HALOGENATED HYDROCARBONS, TOXICITY AND ENVIRONMENTAL IMPACT

1. Introduction

Chlorinated biphenyls, chlorinated naphthalenes, benzene hexachloride, [608-73-1], and chlorinated derivatives of cyclopentadiene are no longer in commercial use because of their toxicity. However, they still impact on the chemical industry because of residual environmental problems. This article discusses the toxicity and environmental impact of these materials.

2. Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) typify halogenated aromatic hydrocarbons (HAHs), industrial compounds, or by-products that have been widely identified in the environment and chemical waste dumpsites (1–8). Other HAHs include the polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), diphenyl ethers (PCDEs), naphthalenes (PCNs), and benzenes (PCBzs). PCBs were used in industry as heat-transfer fluids, organic diluents, lubricant inks, plasticizers, fire retardants, paint additives, sealing liquids, immersion oils, adhesives, dedusting agents, waxes, and as dielectric fluids for capacitors and transformers. After the initial detection of PCBs in the environment in the late 1960s, several studies confirmed their widespread occurrence throughout the global ecosystem. These studies led to the initial ban on all open uses of PCBs in the early 1970s (8–17) and a later ban on their closed uses as dielectric fluids in transformers and capacitors. New transformers and capacitors, as well as PCB-containing electrical equipment, are now filled with alternative fluids.

2.1. Chemistry and Environmental Impact. PCBs are synthesized by the chlorination of biphenyl and the resulting products are designated according to their percent (by weight) chlorine content (2). For example, Aroclors 1221, 1242, and 1260 contain 21, 42, and 60 wt% chlorine. The commercial Aroclors

Table 1. **Estimated Production and Disposition of PCBs**[a]

	United States, 10^6 kg	Worldwide, 10^6 kg
production/use	610	1200
mobile environmental reservoir	82	400
static reservoirs		
in service	340	
dumps	130	
Total static	*470*	*800*

[a] Ref. 8.

were produced by the Monsanto Chemical Corp. and similar PCB mixtures were manufactured worldwide by other chemical companies. Over 600 million kg of commercial PCBs were produced in the United States and the estimated worldwide production is approximately double this quantity (Table 1). Properties of the commercial PCBs varied from highly fluid liquids (Aroclor 1221) to viscous liquids or solids. All of these preparations contained a complex mixture of isomers and congeners and as the degree of chlorination increased, there was a corresponding increase in the relative concentrations of the more highly chlorinated congeners. There are 209 possible PCBs and the properties of these commercial mixtures and the individual PCBs have been extensively investigated. More recent studies indicate that the commercial PCBs contained 132 different compounds (18).

Environmental problems associated with PCBs are the result of a number of factors. Several open uses of PCBs have resulted in their direct introduction into the environment, eg, organic diluents; careless PCB disposal practices have resulted in significant releases into aquatic and marine ecosystems; higher chlorinated PCBs are very stable in their persistence in different environmental matrices; and by a variety of processes (Fig. 1) PCBs are transported throughout the global ecosystem and preferentially bioconcentrate in higher trophic levels of the food chain.

Table 2. **Coplanar Polychlorinated Biphenyls**

PCB isomer	Structure number	Molecular formula	CAS Registry number
Tetrachlorobiphenyls		$C_{12}H_6Cl_4$	[26914-33-0]
3,4,4′,5	(**2**)		[70362-50-4]
3,3′,4,4′	(**3**)		[32598-13-3]
Pentachlorobiphenyls		$C_{12}H_5Cl_5$	[25429-29-2]
3,3′,4,4′,5	(**4**)		[57465-28-8]
2,3′,4,4′,5′	(**6**)		[65370-44-3]
2,3,4,4′,5	(**7**)		[74472-37-0]
2,3′,4,4′,5	(**8**)		[31508-00-6]
2,3,3′,4,4′	(**9**)		[32598-14-4]
Hexachlorobiphenyls		$C_{12}H_4Cl_6$	[26601-64-9]
3,3′,4,4′,5,5′	(**5**)		[32774-16-6]
2,3,3′,4,4′,5′	(**10**)		[69782-90-7]
2,3,3′,4,4′,5	(**11**)		[38380-08-4]
2,3′,4,4′,5,5′	(**12**)		[52663-72-6]
Heptachlorobiphenyl		$C_{12}H_3Cl_7$	[28655-71-2]
2,3,3′,4,4′,5,5′	(**13**)		[39635-31-9]

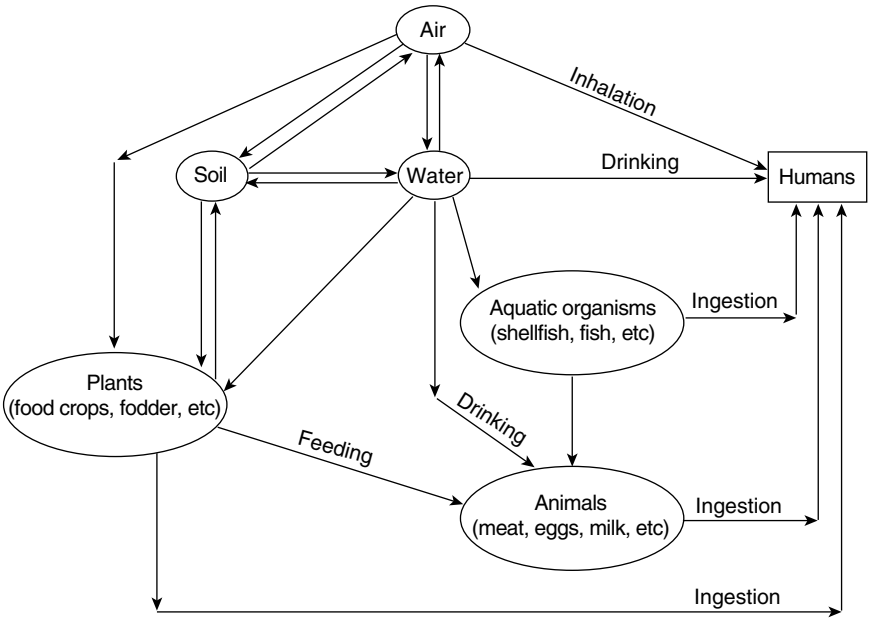


Fig. 1. Transport routes for PCBs and related halogenated aromatic hydrocarbons in the environment.

PCBs have been identified in ambient air samples from diverse locations (15–17,18). In one study of the atmospheric levels of several halogenated aromatic hydrocarbons around Kobe, Japan (19), the average concentration of PCBs was 2800 pg/m^3, whereas the PCDD and PCDF levels were 8.6 and 8.8 pg/m^3, respectively. The PCB levels were probably the result of emissions from sites where commercial PCBs were spilled or dumped, whereas the other compounds were from combustion-derived sources. PCBs are also routinely identified in aquatic and marine sediments at highly variable levels dependent on the proximity to a point source pollution problem.

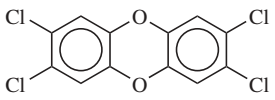
The identification of PCB residues in fish, wildlife, and human tissues has been reported since the 1970s (9–13,20–26). The results of these analytical studies led to the ultimate ban on further use and production of these compounds. The precise composition of PCB extracts from biota samples is highly variable and depends, in part, on the specific analyte and the commercial PCB preparations associated with a contaminated area (14). PCBs found in a composite human milk sample from Michigan (26) were highly complex, and the congener composition and their relative concentrations did not resemble any of the commercial PCB preparations. This fact raises obvious problems with regard to the hazard assessment of PCB mixtures (27).

2.2. Commercial PCBs: Toxic and Biochemical Effects. PCBs and related halogenated aromatic hydrocarbons elicit a diverse spectrum of toxic and biochemical responses in laboratory animals dependent on a number of factors including age, sex, species, and strain of the test animal, and the dosing regimen

(single or multiple) (27–32). In Bobwhite and Japanese quail, the LC_{50} dose for several different commercial PCB preparations ranged from 600 to 30,000 ppm in the diet; the LC_{50} values for mink that were fed Aroclors 1242 and 1254 were 8.6 and 6.7 ppm in the diet, respectively (8,28,33). The toxic responses elicited by most PCB preparations are also observed for other classes of HAHs (27–32) and include a progressive weight loss not simply related to decreased food consumption and accompanied by weakness, debilitation, and ultimately death, ie, a wasting syndrome; lymphoid involution, thymic, and splenic atrophy with associated humoral and/or cell-mediated immunosuppression and/or associated bone marrow and hematologic dyscrasia; a skin disorder called chloracne accompanied by acneform eruptions, alopecia, edema, hyperkeratosis, and blepharitis resulting from hypertrophy of the Meibomian glands; hyperplasia of the epithelial lining of the extrahepatic bile duct, the gall bladder, and urinary tract; hepatomegaly and liver damage accompanied by necrosis, hemorrhage, and intrahepatic bile duct hyperplasia; hepatotoxicity also manifested by the development of porphyria and altered metabolism of porphyrins; teratogenesis, developmental and reproductive toxicity observed in several animal species; carcinogenesis as caused by PCBs in laboratory animals and primarily associated with their effects as promoters; and endocrine and reproductive dysfunction, ie, altered plasma levels of steroid and thyroid hormones with menstrual irregularities, reduced conception rate, early abortion, excessive menstrual and postconceptional hemorrhage, and anovulation in females, and testicular atrophy and decreased spermatogenesis in males.

The biochemical responses elicited by PCBs are also numerous and include the induction of CYP1A1 and CYP1A2 gene expression and the associated monooxygenase enzyme activities, ie, aryl hydrocarbon hydroxylase (AHH) and ethoxyresorufin *O*-deethylase (EROD), and several other cytochrome P-450 dependent monooxygenases; the induction of steroid metabolizing enzymes, DT diaphorase, UDP glucuronosyl transferase, epoxide hydrolase, glutathione (*S*)-transferase, and δ-aminolevulinic acid synthetase; increased Ah receptor binding activity; decreased uroporphinogen decarboxylase activity; and decreased vitamin A levels (27).

2.3. Structure–Function Relationships. Since PCBs and related HAHs are found in the environment as complex mixtures of isomers and congeners, any meaningful risk and hazard assessment of these mixtures must consider the qualitative and quantitative structure–function relationships. Several studies have investigated the structure–activity relationships for PCBs that exhibit 2,3,7,8-tetrachlorodibenzo-*p*-dioxin [1746-01-6] (**1**) (TCDD)-like activity (27,28,34–43).



(**1**)

Figure 2 illustrates the two primary classes of PCBs that exhibit this type of activity, viz, the coplanar PCBs and their monoortho coplanar analogues. The

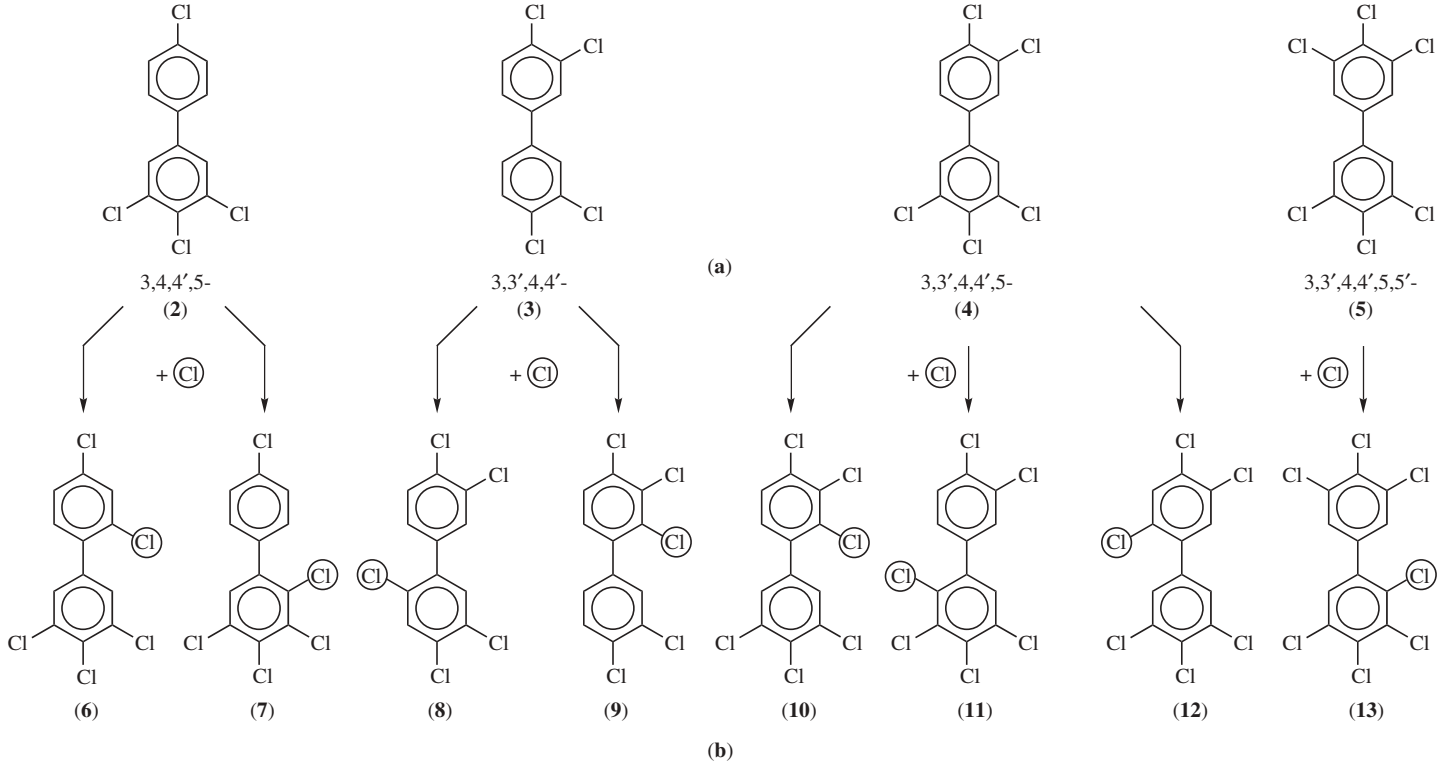


Fig. 2. Toxic PCB congeners: coplanar (**a**) and monoortho coplanar compounds (**b**). See Table 2.

coplanar PCBs, 3,4,4′,5-tetrachlorobiphenyl, 3,3′,4,4′-tetrachlorobiphenyl, 3,3′,4,4′,5-pentachlorobiphenyl, and 3,3′,4,4′,5,5′-hexachlorobiphenyl, which are substituted in both para, at least two meta, and no ortho positions, are the most toxic members of the class of halogenated aromatics. The relative toxic and biochemical potencies of the coplanar PCB congeners exhibit considerable variations that are dependent on the specific response and the test species.

The data show that 3,3′,4,4′,5-pentachlorobiphenyl is the most toxic coplanar PCB congener and the 2,3,7,8-TCDD 3,3′,4,4′,5-pentachlorobiphenyl potency ratios are 66:1 (body weight loss, rat); 8.1:1 (thymic atrophy, rat); 10:1 (fetal thymic lymphoid development, mouse); 125:1 (AHH induction, rat); 3.3/1 (AHH induction, hepatoma H-4-II E cells, rat); and 100/1 (embryo hepatocytes, chick). Both the 3,3′,4,4′-tetra- and 3,3′,4,4′,5,5′-hexachlorobiphenyl congeners are considerably less toxic than 3,3′,4,4′,5-pentachlorobiphenyl and their relative potencies are highly variable. Results from *in vivo* studies in the rat have shown that 3,3′,4,4′-tetrachlorobiphenyl is >30 times less toxic than 3,3′,4,4′,5,5′-hexachlorobiphenyl, whereas in most of the *in vitro* assays these compounds exhibit similar potencies or the reverse order of potency. Using a potency scheme relative to TCDD, toxic equivalence factors (TEFs) of 0.1, 0.05, and 0.01 for 3,3′,4,4′,5-pentachlorobiphenyl, 3,3′,4,4′,5,5′-hexachlorobiphenyl, and 3,3′,4,4′-tetrachlorobiphenyl, respectively, have been assigned (27) (TEF for TCDD = 1.0). Similarly, the relative potencies for the monoortho coplanar PCBs (Fig. 2) were also dependent on the test animal/cell and the response; however, for risk assessment purposes, a TEF value of 0.001 was provisionally assigned to this group of PCB congeners (27). Other structural classes of PCBs also exhibit TCDD-like activities (44); however, the potential contribution of these congeners to the TCDD-like activity of commercial mixtures and PCBs in environmental samples is minimal (27).

The TEF values for PCBs and related halogenated aromatics can be utilized for the hazard and risk assessment of these compounds in environmental mixtures. This subgroup of congeners constitutes only a small fraction of the total number of possible PCBs. Therefore, the proposed TEFs for PCBs do not account for the potential toxicity of the non-TCDD-like congeners or their interactive effects. There are several reports showing that some members of this structural class of PCBs elicit biochemical and toxic responses (30). For example, several PCB congeners resemble both phenobarbital (PB) and dexamethasone as inducers of hepatic microsomal cytochrome P-450 isozymes, ie, cytochromes *b*/*e* and cytochrome *p*, respectively (30). Both 2,2′,4,4′,5,5′-hexachlorobiphenyl [35065-27-1] and hexabromobiphenyl have been characterized as PB-type inducers of hepatic drug-metabolizing enzymes (30). Moreover, like PB, 2,2′,4,4′,5,5′-hexabromobiphenyl [59080-40-9] promoted diethylnitrosamine-initiated enzyme altered foci in Sprague-Dawley rats using a two-stage hepatocarcinogenesis protocol (45). These data suggest that the corresponding PCB congeners may also exhibit comparable tumor-promoting activities, and it is clear that future studies should focus on the development of hazard and risk assessment approaches for those congeners not covered in the current TEF schemes (27).

2.4. Human Health Effects. Any assessment of adverse human health effects from PCBs should consider the route(s) of and duration of exposure; the

composition of the commercial PCB products, ie, degree of chlorination; and the levels of potentially toxic PCDF contaminants. As a result of these variables, it would not be surprising to observe significant differences in the effects of PCBs on different groups of occupationally exposed workers.

The accidental leakage of a PCB-containing heat-transfer fluid into rice oil resulted in serious poisoning incidents in Japan (Yusho poisoning, 1966–1968) and Taiwan (Yucheng poisoning, 1978–1979) (46–50). Many of the poison victims received a relatively high oral dose of PCBs over a limited time period (from weeks to months) and these groups were used as a benchmark for the effects of PCBs on humans. However, it is clear from the results of several studies that the principal etiologic agents in the Yusho/Yucheng accidents were not the PCBs but the unusually high levels of PCDFs found as contaminants in the PCB-containing fluid (51–56).

Several studies have reported relatively high levels of PCBs in the serum or adipose tissues of occupationally exposed individuals, eg, >3000 ppb in the serum (57,58). Not surprisingly, after these exposures were terminated, the PCB serum concentrations tended to decrease (59–61).

Chloracne and related skin problems have been observed in several groups of workers and it was suggested that the air concentrations of commercial PCBs >0.2 mg/m^3 were associated with this effect (62). It was also reported that after occupational exposure to PCBs was terminated there was a gradual decrease in the severity and number of dermatological problems in the exposed workers, and this paralleled a decrease in their serum levels of PCBs (61).

The effects of occupational exposure to PCBs on the concentrations of several serum clinical, chemical, and hematological parameters have been reported (58). Mildly elevated SGOT and γ-glutamyl transpeptidase (GGTP) suggest some liver damage and induction of hepatic monooxygenase enzymes; these results are similar to those observed in animal studies. In one study, it was reported that as PCB serum levels decreased over time the GGTP serum levels also decreased to normal values. A relatively high incidence of pulmonary dysfunction in capacitor-manufacturing workers has been reported (62) with symptoms including coughing, 13.8%; wheezing, 3.4%; tightness in the chest, 10.1%; and upper respiratory or eye irritation, 48.2%. The pulmonary toxicity of PCBs in laboratory animals has not been widely reported (30).

Retrospective mortality studies (63) in 2567 workers (>3 months employment) from two capacitor manufacturing plants indicated that the mortality of the workers in both plants was lower than the control group, and there were no significant increases in either liver or rectal cancer. An update of the mortality study (64) in which seven additional years had elapsed, and therefore there were more deaths in the exposed group, did not alter the initial findings. Otherwise, workplace studies report various effects of PCBs on the incidence of cancer at different organ sites; however, it is apparent that there are no consistent increases in any one cancer in all the epidemiological studies. It is apparent from most reports that workplace exposure to relatively high levels of PCBs results in limited and moderate toxicity in humans. These toxic symptoms appear to be reversible after exposure to PCBs is terminated and this is accompanied by a decline in serum levels of PCBs.

Environmental exposures to PCBs are significantly lower than those reported in the workplace and are therefore unlikely to cause adverse human health effects in adults. However, it is apparent from the results of several recent studies on children that there was a correlation between *in utero* exposure to PCBs, eg, cord blood levels, and developmental deficits (65–68) including reduced birth weight, neonatal behavior anomalies, and poorer recognition memories. At four years of age, there was still a correlation between prenatal PCB exposure levels and short-term memory function (verbal and quantitative). In these studies, the children were all exposed to relatively low environmental levels of PCBs. The potential adverse neurodevelopmental effects of pre- and postnatal exposures to PCBs have continued in North America and Europe, and the results are somewhat variable (69,70). In a followup study on a Michigan cohort exposed to PCBs in the 1980s, there was a significant association between prenatal exposure to PCBs and some neurodevelopmental deficits in 11 year-old children in Michigan (71). In contrast, no association was observed between postnatal exposure to PCBs and these deficits. Since PCB levels in humans have decreased substantially over the past two decades, it was suggested that these impairments were unlikely to be observed in children exposed to current background levels of PCBs (70). Nevertheless, several more recent studies have reported correlations between pre- and/or postnatal PCB exposures with some neurodevelopmental deficits (72,73), and these reports have recently been reviewed (69). It was concluded that "the lack of adequate quantitative exposure data, do not allow the derivation of the degree of risk associated with neurodevelopmental effects at current exposure levels" (69).

3. Polybrominated Diphenyl Ethers

Polybrominated diphenyl ethers (PBDEs) are synthesized by the bromination of diphenyl ether to give PBDE mixtures that are highly stable and resistant to chemical, thermal and biological breakdown (74,75). Several commercial PBDE formulations have been used as flame retardants in electronic equipment, electrical appliances, and building materials. Most formulations contain the more highly brominated PBDE congeners and the octa-decabromo mixtures are the mostly widely used compounds in commercial flame retardants. An estimated 40,000–50,000 metric tons of PBDEs are produced worldwide, and these compounds are among a group of halogenated aromatics used as flame retardants (74,75). Most analytical studies on the occurrence and levels of halogenated aromatic compounds in the environment (including biota) have focused on PCBs, PCDDs, and PCDFs that tend to be decreasing in most regions; however, recent studies have identified levels of PBDEs throughout the global ecosystem including air, water, sediments, fish, wildlife, and humans (76–78). Moreover, in contrast to many other halogenated aromatic pollutants, there is evidence that PBDE levels are increasing. For example, Noren and Meironyte report that PBDE levels in human milk exponentially increased between 1992–1997 and, in 1997, the estimated concentrations in Swedish human milk were approximately 4-ng/g lipid (77). This value is low compared to the 324 ng/g lipid of

total PCBs (77). Nevertheless, the trend of increasing levels of PBDEs is clearly of concern.

3.1. Animal and Human Toxicology. The toxicology of PBDEs has not been extensively investigated and their impacts on human health are unknown (74,75,79,80). Based on analogies with chlorinated biphenyl ethers and PCBs, it is likely that many of the meta/para-substituted analogues will exhibit some Ah receptor agonist activities; however, most of these compounds are not associated with environmental samples. Like most halogenated aromatics, PBDEs induce phase I and phase II hepatic drug-metabolizing enzyme activities in rodents. Since these compounds resemble thyroid hormones, there is concern that PBDEs may affect thyroid hormone action by interacting either with the thyroid hormone receptor or transthyretin (TTR), the thyroid hormone transport protein. Initial studies indicate that although PBDEs did not interact with these receptors, some oxidized PBDE metabolites interacted with TTR (81); however, interactions of PBDEs with human transthyretin have been reported (82). Future studies will be required to determine the potential effects of PBDEs and metabolites on thyroid hormone function.

4. Hydroxylated PCBs

The widespread environmental contamination with DDT and PCBs triggered the concern for the potential adverse impacts of these persistent environmental compounds. However, Hutzinger and co-workers (83) first showed that PCBs were metabolized into hydroxylated metabolites that could then be excreted and thereby provide a pathway for decreasing body burdens of these compounds. However, in 1994, it was reported that hydroxylated-PCBs were present in human serum and wildlife samples, and subsequent studies have identified hydroxy-PCB congeners in wildlife and humans (78,84–86). Most of the hydroxy-PCBs are metabolites of persistent higher chlorinated biphenyls and some of these compounds include 2,2′,3,4′,5,5′-hexachloro-4-biphenylol; 2,3,3′,4′,5-pentachloro-4-biphenylol; 2′,3,3′,4′,5-pentachloro-4-biphenylol; 2,2′,3,3′,4′,5-hexachloro-4-biphenylol; 2,2′,3,3′,4′,5,5′-heptachloro-4-biphenylol; 2,2′,3,4′,5,5′,6-heptachloro-4-biphenylol; and 2,2′,3′,4,4′,5,5′-heptachloro-3-biphenylol.

4.1. Biochemical Effects of Hydroxy-PCBs. 2′,3′,4′,5′-Tetrachloro-4-biphenylol (HO-PCB4) and 2′,4′,6′-trichloro-4-biphenyl (HO-PCB3) were first identified as weakly estrogenic compounds (87) and subsequent studies in several laboratories have demonstrated that the estrogenic activity of most hydroxy-PCBs is weak and some of the congeners identified in humans exhibit both weak estrogen receptor agonist and antagonist activities. In contrast, many of the same hydroxy-PCBs are potent inhibitors of sulfotransferase activities and this response may indirectly increase estrogen levels by preventing sulfation and excretion.

Several studies have also reported that hydroxy-PCBs are highly active ligands for binding TTR (94–96). It has been suggested that interactions of hydroxy-PCBs and other hydroxylated organochlorine (aromatic) compounds may interfere with fetal thyroid hormone transport (97,98) and thereby contribute

to the neurodevelopmental deficits that correlate with exposure to PCBs (65–73). This is an area which is now under investigation in several laboratories and could provide important new data that might clarify the reported associations between exposure to PCBs and neurodevelopmental deficits in children. These effects may also be related to other contaminants and this is an area which requires forther investigation.

5. Polychlorinated Naphthalenes

Polychlorinated naphthalenes (PCNs) are halogenated aromatic hydrocarbons that are no longer produced. They can be synthesized by the chlorination of naphthalene. The commercial products were graded and sold according to their chlorine content (wt%), and used as waxes and impregnants (for protective coatings), water repellents, and wood preservatives (3,6,7).

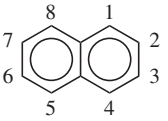
Commercial PCNs were produced by several companies, eg, Koppers Chemical Co., Halochem, Prodelec, Bayer, and ICI, and marketed under a number of trade names including Halowaxes, Nibren waxes, Seekay waxes, and Clonacire waxes. However, the exact yearly or total production figures are obscure. In 1972, the estimated market for PCNs was >2300 t. This figure subsequently decreased as a result of the periodic reported toxicities that have accompanied the production and use of PCNs and the decreased overall utilization of HAHs because of their unacceptable environmental properties.

Like the PCBs, most of the commercial PCNs were complex mixtures of isomers and congeners, although two products, viz, monoPCN and Halowax 1051/N-Wax 80, contained primarily 1-chloronaphthalene [90-13-1], $C_{10}H_7Cl$, and octachloronaphthalene [2234-13-1], $C_{10}C_{l8}$, respectively.

The environmental impact of PCNs has not been extensively investigated and PCNs are not routinely measured in analytical studies of extracts from environmental samples. However, PCNs have been identified in birds of prey in Britain (99) and The Netherlands (100), in a drainage ditch in Florida, and in sediments from San Francisco Bay (101).

5.1. Animal and Human Toxicology. The mammalian toxicology of PCNs has not been studied in detail; however, it is believed that these compounds elicit mixture- and structure-dependent biochemical and toxic responses resembling those reported for PCBs and other toxic HAHs (32). For example, the effects of the commercial Halowax PCNs as microsomal enzyme inducers were dependent on their degree of chlorination. Halowax 1000, the PCN with the lowest degree of chlorination (26 wt%), did not induce AHH activity (102). In contrast, Halowax 1099 (52 wt% Cl) enhanced microsomal AHH activity and cytochrome P-450 content. At dose levels of 600 μmol/kg, Halowaxes 1099, 1013, 1014, and 1051 significantly induced AHH activity (102). Subsequent studies on a limited number of PCN congeners showed that octachloronaphthalene, 1,2,3,4,5,6,7-hepta-1,2,3,4,5,6,8-hepta-, and 1,2,3,4,5,6-hexachloronaphthalene induced rat hepatic microsomal AHH activity, whereas the 1-chloro, 2-chloro-, 1,8-dichloro-, 1,5-dichloro-, 2,7-dichloro-, and 1,2,3,4-tetrachloronaphthalene congeners were inactive. The most active compounds were substituted in three of four of the lateral 2,3,6, or 7 positions and the SARs for PCNs were

comparable to those reported for other HAHs (103,104).

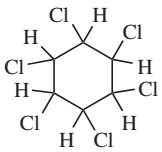


There have been several reported accidental exposures to commercial PCNs. One of the earliest incidents, the poisoning of cattle, was first reported in 1941 in New York State, and became known as X-disease because of its unknown etiology. Eventually it was traced to the use of PCNs as high pressure lubricants in feed pelleting machines which resulted in contamination of the feed and ingestion of the PCNs by the animals (105,106). The symptoms exhibited by the cattle included a thickening of the skin referred to as hyperkeratosis, excess lacrimation and salivation, anorexia, depression, and a decrease in plasma vitamin A. A similar outbreak in cattle was reported in Germany in 1947 (105–109). An isolated case of PCN poisoning involving chickens, referred to as Chick Edema Disease (107) , occurred in 1957 and was the result of contamination of the feed by a mixture of the penta- and hexachlorinated isomers and congeners.

Human incidents have been reported in workers involved in the production or uses of PCNs. In the United States as well as in Germany and Australia, the severity of the PCN-induced toxicosis was higher after exposure to the higher chlorinated PCN mixtures. In humans the inhalation of hot vapors was the most important route of exposure and resulted in symptoms including rashes or chloracne, jaundice, weight loss, yellow atrophy of the liver, and in extreme cases, death (105,107–109).

6. Lindane and Hexachlorocyclopentadiene

Both lindane [58-89-9] (**14**) and hexachlorocyclopentadiene [77-47-4] (**15**) are halogenated hydrocarbons; unlike the PCBs and PCNs, they do not contain an aromatic ring.



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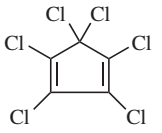

(**15**)

Lindane is one of eight different hexachlorocyclohexane (HCH), $C_6H_6Cl_6$, isomers and its *Chemical Abstract* name is 1α, 2α 3β, 4α, 5α 6β-hexachlorocyclohexane [58-89-9] (γ-HCH or γ-BHC, benzene hexachloride) (110). Commercial products containing lindane are marketed as either a mixture of isomers or as the pure γ-BHC isomer. Not unexpectedly, lindane is a highly stable lipophilic compound and it has been used extensively worldwide as an insecticide. In contrast, hexachloropentadiene, C_5C_{l6}, is an extremely reactive industrial

intermediate used as a chemical intermediate in the synthesis of a broad range of cyclodiene-derived pesticides, which include endosulfan, endrin, heptachlor, and several different organohalogen flame retardants (111).

6.1. Chemistry and Environmental Impact. Lindane is produced by the photocatalyzed addition of chlorine to benzene to give a mixture of isomers. The active γ-HCH isomer can be preferentially extracted and purified. Composition of the technical-grade product is α (65–70%), β (7–10%), γ (14–15%), δ (7%), and ε (1–2%). Lindane has been produced worldwide for its use as an insecticide and for other minor uses in veterinary, agricultural, and medical products.

The relatively high stability and lipophilicity of lindane and its global use pattern has resulted in significant environmental contamination by this hydrocarbon. For example, lindane has been identified in low ppb levels in sediments in the Elbe River, Elbe Estuary, and Corpus Christi Bay (112,113), and in birds from the Falkland Islands (114) and the Shenandoah Valley, Virginia (115) (20 ppb median level, 86% detection frequency). In the National Pesticide Monitoring program (United States), lindane concentrations in fish were 30 ppm (wet weight basis) and the frequency of detection was 16% (116). In contrast, relatively high levels of α-hexachlorocyclohexane [319-84-6] were observed in this study, accompanied by higher frequencies of detection. The mean adipose tissue concentrations of lindane in humans (wet weight basis) has been reported as 19.5 ppb (Germany) and 6.7 ppb (The Netherlands) (117). In surveys of adipose tissue in Canadians, β-hexachlorocyclohexane [319-85-7] is the dominant HCH contaminant with mean levels of 31 ppb with a detection frequency of 100% (118). In another Canadian study, comparable results were obtained and the β-HCH was detected in all samples, whereas the detection frequencies of lindane varied from 0–19% (119). In contrast, studies in the early 1990s showed that β-HCH levels in adipose tissue from individuals in several European countries, such as Italy, Poland, and Spain, were considerably higher (2.26, 0.221, and 2.99 ppm, respectively) than observed in the Canadian studies (120–122). The results suggest that overall lindane contamination may be higher in Europe than in North America. The residues of lindane are probably derived from various foods that contain this compound (123). The environmental impact of lindane on exposed populations has not been determined.

The highly reactive hexachlorocyclopentadiene is rapidly degraded in the environment and is not routinely detected as an environmental pollutant (111).

6.2. Animal and Human Toxicity. The acute toxicity of lindane depends on the age, sex, and animal species, and on the route of administration. The oral LD_{50} in mice, rats, and guinea pigs is 86, 125–230, and 100–127 mg/kg, respectively. In contrast, most of the other isomers were considerably more toxic (124,125). Some of the other toxic responses caused by lindane in laboratory animals include hepato- and nephotoxicity, reproductive and embryotoxicity, mutagenicity in some short-term *in vitro* bioassays, and carcinogenicity (110). The mechanism of the lindane-induced response is not known. Only minimal data are available on the mammalian toxicities of hexachlorocyclopentadiene.

The effects of occupational exposure to lindane have been investigated extensively (126–130). These studies indicated that occupational exposure to lindane resulted in increased body burdens of this chemical; however, toxic effects associated with these exposures were minimal and no central nervous system

disorders were observed. This is in contrast to the polyneuropathies that are often observed after exposure to other haloorganic solvents.

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