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Polychlorinated biphenyls: New evidence from the last decade

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Abstract

Millions of pounds of polychlorinated biphenyl (PCB) compounds have been produced in multiple countries for industrial applications over the last several decades. PCB exposure induces various adverse health effects in animals and humans. Environmental and occupational exposures to PCBs have been associated with liver, kidney, endocrine, and neurodevelopmental adverse effects. We have collected and reviewed animal and human data cited in the U.S. National Library of Medicine from 2000–2010. In brief, our review shows new evidence that demonstrates:

In animal studies, exposure to one of the PCBs, A1221, induces a significant alteration of serum luteinizing hormone. The effects were more profound in the F2 generation, particularly with respect to fluctuations in hormones and reproductive tract tissues across the estrous cycle. Morphological analyses of brain tissue from rats exposed to A1254 confirmed earlier work that showed the relative size of the intra- and infra-pyramidal (II-P) mossy fibers was smaller than in controls, and reduction in growth was selective for the II-P mossy fibers. PCB exposure increased anogenital distance and prostate size but decreased epididymal weight, epididymal sperm count, and motile epididymal sperm count. No effects were observed on testicular weight or size.

The epidemiological data showed an association between diabetes mellitus prevalence and elevated concentrations of PCB-153. Additionally, prenatal PCB exposure studies were associated with a smaller thymic index at birth and could adversely affect immune responses to childhood vaccinations and resistance to respiratory infections. PCB exposure was also reported to adversely affect enamel development in children in a dose-dependent manner.

Because PCBs and their metabolites are potential health hazards, understanding the risk factors associated with individual PCBs, PCB mixtures, and PCB metabolites is important. PCB exposures of vulnerable populations (pregnant women, fetuses, infants, and children) are of particular concern because of heightened sensitivity during this period of brain development.

Keywords

Polychlorinated Biphenyls; PCB congeners; Cancer; diabetes mellitus; Developmental neurotoxicity; Endocrine Disrupters

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Introduction

Polychlorinated biphenyls (PCBs) are a category of chemicals that were manufactured in the United States between about 1930 and 1977 (Hopf et al., 2009). Because of their general chemical inertness and heat stability, PCBs were predominantly used as coolants and lubricants in electrical equipment such as capacitors and transformers. Because of their non-flammability, chemical stability, high boiling point, and electrical insulating properties, PCBs were used in hundreds of industrial and commercial applications including electrical, heat transfer, and hydraulic equipment; as plasticizers in paints, plastics, and rubber products; in pigments, dyes, and carbonless copy paper; and many other industrial applications (EPA 2014). Their high dielectric properties made them so useful.

PCBs were manufactured as a mixture of PCB congeners under a variety of names, the most common being Aroclor. Aroclor mixtures of chlorinated biphenyl congeners vary in degree of chlorination. One example is the commercial product Aroclor 1254, a mixture of mono- through hepta-chlorinated biphenyl congeners with an average chlorine content of approximately 54%. In 1977, the United States stopped the manufacture of PCBs after finding they accumulate and persist in the environment and can cause adverse health effects in humans and animals. No known consumer product currently manufactured in the United States contains PCBs, although some industrial processes still release them. Once commercial PCB mixtures are released into the environment, processes such as volatilization, partitioning, chemical or biological transformation, and preferential bioaccumulation alter them and dictate their environmental fate. These processes are dependent on the degree of chlorination of the biphenyl molecule (ATSDR 2000) (Figure 1). The higher chlorinated PCB congeners adsorb strongly to sediment and soil, where they tend to persist with half-lives of months to years.

PCBs also bioaccumulate in the food chain (Ivanciuc et al., 2006). Because of stability and lipophilicity, PCBs preferentially bioaccumulate in fatty tissues. Bioaccumulated PCBs persist in the body and are therefore of special relevance to human health. PCB exposure may occur as a result of ingesting contaminated food or inhaling contaminated air. However, food consumption has been and continues to be the major source of PCB exposure and thus, body burdens (Patandin et al., 1999). In 1978, the estimated dietary intake of PCBs for an average adult was about 0.03 μg/kg/day. By 1991, dietary intake had declined to <0.001 μg/kg/day (ATSDR 2000). No current or systematic estimation of dietary intake of non-dioxin-like PCBs in the U.S. is available, either on a total PCB basis or on the basis of individual PCB congeners (Aylward et al., 2014). However, Schecter et al. (2001) estimated mean daily TEQ intakes of dioxin and dioxin-like compounds of adult males and females to be 2.4 and 2.2 pg/kg/body weight, respectively. Evidence suggests that diets high in fish from PCB-contaminated waters, such as in the Great Lakes-St. Lawrence River basins, can significantly increase a person’s dietary PCB intake (Johnson et al., 1999). Breast-fed infants of mothers who have diets high in contaminated fish may have an increased risk for exposure resulting from PCB presence in breast milk (Lehmann et al., 2014). Human PCB exposure has also been attributed to inhalation of indoor air—especially at locations that still use electrical equipment containing PCBs (U.S. EPA 2012) Determination of body burdens of PCBs is a difficult process but can be accomplished by analytical measurement of PCBs

and their metabolites in organs and tissues. PCB exposure has mainly been assessed by measuring PCBs in blood, breast milk, and adipose tissue. Umbilical cord blood also has been used to estimate exposure *in utero*. When tissue and organ data are not available, exposure data can serve as a reasonable estimate of body burdens or adverse effect levels. Measurements of PCB levels in soil, sediment, air, food, and water have all been used to estimate human body burdens of PCBs. Of particular importance has been estimating fish consumption, particularly in contaminated areas and in subsistence fishing populations. For example, persons whose diets do not contain high levels of fish intake have serum PCB levels in the range of 0.9–1.5 ppb PCB. In populations with high fish intake (Greenlander), the mean concentration of total PCBs in omental fat samples was 5,719 μg/kg lipid basis (range=1,019–12,716 μg/kg lipid basis) (ATSDR 2000).

The human health assessment community uses the body burden and exposure information for PCBs to evaluate the public health impact of past, ongoing, and future exposures to PCBs. Our objective was to review the literature aiming to summarize and evaluate the current evidence of an association between PCBs and the exposure levels effects using the recently published literature included at the ATSDR Toxicological Profiles of PCBs Addenda, which provides to the public and other federal, state, and local agencies a non-peer reviewed supplement of scientific data published in the open peer-reviewed literature since the release of the profile.

General Population and Occupational Exposure

The general population may be exposed to PCBs from a variety of routes and sources, including diet, ambient air, occupational settings, and consumer products. Measurement of PCBs in biological samples generally reflects cumulative, prior exposures. The half-life of congeners varies from months to several years; congeners with few chlorine substitutions have shorter half-lives than the highly chlorinated congeners. Because highly chlorinated congeners are more slowly metabolized, they accumulate to higher levels. Thus, the profile of congeners detected in the environment may differ from the profile of the initially released PCBs. Exposure profiles may change over time also.

The major exposure route for humans is through food. Inhalation and dermal routes factor into occupational exposures in buildings containing PCBs, during PCB clean-up activities, in exposures at hazardous waste sites containing PCBs, and for swimmers in PCB-polluted waters. In all cases, total PCB levels must be based on specific congener analysis rather than in terms of commercial mixtures (Aroclors) because the congener patterns in environmental media and biological tissues usually do not match those in the parent Aroclors.

Cohort studies, community studies, and ongoing risk assessment activities at different sites in the United States have addressed how the environment will affect PCB body burden. Several published studies report levels of individual PCBs, total PCBs, hydroxylated PCB metabolites (OH-PCBs), total OH-PCBs, and mixtures of parents and metabolites. In general, the measured PCBs levels are comparable across studies; some examples include California mothers cohort (Park et al., 2009), East Chicago and Columbus Junction (Marek et al., 2013), Great Lakes cohort of pregnant African American women (McGraw and Waller

2009), The Adult Native American cohort (De Caprio et al., 2005), Hudson River communities (Fitzgerald et al. 2007, 2011), Anniston community (Silverstone et al., 2012, Goncharov et al., 2009), and the National Health and Nutrition Examination Survey (NHANES) (CDC 2009).

Indoor inhalation exposure with low chlorinated PCB congeners resulted in an increase of PCB 28 and PCB 52 blood levels in teachers working in a PCB-contaminated school (Schwenk et al., 2002). Accumulation of non-dioxin-like PCBs has been detected in several studies. Breastfeeding and consumption of fish from the Great Lakes contributed significantly to the increase of non-dioxin-like PCBs in the U.S. (Carpenter et al., 2005; Patterson et al., 1994; Turyk et al., 2006). The highest detection frequencies in the U.S. population were for PCBs 138, 153, and 180. These three congeners contributed 65% of total PCB body burdens (Needham et al. 2005). Generally, highly chlorinated PCB congeners (with 5, 6, or 7 chlorine atoms) contributed to 80% of the total PCBs in human serum. Comprehensive human serum analysis of coplanar, mono-ortho, and non-dioxin-like PCBs have been reported in the Fourth National Report on Human Exposures to Environmental Chemicals (CDC 2009).

The Centers for Disease Control and Prevention (CDC) publishes the National Report on Human Exposures to Environmental Chemicals, is an ongoing assessment of exposure to environmental chemicals in the general U.S. population. The Fourth Report contains data for years 1999–2000, 2001–2002, and 2003–2004, from participants in the National Health and Nutrition Examination Survey (NHANES). Detailed information on the design and conduct of NHANES is available at http://www.cdc.gov/nchs/nhanes/about_nhanes.htm. In general, the NHANES Fourth Report found that serum concentrations of PCBs reflected cumulative past exposure in the general U.S. population.

CDC measured polychlorinated biphenyls in serum from a random one-third subsample of participants aged 12 years and older in 1999–2000 and in 2003–2004. In 2001–2002, coplanar PCBs were measured in a random one-third subsample of participants aged 20 years and older, while other PCBs were measured in a random one-third subsample of participants aged 12 years and older. Table 1 lists the dioxin-like PCBs (coplanar and mono-ortho-substituted PCBs) and non-dioxin-like PCBs discussed in the Fourth Report. Included were the measured levels of 38 PCB congeners. Of these, six have previously documented animal and human health effects: PCB 118, PCB 126, PCB 138, PCB 153, PCB 170, and PCB 180.

Polychlorinated Biphenyls Health Effects

The following sections provide summaries of some of the scientific literature published since 2000 regarding the human and animal health effects of PCB exposure. Tables 2 and 3 provide more detailed information about studies summarized in the text.

Systemic Effects

Jokinen et al.(2003) evaluated the effects of chronic exposure to dioxin (2,3,7,8,-tetrachlorodibenzo-p-dioxin [TCDD]) and a dioxin-like compound (3,3′,4,4′,5-

pentachlorobiphenyl [PCB-126]) on the cardiovascular system in female Harlan Sprague-Dawley rats. Results indicated that the rat cardiovascular system was a target for dioxin and PCB-126 toxicity, based on increases in the incidence of spontaneous cardiomyopathy and arteritis of the coronary vessel. Lind et al. (2004) showed that female rats treated with PCB-126 had increased levels of serum cholesterol, increased blood pressure, and increased myocardial mass, all exposure-attributable. In the Lind et al. (2004) experiment, rats received a total dose of 224 μg/kg-bw in five intraperitoneal injections once every other week. The first two doses were 64 μg/kg-bw each, to attain a significant body burden rapidly. The remaining three doses were 32 μg/kg-bw each.

Effects on Bone Mineral Density (BMD)

Glynn et al. (2000) investigated the effect of PCB exposure on bone mineralization in 115 Swedish men from the general population. Researchers observed no statistically significant relationship between PCBs exposure and bone mineral density (BMD). Wallin et al. (2004, 2005) conducted similar studies, investigating the effects on bone in Swedish male and female adults. Although a weak association appeared between PCB-153 exposure and osteoporotic fractures, the relationship was not significant.

Weiss et al. (2006) reported similar findings. They assessed serum levels of the persistent PCB-153, hydroxylated polychlorinated biphenyl metabolites (OH-PCBs), polybrominated diphenyl ethers (PBDEs), and hexabromocyclododecanes (HBCDDs) in a group of Swedish middle-aged and elderly women. They found no association between BMD or the biochemical markers of bone metabolism and PCB-153 and PCB-hydroxylated metabolites. Still, the small number (184 women) of study participants limited the ability to detect any weak or moderate associations. Hodgson et al. (2008) conducted another study from a population 60–81 years of age (154 males, 167 females) living near the Baltic Coast. The results showed that the subjects (mainly males) who lived near a PCB-contaminated river and who were exposed to relatively low levels of PCB congeners had reduced BMD after controlling for major confounding variables. In males, PCB-118 (dioxin-like PCB) exposure was negatively associated with BMD: the odds ratio for low BMD (Z-score less than −1) was 1.06 (95% confidence interval, 1.01–1.12) per 10 pg/mL PCB-118. The sum of the three most abundant non-dioxin-like PCBs (PCB-138, PCB-153, PCB-180) was positively associated with BMD. In females, although PCB-118 was positively associated with BMD, this congener did not influence women's low BMD risk.

Lundberg et al. (2006) studied the effects of perinatal exposure to PCB-153 and PCB-126 in female goat offspring. The goat dams were exposed to 98 μg/kg/day of PCB-153 or 49 ng/kg/day of PCB-126 in corn oil on gestation day (GD) 60 until delivery. The offspring were also exposed to PCBs during the lactation period of 6 weeks. Diaphyseal bone was analyzed at a distance of 18%, and 50% of the total bone length and metaphyseal bone at a distance of 9%. Also, researchers conducted a biomechanical three-point bending of the bones, with the load applied to the mid-diaphyseal peripheral quantitative computed tomography (pQCT) measure point (50%). PCB-153 exposure significantly decreased the total cross-sectional area (125±4 mm^2) versus non-exposed (142±5 mm^2), decreased that of the marrow cavity (38±4 mm^2) versus non-exposed (50±3 mm^2), and decreased the moment

of resistance (318±10 mm^3) versus non-exposed (371±20 mm^3) at the diaphyseal 18% measure point. At the metaphyseal measure point, the trabecular bone mineral density (121±5 mg/cm^3) was increased versus non-exposed (111±3 mg/cm^3). PCB-126 exposure did not produce any observable changes in bone tissue. Researchers observed no significant changes in bone parameters in the PCB-126-exposed group. For either congener, the biomechanical testing showed no significant differences between the exposed and control groups.

Endocrine Effects

Rylander et al. (2005) measured serum PCB 153 concentrations in Swedish fishermen and their wives: 196 men (median age 60 years) and 184 women (median age 64 years). Participants answered questions about diabetes, medication, and disease onset. Elevated PCB-153 serum concentrations were significantly associated with diabetes mellitus type 2 prevalence, even after adjustment for confounding variables. An increase of 100 ng PCB-53/g lipids was related to an odds ratio of 1.16 with 95% confidence interval (CI) 1.03–1.32, p value= 0.03. This study suggested that PCB exposure was strongly related to prevalence of type 2 diabetes mellitus. Others also have reported associations between incidences of type 2 diabetes mellitus and exposure to PCBs (Vasiliu et al. 2006; Chen et al. 2008; Codru et al. 2007; and Wang et al. 2005).

A cross-sectional study showed an association between diabetes mellitus prevalence and the concentrations of PCB-153 and p, p′-DDE in 544 serum samples among Swedish fishermen's wives (Rignell-Hydborn et al. 2007). Lee et al. (2006, 2007a, b) reported similar findings, in which striking dose-response relationships appeared between serum concentrations of six selected persistent organic pollutants (POPs) and the prevalence of diabetes.

Turyk et al. (2009) conducted a study on a cohort of Great Lakes sport fish consumers. Established in 1990 and followed through 2005, this study investigated in the studied cohort the relationship between POPs, including several PCBs, body burdens, and the incidence of diabetes mellitus. Diabetes (Type 2) incident was not associated with mono-ortho PCB-118, total PCBs, or years of sport fish consumption.

Steinberg et al. (2008) administered to pregnant Sprague-Dawley rats 0, 0.1, 1, or 10 mg/kg Aroclor 1221 (A1221) on GD 16 and 18. With the low doses of A1221 given during this critical period of development on F1 and F2 female rats, litter sex ratio skewed toward females. In the F1 generation, additional effects were found, including a significant alteration of serum luteinizing hormone in the 1 mg/kg A1221 group. The F2 generation showed more profound alterations, particularly with respect to fluctuations in hormones and reproductive tract tissues across the estrous cycle.

Lilienthal et al. (2000) measured in rat dams and offspring the serum concentrations of vitamin D_3 metabolites 25-hydroxycholecalciferol (25-D) and 1, 25-dihydroxycholecalciferol (1, 25-D). Measurements occurred after exposure to a PCB mixture reconstituted according to the congener pattern found in human milk. The PCB

pattern in human breast milk has been reported elsewhere in the literature. Exposure of rat dams to the reconstituted PCB mixture at doses of 0, 5, 20, or 40 mg PCBs/kg diet caused dose-dependent reductions in their serum concentrations of 25-D during delivery but not at weaning. This effect was also seen for the two high-dose exposure levels in the offspring at birth and at weaning. In the offspring, there was also a PCB-induced decrease of 1, 25-D and 25-D levels in the group exposed to the highest dosage of PCBs. The results demonstrate that exposure to a human milk-like PCB mixture leads to a decrease in concentrations of a hormone involved in calcium homeostasis.

Immunological and Lymphoreticular Effects

Park et al. (2008) examined the effects of prenatal exposure to PCBs on thymus size at birth in Eastern Slovakian neonates. Prenatal PCB exposure was associated with a smaller thymic index at birth [beta= −36 (natural log-transformed; nanograms per gram lipids); p = 0.047]. District of residence and delivery also predicted thymic index. Male sex, later gestational age, larger birth weight z-score, and Roma ethnicity were associated with a larger thymic index, whereas respiratory illness was associated with a lower thymic index (Park et al. 2008). This evidence is the first to date suggesting that PCB exposure in neonates is associated with a smaller thymic volume, suggesting the possibility of impaired immunologic development.

In another study, Heilman et al. (2006) implied that PCB exposure was a possible cause of deficient immune function in children. They demonstrated that increased perinatal exposure to PCBs can adversely affect immune responses to childhood vaccinations. The study examined sera for antibody responses against diphtheria and tetanus vaccines from 119 children at 18 months and 129 children at 7 years of age. The antibody response to diphtheria vaccine decreased at age 18 months by 24.4% (95% CI, 1.63–41.9; p=0.04) for each doubling of the PCB exposure at the time of examination. At age 7 years, antibody response to tetanus vaccine decreased by 16.5%. Langer et al. (2002) also evaluated the possible long-term effects of PCBs by comparing the prevalence of anti-glutamic acid decarboxylase antibodies (anti-GAD) with the development of diabetes mellitus. Although this retrospective study could not determine the prevalence of diabetes, the relationship between PCBs and the prevalence of anti-GAD antibodies supports the concept of an immunomodulatory effect of PCBs.

Neurological Effects

An occupational cohort study involving 17,321 workers indicated that exposure to PCBs likely has an effect on neurodegenerative diseases for women, but not for men. The total cohort showed no excess of neurodegenerative disease mortality compared with expectations in the U.S. population. Nevertheless, the data did show mortality excesses of amyotrophic lateral sclerosis (ALS, also known as motor neuron disease) among women and, in the high-exposure group, of Parkinson disease and dementia (other than cerebrovascular dementia) among women (Steenland et al. 2006).

Cromwell et al. (2007) examined the effect of PCBs on maternal odor conditioning in rat pups 12–14 days of age. PCB-77 exposure changed aspects of maternal-offspring interaction in these rodents. The results suggest that PCB exposure decreased the preference for the maternal-associated cue, but it did not impair discrimination for a novel odor. Pups exposed to perinatal PCBs did not remain in the cue-associated location longer relative to the noncue-related location, nor did they remain longer for the lower (12.5 ppm) maternal PCB dose. The pups actually spent significantly longer time in the noncue location. These observed shifts in maternal cue preference were without significant changes in body weight, feeding, or olfactory function. Similarly, Cumming et al. (2005) reported that behavioral changes discerned through use of a cross-fostering paradigm suggested that maternal behavior changes were likely to emerge from direct effects of PCB-77 on the dams as well as in response to effects of the PCB on the litter.

Orito et al. (2007) exposed female rat dams orally at GD15 to 30 μg/kg/day of PCB-126 in corn oil. At 4–5 weeks of age, they assessed male offspring by use of an open field test. Intrauterine exposure to PCBs resulted in a reduction in time spent in the center of an open field, a reduction in the number of rearings, and an extension of grooming duration. Interaction behavior—an anxiety level index—was shortened in social interaction. The results suggest that exposure to PCBs may exert anxiogenic behavior in rats. The results of another study show that exposure to PCB-77 can have complex effects on behavioral interactions between dams and their litters, with a potential effect on offspring development (Cummings et al. 2005, 2008).

Moreover, exposure to PCB-77 during gestation and lactation can have a significant effect on the maternal behavior of rat dams, as reported by Simmons et al. (2005). Exposure to 2 and 4 mg/kg of PCB-77 during GD 6–18 reduced the amount of nursing time in which the dams displayed high-crouch posture over postnatal days 1–6. The amount of maternal licking and grooming of the litters, the amount of time the dams spent on the nest, and pup mortality increased at the high dose. At both the higher and lower doses, the weight gain of the litters during the first 6 days of life was reduced.

Coburn et al. (2005) assessed the effect of PCBs on brain mechanisms of body fluid regulation. Particularly, they focused on both central and systemic vasopressin (VPs) release in response to acute dehydration after oral exposure to Aroclor 1254 in adult male rats. Central vasopressin release from magnocellular neuroendocrine cells in the supraoptic nucleus (SON) occurs within several hours after acute dehydration and is an important autoregulatory mechanism. SON from dehydrated PCB-naive rats released significantly more VP than did SON from control rats (4.9±0.8 vs. 2.7±0.4 pg/ml/μg of tissue weight). In contrast, PCB exposure had no effect on baseline water intake, weight gain, or plasma osmolality responses to dehydration in PCB-fed rats. But the SON failed to respond with increased VP release during dehydration. Dehydrated PCB-fed rats had an exaggerated increase in plasma VP. This finding indicates a limited inhibitory effect of central VP on plasma VP level.

In a study by Pruitt et al. (1999), rat pups were exposed to PCBs from conception to ages 16, 30, or 60 days. They were then sacrificed and their brain tissues were stained with Timm’s

silver sulfide solution for mossy fiber in hippocampal tissue evaluation. Results from morphological analyses of brain tissue confirmed that in rats continuously treated with Aroclor 1254 at doses of 125 ppm, the relative size of the intra-and infra-pyramidal (II-P) mossy fiber was smaller than in control rats in all ages tested. Furthermore, this reduction in growth was selective for the II-P mossy fibers.

Dziennis et al. (2008) exposed rats to Aroclor 1254 (A1254) at 0.1 or 1 mg/kg/day in the maternal diet throughout gestation and lactation. Focal cerebral ischemia was induced at 6–8 weeks of age via middle cerebral artery occlusion, and infarct size was measured in the cerebral cortex and striatum at 22 hr of reperfusion. PCB levels and cortical and striatal expression of Bc12 and Cyp2c11 were quantified in the brain by gas chromatography and quantitative reverse transcriptase-polymerase chain reaction, respectively. Exposure during the development period resulted in significantly decreased striatal infarct in females and males at 0.1 and 1 mg/kg/day, respectively. Effects of A1254 exposure during development on Bcl2 and Cyp2C11 expression did not correlate with effects on infarct volume.

Reproductive Effects

The associations of time to menopause and environmental exposure to PCBs and related compounds were assessed in Michigan women (n=874, age 24y and older) (Blanck et al. 2004). During enrollment, between 1976 and 1978, the women provided serum PCBs samples. In 1997—19 years later—the women were interviewed about their menstrual periods, and PCBs were again measured in blood samples. Aroclor 1254 was measured with a level of detection of 5 ppb. The serum level of PCBs was divided into low (≤5 ppb), moderate (>5–11 ppb), and high (≥11 ppb) serum concentrations. No significant association between PCB levels and time to menopause was observed.

Gupta (2000) investigated the fetal long-term effect on the reproductive parameters of male mice offspring of pregnant mice fed 100 μg/kg/d of diethylstilbestrol (DES), 50 μg/kg/d of bisphenol A (BPA), and 50 μg/kg/d of Aroclor 1016 during GDs 16–18. The male offspring were examined at 3, 21, and 60 days after birth. The effects of PCB exposure were an increased anogenital distance, increased prostate size, and decreased epididymal weight. However, compared with controls, no effects were observed on testicular weight or size.

Pregnant rats were gavaged a single dose of 375 μg of PCB-118/kg body weight on GD 6 (Kuriyama et al. 2004). This dose was 100-fold higher than that found in human tissue reported by WHO in 1996. The rat offspring were hyperactive at PND 70–74; at adulthood (PND 170), the exposure had adverse effects on the male reproductive system. Rat offspring had smaller testes, epididymides, and seminal vesicles; the offspring also had decreases in sperm and spermatid numbers and impairment of daily sperm production.

Hsu et al. (2007) treated pregnant rats with a single dose of PCB-132 at 1 or 10 mg/kg on GD15 and assessed male offspring at adulthood (PND 84). The adult male rats had a decrease in the cauda epididymus weight, epididymal sperm count, and motile epididymal sperm count. The spermatozoa of PCB-132-exposed offspring produced significantly higher levels of reactive oxygen species (*ROS*) than did the controls. In the 1 mg/kg dose group,

p53 was significantly induced and caspase-3 was inhibited, while in the 10 mg/kg dose group, activation of caspase-3 and -9 was significantly increased. At the same time, expressions were significantly decreased of Fas, Bax, bcl-2, and p53 genes.

Developmental Effects

In Finland, 34,457 infants born between 1997–2000 were examined for natal and neonatal teeth (Alaluusua et al. 2002). Exposure of the infants to 36 PCB congeners and other related contaminants was evaluated by measuring PCB congener levels in the children's mothers' milk samples when the children were 4–8 weeks old. The PCB median exposure level in milk was 7.24 picograms/gram (pg/g) in fat (measured as 2,3,7,8-TCDD toxicity equivalent). Thirty-four infants with teeth were observed (29 infants had one or two natal teeth, and five neonates had neonatal teeth). The prevalence of natal and neonatal teeth was 1:1000. Therefore, no association was found between pollutant levels and occurrence of natal and neonatal teeth. This study suggested that PCB exposure levels in Finland were likely below the threshold to cause perinatal tooth eruption.

Jan and Vrdic (2000) and Jan et al. (2007) evaluated 432 Slovenian children 8–9 years of age for long-term PCB exposure. The total PCB serum concentrations in children were <200, 200–600, and >600 ng PCBs/g serum lipids. They used standard dental indices to evaluate caries susceptibility, gingival health, and enamel defects. The proportion of deciduous and permanent teeth affected with enamel defects was significantly higher in the highest exposed children (>600 ng PCB/g group). Compared with controls, caries susceptibility, gingival health, or number of teeth was not affected significantly. Still, a dose-response relationship was observed between PCB exposure and developmental enamel defects of permanent teeth in children.

Brucker-Davis initiated a prospective case-control study of 151 cord bloods (67 cryptorchid/84 matched control) and 125 colostrums (56 cryptorchid/69 matched control) to assess the incidence of cryptorchidism in male children exposed to PCBs during prenatal and postnatal life. Study results suggested a positive association (p=0.045) between high total PCB concentrations (perinatal exposure) and cryptorchidism in boys.

Patterson et al. (2009) studied a randomly selected cohort of 615 children from 12 U.S. study centers born during 1959–1965. A complete data set was available for 195 children with sensorineural hearing loss. Exposures to PCBs were measured as total PCB concentration in maternal serum, with the median measured as 2.8 μg/L during the third trimester. This level was about twofold higher than in recent background levels in the U.S. The geometric mean PCB concentration in whole blood for the 2003–2004 NHANES 12-year and older study population was 0.820 ppb (ng/g). Longnecker et al. (2004) evaluated hearing when the children were about 8 years old, observing no significant adverse effects on the average hearing threshold across the frequencies required for speech recognition.

Riva et al. (2004) established a prospective cohort study for randomly selected children who breastfed exclusively for at least 4 months—25 of 353 healthy, full-term children who were born between April and June of 2000. Levels of PCB congeners (PCBs 105, 118, 138, 153,

156, and 180) were measured in colostrum and breast milk at 1 and 3 months after delivery. Visual function evaluations were carried out by P100. (The major component of the visual evoked potentials [VEP] is the large positive wave peaking at about 100 milliseconds [also called P100]). The P100 is very reliable and stable between individuals from 5 to 60 years of age, with latency visual evoked potentials (VEPs) being measured starting at 12 months of age. At 15 months of age, impaired VEP was significantly correlated (r=0.401–0.618) with all PCB congeners except for PCB-105. But VEP at 1 hour correlated (r=0.504) with PCB-180 only. This study suggests a weak correlation at 12 months of age between PCB levels and impaired visual functions.

Wang et al. (2005) selected pregnant women (n=118, age 25–34 years of age) to participate in a study to examine the association between transplacental exposure to dioxins/PCBs and thyroid and growth hormones in newborns. Cord sera from 118 newborns were analyzed for 12 dioxin-like PCB congeners, for other related compounds such as dioxins, and for thyroid and growth hormones. Statistical analyses showed independently and significantly decreased concentrations of free T4 (FT4) x TSH with increasing non-ortho PCBs ($r = -0.2$; $p < 0.05$). Differences in compositions and exposure levels to PCBs might result in different health effects.

Cao et al. (2008) recruited a cohort of 232 pregnant German women 18–42 years of age for a 2000–2002 study. The authors investigated PCB and dioxin effects on gonadal hormones. Maternal blood and milk samples were collected from a subset of 104 mother-infant pairs for chemical analyses of Σ_6 PCBs (28, 52, 101, 138, 153, and 180) as indicator PCBs and of 17 PCDD/F congeners. The median concentrations in maternal blood fat and milk fat for the sum of the indicator PCBs (28, 52, 101, 138, 153, and 180) were 149 and 177 ng/g. The median concentrations of PCDD/F in maternal blood fat and milk fat were 15.3 and 13.1 pg WHO-TEQs/, respectively.

Cao et al. (2008) analyzed maternal sera and cord sera for testosterone and estradiol. In girls, the adjusted means ratio (MR) for testosterone hormonal level in cord serum samples was significantly reduced (MR = 0.81, 95% CL 0.69–0.94 for Σ non-o-PCBs; MR = 0.72, 95% CL 0.57–0.90 for Σ mono-o-PCBs; MR = 0.76, 95% CL 0.61–0.96 for Σ_6 PCBs; MR = 0.69, 95% CL 0.53–0.90 for ΣPCDD/F)—but not in boys. On other hand, after PCB exposures estradiol levels were significantly reduced in boys but not in girls. Estradiol levels were not significantly associated with any PCB category level. This study suggested that even low levels of PCBs had a robust negative effect on gonadal hormones in newborns.

Another study, however, found no strong association between umbilical cord PCB levels and testicular sizes, serum testosterone concentrations, or spermaturia in boys at 7 and 14 years of age (Mol et al. 2002).

Denham et al. (2005) studied a cohort of 138 girls (10–16.9 years old) from the Akwesasne Mohawk Nation, New York, who had been exposed to PCBs via food. They compared blood PCB levels against attainment of menses. More than 50% of the blood samples contained 16 PCB congeners. In this study, the presence or absence of menses at the time of the interview was recorded. The geometric mean (0.12 ppb) of estrogenic PCBs (PCB 52, 70, 90/101,

187) was associated with a significantly greater probability of having started menarche early (β=2.12). Among 12-year-old girls, 86% were predicted to have reached menarche at the 75th percentile of estrogenic PCBs levels. The study suggested that even at low levels of estrogenic PCBs, the time to menarche attainment decreased. The median age at menarche for this cohort (138 girls) was 12.2 years. But Vasiliu et al. (2004) reported no association with maternal PCBs exposure. The serum concentrations of PCBs 138, 153, and 180 and other related contaminants were measured in 200 persons who lived in high-, moderate-, low-, or non-contaminated areas, with a mean age of 17.4 years. In boys, the testicular volumes and pubic hair growth were measured. In girls, the adult stage of breast development was measured. In the highest contaminated areas, significantly fewer boys reached the adult stage of genital and pubic hair development, in comparison with controls. In the highest contaminated areas, fewer girls reached the adult stage of breast development. The present study indicated that exposure to certain PCB congeners may interfere with human reproductive development (Den Hond et al. 2002).

Meerts et al. (2004) investigated developmental effects of *in-utero* exposure to 4-hydroxy-2,3,3′,4′,5-pentachlorobiphenyl (4-OH-PCB107). They focused on rat sex-steroid hormone levels and female reproduction. The developmental effects observed following exposure to 4-OH-PCB 107 were a dose-related prolongation of the estrous cycle in female offspring, measured between PNDs 210 and 231 and increased estradiol progesterone ratios. The effects of 4-OH-PCB 107 were considered sex-related—at PNDs 310 to 325, no effects could be detected on male accessory sex organ weights or testosterone levels.

Kobayashi et al. (2008) exposed Sprague-Dawley rat dams to PCB-153 (0, 16, or 64 mg/kg/day) orally from GD 10 through GD 16. At age 1 or 3 weeks, the male and female offspring were examined for changes in developmental parameters. Changes were dose-dependent in body weight, body length, tail length, and weights of kidneys, testes, ovaries, and uterus. A significant dose-dependent decrease occurred in plasma concentrations of thyroxine (T4) and tri-iodothyronine (T3). But no changes occurred in any dose group in plasma concentrations of growth hormone and insulin-like growth factor-1.

Gupta (2000) fed pregnant Charles River rats 50 μg/kg/day of Aroclor 1016 dissolved in corn oil at GD 16–18. Compared with control, Aroclor 1016 increased anogenital distance, increased prostate size, and decreased epididymal weight. No effects were found on testicular weight or size in offspring.

Steinberg et al. (2007) exposed pregnant female rats by IP injection to low levels of Aroclor 1221 (0, 0.1, 1, or 10 mg/kg) on embryonic day 16 of F1. The exposure of offspring to Aroclor 1221 resulted in a significant reduction in their mating-trial pacing, vocalizations, ambulation, and the female's likelihood to mate. Shirota et al. (2006) reported similar results in the reproductive developmental effects of female rats exposed to PCB 126.

Lyche et al. (2004) examined the possible adverse effects on the hypothalamic-pituitary-gonadal axis. They measured gonadotrophins and gonadal steroid hormone concentrations in goat offspring exposed during gestation and lactation to environmental doses of PCB-153 and PCB-126. The doses of PCBs 153 and 126 were estimated at 98 μg/kg/day and 0.049

μg/kg/day, respectively. The results indicated that maternal exposure to low doses of PCB 153 during gestation and lactation suppressed prepubertal plasma luteinizing hormone concentrations and delayed the onset of female offspring puberty. PCB 126 did not produce any observed effects at the exposure level tested in this study. The resulting concentrations in adipose tissue 9 months post-partum in the goat offspring were 5.8 μg/g (fat weight) and 0.00049 μg/g (fat weight) for PCBs 153 and 126, respectively.

Crofton et al. (2000) compared the effect of prenatal versus postnatal rat exposure to Aroclor 1254. In this study, primiparous rats received 0 or 6 mg/kg A1254 (po in corn oil) from GD 6 to PND 21. On the day of birth, half of treated litters and half of the control litters were cross-fostered. As a result, the experiment consisted of the following groups: Ctrl/Ctrl, A1254/A1254 (perinatal exposure), A1254/Ctrl (prenatal exposure only), and Ctrl/A1254 (postnatal exposure only). Serum thyroid hormone concentrations were assessed, as were liver and brain concentration of PCBs, body weight, mortality, and age at eye opening, auditory startle amplitudes, and auditory thresholds for 1 kHz and 40 kHz tones. The results demonstrated that postnatal exposure alone was responsible for ototoxicity. These cross-fostering experiments also showed that prenatal-only exposure led to small postnatal hypothyroxinemia, which recovered by the end of lactation. But the hypothyroxinemia that occurred following postnatal-only exposure matched that seen with perinatal exposure within a few days after birth.

Kenet et al. (2007) exposed pregnant rats orally to non-coplanar PCBs (6 mg/kg/day of PCB-95) during the gestational period and throughout 3 subsequent suckling weeks. Exposure to non-coplanar PCBs resulted in abnormal development of the primary auditory cortex in pups. Still, the pups' hearing sensitivity and brainstem auditory responses were normal.

Cancer

In a population-based case-control study in the United States, De Roos et al. (2005) investigated how exposure to PCBs and to other organochlorines might affect the risk of non-Hodgkin's lymphoma. Certain PCB congeners, particularly the higher chlorinated PCBs (PCB 156,180,194) were associated with increased risk of non-Hodgkin's lymphoma development, with odds ratios for the highest versus lowest quartile ranging from 2.7 to 3.5, and significant trends ($p<0.05$) across categories.

Hardell et al. (2004) found that PCB blood concentrations were higher in mothers of patients with testicular cancer than in controls—a finding that supported the hypothesis regarding the fetal etiology of testicular cancer (Hardell et al. 2003).

Hardell et al. (2006) reported an association between persistent organophosphate pollutants (POPs) and prostate cancer, significantly so for PCB 153 in the total study population of 58 cases. Of the 38 PCB congeners studied, PCB-153 had the highest adipose tissue concentration. For most of the studied POPs, OR increased further in the case group with PSA greater than 16.5 ng/mL. Similar studies suggested that long-term, low-dose exposure to specific organochlorine pesticides and PCBs in the general population may contribute to

an increased risk of prostate cancer; those studies also recommended further investigation (Ritchie et al. 2003, 2005).

Nyska et al. (2004) evaluated the effects of chronic exposure to dioxin and multiple dioxin-like PCBs on the pancreas of the female Harlan Sprague-Dawley rat. Animals were treated with PCB-126 by gavage for up to 2 years. The specific dose used in the TEF mixture study was 33.3 ng/kg PCB-126. The study indicated that the pancreatic exocrine acini represented a target tissue of the PCB-126, inducing mainly degenerative, inflammatory, and atrophic lesions and possibly also sporadic acinar adenomas and carcinomas.

Exposure by gavage of female Harlan Sprague–Dawley rats to PCB-126 at doses of 0, 30, 100, 175, 550, and 1,000 ng/kg/day—assuming a PCB-126 TEF of 0.1 for up to 2 years—resulted in a dose-related increase in the incidence of bronchiolar metaplasia of the alveolar epithelium, as reported by Brix et al. (2004). Exposure to PCB-126 increased the incidences and severity of neoplastic and nonneoplastic lesions in the lung.

Groups of Harlan Sprague-Dawley rats were treated by gavage with PCB-153 in corn oil acetone: (99:1) at doses of 10, 100, 300, 100, or 3,000 μg/kg 5 days/week for up to 105 weeks. Exposure at the highest dose (3,000 μg/kg) continued for 30 weeks. Treatment then changed to vehicle only for the rest of the study. This 2-year gavage study found equivocal evidence of carcinogenic activity of PCB-153 in female Harlan Sprague-Dawley rats; the evidence was based on the occurrence of cholangioma of the liver. PCB-153 administration caused increased incidences of nonneoplastic lesions of the liver, thyroid gland, ovary, oviduct, and uterus in female rats (NTP 2006a).

Groups of 81 female Harlan Sprague-Dawley rats were treated by gavage with PCB-126 in corn oil: acetone (99:1) at doses of 30, 100, 175, 300, 550, or 1,000 ng/kg 5 days/week for up 104 weeks. Another 50 female rats were exposed to the highest dose (1,000 μg/kg) for 30 weeks and then only to vehicle for the rest of the study. This 2-year oral gavage study revealed clear evidence of carcinogenic activity of PCB-126 in female Harlan Sprague-Dawley rats on the basis of increased incidences of cholangiocarcinoma of the liver, squamous neoplasms of the lung (cystic keratinizing epithelioma and squamous cell carcinoma), and gingival squamous cell carcinoma of the oral mucosa. Administration of PCB-126 was also possibly associated with hepatocellular adenoma and hepatocholangioma of the liver. Neoplasms of the adrenal cortex and cholangioma of the liver may have been related to administration of PCB-126 (NTP 2006b). In female rats, the administration of PCB-126 by oral gavage for 2 years produced an increased incidence of nonneoplastic lesions of the liver, lung, adrenal cortex, pancreas, kidney, heart, thyroid gland, thymus, spleen, clitoral gland, and mesenteric artery (NTP 2006b).

Another 2-year oral gavage NTP study showed clear evidence of carcinogenic activity of a constant ratio binary mixture of PCB-126 and PCB-153 in female Harlan Sprague-Dawley rats. The daily doses were 10, 100, 300, or 1,000 ng of PCB-126, each with 1,000 times more PCB-153, per kilogram body weight. The evidence was based on increased incidences of cholangiocarcinoma, hepatocholangioma, and hepatocellular neoplasms (predominantly adenomas) of the liver, squamous neoplasms of the lung (predominantly cystic keratinizing

epithelioma), and gingival squamous cell carcinoma of the oral mucosa. Increased incidences of pancreatic acinar neoplasms were also possibly related to the administration of the binary mixture of PCB-126 and PCB153. The increased incidences of uterine squamous cell carcinoma may have been related to administration of the binary mixture of PCB-126 and PCB-153. The uterine squamous cell carcinoma is rare type of cancer. Administration of the binary mixture of PCB-126 and PCB-153 caused increased incidences of nonneoplastic lesions in the liver, lung, oral mucosa, pancreas, adrenal cortex, thyroid gland, thymus, kidney, nose, and forestomach (NTP 2006c). In a 2-year oral gavage study, similar results of carcinogenic activity were found for the binary mixture of PCB-126 and PCB-118 (NTP 2006d).

In another 2-year oral gavage study, female rats were exposed to ratios of 1 part TCDD, 2 parts PeCDF, and 10 parts PCB-126. The dose formulation was intended to give approximately equal toxic contributions from each substance. The administered doses were 10, 22, 46, or 100 ng toxic equivalents/kg body weight in corn oil: acetone (99:1) by gavage daily for 5 days/week for up to 105 weeks. In female Harlan Sprague-Dawley rats, clear evidence of carcinogenic activity appeared for the mixture of TCDD, PeCDF, and PCB-126. The evidence was based on increased incidences of hepatocellular adenoma and cholangiocarcinoma of the liver and cystic keratinizing epithelioma of the lung. Neoplasms of the pancreatic acinus may have been related to administration of this mixture. This cancer is rare, forming only 1% of all pancreatic tumors. In this case, cancer arises from acinar cells of the pancreas and secretes pancreatic enzymes, mostly lipase. Also, in female rats this mixture caused increased incidences of nonneoplastic lesions of the liver, lung, pancreas, adrenal cortex, oral mucosa, uterus, thymus, ovary, kidney, heart, bone marrow, urinary bladder, mesenteric artery, and thyroid gland (NTP 2006e). Table 2 and 3 contain summaries of recent epidemiologic studies of human exposures to PCBs, and animal studies, respectively.

Conclusion

Biomedical data from human and laboratory and mammal studies provide evidence of PCB exposure’s toxic potential. Information on health effects of PCBs is available from studies of people who

- Were exposed in the workplace,
- Consumed contaminated fish, and
- Were exposed to environmental levels.

As summarized in this article, recent advances in the study of PCBs effects have associated exposure to PCBs in humans, in animals, or in both with

- Endocrine changes,
- Dental changes,
- Immunological alterations,
- Neurodevelopmental and reproductive changes, and

- Cancer.

The human studies of occupational exposure, contaminated fish consumption, and general populations are complicated by the mixture-nature of PCB exposure and possible interactions between congeneric components and other chemicals. Although PCBs may have contributed to adverse health effects in these human populations, which congeners may have caused the effects cannot be determined with certainty. That said, however, animal studies have shown that PCBs induce effects in non-human primates at lower doses than in other species. Immunological, dermal/ocular, and neurobehavioral changes have been shown to be particularly sensitive indicators of toxicity in non-human primates exposed either as adults, or during pre- or postnatal periods.

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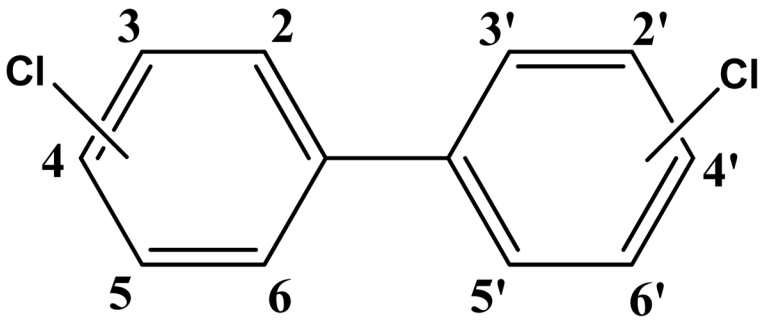

Figure 1.
Chemical structure of Polychlorinated Biphenyls (PCBs)

Table 1

Coplanar, Mono-ortho and Non-Dioxin-like Polychlorinated Biphenyls (PCBS) from the Fourth National Report on Human Exposure to Environmental Chemicals.

Coplanar PCBs	**Geometric Mean‡**	**50th Percentile**	**75th Percentile**	**95th Percentile**
3,4,4′,5-Tetrachlorobiphenyl (PCB 81)	*	< LOD	< LOD	13.4
3,3′,4,4′,5-Pentachlorobiphenyl (PCB 126)	16.3	14.7	24.8	68.7
3,3′,4,4′,5,5′-Hexachlorobiphenyl (PCB 169)	*	< LOD	19.5	40.6
Mono-*ortho*-PCBs				
2,3,3′,4,4′-Pentachlorobiphenyl (PCB 105)	1.20	1.09	1.90	6.24
2,3′,4,4′,5-Pentachlorobiphenyl (PCB 118)	6.00	5.19	10.4	31.3
2,3,3′,4,4′,5-Hexachlorobiphenyl (PCB 156)	2.54	3.29	7.00	15.3
2,3,3′,4,4′,5′-Hexachlorobiphenyl (PCB 157)	0.605	0.80	1.73	3.80
2,3′,4,4′,5,5′-Hexachlorobiphenyl (PCB 167)	0.494	0.70	1.60	4.10
2,3,3′,4,4′,5,5′-Heptachlorobiphenyl (PCB 189)	*	< LOD	< LOD	1.47
Non-dioxin-like PCBs				
2,4,4′-Trichlorobiphenyl (PCB 28)	4.90	4.96	6.79	11.3
2,2′,3,5′-Tetrachlorobiphenyl (PCB 44)	2.06	2.05	3.03	5.70
2,2′,4,5′-Tetrachlorobiphenyl (PCB 49)	1.29	1.35	1.90	3.53
2,2′,5,5′-Tetrachlorobiphenyl (PCB 52)	2.66	2.74	4.17	7.60
2,3′,4,4′-Tetrachlorobiphenyl (PCB 66)	1.39	1.37	1.97	4.10
2,4,4′,5-Tetrachlorobiphenyl (PCB 74)	4.81	4.36	8.72	22.3
2,2′,3,4,5′-Pentachlorobiphenyl (PCB 87)	0.656	0.90	1.32	2.70
2,2′,4,4′,5-Pentachlorobiphenyl (PCB 99)	4.16	3.79	6.53	18
2,2′,4,5,5′-Pentachlorobiphenyl (PCB 101)	1.65	1.7	2.70	5.83
2,3,3′,4′,6-Pentachlorobiphenyl (PCB 110)	1.22	1.20	1.96	4.42
2,2′,3,3′,4,4′-Hexachlorobiphenyl (PCB 128)	*	< LOD	< LOD	0.60
2,2′,3,4,4′,5′-Hexachlorobiphenyl (PCB 138) & 2,3,3′,4,4′,6-Hexachlorobiphenyl (PCB 158)	15.1	15.1	30.5	75.3
2,2′,3,4′,5,5′-Hexachlorobiphenyl (PCB 146)	2.17	2.21	4.80	11.7
2,2′,3,4′,5′,6-Hexachlorobiphenyl (PCB 149)	0.598	0.60	0.90	1.90
2,2′,3,5,5′,6-Hexachlorobiphenyl (PCB 151)	*	< LOD	0.42	1.00
2,2′,4,4′,5,5′-Hexachlorobiphenyl (PCB 153)	19.8	20.8	43.3	97.1
2,2′,3,3′,4,4′,5-Heptachlorobiphenyl (PCB 170)	5.46	6.30	12.9	28.2
2,2′,3,3′,4,5,5′-Heptachlorobiphenyl (PCB 172)	0.647	0.90	1.80	4.16
2,2′,3,3′,4,5′,6′-Heptachlorobiphenyl (PCB 177)	1.13	1.30	2.77	7.20
2,2′,3,3′,5,5′,6-Heptachlorobiphenyl (PCB 178)	0.933	1.20	2.50	6.10
2,2′,3,4,4′,5,5′-Heptachlorobiphenyl (PCB 180)	15.1	18.0	37.1	81.5
2,2′,3,4,4′,5′,6-Heptachlorobiphenyl (PCB 183)	1.45	1.60	3.29	7.90
2,2′,3,4′,5,5′,6-Heptachlorobiphenyl (PCB 187)	4.23	4.60	10.1	24.3
2,2′,3,3′,4,4′,5,5′-Octachlorobiphenyl (PCB 194)	2.69	4.19	8.47	19.1

Coplanar PCBs	Geometric Mean‡	50th Percentile	75th Percentile	95th Percentile
2,2′,3,3′,4,4′,5,6-Octachlorobiphenyl (PCB 195)	*	0.90	1.98	4.51
2,2′,3,3′,4,5,5′,6′-Octachlorobiphenyl (PCB 199)	2.81	3.80	8.30	18.9
2,2′,3,3′,4,4′,5,6′-Octachlorobiphenyl (PCB 196) & 2,2′, 3,4,4′,5,5′,6-Octachlorobiphenyl (PCB 203)	2.61	3.40	6.70	15.0
2,2′,3,3′,4,4′,5,5′,6-Nonachlorobiphenyl (PCB 206)	2.13	2.34	5.00	13.7
2,2′3,3′4,4′5,5′6,6′-Decachlorobiphenyl (PCB 209)	1.40	1.18	3.20	11.1

*not calculated; LOD: Limit of detection (0.4).

‡Concentration units (ng/g of lipid)

Table 2

Summaries of Recent Epidemiologic Studies of Human Exposures to PCBs

Health effect/outcome	Levels of Exposure	Outcome	Reference
Cancer/Non-Hodgkin's lymphoma	PCBs and other organochlorines	PCBs 156,180, and 194 associated with increased risk of non-Hodgkin's lymphoma	De Roos et al. 2005
Cancer/Prostate cancer	30 PCBs and 18 organochlorine pesticide	PCB 180 were associated with an increase of risk of prostate cancer	Ritchie et al. 2003
Cancer/PSA levels	PCBs and other POPs (Chlordane, DDE)	In cases with PCB 153 > than the median concentration among controls, the OR=3.15 (95% CL =1.04–9.54)	Hardell et al. 2006
Cancer/prostate	30 PCB congeners in serum	Odds of high exposure group > twice that of lowest exposure group	Ritchie et al. 2005
Cancer/Prostate cancer	Both high exposure to electromagnetic fields and PCBs	No association after adjusting for confounders	Charles et al. 2003
Cancer/Testicular/Seminoma	38 PCB congeners, DDT, hexachlorobenzene, chlordanes	PCBs yielded odds ratio 3.8, 95% CL, 1.4–10 among case mothers	Hardell et al. 2003
Cancer/Testicular Cancer	37 PCBs exposure	The concentrations of PCBs are higher in mothers to patients with testicular cancer	Hardell et al. 2004
Developmental/Sensorineural hearing loss (SNHL)	2.8 μg/L serum total PCBs; mothers in 3rd trimester	The mean of mother's serum PCB concentrations not related to the adjusted odds of SNHL	Longnecker et al. 2004
Developmental Natal and neonatal teeth	TEQ 11.9 pg/g fat PCDD/F TEQ 7.24 pg/g fat	No association	Alaluusua et al. 2002
Developmental	PCBs (138, 153, 180) Dioxin-like compounds	Doubling of serum PCB 153 and dioxin-like chemicals significantly affected sexual maturation clarify	Den Hond et al. 2002
Developmental	**X**	In Polish cohort of this study, PCB-153 correlated negatively with the portion of y-bearing fraction of spermatozoa	Rignell-hydbom et al. 2006
Developmental	French cohort	At birth, Cryptorchidism associated with higher prenatal exposure to PCBs.	Brucker-Davis et al. 2008
Developmental/Age at menarche in offspring	PCBs and DDTs. Retrospective cohort study for two generations	No association with maternal PCB exposure	Vasiliu et al. 2004
Developmental/Gingival health by standard dental indices and enamel by FDI index	Children living near industrial area contaminated with PCBs	Enamel defects in deciduous teeth significantly high in higher exposed children (Chi (2) = 8.35; p=0.03). For permanent teeth with any enamel defects (Chi (2) 7.237; p=0.027). The extent of enamel defects is significantly greater in high PCB exposure group (Chi (2) 10.714; p=0.005)	Jan et al. 2007
Developmental/Menses attainment	16 PCB congeners	PCBs levels are significant predictors of menarcheal status	Denham et al. 2005
Developmental/Visual function	Breastfed for 4 month and examined at12 month of age	P100 with latency evoked potentials (VEPs) at 60 min. related to PCB 180 (r= −0.504)	Riva et al. 2004

Health effect/outcome	Levels of Exposure	Outcome	Reference
Developmental/Dental enamel	Concentration of PBCs in diet/	Enamel development defects were found in 71.3% exposed vs. 49.5% control	Jan and Vrbic 2000
Developmental/Hormone levels and sexual differentation	Prenatal exposure to PCBs. Umbilical cord specimens were collected.	20 boys with cryptochidism; oOther 58 with spermaturia.	Mol et al. 2002
Endocrine/type 2 diabetes mellitus	POPs	OR=1.6; 95% CL 1.0–2.7 associated with an increase of CB-153 of 100 ng/g lipid;	Rignell-hydbom et al. 2007
Endocrine/type 2 diabetes mellitus	PCBs exposure	Positive linear association of PCB levels with diabetes at the time of enrolment in women	Vasiliu et al. 2006.
Endocrine/thyroid	Retrospective study	Anti-GAD was 4 times higher than that of all controls	Langer 2002
Endocrine/Testosterone and estradiol	PCBs concentrations 149 ng/g in blood and 177 ng/g in milk	Testosterone and estradiol levels were less in babies with high PCB concentrations	Cao et al. 2008
Endocrine/Thyroid and growth hormones	118 pregnant women (ages 25–34 years); Placental and cord blood samples. 12 dioxin-like PCBs	Significant negative associations between FT4, TSH and the increase of non-ortho PCBs ($r=-0.2$; $p<0.05$)	Wang et al. 2005
Endocrine/Diabetes mellitus	PCBs 153	PCB 153 significantly associated with diabetes (an increase of 100 ng/g lipid corresponded to OR =1.16 95% CL 1.03–1.32, p=(0.03)	Rylander et al. 2005
Endocrine/Diabetes mellitus	Cross-sectional study.	OR = 2.1 (95% CL 1.1–4.5) for women. Women with chloracne OR= 5.5 (95% CL 2.3–13.4) for diabetes	Wang et al. 2008
Endocrine/Diabetes mellitus	PCB congeners, and chlorinated pesticides	The prevalence of diabetes was 20.2%. The OR of having diabetes for participants in the highest tertile of total PCB concentration compared with the lowest tertile was 3.9 (95% confidence interval, 1.5–10.6).	Cordru et al. 2007
Endocrine/Diabetes mellitus/Insulin sensitivity	12 PCB congeners exposure	PCBs (123,126 and 169) were significant associated with insulin activity ($r = -0.34$, $p < 0.05$)	Chen et al. 2008
Endocrine/type 2 diabetes	Persistent organic pollutants (POPs); 19 POPs in 5 subclasses	Association observed between HOMA-IR and two nondioxin-like PCBs	Lee et al. 2006, 2007
Immunological/Antibodies for tetanus and diphtheria toxoids	Two cohorts from Faroe Islands, mother serum (during pregnancy) and milk PCB levels were analyzed. Antibodies for tetanus and diphtheria were measured.	For each doubling of PCBs serum conc, Ab for diphtheria toxoid decreased by 24.4% at age 18 months (95% CL, 1.63–41.9; p=0.04). Ab for tetanus toxoid decreased by 16.5% at age 7 y (95% CL, 1.51–29.3; p=0.03)	Heilmann et al. 2006
Immunological/rheumatoid arthritis	Cross-sectional study, 1721; 20y or more of age; dioxin and non- dioxin- like PCBs	Ors 1.0, 2.1, 3.5, and 2.9 across quartiles of DL PCBs. ODs for non dioxin-like PCBs quartiles are 1.0, 1.6, 2.6, and 2.5.P for trends =0.02. Men: no clear association	Lee DH, 2007
Immunological/thymus atrophy	15 PCB congeners in neonates?	Smaller thymus	Park et al. 2008
Metabolism/Enzyme biomarker/	PCBs exposures via food (serum PCB concentrations)	Positive association with the serum levels of 9 PCB congeners	Fitzgerald et al. 2005
Musculoskeletal	This is part of the study of Swedish fisherman's wives	No association found between PCB-153 and OH-PCBs and bone mineral density or biochemical markers of bone metabolism	Weiss et al. 2006

Health effect/outcome	Levels of Exposure	Outcome	Reference
Musculoskeletal/Bone mineral density (BMD)	Swedish fishermen and their wives	After adjustment for age and body mass index, the significant negative relationship between PCB-153 and BMD was not valid anymore	Wallin et al. 2005
Musculoskeletal/Bone mineral density (BMD)	5 dioxin-like PCBs and 3 non-dioxin- like PCBs blood levels.	Male odds ratio negatively associated with BMD 1.6 (95% CL, 1.01–1.2) per 10 pg/ml CB-118	Hodgson et al. 2008
Musculoskeletal/Bone mineral density	Persistent organochlorines (PCBs, DDT)	PCBs do not cause (were not associated with?) significant effects on bone density	Glyn et al. 2000
Neurological/Neurodegenerative diseases.	PCB levels of workers were about 10 times higher than the PCB levels in community	Overall no significant effects (SMR= 1.40, 1.11, and 1.26, respectively. Women's amyotropic lateral (SMR = 2.26; 95% CL = 1.08–4.15)	Steenland et al.2006
Reproductive/Time to menopause	Halogenated biphenyl (PCBs, PBB) blood samples	No association with either PCBs or PBB	Blanck et al., 2004

Table 3

Summaries of Recent Animal Studies on Health Effects from Exposure to PCBs

Species	Study designs	Health effects (Findings)	Reference
Rats (Sprague-Dawley)	Aroclor 1221 (0, 0.1, 1, or 10 mg/kg). In utero exposed female offspring (F1) and (F2); Gd 16 and 18	In both generations, litter sex ratio was skewed toward females.	Steinberg et al. 2008
Mice (CD-1)	Aroclor 1016, fed 50 ug/kg/d; Gd 16–18; offspring examined at D3, D21, and D60	Increase prostate size, anogenital distance, decrease epididymal weight	Gupta C. 2000
Rats (Sprague-Dawley)	Gavage 5 d/wk, 1000 ng/kg, PCB 126; for 2 years or corn oil/acetone vehicle (99:1 mixture)	Increase of degenerative cardiovascular lesions, cardiomyopathy and chronic active arthritis with dose	Jokinen et al. 2003
Rats	Diets containing 0, 5, 20, or 40 mg PCBs/kg diet; exposure started 50 days before mating and terminated at birth	Reduced 1, 25-dihydroxycholecalciferol during pregnancy	Lilienthal et al. 2000
Rats (Sprague-Dawley)	2 years, Gavage, PCB 126. Control corn oil-acetone vehicle	Cytoplasmic vacuolation, chronic active inflammation, atrophy in exocrine pancreas	Nyska et al. 2004
Rats (Sprague-Dawley)	125 ppm Aroclor 1254 in diet, pregnant rats	Reduce growth of hippocampal intra-and infra-pyramidal (II-P) mossy fiber	Pruitt et al. 1999
Rats (22–24/dose) clarify	0 or 6 mg/kg A1254 (po in corn oil) GD6-PND 21. Cross fostered the offspring resulted in 4 groups (ctrl/ctrl; A1254/A/1254 perinatal exposure; A1254/ctrl, prenatal exposure only; ctrl/A1254, postnatal exposure only	Permanent hearing deficits in A1254/A1254 and ctrl/A1254 groups	Crofton et al. 2000
Rats (Sprague-Dawley)	females, gavage exposure to PCB 126	Bronchiolar metaplasia	Brix et al. 2004
Adult male rats	A1254 (diet) (30 mg/kg/day for 15 days)	Dehydrated PCB-fed rats had 863% increase in plasma vasopressin (VP); for the dehydrated control, a 241% increase in VP	Coburn et al., 2005
Rats (Sprague-Dawley)	Single dose Gavage of 375 ug PCB 118/kg on GD 6	Hyperactivity and smaller testes, epididymides, seminal vesicles, decrease in sperm and spermatid numbers in offspring on PND 170.	Kuriyama et al. 2004
Rats (females)	40 rats exposed to PCB 126 alone, vehicle, ovariectomy, or sham operation (2×2 factorial design) for 12 weeks	PCB 126 increases heart weight and serum cholesterol in both groups. PCB 126 increases blood pressure in sham-operated rats only.	Lind et al. 2004
Goat (kids)	Goat kids exposed to PCB 153 and PCB 126 during gestation and lactation. The average PCB concentrations in goat kids' fat at age of 9 months were 5800 ng/g and 0.49 ng/g fat weight for PCB 153 and PCB 126 respectively.	At puberty, low LH, delayed puberty, higher progesterone level in group exposed to PCB 153. PCB 126 has no effect at these levels	Lyche et al. 2004
Pregnant rats	0, 0.5, and 5.0 mg/kg bt of 4-OH-CB107 or Aroclor 1254 (25 mg/kg bt) during GD 10-GD16.	At 0.5 and 5.0 mg of 4-OH-PCB 107 a significant prolongation of the estrous. A 50% increase in plasma estradiol levels in female offspring in animals treated with 5 mg 4-OH-CB107/kg bw. Aroclor 1254 treatment had no significant effects of estradiol levels	Meerts et al. 2004
Female rats (Sprague-Dawley)	Binary mixture of 1000 ng/kg PCB 126 + 1000 ng/kg PCB 153; PCB 126 = PCB 118 (216 and 360 ng TCDD equivalent/kg	Hyperplasia of respiratory epithelium and metaplasia of olfactory epithelium, acute inflammatory exudates observed within the lumen of nasal cavity on the affected area	Nyska et al. 2005
Long-Evans 5 day pregnant rats	2 or 4 mg/kg/subcutaneous injection of PCB 77 on GD 6–18	Nursing time was reduced in both treatments. At 4 mg/kg body wt, the amount of licking time and pup mortality were increased	Simmons et al. 2005

Species	Study designs	Health effects (Findings)	Reference
Rats (Sprague-Dawley)	PCB 126 + PCB 153; PCB 126+PCB 118; PCB 126 alone; PCB 153 alone; TCDD+PCB 126+PeCDF; By Gavage/2 years	In all mixtures, the incidences of gingival squamous cell hyperplasia were increased significantly. In TCCD, PCB 126, and PCB 126+PCB 153 treated groups, squamous cell carcinoma increased significantly	Yoshizawa et al. 2005
Pregnant Rat	2 mg/kg PCB 77 Gd 6–18 and gestation	Increase frequency of nursing bouts and amount of maternal auto-grooming.	Cummings et al. 2005
Rats	2-yrs gavage PCB 153 dose?	Increased incidences of non-neoplastic lesions of the liver, thyroid gland, ovary, oviduct, and uterus in female rats	NTP 2006a
Rats	2-yrs gavage PCB 126 dose?	Increased incidences of cholangiocarcinoma of the liver, squamous neoplasms of the lung (cystic keratinizing epithelioma and squamous cell carcinoma), and gingival squamous cell carcinoma of the oral mucosa	NTP 2006b
Rats	PCBs on maternal odor conditioning in rat pups 12–14 days of age.	Significantly depressed the preference for the maternal-associated cue, but did not impair discrimination for a novel odor.	Cromwell et al. 2007
Rats	Pregnant rats administered single doses of PCB 132 at 1 or 10 mg/kg on gestational day 15. Male offspring were assessed on postnatal day 84	Decreased cauda epididymal weight, epididymal sperm count, and motile epididymal sperm count in adult offspring. The spermatozoa of PCB 132-exposed offspring produced significantly higher levels of ROS than the controls. Low-dose PCB 132 group, p53 was significantly induced and caspase-3 was inhibited. High-dose group, activation of caspase-3 and -9 was significantly increased, while the expressions of Fas, Bax, bcl-2, and p53 genes were significantly decreased	Hsu et al. 2007
Rats	Noncoplanar PCBs were fed to rat dams during gestation and throughout three subsequent nursing weeks.	Abnormal development of the primary auditory cortex (A1)	Kenet et al. 2007
Female Goat	Goat dams were orally dosed with PCB 153 in corn oil (98 microg/kg body wt/day) or PCB 126 (49 ng/kg body wt/day) from day 60 of gestation until delivery. The offspring were exposed to PCB in utero and through maternal milk. The suckling period lasted for 6 weeks.	Perinatal exposure to PCB 153, but not PCB 126, resulted in altered bone composition in female goat offspring	Lundberg et al. 2006
Female Rats (Sprague-Dawley)	Binary Mixture PCB 126 and PCB 153 dose?	Increased incidences of non-neoplastic lesions in the liver, lung, oral mucosa, pancreas, adrenal cortex, thyroid gland, thymus, kidney, nose, and fore stomach	NTP 2006c
Female Rats (Sprague-Dawley)	Binary Mixture PCB 126 and PCB 118	Increased incidences of non-neoplastic lesions in the liver, lung, oral mucosa, pancreas, adrenal cortex, thyroid gland, thymus, kidney, nose, and fore stomach	NTP 2006d
Female Rats (Sprague-Dawley)	Mixture of TCDD, PeCDF and PCB 126	Increased incidences of non-neoplastic lesions of the liver, lung, pancreas, adrenal cortex, oral mucosa, uterus, thymus, ovary, kidney, heart, bone marrow, urinary bladder, mesenteric artery, and thyroid gland in female rats	NTP 2006e
Female Rats (Sprague-Dawley)	Daily oral administration of vehicle (corn oil) or 1 or 3 μg/kg of PCB-126 from 2 weeks prior to mating with intact males until 20 days after delivery, examined from birth until puberty.	Direct effect on the ovary and adverse effects female puberty by altering the morphological and functional development of the female reproductive system	Shirota et al. 2006
Adult Female Rats (Sprague-Dawley)	Prenatal exposure to the PCB mixture Aroclor 1221 on adult female	Mating trial pacing, vocalizations, ambulation, and the female's likelihood to mate. Were these impaired?	Steinberg et al. 2007

Species	Study designs	Health effects (Findings)	Reference
Female Mice (C57BL/6)	Temporal analysis, mice were orally gavaged with PCB126 or sesame oil as vehicle and sacrificed after 2, 4, 8, 12, 18, 24, 72, 120, or 168 h. In the dose-response study, mice were gavaged with 0.3, 1, 3, 10, 30, 100, 300, 1000 μg/kg PCB126, 30 or 100 μg/kg TCDD and sacrificed after 72 h	251 and 367 genes were differentially expressed by PCB 126 at one or more time points or doses, respectively, significantly less than elicited by TCDD. At 300 μg/kg PCB 126 elicited a subset of weaker effects compared with 30 μg/kg TCDD in immature, ovariectomized C57BL/6 mice	Kopec et al. 2008
Rats	Pregnant rats were treated orally with PCB 126 at a dose of 30 microg/kg or corn oil, its vehicle, on gestational day 15, and their male offspring were subjected to locomotor activity and anxiety related test, social interaction, and rotating test at 4–5 weeks old.	% time spent in the center, social interaction time, and number of rearing were significantly reduced in PCB treated group.	Orito et al. 2007
Female Rats (Sprague-Dawley)	The rats were treated orally for up to 2 years with a ternary mixture of TCDD, PCB 126 and PeCDF dose?	A variety of pulmonary lesions was observed in all the studies. Non-neoplastic lesions were bronchiolar metaplasia and squamous cell metaplasia of the alveolar epithelium. Cystic keratinizing epithelioma was the most commonly observed neoplasm	Walker et al. 2007
Female Rats	Pre- and/or postnatal exposure to PCB 77. Pregnant rats were treated with oil or PCB dissolved in oil (2 mg/kg b.w.) on gestation days 6–18 and then given pups that had been exposed to either the oil vehicle or PCB during gestation. Female offspring were monitored until adulthood	None of the treatments (preferred to exposed) affected female sexual behavior	Cummings et al. 2008
Adult Rats	PCB mixture Aroclor 1254 (A1254) at 0.1 or 1 mg/kg/day in the maternal diet throughout gestation and lactation. Focal cerebral ischemia was induced at 6–8 weeks of age via middle cerebral artery occlusion, and infarct size was measured in the cerebral cortex and striatum at 22 hr of reperfusion	Significantly decreased striatal infarct in females and males at 0.1 and 1 mg/kg/day, respectively. Effects of developmental A1254 exposure on Bcl2 and Cyp2C11 expression did not correlate with effects on infarct volume	Dziennis et al. 2008
Female Rats (Sprague-Dawley)	Pregnant Sprague-Dawley rats (Crj: CD (SD) IGS) were given PCB 153 (0, 16, or 64 mg/kg/day) orally from gestational day (GD) 10 through GD 16. Male and female offspring 1 or 3 weeks of age clarify	Significant dose-dependent decrease in T3 and T4 plasma concentrations in treated group. However, thyroid stimulating hormone levels not changed significantly.	Kobayashi et al. 2008
Mice	Single gavage dose (150 micromol/kg body weight) of PCB 77, PCB 104, PCB 153 (as a mixture)	Induction of pro-inflammatory mediators in livers, lungs and brains. The strongest expression of pro-inflammatory proteins occurred 24 h following the PCB administration independent of the class of PCB	Sipka et al. 2008