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Polychlorinated Biphenyls (PCBs): Routes of Exposure and Effects on Human Health

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ABSTRACT

The polychlorinated biphenyls (PCBs) are synthetic organochlorine chemicals that were useful industrial products in the past, but their production was ended because they persist in both the environment and living organisms. The PCBs are mixtures of up to 209 different components (congeners), depending on the number and position of chlorines around the biphenyl ring. The PCBs are fat-soluble substances to which everyone is exposed through ingesting animal fats, inhalation, or dermal contact. Exposure to PCBs suppresses the immune system, thereby increasing the risk of acquiring several human diseases. Both ortho-substituted and coplanar (dioxin-like) congeners are tumor promoters that enhance the effects of other carcinogenic substances. PCB exposure, especially during fetal and early life, reduces IQ and alters behavior. The PCBs alter thyroid and reproductive function in both males and females and increase the risk of developing cardiovascular and liver disease and diabetes. Women are at high risk of giving birth to infants of low birth weight, who are at high lifetime risk for several diseases. As knowledge of their toxic effects has grown faster than environmental levels have declined, PCBs remain dangerous contaminants.

BACKGROUND

The polychlorinated biphenyls (PCBs), synthetic chemicals manufactured in the United States (U.S.) from 1929 to 1976, were useful compounds for a variety of purposes. These heavy oils were used in transformers and electrical capacitors because of their relatively good electrical insulating properties. They were also used as hydraulic fluid, oil additives to paints, window caulking, ceiling/floor tiles, and for many other uses. The PCBs were sold in the U.S. primarily as Aroclor mixtures, based on the average degree of chlorination.

Polychlorinated biphenyls are made from the biphenyl molecule, two six-carbon rings linked by a single carbon-carbon bond. The PCB molecule comprises 12 carbon atoms with chlorine atoms substituted for hydrogen atoms at any of 10 possible positions (Fig. 1). Thus theoretically, 209 individual PCB components (congeners) can be formed, depending upon the number of chlorines and their location on the biphenyl rings. The name of a congener specifies the total number of chlorine substitutions and the position of chlorine. Figure 1 shows the conventional nomenclature, with the 1 and 6 positions closest to the biphenyl bond described as ortho, those opposite called para, and the remainder called meta. For example, a 4,4'-dichlorobiphenyl congener would consist of the biphenyl structure with two chlorine substitutions, one on each of the two carbons at the ‘4’ (para) positions of the two rings. The number and position of the chlorines determine both the physical and the biological properties of each
congener. For example, congeners containing few chlorine atoms are in general more water soluble, more volatile, and more easily metabolized than are those having a high number. Conversely, PCBs with large numbers of chlorines are resistant to biodegradation and therefore bioaccumulate in the environment. Congeners containing chlorine only in the meta and para positions tend to assume a planar configuration and show dioxin-like activity, whereas those having more than one ortho chlorine do not show significant dioxin-like activity.

The toxicity of PCB congeners that exist in a planar configuration occurs through the activation of a protein called the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor that controls the expression of cytochrome P450 1A (CYP1A) genes. The AhR is a member of the steroid-hormone receptor family and acts by gene induction, increasing or decreasing the levels of a large number of gene products. Unlike the steroid-hormone receptors, however, the AhR has no known physiological ligand. The known AhR ligands are foreign planar aromatic compounds, such as certain polycyclic aromatic compounds and halogenated aromatic compounds like the dioxins. Thus, the actions of the coplanar PCBs on the AhR are identical to those of the dioxins and furans.

Four coplanar PCB congeners having at least four chlorines each, as well as several mono-ortho congeners, have significant AhR-activating potential. As all chemicals that activate the AhR have similar actions but different potencies, a toxic equivalent factor (TEQ) (toxicity of a particular formulation relative to 2,3,7,8-tetra-chlorodibenzo-p-dioxin [TCDD]), was developed as a way to deal with mixtures of compounds that act on a common receptor /1–2/. Although the coplanar PCBs are not as potent in activating the AhR as TCDD, the most toxic dioxin congener, in many circumstances the concentration of the PCBs is sufficiently greater than that of dioxins and furans, such that most AhR receptor activity comes from PCBs /3/.

No person exposed to PCBs is exposed only to dioxin-like PCB congeners. Because the non-dioxin-like PCB congeners have a different mechanism of action and because exposure to such congeners results in different diseases, a PCB-exposed person is at risk for all diseases caused by dioxin, as well as for those caused by non-dioxin-like congeners. Each individual congener has its
own profile of actions in biological systems. Thus, although having the measurements of individual congeners is important, we do not always have adequate information on the actions of each individual congener /4/.

Various investigators have proposed grouping PCB congeners according to their degree of chlorination, pattern of enzyme induction, or endocrine-disrupting activity /3, 5–6/. Different PCB congeners induce different cytochrome P450 (CYP) isoenzymes, which are responsible for the oxidative metabolism (Phase I, activation) of many drugs, steroids, and carcinogens /7–8/. Dioxins and coplanar PCBs induce the activity of cytochromes P450 1A1, 1A2, 2A1, and 1B1 (numbers indicate the family, subfamily, and gene). These actions result in the proliferation of endoplasmic reticulum in the liver, resulting in an increase in liver size and an alteration in many, if not all, aspects of liver function, including the perturbation of endocrine function. The immune system is altered and the size of the thymus gland is reduced. Fitzgerald et al. /9/ demonstrated that individuals with high exposure to nine mono- or di-ortho-substituted PCB congeners metabolize caffeine more rapidly than do those with low exposure, a measure of CYP1A2 activity in the liver. These observations demonstrate that exposure to PCBs alters liver function in ways that can affect the metabolism of other substances, through the induction of P450s, in this case CYP1A2, which is involved in the metabolic activation of certain carcinogens.

Other congeners cause the induction of CYP 2B1 and 2B2, a pattern similar to that induced by phenobarbital. These congeners have carcinogenic, neurotoxic, and endocrine disrupting actions that differ from those of the dioxin-like congeners. A third major group of congeners have activities at both sites and are called “mixed” congeners—mono-ortho congeners that activate both CYP1A and CYP1B enzymes, as well as CYP2B. This group contains nine major congeners and contributes significantly to the total TEQ because some are present in relatively high concentrations /10/. Some congeners induce CYP3A enzymes, whereas others do not induce any P450s but can act at other sites /7/.

Congeners containing ortho chlorines, but not having AhR activity, have a different profile of actions and health effects, many unrelated to any P450 enzyme. Such PCBs alter the cells of the nervous /11–13/ and immune systems /14–15/, causing a relatively rapid cell death that results from disruption of the membrane structure /16/, an effect not seen by coplanar PCBs at comparable concentrations. These congeners also stimulate insulin release from a human beta-receptor cell line, reduce synthesis of the neurotransmitter dopamine in neurons, and activate neutrophils to produce reactive oxygen species /17/.

Not only do different PCB congeners have unique sites and mechanisms of action but also their metabolites have biological activity and are persistent in living organisms for a long period of time /18–19/. The endocrine disruptive actions of PCBs can be a result of the parent PCB, the enzymes induced by the parent PCB, or due to an action of metabolites /20/. The coplanar and AhR-activating PCBs, for example, are anti-estrogenic because they induce P450s 1A1 and 1B1, which degrade estrogen /21/. In contrast, most other PCBs, and especially their hydroxylated metabolites, are estrogenic. Because the great majority of PCBs are not AhR activators, the net activity of most PCB mixtures is to mimic the actions of estrogen. This variation in action found in different PCB congeners is particularly important in developing an understanding of the relation between exposure to PCBs and the risk of breast cancer. Estrogen is by far the best-documented risk factor for breast cancer /22/. Thus, exposure to AhR-activating PCBs might be expected to be protective against breast cancer based only on this action, whereas exposure to the estrogenic congeners might be expected to promote risk.

Because PCBs are found in the lipid fraction,
blood levels are reported either as wet weight concentrations or with the results lipid-adjusted. Studies from the U.S. Centers for Disease Control and Prevention (CDC) have shown no difference between fasting and non-fasting results, providing that a lipid adjustment is made /23/. Nevertheless, lipid adjustment also has some problems in that PCBs can alter lipid metabolism /24/ and because the method has been reported to be highly prone to bias /25/. The various ways in which PCB levels are reported and the varying numbers of PCB congeners determined by various laboratories often make it difficult to compare across studies.

The half-life of PCBs in the human body is long, but varies with the congener, in that the lower chlorinated congeners are more rapidly metabolized and many of the highly chlorinated congeners persist for many years. The rate of removal is also a function of body burden. Wolff et al. /26/ reported a half-life of 3–5 years for individuals with high serum PCBs, but 13–17 years for those having lower values.

The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) /27/ states that PCB levels in persons without unusual exposure range from 0.9 to 1.5 ppb wet weight and summarizes information from many studies showing that PCB levels increase with age. A recent study of older pregnant women (mean age 39 y) in Western Canada reported a mean wet weight concentration of 0.78 ppb, with the range being 0.43 to 3.34 ppb /28/. Thus, it is likely that the ATSDR values overestimate the background serum concentrations of PCBs in persons without some unusual source of exposure and in persons < 50 years of age. At older ages, the ATSDR values are probably accurate.

**ROUTES OF EXPOSURE**

Ingestion has usually been assumed the primary route of exposure to PCBs /27/. These compounds are fat soluble and bioaccumulative. The tissues of fish taken from contaminated fresh water are particularly high in PCBs /27/, although farmed fish like salmon are also an important route of exposure /29/. Everyone in developed countries has a certain amount of PCBs in their bodies, primarily from contamination of the food supply /30/. Inhalation and dermal absorption are also possible routes of exposure. Animal studies have shown that the inhalation of vapor-phase PCBs is an important route of exposure and that inhaled vapor phase PCBs can bioaccumulate and cause pathological changes /31/. Vapor-phase PCBs are significantly elevated near PCB-contaminated hazardous waste sites /32–33/. The results of our investigations provide evidence that inhalation is also an important route of exposure in humans /4/ and a cause of various health effects among individuals who live near such contaminated sites /34–36/. Liebl et al. /37/ also demonstrated the accumulation of lower-chlorinated PCB congeners in humans, a result of breathing contaminated indoor air. The lower-chlorinated congeners are more volatile but more easily metabolized by the body. Thus, the appearance of transient congeners in human blood reflects relatively recent exposure, independent of the route of exposure, but is characteristic of inhalation. Because of the relatively rapid disappearance of the more volatile congeners, the relative magnitude of exposure by inhalation may be underestimated upon serum PCB measurement.

**HUMAN HEALTH EFFECTS**

The human health effects of PCB exposure has been reviewed previously by Carpenter /38/ and by ATSDR /27/. The present report is meant as an update, focusing on positive human studies that provide some indication of dose-response relations. Although PCB levels are declining in developed countries, our knowledge of the adverse health effects is growing. PCBs are carcinogens; alter
immune system function; cause adverse alterations of the nervous system, skin, thyroid, and sex steroid hormonal systems; liver, kidney, pancreas, and the cardiovascular system. As a result of these actions on multiple organ systems, humans who are exposed to PCBs are at increased risk of cancer, infections, reduced cognitive function accompanied by adverse behavioral effects, hypothyroidism, infertility, ischemic heart disease, hypertension, diabetes, liver disease, asthma and arthritis, as well as giving birth to infants of lower than normal birth weight. Some of these adverse effects, such as IQ deficits that result from perinatal exposure, are irreversible and cannot be treated but many other diseases, such as cancer, can be treated successfully if diagnosed early. The evidence for various PCB-associated diseases is given below.

1. **Cancer**

PCBs are complete carcinogens and act as general cancer promoters, agents that are not directly carcinogenic but act to enhance the effects of other carcinogenic substances via the generation of reactive oxygen species and the induction of a variety of genes /39/. Chronic exposure to PCBs results in chromosomal aberrations /40/, an action probably mediated primarily by metabolites of the PCBs, although they are generally not viewed as being cancer initiators /41/. Nevertheless, evidence from one study indicates that dioxin-like congeners and dioxin itself produce oxidative DNA damage /42/. In a study investigating the induction of hepatic tumors in rats, van der Plas et al. /43/ concluded that ...the majority of the tumor promotion potential of PCB mixtures resides in the non-dioxin-like fraction, which is not taken into account in the toxic equivalency factor (TEF) approach for risk assessment of PCBs.

Therefore, one cannot adequately assess cancer risk from PCB exposure by using TEFs. The situation is further complicated by evidence for interactions, both antagonistic and synergistic, in certain combinations of PCB congeners, with or without dioxins /44–45/. By virtue of these actions, one would expect that they would result in an increased risk of every kind of cancer /46/.

Studies of cancer in human populations are primarily of two major types—occupational studies of workers and case-control studies of individuals with a specific kind of cancer. Polychlorinated biphenyls are classified as “probable human carcinogens” by the World Health Organization, based on proof in animals and results consistent with this conclusion in humans, whereas dioxins are classified as “known human carcinogens”. A major reason that the evidence for PCB carcinogenicity does not reach the level of proof in humans is that PCBs accumulate with many other fat-soluble contaminants, therefore, it is impossible to be 100% confident that the cancer is caused by PCBs and not by DDT or other fat-soluble chemicals. Nevertheless, it is almost certain that a substance will be carcinogenic in humans if that chemical is carcinogenic in animals who share a majority of our genes. Therefore, when evaluating the impact of PCB exposure on human health, discounting animal carcinogenic studies has no merit.

Occupational studies are limited in power, especially because (a) the number of employees is usually small and (b) cancer is a relatively rare disease, for which the incidence in a small population will not be large, even if the risk is elevated. A number of occupational studies have reported increased numbers of various PCB-associated cancers—liver, gall bladder, biliary tract, leukemia, gastrointestinal, skin (especially malignant melanoma), lymphoma, lung, pancreatic /27, 47/, but these studies do not report PCB levels and are not of great use in defining risk. The other problem is that not all occupational studies show elevations of the same type of cancer, probably because of the size of the groups studied. In
addition, many occupational studies are going to show what is known as the ‘healthy worker effect’, which is that employed persons are in general healthier than those who are unemployed. Such limitations are clearly shown in the studies conducted by Kimbrough et al. /48–49/. Although widely reported to be “the largest occupational cohort studied”, the study of over 7,000 employees at two General Electric capacitor plants in New York included everyone who had worked at the plant for a period as short as 90 days, including secretaries and workers that we would not expect to be exposed. These studies focused on mortality, not incidence, and suffered from exposure misclassification, failure to account for latency of cancer development, and poor statistical power /50–51/.

**Brain cancer.** Sinks et al. /52/ reported an elevated incidence of brain cancer in workers in an Indiana capacitor-manufacturing plant. Ruder et al. /53/ recently published a follow-up study of the same population and found a SMR of 1.91 (1.0–3.3) and a significant dose-response trend (p = 0.016). The highest SMRs were found among workers in the highest tertile of PCB exposure.

**Breast cancer.** Many small clinic-based breast cancer studies have been published, some of which suggest a dose-dependent relation to total PCB exposure, but most large retrospective and nested epidemiologic studies have not demonstrated a relation between elevated total PCB levels and breast cancer. These have been reviewed by Moysich, et al. /54/. As discussed above, such conflicting observations may be a result of the different endocrine actions of different PCB congeners. Nevertheless, some evidence has been found for a relation between PCB exposure and risk of breast cancer in individuals with exposure to certain PCB congeners and in persons from certain racial or genetically susceptible subgroups.

PCBs are potent inducers of the enzyme cytochrome CYP1A1, which has several variant genotypes. In a retrospective case-control study, Moysich et al. /55/ looked at the risk of breast cancer in relation to serum PCB levels in relation to the specific genetic polymorphism of P450 1A1, which codes for a isoleucine to valine substitution. Overall, postmenopausal women having a higher body burden of PCBs were not at greater risk of breast cancer than were women with lower levels. When stratified by genotype, however, among women with serum PCB levels above the median of the distribution in the control group, increased risk of breast cancer was associated with the presence of at least one valine allele (either CYP1A1 Ile:Val or Val:Val) (OR 2.93; 95% CI 1.17–7.36) when compared with women who were homozygous for the isoleucine alleles (CYP1A1 Ile:Ile). Women with lower PCB levels and the CYP1A1 Ile:Val or Val:Val genotypes were not at greater risk for breast cancer, nor were women with elevated PCB levels and CYP1A1 Ile:Ile.

Millikan et al. /56/ studied plasma DDE (1,1-dichloro-2,2-bis(p-chlorophenyl)-ethylene) and PCB levels in relation to breast cancer in a population-based, case-control study of African-American and Caucasian women. The ORs for the highest to lowest third for total PCBs were 1.74 (95% CI: 1.00–3.01) for African-American women and 1.03 (95% CI: 0.68–1.56) for Caucasian women. For obese African-American women, the OR was 4.92 (95% CI: 1.63–14.83). These observations are consistent with the presence of subpopulations that are genetically at greater risk of developing breast cancer following exposure to PCBs.

Aronson et al. /57/ examined breast tissue from 217 hospital cases of cancer and 213 controls. The authors found no relation with total PCBs but significant correlations with PCBs 105 and 118. The ORs for these two congeners increased linearly across categories (p for trend < 0.01). The elevated risk associated with PCBs 105 and 118 were higher among premenopausal women, whereas for postmenopausal women the risks were elevated with PCBs 170 and 180.

Demers et al. /58/ studied 315 cases of breast
cancer and 523 hospital and population controls. The authors reported significant elevations of three individual PCB congeners, PCB 99, 118, and 156, with significant associations between breast cancer risk and PCB 118 (OR = 1.60, 95% CI: 1.01–2.53) or PCB 156 (OR = 1.80, 95% CI: 1.11–2.94). The group also found a significant relation with the sum of mono-ortho-PCBs 105, 118, and 156 (OR = 2.02; 95% CI: 1.24, 3.28, 1st vs 4th quartile). These observations suggest that certain congeners or combinations of congeners cause a dose-dependent increase in the risk of breast cancer, whereas others do not. Although less information is available on the PCB-induced risk of other estrogen-dependent cancers, what is true for breast cancer is likely true for other types of cancers.

Holford et al. \cite{59} analyzed nine congeners in a hospital-based case-control study and reported that although no relation between total PCBs and breast cancer risk could be established, an anti-estrogenic and dioxin-like congener, PCB 156, had a protective effect, whereas two phenobarbital-like congeners PCBs 180 and 183 had adverse effects. The latter report indicates the importance of obtaining congener-specific information.

Liver/biliary cancers. Liver and biliary cancers are some of the most common neoplasms induced in experimental animals exposed to PCBs \cite{64–65}. Such tumors have also been reported in human occupational studies \cite{66–67}. In the capacitor study of Mallin et al. \cite{60}, an SMR of 6.2 was found for liver/biliary cancer in women employed in the plant for 10 or more years.

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of non-Hodgkin’s lymphoma with increasing serum total lipid-corrected serum PCB concentration. The authors studied 74 cases of non-Hodgkin’s lymphoma occurring among a retrospective cohort of 25,802 adults from Washington County, Maryland in the U.S., from whom blood samples were obtained in 1974, and 147 controls from the same population. Taking the lowest lipid-adjusted PCB levels (247–641 ppb) as controls, the matched adjusted OR was 1.3 (95% CI 0.5–3.3) for serum levels of 649–806 ppb, 2.7 (95% CI: 0.9–7.8) for 814–1060 ppb, and 4.1 (95% CI: 1.4–11.9) for 1070–2070 ppb. The latter value is statistically significant by itself, with a positive p value for trend (p = 0.002). For those individuals who were not positive for Epstein-Barr virus, the level of significance was even greater. Rothman’s table also shows the PCB levels as absolute serum values (not lipid-adjusted). The respective mean values of the four groups are 3.8, 5.5, 6.7, and 10.3 ppb. A later report from the same group /73/ did not find a relation between non-Hodgkin’s lymphoma and any of nine other chlorinated pesticides, suggesting that the relation is specific to PCBs.

Hardell et al. /74/ studied 29 cases of B-cell non-Hodgkin’s lymphoma and 17 controls and found that almost all levels of the PCB congeners analyzed were higher in cases than in controls. The mean sum of PCBs was 1,614 ppb (range 637–4,705, lipid-adjusted) for cases and 1,213 ppb (range 366–2,282) for controls. Compared with controls, the elevated congeners were 156, 157, 171, 172, 182, 187, 189, 190, 194, 201, 202, and 208, with p < 0.05 for all. Hardell found no difference for hexachlorobenzene (HCB) and DDE.

Epstein-Barr virus is a human herpes virus that has been associated with certain subgroups of non-Hodgkin’s lymphoma. In a 2001 report, Hardell and coworkers /75/ reported an OR of 4.0 (95% CI: 1.2–14) for total PCBs and an OR of 6.4 (95% CI: 1.9–24) for the sum of immunotoxic PCBs in individuals who also had elevated antibodies to Epstein-Barr virus (indicating that they had been infected).

Nordstrom et al. /76/ studied 54 cases of hairy cell leukemia (a form of non-Hodgkin’s lymphoma) and 54 controls. Although no significant difference was found between cases and controls in total lipid-adjusted blood PCB concentrations, in a subset of the population who had high serum antibody titers to Epstein-Barr virus, increased risk was found for the sum of a subgroup of immunotoxic PCB congeners (PCBs 66, 74, 105, 110, 118, 128/167, 138, 156, and 170/190). The OR was 1.7 for low levels of these congeners and 11.3 for high levels, indicating a more than 10-fold increased risk. Colt et al. /77/ investigated the incidence of non-Hodgkin’s lymphoma in relation to the PCB concentration in household dust. The authors found that risk was elevated if any one of six monitored PCB congeners was detected (OR 1.5, 95% CI 1.2–2.0). The relation was particularly striking with PCB 180 (OR 1.7, 95% CI 1.1–2.6; p = 0.03).

Hoque et al. /63/ studied various cancers in 187 persons exposed to PBBs, which would be expected to have the same effect as PCBs, and 696 unexposed controls. The authors found no overall increased risk of cancer related to serum PBB level, but did find a PBB-related dose-dependent elevated risk for both lymphoma and digestive system cancers. For lymphoma, taking a PBB level of < 3 ppb as control, the ORs were 3.85, 19.6, and 48.9 for the respective PBB levels of 4–20, 21–50, and > 50 ppb, all of which are highly significant.

Pancreatic cancer. Yassi et al. /78/ reported a significant elevation of pancreatic cancer mortality in workers in a transformer manufacturing plant using transformer fluids, some containing PCBs (SMRs ranging from 2.92–7.64). Studying a group of 108 cases and 82 controls, Hoppin et al. /79/ have shown that exposure to PCBs results in a significant dose-dependent increased risk of pancreatic cancer (p for trend < 0.0.001). Total PCBs were measured in serum and reported as lipid-adjusted values. Taking lipid-adjusted PCB levels in serum below 185 ppb as reference, a 1.3-
fold risk (95% CI: 0.6–2.8) was found for levels between 185–360 ppb, and a 4.2-fold increased risk for levels over 360 ppb (95% CI: 1.9–9.4). Not only is the last number statistically significant but also a p for trend and a continuous (OR = 1.003 for each ppb increase in concentration) variable are significant as well. Significantly elevated ORs were reported for the highest tertiles of PCB congeners 153 (OR 3.0, 95% CI: 1.4–6.6) and PCB 180 (OR = 8.4, 95% CI: 3.4–21).

In a study of 51 cases of pancreatic cancer by Porta et al. /80/, cases with wild-type K-ras gene1 (n=17) were frequency matched for age and sex to cases having a K-ras mutation (n=34, case-case study). The authors found that cases having a K-ras mutation had higher concentrations of PCBs 153, 180, and 138 (the only congeners measured). When compared with 26 hospital controls (case-control comparison), the total concentrations of the three PCBs were higher in the 51 cases than in the 26 controls, but the differences were significant only for PCB 180. The 51 cases were more than four times more likely than the 26 controls to be in the upper tertile of PCB 180 (OR = 4.6, 95% CI: 1.1–19.0, p for trend = 0.037). The OR for the 34 K-ras-mutated cases was 7.4 (95% CI: 1.6–34.4, p for trend = 0.012). Considered alone, lipid adjusted, and taking non-detected values as OR = 1.0, in tertiles, the ORs for PCB 138 increased from 1.0 to 2.9 (95% CI: 0.5–17.2) to 6.9 (95% CI: 1.1–41.5), with a p for trend of 0.034. For PCB 153, the ORs ranged from 1.0 to 1.8 (95% CI: 0.4–7.6) to 7.2 (95% CI: 1.1–45.6); p for trend = 0.035. For PCB 180, the ORs ranged from 1.0 to 2.8 (95% CI: 0.6–14.3) to 6.3 (95% CI: 1.0–38.8); p for trend = 0.028.

Prostate cancer. For three specific groups of PCB congeners, Ritchie et al. /81–82/ demonstrated a dose-dependent increased risk of prostate cancer as a function of serum PCB concentration. Interestingly, the authors did not find an increased risk with dioxin-like congeners, but did find a dose-dependent increased risk of up to more than 2 orders of magnitude for moderately chlorinated congeners and transient and persistent phenobarbital-like inducers. This study is one of the clearest demonstrations that not only dioxin-like PCB congeners can increase the risk of cancer. In an occupational nested case-control study, Charles et al. /83/ reported an OR of 1.47 (95% CI: 0.97–2.24) for serum PCB levels and prostate cancer mortality after adjustment for suspected confounding factors.

Thyroid cancer. Thyroid cancer is commonly induced in animals upon exposure to PCBs /65, 84/. The occupational study of capacitor workers conducted by Mallin et al. /60/ reported a significant SMR of 15.2 for thyroid cancer in men.

2. Recurrent Infections

Suppression of the immune system is an important factor because individuals with subnormal immunity show increased susceptibility to infections and to cancer. As exposure to PCBs can suppress both the antibody (immunoglobulins) and the cellular immune response, frequent infections can be a direct result of PCB exposure. Until recently, the ATSDR considered immune suppression to be the biologic effect that occurred at the lowest PCB concentration, although they now believe that effects on neurobehavior occur at even lower doses.

Human studies have clearly shown that persons exposed to PCBs have a greater incidence of all kinds of infections. One year after the event, Lu and Wu /85/ studied patients in Taiwan who were exposed to PCB-contaminated rice oil in 1979. As compared with controls, exposed patients had more infections, especially of the respiratory tract and skin. The initial PCB levels in the patients varied between 3 to 1156 ppb (mean = 89 ppb). When tested later, a subgroup showed elevated

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1 Family of retrovirus-associated (ras) DNA sequences isolated from Harvey (H-ras, Ha-ras, rasH) and Kirsten (K-ras, Ki-ras, rasK) murine sarcoma viruses. Sequences corresponding to both H-ras and K-ras genes have been detected in human, avian, murine, and non-vertebrate genomes.
immunoglobulin classes IgA and IgM, a reduced delayed-type response to skin test antigens, and a reduced number of several classes of white blood cells involved in the immune response. This study does not report PCB levels in these subjects, but the differences are significant relative to unexposed controls.

Weisglas-Kuperus et al. /86/ showed that at 3 months of age, Dutch children exposed to a mixture of PCBs and dioxins had lower levels of monocytes and granulocytes than did less exposed children. As these white blood cells scavenge and kill microbes, an abnormally low concentration reduces the body’s resistance to many infections. In a later study /87/ of 207 Dutch mother-infant pairs, the same group measured the sum of PCB congeners 118, 138, 153, and 180 in the mothers’ serum, in cord blood, and in breast milk. The authors state that these four congeners constituted 46% of the total PCBs. The range of PCB levels in children at 42 months of age was from 0.08 to 5.90 ppb, with the average being well below 1 ppb. Adjusted for confounders, higher PCB levels were associated with a higher incidence of recurrent middle-ear infections (elevated 3-fold) and of chicken pox (elevated 7.6-fold), but a lower prevalence of asthma. The children with higher PCB levels had more coughing, chest congestion, and phlegm. The authors conclude that the higher the PCB level, the greater the frequency and severity of infections, but the lower the frequency of allergic diseases.

These children were followed up until school age and found to have a persistently higher prevalence of ear infections /88/. Dewailly et al. /89/ found that one-year-old infants fed milk contaminated with PCBs had a 20-fold higher incidence of infectious diseases, such as measles, meningitis, and middle ear infections than did children with less exposure.

Immunoglobulins (Ig) produced by lymphocytes are good markers for the integrity of the immune system. In a study of Belgian adolescents, Van Den Heuvel et al. /90/ found that as levels of three PCB congeners and total dioxin equivalents (TEQs) increased, serum IgA levels increased and IgG and IgE levels decreased.

We recently studied the hospitalization rates for infectious diseases in relation to residence near PCB-contaminated sites. Kudyakov et al. /35/ found that the hospitalization rates for acute and chronic infectious respiratory diseases were significantly elevated in persons living in PCB-contaminated zip codes in upstate New York when compared with ‘clean’ zip codes without hazardous waste sites or with zip codes having hazardous waste sites containing other kinds of wastes. As a control for other well-documented confounders, the authors report that the family income of individuals living along the Hudson River is greater than that of other upstate residents and, based on the Behavioral Risk Factor Surveillance System, such persons smoke less, exercise more, and eat more fruits and vegetables than do other New Yorkers. Yet the Hudson River residents show significantly higher rates of hospitalization for chronic respiratory infections. We attribute the elevated rates to inhalation exposure to PCBs coming from the Hudson River, resulting in suppression of immune function.

3. Neurobehavioral Effects

In utero exposure to PCBs has been linked to adverse effects on intellectual function in infants and young children. Jacobson and Jacobson /91/ assessed whether such effects persist through school age in children born to women who during pregnancy had eaten fish contaminated with PCBs. The authors followed 212 children from birth to 11 years of age. PCB levels were determined in maternal serum, in breast milk, in the umbilical cord blood at delivery, and in the children’s blood 11 years later. The authors then administered a battery of IQ and achievement tests. The average
maternal serum level at the time of the child’s birth was 6 ppb, whereas the child’s was 1 ppb at age 11 years (not lipid adjusted). The breast milk on average contained 841 ppb of PCBs, lipid adjusted. The results show a significant reduction in full-scale IQ in children of mothers whose breast milk contained PCBs at a concentration of 1,250 ppb (lipid adjusted) or greater and poorer performance on reading mastery in children whose mothers had 1,000 ppb or greater PCBs in breast milk. The authors conclude that perinatal exposure to PCBs causes an irreversible decrement of IQ.

Chen et al. /92/ reported on the cognitive development of children born to mothers who had eaten PCB-contaminated rice oil and dibenzofurans in Taiwan in 1976. These authors studied 118 children born to exposed mothers (some born years after the poisoning) and 118 matched controls. The exposed children scored approximately 5 points lower on the Wechsler Intelligence Scale for Children. The children were followed through ages 4, 5, 6, and 7 years, but no obvious improvement occurred with time. This study did not obtain PCB levels but reports that after the exposure, the average levels were 49.3 ppb in adults (range 2.0–456 ppb) in the exposed population, whereas the mean PCB level was 9.8 ppb in 92 Taiwanese blood donors (not used as controls in this study, but perhaps reflective of the population).

Lonky et al. /93/ attempted to replicate the studies carried out by Jacobson through studying children born to mothers who had eaten PCB-contaminated Lake Ontario fish. This paper does not give PCB values (they studied only cord blood, but the data appear in a different paper), but categorizes mothers either as “no fish”, “low fish”, or “high fish”. Each group comprised over 150 mother-infant pairs. Using the Neonatal Behavioral Assessment Scale to study neurologic development over the first 48 h of life, the investigators found that infants in the “high fish” category showed more abnormal reflexes, greater responses to stress, and less habituation to repeated stimuli than did “no fish” and “low fish” babies. The results are consistent with known effects of PCBs on the brain before birth.

Rogan et al. /94/ studied 912 children in North Carolina born to mothers with no known special exposure to PCBs and performed the Brazelton Neonatal Behavioral Assessment Scales (psychologic and neurologic tests designed for use in newborn infants) in relation to the PCB levels in breast milk. Children who were more exposed showed low muscle tone and depressed reflexes. Relating the breast milk PCB levels reported in this study to those of other studies is hard, but the Rogan study is important because it shows that levels that are present in the general population (about 1980 ppb) alter the nervous system performance of children.

Walkowiak et al. /95/ reported on 171 mother-infant pairs from Germany who were recruited into the study between 1993 and 1995. The children were examined repeatedly for psycho-development at 7, 18, 30, and 42 months of age. Prenatal and perinatal PCB levels were determined in cord blood and breast milk and in the children’s serum at 42 months of age. Only three PCB congeners were measured at levels representing European ambient background exposure. Prenatal exposure to PCBs had a negative effect on both mental and motor development in children at all ages. The results show that even at background exposure levels, more is worse, but because the investigators measured only three congeners, determining the relative risk is difficult.

Yu et al. /96/ studied behavior in 118 children born to the Taiwanese mothers who were exposed to PCBs by consuming rice oil and matched controls. Consistent and significant differences were found on the Chinese version of Rutter’s Child Behavior Scale A measuring emotional and behavioral disorders on health, habit, and behavior. The exposed children were examined annually from 1985 to 1991 and performed more poorly than controls on all three components, which
persisted as the children aged.

In an assessment of impact of PCB exposure during adulthood on intellectual functioning, Schantz et al. /97/ studied memory function in 572 49- to 86-year-old adults who eat a great amount of contaminated Great Lakes fish and 419 people who do not. Three memory tests were used, as well as several visual tests, and serum PCBs and a number of other contaminants were measured. The PCB levels were divided into four groups: ND–4.6 ppb, 4.7–7.8 ppb, 7.9–13.8 ppb, and 13.9–75.0 ppb. In all three memory tests, performance decreased as the PCB dose increased, but PCB exposure had no effect on the visual tests. No other contaminant studied was associated with poor performance on memory tests. This study is important because it is the only one clearly showing that even adults can suffer from a specific loss of IQ and memory upon PCB exposure.

The general conclusion is that the higher the child’s exposure to PCBs in early life, the lower the IQ and the more the child exhibits anti-social behavior, depression, and attention deficit hyperactivity disorder-type symptoms. These effects are found over the full range of IQ, however, and even bright kids would have been brighter had they not been exposed. In adults exposed to PCBs, a decrement in IQ is paralleled by a reduction of memory.

4. Hypothyroidism

Thyroid hormones have some structural similarity to PCBs but have iodine rather than chlorine substitutions on the two phenyl rings. A number of animal studies clearly show that PCBs interfere with thyroid hormone at multiple sites /98/.

Koopman-Essenboom et al. /99/ studied thyroid function in mother-infant pairs in the Dutch study /88/ and found that high organochlorine levels in mother’s milk correlates with low plasma maternal T3 and T4 levels and with high thyroid stimulating hormone (TSH, thyrotropin) levels in their infants. Osius et al. /100/ measured thyroid hormones and eight PCB congeners in blood samples obtained from 1,091 second-grade children living near an incinerator in Germany. One congener (PCB 118) correlated positively with TSH, whereas five other congeners were negatively correlated with free T3, the active form of thyroid hormone.

Schell et al. /101/ studied PCBs and thyroid hormones in Native American adolescents living near the St. Lawrence River where the fish are contaminated with PCBs. The mean PCB level was 1.82 ppb and the maximum level 4.75 ppb. Schell found a statistically significant positive and dose-dependent relation between total PCBs and TSH levels and a significant negative relation with both free and total thyroxine (T4). A negative relation to T3 (triiodothyronine) was found, but not at a level that was significant. This study shows clearly that PCBs at levels common in the population reduce thyroid function. Wang et al. /102/ reported reduced levels of free T4 FT₄ × TSH (based on the normal hypothalamic–pituitary axis in which decreased T₄ feeds back to the hypothalamus and stimulates the anterior pituitary to secret TSH) with increasing levels of placental non-ortho PCBs in neonates from the general population.

5. Infertility and Reproductive System Disorders

Polychlorinated biphenyls are potent inhibitors of the synthesis of the male sex hormone testosterone /103/, the basis of sexual arousal and secondary sexual characteristics /104/. Animals exposed to PCB-containing transformer fluids show decreased levels of testosterone /105/. In addition, PCBs compete with testosterone for binding at the testosterone receptor /106/, which even further reduces masculinity. In healthy, young humans, serum levels of PCB 153 were shown to be inversely correlated with free testosterone levels /107/. In addition, high PCB levels have been
correlated with reduced sperm mobility /107–108/. Men in Taiwan exposed to PCBs in 1978–1979 and studied by Hsu et al. /109/ in 1999–2002 were found to have more abnormal sperm than did controls; the sperm they did have showed a reduced capability to bind and penetrate oocytes.

For both dioxins /110/ and PCBs /111/, clear evidence shows that the ratio of male to female births is strikingly reduced following parental exposure. Exposure to these compounds also alters female reproduction. Both PCB /112/ and PBB /113/ exposure causes an earlier menarche in girls. Cooper et al. /114/ reported that women show a positive association between PCB levels and increasing menstrual cycle length (p = 0.02). The exposure of monkeys to dioxins and dioxin-like PCBs results in endometriosis /115–117/. Pauwels et al. /118/ showed an elevated incidence of endometriosis in humans with higher dioxin toxic equivalents, and Buck-Louis et al. /119/ reported that women in the third tertile of anti-estrogenic PCBs have an OR of 3.77 (95% CI: 1.12–12.68) for visually confirmed endometriosis, which is consistent with the monkey evidence.

6. Cardiovascular Disease (CVD) and Elevated Serum Lipids

Baker et al. /120/ first reported that workers exposed to PCBs showed a significant direct correlation between serum PCB levels and plasma triglyceride levels, a relation later confirmed in animal studies /121–124/. Elevated serum lipid levels along with hypertension are the best-documented risk factors for ischemic heart disease /125/. Baker et al. found that blood levels of PCBs in persons working in a sewage sludge plant in Indiana and their families were between 17.4 and 75.1 ppb, with a highly significant relation between plasma triglyceride levels and serum PCB concentrations.

In the U.S., Kreiss et al. /126/ determined serum lipids as a function of serum PCB levels in 458 individuals over 12 years of age in Triana, Alabama, which had significant PCB contamination, primarily through eating contaminated fish. This group found that the higher the PCB level, the higher the serum cholesterol level and the higher the blood pressure. The mean PCB level was 17.2 ppb, with a range from 3.2 to 157.9. Sixty of the 458 residents had levels greater than 30 ppb. Chase et al. /127/ found significantly elevated serum triglyceride levels in PCB-exposed workers (p < 0.0001), after controlling for either age or length of employment. The frequency of reported direct contact with PCB levels suggested a dermal route of exposure. Martin /128/ reported that workers exposed to dioxin in an accident still had statistically significant elevations of serum cholesterol and triglyceride concentrations 10 years later.

Gustavsson and Hogstedt /67/ studied 242 male capacitor manufacturing workers exposed for at least 6 months to PCBs and found significantly increased mortality from CVD among those employed for at least 5 years in high-exposed jobs, with a latency of 20 years. The latter study did not control for smoking habits, however. Another occupational study reported similar results for workers using a phenoxy-herbicide spray mixture containing 10% waste transformer oil /129/, but did not really provide any direct PCB exposure data. Occupational exposure to dioxins/furans has been correlated with an excess incidence of CVD in two studies /130, 131/, but not in another /132/. The ATSDR /27/ concluded, however, that the existing data at that point in time (2000) were insufficient to incur possible cardiovascular toxicity of PCBs in humans.

In a study of anglers in New York, Moysich et al. /133/ reported a significant correlation between total lipids and serum PCB levels even after age adjustment. Tokunaga and Kataoka /134/ reported on the relation between PCB exposure (Kanechlor) and serum lipids in Japanese Yusho patients exposed through contaminated rice oil in the 1970s. The authors found that a 10-fold elevation of PCB
levels was associated with an elevation of serum total cholesterol by 18.4 mg/dL (p < 0.001) in men and 17.5 mg/dL in women, and of serum triglycerides by 43.3% in men and 42.8% in women, compared with controls.

Sergeev and Carpenter /36/ reported hospitalization discharge diagnosis rates for coronary heart disease and myocardial infarction among New York State residents living in a zip code that contains or abuts a hazardous-waste site containing persistent organic pollutants (POPs), of which PCBs are the most frequent contaminant. The authors found that the rate of diagnosis of coronary heart disease were 15% higher in residents who live in zip codes containing or abutting a POPs sites, and that rates of myocardial infarction were 20% higher in these zip codes. Sergeev and Carpenter also studied a subset of zip codes along the Hudson River, 200 miles of a National Priority Site highly contaminated with PCBs, where the average income is higher, smoking rates are lower, residents exercise more frequently and consume fruits and vegetables more regularly than in the other parts of the state. Despite a higher socio-economic status and healthier life style, the authors found a 35.8% higher frequency diagnosis of coronary heart disease and a 39.1% more frequent diagnosis of myocardial infarction in this population.

7. Hypertension

Kreiss et al. /126/ reported that residents of Triana, Alabama having high serum PCB concentrations from eating local contaminated fish showed a significantly higher incidence of high blood pressure than those with lower PCB levels. The increase in blood pressure was independent of age, sex, body mass index, and social class. In a population of 458 persons with an average serum PCB concentration of 17.2 ppb, the rate of borderline or definite hypertension was 30% higher than expected from national rates. The relation with PCB concentration was highly significant for diastolic blood pressure and of borderline significance for systolic blood pressure. Excess hypertension has been reported in several occupational studies of PCB exposure/135–137/.

8. Diabetes

Although diabetes is rarely considered an environmentally induced disease, the evidence is strong that environmental PCB exposure contributes to the incidence of diabetes. Some of the best evidence emerged from a study of the U.S. Air Force personnel who dropped Agent Orange (contaminated with dioxin) during the Vietnam War. A highly significant relation between dioxin exposure and the onset and severity of diabetes was found in those individuals having the greatest exposure /138/. This observation led to a report by the committee of the U.S. Institute of Medicine of the National Academies of Sciences /30/, which concluded that there was suggestive evidence of an association between dioxin exposure and diabetes.

Pesatori et al. /139/ and Bertazzi et al. /140/ studied individuals exposed to dioxins in an industrial accident that occurred in the town of Seveso, Italy, in 1976 and found elevated diabetes in exposed individuals. A similar conclusion was drawn by Vena et al. /132/ from a study of phenoxycacid herbicides and chlorophenol production workers exposed to dioxins. Cranmer et al. /141/ studied a population of individuals exposed to dioxin from a Superfund site and found that plasma insulin concentrations were significantly higher in individuals with elevated dioxin levels, concluding that high serum dioxin levels cause insulin resistance.

Longnecker et al. /142/ studied 2,245 pregnant women, 44 of whom had diabetes. The mean serum PCB level in the women with diabetes (3.77 ppb) was 30% higher than the controls (2.79 ppb), and the relation of PCB level to the adjusted OR
for diabetes was linear. Taking PCB levels < 2.50 ppb to have an OR of 1.0, the OR was 2.9 for PCB levels 2.50–3.75 ppb, 4.4 for PCB levels 3.75–5.00 ppb, and 5.1 for PCB levels > 5.0 ppb. All values were statistically significant. This is an excellent study showing a dose-response relation between PCB levels and diabetes. Strong support for this relation between exposure and diabetes is also found in population-based study of Fierens et al. /143/, in which they found, after adjustment for age and other covariates, that total TEQ and 12 marker PCB concentrations were 62% and 39% higher, respectively, than in controls. The ORs were 5.1 (95% CI: 1.18–21.7) for dioxins, 13.3 (95% CI: 3.31–53.2) for coplanar PCBs, and 7.6 (95% CI: 1.58–36.3) for 12 marker PCBs.

9. Liver Disease

The U.S. Environmental Protection Agency’s Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds National Academy Sciences (NAS) Review Draft document gives the following statement:

*Increased liver size is consistently reported in treated animals after exposure to 2,3,7,8-TCDD...Among exposed human populations, four case reports in three populations, but not controlled epidemiologic studies, described evidence of enlarged livers or hepatomegaly.*

With regard to enzyme changes following dioxin exposure, the following statements:

*Laboratory studies have demonstrated changes in hepatic enzyme levels after 2,3,7,8-TCDD exposure, although there is considerable interspecies variation in the observed effect.*

*Epidemiologic studies and case reports describe elevated liver enzymes among exposed TCP production workers and among Severso residents.*

Although this report is still not official, the references to the studies indicated below are included in the draft document.

Damage to liver cells causes the release of several enzymes. Among the most sensitive and widely enzyme assays are the aminotransferases, aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT), as well as other enzymes, such as gamma-glutamyl transpeptidase (GGTP) and the liver-specific ornithine carbamoyltransferase (OCT).

In studies focusing specifically on PCBs, Kreiss et al. /126/ reported that the exposed residents of Triana, Alabama showed a positive relation between serum PCBs levels and GGTP enzymatic activity levels. Chase et al. /127/ and Fischbein /144/ both reported significantly elevated serum SGOT activity levels in 120 workers who were exposed to PCBs. Smith et al. /145/ surveyed three groups of PCB workers and found that significant elevations of both SGOT and GGTP positively correlated with serum PCB levels. Maroni et al. /146/ found that 16 of 80 workers exposed to PCBs had hepatomegaly, with an increase in serum enzymes GGT (GGTP), AST, ALT, and OCT. The studies of Fitzgerald et al. /9/ mentioned above demonstrated that PCB exposure increases the rate of the metabolism of caffeine in the liver.

10. Asthma

Whereas dioxin exposure is known to reduce the incidence of asthma /87/, PCB exposure is associated with a significant increase in the risk of asthma /90/. The latter report demonstrated an increased risk of 2.12 orders of magnitude based on the concentrations of PCBs 138, 153, and 180. The report confirmed the opposite effect of dioxin-
like compounds using the CALUX assay, which measures total dioxin-like activity, including that of the dioxin-like PCBs. It is likely that the specific PCB effect on asthma is secondary to the immune system alterations induced by the ortho-substituted PCBs, as have been studied by Tan et al. /15/.

11. Arthritis

An elevation in the incidence of joint disease has been seen in both Asian populations that were exposed to PCBs in cooking oil. Kuratsune /147/ reported an elevated incidence of joint inflammation in Yushu-exposed persons in Japan. Guo et al. /148/ report that Taiwanese men exposed to PCBs in the same accident had a 4.1-fold elevated risk of developing arthritis. Guo et al. /148/ also reported that Taiwanese men exposed to PCBs had a 2.9-fold increased risk of developing back problems because of intervertebral disc disease. As with asthma, the mechanism responsible is not known, but both studies show highly significant effects in relation to PCB exposure.

12. PCB exposure and Low Birth Weight: A Factor for Increased Risk of Diabetes, Cardiovascular Disease and Hypertension

Several studies (see reference /34/) have shown that PCB exposure increases the risk of babies having low birth weight. Taylor et al. /149/ showed that women working in a capacitor plant in areas where they were presumed to be exposed to PCBs gave birth to children 153 g lower in weight and with an average of 6.6 days shorter gestation than babies born to unexposed mothers. This effect has been seen in a number of other studies and the effect appears to be greater in male than in female infants.

We /34/ have shown that maternal residence in a zip code containing or abutting a PCB-contami- nated site significantly increases the risk of giving birth to a low-birth-weight infant and that the risk is greater for male than for female infants. This finding is particularly important in relation to adult diseases because low birth weight has been clearly shown that to increase the risk of several chronic diseases in adulthood, including CVD /150/, hypertension /151/, and diabetes /152/.

CONCLUSIONS

Polychlorinated biphenyls alter the functioning of many different organ systems in both animals and humans and are risk factors for a large number of human diseases. Although levels in the environment and in populations are declining since their manufacture and use has been reduced, these substances are persistent and remain in the environment and in the human body. It is imperative to continue to reduce human exposure to these dangerous compounds.

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