducción en la concentración de las vitaminas A, B_1, B_2 y B_6.

1.14 Factores modificadores de la toxicidad, mecanismo de acción

Los productos comerciales de BPCs muestran un espectro de respuesta tóxica en parte parecido al de los DDPCs y DFPCs. Además, los distintos BPCs tienen unas relaciones análogas entre estructura y actividad con respecto a la mayor parte de sus respuestas tóxicas y a su capacidad de inducción de AHH dependiente del P448, lo cual indica que los BPCs que son aproximadamente esteroisómeros del 2,3,7,8-DDTC son los más activos. Estos resultados parecen indicar que hay un mecanismo común de acción basado en la afinidad de estos compuestos por la proteína citosólica receptora de AH. Se han propuesto factores de equivalencia tóxica para estos compuestos coplanares en relación con el 2,3,7,8-DDTC. No se ha investigado adecuadamente la naturaleza de las probables interacciones entre BPCs, DFPCs y DDPCs. Como los BPCs estimulan la actividad de las enzimas microsomales, pueden influir en la acción de otros productos químicos que se ven sometidos al metabolismo microsomal. Otros compuestos, llamados no planares, pueden producir otras toxicidades más sutiles. Además, los distintos BPCs, especialmente los menos clorados, se pueden metabolizar a través de óxidos de areno intermedios y metabolitos de metilsulfonilo.

1.15 Efectos en el ser humano

La evaluación toxicológica de los BPCs presenta muchos problemas. Los BPCs normalmente se encuentran como mezclas de numerosos compuestos distintos, y muchos de los datos sobre su toxicidad se basan en las pruebas de estas mezclas. Algunos de los componentes de la mezcla se degradan más fácilmente que otros en el medio ambiente. Así, la población general puede estar expuesta a mezclas que son diferentes de las que soportan las personas que trabajan con BPCs.

La población general está expuesta a BPCs fundamentalmente a través de alimentos contaminados (organismos acuáticos, carne y productos lácteos). La ingesta diaria de BPCs en la mayoría de los países industrializados es del orden de unos microgramos por persona. Tales exposiciones no se han asociado con enfermedades. Los lactantes están expuestos a través de la leche materna. La ingesta diaria de BPCs puede ser de unos microgramos/kg de peso corporal.

Es muy difícil evaluar por separado los efectos para la salud humana de los BPCs, DFPCs o DDPCs, puesto que con mucha frecuencia las mezclas de BPCs contienen DFPCs. Ocasionalmente se ha detectado también la presencia de DDPCs en accidentes con ciertas mezclas. Se ha demostrado que los BPCs comerciales están contaminados con DFPCs y, por consiguiente, en muchos casos no está claro qué efectos son atribuibles a los BPCs y cuáles a los DFPCs, mucho más tóxicos. Así pues, muchos de los datos procedentes de casos importantes de intoxicaciones en el ser humano, por ejemplo las de Yusho, Yu-Cheng y otras, probablemente reflejan los efectos de la exposición tanto a los DFPCs como a los BPCs.

Los síntomas de la intoxicación en los pacientes de Yusho y de Yu-Cheng fueron hipersecreción de las glándulas meibomianas de los ojos, inflamación de los párpados y pigmentación de las uñas y de las membranas mucosas, ocasionalmente acompañados de cansancio, náuseas y vómitos. Estos efectos normalmente iban seguidos de hiperqueratosis y oscurecimiento de la piel, con agrandamiento folicular y erupción acneiforme. Además, se observaron edemas en brazos y piernas, aumento del tamaño del hígado y trastornos hepáticos, alteraciones del sistema nervioso central, problemas respiratorios, por ejemplo alteraciones del tipo de la bronquitis, y cambios en el estado inmunitario de los pacientes. En los hijos de pacientes de Yusho y Yu-Cheng se detectó disminución del crecimiento, pigmentación oscura de la piel y las membranas mucosas, hiperplasia gingival, edema xeroftálmico ocular, dentición al nacer, calcificación anormal del cráneo, curva del talón más baja y una alta frecuencia de escasez de peso al nacer. No se pudo concluir de manera definitiva si existía o no correlación entre la exposición y la formación de neoplasmas malignos en esos pacientes, porque el número de muertes fue demasiado pequeño. Sin embargo, en pacientes varones se observó un aumento estadísticamente significativo de la mortalidad producida por todos los neoplasmas, el cáncer de hígado y el de pulmón.

En condiciones profesionales, tras unas horas de exposición aguda se produjo una erupción cutánea. Además, después de una exposición a altas concentraciones de BPC se observó prurito, escozor, irritación conjuntival, pigmentación de dedos y uñas y cloracné. La cloracné es uno de los resultados predominantes entre los trabajadores

expuestos a BPCs. Además de estos signos cutáneos de intoxicación, diferentes autores han encontrado trastornos hepáticos, cambios en la inmunosupresión, irritación transitoria de las membranas mucosas del tracto respiratorio y efectos neurológicos y psicológicos o psicosomáticos inespecíficos, como dolor de cabeza, mareos, depresión, trastornos del sueño y de la memoria, nerviosismo, cansancio e impotencia. La conclusión general es que la exposición profesional constante a altas concentraciones de BPCs y DFPCs puede tener consecuencias en el hígado y la piel.

Se han llevado a cabo dos amplios estudios de mortalidad en cohortes de trabajadores. Tras la exposición a Aroclor 1254, 1242 y 1016, en un estudio se observó un aumento de la mortalidad por cáncer de hígado y de vesícula biliar, y en el otro por neoplasmas y cáncer del tracto gastrointestinal. Ninguno de los estudios epidemiológicos disponibles aporta pruebas concluyentes de una asociación entre la exposición a BPCs y el aumento de la mortalidad por cáncer, debido al pequeño número de muertes en las poblaciones expuestas, la falta de relación dosis-respuesta y el problema de los contaminantes en las mezclas de BPCs.

2. Conclusiones

2.1 Distribución

Debido a sus propiedades físicas y químicas, los BPCs se han dispersado en el medio ambiente de todo el mundo.

Los BPCs están casi universalmente presentes en los organismos del medio ambiente y se bioacumulan fácilmente. También se ha demostrado una bioamplificación en las cadenas alimentarias.

Se acumulan preferentemente los compuestos más clorados.

2.2 Efectos en animales de experimentación

Los resultados de los estudios en animales indican que los BPCs tienen una actividad inmunosupresora, evaluada por alteraciones importantes de la función inmunitaria (peso del bazo, peso del timo y recuento de linfocitos). En monos, se han estimado unos NOELs de 100 μg/kg para el Aroclor 1248 y < 100 g/kg de peso corporal

para el Aroclor 1254. La inmunosupresión parece ser un efecto específico de cada compuesto.

En general, sólo se observa toxicidad en la reproducción con dosis que producen toxicidad sistémica en la madre. Los neonatos que se alimentan de leche materna contaminada (en monos y otras especies animales utilizadas como modelo) parecen ser particularmente sensibles a los BPCs, y muestran una disminución del crecimiento y otros síntomas tóxicos. El NOEL para los efectos del Aroclor 1016 en la reproducción es de 30 μg/kg de peso corporal en monos; no se pudo establecer el NOEL para los efectos en la reproducción del Aroclor 1248.

Los BPCs no son genotóxicos y no hay pruebas definitivas de su acción como desencadenantes de tumores. Los BPCs sí actúan como estimulantes de tumores. Se puede concluir que la toxicidad de las mezclas de BPCs se pueden evaluar sólo en función de su umbral.

2.3. *Efectos en el ser humano*

La exposición de la población general a los BPCs se produce sobre todo por los artículos alimenticios. Los lactantes están expuestos a través de la leche materna.

Se han registrado dos importantes casos de intoxicación humana en el Japón (Yusho) y en la provincia de Taiwán (Yu-Cheng). Los principales síntomas de los pacientes de Yusho y Yu-Cheng se han atribuido con frecuencia a contaminantes de las mezclas de BPCs, en particular a los DFPCs. Sin embargo, los causantes de algunos de los síntomas, principalmente los efectos respiratorios crónicos, pueden haber sido los metabolitos de metilsulfona de algunos compuestos del grupo de los BPCs.

2.4 *Efectos en el medio ambiente*

Aunque se han notificado efectos en poblaciones locales de aves, el efecto más importante de los BPCs en organismos del medio ambiente ha sido sobre la insuficiencia reproductora de los mamíferos marinos. Este efecto se ha observado principalmente en mares semicerrados, y se ha traducido en la reducción de las poblaciones locales. El pronóstico de que los residuos de BPCs en el medio ambiente se

redistribuirán gradualmente hacia el entorno marino indica que hay un peligro creciente en el futuro para los mamíferos marinos.

3. Recomendaciones

- Se recomienda un acuerdo internacional sobre los procedimientos analíticos, para mejorar la comparabilidad de los resultados de los programas de vigilancia. Se debe continuar perfeccionando la metodología del análisis de los distintos compuestos, aunque se reconoce el valor de los análisis de mezclas.

- Para asegurar que los datos analíticos sean fidedignos, se recomiendan firmemente estudios de control de calidad entre laboratorios. Se recomienda asimismo el establecimiento de una red internacional de asistencia y supervisión técnica, para permitir la participación de los países en desarrollo en la vigilancia.

- Se recomiendan estudios de larga duración utilizando distintos compuestos, y estudios sobre el mecanismo de acción de los componentes de las mezclas de BPCs, prestando particular atención al estímulo de los tumores, a fin de mejorar la precisión de la evaluación del riesgo de los BPCs.

- Son necesarios estudios epidemiológicos que permitan evaluar mejor los riesgos para los neonatos, dado que los recién nacidos parecen ser el sector más vulnerable de la población general, debido a su elevada exposición a través de la leche.

- Se deben poner a punto biomarcadores sensibles y específicos para algunos de los tipos más sutiles de toxicidad de los BPCs (como la toxicidad sobre los sistemas reproductor, inmunitario y nervioso), a fin de utilizarlos en futuros estudios epidemiológicos.

- La eliminación de los BPCs se debería llevar a cabo mediante incineración en instalaciones con un diseño y un funcionamiento apropiados que puedan garantizar la temperatura alta constante (superior a 1000°C), el tiempo de permanencia y la turbulencia que se necesitan para asegurar su completa descomposición.

- Hay que investigar sistemas de eliminación de los BPCs que se encuentran ya en vertederos.
- Se ha de promover una vigilancia mundial de los BPCs en el medio ambiente y en la fauna y flora silvestres, para seguir de cerca la redistribución prevista de los residuos ya existentes.
- Los mamíferos marinos son susceptibles a una insuficiencia reproductora a causa de la contaminación con BPCs. Se deben promover estudios sobre el tamaño de las poblaciones y la eficacia reproductora de los cetáceos, además de otros estudios para identificar los compuestos causantes de estos efectos.

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