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The Role of Structure in the Disposition of Halogenated Aromatic Xenobiotics

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Halogenated aromatic xenobiotics such as the chlorinated and brominated biphenyls, naphthalenes, dibenzodioxins, and dibenzofurans are widespread environmental contaminants. The number, position, and nature of the halogen atoms as well as the structure of the aromatic rings influence the disposition of these chemicals in living systems. Absorption is governed primarily by the physical properties of lipophilicity and solubility. Distribution through the blood occurs by nonspecific binding to plasma proteins and cellular components. Liver and adipose tissue are the major depots. Metabolism is a prerequisite for excretion. The highly substituted isomers tend to be resistant to metabolism. The route of excretion shifts from urine to feces with increasing size and number of halogen atoms. Although pharmacokinetic modeling has allowed some predictions to be made from one compound to another or across species, more information on metabolism is required in order to improve the ability to predict the disposition in humans of this class of toxic environmental pollutants.

Halogenated aromatic hydrocarbons constitute a broad class of compounds with varying structure, uses, environmental occurrence, and toxicity. The nature of the halogen atoms(s) involved and the structure of the aromatic ring(s) determines the physical properties of these molecules as well as influencing the response of biological systems to them. The availability of these compounds to their biological target site is governed by a complex interaction of physical and biological factors. In this paper, the structure of halogenated aromatic hydrocarbons will be correlated with their disposition in living systems. Since extensive reviews have been written on the less complex compounds, such as the halogenated benzenes, only the multiring structures such as the halogenated naphthalenes, biphenyls, dibenzodioxins, and dibenzofurans will be considered. Several recent reviews have concerned the pharmacokinetics of polyhalogenated aromatic hydrocarbons (*1–4*); 2,3,7,8-tetrachlorodibenzofuran (TCDF) (*5*); 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (*6,7*); and a comparison of dioxins and furans (*8*). I shall attempt to emphasize the similarities and differences in the disposition of these compounds as well as discuss the results of some current investigations both in our laboratory and others.

There are 75 possible chlorinated dibenzodioxins and 135 chlorinated dibenzofuran isomers. The total number of chlorinated biphenyl and naphthalene isomers is in the hundreds. Most of these isomers exist in complex industrial mixtures and others have been detected in the environment due both to industrial contamination and to breakdown, rearrangement, and pyrolysis of other halogenated compounds. A wide variety of brominated biphenyls have also been made for industrial purposes but they are less widespread in the environment. Likewise, brominated dioxins, furans, and naphthalenes are rare, although brominated naphthalenes have been shown to exist as toxic impurities in polybrominated biphenyls (PBBs) (*9*). Iodinated and fluorinated biphenyls and dioxins have been synthesized for pharmaceutical and research purposes (*10,11*) but have not been detected as environmental pollutants.

An analysis of the effect of structure on the disposition of these compounds can be divided into the areas of absorption, distribution, metabolism and excretion. Certain general patterns exist in the disposition of these compounds, but these are modulated by both the ring structure and the halogen atoms, varying with type, number, and position.

Absorption into blood is the first step which must occur for a compound to be able to reach its site of action other than direct local effects, for example, on skin. All of the halogenated dioxins, furans, biphenyls, and naphthalenes are uncharged, nonpolar, lipophilic compounds whose absorption occurs by diffusion across the semipermeable membranes of the body. In general, the ability of a compound to diffuse across membranes is related to its solubility in the membrane or its hydrophobicity, a property commonly approximated by measuring a partition coefficient between an organic and aqueous solvent. The partition coefficients determined between

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Table 1. Partition coefficients of representative aromatics.

Compound	Log p[a]	Reference
Benzene	2.13	(*12*)
Fluorobenzene	2.27	(*12*)
Chlorobenzene	2.84	(*12*)
Bromobenzene	2.99	(*12*)
Iodobenzene	3.25	(*12*)
Dichlorobenzene	3.38	(*12*)
Naphthalene	3.37	(*12*)
Biphenyl	4.07	(*13*)
4-Chlorobiphenyl	4.26	(*14*)
2-Chlorobiphenyl	4.54	(*15*)
3-Chlorobiphenyl	4.95	(*15*)
6-Chlorobiphenyl	5.08	(*15*)
2,2′-Dichlorobiphenyl	5.58; 5.18	(*12,14*)
4,4′-Dichlorobiphenyl	4.04	(*14*)
2,3,2′,3′-Tetrachlorobiphenyl	4.63	(*14*)
2,3,5,6-Tetrachlorobiphenyl	5.46	(*14*)
3,4,3′,4′-Tetrachlorobiphenyl	6.04	(*14*)
3,5,3′,5′-Tetrachlorobiphenyl	6.85	(*14*)
2,4,5,2′,5′-Pentachlorobiphenyl	6.11	(*12*)
2,4,5,2′,4′,5′-Hexachlorobiphenyl	6.72	(*12*)
3,5-Dibromobiphenyl	5.78	(*14*)
3,5,4′-Tribromobiphenyl	6.41	(*14*)
3,5,3′,5′-Tetrabromobiphenyl	7.41	(*14*)
Dibenzofuran	4.12	(*13*)
2,3,7,8-Tetrachlorodibenzodioxin	5.38	(*16*)

[a] p = partition coefficient (n-octanol/water); log p is taken directly or calculated from cited reference.

n-octane and water are given for a number of aromatic hydrocarbons in Table 1. It is clear that lipid solubility, which is reflected by an increased solubility in octanol, increases as the ring complexity increases and as the size and number of the halogen atoms vary. Thus, naphthalene is less soluble in water than benzene, while dibenzofuran is much more lipophilic than naphthalene. Iodobenzene is less water-soluble than fluorobenzene, and dichlorobenzene is more lipophilic than monochlorobenzene. Likewise, tetrabromobiphenyl is relatively more soluble in n-octanol than is tetrachlorobiphenyl. It is interesting that TCDD has a partition coefficient in the range of the tetrachlorobiphenyls. However, because of the extremely limited solubility of the highly halogenated aromatics in water, the partition coefficients may be underestimated. Also, many of the partition coefficients in the literature are calculated from solubility data and not actually measured, which may impart some error (*15*).

Absorption across the body surfaces is primarily governed by lipid solubility. However, for compounds with extremely high partition coefficients (i.e., >7), absorption into the blood tends to be less than expected. This may reflect either the extreme insolubility in the aqueous milieu of the body fluids, since chemicals must be in solution in order to be absorbed—particulates can only be taken up by endocytic means which seem to play little role in the absorption of xenobiotics—or because they are so lipid-soluble that they become essentially trapped in the lipid bilayer of cellular membranes instead of continuing to cross from one side to the other. The extent of absorption of several halogenated aromatics is given in Table 2. While all the less halogenated compounds seem to be completely absorbed, absorption tends to decrease with increasing halogenation (*25*). The relative lack of toxicity of compounds such as octachlorodibenzodioxin (*22*) may in part be due to its low extent of absorption. Of course, absorption can also be strongly influenced by the vehicle in which the compound is administered. Poiger and Schlatter (*26*) reported that the presence of dirt or charcoal significantly reduced the oral absorption of TCDD. TCDD in vaseline was less absorbed dermally than if it were in polyethylene glycol. These results are supported by a recent study by McConnell and co-workers (*27*) which has shown that three to five times higher levels of TCDD are needed to cause toxic effects in guinea pigs when the animals are treated orally with TCDD mixed with dirt as compared to TCDD in corn oil. In contrast, no differences in oral absorption were detected when hexabromonaphthalene was given in corn oil or in a mixture of Emulphor:ethanol:water (1:1:2) (*24*). Emulphor EL-620 is a polyethoxylated vegetable oil (GAF Corp., New York, NY) that has been used successfully in solubilizing highly lipophilic compounds.

Table 2. Relative absorption after oral exposure.

Compound	Relative absorption	Reference
4-Chlorobiphenyl	+ + + +	(*17*)
4,4′-Dichlorobiphenyl	+ + + +	(*17*)
2,4,5,2′,5′-Pentachlorobiphenyl	+ + + +	(*17*)
2,4,5,2′,4′,5′-Hexachlorobiphenyl	+ + + +	(*17*)
2,4,5,2′,4′,5′-Hexabromobiphenyl	+ + + +	(*18*)
2,3,7,8-Tetrachlorodibenzofuran	+ + + +	(*19–21*)
1,2,4,6,8,9-Hexachlorodibenzofuran	+ +	Birnbaum, unpublished
2,3,7,8-Tetrachlorodibenzodioxin	+ + +	(*7*)
1,2,3,4,6,7,8,9-Octachlorodibenzo-p-dioxin	+	(*22*)
1,2-Dichloronaphthalene	+ + + +	(*23*)
1,2,3,4,6,7-Hexabromonaphthalene	+ +	(*24*)

Once a compound is absorbed, its distribution throughout the body is governed by its transport in the blood and its ability to diffuse through the membranes between the blood vessels and the tissues. Transport through the blood may involve only the free chemical. However, in the majority of cases, and especially where such lipophilic compounds as the halogenated aromatics are concerned, transport involves adsorption of the compounds to components in the blood, both in whole blood and in plasma. This binding was first suggested by the difficulty observed in extracting the highly lipophilic 2,4,5,2′,5′-pentachlorobiphenyl from blood, which is a hydrophilic medium, into organic solvents (*28*). Association of other chlorinated hydrocarbons having low water solubility, such as halogenated insecticides, has been observed with erythrocytes, albumin, and various other plasma proteins (*29*). Lipoproteins, in particular,

are involved in the transport of such hydrophobic molecules. The binding of such compounds by plasma proteins was found to be nonspecific. Becker and Gamble (*30*) reported that both albumin and low-density lipoprotein bind 2,4,5,2′,4′,5′-hexachlorobiphenyl effectively *in vitro*. They suggested that the binding of various polychlorinated biphenyl (PCB) isomers will depend on three properties of the chemicals: hydrophobicity, aromaticity, and steric configuration. Maliwal and Guthrie (*31*) reported that both 2,4,5,2′,4′,5′-hexachlorobiphenyl and 3-chlorobiphenyl were rapidly bound *in vitro* by albumin and by all three classes (high density, low density, and very low density) of lipoproteins. The bound hydrocarbons rapidly exchanged between the different protein classes. However, at equilibrium, the low-density lipoprotein fraction contained at least half of the halogenated aromatic compound, while the very low-density fraction accounted for less than 15%. The rapid transfer between lipoproteins may help explain the rapid uptake of halogenated aromatic hydrocarbons from blood by the tissues. Vomachka and co-workers (*32*) have recently shown that gamma globulin can also compete with lipoproteins and albumin for binding 2,4,5,2′,4′,5′-hexachlorobiphenyl.

Matthews et al. (*29*) examined the binding of a series of halogenated biphenyls to blood proteins both *in vivo* and *in vitro*. They observed that as the degree of halogenation increased, not only did lipid solubility increase as expected from the partition coefficients, but the binding to lipoproteins also increased. Thus, while only 30% of biphenyl bound to the lipoprotein fraction *in vitro*, 40% of 4-chlorobiphenyl, 50% of 4,4′-dichlorobiphenyl, 60% of 2,4,5,2′,5′-pentachlorobiphenyl, and 80% of both 2,4,5,2′,4′,5′-hexachloro- and hexabromobiphenyls partitioned into the lipoprotein fraction. The opposite situation existed with the binding to cellular components of the blood, but factors other than lipid solubility also seemed involved. Thus, transport of halogenated aromatics in the blood seems to occur by a partitioning process into various lipid-rich phases rather than by specific binding. The compounds can then partition from blood components into cellular membranes thus accounting for the rapid transfer observed *in vivo* from blood to tissues.

Given the highly lipophilic nature of the halogenated aromatic compounds, it is not surprising that their transfer from mother to fetus or from nursing mother to the neonate reflects their partitioning into lipid-rich phases. Very low levels of TCDD are actually passed across the placenta from mother to fetus (*33*). In fact, fetal levels of dioxin are at least 100-fold lower than levels found in the maternal liver. Studies in our laboratory (Birnbaum and Weber, unpublished observations) have shown that less than 0.1% of the total dose of either TCDD or TCDF appeared in the fetuses one day after acute exposure on day 11 of gestation. Nagayama and co-workers (*34*) reported that less than 1% of the total amount of a dietary mixture of polychlorinated dibenzofurans ingested by dams was transferred to the fetuses. However, transfer of the compounds through the milk was extensive, a situation previously reported for PCBs (*35*). The more highly chlorinated PCBs, such as 2,4,5,2′,4′,5′-hexachlorobiphenyl, 2,3,4,2′,4′,5′-hexachlorobiphenyl and 2,3,4,5,2′,3′,4′,5′-octachlorobiphenyl, were more transferable to the offspring through the milk than were the lower chlorinated congeners, 2,4,4′-tri-, 2,5′,3′,4′-tetra-, and 2,4,5,2′,5′-pentachlorobiphenyl.

After absorption, the halogenated aromatic compounds are rapidly distributed throughout the body into various tissues. For example, over 90% of an intravenous dose of 2,4,5,2′,5′-pentachlorobiphenyl moved from the blood into the tissues within 10 min after treatment (*28*). In general, there seems to be little preferential deposition in most tissues. A high percentage of the dose is frequently found in muscle at early time points after injection due to the large volume of this tissue. high initial concentrations are observed in highly perfused tissues such as the adrenal glands (*19*). The primary tissue deposits, however, are liver, adipose tissue, and skin. Brandt (*36*) also observed concentration of specific PCB isomers in the lungs.

There is an interesting correlation between structure and liver/adipose tissue content as seen in Table 3. All the chlorinated biphenyls and hexabromobiphenyl show low levels in liver relative to that seen in adipose tissue. However, the dioxins, furans, and naphthalenes concentrate more in liver than in fat. There also seems to be a tendency for higher levels of halogenation in these compounds to result in higher liver concentrations. The values given in Table 3 are all taken from studies on the rat. Liver/adipose ratios for dichlorobiphenyl are similar in monkeys and dogs (*39*), as are the values in mice for TCDF (*20*). However, the relative liver/adipose tissue levels of TCDD (*40*) or TCDF (*21*) in the guinea pig are lower than in the rat. Hamsters also have lower liver TCDD levels (*41*).

The affinity of these compounds for adipose tissue is most clearly shown in a series of studies in which the distribution of various halogenated aromatic hydrocar-

Table 3. Relative liver and adipose tissue constants in the rat.

Compound	Liver/adipose (% TD)	Reference
4-Chlorobiphenyl	0.16	(*17*)
4,4′-Dichlorobiphenyl	0.12	(*17*)
2,4,5,2′,5′-Pentachlorobiphenyl	0.12	(*17*)
2,4,5,2′,4′,5′-Hexachlorobiphenyl	0.17	(*17*)
2,3,6,2′,3′,6′-Hexachlorobiphenyl	0.05	(*37*)
2,4,6,2′,4′,6′-Hexachlorobiphenyl	0.11	(*37*)
2,3,5,2′,3′,5′-Hexachlorobiphenyl	0.16	(*37*)
4-Iodobiphenyl	0.08	(*11*)
2,4,5,2′,5′-Hexabromobiphenyl	0.43	(*18*)
2,3,7,8-TCDD	6.22	(*38*)
2,3,7,8-TCDF	1.30	(*19*)
1,2,4,6,7,9-Hexachlorodibenzofuran	1.82	Birnbaum, unpublished
1,2-Dichloronaphthalene	1.50	(*23*)
1,2,3,4,6,7-Hexabromonaphthalene	2.51	(*24*)

bons varied with the body composition of the animals in question. In 1981, this laboratory (*20*) reported that 2,3,7,8-tetrachlorodibenzofuran persisted twice as long in DBA/2J (D2) mice as in C57BL/6J (B6) mice. By measuring the levels of dissectable fat, it was observed that the D2 mice had approximately 60% more adipose tissue than the B6 mice. It was suggested that this higher adipose tissue content might serve as a protective reservoir for the animal, i.e., while TCDF is in the fat it cannot execute its toxic effects. This difference in body composition could in part explain the differential sensitivity that these two strains of mice exhibit towards this class of halogenated polyaromatic compounds. These results were extended and confirmed by Gasiewicz et al. (*42*), who studied the distribution of TCDD in B6, D2, and B6d2F1 hybrid mice. As was true for TCDF, more of the dose of TCDD was present in the adipose tissue and persisted for twice as long in the "fat" D2 as opposed to the "lean" B6 or B6D2F1 hybrid. They observed that the D2 mice possessed approximately 90% more dissectable adipose tissue than the B6 mice and supported the hypothesis that the sequestration of lipophilic compounds like TCDD in adipose tissue stores could contribute to the decreased sensitivity of the D2 relative to the B6 mice.

One of the first reports emphasizing the role of adipose tissue in protection against halogenated hydrocarbon toxicity was that of Matthews and Anderson (*17*), who observed that starvation of rats which had previously been acutely exposed to 2,4,5,2′,4′,5′-hexachlorobiphenyl resulted in mobilization of the chemical stored in the fat, resulting in elevation of blood and liver levels and an increase in the amount excreted. This observation was further examined by Wyss et al. (*43*) who investigated the distribution and excretion of 2,4,5,2′,4′,5′-hexachlorobiphenyl in severely dietary restricted rats. They concluded that while in growing rats highly lipophilic compounds like 2,4,5,2′,4′,5′-hexachlorobiphenyl appear to be irreversibly stored in adipose tissue, this situation can be reversed by drastic reduction in volume of this depot. The storage role of adipose tissue was also reported by Birnbaum (*44*), who compared the distribution of 2,4,5,2′,4′,5′-hexachlorobiphenyl in senescent rats having large adipose tissue contents to that previously observed in young growing rats in the same laboratory (*17,37*). In the old rats (24 months), the volume of the adipose tissue deposits was so great that the concentration (nmole/g tissue) of the 2,4,5,2′,4′,5′-hexachlorobiphenyl was less than that observed in young animals who had less total body fat. The role of adipose tissue content as a modifier in the distribution and effects of this chemical was recently examined in the two strains of mice previously used to examine the role of adipose tissue in the disposition of TCDF and TCDD. Ahotupa and Mantyla (*45*) measured the total body fat by extracting the entire carcass with ether. They observed that the DBA mice contained 90% more fat than the B6 mice. Therefore, greater doses of 2,4,5,2′,4′,5′-hexachlorobiphenyl were required to be adipose tissue levels as reached after low doses were administered to the B6 strain. Dietary restriction of the DBA mouse reduced its fat content, thus altering its body composition and resulting in a pattern of 2,4,5,2′,4′,5′-hexachlorobiphenyl distribution resembling that seen in the B6 mouse.

Although tissue volumes play an important role in the distribution and biological effects of lipophilic halogenated aromatic compounds, the major factor which controls the elimination phase of the disposition of these chemicals is their metabolism. The general conclusion that can be drawn from a large number of studies is that metabolism is a prerequisite for excretion. Without metabolism, these chemicals tend to remain sequestered in body fat or membranes, or bound to plasma proteins. Only if high levels of free compound are present in the blood, as occurred for 2,4,5,2′,4′,5′-hexachlorobiphenyl under starvation conditions (*17,43*), do appreciable amounts of the compound diffuse across the gut wall and appear unchanged in the feces. Otherwise, essentially all of the excreted chemical, in either urine or feces, represents the results of metabolic transformations of the original compound.

There are a number of reviews which cover the metabolism of aryl halides (*46,47*). For simple halogenated benzenes, as well as for the more complex halogenated biphenyls and chlorinated naphthalenes, oxidative metabolism occurs primarily at the site of two adjacent unsubstituted carbon atoms via an arene oxide intermediate. However, direct insertion of a hydroxyl group (*48*) has recently been shown to be a major route of metabolism for 2,5,2′,5′-tetrachlorobiphenyl.

The number, position, and types of halogen atoms all play a role in regulating the metabolism of halogenated aromatics. It has been suggested that the metabolism of aryl fluorides is distinct from that of aryl chlorides, bromides, and iodides (*46*). In general, the rate of oxidative metabolism decreases with the electronegativity of the halide substitution (Cl<Br<I). However, the rates of metabolism tend to decrease as the number of halogens in the aromatic rings increase because of steric hindrance (*47*). Parkinson and Safe (*49*) compared the *in vitro* metabolism of biphenyl and the four 4-halobiphenyls (fluoro-, chloro-, bromo-, and iodo-. Their study showed that halogenation with any of the halogen atoms shifted the minor route of metabolism from 2- to 3-hydroxylation, while not changing 4–hydroxylation as the major oxidative pathway. However, the *in vivo* biological response, as measured by the induction of cytochrome P-450 enzymes, varied with fluoro- and bromobiphenyl behaving like biphenyl as distinct from iodo- and chlorobiphenyl which shared common inducing properties. The physicochemical properties and electronic parameters of these biphenyls cannot account for the observed differences in hydroxylation. *In vivo* metabolism studies of 4-iodobiphenyl also showed it to be oxidized primarily to the 4-hydroxy-4′-iodobiphenyl, a situation analogous to the metabolism of 4-chlorobiphenyl (*11*).

The importance of halogen position as opposed to

number was studied by Kato et al. (*50*), who investigated the *in vivo* metabolism of four symmetrical hexachlorobiphenyl isomers, 2,3,5,2′,3′,5′-, 2,3,6,2′,3′,6′-, 2,4,5,2′,4′,5′- and 2,4,6,2′,4′,6′-. They observed that the three isomers without vicinal unsubstituted carbon atoms were slowly metabolized while 2,3,6,2′,3′,6′-hexachlorobiphenyl was readily metabolized and excreted. Identification of the metabolites showed that dechlorination, chemical shifts, and direct hydroxyl insertion occurred in addition to arene oxide formation when there were adjacent unsubstituted carbon atoms.

Biphenyl metabolism has been studied in a variety of species, including rats, mice, dogs, monkeys, humans, fish, and birds (*3*). The above metabolic rules seem to hold in general for all species examined. For example, metabolism of 4-bromo- and 4-chlorobiphenyl in the chicken resulted in the same products as that observed in the rat and rabbit (*51*). The major metabolites of 2,5,4′-trichlorobiphenyl were monohydroxylated derivatives in both the monkey (*52*) and rat (*53*). However, a clear species difference was found between the monkey and dog in the metabolism of 4,4′-dichlorobiphenyl (*39*). The dog tends to resemble the rat (*17*) in being more able to metabolize this isomer than is the monkey. The reverse relationship is true for the metabolism of 2,4,5,2′,4′,5′-hexachlorobiphenyl, where the monkey is more similar to the rat than is the dog (*54*). In fact, the dog seems to be the only species so far examined which can readily metabolize 2,4,5,2′,4′,5′-hexachlorobiphenyl. Recent data from the same laboratory also showed the lack of metabolism of this PCB isomer by human liver microsomes (*55*).

The metabolic rules for the chlorinated biphenyls seem to hold, in general, for the brominated biphenyls as well. Matthews and Anderson (*17*) showed that 2,4,5,2′,4′,5′-hexachlorobiphenyl was metabolized and cleared very slowly. The same brominated isomer, which is a major component of Firemaster BP-6 (*9*), was also shown to be resistant to metabolism (*18*). After treating rats with Firemaster FF-1, Domino et al. (*56*) showed that 2,4,5,2′,5′-pentabromobiphenyl was cleared more rapidly than was 2,4,5,3′,4′-pentabromobiphenyl. This differential excretion was expected due to the absence of adjacent unsubstituted carbon atoms in the latter isomer on one ring and the lack of a free *para* position on the other. The hexabromobiphenyl isomer, 2,4,5,2′,4′,5′, was persistent and stored in the adipose tissue. This study demonstrated that the distribution of this isomer was independent of the distribution of other isomers in the mixture, since the kinetic data observed were in agreement with those previously obtained using the purified isomer (*18*).

The importance of the position of the halogen atoms on the aromatic ring may be further emphasized by examining the metabolism of the halogenated naphthalenes. Takeshita and Yoshida (*57*) could detect no relationship between the degree of chlorination and the extent of tissue retention using a polychlorinated naphthalene mixture. Both 1- and 2-chloronaphthalene were readily metabolized to their corresponding hydroxylated metabolites (*58*). Two dichloronaphthalenes, 1,2- and 1,4-, were hydroxylated via arene oxides to monohydroxy derivatives, as was the more highly chlorinated isomer, 1,2,3,4-tetrachloronaphthalene (*59*). A dihydrodiol was also produced from the metabolism of 1,2-dichloronaphthalene (*23*). Oishi and Oishi (*60*) studied the disposition of 1,8- and 2,7-dichloronaphthalenes and observed that the position of the chlorine atom affected the biological half-life, with 2,7-dichloronaphthalene being more slowly metabolized than the 1,2-isomer. No metabolites of 1,2,3,4,5,6-hexachloronaphthalene (*59*) or octachloronaphthalene were detected (*60*).

Comparison of the effect of the type of halogen atom on metabolism was examined by Ruzo et al. (*59*), who compared the metabolism of 1,4-dichloronaphthalene to that of 1,4-dibromonaphthalene. While metabolism of 1,4-dichloronaphthalene resulted only in one major product, 2,4-dichloronaphthol, two metabolites were produced from 1,4-dibromonaphthalene, 2,4- and 5,8-dibromonaphthol. These products were due to direct hydroxylation of the unhalogenated ring as well as halogen shift accompanying an arene oxide intermediate. Recent work from this laboratory has looked at the disposition of a mixture of two hexabromonaphthalenes, 1,2,3,4,6,7- and 2,3,4,5,6,7- (*24*). These authors speculated that the former isomer was metabolized and excreted, while the latter was persistent. This hypothesis has been confirmed by the isolation and identification of the residual hexabromonaphthalene from the liver 10 days after treatment as 2,3,4,5,6,7-isomer (Birnbaum and McKinney, unpublished observations). The metabolites produced from 1,2,3,4,6,7-hexabromonaphthalene have not yet been characterized.

While the preference for metabolism to occur at adjacent unsubstituted carbon atoms seems clear for the halogenated biphenyls and to a lesser extent for the naphthalenes, the situation with the polyhalogenated dibenzodioxins and dibenzofurans is less clear. No studies have been published on the disposition of any but the chlorinated isomers of these compounds. This may reflect the lack of environmental occurrence of brominated dioxins or furans. Chlorinated dibenzofurans appear to be more readily metabolized than the corresponding dioxin isomers (*61*).

Studies of residue analysis of humans environmentally or occupationally exposed to PCDF or PCDD mixtures can help elucidate the structural rules governing the metabolism and elimination of these classes of halogenated aromatics. In fact, the basic rule that position and extent of halogenation determine persistence clearly holds for humans, as demonstrated for PCB isomer retention in occupationally exposed persons (*62*). In the "Yusho" poisoning incident, almost 2000 people consumed rice oil contaminated with PCBs, polychlorinated dibenzofurans (PCDFs), and polychlorinated quaterphenyls (*63*). The degree of toxicity correlated with the furan content, rather than the PCB levels. The majority of the PCBs and PCDFs in the oil were highly chlorinated isomers which would tend to accumulate (*64*). Rappe et al. (*65*) compared the PCDFs occurring in the

Table 4. Relative levels of PCDFs in livers of Yusho patients.[a]

Time of death	Total PCDF content, ppm	Tetrachlorodibenzofurans, ppm		Pentachlorodibenzofurans, ppm		Hexachlorodibenzofurans, ppm
		2,3,6,8-	2,3,7,8-	1,2,4,7,8-	2,3,4,7,8-	
July 1969	17.6	4.0	1.7	40.3	39.2	14.8
July 1969	2.0	4.0	1.0	60.0	20.0	15.0
May 1972	0.45	6.7	tr[c]	20.0	66.7	6.7
March 1977	0.16	ND[b]	ND	12.5	62.5	25.0

[a]From Kuroki and Masuda (*66*).
[b]ND = not detected.
[c]tr = trace.

toxic rice oil with those present in the livers of two Yusho patients. They observed that isomers with adjacent unsubstituted carbon atoms which were present in the oil were not detectable in the patients. Isomers such as 2,3,6,8- and 2,3,7,8-tetrachlorodibenzofuran, 1,2,4,7,8- and 2,3,4,7,8-pentachlorodibenzofuran and 1,2,4,6,7,8-, 1,2,3,4,7,8-, 1,2,3,6,7,8- and 2,3,4,6,7,8-hexachlorodibenzofuran were detected at equal or higher levels in the patients than in the Yusho oil. One might expect that these isomers would be resistant to metabolism. The presence of 1,2,3,4,6,7,8-heptachlorodibenzofuran in the oil but not in the patients might suggest that this highly chlorinated isomer was not well absorbed. Exposed patients who died shortly after the poisoning occurred had higher total levels of PCDFs and relatively higher amounts of the tetrachlorodibenzofuran isomers than those who died 9 years after exposure (Table 4). However, the relative content of the toxic isomer, 2,3,4,7,8-pentachlorodibenzofuran, was noted to increase with time (*66*). A change in the relative isomeric composition of PCDFs in commercial products such as pentachlorophenols as compared to biological samples also exists in fat samples taken from turtles and seals (*67*).

The metabolism of PCDFs has not yet been studied in great detail. Mono- and dihydroxy derivatives were detected as metabolites from rats given 2-chloro-, 2,8-dichloro-, and 2,3,8-trichlorodibenzofuran (*61*). In a series of studies from this laboratory (*20,21,30,68*), it was reported that 2,3,7,8-tetrachlorodibenzofuran was metabolized and excreted by rats, mice, and monkeys, while it persisted in the guinea pig. At least four metabolites were detected but have not yet been characterized (*57*). An examination of the fate of pure 1,2,4,6,7,9-hexachlorodibenzofuran (HCDF) as compared to a preparation containing approximately 35% pentachlorodibenzofuran contaminants suggested that the HCDF was not readily metabolized, while the pentachloro contaminants were metabolized and excreted (Birnbaum, unpublished observations). Using a mixture of PCDFs, Kuroki and co-workers (*69*) showed that both rats and monkeys excreted 1,2,7,8- and 2,3,7,8-tetrachlorodibenzofuran and 1,2,3,7,8- and 1,2,4,7,8-pentachlorodibenzofuran, while 2,3,4,7,8-pentachlorodibenzofuran and hexachlorodibenzofuran were retained. In fact, the toxic 2,3,4,7,8-pentachlorodibenzofuran isomer was concentrated and retained in the liver of both rats and monkeys, a situation similar to the observed retention of this isomer in Yusho victims (*66*) (Table 4).

More extensive metabolite characteriation has centered on the highly toxic compound, 2,3,7,8-tetrachlorodibenzodioxin. The lower chlorinated isomers are metabolized to hydroxylated derivatives (*70*). Although early *in vivo* studies with TCDD failed to reveal the presence of metabolites, it is now clear that TCDD is metabolized at a finite rate. TCDD metabolites have been detected from rats (*71*) mice (*42*) and hamsters (*41,72*). The primary *in vivo* metabolic products of TCDD seem to be phenols. Using rat heptocytes, Sawahata et al. (*73*) were able to generate at least two metabolites of TCDD which were identified as 1-hydroxy-2,3,7,8-TCDD and 8-hydroxy-2,3,7-trichlorodibenzo-*p*-dioxin. Poiger et al. (*74*) were able to identify five phenolic metabolites produced *in vivo* by dogs. Dogs seem to have more ability to metabolize TCDD than do many other species, a situation reminiscent of that with 2,4,5,2′,4′,5′-hexachlorobiphenyl.

Although metabolism is in general a prerequisite for excretion of these highly lipophilic compounds, exceptions do exist. Unchanged TCDD could be detected in the feces of TCDD-treated hamsters (*7*). Similarly, TCDF could be detected in the feces of TCDF-treated guinea pigs (*21*). Whether this was due to transluminal passage or action of microbial flora has not yet been resolved.

In general, the molecular weight is a major determinant of the route of excretion (*75*). Compounds with a molecular weight of less than 300 tend to be excreted primarily in the urine while those with molecular weights greater than 500 are excreted via the biliary-fecal route. However, this molecular weight cut-off tends to vary with species, with mice and rats tending to have compounds appearing in the feces which would be in the urine of monkeys and dogs. Mainly metabolites are detected in urine and bile, but appreciable amounts of parent chemical may appear in the feces, as mentioned for TCDD, TCDF, and 2,4,5,2′,4′,5′- hexachlorobiphenyl, suggesting the occurrence of passive diffusion into the gastrointestinal tract. Lactation can also serve as a route of excretion.

The elimination kinetics of PCB, PCDD, PCDF, PCN and other halogenated derivatives tend to follow first-order processes. In general, except as modified by var-

Table 5. Half-lives for elimination.

Chemical	Feces/urine[a]	$t_{1/2}$ for excretion, days[b]	Species	Reference
TCDD	15.7	30	Guinea pig	(*20*)
	>99	31	Rat	(*76*)
	2.7	11	Mouse (B6)	(*42*)
	1.2	24	Mouse (D2)	(*42*)
	1.4	11	Hamster	(*41*)
Octachlorodibenzo-*p*-dioxin	17.9	21	Rat	(*22*)
TCDF	2.1	40	Guinea pig	(*21,77*)
	31.4	2	Rat	(*19*)
	6.5	2	Mouse (B6)	(*20*)
	2.8	4	Mouse (D2)	(*20*)
	5.4	8	Monkey	(*68*)
HCDF	13.0	8	Rat	Birnbaum, unpublished
1,2-Dichloronaphthalene	1.2	1	Rat	(*23*)
Hexabromonaphthalene	104.2	5	Rat	(*24*)
2,4,5,2′,4′,5′-PBB	66	2	Rat	(*18*)
4-Chlorobiphenyl	0.7	1	Rat	(*17*)
	0.9	1	Mouse	(*78*)
4,4′-Dichlorobiphenyl	6.7	1	Dog	(*39*)
	0.2	19	Monkey	(*39*)
	1.9	1	Rat	(*17*)
	0.7	1	Mouse	(*78*)
2,5,4′-Trichlorobiphenyl	3.7	3	Rat	(*53*)
2,4,5,2′,5′-Pentachlorobiphenyl	7.4	2	Rat	(*17*)
	12.2	2	Rat	(*17*)
	35.3	1	Mouse	(*78*)
2,3,6,2′,3′,6′-Hexachlorobiphenyl	4.0	1	Dog	(*79*)
	3.7	7	Monkey	(*79*)
	160.0	1	Rat	(*37*)
2,4,5,2′,4′,5′-Hexachlorobiphenyl	21	8	Dog	(*54*)
	17	∞	Monkey	(*54*)
	141.9	∞	Rat	(*17*)
	2.5	∞	Mouse	(*78*)
4-Iodobiphenyl	1.4	1	Rat	(*11*)

[a] Ratio of percent of the total dose excreted in feces to the percent of the total dose excreted in urine.
[b] Measure of the time required to eliminate 50% of the dose.

iations in body composition, i.e., adipose tissue content, the rates of elimination of halogenated aromatics tend to be directly related to their rates of metabolism. Table 5 gives the relative half-lives for elimination of the chemical from the body and the ratio of excretion in feces to that in urine for many of the compounds discussed in this review. Not only is the effect of increasing size on the route of excretion apparent, but as the resistance to metabolism increases, so does the relative amount excreted in the feces, reflecting again the diffusion of unaltered compounds into the gastrointestinal tract and hence into the feces. The presence of the larger fecal route of excretion, probably due both to increased molecular weight and enhanced lipophilicity.

As mentioned, however, most of the material appearing in the feces represents metabolites produced by the liver being excreted via the bile into the small intestines. For the more highly substituted compounds, enterohepatic circulation does not appear to play a major role. However, the interruption of enterohepatic cycling by treatment of mineral oil or chlorostyramine has been shown to enhance elimination of 2,4,5,2′,4′,5′-hexabromobiphenyl in monkeys (*80*). Such treatment would not only prevent reabsorption of biliary metabolites but of lipophilic parent compound. Mineral oil would

also enhance passive diffusion into the gut by increasing the hydrophobicity of gut contents.

The basic structural features governing the disposition of halogenated aromatic hydrocarbons have been known for several years. The size and electronegativity of the halogen, the numbers of halogens, and their position all play a role in determining the physical and biochemical properties of the compound in question. The nature of the ring structure also has a role. Generalizations that lipophilicity of compounds favors absorption and distribution while adjacent unsubstituted carbon atoms predispose towards metabolism and thence excretion seem pertinent. However. the brominated derivatives do seem to be more lipophilic than their chlorinated analogs resulting in such a degree of insolubility that absorption is impeded. A similar situation seems to exist for the completely substituted dioxins, naphthalenes, and furans which may never be absorbed and are therefore low in toxicity.

The presence of the ether linkage in dioxins and furans may enhance their metabolism relative to the biphenyls. The strained ether bond in the furans may explain their ease of oxidation relative to the symmetrical situation which exists in the dioxins. However, the great species variations observed in metabolism is still unclear, as in the position that humans occupy in both the toxic sensitivity disposition picture relative to other species.

Pharmacokinetic modeling may be helpful in this regard. Physiological pharmacokinetic models for several PCB isomers have been developed in the rat (*81*) and mouse (*82*), for 2,4,5,2′,4′,5′-PBB in the rat (*83*), and for 2,3,7,8-TCDF in rats, mice and monkeys (*84*). These studies demonstrate the equilibrium relationship that exists between blood and other tissues, and that if the uptake, accumulation and disposition parameters are known, one can predict the overall distribution. The physiological models derived from rats for PCBs have been successfully applied to the mouse, as have the data for a single TCDF isomer been shown to be applicable to other species. The major limitation to extrapolation of pharmacokinetic data is the fact that metabolism varies between species (*4*). Further measurements of metabolic capabilities are required to be able to improve predictions of species disposition as well as the effects that structure plays on the disposition of this entire class of compounds.

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