Characterization of Potential Endocrine-Related Health Effects at Low-Dose Levels of Exposure to PCBs

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This article addresses issues related to the characterization of endocrine-related health effects resulting from low-level exposures to polychlorinated biphenyls (PCBs). It is not intended to be a comprehensive review of the literature but reflects workshop discussions. "The Characterizing the Effects of Endocrine Disruptors on Human Health at Environmental Exposure Levels," workshop provided a forum to discuss the methods and data needed to improve risk assessments of endocrine disruptors. This article contains an overview of endocrine-related (estrogen and thyroid system) interactions and other low-dose effects of PCBs. The data set on endocrine effects includes results obtained from mechanistic methods and models (receptor-based, metabolism-based, and transport protein-based), as well as from in vivo models, including studies with experimental animals and wildlife species. Other low-dose effects induced by PCBs, such as neurodevelopmental and reproductive effects and endocrine-sensitive tumors, have been evaluated with respect to a possible causative linkage with PCB-induced alterations in endocrine systems. In addition, studies of low-dose exposure and effects in human populations are presented and critically evaluated. A list of conclusions and recommendations is included. Key words: endocrine, estrogen, health, human, low dose, PCBs, risk, thyroid.


A National Institute of Environmental Health Sciences' workshop, "Characterizing the Effects of Endocrine Disruptors on Human Health at Environmental Exposure Levels," was held in Raleigh, North Carolina, on 11–13 May 1998. This workshop was to provide a forum for the discussion on methods and data needed to improve risk assessments of endocrine disruptors. The discussions presented in this paper address the persistent and toxic environmental pollutants polychlorinated biphenyls (PCBs).

PCBs cause a wide range of effects in experimental animals, wildlife, and humans (1,2). This article addresses toxic effects from low-level exposures to PCBs that may be related to endocrine-associated influences on health. The assigned task was a challenge, in part because a) PCBs are a complex mixture that comprise theoretically 209 congeners; b) the toxicity of PCBs is highly dependent on the number and position of chlorine atoms on the biphenyl rings; c) both parent PCBs and their metabolites can cause toxic effects, with the metabolites being mainly associated with endocrine-associated effects; and d) there is a large species difference in toxic effects of PCBs. We also recognize that humans are exposed to high levels of natural compounds in foods that may alter the endocrine activity, if any, of PCBs in humans. Nevertheless, much progress has been made through the study of specific PCB congeners and their metabolic products, which enables an evaluation of potential endocrine-associated adverse health effects of PCBs.

This article is not intended to be a comprehensive review of the literature but reflects workshop discussions. Only data available from peer-reviewed articles were considered for discussion. The following questions were addressed:

• What data and models are needed to estimate human risk?
• What is the spectrum of observed effects?
• What data and models are needed to estimate human risk?
• What is the quality of the human exposure data?
• What has been the utility of specific animal and in vitro models?

The questions and discussions of these issues are addressed in the same order, with appropriate citations of relevant data. Conclusions and recommendations are given at the end of this article.

What Data and Models Are Needed to Estimate Human Risk?

In principle, the strategy to estimate human risk at low-dose exposure to endocrine disrupting chemicals does not differ from that used for other categories of toxic compounds in the sense that one needs exposure–effect relationships and dose–response data in experimental animals; in the case of a suggested problem one may rely on wildlife data or human epidemiologic data to support or reject claims of exposure-related adverse health effects.

The complexity arises, however, when considering the vast number of different cells, tissues, and organs that could possibly be affected when the supportive endocrine system(s) are disrupted. Consequently, many different exposure–effect relationships may have to be studied to evaluate the full spectrum of adverse effects that could arise following endocrine disruption.

The complexity increases further when considering that most essential physiologic functions such as reproduction and behavior, as well as the processes involved in fetal development, are supported by multiple endocrine systems that may communicate (cross-talk) with each other. Hence, even when a chemical affects a physiologic end point such as reproduction or behavior, it may be difficult to prove that this effect results from disruption of an endocrine system. Finally, endocrine systems can be affected in various ways, e.g., at the receptor level, the various metabolic steps, the organ, processes of synthesis and/or release, the transport systems, and various steps of feedback regulation. This complicates the development of suitable and unequivocal mechanism-based (pre)screening and testing methods to predict potential low-dose health risks from...
Although it is difficult to answer the question, What data and models are needed to estimate human risk? based on data and experiences from studies on the effects of PCBs, the PCB database can provide valuable insight on how to evaluate human health risks at environmental exposure levels.

In this article, a concise overview is given of the available data with regard to endocrine-related effects of PCBs, including the full spectrum of low-dose effects observed in animals and effects in humans following accidental or occupational exposure to PCBs. An attempt is made to delineate which of those low-dose end points are to be considered as causally linked to endocrine disruption. The information is structured in subclasses of methods and models used to obtain the data. Although a lot of information on hormonal alterations caused by PCBs was known well before endocrine disruption became a prominent issue, it should be noted that many of the data sets on effects of PCBs were not obtained originally with a focus on putative endocrine-disruptive effects. Categorizing data on effects of PCBs in different classes of methods and models is therefore mainly done in retrospect. It is, however, possible and helpful to use this data set and the experiences obtained with PCBs to assess possible human health risks from exposure to low levels of putative endocrine disruptors.

Overview of Endocrine-Related and Other Low-Dose Effects of PCBs

Endocrine Systems Affected by PCBs

There is extensive data on endocrine-related effects of PCBs. A wide variety of endocrine systems are affected by PCBs, including the estrogen and androgen system (3), the thyroid hormone system (4), retinoid system, corticosteroid system and several other endocrine pathways. In addition, the dioxin-like non-ortho and mono-ortho PCBs that exert their effects mainly through the arylhydrocarbon receptor (AhR) pathway may also affect a number of other pathways through cross-talk of the AhR and AhR nuclear transport protein (ARNT) transcription factors with other members of the Per-Arnt-Sim family of helix-loop-helix proteins (5). The work group agreed to focus their attention on interactions of PCBs with the thyroid and estrogen hormonal systems. The effects observed by PCBs are subdivided into:

- a) endocrine effects on components of the endocrine system such as hormones, metabolic enzymes, carrier proteins, receptors, endocrine glands, and feedback regulation systems, and
- b) effects that may be associated with changes in endocrine systems: neurodevelopment, reproduction, immune effects, and induction of endocrine-sensitive tumors.

Mechanism-Based Models for Endocrine Effects

Mechanism-based models that are used to study endocrine effects focus on certain aspects of the endocrine system. The in vitro models and methods are particularly suitable to study certain aspects of endocrine systems in isolation. These mechanism-based models may be quite useful as (pre)screening tools to identify putative endocrine-disruptive chemicals and may allow the analysis of large numbers of compounds in short periods of time.

Receptor-based methods and models.

These methods and models include receptor-binding assays, receptor-mediated reporter gene assays, and hormone-dependent cell proliferation assays.

Estrogen receptor-mediated effects of PCBs.

Several hydroxylated (OH)-PCBs show binding affinity for the estrogen receptor in in vitro receptor-binding assays (6-8). The most potent congener among the limited set of hydroxy-PCBs tested was 2,4,6,2′,6′-pentachloro-4-biphenyl, which was about 5 times less potent than 17β-estradiol (7), although most compounds show much less potency (6.8). A number of OH-PCBs identified in human serum exhibited antiestrogenic activity in the rat uterine estrogen-binding assay and in the MCF-7 cell proliferation assay (9). OH-PCBs bound to the estrogen receptor and transactivated the estrogen receptor to DNA binding and altered gene expression in in vitro reporter gene assays (9,10). However, these compounds were mainly antiestrogenic rather than estrogenic in these reporter gene assays. PCB mixtures (Aroclors 1221, 1232, 1242, 1248, 1254, and 1260) did not exhibit antiestrogenic activity, based on secretion of procathepsin D, an estrogen-regulated gene in MCF-7 cells (11).

Thyroid receptor-mediated effects of PCBs.

There is little information on the direct effects of PCBs or their metabolites on the thyroid hormone receptor(s). McKinney and co-workers (12) found some indications that dioxins and dioxinlike PCBs may bind to the nuclear thyroid hormone receptor, based on graphics-assisted computer modeling. However, to date no report has been published showing a direct competitive binding of PCBs to thyroid hormone receptors.

Metabolism-based methods and models.

Many different enzyme systems are involved in the synthesis, intracellular bioactivation, and degradation of hormones including cytochrome P450 isozymes, uridine-5'-diphosphate-glucuronosyltransferases (UGTs), deiodinases (IDs), and sulfotransferases (SULTs). It is the intimate interplay between these enzyme systems that determine the intracellular concentrations of active hormones in target cells. Certain chemicals may affect endocrine systems by interfering in metabolic steps and thereby altering the availability of the active natural hormone.

Effects of PCBs on thyroid hormone metabolism.

PCB congeners are capable of inducing UGT enzymes in livers of exposed rats. There are at least two or possibly three UGT isozymes involved in thyroid hormone glucuronidation (13). The so-called bulky phenol types of UGT are inducible by PCBs, in particular by planar non-ortho-PCBs, with the induction mechanism involving the Ah-receptor. For example, T₄ thyroxine glucuronidation is markedly induced in livers of rats exposed to 3,3',4,4'-tetrachlorobiphenyl CB (PCB 77) (13), 3,3',4,4',5,5'-hexaCB (PCB 169) (14), 3,3',4,4'-pentachlorobiphenyl (PCB 126), and 2,3,3',4,4',5,5'-hexaCB (PCB 156) (15,16). However, nonplanar di-ortho PCBs, such as 2,2',4,4',5,5'-hexaCB (PCB 153) are also capable of inducing T₄ thyroid hormone glucuronidation, albeit through another isozyme (17). PCB mixtures are also capable of inducing T₄ glucuronidation (18-21). A negative correlation between plasma T₄ levels and hepatic T₄ UGT activity has been observed (17).

PCBs also affect thyroid hormone ID enzymes as well as SULT isozymes. Exposure of rats to 3,3′,4,4′-tetrachloroCB (PCB 77) resulted in an inhibition of hepatic ID-1 that converts T₄ into T₃ (3,3′,5′-triiodothyronine) as well as reverse T₃ activity (13,22). OH-PCB metabolites competitively inhibited ID-1 activity in isolated rat microsomes (22,23). On the other hand, brain ID-2 (converts T₄ into T₂ exclusively) was enhanced in fetal and neonatal rats born from dams exposed to 3,3′,4,4′,5,5′-hexaCB (PCB 169) and 3,3′,4,4′-tetrachloroCB (PCB 77) (14). OH-PCBs were also potent inhibitors of thyroid hormone sulfation, competitively inhibiting the SULT enzyme involved (24,25). Inhibition of ID activity or SULT activities may compromise the availability of intracellular T₃.

Effects of PCBs on estrogen metabolism.

There is only limited information available on the effects of PCBs on estrogen metabolism. The main enzyme system involved in estrogen metabolism that is also affected by dioxinlike PCBs is the cytochrome P450 system. Caretchol estrogen formation was decreased by 50-75% in hepatic microsomes obtained from 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD)-treated rats (26). 2,3,7,8-TCDD and related...
compounds affect aromatase, thus interfering in the production of estradiol from testosterone (27). Yoshihara et al. (28) reported that 3,3',4,4',5-pentaCB (PCB 126) increased the 7α-hydroxylation but suppressed the 2α-, 6β-, and 16α-hydroxylation and 5α-reduction of progesterone and testosterone in liver microsomes.

**Transport protein methods and models.** Interference with intracellular and/or plasma proteins that transport hormones may greatly enhance (at least momentarily) the availability of free hormone for uptake and biological activity. This may be particularly important during pregnancy, when serum protein binding of hormones plays a crucial role in maintaining a suitable level of free hormone despite large fluctuations in hormone physiology and demand. In addition, transport protein binding may provide special facilitated routes of transport for exogenous chemicals, which may have a considerable impact on their toxicokinetics.

**INTERFERENCE OF PCBs WITH THYROID HORMONE-BINDING PROTEINS.** OH-PCBs competitively displace T4 from the plasma-binding protein transthyretin (TTR), formerly known as prealbumin (29-31). This occurs both in vitro and in vivo in fetal brain and plasma as well as in maternal plasma. The structure-activity relationship of T4-TTR competition by OH-PCBs is well known and involves hydroxylation on meta or para positions with one, but preferably two, estragri-binding proteins such as sex hormone-binding globulin (SHBG) or utero-tropinlike proteins. There is, however, information on the binding of methylsulfone-PCB metabolites to a uterotropinlike protein in livers of rats (34).

**INTERFERENCE OF PCBs WITH ESTROGEN-BINDING PROTEINS.** There is very little information on possible interference of PCBs with estrogen-binding proteins such as sex hormone-binding globulin (SHBG) or uterotropinlike proteins. There is, however, information on the binding of methylsulfone-PCB metabolites to a uterotropinlike protein in livers of rats (34).

All of the mechanisms indicated above may have implications on the availability of thyroid hormones in the fetal brain and other tissues where thyroid hormones play an essential role in normal development. However, in recently performed rat perinatal exposure studies, Aroclor 1254 resulted in little or no effect on fetal and neonatal brain T3 levels, despite the fact that plasma and brain T4 levels were reduced by 90% (32). In addition, no changes in T4-sulfate concentrations were observed in dams or fetuses, despite the fact that considerable amounts of phenolic organohalogens were present in the fetal compartment (35).

**In Vivo Models for Endocrine Effects of PCBs**

**Experimental animal models.** THYROID HORMONE SYSTEM EFFECTS. Most information on thyroid hormone-related effects of PCBs stem from relatively short-term single-dose exposure studies of experimental animals (rats, mice, marmoset monkeys) exposed to either mixtures of PCBs or individual PCB congeners. Exposure to PCB mixtures (Aroclors 1254 and 1260, Clophen A50) or to single PCB congeners (e.g., 3,3',4,4'-tetraCB (PCB 77), 2,3,3',4,4'-pentaCB (PCB 105), 2,3,3',4,5-pentaCB (PCB 118), 3,3',4,4',5-pentaCB (PCB 126), 3,3',4,4',5,5'-hexaCB (PCB 169), or 2,2',4,4',5,5'-hexaCB (PCB 153)) resulted in marked reductions in plasma levels of T4, whereas T3 levels were only marginally affected (14-16,21,36-40). Reductions in plasma thyroid hormone levels were observed 24-48 hr after a single intraperitoneal injection and remained low for prolonged periods of time (several days to months), depending on the half-life of the PCB congener (36).

Effects at lower doses were observed in experiments involving perinatal exposure protocols. For example, severely depressed T4 levels (by 60-90%) were observed in fetal and neonatal rats following in utero exposure to 5 or 25 mg of Aroclor 1254/kg from gestation day 10 to gestation day 16 (32), while much higher doses of Aroclor 1254 were needed in adult rats to cause similar changes in plasma T4 levels (36). At postnatal day 21, there were no observable reductions in plasma T4 levels, indicating that perinatal exposure to PCBs did not cause permanent alterations in thyroid hormone levels in the offspring. Reduced plasma T4 levels were also observed in rat pups born to dams exposed to 4 or 16 mg of 2,3',4,4',5-pentaCB (PCB 118) and 16 or 64 mg of 2,2',4,4',5,5'-hexaCB (PCB 153)/kg/day from gestation day 10 to gestation day 16 (41).

Effects of PCB exposure on thyroid hormone feedback regulation, as measured by thyroid-stimulating hormone (TSH) levels, are equivocal. Some reports indicate an increased TSH concomitant with a low T4 level in adult rats after exposure to PCBs (19,42,43); other reports, mainly from in utero exposure to PCBs, have not observed an effect on TSH despite severely depressed T4 levels (32).

Reduced brain T4 levels (by 90%) were also observed in fetal rats following in utero exposure to Aroclor 1254 (32). However, brain T3 levels were marginally affected because of increased activity of the enzyme ID-2, which bioactivates T4 to the active hormone T3. This indicates that an effective compensatory mechanism is operative in late gestational fetuses that may effectively cope with severely reduced T4 levels in critical target organs such as the brain.

Sustained alterations in peripheral thyroid hormone levels will result in a prolonged activation of the hypothalamic-pituitary-thyroid (HPT) axis. Evaluation of thyroid gland morphology may therefore be a good indicator for compounds that interfere in thyroid hormone metabolism. Thyroid gland abnormalities have been reported following adult and in utero exposure to Aroclor 1254 in rats and adult exposure in cynomolgus monkeys (44-49). The ultrastructural lesions observed in rat thyroid follicular cells after PCB exposure were suggestive of an effect on thyroid hormone synthesis and secretion (47,50). However, these thyroid ultrastructural changes were also interpreted as a sustained thyroid activation through the HPT axis (41,51).

**ESTROGEN SYSTEM EFFECTS.** Decreases in serum estradiol and progesterone were reported in rhesus monkeys exhibiting reproductive dysfunction, following exposure to 2,3,7,8-TCDD (500 ppt in the diet for 7 months) (52) and polybrominated biphenyls (53). Exposure to Aroclor 1248 at doses of 2.5 and 5.0 ppm in the diet caused prolonged menstrual cycles and decreased peak progesterone levels in female rhesus monkeys (54). Aroclor 1242 caused an increase in basal luteinizing hormone and follicle-stimulating hormone secretion by the pituitary in rats (55).

The uterotrophic assay, e.g., an increase in uterine wet weight in prepuberal rats following a short-term exposure (e.g., 4 days) to an estrogenic compound, is frequently used as a functional assay for putative estrogenic compounds. Aroclor mixtures, particularly the lower chlorinated ones including Aroclors 1221, 1232, and 1242, were weakly estrogenic in the uterotrophic assay (55-58). The potency of the Aroclor mixtures was 4-5 orders of magnitude lower than that of 17β-estradiol. The non-ortho 3,3',4,4'-TeCB[PCB 77] was not estrogenic and in fact antagonized the increases in uterine wet weight induced by 17β-estradiol and Aroclor 1242. ortho substitution may be related to the weak estrogenic activity of PCB congeners (7,58).

**Studies in wildlife species.** Possible effects of putative endocrine disruptors in real life are difficult to assess because of the generally very low background levels of exposure.
However, studies in wildlife species that are situated at the top of food chains may be quite useful to establish if there are effects at environmentally relevant concentrations.

**Thyroid hormone system effects.** There is a considerable data set for the effects of PCBs on wildlife species. Some studies also provide information on thyroid hormone system effects. Changes in plasma T₄ levels were observed in wildlife species exposed either experimentally or environmentally to low doses of PCBs. Harbor seals (Phoca vitulina) held in captivity were exposed for almost 3 years to fish diets that were obtained from a highly polluted area (Baltic Sea) or from a relatively clean area (northeast Atlantic). The diets differed by a factor of 10 in PCB concentrations, and feeding was adjusted for fish protein intake (59). Seal reproduction was reduced in the group fed the highly polluted fish diet. In plasma samples taken from the seals during the dietary exposure period, significantly reduced total and free thyroxine (TT₄, FT₄) and total triiodothyronine (TT₃) levels were found in the highly polluted fish diet group (60).

Several studies have been performed on eggs of fish-eating birds that were taken from their nests and artificially hatched in a laboratory incubator. Significant dose-dependent reductions in plasma thyroid hormone concentrations TT₄ and FT₄ were observed in cormorant hatchlings from high PCB-contaminated breeding colonies compared to those from low PCB-contaminated colonies (61). The number of hatchlings and fledglings in the high-contaminated breeding colony was significantly reduced compared to that in the low-polluted colony. In addition, 28-day-old eider ducks exposed to 3,3',4,4'-tetraCB (PCB-77) under semifield conditions showed a significant negative correlation between plasma levels of progesterone and relative high levels of PCBs for 2 years, a lower reproductive success was observed; changes in plasma levels of progesterone were also found (59).

### Other Low-Dose Effects of PCBs in Experimental Animals That May Be Linked to Endocrine Disruption

PCBs induce a wide spectrum of toxic and biochemical effects in experimental animals. In Table 1, a number of the most important effects are given. In addition, the effects are categorized as low-, moderate-, or high-dose effects and whether there is a suggested link with endocrine disruption.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Animal</th>
<th>Dose level</th>
<th>Endocrine link</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid system</td>
<td>Rodents/monkeys</td>
<td>Low</td>
<td>T</td>
</tr>
<tr>
<td>T₄ depletion</td>
<td>Rodents/monkeys</td>
<td>Moderate</td>
<td>T</td>
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<tr>
<td>T₃ depletion</td>
<td>Rodents/monkeys</td>
<td>Moderate</td>
<td>T</td>
</tr>
<tr>
<td>TSH increase</td>
<td>Rodents/monkeys</td>
<td>Low/moderate</td>
<td>T</td>
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<tr>
<td>Thyroid gland abnormalities</td>
<td>Rodents/monkeys</td>
<td>Moderate</td>
<td>T</td>
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<tr>
<td>Estrogen system</td>
<td>Rodents/monkeys</td>
<td>Moderate</td>
<td>T</td>
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<tr>
<td>E-levels</td>
<td>Rodents/monkeys</td>
<td>Moderate</td>
<td>T</td>
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<tr>
<td>Uterotropic effects</td>
<td>Rodents/monkeys</td>
<td>Moderate</td>
<td>T</td>
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<tr>
<td>Growth reduction</td>
<td>Rodents/monkeys</td>
<td>Moderate</td>
<td>T</td>
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<tr>
<td>Neurodevelopment</td>
<td>Rodents/monkeys</td>
<td>Moderate/high</td>
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<td>Rodents/monkeys</td>
<td>Moderate/high</td>
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<td>Neuroproteins (GFAP/synapt)</td>
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<td>Moderate/high</td>
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<td>Rodents/monkeys</td>
<td>Moderate/high</td>
<td>T</td>
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<td>Rodents/monkeys</td>
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<tr>
<td>Auditory function</td>
<td>Rodent</td>
<td>Low/moderate</td>
<td>T</td>
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<tr>
<td>Reprodevelopment</td>
<td>Rodents/monkeys</td>
<td>Low</td>
<td>E</td>
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<tr>
<td>Gonad development</td>
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<tr>
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<td>Rodents/monkeys</td>
<td>Low</td>
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<td>Rodents/monkeys</td>
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<td>Rodents/monkeys</td>
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<td>E</td>
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<td>Immunotoxicity</td>
<td>Rodents/monkeys</td>
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<td>?</td>
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<tr>
<td>Endocrine tumors</td>
<td>Rodents/monkeys</td>
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<td>Rodents/monkeys</td>
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<td>Monkeys</td>
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<td>T</td>
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<tr>
<td>Porphyria</td>
<td>Rodents</td>
<td>Moderate</td>
<td>T</td>
</tr>
<tr>
<td>Biochemical enzyme induction, etc.</td>
<td>Rodents/monkeys</td>
<td>Low</td>
<td>?</td>
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</table>

**Table 1.** Dose- and endocrine system-linked adverse effects induced by PCBs in experimental animals and/or their offspring.

**Abbreviations:** E, estrogen system; ESTERO, estradiol; F₁, first-generation offspring; GFAP, glial fibrillary acidic protein; PCBs, polychlorinated biphenyls; synapt, synaptophysin; T, thyroid system; TSH, thyroid-stimulating hormone; T₂, thyroxine; T₃, triiodothyronine; T₄, thyroxine; T₃, triiodothyronine. Linkage is clear for hormone changes related to estrogen system effects; however, this does not indicate that the effect is mediated by an endocrine mechanism.

**Neurodevelopmental effects.** It is well known that thyroid hormones are very important for normal brain development and that hypothyroidism during fetal and early neonatal life may have profound adverse effects on the developing brain. This may result in reduced axonal and dendritic size and complexity (67) and alterations in the growth and development of a number of different neuronal cell types and glial fibrillary acidic protein (GFAP)-positive astrocytes (68). In fact, changes in GFAP levels have been observed in several brain regions in postnatal day 90 rat offspring that were exposed in utero and via lactation to Aroclor 1254 (69). Hypothyroidism also results in changes in the serotonergic and dopaminergic neurotransmitter systems (70). It is well known that perinatal exposure of rodents to PCB mixtures or to dioxinlike as well as non-dioxinlike PCBs causes changes in dopaminergic and serotonergic neurotransmitter concentrations and metabolism (71-73). In a perinatal exposure study (74), similar influences were observed on the serotonergic system by 3,3',4,4'-tetraCB (PCB 77) and the well-known thyroid suppressive agent...
6-n-propyl-2-thiouracil in rat offspring. Retarded behavioral and cognitive development and profound deafness are consequences of fetal hypothyroidism (79). Rodent and monkey offspring born to mothers exposed to PCBs perinatally also exhibited learning and behavioral deficits and reduced auditory-evoked potentials at low frequencies (40,76-80). Although quite similar changes in neurodevelopment can be induced by fetal hypothyroidism and by perinatal exposure to PHAHs, this does not necessarily mean that the changes observed by PHAHs are causally linked to alterations in the thyroid hormone system. However, the changes observed in auditory-evoked potentials are more likely linked directly to alterations in the thyroid hormone system (40).

Effects on reproductive development. Gonadal development, sex determination, and reproductive success of the offspring are highly dependent on the sex hormonal systems. Disruption of the sex steroid system during fetal stages of life results in profound adverse developmental reproductive effects, as is well known from the diethylstilbestrol experience (3). The changes include decreased sperm counts; sperm abnormalities; male gonadal changes such as hypospadia, cryptorchidism, and androgen hormonal balances during fetal life may also impact on gonadal as well as sexual behavioral development. Alterations in reproductive development have been most extensively studied with 2,3,7,8-TCDD. 2,3,7,8-TCDD exposure during development causes changes in both male and female gonadal development, reductions in sperm counts, abnormal sperm, and changes in sexual behavior such as demasculinization and feminization of male offspring (81,82). There is only limited information on reproductive developmental effects following exposure to PCBs. Postnatal lactational exposure of infant male rats to Aroclor 1254 at maternal doses of 8, 32, and 64 mg/kg resulted in adverse effects on subsequent mating behavior and reproductive success (83). There were also decreases in ventral prostate weight and testicular weight in adult male rats exposed to Aroclor 1254 via lactation. In female rats exposed to Aroclor 1254 via lactation, several adverse effects were observed such as delayed puberty, decreased uterine weight, impaired fertility, and irregular estrus cycles (84). Although the reproductive abnormalities induced by 2,3,7,8-TCDD (and to a more limited extent by PCBs) would not be in conflict with an underlying estrogenlike mechanism of action, this possible relationship needs to be studied further.

Endocrine-sensitive tumors. It is well known that tumor incidences of endocrine-sensitive organs such as mammary gland, testis, prostate, ovary, and thyroid gland can be highly influenced by changes in sex steroids or thyroid hormone levels. In fact, quite a number of antitumor therapies take advantage of this knowledge by using anti-hormone or hormone antagonist treatments.

PCBs are carcinogenic in rodents. The principle tumor response to 2,3,7,8-TCDD and related dioxinlike PCBs is seen in the female rat liver (85). The fact that no liver tumors are observed with 2,3,7,8-TCDD in male rat livers suggests a possible role of estrogens in female rat liver tumor formation by 2,3,7,8-TCDD. There is some information on PCB-induced tumors in endocrine tissues. Small increased incidences of thyroid gland follicular cell adenomas were observed for males receiving Aroclor 1242, 1254, or 1260 at 25, 50, or 100 ppm in the diet for 2 years, but the increases did not continue proportionately above the lowest dose. Follicular cell hyperplasia (generally minimal to mild) was increased in a nondose-related manner for males exposed to Aroclor 1242, 1254, or 1260. Thyroid effects were not observed in males fed 50, 100, or 200 ppm Aroclor 1016 or in female Sprague-Dawley rats fed Aroclor 1016, 1242, 1254, or 1260 (86). The morphology of the tumors was characteristic of those that develop as a secondary response to chronic overstimulation by TSH.

A significant decreased trend in the incidence of spontaneously occurring mammary gland tumors was measured in female Sprague-Dawley rats fed up to 100 ppm Aroclors 1242, 1254, and 1260 in the diet for 2 years. The effect was not observed in females fed up to 200 ppm Aroclor 1016 or in female Sprague-Dawley rats fed Aroclor 1016, 1242, 1254, or 1260 (86). This effect was most consistently observed in groups receiving Aroclors 1242 and 1260. The authors speculated that the results may be the consequence of an alteration in the 2-hydroxylation rate versus the 16α-hydroxylation rate of estradiol, as reported by others and demonstrated in this study (87). We also note that 2,3,7,8-TCDD decreases the amount of hepatic estrogen receptors in rats (88). Reduced incidences of mammary tumors in rats have been seen with studies of Aroclor 1260 in Sherman rats (89) or Sprague-Dawley rats fed 2,3,7,8-TCDD (84), but these may have been associated with decreases in body weight.

These data suggest that at relatively high doses, PCBs affect tumor incidence. This may be related to persistent effects on the thyroid system (hypothyroidism resulting in prolonged overstimulation of the HPT axis) or to effects on the estrogen system following chronic exposure.

Exposure and Associations with Health Effects in Human Populations

Data on human exposure to PCBs. Over the past 20 years, measurement of human exposure to PCBs has improved because of developments in methods of extracting PCBs from the specimen source and in clean-up to remove materials that interfere with the assay; control of the proportion of PCBs in the specimen that is extracted for analysis (because of availability of deuterated or surrogate standards); and instrumentation that has resulted in lower detection limits and lower coefficients of variation.

Using modern methods it is now apparent, that the PCBs in human specimens typically comprise three dozen or more specific PCB congeners, with the number detected depending on the analytical sensitivity or the laboratory method, amount of sample, and the population studied. From the 1970s through the mid-1980s, however, PCBs were usually quantified by either the peak pattern method, where PCB peaks in the sample were compared with the corresponding peaks in commercial PCB mixtures, or by the perchlorination method, where all individual PCB congeners were converted to decachlorobiphenyl, followed by back calculation to commercial PCB mixtures, e.g., Aroclor 1260 (1,90,91). Subsequently, analysis of several chromatographic peaks (often seven) reflecting the concentration of the major congeners was used to provide a more precise estimate of total PCBs using the Webb-McCall method (92). Recently, the focus has been on quantification of specific congeners using solid phase (93) or solvent extraction (94). With the earliest measures of PCBs, comparison of results across laboratories is unreliable. Results based on the Webb-McCall method allow a qualitative comparison of concentrations measured in different laboratories. With congener-specific methods, quantitative comparisons across laboratories are feasible but still complicated by variation across laboratories in procedures for extraction and clean-up, methods of analysis including selection of congeners measured, and data handling and presentation.

Expressing organochlorine concentration in relation to the amount of lipid in the specimen is desirable because otherwise variation in lipid introduces variation in wet weight concentration that does not reflect body burden. Furthermore, expressing concentration per unit lipid probably better represents the concentration of free organochlorine that may be directly responsible for toxicity, much like levels of free hormones de-emphasize variation in total concentration because of differences in amounts of binding proteins present. Expressing concentration of organochlorines
relative to lipids, however, introduces another source of variation in measurement across laboratories. Not only do the major approaches to lipid determination (gravimetric and enzymatic) introduce possible variation in results, but for a given approach results may vary substantially across laboratories.

Measurement of specific congeners has become popular, in part, because the toxicology of the individual PCB congeners varies. For example, PCB congener 153, routinely detectable in humans by modern methods, induces phenobarbital-metabolizing enzymes (95). Congener 28 and several others are suspected of being neurotoxic. Congener 118, also routinely detectable in humans, has weak dioxinlike activity.

The dioxinlike activity in a sample can be completely characterized by measurements of PCB congeners that include those with the most potent dioxinlike activity (congeners with no ortho position chlorines [coplanar PCBs] as well as polychlorinated dibenzodioxins (PCDDs; including dioxin itself), and related compounds such as polychlorinated dibenzofurans (PCDFs). These three types of compounds are present at very low concentrations in background-exposed people. Measurement of these very low concentration compounds is expensive and requires relatively large sample volumes. Whether or not these are measured, the total dioxinlike activity of a given sample can be estimated by taking into account the dioxinlike activity of each individual compound and the amount of each compound that is present (95). The dioxinlike activity of a compound is expressed as a toxic equivalency factor, a multiplier that reflects the compound's dioxinlike potency relative to dioxin (range 0–1). The sum of the concentration of each compound multiplied by its toxic equivalency factor yields a toxic equivalency value for the mixture.

Recent studies suggest that among background-exposed people in Europe (96) and North America (97), levels of specific PCB congeners, PCDDs, and PCDFs are highly correlated, raising questions regarding the additional information gained by measuring a large number of specific PCB congeners or related compounds, and about whether effects of specific compounds can be distinguished statistically. Furthermore, methods of grouping congeners with similar toxicologic properties have been proposed for use as exposure measures in epidemiologic analyses, but their value in practice remains to be established.

Finally, we note that with PCB levels expressed relative to the amount of lipid present, the concentrations in various tissues have been considered equivalent. However, few data are available to substantiate this, and the possibility that different congeners equilibrate differently has not been adequately addressed (98).

A comment on the scope of epidemiologic data reviewed. We have focused our discussion of epidemiologic results primarily on studies of health outcomes associated with exposure to PCBs. We have not included a general review of the health effects of exposure to PCDDs or PCDFs, although such data may be informative if PCBs are toxic through an AhR-mediated mechanism. The reader is referred elsewhere for more information on this topic (99). We note that studies on fish intake in relation to health outcomes may be informative regarding PCB effects, but such studies were in general not included in this review because of the possibility that other contaminants in fish might account for health effects associated with fish consumption. Two studies of fish intake in relation to neurodevelopmental outcome, however, are included in this review. We have focused primarily on those relations where the data suggest an association. Thyroid data are reviewed in detail because of the direct tie-in with endocrine disruption. More complete recent reviews are available elsewhere (100).

Epidemiologic associations between early-life PCB exposure and health effects.

ThYROID HORMONES. The results of the two studies of in utero exposure to PCBs and thyroid function in neonates are summarized in Table 2. Both studies were done in Dutch populations with no special PCB exposure. The laboratory assay for TSH used in the study by Koopman-Esseboom et al. (101) had a lower limit of detection. In that study higher PCB exposure was related to increased TSH. In the small study by Pluim et al. (102) also done among a Dutch population, both thyroxine (T4) and TSH increased with higher exposure to dioxin and dioxinlike compounds. Koopman-Esseboom et al. (101) also found that exposure to dioxin and dioxinlike compounds was associated with increased TSH and lower total T4. In another study among subjects in Japan who had no special dioxin exposure (103), exposure to dioxin and dioxinlike compounds was associated with decreased T4 and increased TSH, measured at 1 year of age. Overall, the results of the four modest-size studies on

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<th>Table 3. Summary of epidemiologic results on perinatal PCB or dietary fish exposure in relation to neurodevelopmental outcomes.</th>
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<td>Outcome</td>
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<td>Neonatal reflexes</td>
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Abbreviations: IQ, intelligence quotient; PCBs, polychlorinated biphenyls; *Representative findings are shown from each study; **p < 0.05 level of significance; **p < 0.01 level of significance; Fish: effects of dietary fish exposure in relation to health outcomes are summarized. The laboratory assay for TSH used in the study by Koopman-Eesseboom et al. (101) had a lower limit of detection. In that study higher PCB exposure was related to increased TSH. In the small study by Pluim et al. (102) also done among a Dutch population, both thyroxine (T4) and TSH increased with higher exposure to dioxin and dioxinlike compounds. Koopman-Eesseboom et al. (101) also found that exposure to dioxin and dioxinlike compounds was associated with increased TSH and lower total T4. In another study among subjects in Japan who had no special dioxin exposure (103), exposure to dioxin and dioxinlike compounds was associated with decreased T4 and increased TSH, measured at 1 year of age. Overall, the results of the four modest-size studies on
early-life organochlorine exposure suggest that associations with thyroid function exist and specifically that higher exposure increases TSH. The higher TSH could indicate mild hypothyroidism, which in turn could adversely affect neurodevelopment.

NEURODEVELOPMENT. The results of studies of perinatal PCB or dietary fish exposure in relation to neurodevelopmental outcomes are summarized in Table 3. The populations studied all had essentially background-level PCB exposure typical of the region, though the range of exposure in Michigan may have been increased somewhat due to frequent fish consumption (104). Use of fish intake as a surrogate measure of PCB exposure should attenuate associations due to measurement error, and potential confounding of associations with the fish measure by other neurotoxic contaminants of fish, such as methyl mercury, are a concern. "Measured PCBs" in the right-hand column of Table 3 refers to measurements in mother's milk, cord blood, maternal serum, etc., which are all highly correlated (96,105). The methods of assessing neurodevelopment have been somewhat similar across cohorts. Some parallel findings across cohorts are evident. For example, in the North Carolina and the breast-fed Netherlands subjects, higher PCB exposure was associated with hypotonia at birth and with delayed psychomotor development within 6 months of birth. Furthermore, in both studies the PCB-associated psychomotor delays were no longer evident later in childhood. Findings have not been consistently replicated across studies. For example, hypotonia at birth and subsequent delay in psychomotor aspect of the Bayley scales of infant development showed associations with PCB exposure in the Netherlands and North Carolina studies (106) but not in the Michigan study (not shown in Table 3). Detrimental effects of PCBs on cognition (IQ, visual recognition memory, and short-term memory) have been suggested in the Michigan data (Table 3), but confirmatory findings have not been reported in other studies to date. Despite discrepancies among studies, overall the data suggest subtle neurodevelopmental delays observable in human infant populations exposed in utero to background levels of PCBs.

OTHER OUTCOMES. A host of other outcomes have been examined in relation to early-life PCB exposure. Generally, the results are mixed or isolated positive findings remain uncorroborated (100). For example, data are mixed regarding an association of in utero background-level exposure to PCBs with lower birth weight and shorter gestational age (100,107); one occupational study supports such an association (108). The possibility of detrimental immunologic effects has also been raised (100).

Epidemiologic associations between adult PCB exposure and health effects. Cancer. In the study by Loomis et al. (109) on occupational PCB exposure in relation to cancer risk, a dose–response association was found for malignant melanoma. In that study, 88 deaths due to malignant melanoma occurred among exposed workers. Similarly, a meta-analysis including data from all earlier studies of cancer among those occupationally exposed to PCBs (100) also showed an increased risk of skin cancer. That study, in comparison, included only 15 deaths from skin cancer of all types. Previously, the cancers most suspected of being linked to occupational PCB exposure were liver, brain, and malignant melanoma. The results of Loomis et al. (109) and the meta-analysis are inconsistent with one another regarding whether risk is increased for cancer of the liver. At best, both provide weak support for increased risk of brain cancer.

Among nonoccupationally exposed women, the relation of PCB blood levels to risk of breast cancer has been examined in a number of large studies (110–113). Overall the data do not support an association. In a recent prospective study among subjects with background-level exposure to PCBs, a strong monotonic relation was observed between blood levels of PCBs and subsequent increased risk of non-Hodgkin lymphoma (114).

OTHER OUTCOMES. Occupational exposure to PCBs has consistently been associated with abnormal liver function tests and chloracne (99). In men occupationally exposed to PCBs, thyroid hormone level was not clear relation to measured PCB levels (115). As with early-life exposures, a host of other outcomes have been examined in relation to PCB exposure. Generally, the results are mixed or isolated positive findings remain uncorroborated.

The Asian (Yu-sho/Yu-cheng) Mass Poisonings. Mass poisonings with PCB-containing mixtures have occurred twice—one in Taiwan and once in Japan (116,117). In each instance contaminated rice oil was the source. The contaminating mixture contained PCBs, PCDFs, and other related compounds. The toxic effects of the mixture could be due to dioxinlike activity, with PCDFs the major contributor, or to effects mediated by other mechanisms of potential importance, as the mixture contained primarily PCBs. Studies of the health effects in these incidents are informative about high-dose adult and in utero exposures to the mixtures. Much of the available data on health effects are from case series and may reflect findings in the most severely affected. The standardized mortality ratio for the studied, exposed adult populations in Taiwan (n=1900) and Japan (n=1800) 10 and 20 years after the incident, respectively, was 1.1 in both populations. Deaths from nonmalignant liver disease were increased in both populations. In Japan an excess of deaths from liver cancer was evident (99). In both populations, the exposed subjects had increased prevalence of chloracne, localized hyperpigmentation, abnormalities of the dermal tissues adjacent to the eye, slowed nerve conduction, abnormalities of a number of laboratory tests on blood, and other symptoms. A group of exposed subjects from Japan had elevated T₃ and T₄ levels 16 years later (116). The Taiwanese children exposed to the mixture in utero were systematically followed and studied. Within 4 years of birth, 21% had died. The children had many of the same manifestations of toxicity as the adults, and in addition had delayed, inhibited growth, permanent intellectual impairment, disordered behavior, more frequent infections, and other problems (117). Table 4 is a list of the major findings in the children born to Yu-cheng mothers. Several of the symptoms in human infants resemble the developmental effects observed in experimental animals exposed in utero to PCBs. It is not known if the reproductive, cognitive, and psychomotor effects and the hearing difficulties have been linked with possible endocrine-disruptive effects of PCBs in the Yu-cheng and Yu-sho infants.

Summary and Conclusions

After extensive discussions of the available peer-reviewed literature, the working group on PCBs arrived at the following conclusions:

• Numerous effects of PCBs have been demonstrated in experimental animals, some of which can be induced at tissue concentrations not far from body burdens that are present in background exposure populations in industrialized countries.
• The most sensitive time window of sensitivity for adverse effects by PCBs appears to be the prenatal and the early postnatal period.
Developmental effects on neurobehavior, on the reproductive tract, and on the immune and thyroid systems are induced following exposure to some PCBs in the prenatal and early postnatal periods in experimental animals.

In human infants from accidentally exposed populations (Yusho/Yu-cheng), developmental effects were caused by prenatal exposure to PCDFs or PCBs and included retarded growth, neurobehavioral effects, immune effects, chloracne, and teeth and nail deformities.

In several studies involving human infants at background environmental exposure levels, subtle changes were observed in thyroid hormone levels and neurobehavioral parameters, associated mainly, but probably not exclusively, with prenatal exposure to PCBs.

However, it should be noted that there were some inconsistencies in the neurobehavioral and thyroid hormone findings in the human infant studies, which emphasizes the need for further investigations.

In the following paragraphs information on effects of PCBs on endocrine systems and in experimental animals, wildlife, and in human individuals is evaluated and used to answer the questions raised at the outset of the workshop.

What Data and Models Are Needed to Estimate Human Risk?

Extensive data from experimental animal studies and data from a modest number of human populations are available to estimate human risk from PCB exposure. However, the question is considerably more difficult to answer when we are asked to estimate human risk from endocrine-based effects of PCBs specifically. Several endocrine systems are affected by PCBs and their hydroxylated metabolites. Most information is available on thyroid hormone perturbations; however, the estrogen, androgen, and other systems may also be affected by PCBs. In experimental animal studies, reductions in thyroid hormone levels have been observed in addition to developmental effects on brain, behavior, and reproduction following developmental exposure to PCBs. Although it is tempting to propose an endocrine linkage for the adverse effects, there is evidence only for selected end points. Also, in human infants, associations have been demonstrated between serum or human milk PCB levels and thyroid hormone and neurobehavioral changes. However, these findings do not necessarily imply that neurobehavioral changes are also causally related to thyroid changes. Therefore, it is reasonable to conclude that we do not currently have the data and models that could answer the question on estimates of human risks from low-dose endocrine-related effects.

One of the major problems is that multiple PCB congeners may impact upon multiple endocrine systems, and several of those endocrine systems may be involved in regulating and maintaining the same end point. Given the complexity of PCB mixtures in environmental exposures, it is unlikely that a single endocrine perturbation will exclusively drive all of the observed adverse effects. End points such as auditory thresholds, which seem to be more exclusively regulated by thyroid hormones, may be good candidates for further development into models for low-dose endocrine (thyroid hormone)-related effects. Another problem is the complexity and differences in the mixtures of PCBs that are available commercially, that are present in the environment, or are measured in human samples, e.g., human milk. Different compositions may result in different spectra of toxicity outcomes. Models using defined reconstituted mixtures, relevant to human exposure, may enhance the consistency of findings between different laboratories.

What Is the Quality of the Human Exposure Data (Dose, Timing)?

Although we have voluminous data on PCBs in several studies, the quality of the exposure data from the various human cohorts studied is highly variable. In some cases there is extensive data on congener-specific PCB, PCDD, and PCDF analysis in repetitive samples taken from the same individual over time; in others there may be only a sum PCB measure or just fish consumption data. The methodology used for analyzing PCBs by different laboratories varies greatly. This includes issues such as lipid-adjusted (gravimetrically or triglyceride/cholesterol basis) or wet-weight adjusted, differences in limits of detection, types and numbers of congeners analyzed, etc.

Although there is extensive research literature on the effects of PCBs, failure to adequately describe the test substance or verify the nominal test concentration compromises the utility of some results. Another limitation is the relatively small range of exposure levels within a given human study; this hampers the establishment of significant dose-response relationships. Inter-calibration of laboratory analyses may allow comparisons between several cohorts with different background exposure levels.

What Is the Spectrum of Observed Effects?

The reader is referred to the tables and text presented in this paper.

What Has Been the Utility of Specific Animal and in Vitro Models?

In general, the animal data have been extremely useful in establishing biologic plausibility and suggesting directions for human studies. In vitro and in vivo models have been pivotal in the advancement of our understanding of mechanism(s) of action, of dose-response relationships, of susceptibility differences between strains or species, of critical time windows of exposure and effects, and on hazard identification in general. Studies using wildlife species are of value in assessing health effects when observed effects can be shown not to be due to concomitant exposures.

Recommendations

Confirmation and extension of previous findings in humans should be further investigated. Areas of focus should include neurodevelopmental, thyroid, immunologic, and reproductive effects.

Studies assessing the relation between early-life PCB exposure, thyroid hormone levels, and sensorineural hearing impairment in children are needed. If changes in sensorineural hearing impairment are observed, children should be followed to determine if early impairment results in later deficits in verbal ability.

End points that are more exclusively regulated by single hormonal influences, such as sensorineural hearing and thyroid hormone regulation, should be further studied and developed into validated models for in vivo tests for potential effects of endocrine disruptors.

Given the complex nature of mixtures of PCBs that human individuals are exposed to and the dependency of toxic outcome to the congener composition of mixtures, it is essential to design and distribute environmentally relevant reconstituted PCB mixtures to improve comparability of studies and consistency of results.

A research priority is for studies in appropriate animal models (including wildlife animal models) to determine if there is a causal relationship between PCB congeners, endocrine changes, and developing neurologic parameters. Characterization of dose-response relationships should be a central objective of such studies.

When interpreting study results that appear to be key to establishing an effect (or lack of effect), the quality and completeness of the characterization of the test materials should be part of the interpretation. Analytical chemical criteria should be developed to aid in the objective analysis of such data. The analytical criteria should promote consistency among studies in the PCB congeners measured, with detailed methodology.
EVALUATING RISK FROM LOW-DOSE PCB EXPOSURE

and quality assurance/quality control information presented for all studies. Details on methods of PCB determination for individual congeners, including recoveries and limits of detection, should be reported. The method of lipid determination and adjustment should be included. For truncated data, the number of samples included in any averaged data set should be stated and the methods used to deal with values below the limit of detection must be explained.

Because the distribution of PCB congeners varies with lipid content, this distribution must be determined in order to apply a lipid adjustment to a particular sample matrix to be used as an indication of body burden.

Ideally, a proficiency program would be established to certify all laboratories performing congener-specific analyses. Proficiency samples would be available for all relevant sample matrices, including serum, plasma, whole blood, milk, fat, and relevant tissues as needed. Proficiency would be demonstrated by participating laboratories on a regular basis. This program would contain the analyses at concentrations normally encountered in population studies. Lipid analysis would be included in the proficiency program.

Vectors of exposure and the resulting levels of PCBs in human populations need to be characterized more fully. There is little data on foods that include meats, fish, whole blood, milk, fat, and relevant tissues as needed. Proficiency would be demonstrated by participating laboratories on a regular basis. This program would contain the analyses at concentrations normally encountered in population studies. Lipid analysis would be included in the proficiency program.

Characterization of congener distributions in human tissues of interest is needed, especially for the OH- and sulfonated PCB metabolites.

Interlaboratory quality control of exposure data should stimulate the interactions and comparability of data from various study cohorts with different background exposure levels to PCBs. This will enhance the quality of estimates of dose–response relationships.

Issues of analytical quality and composition of mixtures for experimental studies should be coordinated by a working group under the auspices of an international organization.

REFERENCES AND NOTES


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EVALUATING RISK FROM LOW-DOSE PCB EXPOSURE


Environmental Health Perspectives (EHP) is a forum for the discussion of issues in environmental health, and several formats have been devised for that purpose. All scientific articles are subject to rigorous peer review. The primary criteria for publication are environmental significance and scientific quality. Articles are generally published online within eight weeks after acceptance. Publication in paper form will then occur within about three to four months after Internet publication.

Environmental science and medicine is made up of many fields; therefore, we are prepared to consider scientific progress in all of them. Cross-fertilization and serendipity have proven to be extremely important processes in the advancement of science in general, and this must hold true for the science of environmental health. We will consider for publication articles ranging from the most basic molecular biology to environmental engineering. We particularly encourage those researchers concerned with mechanisms of toxicity and new approaches for detecting and/or remediating environmental damage. We also encourage the submission of articles related to the identification and characterization of genes involved in the manifestation of environment-related diseases.

Opinions and ideas based on scientific observation and argument are welcome. Although the expression of opinions may lead to debate and disagreement, such reactions are healthy and can lead to new research and discoveries. Presentation of ideas and opinions will be promoted, but our policy is to strive for objectivity and balance.

While the condition of all forms of life is of concern to our readers, the ultimate effect of environmental degradation is on human health and, in this regard, our intention is to serve both the scientific and medical communities. Environment-related diseases are a reality of everyday life for practicing physicians and, in order that they might be rendered more aware of current problems, we feature a section dedicated to the examination and evaluation of specific case records. Cases presented must be scholarly, scientifically rigorous, and devoid of unsubstantiated anecdotal opinion.

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Perspectives

The journal is a forum for the expression of ideas and opinions. Opinions and ideas should be carefully considered and based on scientific principles. All articles are subject to peer review. Four formats are offered:

Editorial statements are published by our editors, members of our editorial board, and occasional guest editors. These statements focus attention on important or neglected areas of environmental health, offer opinions and ideas, and stimulate discussion.

Commentaries are up-to-date articles that present ideas and opinions offering perspective and insight on a particular topic. Data may be included to substantiate arguments. Abstracts are required and articles must be appropriately referenced.

Reviews are narrowly focused articles that emphasize recent developments in a particular field of research. Lengthy historical perspectives are not appropriate.

Correspondence is encouraged. Opinions, perspectives, and insight are welcome. Comments on articles published in EHP are also welcome, but criticism will always be balanced by the opportunity for defense and clarification.

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This section is targeted to medical workers and others engaged in the environmental and occupational health arenas. Articles are subject to peer review.

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Research Articles are original manuscripts reporting scientific research and discovery in the broad field of environmental health. Research articles may come from any field of scientific research, from the most basic molecular biology and biochemistry to atmospheric physics, ecology, and engineering. The criteria for publication are weighted toward scientific quality and environmental significance. The work will be assessed according to its originality, scientific merit, and experimental design; the manuscript will be evaluated on the basis of its conciseness, clarity, and presentation. We also attempt to address certain ethical problems during the review process. We require assurances that all human and animal subjects have been treated humanely and with due regard for the alleviation of suffering. Manuscript review also considers scientific integrity as part of the process.

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Workshop Summaries are reports by expert scientific committees that include reviews of existing information and that summarize research findings on specific topics, present new information, and recommend methods, courses of action, or further research needs for the scientific community. Abstracts are required for Workshop Summaries.

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The Environews section provides up-to-date information on important issues in environmental health, covering a variety of areas including but not limited to policy, legislative, and regulatory actions; innovative technological and conceptual research advances; conference and meeting summaries; and emerging environmental problems. The Environews section consists of several components:

Forum articles are brief reports on topics of environmental health significance such as recent research advances, national and international meetings, contamination...