Chapter 1

Introduction

In this section the general aspects of polychlorinated biphenyls (PCBs) and dioxins are discussed. In addition, the effects of chronic and acute exposure to these compounds that have been found in animals and humans are described, with special emphasis on the '*Dutch PCB/Dioxin-Breast Milk Study*'.

POLYCHLORINATED BIPHENYLS (PCBS) AND DIOXINS

The first finding of PCBs in environmental extracts was described in 1966[1]. At present, PCBs and dioxins can be detected in almost every compound of the eco-system. PCB and dioxin levels in The Netherlands and other densely populated parts of Europe and the United States belong to the highest in the world, although comparison is difficult due to differences in analytical methods.

Chemical structure

PCBs and dioxins are polycyclic halogenated aromatics. The term dioxins refers to the group of polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs). PCBs, PCDDs, and PCDFs are non-polar, lipophilic compounds[2]. Their basic molecular structure is shown in figure 1. PCBs, PCDDs, and PCDFs have two connected benzene rings. In the case of PCDDs, the benzene rings are connected by two oxygen atoms, whereas in the PCDFs the benzene rings are connected by one oxygen atom. Hydrogen atoms attached to the carbon atoms may be substituted with a chlorine atom.

Differences in the chlorine-substitution pattern and the degree of halogenation lead to different compounds. There are 209 possible PCBs, 135 PCDFs, and 75 PCDDs. The individual PCB, PCDD, and PCDF isomers are generally referred to as congeners. A numbering system for PCB congeners was proposed by Ballschmitter and Zell in 1980[3], which was later adopted by the International Union of Pure and Applied Chemistry (IUPAC).

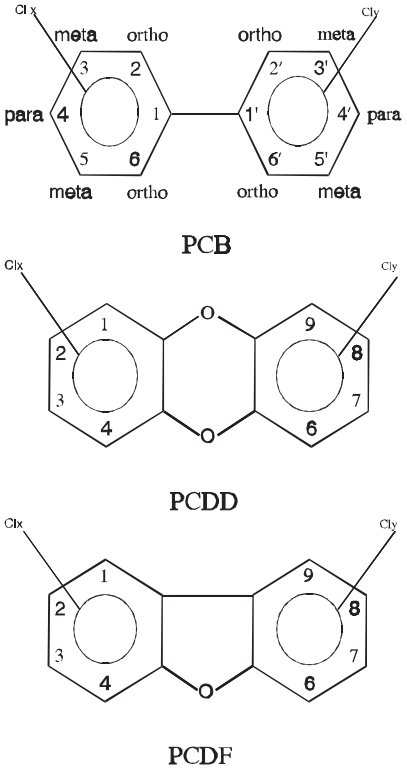

***Figure 1**: Molecular structure of polychlorinated biphenyls (PCBs), and polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs).*

Sources, environmental distribution, and disposition

Industrial production of PCBs started in 1930. The lower chlorinated PCBs appear as a clear and mobile oil, whereas the higher-chlorinated PCBs are white and solid. The technical mixtures have been marketed world-wide under trade names such as Aroclor (Monsanto Chemical Corporation, USA), Phenoclor (Prodelec, France), Kanechlor (Kanegafuchi Chemical Co., Japan), Soval (Sovol, Russia), and Delor (Chemko, Czechoslovakia)[4]. The high chemical stability and electrical resistance of PCBs, together with their low volatility and poor tendency to combustion, favoured wide-spread application in heavy-duty transformers and capacitators[5]. Other industrial uses are the formulation of hydraulic and heat-exchange fluids, incorporation into protective coatings for wood, metal, and concrete, usage

in plastics, printing inks, plasticiser, adhesives, and lubricating additives. In the late 1970s, in most Western countries, the production of PCBs was banned. In Western Europe and the United States, over 800 million tons of PCBs have been produced, and a large part has become distributed in the environment. Significant quantities are still being used in old transformers and capacitators.

Dioxins are unwanted byproducts of thermal processes and of chemical formulations. The following major categories of sources can be distinguished[6, 7]: (1) Formation during incineration processes. This includes municipal waste combustion, scrap metal recycling, vehicle fuel combustion, cigarette smoking, and combustion of wood. (2) Formation as by-products in industrial processes, such as in the production of pesticides and in the pulp and paper industry. (3) Mobilization of dioxins from secondary sources, such as waste dumps and the application of sewage sludge for fertilization.

The predominant mode of environmental transport of PCBs and dioxins is the atmosphere[5]. They can be dispersed in the air either in vapour or in aerosol form, especially during inefficient incineration and during incineration of PCB-containing materials. Subsequently, the more highly chlorinated PCBs and dioxins, which are virtually insoluble, remain associated with the soil. The lower-chlorinated congeners have a small solubility in water. Traces of these substances leach out into the water, where they probably cling to the sediment and are washed down-stream.

Metabolism of PCBs and dioxins is very slow, and, therefore, these compounds bioaccumulate and biomagnify in the food chain. For example, in humans half-lives of 2,3,7,8 substituted PCDFs have been found to range from two to 10 years. Elimination of PCBs appeared to be somewhat faster (t½ between 1 and 5 years)[8]. In vivo, metabolism involves preferential hydroxylation at the lateral (2,3,7,8) position in case of dioxins, and on the para position when PCBs are concerned. The highly substituted isomers have been found to be more resistant to metabolism than the lower chlorinated congeners[9]. In abiotic samples, aerobic and anaerobic microbial degradation of these compounds have been reported from laboratory studies. In soil, degradation is insignificant, or at least extremely slow[10].

Mechanism of action

The toxic effects of PCBs and dioxins have been shown to be mediated through binding to the cytosolic arylhydrocarbon (Ah) receptor[11]. For PCDDs and PCDFs, the affinity for the Ah receptor increases when the congeners are substituted in all four lateral positions[12]. Such congeners have a planar configuration. For example, 2,3,7,8 tetrachlorodibenzo-*p*-

dioxin (TCDD) is the most toxic congener. PCBs which contain two para and at least two meta chlorine atoms (see figure 1), also referred to as the non-ortho or planar PCBs, resemble 2,3,7,8 TCDD most in their affinity for the Ah receptor. The addition of chlorine atoms on the ortho position reduces planarity and the affinity for the Ah receptor[13]. But, despite their low affinity for the Ah receptor, several important toxic responses have been found as a result of exposure to mono- and di-ortho PCB congeners, including neurotoxic[14], carcinogenic[15], and endocrinological changes[16]. The mechanism behind these effects remain unknown.

Based on the Ah receptor model, the toxic equivalency approach was developed. This concept makes it possible to express the toxicity of a complex mixture in biological samples by a single value. According to this concept, the PCDD-, the PCDF-, and the dioxin-like planar PCB congeners are assigned an toxic equivalent factor (TEF)[17, 18] which refers to its relative toxicity towards 2,3,7,8 TCDD. In addition, for some mono-ortho (PCB 105, 114, 118, 123, 156, 157, 167, and 189) and di-ortho PCBs (PCB 170 and 180) a TEF was proposed at a World Health Organization-consultation meeting in Bilthoven, The Netherlands[19]. The toxic equivalency (TEQ) for each congener is calculated by the multiplication of the concentration of the congener with its assigned TEF. For the total PCB/dioxin TEQ, the congener-specific TEQs are added.

PCBs and dioxins in animals

The toxic effects elicited by PCB and dioxins on diverse animal systems have been described in numerous review articles[4, 20-26]. The effects of exposure to PCBs and dioxins are summarized in table 1. In addition to variations in species sensitivity, the effects seem to be sex, strain, and age dependent.

PCBs and dioxins in humans

Human populations have been exposed to PCBs and dioxins via three major pathways, i.e. accidental, occupational, and environmental. As compared to the latter category, levels of exposure in the first two groups are significantly higher. PCBs and dioxins can be found in all compartments of the human body, including adipose tissue and blood lipids[27]. PCBs and dioxins pass the placenta[28, 29], and they are transferred into human breast milk fat[27, 28, 30].

***Table 1**: Toxic effects due to exposure to chronic and acute PCBs and dioxins in laboratory animals.*

Effect	Description
Wasting	*Progressive weight loss*
Dermal lesions and acne	*Hyperplasia, hyperkeratosis, hyperpigmentation, alopecia, folliculitis, chloracne*
Neurotoxicity	*Impaired avoidance response, alterations in neurotransmitter levels, neurobehavioural problems, deficits in cognitive ability*
Immunotoxicity	*Atrophy of lymphoid tissues, decreased immunocompetence, decrease in number of circulating leucocytes and lymphocytes and suppression of antibody response*
Hepatotoxicity	*Hepatomegaly, hepatonecrosis*
Reproductive and hormonal effects	*Impaired ability to maintain pregnancy, prolonged menstrual cycles, reduction in the number of live births, decrease in survival and mating successes, decreased weight of the uterus, thyroid effects*
Mutagenic and carcinogenic effects	*Hepatocellular carcinomas*
Metabolism	*Induction of the hepatic microsomal mixed function oxidase system (cytochrome P450), effects on lipid metabolism*
Other effects	*Porphyria, reduced vitamin A storage, vitamin K deficiency*

Three general populations, that have accidentally been poisoned with PCDDs and PCDFs exist. The first incident took place in Japan in 1968 in which 1700 persons were affected. This incident was called ‘Yusho’. In that event, cooking oil was contaminated with a complex mixture of PCBs, dibenzofurans, and quaterphenyls[31]. A similar incident occurred in Taiwan in 1979, with more than 2000 victims. This was called ‘Yu-cheng’ (oil disease)[32]. The clinical manifestations of chronic poisoning consisted of acneiform eruptions, hyperpigmentation, peripheral neuropathy, abdominal pain and, deformation of the nails. Because these chemicals persist in

human tissue, and because they pass the placenta the offspring of female patients was exposed in utero. The exposed children tended to have a low birthweight[33] and more frequently showed dystrophic finger-nails and pigmented or dystrophic toe-nails than did controls. These babies also had an increased rate of hyperpigmentation and acne, and a higher rate of generalized itching, localized skin infections and hair loss[34]. In addition, neonatal conjunctival hypersecretion and jaundice occurred more frequently[35]. At follow-up, the exposed children showed a delay in growth[33], cognitive[36, 37] and motor development[38]. Another population that has overtly been exposed to these classes of compounds is that in and around Seveso (Italy). In 1976, the Seveso population was exposed to 2,3,7,8 TCDD as a result of an accidental release from a 2,4,5-trichlorophenol-manufacturing plant. The main route of exposure to the nearby residents was inhalation of and dermal contact with the contaminated fall-out and ingestion of contaminated food products.

The effects of high levels of exposure can also be studied in the workers employed in, for example, industries manufacturing PCBs or PCB-containing products. Exposure takes place mainly via skin absorption or inhalation.

The major route of environmental exposure (>90%) is the consumption of contaminated food[39-42], from which almost complete absorption takes place[43]. In The Netherlands, dairy products accounted for half and industrial oils (a mixture of animal and vegetable oils in e.g. savory snacks, sauces, pastry, and biscuits) accounted for a quarter of the PCB and dioxin intake[44]. In other regions, contaminated fish is an important source of exposure[45, 46]. The developmental effects of environmental exposure to PCBs are studied in two prospective longitudinal US studies; one in Michigan, and one in North-Carolina study. The effects of perinatal PCB- and dioxin exposure on child development was investigated in The Netherlands (the '*Dutch PCB/Dioxin-Breast Milk Study*').

The Michigan and North-Carolina studies

The Michigan cohort involved 313 mothers and their newborn infants delivered at four hospitals in western Michigan; 242 of the mothers had consumed Lake Michigan fish which is contaminated with PCBs[47]. About 90 percent of the 'Michigan children' were breast-fed. The North-Carolina cohort consisted of 912 mother/infant pairs that were drawn from the general population[48, 49]. Sixty-one percent of the mothers enroled in the North-Carolina cohort breast-fed their infant. In both studies, prenatal exposure was established on the basis of maternal serum samples collected following delivery. Based on the methodology available when

these studies were initiated, a majority of the cord serum PCB concentrations were below laboratory detection limits. Postnatal exposure was assessed in terms of PCB levels in breast milk fat and the duration of nursing. In addition, in Michigan, serum samples from 285 4-year-old children were obtained[50].

Both in the Michigan and the North-Carolina study, the neonatal behavioral performance in relation to PCB exposure was assessed by means of the Brazelton Neonatal Behavioral Assessment Scale[51]. In Michigan, Jacobson and co-workers found a negative relationship between Lake Michigan fish consumption and the performance on three clusters of the Brazelton Scale: autonomic maturity, reflexes, and range of state[52]. Rogan *et al.*, in North-Carolina, found that higher PCB levels were associated with hypotonicity and hyporeflexia[53].

In Michigan, 123 infants were administered Fagan's test of visual recognition at 7 months of age. Both cord serum PCB level and maternal report of contaminated fish consumption predicted less preference for a novel stimulus[54]. Postnatal exposure from nursing was not related to visual recognition memory. At 4 years of age, prenatal exposure was found to be associated with poorer short-term memory function on both verbal and quantitative tests which are part of the McCarthy Scales[55]. At this age, prenatal exposure also was associated with lower body weight[56]. The child's contemporary body burden, assessed by 4-year serum PCB levels, was associated with reduced behavioral activity at four years of age[56]. Recently it was found that prenatal exposure (assessed by the average of the detectable PCB values from cord and maternal serum and maternal milk) to PCBs was associated with lower full-scale and verbal IQ at 11 years of age[57].

In North-Carolina, a relationship between prenatal PCB exposure and poorer psychomotor performance on the Bayley Scales at 6, 12, and 24 months was found[58, 59]. Neither transplacental nor breast-feeding exposure to PCBs affected the McCarthy scores at 3, 4, or 5 years[60].

The 'Dutch PCB/Dioxin-Breast Milk Study'

From June 1990 to June 1992, healthy pregnant women were asked to participate in two study centres, Groningen and Rotterdam (The Netherlands). The Groningen region is a semi-urban area in the northeast of The Netherlands, whereas the Rotterdam region is a highly industrialized area in the midwest of The Netherlands. The study population consisted of 418 mothers and their infants. As a result of the implementation of stringent inclusion criteria, children were presumed to be at low risk for neurological and cognitive deficit. Fifty percent of the children was breast-fed, and another fifty percent was formula-fed for at

least six months after birth. To guarantee a certain amount of lactational exposure, only children that were actually breast-fed for at least six weeks after birth were included in the breast-fed group. Prenatal exposure was reflected by PCB levels (sum of the congeners 118 (2,4,5,3',4'-Pentachlorobiphenyl (CB)), 138 (2,3,4,2',4',5'-HexaCB), 153 (2,4,5,2',4',5'-HexaCB), and 180 (2,3,4,5,2',4',5'-HeptaCB) in plasma sampled from the umbilical cord and maternal plasma taken in the last month of pregnancy. 24-h breast milk samples were collected in the seventh week after delivery, and analyzed for 17 dioxins and 26 PCB congeners (appendix 1). Milk PCB and dioxin levels were used as a measure of lactational exposure. In addition, the duration of breast-feeding was recorded.

In the second week after delivery, pre- and early postnatal levels of PCB exposure were found to be negatively related to the neonatal neurological condition measured by means of the technique according to Prechtl[61] and the incidence of hypotonia[62]. In addition, transplacental PCB passage was found to have a small negative effect on the neurological condition (method according to Touwen and Hempel[63]) in 18-month-old toddlers[64]. In 207 infants, pre- and postnatal exposure to PCBs and dioxins was unrelated to cognitive development as assessed by Fagan's visual recognition memory test at 3 and 7 months of age[65]. At 3 months of age, *in utero* exposure to PCBs was negatively related with psychomotor development measured with the Bayley Scales of Infant Development, but not at 7 and 18 months[66].

No effects of lactational exposure on neurological and cognitive development were found. Despite the presence of PCBs and dioxins in breast milk, a small beneficial effect of breast-feeding on the quality of movements in terms of fluency was found among 18-month-old toddlers[64]. Moreover, at 7 months of age, breast-fed children even had higher mean scores on both the Fagan and the Bayley test as compared to formula-fed infants[65, 66].

THE PRESENT INVESTIGATIONS

The present study is an extension of the above-mentioned '*Dutch PCB/Dioxin-Breast Milk Study*', and it aims at investigating the effects of prenatal PCB exposure and lactational exposure to PCBs and dioxins on the neurological and cognitive development at 42 months of age. In

addition, we report on the effect of breast-feeding on long-term neurological development.

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Appendix I

Polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), planar PCBs, and mono-, di-, and non-ortho PCBs that were measured in breast milk samples obtained in the 'Dutch PCB/Dioxin-Breast Milk Study'.

Structure	IUPAC nr.	Structure	IUPAC nr.
PCDDs		*PCBs*	
2,3,7,8-TCDD	48	2,4-4'-CB	28
1,2,3,7,8-PeCDD	54	2,5-2'5'-TCB	52
1,2,3,4,7,8-HxCDD	66	2,4-3'4'-TCB	66
1,2,3,6,7,8-HxCDD	67	2,5-3'4'-TCB	70
1,2,3,7,8,9-HxCDD	70	2,4,5-2'4'-PeCB	99
1,2,3,4,6,7,8-HpCDD	73	2,4,5-2'5'-PeCB	101
1,2,3,4,6,7,8,9-OCDD	75	2,3,4-3'4'-PeCB	105[A]
PCDFs		2,4,5-3'4'-PeCB	118[A]
2,3,7,8-TCDF	83	2,3,4-2'3'4'-HxCB	128
1,2,3,7,8-PeCDF	94	2,3,4,5-2'4'-HxCB	137
2,3,4,7,8-PeCDF	114	2,3,4-2'4'5'-HxCB	138
1,2,3,4,7,8-HxCDF	118	2,3,4,5-2'5'-HxCB	141
1,2,3,6,7,8-HxCDF	121	2,3,5,6-2'5'-HxCB	151
1,2,3,7,8,9-HxCDF	124	2,4,5-2'4'5'-HxCB	153
2,3,4,6,7,8-HxCDF	130	2,3,4,5-3'4'-HxCB	156[A]
1,2,3,4,6,7,8-HpCDF	131	2,3,4,5-2'3'4'-HpCB	170[B]
1,2,3,4,7,8,9-HpCDF	134	2,3,5,6-2'3'4'-HpCB	177
1,2,3,4,6,7,8,9-OCDF	135	2,3,4,5-2'4'5'-HpCB	180[B]
Planar PCBs		2,3,4,6-2'4'5'-HpCB	183
3,4,3'4'-TCB	77	2,3,5,6-2'4'5'-HpCB	187
3,4,3'4'5-PeCB	126	2,3,4,5-2'3'4'5'-OCB	194
3,4,5,3'4'5'-HxCB	169	2,3,4,5,6-2'3'4'-OCB	195
		2,3,5,6-2'3'5'6'-OCB	202

[A] Mono-ortho PCB; [B] Di-ortho PCB; IUPAC International Union of Pure and Applied Chemistry.