Exposure to Mixtures and Congeners of Polychlorinated Biphenyls

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There are 209 congeners of polychlorinated biphenyls (PCBs), the metabolism and toxicity of which vary by congeners. Use of PCBs is now restricted, but environmental contamination and human exposure persist. Analysis for "total PCBs" in biological samples gives limited information; congener-specific analysis is far more informative, but more complicated. Concentrations of congeners in serum/plasma, adipose tissue, or milk are useful biomarkers of exposure. Lipids may contain similar concentrations and congener patterns, but these vary between exposures and are different from those of the corresponding exposure mixtures; hence, analysis of lipids cannot be used to identify the original exposure. Some non- and mono-ortho congeners may attain a coplanar conformation, which renders them capable of a dioxin-like action. Toxic equivalency factors (TEFs) have been used to sum that risk as toxic equivalents (TEQs), which are considerably different from congener concentrations. No reliable data have been developed on the relationship between concentrations of "total PCBs" or congeners in biological samples and effects of PCBs on human health, mainly because of the various analytical procedures involved and confounding exposures.

Indexing Terms: blood/breast milk/adipose tissue/fish/toxicology/environmental hazards

Polychlorinated biphenyls (PCBs) were widely used in industry and various products for several decades. Thus, both "normal" and accidental occupational exposures have produced outbreaks of poisoning. Also, because of environmental pollution, there is still a general exposure in the population, the health consequences of which are unclear. Thus, reliable biomarkers of exposure/risk and effects are needed.

Several comprehensive reviews on health aspects of PCBs have been published recently (1-4). The present review is partly based on these.

PCB Structure, Chemical and Physical Properties, and Commercial Use

There are 209 individual PCB congeners. The numbering system adopted by the International Union of Pure and Applied Chemistry (IUPAC) shown in Fig. 1, will be used here. From a toxicological point of view, both the degree of chlorination and the stereochemical structure of these compounds is important. Not all congeners are present in individual commercial mixtures or in the environment.

PCBs have several technically interesting properties, including high heat and fire resistance, low electrical conductivity, and high thermal conductivity. Accordingly, PCBs had a wide commercial use, starting in 1929, mainly as dielectric (in transformers and capacitors) and heat-exchange fluids and lubricating oils. They were always used as mixtures of congeners (e.g., Aroclor 1016, 1248, 1260; Clophen A40, A50, A60; Kanechlor 300, 400, 500; Phenoclor DP6), and the degree of chlorination ranged from 210 to 680 g/kg.

PCBs are also persistent in the environment. Being lipophilic (increasingly so with increasing degree of chlorination), they accumulate in the food chain. Jensen discovered PCBs in environmental samples in 1966 (5). This led to administrative actions in many countries: in Sweden, the use of PCBs was restricted in 1972, and new PCBs-containing products were prohibited in 1978; by 1995, all PCBs will be replaced. However, environmental exposure will remain for a long time.

Analysis

PCBs can be separated chromatographically and detected by electron capture or mass fragmentography. Methods for determination of total PCBs have considerable limitations. Results are highly dependent on the chromatographic method used, which calibrator mixtures are used, and which peaks are selected for quantification.

Generally, the sum of one or more peaks are compared with those of the corresponding peaks in one or several commercial mixtures (6). However, the congeners dominating in biological samples, because of selective degradation, as well as absorption, distribution, biotransformation, and excretion (see below), differ from those in the mixtures (6), greatly complicating analysis. Also, the congener patterns in biological samples vary.

Historically, packed-column gas chromatography has been used for assessing total PCBs in humans. However, because this technique cannot adequately account for some congeners, it is now used only as a quick screening method (7). Capillary gas chromatography, with better resolution, gives more adequate results (7, 8). Nonethe-
Fig. 1. Structure of 10 polychlorinated biphenyls, named according to terminology of the International Union of Pure and Applied Chemistry (IUPAC).

less, the concentrations of total PCBs reported by laboratories using different analytical procedures may vary by as much as one order of magnitude (3).

A better alternative is the quantitative determination and reporting of relevant individual congeners (6). Recently, the availability of standards, as well as high-resolution gas chromatography/mass spectrometry, has made it possible to determine even the extremely low concentrations of non-ortho-PCB congeners in biological samples, which are two to five orders of magnitude lower than the most prevalent congeners (9–11). Particular preparation methods are used, usually involving activated carbon or a 2(1-pyrenyl)ethyldimethysilylated silica gel HPLC column. However, large amounts of sample are required, e.g., 45 mL of plasma (11).

To minimize variations in concentration between different types of biological samples, and to reduce the interindividual variation, the concentration is often related to the lipid content of the sample. However, the lipid determinations have often been unsatisfactory, possibly because of the variety of methods used (12).

Toxicology

A large amount of information is available on the toxicological properties of PCB mixtures and individual congeners (3). The general picture is of considerable variation between different species and, within a species, between the different congeners. In the following, we will briefly review only information of immediate relevance for the use of biomarkers in humans.

Metabolism

PCBs are readily absorbed from the gastrointestinal tract (3) and somewhat through the skin and lungs. Widely distributed in the body, all PCB congeners accumulate in the highest concentrations in the adipose tissue. PCBs also cross the placenta and are excreted into milk (3, 13, 14).

PCBs are slowly eliminated in humans. In one volunteer, the half-life for di-ortho IUPAC 153 was 11 months (15). Similar half-lives were found for the mono-ortho IUPACs 105 and 118 in Yu-Cheng patients (see below) followed for 1–2 years after an outbreak of poisoning (16). However, other studies of these and other individual congeners, as well as of congener combinations, in occupationally exposed workers (17–21) and Yusho patients (22) followed for 4–8 years after exposure ceased, have shown half-lives of several years. The reasons for these discrepancies are not known. Some data indicate a nonlinear elimination, which may be due to enzyme induction by PCBs or other contaminants at high concentrations.

Hence, accumulation for many years after an increase in exposure would be expected. This may explain the relation between long-term exposure and the concentration of PCBs in serum (23, 24), as well as between age and the serum concentration (11, 25, 26).

Effects

Information on the toxic effects of PCBs are limited in some aspects (3, 27). Experimental studies in animals often refer to commercial preparations, and the human exposures always involve a mixture of congeners. Also, variation between species is wide. Moreover, the data on humans is from subjects exposed to mixtures that are often contaminated with other polychlorinated compounds.

Human studies. In 1968 and 1979, there were outbreaks of poisoning in Japan and Taiwan, caused by rice oil contaminated with PCBs (and other polychlorinated compounds, see below; 2, 3). The syndromes were called Yusho and Yu-Cheng (rice oil disease), respectively. The ~4000 patients affected had skin disease (chloracne), liver damage, immunosuppression, and neuropathy. Infants delivered by poisoned mothers were affected, having retarded postnatal physical and neurobehavioral development (28). Further, follow-up of Yusho patients indicated an increased risk of deaths from liver and lung cancer (29).

A series of cases of occupational poisoning have been reported (3), with reported effects similar to those in Japan and Taiwan. Also, studies of occupationally exposed workers have indicated increased deaths from cancer (3).

The Yusho/Yu-Cheng outbreaks, as well as the studies of occupational exposure, have serious limitations regarding possible conclusions to draw on the risks of "pure" exposure to PCBs. The rice oils were also contaminated with other polychlorinated compounds, mainly polychlorinated dibenzofurans (PCDFs), which may cause the same effects and which are more toxic than the PCBs (30), polychlorinated dibenzo-p-dioxins (PCDDs), and polychlorinated naphthalenes and quar-terphenyls. The occupational poisonings may also involve confounding exposures.

Other experiments. Animal experiments with PCB
mixtures or individual congeners have also displayed effects on the skin, liver, and immune and nervous systems, as well as reproductive and developmental disturbances, and liver tumors (3). There is a striking similarity between the toxic syndrome induced by the non-ortho- and, to a lesser extent, the mono-ortho-PCBs and that caused by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (3, 27). However, the majority of the individual PCBs do not produce the full dioxin-like syndrome.

PCBs cause induction of hepatic cytochrome P450-dependent monoxygenases (31). Thus, the non-ortho-PCB (e.g., IUPACs 77, 126, and 169) cause 3-methylcholanthrene-type induction (cytochromes CYP1A1/A2); the mono-ortho-PCB (e.g., IUPACs 105, 118, 156, and 157) also induce in a phenobarbital-like way (cytochromes CYP2B1/B2). The di-ortho congener IUPAC 153 causes a phenobarbital-type induction only.

It has been suggested that methylcholanthrene-type induction is mediated through binding of the PCB congener to the cytosolic aryl hydrocarbon receptor protein (27). This kind of binding is well-known for the PCDDs. The congeners that bind most strongly cause the most pronounced induction. Binding of PCBs to the receptor depends on the stereochemical similarity between the PCB congener and TCDD. Only PCBs that can attain a coplanar conformation and which have lateral (para and meta) chlorines can bind (i.e., non-ortho congeners; Fig. 1). Chlorination at one (mono-ortho) or two (di-ortho) positions stepwise decreases the probability of attaining a coplanar formation and thus binding.

Safe (27) used experimental data for individual PCB congeners, and their extent of structural similarities to TCDD, to establish a series of TCDD TEFs for PCB congeners. This makes it possible to calculate TCDD TEQs for amounts and concentrations of individual PCB congeners, and for the sum of mixtures. Later, Ahlborg et al. (3) proposed a slightly different set of TEFs, based more upon methylcholanthrene-type enzyme induction in vivo (Table 1). The latter TEFs and TEQs will be used here. A WHO meeting in 1993 (32) modified the values for some congeners.

We stress that the TEF concept has several problems. TEFs are based mainly on short-term studies and may not adequately predict chronic toxicity, partly because of differences in toxicokinetics between congeners. Also, different congeners may interact and, in at exposures to mixtures, depending on their relative concentrations, the effects of the different components in the mixture are not always additive. Moreover, the uncertainty may vary over a wide range. Further, as said above, many congeners have effects other than dioxin-like ones.

Probably, other mechanisms account for the toxic effects of PCBs than just the dioxin-like ones. However, at present, insufficient information is available for estimating the relative potency for possible non-dioxin-like effect.

**Biomarkers of Exposure to PCBs**

In the occupational setting and in accidents, people are exposed to the PCB congeners in a commercial mixture. Given the different metabolic fates of the individual congeners, the pattern of composition in biological samples will, as said above, differ from that of the original mixture. Environmental pollution, in addition, involves selective degradation and bioaccumulation of different PCB congeners.

Because exposure to PCBs is always (except in experiments) to a mixture, some components of which have similar effects, there is a need for summary indices.

**Serum/Plasma Concentrations**

Serum concentrations of PCBs have been rather widely used as a biomarker of exposure in occupational settings (23, 33, 34), accidents such as food contamination (i.e., Yusho/Yu-Cheng; 14) and capacitor leakage and fire (35); and intake of contaminated foods (fish; 11, 24, 36–38). In Norway, the average total PCBs concentration in subjects without particular exposure is ~10 µg/L (39), which corresponds to ~2 µg/g lipid.

Workers engaged in capacitor manufacture exhibited an association between years of exposure to PCB mixtures and plasma concentrations of highly chlorinated PCBs (23). For less highly chlorinated ones (2–4 chlorines), there was no such correlation, probably because of recent high exposure but possibly also due to metabolic differences; however, there was an association with current intensity of exposure.

The congener pattern in serum differed between workers with regular or accidental occupational exposure and unexposed subjects (34, 35, 40).

Fat fish from the Baltic Sea contain high concentrations of polychlorinated compounds, including PCBs (41–43). In a study of Swedish men with various intakes of such fish, there were cutclear associations of intake with plasma concentrations of 10 different non- (Fig. 2), mono-, and di-ortho congeners (11). The di-ortho IUPAC 153 was the most prevalent congener being present in concentrations three to four orders of magnitude greater.

**Table 1. Plasma PCB concentrations (means) in 11 men with fish intake from the Baltic Sea.**

<table>
<thead>
<tr>
<th>Congener (IUPAC)</th>
<th>Mean plasma PCBs conc, pg/g lipid*</th>
<th>TEF*</th>
<th>Mean plasma TEQ conc, pg/g lipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ortho</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>77</td>
<td>50</td>
<td>0.0005</td>
<td>0.025</td>
</tr>
<tr>
<td>126</td>
<td>790</td>
<td>0.1</td>
<td>79</td>
</tr>
<tr>
<td>169</td>
<td>570</td>
<td>0.01</td>
<td>5.7</td>
</tr>
<tr>
<td>Mono-ortho</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>39 000</td>
<td>0.0001</td>
<td>3.9</td>
</tr>
<tr>
<td>118</td>
<td>160 000</td>
<td>0.0001</td>
<td>16</td>
</tr>
<tr>
<td>156</td>
<td>90 000</td>
<td>0.001*</td>
<td>90</td>
</tr>
<tr>
<td>157</td>
<td>18 000</td>
<td>0.001*</td>
<td>18</td>
</tr>
<tr>
<td>Di-ortho</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>153</td>
<td>1 000 000</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>28</td>
<td>11 000</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>101</td>
<td>17 000</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Source: 11.
* Source: 3.
* According to WHO (32), 0.0005.
than the non-orthos (Table 1). The serum concentrations of non-ortho congeners in the Swedes are in rough agreement with reports from Finland (34) and the US (44) and in good accordance with those found among Canadian "fish eaters" (37).

In subjects with moderate intake of fish (average ~50 g/day), about one-third of the exposure to the non-ortho congener IUPAC 126 is through direct intake of fat fish (Fig. 3). This agrees with food-basket studies in Finland on total PCBs (45). In subjects with extreme intake of fat fish, intake may be sevenfold that from other sources. The relative distribution of the congeners in plasma in high consumers of fish differed from the congener pattern in the fat fish (Table 2), indicating the selective metabolism by humans of different congeners.

When TEF values (3) were applied to the measured plasma PCBs concentrations, the two dominating congeners were the non-ortho IUPAC 126 and the mono-ortho IUPAC 156; non-ortho IUPAC 77 (e.g.) played a minor role (Table 1). However, there are also considerable concentrations of other polychlorinated compounds in fish. Thus, the intake of fish was associated with the plasma concentrations of 1,1-dichloro-2,2-bis(4-chlorophenyl)ethane (DDT/DDE) (11, 46) and PCD(D/F)s (47). Accordingly, PCBs and PCD(D/F) concentrations in plasma were associated (Fig. 4). The TEQ for PCBs was far higher than for PCD(D/F)s among high consumers, 234 vs 62 μg/g lipid, respectively, based on TEFs according to Ahlborg et al. (3, 48). The relative importance of PCBs is in accordance with findings in adipose tissue from Japanese (49) and Welsh (10) autopsies.

Adipose Tissue

Concentrations of PCBs in adipose tissue have been widely used as an index of exposure and risk. Mostly, the samples have been obtained at autopsy (10, 31, 35, 49) or during surgery (50), but sometimes by open or needle biopsy (23, 33). However, the amounts obtained at needle biopsy are small, and thus insufficient, at present, for determining the congeners having the lowest concentrations.

The concentrations of total PCBs, expressed on a fat basis, are similar in serum and adipose tissue. In Norway, the concentration in subjects without particular exposure was ~1 μg/g lipid (39). Similarly, for groups of congeners with different degrees of chlorination, plasma and adipose tissue concentrations were correlated in capacitor workers (23, 33). Capacitor (23, 33) and transformer repair (51) workers had higher concentrations of a series of PCB congeners than had unexposed subjects. In samples from Finnish subjects without particular

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**Table 2. PCB congeners in Baltic herring and in plasma from 11 men with high intake of such fish.**

<table>
<thead>
<tr>
<th>Congener (IUPAC)</th>
<th>Herrings*</th>
<th>Humans*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ortho</td>
<td></td>
<td></td>
</tr>
<tr>
<td>77</td>
<td>4200</td>
<td>50</td>
</tr>
<tr>
<td>126</td>
<td>2700</td>
<td>790</td>
</tr>
<tr>
<td>169</td>
<td>710</td>
<td>570</td>
</tr>
<tr>
<td>Di-ortho</td>
<td></td>
<td></td>
</tr>
<tr>
<td>153</td>
<td>550 000</td>
<td>1 000 000</td>
</tr>
</tbody>
</table>

* Source: 41. Concentrations were similar in salmon (42).
† Source: 11.
* Source: 43.

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**Fig. 3. Blood plasma concentrations of the non-ortho-PCB (polychlorinated biphenyl) congener IUPAC 126 and intake this congener from fat fish among Swedish men with no (C; n = 8), moderate (□; n = 7), or high (●; n = 11) consumption of fish.**

Source: 11; r = 0.81, P = 0.0001; y = 66x + 270.

**Fig. 4. Relationship between blood plasma concentrations of 2,3,4,7,8-pentachloro-p-dibenzofuran and PCB (IUPAC 126) among Swedish men with no (C; n = 8), moderate (□; n = 3), or high (●; n = 11) consumption of fish.**

Source: 11; r = 0.78, P = 0.0007.
exposure, the congener pattern was again similar in adipose tissue and serum (35). However, in U.S. capacitor workers, the adipose tissue/plasma partition varied for different congeners, ranging from 50 to 370 (lipid basis in adipose tissue/wet weight in plasma) (33).

Three major congeners (IUPAC 153, 180, and 138) make up 50% of the total PCBs content in adipose tissue in "unexposed" subjects (45). As regards TEQs (27) in adipose tissue from Wales, the mono-ortho congeners (IUPAC 118, 156, and 105) dominated (10).

Cord Blood

Cord blood has sometimes been used to monitor the exposure of the fetus to PCBs. The concentrations are lower (by ~30–50%) than in maternal blood (39, 52), mainly because of the lower fat content in cord blood (39).

Breast Milk

Concentrations of PCBs in breast milk have been fairly widely used as a biomarker of exposure, as well as an index of the exposure in the sucking infant. Milk is of particular interest, given its high lipid content and its consumption in large amounts by infants. Under steady-state conditions, the concentration of PCBs in milk seems to reflect the concentration in the maternal fat depot (13, 14, 39). In Norway, the total PCBs concentration in breast milk, as well as adipose tissue, was ~1 μg/g lipid (39).

During the lactation period, the blood concentrations of PCBs in the breast-fed infant increase to exceed the mother’s (52), while the maternal blood concentration (52) and the excretion into milk (39) decrease. The excretion into milk is considerably higher in primiparas than after later births. Thus, comparisons of breast milk concentrations of PCBs between populations can be made only if the sampling has been standardized for parity and time of collection during lactation.

Intake of contaminated fish has been associated with the total PCBs concentration in breast milk (36). The great impact of exposure through fish is illustrated by the association between PCBs concentrations in serum at age 4, on the one hand, and the concentration in milk and duration of breast feeding, on the other (53). Women with occupational or accidental exposure to PCBs may have high concentrations of total PCBs in milk (14).

The patterns of PCB congeners are similar in breast milk from Swedish women and blood plasma from Swedish men with moderate fish intake (9, 11) (Fig. 5). Also, on a lipid basis, the concentrations were approximately the same.

Biomarker Concentrations vs Effects

Reliable information on the relationship between PCB concentrations and health effects is scarce. Some information on serum concentrations of total PCBs in a few Yu-Cheng cases has been published (16); median 44 (range 28–110) μg/L at 9–12 months after the outbreak. Further, in the worker population at a capacitor factory, which showed chloracne and an increased cancer incidence at follow-up, the concentrations were 280 μg/L (in a fraction with 54% chlorine) and 140 μg/L (42% chlorine) (54). As we emphasized earlier, however, values for total PCBs are highly dependent on the analytical method.

In studies of children whose mothers had high intake of contaminated fish from Lake Michigan, the average total PCBs concentration was 4.7 μg/L in maternal serum, 2.0 μg/L in cord serum, and 730 ng/g milk fat (36). There were statistically significant associations between several gestational and developmental outcome variables, on the one hand, and cord-serum and milk concentrations, on the other. However, there are several possible sources of bias, regarding comparability of study groups and confounding (3). In a population from North Carolina, which was probably much less exposed to PCBs, a psychomotor index was inversely correlated with milk PCBs (28). We should point out that the effects recorded in the Lake Michigan and North Carolina studies are not fully consistent.

In a study of Swedes with variable intakes of fish from the Baltic Sea, serum concentrations of several PCB congeners were associated with enzyme activities in serum (γ-glutamyltransferase and aspartate aminotransferase) that might indicate an effect on the liver, though there is a possibility of confounding (11, 55). Also, the fraction of natural killer lymphocytes in peripheral blood decreased with increasing plasma concentration of the non-ortho congener IUPAC 126, as well as with increasing TEQs of PCBs (55, 56). Furthermore, fishermen in the Baltic Sea had an increased risk of certain tumors (55, 57).

Of course, if at all related to exposure to PCBs, serum activities of liver enzymes and effects on lymphocytes in peripheral blood are far too nonspecific to be used as biomarkers of effects. Further, fish intake may cause exposure to several other potentially confounding pollutants, e.g., other polychlorinated compounds (DDT/ DDE, PCBs, PCDDs) (11, 47), methylmercury (58–61), methyamines (55, 62), arsenic, and polycyclic aromatic compounds, which may explain at least some of the effects.
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