Polychlorinated Biphenyls and Human Health

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Abstract: Polychlorinated biphenyls (PCBs) were manufactured and used widely for many years. Because they are very persistent in both the environment and biological systems, there has been significant global contamination. This review presents a summary of known or suspected health effects of various PCB congeners documented on the basis of both human and animal studies. As our knowledge increases several important points become apparent. PCBs interfere with many biological functions, including the immune system, the nervous system and several endocrine systems, and the fetus appears to be particularly vulnerable to these actions. PCBs cause certain cancers in animals. PCBs are mixtures of multiple congeners, differing on the basis on the numbers and positions of chlorines around the biphenyl ring, and it is becoming increasingly apparent that different congeners may have very different actions. These observations suggest that the potential human health hazards from PCB exposure have been underappreciated.

INTRODUCTION

Polychlorinated biphenyls (PCBs) are 209 distinct chemicals that consist of a biphenyl backbone on which chlorines are added in various numbers (from 1 to 10) and at different positions (ortho, meta and para to the phenyl ring). PCBs were manufactured for industrial purposes from about 1930. Their production was banned in most countries in the late 1970s because of evidence that they were persistent in the environment. The principal manufacturer in the US was the Monsanto Company, which produced PCB mixtures which they marketed under the trade name Aroclor from 1930 to 1977.

PCBs were manufactured in several countries under different names (Clophens in Germany, Sovol in the former USSR. Chlorofen in Poland and Kanechlors in Japan). The synthetic process involved chlorination of biphenyl with chlorine has, and Monsanto and other producers sold several different mixtures, distinguished by varying degrees of chlorination. The most widely used mixtures in the US were Aroclor 1016 and 1949, with an average of 3 chlorines per molecule, Aroclor 1248 with an average of 4, 1954 with 5 and 1260 with an average of 6-6.3 chlorines (26). Production of PCBs continues to the present in Russia and probably in North Korea.

The structures of PCB and the conventional designation of positions are showning Fig. 1. Individual PCBs are called congeners, and are identified by the positions of chlorine atoms. For many purposes

they are divided into classes based on whether chlorines are found on ortho positions (mono-, di-. etc.) or are not present in any ortho position, where the compound is called a coplanar PCB, since without ortho-substituted chlorines the molecule can assume a coplanar configuration and exert some actions similar to 3,4,7,8-tetrachloro-dibenzo-dioxin (TCDD), the most toxic of the dioxin congeners. Safe (1994) has defined toxic equivalency factors (TEFs) for a number of PCB congeners on the basis of the ability of each to act through the aryl hydrocarbon (Ah) receptor pathway. While this has been a very valuable contribution for quantitation of relative PCB actions mediated via Ah receptor activity, it has unfortunately had the effect of leading many to consider that this is the only form of PCB toxicity. This is not the case, however, as discussed below.

PCBs had many uses. Because they were chemically and physically stable, they were used in transformers, capacitors, printing inks, paints, dedusting agents, pesticides and insulating fluids. Over 9.4 billion pounds of PCBs have been produced, of which Monsanto produced l.25 billion pounds in the US (27). Even in the US many PCB-containing transformers and other products are still in use. In the meantime PCBs have become ubiquitous environmental pollutants, present in essentially every living animal, including humans, on the face of the earth.

PCB PERSISTENCE AND METABOLISM IN NATURE AND IN ANIMALS

PCBs are among the most persistent of all known chemicals, and they are persistent both in the environment and in the human body. However, the individual congeners vary considerably in vulnerability to metabolism, just as they do in biological effects. The congeners also differ in physicochemical properties, with the lower chlorinated congeners being more water soluble and volatile, and these factors influence both migration and rates and modes of degradation.

PCBs are degraded, albeit slowly, by both anaerobic and aerobic processes (l). Anaerobic processes are of particular importance in sediments and soils. There are a host of bacterial species, most unidentified, that are able to derive energy from removal of chlorines. However, these bacteria can remove chlorines only from the meta and para positions, so that there is only an alteration in the congener profile, not a net loss of PCBs (3O,48,65-67). This leads to an accumulation of lower chlorinated, ortho substituted congeners. However, the process of anaerobic biodegradation does not go to completion, but stops when the concentration of PBCs reaches a threshold value (48). In contrast, aerobic biodegradation is most effective against lightly chlorinated congeners (41).

The issues around biodegradation of PCBs have major political as well as practical consequences. For example, the position of the General Electric Company, responsible for the PCB contamination of the Hudson River in New York State, has been and is that the PCBs are being removed by the process of biodegradation (l,7,30,41). They conclude that the River will ultimately clean itself, and that any action such as dredging will only aggravate the program by stirring up the contaminated sediments. In contrast, MP Brown et al, (8), the USEPA, and Rhee and colleagues (66,67) conclude that while anaerobic biodegradation may alter the congener profile to lower chlorinated congeners, there is little net loss of PCBs. The EPA report documents that while there has been up to a 40% loss of PCB content at several specific hot-spots of contamination just below the old General Electric plant at Hudson Falls, NY, no more than 10% of this is a net loss of PCBs (via aerobic dechlorination and volatilization), the remainder is due to a redistribution to the water column, redeposition to other areas of the River, and a likely increased availability of these migrating PCBs to the food chain.

PCBs enter the food chain through several mechanisms. Fish both accumulate PCBs by direct

absorption through the gills (IO) and by eating contaminated sediments, insects and smaller fish. Evans et al. (28) showed that PCBs bioconcentrate by a factor of 12.9 fold in going from plankton to fish. Wood et al. (86) demonstrated that dipteran larvae selectively accumulate congeners with 2-4 chlorines over those with both more and fewer, and noted that the release rate of the congeners from the sediment was inversely related to the octanol/water partition coefficients. They specifically commented that various species show different patterns of bioaccumulation. However, Pullman et al. (83) have reported that the process of bioaccumulation results in relative enrichment of the higher chlorinated congeners, because of the fact that they show the greatest lipophilicity. Thus it would appear that there are at least two processes involved: letting the PCBs off sediment particles and into a biologic system (a process involving water solubility), and then consumption and concentration of PCBs from biologic sources, a process more efficient the more lipophilic the congener. Birnbaum (4) notes that gut absorption of PCBs is also a function of lipophilicity, but that with extreme decrees of chlorination there is less absorption, probably because of the extreme insolubility of these compounds in an aqueous medium.

Species differ in ability to metabolize PCBs (6). In fish most PCB clearance is simple extraction from gill membranes into the surrounding water column, which results in a relative depletion of lower chlorinated congeners. However, in animals breathing air, most PCB loss is secondary to metabolism by the liver through several different cytochrome P450s. In general these P450s are much more efficient in metabolizing the lower chlorinated PCBs, and do so by generating hydroxylated products that are further metabolized. These observations indicate that different congeners have very different half-lives in humans, where some of the lower chlorinated congeners may last only a matter of hours or days (73), while the more highly chlorinated congeners last ten or more years (6). However, some of the hydroxylated PCB metabolites formed in the liver may also persist for periods of time in blood, and may have biologic activities that are not necessarily identical to that of the parent compounds (3,33). Shain et al. (78) studied bioaccumulation in rats during gestation and lactation. They found that the lower chlorinated congeners did not bioaccumulate to any great degree, while the most highly chlorinated congeners bioaccumulate. Intermediate PCBs with five or six chlorines showed various degrees of bioaccumulation. None of these studies, of course, consider relative health effects of the different congeners. Since those congeners with the longest half-lives are for the most part stored in body fat, they may not be the ones which alter physiological processes the most.

PCB LEVELS IN HUMANS

While there have been a large number of studies of PCB concentration in human blood, breast milk, and urine, it is somewhat difficult to compare results from different laboratories because of a lack of uniformity in methods of measurement. Most laboratories determine total PCB content, not individual congeners. The ATSDR (2) has recently summarized results from numerous investigators who measured PCBs in serum in different populations. Of 12 studies from a total of 4889 US people without any known specific exposure, the geometric mean serum PCB concentration varied between 3.38 and 15 ug/L. In 11 of these studies the mean values were all less than 7 ug/L. and the study reporting 15 ug/L was of only 29 people. In 8 different studies of occupational exposure the mean PCB serum values ranged from 3 to 119 ug/L. and in only one study was the value greater than 50 ug/L.

The individual congeners found in humans are not reflective of what is present in the original PCB mixtures. In human adipose tissue, IUPAC numbers 138 (2,3,4,2',4',5'), 153(2,4,5,2',4',5') and 180(2,3,4,5,4',5') comprise 55%of total PCBs (22), while in breast milk these three plus IUPAC 28 (2,4.4') account for 50% of total PCBs (23). The first three congeners listed above are particularly

resistant to degradation in the body and therefore accumulate. However, because individual congeners vary so much in their biological effects, the total PCB content of serum adipose tissue or breast milk is not very valuable information except perhaps as an indicator of total exposure. The congener profile in any particular individual does provide some information about the route of exposure, and also should predict the type of health outcome to be expected if the biological effects of each of the individual congeners were known, which unfortunately is not the case at present. This is not a trivial issue, however, given that the lower chlorinated congeners present in serum probably reflects recent exposure, since these are more rapidly cleared or metabolized, while the higher chlorinated congeners are more likely to reflect long-term accumulation, since they are more resistant to metabolism. It is clearly possible, and indeed likely, that lower chlorinated congeners which are neuro or immunotoxic and disrupt endocrine systems may have physiologic effects (see below), but are then metabolized. Even in light of metabolism the serum concentration of individual PCBs provides important information.

A number of health effects of PCBs have been reported in human and animal exposure studies, although the evidence from the animal studies is in general, much stronger than that from humans (see recent reviews 38, 80). These include:

Cancer: PCBs have been known for a long time to cause cancer. The evidence for this is summarized in recent reviews by Cogliano (19) and the EPA (25). All of the Aroclor mixtures have been shown to produce liver cancer in rats (9.56), and humans working in capacitor manufacturing have been reported to have elevated incidence of liver, gall bladder, and biliary tract cancers (7). Other specific cancers reported to be increased in exposed humans include gastrointestinal tract, malignant melanoma, lung, brain and non-Hodkin's lymphoma (19). In rats, females show a higher incidence of liver cancers than males, but actually have a lower life expectancy due to a reduced incidence of mammary cancers, probably resulting from the antiestrogen actions of coplanar congeners (56).
It has been generally accepted that PCB carcinogenesis is mediated by coplaner congeners via activation of Ah receptors, although recent evidence raises the possibility that PCBs with lower chlorine content may also contribute. Oakley et al. {62) have suggested that the dihydroxy metabolites of lower chlorinated PCBs can be changed to reactive intermediates that produce oxidative DNA damage. In a case- control study of non-Hodgkin's lymphoma, cases showed higher concentrations of both coplaner and non-coplanar PCB congeners than controls (39). Safe (73) notes that the Aroclor 1260 is much more carcinogenic than can be explained by the summed TEQs, and suggests that the phenobarbital-type PCBs, which are not coplanar but are highly chlorinated, may contribute to the carcinogenicity. In spite of d degree of uncertainty, however, it is likely that the more carcinogenic PCBs are dioxin-like coplanars with a relatively high chlorine content.

Immune system depression: PCBs cause immunosuppression, which may in part explain their carcinogenic actions. Chang et al. (14) have reported that exposed humans have reduced concentrations of IgA and IgM, but not IgG, and that some but not all T cell subpopulations were reduced. Similar changes have been observed in monkeys chronically exposed to Aroclor 1254 (81). There is evidence that PCB immunotoxicity is mediated by Ah receptors (79), although there is also strong evidence that at least a component of immunotoxicity is independent of activation of An receptors (43).

Several components of the immune system are altered by PCBs. Neutrophils are activated by Aroclor mixtures to produce reactive oxygen species and undergo secretion of lysosomal products (31). This action appears to be due to non-coplanar congeners, and is independent of activation of Ah receptors.

Effects on the nervous system and behavior: There have been two incidents with mass poisoning by PCB mixtures in Japan and Taiwan, respectively, and in both a variety of illnesses resulted in exposed adults (14,72). However, the most significant effects appeared in children born to exposed women. Since many of the children were born years after the exposure of the mother, the effects appear to be mediated via exposure of the fetus from the PCB stores in the mother's body fat. In addition, the child may be exposed to PCBs via breast feeding. Many of the defects seen in these children were related to the nervous system, including abnormalities on behavioral assessment and increased activity level (15) significant delays in behavioral milestones, deficits in formal developmental testing and lower scores on several tests of cognitive function (53,72). Three groups have investigated the development of US children as a function of exposure to PCBs. Roman and colleagues (34,71) have investigated the effects of ambient levels of PCBs in a population in North Carolina and found that children with the greatest transplacental exposures demonstrate hypotonia and hyperreflexia. Jacobson and colleagues (44-46) have studied children of Great Lakes fish eaters, where PCBs are presumed to be the major contaminants, and have shown that children with significant exposure show deficits in visual recognition memory and poorer short-term memory on both verbal and quantitative tests. When these children were tested at 11 years of age, the most highly exposed children were found to have a 6.2 point decrement of full scale and verbal IQ scores, and were at least twice as likely to lag in reading comprehension. These decrements were related to prenatal, not postnatal, exposure to PCBs. Lonky et al. (54) have reported results of neurobehavioral assessment of infants born to mothers who ate a significant amount of PCB-contaminated Lake Ontario fish. They found that infants born to mothers who ate these fish did more poorly on the reflex, autonomic and habituation clusters of the National Behavioral Assessment Scale.

There have been animal studies of PCB effects on the nervous system as well, Rice and Hayward (68) report that monkeys subjected to postnatal PCB exposure show variable increases in mean response latencies in a nonspatial discrimination reversal problem followed by a spatial delayed alternation task. On the delayed alternation task the PCB exposed animals showed retarded acquisition of the task and increased errors at short, but not long, delay values. Treated monkeys showed perseverative responding. They conclude that PCB exposure results in a learning, performance/decrement rather than an effect on spatial memory *per se*. Schantz et al. (74) have shown that ortho-substituted congeners caused spatial learning deficits, while Holene et al. (42) showed deficits in a visual discrimination task accompanied by increase in overall activity. Eriksson and Fredriksson (27) showed that several ortho-substituted congeners cause an increase in spontaneous motor activity and a disruption of habituation in exposed mice, and also resulted in a poorer performance in a radial arm maze and a Morris water maze. A variety of toxic actions on neurons have been reported in cellular studies. Shain et al. (77) reported that ortho-substituted, but not coplanar, congeners cause a reduction in cell dopamine concentration in PC l2 cells, thought to be mediated by a direct inhibition of the activity of tyrosine hydroxylase, the rate limiting enzyme in the synthesis of dopamine. Niemi et al. (60) have demonstrated that long-term potentiation (LTP), documented to be an adequate model system for some forms of learning and memory, is blocked by Aroclor mixtures and single PCB congeners. Three laboratories have studied cytotoxic actions of PCBs on neurons. Kodavanti and colleagues (49-51) have shown that ortho-substituted, but not coplanar, PCB congeners cause death of cultured cerebellar granule coil neurons, probably by disruption of calcium homeostasis, and Carpenter et al. (13) have shown similar findings in acutely isolated cerebellar granule cells studied by flow cytometry. Pessah and colleagues (84-85) have demonstrated cytotoxic actions of noncoplanar PCBs acting through ryanodine receptors. Therefore it appears that PCBs, especially ortho-substituted congeners, can exhibit a variety of neurotoxic actions

(12).

Disruption of thyroid function: PCBs cause alterations of several hormonal systems, including insulin (29), thyroid and sex steroids (57), but that of thyroid function is probably the most serious, Collins and Capen (20) reported that PCBs caused alterations in thyroid structure and reduction in serum thyroid hormone levels, and these observations have been confirmed by a number of other investigators (36,58). Others have shown that the immediate response to PCBs is an elevation of thyroid hormones, followed by a fall (38). Not all PCB congeners alter thyroid function, and it is nor yet clear what the structure-activity relationships are. It should be noted that the structure of PCBs have many common features with that of thyroxine, although PCBs have chlorine substitutions while thyroxine has iodines. Because thyroid hormone regulates metabolism, interference with thyroid function has serious consequences at all ages, but particularly during development (64). Since normal thyroid function is essential for mental development, it is possible that some of the cognitive deficits associated with PCB exposure are secondary to the resultant hypothyroidism, since LTP is blocked both by hypothyroidism (61) and PCBs (60).

Sex steroid alterations: PCBs alter sex steroid function in several ways. Coplanar PCBs, like TCDD, activate the Ah receptor and cause the induction of cytochrome P450s of the CYP1A and CYP1B families. These P450s catalyze the metabolism of many PCB congeners as well as other aromatic moieties such as endogenous hormones, including estradiol. Estradiol can be oxidized at two positions, and the products are reactive and rapidly metabolized further and excreted. These P450s are estradiol hydroxylases, but insert the hydroxyl group at different sites, CYP1A at the 2 position and CYP1B1 at the 4 position. When metabolism of estradiol is increased, functional levels fall and an altered estrogenic function ensues.

A number of the ortho-substituted PCBs, but not the coplanars, produce a pattern of enzyme induction similar to that elicited by phenobarbital (63). Although the precise biochemical mechanisms and protein factors involved in this induction process are not well characterized, elevated levels of CYP2B, CYP2C and CYP3A result, and have the same effect in increasing metabolism and excretion of estradiol. These enzymes are primarily expressed in the liver, although there may be limited expression in other tissues. Elevated rates of hepatic metabolism of estradiol are observed in animals exposed to PCBs (59). Unlike the other P450s, CYP1Al and CYP1B1 appear to be inducible in a number of extrahepatic tissues, including breast, uterus and pituitary (37).

Some of the metabolites produced from PCBs, especially mono- and dihydroxy PCBs, have estrogenic or antiestrogenic activities of their own (33). But in addition to inducing P450s, some of the PCBs and metabolites can directly inhibit these enzymes. While some lightly chlorinated PCBs bind to the active site of the P450s and hydroxylation of the compound occurs, some of the more heavily chlorinated congeners bind but are difficult to hydroxylate, so are very effective inhibitors. Finally, through activation of the Ah receptor, TCDD and probably also coplanar PCBs may have inhibitory effects on estroen-regulated gene transcription by exclusive binding at gene regulatory elements found in the 5' flanking regions of estrogen responsive genes. The ligand-bound Ah receptor appears to disrupt the estrogen receptor-Sp1 complex that is involved in transcriptional activation of human cathepsin D by interaction at an overlapping xenobiotic response element (52). There may be similar negative regulation of other estrogen-regulated genes by the Ah receptor.

Individual congeners and hydroxymetabolites have been shown to be either estrogenic or antiestrogenic on the basis of effects of immature rat uterine weights (47). Because PCB mixtures and

their metabolites have a combination of estrogenic and antiestrogenic effects, it is difficult to predict how humans will be affected upon exposure. While the metabolites are transient, there is clear evidence that they may have effects that supersede the antiestrogenic actions of the parent PCBs. Seegal et al. (76) have recently shown that developmental exposure of rats to the coplanar congener, 3,4,3',4', resulted in an increase in brain dopamine, and that this effect was due to the estrogenic actions of the metabolite of this congener. PCBs have been reported to alter sexual function in everything from turtles (21) to polar bears (75), presumably through estrogenic mimicry. Thus study of the biologic actions of PCB congeners that are relatively rapidly metabolized and of the metabolic products is a very important problem.

SOURCES OF EXPOSURE

There are three obvious possible sources of exposure to PCBs: ingestion, inhalation and dermal. Ingestion as a major source of exposure is well documented, especially upon consumption of contaminated fish (2). Other meats, including poultry, also contribute to body burdens of PCBs, especially of the more highly chlorinated and persistent congeners. Dermal absorption has been demonstrated, but is unlikely to be a significant source of exposure outside of some occupational activities that in the past involved extensive skin contact. There is certainly the possibility that certain individuals who spend significant periods of time swimming in contaminated waters might absorb PCBs from the water column, as is well documented for such chlorinated hydrocarbons as chloroform (cf.35). There has been little investigation of effects of inhaled PCBs in either animals or man, but ATSDR (2) has listed inhalation as a significant source of human exposure to PCBs, especially from indoor air in buildings using PCBs in various ways.

PCBs have been known to volatilize and be transported for deposition at sites far from their origin for many years (55). Gaseous PCB escape can be quantified by using a combination of Fick's and Henry's Laws, as has recently been elegantly done from both a theoretical and experimental basis for the New Bedford Harbor Superfund Site (32). The process of volatilization is dependent upon the medium. For pure PCB mixtures, individual congeners will have different equilibria between gas and liquid phases depending on the partial pressure of the gas constituent the contaminant specific distribution coefficient and the concentration, which is partly described by Henry's Law. However, pure Aroclor mixtures are not usually an environmentally relevant source of exposure. In contaminated soils or dry sediments, some of the PCBs are bound to soil particles, and therefore are unlikely to volatilize without desorption from the particles (32). However, in wet soils or sediments there is an equilibrium between the PCBs bound to the soil particles and the aqueous solution; this depends upon organic carbon content, particle size and the octanol/water coefficient. Once in an aqueous medium PCB volatilization can be calculated using Henry's and Fick's Laws. When sediments are allowed to dry a process called wicking may occur, where the contaminant is concentrated at the evaporative surface. This may facilitate evaporative loss of PCBs (24).

In a series of laboratory studies Chiarenzelli et al. (16-18) studied evaporative loss of PCBs (Aroclors l242,1248, 1254, and 1260) from small contaminated sediment samples during drying or after repeated wetting and drying. They found that with repeated wetting and drying they could net up to 63% loss of total PCB content. The degree of volatilization was inversely correlated with the chlorine content (R^2=0.97). When they studied a natural sediment contaminated with Aroclor l248, but having undergone a degree of biodegradation, they found that 195 of the PCBs were lost by volatilization and that 55% of the loss was due to

volatilization of several lower chlorinated, ortho-substituted congeners (2, 2.2,2.6,2.6.2') that were the products of biodegradation. These observations have been extended by Bushart et al. (l1) who observed volatile PCB loss of a contaminated St. Lawrence River sediment containing about 600 ppm PCBs. They found that the sediments lost 0.7-1.7% of total PCBs to the air during a 24-hour drying cycle. Sediments submerged lost less PCBs than wet sediments with no overlying water. The PCB loss was correlated to PCB concentration and to water loss. The ortho-substituted mono-, di-, and trichlorobiphenyls constituted greater than 90% of the volatilized congeners. These observations suggest the atmospheric transport, especially of lower chlorinated PCB congeners, is an important factor in the global distribution of PCBs, and is probably the cause of the significant contamination known to exist in both the Arctic and Antarctic regions (40,70). Once these more volatile congeners precipitate due to the cold temperatures, they are then available for bioaccumulation in the food chain and presumably are the cause of the significant levels of PCBs found in indigenous peoples in the polar regions (21).

CONCLUSIONS

PCBs are a complex mixture of biolooically active substances. PCBs are persistent in both the environment and within biological systems and tend to bioaccumulate in the food chain due to their lipophilic nature. The various PCB congeners, differing in the numbers and positions of chlorines around the biphenyl rings, may have unique biological effects, which enormously complicate valuation of human health effects predicted on the basis of knowledge of serum PCB levels. The best documented effects of PCBs in humans are irreversible effects on brain development and IQ following exposure during gestation. PCBs are also immuno-suppressants, and have been shown to cause certain kinds of cancer. Certain congeners disrupt both the thyroid and sex steroid endocrine systems. Because of their long and multiple uses, their persistence and the fact that they can volatilize and be transported over long distances, PCBs contaminate even remote regions. The degree to which PCBs constitute a health hazard to humans is not yet clear, but recent studies demonstrating particularly vulnerability of the developing fetus raise the likelihood that these substances constitute a greater hazard to human health than previously appreciated.

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