Chapter 5.10 Polychlorinated biphenyls (PCBs)

General description

Physical and chemical properties

Polychlorinated biphenyls (PCBs) are aromatic, synthetic chemicals which do not occur naturally in the environment. They consist of the biphenyl structure with two linked benzene rings in which some or all of the hydrogen atoms have been substituted by chlorine atoms. The basic molecular structure, including the conventional numbering of the substituent positions, is shown in Fig. 1.

Fig. 1. Structural formula of PCBs

The chemical formula of PCBs is $C_{12}H_{10-n}Cl_n$, where n ranges from 1 to 10. Theoretically, 209 different congeners are possible, but only about 130 of these have been identified in commercial products. Ballschmiter and Zell *(1)* proposed a numbering system for the PCB congeners which has been adopted by the International Union of Pure and Applied Chemists (IUPAC) (Table 1).

All congeners of PCBs are lipophilic and their lipophilicity increases with increasing degree of chlorination. However, they have very low water solubilities. Congeners with a lower degree of chlorination are more volatile than those with a higher degree. Pure individual PCB congeners are colourless and often crystalline. Commercial PCB mixtures are clear to light yellow oils or resins and they do not crystallize, even at low temperatures.

PCBs are practically fire resistant because of their high flash points (170–380 °C). They form vapours which are heavier than air, but are not explosive. They have low electrical conductivity, high thermal conductivity and high resistance to thermal degradation. On the basis of these properties they have been used as dielectric isolators in electrical equipment. Like many organochlorine compounds, many of the congeners are highly persistent and accumulate within food chains. Investigations in many parts of the world have revealed widespread distribution of PCBs in the environment.

The universal distribution of PCBs throughout the world, suggests that PCBs are transported in air *(2)*. The ability of PCBs to co-distil, volatilize from landfills into the atmosphere (adsorption to aerosols with a particle size of < 0.05–20 μm), and resist degradation at low incinerating temperatures, makes atmospheric transport the primary mode of global distribution. In a study in the USA, 92% of the PCBs detected were in the vapour phase *(2)*. In a German study, congeners with a low degree of chlorination were dominant in filtered air, whereas those with a high degree dominated in aerosols and rainfall *(2)*.

Table 1. IUPAC numbers and chlorine atom positions of all PCB congeners *(1)* [a]

No.	Structure	No.	Structure	No.	Structure	No.	Structure
1	2	56	2,3,3',4'	111	2,3,3',5,5'	166	2,3,4,4',5,6
2	3	57	2,3,3',5	112	2,3,3',5,6	167**	2,3',4,4',5,5'
3	4	58	2,3,3',5'	113	2,3,3',5',6	168	2,3',4,4',5',6
4	2,2'	59	2,3,3',6	114**	2,3,4,4',5	169*	3,3',4,4',5,5'
5	2,3	60	2,3,4,4'	115	2,3,4,4',6	170***	2,2',3,3',4,4',5
6	2,3'	61	2,3,4,5	116	2,3,4,5,6	171	2,2',3,3',4,4',6
7	2,4	62	2,3,4,6	117	2,3,4',5,6	172	2,2',3,3',4,5,5'
8	2,4'	63	2,3,4',5	118**	2,3',4,4',5	173	2,2',3,3',4,5,6
9	2,5	64	2,3,4',6	119	2,3',4,4',6	174	2,2',3,3',4,5,6'
10	2,6	65	2,3,5,6	120	2,3',4,5,5'	175	2,2',3,3',4,5',6
11	3,3'	66	2,3',4,4'	121	2,3',4,5',6	176	2,2',3,3',4,6,6'
12	3,4	67	2,3',4,5	122	2',3,3',4,5	177	2,2',3,3',4',5,6
13	3,4'	68	2,3',4,5'	123**	2',3,4,4',5	178	2,2',3,3',5,5',6
14	3,5	69	2,3',4,6	124	2',3,4,5,5'	179	2,2',3,3',5,6,6'
15	4,4'	70	2,3',4',5	125	2',3,4,5,6'	180***	2,2',3,4,4',5,5'
16	2,2',3	71	2,3',4',6	126*	3,3',4,4',5	181	2,2',3,4,4',5,6
17	2,2',4	72	2,3',5,5'	127	3,3',4,5,5'	182	2,2',3,4,4',5,6'
18	2,2',5	73	2,3',5',6	128	2,2',3,3',4,4'	183	2,2',3,4,4',5',6
19	2,2',6	74	2,4,4',5	129	2,2',3,3',4,5	184	2,2',3,4,4',6,6'
20	2,3,3'	75	2,4,4',6	130	2,2',3,3',4,5'	185	2,2',3,4,5,5',6
21	2,3,4	76	2',3,4,5	131	2,2',3,3',4,6	186	2,2',3,4,5,6,6'
22	2,3,4'	77*	3,3',4,4'	132	2,2',3,3',4,6'	187	2,2',3,4',5,5',6
23	2,3,5	78	3,3',4,5	133	2,2',3,3',5,5'	188	2,2',3,4',5,6,6'
24	2,3,6	79	3,3',4,5'	134	2,2',3,3',5,6	189**	2,3,3',4,4',5,5'
25	2,3',4	80	3,3',5,5'	135	2,2',3,3',5,6'	190	2,3,3',4,4',5,6
26	2,3',5	81	3,4,4',5	136	2,2',3,3',6,6'	191	2,3,3',4,4',5',6
27	2,3',6	82	2,2',3,3',4	137	2,2',3,4,4',5	192	2,3,3',4,5,5',6
28	2,4,4'	83	2,2',3,3',5	138	2,2',3,4,4',5'	193	2,3,3',4',5,5',6
29	2,4,5	84	2,2',3,3',6	139	2,2',3,4,4',6	194	2,2',3,3',4,4',5,5'
30	2,4,6	85	2,2',3,4,4'	140	2,2',3,4,4',6'	195	2,2',3,3',4,4',5,6
31	2,4',5	86	2,2',3,4,5	141	2,2',3,4,5,5'	196	2,2',3,3',4,4',5,6'
32	2,4',6	87	2,2',3,4,5'	142	2,2',3,4,5,6	197	2,2',3,3',4,4',6,6'
33	2',3,4	88	2,2',3,4,6	143	2,2',3,4,5,6'	198	2,2',3,3',4,5,5',6
34	2',3,5	89	2,2',3,4,6'	144	2,2',3,4,5',6	199	2,2',3,3',4,5,6,6'
35	3,3',4	90	2,2',3,4',5	145	2,2',3,4,6,6'	200	2,2',3,3',4,5',6,6'
36	3,3',5	91	2,2',3,4',6	146	2,2',3,4',5,5'	201	2,2',3,3',4',5,5',6
37	3,4,4'	92	2,2',3,5,5'	147	2,2',3,4',5,6	202	2,2',3,3',5,5',6,6'
38	3,4,5	93	2,2',3,5,6	148	2,2',3,4',5,6'	203	2,2',3,4,4',5,5',6
39	3,4',5	94	2,2',3,5,6'	149	2,2',3,4',5',6	204	2,2',3,4,4',5,6,6'
40	2,2',3,3'	95	2,2',3,5',6	150	2,2',3,4',6,6'	205	2,3,3',4,4',5,5',6
41	2,2',3,4	96	2,2',3,6,6'	151	2,2',3,5,5',6	206	2,2',3,3',4,4',5,5',6
42	2,2',3,4'	97	2,2',3',4,5	152	2,2',3,5,6,6'	207	2,2',3,3',4,4',5,6,6'
43	2,2',3,5	98	2,2',3',4,6	153	2,2',4,4',5,5'	208	2,2',3,3',4,5,5',6,6'
44	2,2',3,5'	99	2,2',4,4',5	154	2,2',4,4',5,6'	209	2,2',3,3',4,4',5,5',6,6'
45	2,2',3,6	100	2,2',4,4',6	155	2,2',4,4',6,6'		
46	2,2',3,6'	101	2,2',4,5,5'	156**	2,3,3',4,4',5		
47	2,2',4,4'	102	2,2',4,5,6'	157**	2,3,3',4,4',5'		
48	2,2',4,5	103	2,2',4,5',6	158	2,3,3',4,4',6		
49	2,2',4,5'	104	2,2',4,6,6'	159	2,3,3',4,5,5'		
50	2,2',4,6	105**	2,3,3',4,4'	160	2,3,3',4,5,6		
51	2,2',4,6'	106	2,3,3',4,5	161	2,3,3',4,5',6		
52	2,2',5,5'	107	2,3,3',4',5	162	2,3,3',4',5,5'		
53	2,2',5,6'	108	2,3,3',4,5'	163	2,3,3',4',5,6		
54	2,2',6,6'	109	2,3,3',4,6	164	2,3,3',4',5',6		
55	2,3,3',4	110	2,3,3',4',6	165	2,3,3',5,5',6		

[a] Marked congeners have been assigned "toxic equivalency factors" (TEFs): * non-*ortho* congener; ** mono-*ortho* congener; *** di-*ortho* congener. These congeners are also chlorinated in both *para* and at least two *meta* positions.

Sources

Polychlorinated biphenyls (PCBs) have been used commercially since 1929 as dielectric and heat exchange fluids and in a variety of other applications. However, the distribution of PCBs in the environment was not recognized until 1966, when Jensen identified PCBs in human and wildlife samples *(3)*. Many countries and intergovernmental organizations have now banned or severely restricted the production, use, handling, transport and disposal of PCBs. It should also be mentioned that when *de novo* synthesis of PCBs occurs, e.g. in combustion processes, the congener composition is different from that of commercial mixtures.

Occurrence in air

Few studies have been conducted to measure ambient air levels of PCBs, but concentrations appear to differ markedly between locations. Owing to variations in the analytical procedures used, concentrations measured in independent studies must be evaluated with caution. The lowest levels, from 0.002 ng/m^3, are found in non-industrialized and non-contaminated areas, whereas levels of 3.3 ng/m^3 have been measured in the Ruhr area in Germany *(2)*. Near a waste landfill in Yugoslavia and close to industrial plants in Japan, levels of up to 45 and 650 µg/m^3, respectively, were found *(2)*.

Higher levels are found indoors than outdoors. In the USA indoor levels ranged from 44 to 240 ng/m^3, while maximum outdoor levels were 18 ng/m^3 *(2)*. The levels of airborne PCBs were two times higher (457 ± 223 ng/m^3) in buildings with PCB transformers, than in buildings without them (229 ± 106 ng/m^3) *(2)*. The highest indoor levels (up to 7500 ng/m^3) have been reported in buildings constructed from prefabricated concrete elements sealed with elastic materials containing PCBs *(4)*. These buildings were constructed between 1960 and 1975. High concentrations of PCBs may also be found in buildings containing electrical equipment. In 39% of over 120 German buildings suspected to be contaminated, PCB levels exceeding 300 ng/m^3 were reported. High PCB levels were also found in buildings where particle boards containing PCBs had been used for panelling ceilings. Indoor PCB levels were inversely related to the degree of chlorination of the PCB mixtures used *(4,5)*. In a Swedish study, an indoor PCB concentration of 80 ng/m^3 was measured in an apartment house built with PCB-containing joint sealants *(6)*. In three other buildings, with few or no PCB-containing materials, the levels were 1.9–3.6 ng/m^3. Outside these buildings, the levels were lower, 0.5–4.6 ng/m^3.

Plant foliage is a reliable biomonitor of ambient levels of vapour-phase compounds in air. Analysis of archive herbage samples from the period 1965–1989 showed that air concentrations of lower chlorinated PCBs in rural England decreased by a factor of 50 during that time. High-molecular-weight PCBs have also decreased in concentration, but not to such a great extent *(7)*. The lower chlorinated PCBs (IUPAC No. 18, 28 and 52) constitute up to 40% of the total PCBs.

Conversion factors

Conversion factors for different PCB mixtures depend on the degree of chlorination and are between 0.065 (Aroclor 1260) and 0.12 ppm (Aroclor 1221) for 1 mg/m^3 *(2)*.

The concept of toxic equivalency factors

Owing to the fact that dioxin-like compounds normally exist in environmental and biological samples as complex mixtures of congeners, the concept of toxic equivalents (TEQs) has been introduced for risk assessment and regulation. In applying this concept, relative toxicities of

dioxin-like compounds in relation to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (i.e. toxic equivalency factors, TEFs) are determined from *in vitro* and *in vivo* studies. This approach is based on the evidence that there is a common, receptor-mediated mechanism of action for these compounds, but it has its limitations owing to a number of simplifications. The most important limitation is that the combined toxic effects of the components of a given mixture are assumed to be additive, neglecting possible synergism or antagonism. Furthermore, differences in the toxicokinetics of individual congeners are not always taken into account.

The criteria for including a compound in a TEF-scheme has been discussed elsewhere *(8–10)* and the following criteria should be met for a compound to be considered:

18. it should show structural relationship to the PCDDs and PCDFs
19. it should bind to the Ah-receptor
20. it should elicit dioxin-specific biochemical and toxic responses
21. it should be persistent and accumulate in the food chain.

On the basis of these criteria and after evaluating the present database, The WHO European Centre for Environment and Health and the International Programme on Chemical Safety (IPCS) have recommended interim TEFs for three non-*ortho*-, eight mono-*ortho*- and two di-*ortho*-substituted PCBs *(11)* (Table 2).

Table 2. WHO/IPCS interim toxic equivalency factors for human intake of dioxin-like PCBs

Type	IUPAC No.	Congener structure	TEF
Non-*ortho*	77	3,3',4,4'-tetrachlorobiphenyls	0.0005
	126	3,3',4,4',5-pentachlorobiphenyls	0.1
	169	3,3',4,4',5,5'-hexachlorobiphenyls	0.01
Mono-*ortho*	105	2,3,3',4,4'- pentachlorobiphenyls	0.0001
	114	2,3,4,4',5- pentachlorobiphenyls	0.0005[a]
	118	2,3',4,4',5- pentachlorobiphenyls	0.0001
	123	2',3,4,4',5- pentachlorobiphenyls	0.0001
	156	2,3,3',4,4',5- hexachlorobiphenyls	0.0005
	157	2,3,3',4,4',5'- hexachlorobiphenyls	0.0005
	167	2,3',4,4',5,5'- hexachlorobiphenyls	0.00001[a]
	189	2,3,3',4,4',5,5'-heptachlorobiphenyls	0.0001[a]
Di-*ortho*	170	2,2',3,3',4,4',5- heptachlorobiphenyls	0.0001[a]
	180	2,2',3,4,4',5,5'- heptachlorobiphenyls	0.00001[a]

[a]Based on very limited data.

Analytical methods (for air)

Analytical methods used for the quantification of PCBs in air have been described in *(2)*. During the 1970s, improved analytical techniques and methods for the synthesis of pure standards of individual congeners made it possible to use single PCB congeners for quantification purposes *(12)*. At present, several recommended analytical procedures exist for the analysis of PCBs in samples of technical products, air, soil and of biological origin. There are various ways of extraction, clean-up and fractionation of the extracts are used; however, all acceptable methods are based on the determination of individual congeners. Final separation of the PCBs is performed by temperature-programmed high-resolution capillary

gas chromatography, preferentially attached to a mass spectrometric detector, although an electron capture detector can also be used. Identification and quantification of the individual PCB congeners are performed by comparing the retention times and heights of peaks in the sample chromatogram with corresponding peaks in a chromatogram of a mixture of selected, pure reference ^{13}C12-labelled PCB congeners added before the extraction. For the identification and quantification of the non-*ortho* PCB congeners, and preferably also for the mono-*ortho*-substituted PCBs, gas chromatography-mass spectrometry (MS) must be used,. In Germany, a comparison between 22 laboratories analysing PCBs in indoor air found an interlaboratory standard deviation of 25–50 % *(13)*.

Routes of exposure

Air

PCB levels in air are generally higher indoors than outdoors. In addition, most people in the Western world spend most of their time indoors. Subsequently, an exposure assessment is most relevantly based on indoor levels of PCBs. In Germany, indoor levels of up to 7500 ng/m^3 have been determined *(4)*. In another German study of buildings suspected to be contaminated, 39% of the buildings had levels exceeding 300 ng/m^3, which would result in a daily exposure dose of > 0.1 µg/kg. Indoor air levels in noncontaminated buildings, which were reported to be 1.9–3.6 ng/m^3 *(6)*, would result in a daily exposure dose of 0.6–1.2 ng/kg.

In a German office building constructed with PCB-containing rubber sealants, PCB levels of 200–1800 ng/m^3 were determined *(14)*. However, no elevated blood levels of PCB were detected among 30 employees.

Drinking-water

Levels reported in drinking-water are typically between 0.1 and 0.5 ng/litre *(2)*. A person drinking 2 litres of water a day containing 0.5 ng/litre will be exposed to a daily dose of 0.01–0.02 ng/kg (body weight 100–50 kg).

Food

It is currently assumed that the general population receives its major exposure to PCBs through food intake. Since PCBs are lipophilic and accumulate in the food chain, foods of animal origin are an important source of exposure. In general, plants contain lower levels of PCBs, which are commonly close to the detection levels for these chemicals.

A few studies have analysed PCB concentrations in a variety of food commodities and calculated the dietary intake. In Finland, Moilanen et al. *(15)* estimated the total dietary intake of PCBs to be 14.35 µg/day, corresponding to a daily dose of 0.24 µg/kg for a person weighing 60 kg. Of this, 38% came from fish, and especially Baltic herring. However, in a more recent estimation from the Swedish Food Administration *(16)*, the total intake of PCBs in Sweden was calculated to be 3.2 µg/day, corresponding to a daily dose of 0.05 µg/kg body weight (bw). Fish consumption represented 50% of the intake of PCBs. In Germany, daily intakes of around 0.1 µg/kg bw have been reported *(17)*.

Intake calculations based on data from Norway and Sweden *(18,19)* indicated a daily TEQ intake of about 1 pg/kg bw for dioxin-like PCBs using recent Norwegian data on levels in food and food consumption *(19)*. Higher daily TEQ intakes of up to 3.1 pg/kg bw were estimated from calculations based on levels of dioxin-like PCBs in blood *(20,21)* and breast

milk *(22–24)* in individuals exposed to background levels in Norway and Sweden. The discrepancy can most probably be explained by the fact that the calculations based on levels found in human samples represent accumulated intake over many years, while the food data are recent and probably mirror a decrease in environmental levels due to extensive control of known sources in the Nordic countries.

Local eating habits, e.g. intake of fatty fish from contaminated waters, may significantly increase the daily intake of PCBs. Thus, Swedish fishermen active in the Baltic sea and with much higher than average intakes of herring and salmon, were found to have blood levels of PCBs two times higher than those in the general population *(20)*.

Population groups at higher exposures

PCBs are found in human milk at comparatively high concentrations. Infants with human milk as the dominant food source will consequently have a much higher PCB intake than adults. The factors determining the levels found in humans include both lifestyle and the degree of industrialization. Monitoring programmes have indicated a declining trend in PCB-concentrations in breast milk during the last 20–25 years. The decline appears to be somewhat congener specific *(17,25)*.

In addition to individuals who consume large amounts of contaminated food (e.g. fish, breast milk) and those who work with PCBs or PCB-contaminated materials, people living or working in PCB-contaminated buildings may also be subject to high exposures. However, at present, elevated blood levels have not been detected in humans living in such contaminated buildings *(14)*.

Toxicokinetics

Absorption

Several studies confirm that individual congeners and their mixtures are readily absorbed from the gastrointestinal tract of rodents and monkeys. Gastrointestinal absorption of individual congeners in rats has been reported to vary between 66% and 96% *(26)*. The degree of absorption decreases with increasing chlorination *(27)* The effect of vehicles on gastrointestinal absorption of PCBs has not been systematically evaluated.

Rapid absorption and distribution, comparable to that after oral exposure, has been observed in rats exposed to an aerosol of a PCB mixture (Pydraul A200) via inhalation *(28)*.

Several studies with PCB congeners or mixtures have demonstrated effective dermal absorption. In guinea pigs absorption of mixtures was at least 33–56% during 16 days of exposure, whilst monkeys absorbed at least 20% during 28 days of exposure *(29)*. In rats, up to 60% of 3,3',4,4'-tetrachlorobiphenyl was absorbed after 3 days of exposure *(30)*.

Distribution

The distribution of PCBs in the body is dependent on the structure and the physicochemical characteristics of the individual congeners, and is also dose dependent. In most animal species investigated there is an initial uptake in the liver and muscle, probably due to high blood perfusion in the liver and the relatively large volume of muscle *(31)*. Subsequently, the higher chlorinated congeners in particular are redistributed into adipose tissue and skin, reflecting their high affinity for tissues with a high lipid content. In rodents, non-*ortho*-substituted

PCBs, such as 3,3',4,4',5-PeCB, show a higher affinity for the liver than for adipose tissue when compared to those PCB congeners which have chlorine atoms in *ortho* positions *(32–34)*. The increased liver affinity is associated with induction of hepatic binding protein(s).

Metabolism and excretion

Several reviews on the metabolism and excretion of PCBs are available (e.g. *2,35*). The rate limiting step in the elimination of PCBs is metabolism, which primarily occurs via the hepatic cytochrome P-450-dependent monooxygenase system, and which varies depending on the chlorination pattern of the congener. Hydroxylated products are major metabolites, with hydroxylation occurring primarily at the *para* or *meta* positions if these sites are unsubstituted.

Arene oxides occur as intermediate metabolites in the oxidation of some PCBs. They are reactive and can be converted both spontaneously and enzymatically to detoxified products (phenols, dihydrodiols, glutathione conjugates), which are excreted. Alternatively, they can form other potentially toxic (cytotoxic, mutagenic, carcinogenic), covalently-bound substrate-macromolecular adducts.

Besides hydroxylation and subsequent conjugation, sulfur-containing metabolites (e.g. methyl sulfones) and partially dechlorinated metabolites have also been identified. The methyl sulfonyl and hydroxylated PCB metabolites have been detected in human milk and plasma as well as in other biological samples from the environment. Both types of PCB metabolites can preferentially accumulate in specific tissues such as the lung and the fetus. The rate of metabolism of PCB and the resultant metabolite pattern vary between different species.

The excretion of PCB congeners is, to a large extent, dependent on their rate of metabolism to more polar compounds. Most congeners show a biphasic elimination, where the initial half-life is relatively short for all congeners, but the later half-life is much longer and clearly structure-dependent. There is a large variation in half-lives between different PCB congeners depending on the number and position of the chlorine atoms; the range is from a few days to 450 days depending on the congener.

Metabolites of all the congeners studied so far are eliminated primarily via the bile and the faeces. However, those congeners chlorinated to a lower degree are excreted to a greater extent (although less than 5%) via the urine than those chlorinated to a higher degree.

Several experiments in both rodents and monkeys demonstrate that PCBs cross the placental barrier and distribute to fetal tissues *(31)*. At birth, approximately equal or lower levels of PCBs are found in the young as compared to the dam. In contrast to this, transfer of PCBs through suckling accounts for much higher exposure of the young than does placental transfer. In studies with PCB mixtures, postnatal exposure generally resulted in higher concentrations in the weaning young than in the mother. For PCBs it has been observed that transplacental transport in rodents is influenced by the number of chlorine atoms in the molecule. Possible differences in toxicokinetics (e.g. absorption and metabolism) between adult and neonatal mammals have not been studied in detail.

Biomarkers of exposure

PCBs induce several cytochrome P-450-dependent monooxygenases through Ah-receptor-dependent or independent pathways. Several of these enzyme activities can be used as

biomarkers of exposure in both animals and humans. However, these enzyme activities are also influenced by other contaminants in the environment (e.g. polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs)) and the feasibility of using them as markers for human exposure specifically to PCBs seems very limited. However, some of them have been used quite extensively as biomarkers in animal experiments.

Physiologically-based pharmacokinetic modelling
Owing to the complex nature of the mixtures of PCBs, no recent data from physiologically-based pharmacokinetic modelling (interspecies and interindividual differences) are available. However, early attempts have been made to model individual congeners in rats *(36)* and mice *(37)*.

Health effects

Effects on experimental animals and *in vitro* test systems
Evaluation of the toxicity of commercial PCB mixtures is complicated by numerous factors, including congener composition, the varying degree of contamination with toxic compounds, such as PCDFs, and the differences in species susceptibility. Owing to the complex mixture characteristics of PCB exposure, there are a multitude of mechanisms of toxicity involved, consequently resulting in a multitude of responses. No data on the toxicity of PCBs after exposure via inhalation are available.

Toxicological effects

Acute toxicity
Only a few LD_{50}-values for individual congeners have been reported. However, for commercial mixtures there are several studies reporting oral LD_{50}-values in rats ranging from 0.4–11 g/kg bw *(38)*. For technical PCB mixtures, death was reported to occur within 3 days after oral exposure, but in the case of intravenous administration the time to death was even shorter.

Short- and long-term toxicity
The toxic effects commonly observed after acute, subchronic and chronic administration of PCB mixtures and/or individual congeners to animals include a wasting syndrome (a progressive weight loss which is not simply related to decreased food consumption), effects on the liver, skin, immune system, vitamin A homeostasis and the reproductive system, the induction of oedema at various sites, disturbances of the gastrointestinal tract and thyroid gland and the induction of cancer and of different enzyme activities. A recent subchronic study with 2,2',4,4',5,5'-HexaCB in rats has indicated a lowest-observed-adverse-effect level of < 0.6 mg/kg bw per day based on a variety of toxicological and biochemical parameters. In similar studies using dioxin-like PCBs in rats it was found that no-observed- and lowest-observed-adverse effect levels were three to five orders of magnitude lower *(32,33,39)*.

Species differences in sensitivity to PCB toxicity have been identified from chronic exposure studies. Monkeys, guinea pigs and mink appear to be more sensitive to PCB toxicity than rats and mice. The reasons for the variation in species sensitivity have not been elucidated; however, it cannot be explained by different rates of metabolism. Adverse health effects of PCBs which have been observed in wildlife species could be used as possible indicators to study similar effects in humans.

In order to evaluate the relation between the structure of individual congeners and their toxicological potency, Safe *(35)* summarized the available studies which can be used for such a comparison. As in the case of PCDDs and PCDFs, at least some of the toxic effects are mediated through the binding of the PCB congener to the cytosolic Ah receptor. This binding is, in turn, dependent on the presence of lateral chlorines on the molecule. From the results of the studies on individual PCB congeners, and from their structural similarities to TCDD, it is apparent that the non-*ortho* congeners 3,4,4',5-, 3,3',4,4'-, 3,3',4,4',5- and 3,3',4,4',5,5'-CB, which are substituted in both *para*, at least two *meta* and no ortho positions, are clearly the most toxic PCB congeners. Chlorination at one (mono-*ortho*-PCB congeners) or two (di-*ortho*-PCB congeners) *ortho* positions further decreases the toxic potency, owing to a lower probability of attaining a coplanar conformation. PCB congeners that do not bind to the Ah receptor elicit other types of toxic responses which are independent of the Ah receptor.

Carcinogenic effects

Carcinogenicity

Several carcinogenicity experiments with dietary administration of PCBs in mice and rats have been performed and there are several reviews available *(2, 40)*. Besides liver tumours, which are the most frequent tumours observed after PCB exposure, stomach and lung tumours have also been reported.

Some of the bioassays for cancer *(41–44)* have been re-evaluated by a panel of pathologists, applying today's accepted classification for liver pathology *(45)*. The outcome of the evaluation was that only the higher chlorinated mixtures, i.e. Aroclor 1260 and Clophen A60, can be considered to give a clear hepatocarcinogenic response. However, in many of the other studies, there were high incidences of hepatocellular proliferative lesions in both male and female rats, which were related to the administration of the various mixtures (Aroclor 1254, Clophen A30).

Tumour initiation

The ability of various PCB mixtures and individual congeners to initiate the formation of GGT-positive foci in F344 rats has been examined by Hayes et al. *(46)*. None of the PCBs generated GGT-positive foci, whilst known initiators were active in the assay system used.

Tumour promotion

The tumour-promoting potential of PCBs has been studied extensively in two-stage carcinogenesis models in rat liver and also in mouse lung and skin. The administration of PCB mixtures, such as Aroclor 1254 *(47)*, Kanechlor 400 *(48)*, Clophen A50 *(49)*, and Kanechlor 500 *(50–52)* to rats after treatment with different initiating agents has been demonstrated to increase the number and size of altered hepatic foci. Aroclor 1254 has also been shown to cause tumour promotion in liver and lung in mice *(53)*.

Promotion effects have been reported for most of the individual PCB congeners studied in this respect, e.g. 3,3',4,4'-, 4,4'-, 2,2',4,4'-, 2,2',5,5'- and 2,2',4,4',5,5'-CB *(54–56)*, 2,3,4,4',5- and 2,2',4,5'-CB *(57)* and 2,3,3',4,4'- and 3,3',4,4',5-CB *(58)*. Thus, tumour promotion has been demonstrated both for dioxin-like and non-dioxin-like PCBs.

Genotoxicity

There is no convincing evidence that PCBs induce point mutations, either in *Salmonella typhimurium* (Ames test) or in V79 Chinese hamster cells *(2,38)*. Although the results of most assays on cytogenetic effects are negative, some reports demonstrate a significant increase in chromosomal aberrations in mammalian cells, such as chromatid breaks and rearrangement *(2,38)*. PCBs have been reported to bind to DNA both *in vivo* and *in vitro* and both single-strand DNA breaks and the induction of DNA repair have been detected in mammalian cells *in vitro (2,38)*. When taken together, the data indicate that PCBs have little, if any, *in vivo* genotoxic potential. However, some of the congeners, especially those with a low degree of chlorination, may cause mutagenicity and DNA damage. A proposed mechanism for this genotoxicity is the metabolism of these compounds to arene oxide intermediates which are able to alkylate critical cellular macromolecules *(8,35)*.

In summary, several PCB mixtures are hepatocarcinogenic in rodents and are effective promoters of hepatocarcinogenesis in both mice and rats. Several individual PCB congeners, representing various structural groups, have been shown to act as liver tumour promoters in model systems of multistage carcinogenesis in rats. The promoting effects of PCBs have been reported primarily in the liver, but there is also some evidence for promoting effects in the lung and the skin. PCB congeners may act as promoters by multiple mechanisms. No tumour-initiating effects of PCBs have been revealed.

Owing to the lack of dose–response data from animal bioassays, it is presently impossible to perform any quantitative risk evaluation including the establishment of a no-observed-adverse-effect level. Differences in congener composition between commercial mixtures and environmental exposures also imply that the predictive value of these studies are limited with respect to the assessment of the risks from environmental exposure.

Critical organs, tissues and effects

The toxic effects of PCBs have been reported in detail *(2,38)*. The effects on the immune system and on the behavioural development of the young observed at low doses are described briefly below.

Immunotoxic effects

Long-term, low-level exposure to Aroclor 1254 has been shown to produce moderate, but statistically significant, effects on certain immunological parameters (both humoral and cell-mediated) in rhesus monkeys *(59)*. The effects are already apparent at a daily dose of 5 µg/kg bw, corresponding to a whole-blood total PCB level of 10 µg/litre.

Behavioural effects

Hyperactivity and impaired learning ability have been reported for rhesus monkey infants exposed to different Aroclors *in utero* and through suckling *(60–63)*. The lowest dose studied (0.5 ppm Aroclor 1248 in the diet given to the dams), caused hyperactivity in their infants. The authors estimated the weekly intake for the mothers to be approximately 0.04 mg/kg bw – a daily intake of 6 µg/kg bw. The experiments were performed with several cohorts of animals, although the number of animals in each cohort was rather limited at 3–5 animals plus controls. The outcomes in all the studies were similar, i.e. an increase in behavioural activity. Studies of this type in monkeys have not been performed by other laboratories, but supportive data are available from studies in rats, mice and quails (for review, see *64*).

The rhesus monkeys in the studies by Bowman et al. *(59,60)* were exposed to commercial mixtures of PCBs (Aroclor 1248 or 1016). The congener patterns of these mixtures are, however, quite different from that seen in most biological samples, including fish and human milk.

Other effects
Recent studies have demonstrated a multiplicity of adverse effects following exposure both to complex PCB mixtures and to individual congeners *(65)*. PCB exposure results in decreased thyroid hormone levels. Certain PCBs and/or their metabolites are estrogenic while others are anti-estrogenic. Exposure to Aroclor 1254 at a concentration of 5 ppm in the diet causes reproductive and developmental toxicity in rhesus monkeys *(66,67)*. Effects on the offspring of prenatally and lactationally exposed rats, mice and guinea pigs such as delayed puberty, decreased weight of sexual organs and reproductive deficiencies have been observed *(68–70)*. Subtle effects in the offspring due to exposure to PCB 169, similar to those observed for TCDD *(71–74)* have been noted in rats *(75)*. Hearing deficits have recently been reported in rat pups exposed to Aroclor 1254 perinatally and through suckling; these effects can be blocked by thyroxin administration *(76)*.

Interactions with other chemicals
Highly toxic contaminants, such as PCDFs, have been identified in different commercial PCB mixtures. In many studies using such mixtures, the quantitative contribution of these impurities to the observed toxic responses is mainly unknown, as the biological and toxic effects induced in animals treated with dioxin-like PCBs and PCDFs are qualitatively similar. In general, the most toxic PCDF congeners are much more potent than the corresponding PCBs. The toxic effects of PCB mixtures with a similar composition to that in contaminated rice oil, with or without PCDFs, have been compared in rats and monkeys *(77)*. Less severe effects were seen with PCBs without contamination, and only mixtures containing PCDFs caused dermal effects in monkeys. Interaction also occurs with PCDDs and PCDFs (see below).

Effects on humans

Toxicokinetics
Most studies describing the toxicokinetic properties of PCBs in humans indicate that the kinetics of PCBs are qualitatively similar in humans and experimental animals, such as the rat. However, the rates of metabolism and excretion seem to be slower in humans, as illustrated by the longer half-lives of certain congeners in humans (4.1–11.3 months for IUPAC No. 99, 105, 138, 153 and 180 *(78,79)*. However, the database thus far accumulated is very limited. On the basis of *in vivo* and *in vitro* comparative studies, it has been suggested that the metabolism of PCBs in humans would most closely resemble that in rats and monkeys, but not dogs *(80,81)*. The intestinal absorption of PCB in a breast-fed infant was more than 95% *(82)*.

A study of the elimination of PCB congeners from the blood of intoxicated patients in Taiwan found the same chlorination pattern dependence for rapid metabolism and excretion as that described for rats *(79)*. Because of the preferential elimination of certain PCB congeners, the PCB congener pattern of human fat and breast milk clearly differs from that found in common, commercial PCB mixtures.

Under environmental exposure circumstances, the levels of organohalogens in human milk reflect, to a great extent, adipose tissue levels, a reservoir which is built up during several years and is mobilized during lactation *(83)*.

The presence of PCBs in human cord serum, placenta and fetal tissue indicates that they cross the placental barrier. The concentrations are, however, lower than the corresponding maternal levels, mainly due to a lower concentration of lipid in cord blood as compared to maternal blood *(84)*. As in experimental animals, PCB levels in breast-fed children at weaning are generally higher than the corresponding maternal levels. However, only total PCB levels have been measured. After weaning, the concentration of PCBs in children generally declines, mainly owing to dilution in the increasing fat deposits.

Toxicological effects
Several effects of PCB exposure to humans have been reported. Best characterized are the effects following the accidental consumption of PCB- and PCDF-contaminated rice oil in Japan in 1968 (Yusho) and Taiwan in 1979 (Yu-Cheng). About 2000 patients were identified at each accident. The symptoms and toxic effects included chloracne, hyperpigmentation and other dermal effects, liver effects, chronic bronchitis, immunosuppression, hormonal effects, neuropathy, enzyme induction and effects on infants born to exposed mothers such as endocrinological and neurobehavioural effects and hearing deficits. These effects and other exposure situations have been described in detail *(2,38);* the carcinogenic and neurobehavioural effects are described briefly below.

Carcinogenic effects
A few epidemiological studies on the possible association between the incidence of cancer and exposure to PCBs are available (reviewed in *2*). Some indicate an increased incidence of liver and biliary tract cancer and a recent study also indicated a possible association with brain cancer *(85)*. However, the findings are inconsistent and the studies have several limitations, such as the small sample sizes, the limited observation periods, mixed exposures to other chemicals and other confounding variables. In all these studies, the PCB mixtures were contaminated, to various extents, with PCDFs in particular, which may or may not have contributed to the observed effects.

Neurobehavioural effects
A series of epidemiological studies was undertaken in a population eating fish from Lake Michigan. The effects of PCBs were investigated in 242 pregnant women with a high or moderate intake of contaminated Lake Michigan fish and in 71 pregnant women who did not consume fish *(86)*. There were significant associations between the intake of fish and the PCB levels in maternal serum and milk, and also between maternal and cord serum concentrations. PCB levels in maternal serum and breast milk and in cord serum for each mother/infant pair were similar on a fat basis *(87)*. Levels of PCDDs and PCDFs and other contaminants such as methyl mercury were not reported.

There were significant inverse associations between the intake of fish and cord serum PCB levels with gestational age, birth weight, head circumference and size. Furthermore, delayed neonatal autonomic maturity and abnormally weak reflexes were associated with fish intake *(88)*. When the infants were followed up at the age of 7 months, there was an inverse association between the cord blood PCB level and visual recognition (preference for a new stimulus) *(89)*. Associations were found between cord serum level of PCB and poorer

performance in verbal and numerical memory tests at 4 years age (McCarthy memory scale) *(90)*. These children also performed less well in other tests of cognitive development and sustained attention *(91)*. Prenatal exposure to PCBs was correlated to lower body weight at 4 years *(92)*. All these effects correlate with prenatal, but not postnatal exposure. However, the PCB content in breast milk and the duration of breast-feeding, as well as serum PCB level at 4 years were all inversely associated with a composite activity rating. The association with breast-feeding was most marked for children exposed to high milk concentrations of PCBs for more than 12 months. Serum levels at 4 years correlated with the PCB levels in mother's milk and the duration of breast-feeding *(93)*. Decreased ability in tests was associated with cord serum PCB levels of 1.5 μg/litre (0.48 μg per gram of fat).

In a cohort of more than 800 children from the general population in North Carolina, psychomotor development at 6, 12 and 24 months of age correlated inversely with prenatal exposure to PCBs *(94)*. Neonatal hypotonicity and hyporeflexia were also associated with prenatal PCB exposure *(95)*. The effects had no association with exposure through breast-feeding. In a follow-up on the cohort no correlations between McCarthy developmental scores and either exposure to PCBs via the placenta or through breast-feeding were found at 3–5 years of age and there was no association between PCB exposure and the children's school grades at 8–10 years *(96)*.

A recent Dutch study examined the effects of PCDDs, PCDFs and PCBs on neurological development and thyroid hormone status in breast-fed infants exposed to background levels. Lower plasma levels of thyroid stimulating hormone correlated significantly with increasing levels of these compounds *(97)*. In the same cohort, higher levels of these compounds were associated with a higher incidence of reduced neonatal neurological optimality and a higher incidence of hypotonia *(98)*. Although both studies reported concentration-dependent effects at background levels, their clinical significance is presently unknown.

Interaction with other chemicals

As noted above, certain PCB congeners bind to the Ah receptor and elicit TCDD-like responses. Ah-receptor-dependent responses in humans consequently depend on the combined exposure to both PCBs, PCDDs, PCDFs and other environmental contaminants that act by the same mechanism. Additive and even synergistic interactions between dioxin-like and non-dioxin-like PCBs have been demonstrated, e.g. on tumour promotion *(99)*. However, while additive interactions have been demonstrated between some dioxin-like PCBs and PCDDs and PCDFs, both synergistic and antagonistic interactions have also been observed. These interactions are specific for dose, endpoint, congener, mechanism and species.

Evaluation of human health risks

Exposure

PCB analysis should be performed by congener-specific methods. The method of quantifying total PCBs, by comparing the sample peak pattern with that of a commercial mixture, is accurate only when the sample under investigation has been directly contaminated by a commercial mixture. However, because of substantial differences in PCB patterns between biological samples and technical products, this method leads to errors in the quantification of biological samples and also to differences between laboratories owing to the use of different standard mixtures. As a consequence, data have to be interpreted with great care.

Comparisons can only be made between data either from the same laboratory, using the same validated technique and the same standards over a longer period, or from different laboratories when very strict inter-laboratory controls have been applied. Indications of trends can only be obtained when these considerations are taken into account.

Food

Food is the main source of human intake of PCBs; intake through drinking water is negligible.

Daily intake of total PCBs in Sweden was recently estimated at 0.05 µg/kg bw, with a 50% contribution from fish *(16)*. This is markedly lower than an earlier Finnish estimate of 0.24 µg/kg bw *(15)*, and might reflect the decreasing trends in PCB levels in Nordic food. The decline is similar in Germany, where daily intake is currently estimated to be somewhat below 1 µg/kg bw *(17)*. Recent data from the Nordic countries indicate that the current average daily intake in TEQs of dioxin-like PCBs may be slightly above 1 pg/kg bw *(18,19)*.

If the contributions of PCDDs and PCDFs (using the international TEFs of the NATO Committee on the Challenges of Modern Society) are also taken into account, the daily intake in TEQs would be in the range 2–6 pg/kg bw for many European countries and the USA. For certain risk groups, e.g. fishermen from the Baltic sea and Inuits in the Arctic who consume large amounts of contaminated fatty fish, the intake may be up to four times higher.

Air

PCB levels have been shown to be higher in indoor air than in ambient air. Inhalation exposure to PCBs, assuming an indoor air level of 3 ng/m^3 in an uncontaminated building and an inhaled volume of 20 m^3 of air per day for adults, is approximately 0.001 µg/kg bw per day. In contaminated buildings concentrations above 300 ng/m^3 have been found, corresponding to a daily dose of at least 0.1 µg/kg bw. In buildings using PCB-containing sealants, levels up to 7500 ng/m^3 have been found (corresponding to a daily dose of 2.5 µg/kg bw). In ambient air there is a wide variation in the measurements from nonindustrialized (e.g. 0.003 ng/m^3) and industrial/urban areas (e.g. 3 ng/m^3). The levels of dioxin-like PCBs cannot be estimated owing to the lack of congener-specific analytical data.

Health risk evaluation

In 1990, the Joint FAO/WHO Expert Committee on Food Additives concluded that, owing to the limitations of the available data, it was impossible to establish a precise numerical value for a tolerable intake of total PCBs for humans *(100)*. IARC *(101)* concluded that available studies suggested an association between human cancer and exposure to PCBs. Overall, PCBs were classified as probably carcinogenic to humans (group 2A). However, several national governments are employing tolerable daily intakes (TDIs) for PCBs for the purpose of risk management.

In Germany a TDI for PCB of 1–3 µg/kg bw has been suggested. It was also recommended that, for precautionary reasons, the proportional daily intake via indoor air should not exceed 10% of the TDI for long periods. On this basis an action level for source removal of 3000 ng/m^3 has been derived. For concentrations between 3000 ng/m^3 and 10 000 ng/m^3 (i.e. between 3 and 10 µg/m^3) a concrete health risk is not assumed. However, mitigation measures should be undertaken as soon as possible to reduce the level to 300 ng/m^3, below which concentrations are thought to be of no concern. Source removal should also be undertaken if levels are found to be between 300 and 3000 ng/m^3 *(102)*.

Neurobehavioural and hormonal effects have been observed in infants exposed to background concentrations of PCBs, prenatally and/or through breast-feeding. The clinical significance of these observations is, however, unclear.

On average, the contribution from inhalation exposure is approximately 1% of the dietary intake but may approach that intake in certain extreme situations (areas close to sources or contaminated indoor air).

Exposures to dioxin-like PCBs can be converted to TEQs using the WHO/IPCS interim TEFs *(11)* and subsequently be assessed using the TDI for TCDD. In 1992 WHO established a TDI for TCDD of 10 pg/kg bw. This was derived on the basis of TCDD-induced liver cancer in rats *(104)* for which a no-observed-adverse-effect level of 1 ng/kg bw per day, corresponding to a liver concentration of 540 ng/kg on a wet weight basis, was calculated. Owing to toxicokinetic differences between humans and rats, this would correspond to a daily intake in humans of 100 pg/kg bw, to which value an uncertainty factor of 10 to cover interindividual variation was applied. Although not explicitly stated, the TDI can be looked upon as applicable to the total intake of TEQs derived from PCDDs, PCDFs and other dioxin-like compounds that act by the same mechanisms and cause similar types of toxicity.

For the average consumer, the daily intake of dioxin-like PCBs determined as TEQs would be 10–30% of the TDI. When the contribution from the PCDDs and PCDFs is taken into account, the intake would increase to 20–60%. There are, however, groups with specific dietary habits (e.g. a high intake of contaminated food) or occupational exposure that may exceed the TDI for PCDDs and PCDFs.

The recent WHO human milk exposure study *(105)* indicated that the daily intake in TEQs of PCDDs and PCDFs in breast-feeding infants in industrialized countries ranged from about 20 pg/kg bw in less industrialized areas to about 130 pg/kg bw in highly industrialized areas. This indicates intakes which are 2–13 times higher than the TDI. When the contribution from dioxin-like PCBs is taken into account, the intakes may be up to two times higher. However, it has been noted *(103)* that the TDI should not be applied to such infants because the TDI concept relates to a dose ingested throughout a lifetime. The quantity of PCDDs and PCDFs ingested over a 6-month breast-feeding period would be less than 5% of the quantity ingested over a lifetime.

Guidelines

An air quality guideline for PCBs is not proposed because direct inhalation exposures constitute only a small proportion of the total exposure, in the order of 1–2% of the daily intake from food. WHO has not developed a TDI for total PCB exposure. Owing to the multiplicity of mechanisms underlying PCB-induced health effects, there may not be a scientifically sound rationale to set such a TDI. Average ambient air concentrations of PCBs are estimated to be 3 ng/m^3 in urban areas. Although this air concentration is only a minor contributor to direct human exposure, it is a major contributor to contamination of the food chain. It would also be possible to perform such calculations using TEQs for dioxin-like PCBs in ambient air. However, no such analytical data have been published.

Although indoor air levels of PCBs are generally very low, in certain instances, levels of up to several µg /m^3 have been detected. For people living or working in such buildings, exposure to PCBs via air could contribute significantly to the overall PCB exposure.

Because of the potential importance of the indirect contribution of PCBs in air to total human exposure, it is important to control known sources as well as to identify new sources.

References

1. BALLSCHMITER, K. & ZELL, M. Analysis of polychlorinated biphenyls (PCB) by glass capillary gas chromatography. Composition of technical Aroclor- and Clophen-PCB mixtures. *Fresenius Zeitung der Analytische Chemie,* **302:** 20–31 (1980).
2. *Polychlorinated biphenyls and terphenyls,* 2nd ed. Geneva, World Health Organization, 1993 (Environmental Health Criteria, No. 140).
3. JENSEN, S. Report of a new chemical hazard. *New scientist,* **32:** 612 (1966).
4. BALFANZ, E. ET AL. Polychlorinated biphenyls (PCB) and polychlorinated dibenzofurans and dibenzo(*p*)dioxins (PCDF/D) in indoor air due to elastic sealants and coated particle boards. *Extended abstracts, Dioxin '93*.
5. BALFANZ, E. ET AL Sampling and analysis of polychlorinated biphenyls (PCB) in indoor air due to permanently elastic sealants. *Chemosphere,* **26:** 871–880 (1993).
6. HAMMAR, T. PCB i fogmassor. Rapport, Länsstyrelsen i Kalmar län (1992) [in Swedish].
7. JONES, K.C. ET AL. Evidence for a decline of PCBs and PAHs in rural vegetation and air in the United Kingdom. *Nature,* **356:** 137–140 (1992).
8. SAFE, S. Polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: Environmental and mechanistic considerations which support the development of toxic equivalency factors. *CRC critical review of toxicology,* **21:** 51–88 (1990).
9. BARNES, D. ET AL. Toxicity equivalency factors for PCBs? Quality Assurance. *Good practice, regulation, and law,* **1:** 70–81 (1991).
10. AHLBORG, U.G. ET AL. Impact of polychlorinated dibenzo-*p*-dioxins, dibenzofurans and biphenyls on human and environmental health, with special emphasis on application of the toxic equivalency factor concept. *European journal of pharmacology,* **228:** 179–199 (1992).
11. AHLBORG, U.G. ET AL. Toxic equivalency factors for dioxin-like PCBs. Report on a WHO-ECEH and IPCS consultation, December 1993. *Chemosphere,* **28:** 1049–-1967 (1994).
12. JENSEN, S. & SUNDSTRÖM, G. Structures and levels of most chlorobiphenyls in two technical PCB products. *Ambio,* **3:** 70–76 (1974).
13. ULLRICH, D. Results of an intercomparison exercise to determine PCB in indoor air. In: *Proceedings of the 6th International Conference on Indoor Air Quality and Climate.* Vol. 2, 1993, pp. 363–368.
14. BENTHE, C. ET AL. Polychlorinated biphenyls. Indoor air contamination due to Thiocol-rubber sealants in an office building. *In: Dioxin '91: 11th International Symposium on Chlorinated Dioxins and Related Compounds, Research Triangle Park, NC, 23–27 September 1991.*
15. MOILANEN, R., PYYSALO, H. & KUMPULAINEN, J. (1986) Average total dietary intakes of organochlorine compounds from the Finnish diet. *Zeitung fur Lebensmittel Untersuchung und Forschung,* **182:** 484–488
16. DARNERUD, P.O. ET AL. Bakgrund till de reviderade kostråden. PCB och dioxiner i fisk. *Vår föda,* **47:** 10–21 (1995).

17. BECK, H. Occurrence in food human tissues and human milk. *Proceedings from the Toxicology Forum on Chlorinated organic chemicals. Their effect on human health and the environment, Berlin, Germany 19–21 September 1994*.
18. SVENSSON, B.-G. ET AL. Exposure to dioxins and dibenzofurans through consumption of fish. *New England journal of medicine,* **324:** 8–12 (1991).
19. FÆRDEN, K. *Dioksiner i næringsmidler. Oppsummering av analyser i 1989 og 1990* [Dioxins in food]. Oslo, National Food Control Authority, 1991 (SNT-Rapport 4).
20. ASPLUND, L. ET AL. Polychlorinated biphenyls, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (p,p'-DDT) and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE) in human plasma related to fish consumption. *Archives of environmental health*, 49: 477–486 (1994).
21. JOHANSEN, H.R. ET AL. PCDDs, PCDFs and PCB in human blood in relation to consumption of crabs from a contaminated fjord area in Norway. *Environmental health perspectives*, 104: 756–764 (1996)..
22. CLENCH-AAS, J. ET AL. *Polychlorinated biphenyls (PCB), dibenzo-p-dioxins PCDD and dibenzofurans (PCDF) in human milk from three geographic areas in Norway.* Lillestrøm, Norwegian Institute for Air Research, 1988 (NILU-Report 56/88).
23. JOHANSEN, H.R. ET AL. Congener-specific determination of polychlorinated biphenyls and organochlorine pesticides in human milk from Norwegian mothers living in Oslo. *Journal of toxicology and environmental health,* **42:** 157–171 (1994).
24. BECHER, G. ET AL. PCDDs. PCDFs and PCBs in human milk from different parts of Norway and Lithuania. *Journal of toxicology and environmental health*, 46: 133-148 (1995).
25. NORÉN, K. & LUNDÉN, A. Trend studies of polychlorinated biphenyls, dibenzo-p-dioxins and dibenzofurans in human milk. *Chemosphere,* **23:** 1895–1901 (1991)
26. TANABE, S., NAKAGAWA, Y. & TATSUKAWA, R. Absorption efficiency and biological half-life of individual chlorobiphenyls in rats treated with Kanechlor products. *Agricultural biology and chemistry,* **45:** 717–726 (1981).
27. BERGMAN, Å., LARSEN, G.L. & BAKKE, J.E. Biliary secretion, retention and excretion of five ^{14}C-labelled polychlorinated biphenyls in the rat. *Chemosphere,* **11:** 249–253 (1982).
28. BENTHE, H.F., KNOP, J. & SCHMOLDT, A. Aufnahme und verteilung nach inhalation polychlorierter biphenyle (PCB). *Archiv fur Toxicologie,* **29:** 85–95 (1972).
29. WESTER, R.C. ET AL. Polychlorinated biphenyls (PCBs): Dermal absorption, systemic elimination, and dermal wash efficiency. *Journal of toxicology and environmental health,* **12:** 511–519 (1983).
30. JACKSON, J.A., DILIBERTO, J.J. & BIRNBAUM, L.S. Estimation of octanol-water partition coefficients and correlation with dermal absorption for several polyhalogenated aromatic hydrocarbons. *Fundamental and applied toxicology,* **21:** 334–344 (1993).
31. *Drinking water criteria document for polychlorinated biphenyls (PCBs).* Cincinnati, OH, US Environmental Protection Agency, 1990.
32. VAN BIRGELEN, A.P.J.M. ET AL. Toxic potency of 3,3',4,4',5-pentachlorobiphenyl relative to and in combination with 2,3,7,8-tetrachlorodibenzo-p-dioxin in a subchronic feeding study in the rat. *Toxicology and applied pharmacology,* **127:** 209–211 (1994).
33. VAN BIRGELEN, A.P.J.M. ET AL. Toxic potency of 2,3,3',4,4',5-hexachlorobiphenyl relative to and in combination with 2,3,7,8-tetrachlorodibenzo-p-dioxin in a subchronic feeding study in the rat. *Toxicology and applied pharmacology,* **126:** 202–213 (1994).

34. YOSHIMURA, H. ET AL. Inductive effect on hepatic enzymes and toxicity of congeners of PCBs and PCDFs. Environmental health perspectives, **59:** 113–119 (1985).
35. SAFE, S. Polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs): Biochemistry, toxicology and mechanism of action. *CRC Critical reviews of toxicology,* **13:** 319–395 (1984).
36. LUTZ, R.J. ET AL. A preliminary pharmacokinetic model for several chlorinated biphenyls in the rat. *Drug metabolism and disposition,* **5:** 386 (1977).
37. TUEY, D.H., & MATTHOEWS H.B. Use of a physiological compartment model for the rat to describe the pharmacokinetics of several chlorinated biphenyls in the mouse. *Drug metabolism and disposition,* **20:** 397 (1980).
38. AHLBORG,U.G., HANBERG, A. & KENNE, K. *Risk assessment of polychlorinated biphenyls (PCBs).* Nordic Council of Ministers, Nord 1992:26.
39. VAN BIRGELEN, A. ET AL. Toxicity and biochemical potencies of polychlorinated biphenyl congeners relative to 2,3,7,8-tetrachlorodibenzo-p-dioxin in three month feeding studies in the rat. *Dioxin '92*, **10:** 373–376 (1992).
40. SILBERHORN, E.M., GLAUERT, H.P. & ROBERTSSON, L.W. Carcinogenicity of polyhalogenated biphenyls: PCBs and PBBs. *CRC critical review of toxicology,* **20:** 440–496 (1990).
41. KIMBROUGH, R.D. ET AL. Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Aroclor 1260. *Journal of the National Cancer Institute,* **55:** 1453–1459 (1975).
42. *Bioassay of Aroclor 1254 for possible carcinogenicity.* National Cancer Institute, 1978 (Carcinogenesis Technical Report Series, No. 38).
43. SCHAEFFER, E., GREIM, H. & GOESSNER, W. Pathology of chronic polychlorinated biphenyl (PCB) feeding in rats. *Toxicology and applied pharmacology,* **75:** 278–288 (1984).
44. NORBACK, D.H. & WELTMAN, R.H. Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. *Environmental health perspectives,* **60:** 97–105 (1985).
45. *Reassessment of liver findings in five PCB studies in rats.* Washington, DC, Institute for Evaluating Health Risks, 1991.
46. HAYES, M.A. ET AL. Influence of cell proliferation on initiating activity of pure polychlorinated biphenyls and complex mixtures in resistant hepatocyte in vivo assays for carcinogenicity. *Journal of the National Cancer Institute,* **74:** 1037–1041 (1985).
47. PRESTON, B.D. ET AL. Promoting effects of polychlorinated biphenyls (Aroclor 1254) and polychlorinated dibenzofuran-free Aroclor 1254 on diethylnitrosamine-induced tumorigenesis in the rat. *Journal of the National Cancer Institute,* **66:** 509–514 (1981).
48. KIMURA, N.T., KANEMATSU, T. & BABA, T. Polychlorinated biphenyl(s) as a promotor in experimental hepatocarcinogenesis in rats. *Zeitung fur Krebsforschung,* **87:** 257–266 (1976).
49 OESTERLE, D. & DEML, E. Dose-dependent promoting effect of polychlorinated biphenyls on enzyme-altered islands in livers of adult and weanling rats. *Carcinogenesis,* **5:** 351–355 (1984).
50. NISHIZUMI, M. Enhancement of diethylnitrosamine hepatocarcinogenesis in rats by exposure to polychlorinated biphenyls or phenobarbital. *Cancer letters,* **2:** 11–16 (1976).
51. ITO, N. ET AL. Enhancing effect of chemicals on production of hyperplastic liver nodules induced by N-2-fluorenyl-acetamide in hepatectomized rats. *GANN,* **69:**143–144 (1978)

52. TATEMATSU, M. ET AL. Enhancing effect of inducers of liver microsomal enzymes on induction of hyperplastic liver nodules by *N*-2-fluorenyl-acetamide in rats. *Journal of the National Cancer Institute,* **63:** 1411–1416 (1979).
53. ANDERSON, L.M. ET AL. Promotion to polychlorinated biphenyls of lung and liver tumours in mice. *Carcinogenesis,* **15:**2245–2248 (1994).
54. OESTERLE, D. & DEML, E. Promoting effect of various PCBs and DDT on enzyme altered islands in rat liver. *Archives of pharmacology supplement,* **316:** R16 (1981).
55. BUCHMANN, A. ET AL. Polychlorinated biphenyls, classified as either phenobarbital-or 3-methylcholantrene-type inducers of cytochrome *P*-450, are both hepatic tumor promoters in diethylnitrosamine-initiated rats. *Cancer letters,* **32:** 243–253 (1986).
56. SARGENT, L. ET AL. Study of the separate and combined effects of the non-planar 2,5,2',5'- and the planar 3,4,3',4'-tetrachlorobiphenyl in liver and lymphocytes *in vivo*. *Carcinogenesis,* **12:** 793–800 (1991).
57. BUCHMANN, A. ET AL. Effects of polychlorinated biphenyls in rat liver: Correlation between primary subcellular effects and promoting activity. *Toxicology and applied pharmacology,* **111:** 454–468 (1991).
58. HEMMING, H. Relative tumour promoting activity of three polychlorinated biphenyls in rat liver. *European journal of pharmacology,* **248:** 163–174 (1993).
59. TRYPHONAS, H. ET AL. Effect of chronic exposure of PCB (Aroclor 1254) on specific and nonspecific immune parameters in the rhesus (*Macaca mulatta*) monkey. *Fundamental and applied toxicology,* **16:** 773–786 (1991).
60. BOWMAN, R.E., HEIRONIMUS, M.P. & ALLEN, J.R. Correlation of PCB body burden with behavioral toxicology in monkeys. *Pharmacology, biochemistry and behaviour,* **9:** 49–56 (1978).
61. BOWMAN, R.E., HEIRONIMUS, M.P. & BARSOTTI, D.A. Locomotor hyperactivity in PCB-exposed rhesus monkeys. *Neurotoxicology,* **2:** 251–268 (1981)
62. LEVIN, E.D., SCHANTZ, S.L. & BOWMAN, R.E. Delayed spatial alteration deficits resulting from perinatal PCB exposure in monkeys. *Archives of toxicology,* **62:** 267–273 (1988).
63. SCHANTZ, S.L., LEVIN, E.D. & BOWMAN, R.E. Long-term neurobehavioral effects of perinatal polychlorinated biphenyl (PCB) exposure in monkeys. *Environmental toxicology and chemistry,* **10:** 747–756 (1991).
64. TILSON, H.A. ET AL. Polychlorinated biphenyls and the developing nervous system: Cross-species comparisons. *Neurotoxicology and teratology,* **12:** 239–248 (1990).
65. BIRNBAUM, L.S., Developmental effects of dioxins. *Environmental health perspectives*, 103 (Suppl. 7): 89-94 (1995).
66. ARNOLD, D.L. ET AL. Toxicological consequences of Aroclor 1254 ingestion by female Rhesus (Macaca Mulatta) monkeys. Part 1A. Prebreeding phase: Clinical health findings. *Food chemistry and toxicology,* **31:** 799–810 (1993).
67. ARNOLD, D.L. ET AL. Toxicological consequences of Aroclor 1254 Ingestion by female Rhesus (Macaca Mulatta) monkeys. Part 1B. Prebreeding phase: Clinical and analytical laboratory findings. *Food chemistry and toxicology,* **31:** 811–824 (1993).
68. SAGER, D.B. Effects of postnatal exposure to polychlorinated biphenyls on adult male reproductive function. *Environmental research,* **31:** 76–94 (1983).
69. SAGER, D., GIRARD, D. & NELSON, D. Early postnatal exposure to PCBs: Sperm function in rats. *Environmental toxicology and chemistry*, **10:** 737–746 (1991).
70. SAGER, D.B. & GIRARD, D.M. Long-term effects on reproductive parameters in female rats after translactational exposure to PCBs. *Environmental research,* **66:** 52–76 (1994).

71. MABLY, T.A., MOORE, R.W. & PETERSON, R.E. *In utero* and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. I. Effects on androgenic status, *Toxicology and applied pharmacology,* **114:** 97–107 (1992).
72. MABLY, T.A. ET AL. *In utero* and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-*p*-dioxi. II. Effects on sexual behavior and the regulation of luteinizing hormone secretion in adulthood, *Toxicology and applied pharmacology,* **114:** 108–117 (1992).
73. MABLY, T.A. ET AL. *In utero* and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. III. Effects on spermatogenesis and reproductive capability, *Toxicology and applied pharmacology,* **114:** 118–126 (1992).
74. GRAY, L.E. JR ET AL. Exposure to TCDD during development permanently alters reproductive function in male Long Evans rats and hamsters: reduced ejaculated an epididymal sperm numbers and sex accessory gland weights in offspring with normal androgenic status. *Toxicology and applied pharmacology,* **131:** 108–118 (1995).
75. MORSE, D.C. ET AL. Interference of polychlorinated biphenyls in thyroid hormone metabolism: Possible neurotoxic consequences in fetal and neonatal rats. *Chemosphere,* **25:** 165–168 (1992).
76. GOLDEY, E.S. ET AL. Developmental exposure to polychlorinated biphenyls (Aroclor 1254) reduces circulating thyroid hormone concentrations and causes hearing deficits in rats. *Toxicology and applied pharmacology*, 135: 77-88 (1995).
77. KUNITA, N. ET AL. Biological effect of PCBs, PCQs and PCDFs present in the oil causing Yusho and Yu-Cheng. *Environmental health perspectives,* **59:** 79–84 (1985).
78. BÜHLER, F., SCHMID, P. & SCHLATTER, CH. Kinetics of PCB elimination in man. *Chemosphere,* **17:** 1717–1726 (1988)
79. CHEN, P.H. ET AL. Comparative rates of elimination of some individual polychlorinated biphenyls from the blood of PCB-poisoned patients in Taiwan. *Food chemistry and toxicology,* **20:** 417–425 (1982).
80. SCHNELLMANN, R.G., PUTNAM, C.W. & SIPES, I.G. Metabolism of 2,2',3,3',6,6'-hexa-chlorobiphenyl and 2,2',4,4',5,5'-hexachlorobiphenyl by human hepatic microsomes. *Biochemistry and pharmacology,* **32:** 3233–3239 (1983).
81. SCHNELLMANN, R.G. ET AL. The hydroxylation, dechlorination and glucuronidation of 4,4'-dichlorobiphenyl by human hepatic microsomes. *Biochemistry and pharmacology,* **33:** 3503–3509 (1984).
82. MCLACHLAN, M.S. Digestive tract absorption of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in a nursing infant. *Toxicology and applied pharmacology,* **123:** 68–72 (1993).
83. JENSEN, A.A. Transfer of chemical contaminants into human milk. *In*: Jensen, A.A. & Slorach, S.A. ed. *Chemical contaminants in human milk.* CRC Press, 1991, pp 9–19
84. JACOBSON, J.L. ET AL. The transfer of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) across the human placenta and into maternal milk. *American journal of public health,* **74:** 378–379 (1984).
85. SINKS, T. ET AL. Mortality among workers exposed to polychlorinated biphenyls. *American journal of epidemiology,* **136:** 389–398 (1992).
86. FEIN, G.G. ET AL. Prenatal exposure to polychlorinated biphenyls: Effects on birth size and gestational age. *Journal of paediatrics,* **105:** 315–320 (1984).
87. JACOBSON, S.W. ET AL. Intrauterine exposure of human newborns to PCBs: measures of exposure. In: D'ITRI, F.M. & KAMRIN, M. ed. *PCBs: human and environmental hazards.* Boston, Butterworth, 1983, pp. 311–343.

88. JACOBSON, J.L. Prenatal exposure to an environmental toxin: A test of the multiple effects model. *Developmental psychology,* **20:** 523–532 (1984).
89. JACOBSON, S.W. ET AL. The effect of intrauterine PCB exposure on visual recognition memory. *Child development,* **56:** 853–860 (1985).
90. JACOBSON, J.L., JACOBSON, S.W. & HUMPHREY, H.E.B. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. *Journal of pediatrics,* **116:** 38–45 (1990).
91. JACOBSON, J.L. ET AL. Effects of prenatal PCB exposure on cognitive processing efficiency and sustained attention. *Developmental psychology,* **28:** 297–306 (1992).
92. JACOBSON, J.L., JACOBSON, S.W. & HUMPHREY, H.E.B. Effects of exposure to PCBs and related compounds on growth and activity in children. *Neurotoxicology and teratology,* **12:** 319–326 (1990).
93. JACOBSON, J.L. ET AL. Determinants of polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), and dichlorodiphenyl trichloroethane (DDT) levels in the sera of young children. *American journal of public health,* 79:1401-1404 (1989).
94. GLADEN, B.C. ET AL. Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene transplacentally and through human milk. *Journal of paediatrics,***113:** 991–995 (1988).
95. ROGAN, W.J. ET AL. Neonatal effects of transplacental exposure to PCBs and DDE. *Journal of pediatrics,* **109:** 335–341 (1986).
96. GLADEN, B.C. & ROGAN, W.J. Effects of perinatal polychlorinated biphenyls and dichlorodiphenyl dichloroethene on later development. *Journal of paediatrics,* **119:** 58–63 (1991).
97. KOOPMAN-ESSEBOOM, C. ET AL. Effects of dioxins and polychlorinated biphenyls on thyroid hormones status of pregnant women and their infants. *Pediatric research,* **36:** 468–473 (1994).
98. HUISMAN, M. ET AL. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. *Early human development,* **41:** 111–127 (1995).
99. BAGER, Y. ET AL. Interaction of 3,4,5,3′,4′-pentachlorobiphenyl and 2,4,5,2′,4′,5′-hexachlorobiphenyl in promotion of altered hepatic foci in rats. *Toxicology and pharmacology*, 77: 149-154 (1995).
100. *Evaluation of certain food additives and contaminants. Thirty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives*. Geneva, World Health Organization, 1990 (Technical Report Series, No. 789).
101. *Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42*. Lyon, International Agency for Research on Cancer, 1987 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Suppl. 7).
102. ROSSKAMP, E. Polychloriente Biphenyle ub der Innerraumluft - Sachstand, *Bundesgesundheitsblatt,* **35:** 434 (1992).
103. AHLBORG, U.G., KIMBROUGH, R.D. & YRJÄNHEIKKI, E.J., ed. Special issue: Tolerable daily intake of PCDDs and PCDFs. *Toxic substances journal,* **12:** 101–131 (1992).
104. KOCIBA, R.J. ET AL. Results of a two-year toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats, *Toxicology and applied pharmacology,* **46:** 279 (1978).
105. *Levels of PCBs, PCDDs and PCDFs in human milk. Second round of WHO coordinated exposure study.* Geneva, World Health Organization, 1992 (Environmental Health Series, No.3).

