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PHARMACOKINETICS OF PCBs

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INTRODUCTION

Polychlorinated biphenyls (PCBs) are the products of varying degrees of chlorination of the biphenyl molecule (Figure 1). Given 10 available positions for chlorination, 209 different chlorinated biphenyls (PCB congeners) are possible. These compounds are named according to their positions and degrees of chlorination, i.e. a biphenyl molecule having chlorine atoms at the 2 and 5 positions of each ring (Figure 1) is named 2,5,2',5'-tetrachlorobiphenyl.PCBs were first synthetized over one hundred years ago (1), and commercial production of PCBs in the US began in 1929 (2). Commercial PCB formulations do not consist of a single chlorinated biphenyl but are complex mixtures of chlorinated biphenyls named according to the percent weight accounted for by chlorine. For example, Aroclor® 1248 contains 48 percent by weight of chlorine and several dozen individual chlorinated biphenyls. Because of their desirable physical properties, PCBs have been widely used in a diverse number of commercial products, including heat transfer agents, hydraulic fluids, plasticizers, adhesives, cutting oils, and inks. However, due to their dielectric properties, thermal stability, and nonflammability, PCBs were used most extensively in electrical capacitors and transformers (3). Annual use of PCBs in the US peaked at approximately 85 million pounds in 1970. After 1970, the use of PCBs in the US declined, but it is estimated that almost one billion pounds had been sold up to that date (2).

Given the volume of PCBs used and the period of time during which they were used, the safety record for these compounds was relatively uneventful.

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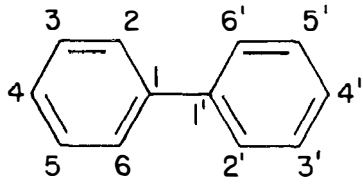

Figure 1 Biphenyl

For a number of years, reports and concern regarding the health effects of PCBs were restricted to workers in direct contact with the compounds in the course of their production or use (4–7). Possibly because they were present as diverse mixtures rather than as one or two individual compounds, PCBs were not recognized as environmental contaminants until 1966 (8). Once their presence had been pointed out and the methods for their detection perfected, PCB contamination was found to be worldwide and in virtually every type of biological sample assayed. The first incident in which PCBs were recognized as the causative agent in the intoxication of the general public occurred in 1968 in Japan, when a PCB mixture used in the cooling system of a rice oil plant leaked into rice oil subsequently consumed by over 1600 persons (9, 10). A similar incident occurred in Taiwan in 1979 (11). The PCB formulation involved in the Japanese incident and to a lesser extent in the Taiwanese incident contained a number of chlorinated dibenzofurans (11, 12). Therefore, it is not known to what extent the diverse symptoms observed in the exposed individuals were due to PCB intoxication or were due in part to the very much more toxic chlorinated dibenzofuran contaminants.

Studies of PCB toxicity in laboratory animals indicate that sensitivity to physiological intoxication by these compounds varies widely with species. Laboratory rats are largely resistant to intoxication by PCBs (13, 14), whereas rhesus monkeys are quite sensitive (15, 16). Human sensitivity to intoxication by PCBs appears to be related to the source of exposure. Numerous industrial exposures have resulted in relatively mild symptoms, primarily chloracne, whereas exposure in the Yusho incident resulted in a number of diverse and marked symptoms of intoxication (9, 10, 17). Studies of PCB carcinogenicity in laboratory animals have resulted in mixed conclusions. A bioassay of Aroclor 1254 for possible carcinogenicity by the National Cancer Institute concluded that this PCB formulation was not carcinogenic (18). However, the results of several other studies indicate that PCBs may be carcinogenic to laboratory animals (19–21).

Tissue Distribution

Due to the incidents of human poisoning and widespread environmental contamination, the production and use of PCBs has virtually ceased worldwide. However, concern regarding PCBs remains, due to their lingering existence in

products manufactured prior to their discontinued use and their bioaccumulation and persistence in higher animals and the environment. Since PCBs may be very persistent in tissues of higher animals, knowledge of the pharmacokinetics of these chemicals was and is an essential complement to an assessment of health effects likely to result from long-term, low-dose exposure to these compounds. However, classical pharmacokinetic modeling of PCB disposition in higher animals has been complicated by the existence of PCBs as complex mixtures and by the variable capacity of different animal species to metabolize and clear these compounds. Therefore, most pharmacokinetic studies of PCBs have concentrated on establishing the basic parameters that determine their absorption, tissue distribution, metabolism, and clearance.

The lipid solubility of PCBs promotes passive absorption of these compounds from the aqueous environment of the intestine across the more lipophilic cell membranes of the intestine wall (22–25); the concentration gradient favors partition across the cells into blood. Once absorbed, PCBs are rapidly transported by the blood to all tissues. Transport in blood is apparently achieved by nonspecific association of PCBs with both blood cells and plasma proteins (26–28). Distribution of PCBs in plasma is apparently determined primarily by partition among the various proteins according to lipid solubility and concentration. Similarly, the partition of PCBs between blood and tissues is determined by lipid content and concentration gradient. Therefore, initial distribution of PCBs to tissues is largely determined by the volume, affinity, and rate of perfusion of the tissue in question.

The initial distribution of PCBs is determined by biophysical factors such as tissue volume, tissue/blood partition ratios, absorption to proteins, and perfusion rate, and is therefore similar in all species studied (24–31). Liver and muscle are the primary early depots because liver is highly perfused and has some affinity for these compounds, and muscle is by far the largest tissue volume. However, since PCBs are highly lipid-soluble compounds, they have a higher affinity for lipid-rich tissues, particularly adipose tissue, and a slower process of redistribution begins simultaneously with initial distribution. Therefore, these compounds are eventually most concentrated in adipose tissue and skin (24, 32), and a dynamic equilibrium of PCB concentrations is established among all tissues for each PCB homolog.

The interrelationship between PCB concentrations in all tissues is illustrated by the flow diagram in Figure 2 (33). At equilibrium, a change in the PCB concentration or tissue volume of any one tissue will result in a corresponding change in all tissues. For example, if the concentration of a PCB in liver is decreased by metabolism and excretion, then the concentration of that PCB in all tissues will be decreased proportionally. If another PCB cannot be metabolized and excreted, then that homolog will be concentrated in adipose tissue but not isolated there. PCBs that are concentrated in adipose tissue are still

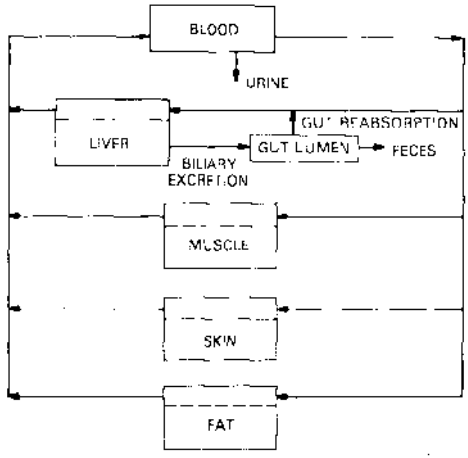

Figure 2 Flow diagram for pharmacokinetic model of chlorinated biphenyls. Source: Lutz et al (33)

circulated to all other tissues by the blood, and the exposure of each tissue is proportional to the respective tissue/blood ratios and the concentration in the major tissue depots, e.g. adipose tissue. The result is that the PCB congeners that can be cleared are depleted from all tissues and those that can not be cleared persist.

Examples of clearance of some PCB congeners and retention of others have been seen, though sometimes not recognized, in reports of human and animal samples in which the PCB profile of the samples did not match the profile of the mixture to which the organism was exposed. Documented examples have been provided by Bush et al (34), who demonstrated that the composition of Aroclor 1254 changed as it passed through the hen and the rat. Chen et al (35) reported that PCB residues in tissues of humans exposed in the Taiwan rice oil incident were preferentially depleted of homologs with adjacent unsubstituted carbon atoms at the 3 and 4 positions. Therefore, it follows that the concentration of an individual PCB in tissues of exposed animals and humans will be a function of level and duration of exposure, the ability of the exposed organism to clear the given PCB, and the time period following exposure.

Metabolism

Polychlorinated biphenyls are highly lipophilic molecules that are virtually insoluble in water. On the other hand, all biological excretory mechanisms are polar systems that involve intimate contact of aqueous fluids with cell membranes containing the usual complement of proteins and lipids. For this reason, intact PCBs are not readily excreted. Even if they were to enter the excretory systems of kidney or liver they would partition from the aqueous media into

the more lipophilic membranes and from these membranes back into blood according to the concentration gradient. Some passive elimination occurs, but PCBs are excreted to an appreciable extent only after they are metabolized and conjugated to form more polar molecules.

The metabolism of all 209 chlorinated biphenyls has not been studied, but enough of these compounds have been studied to permit general conclusions about the mechanisms involved. Metabolism of chlorinated biphenyls is achieved primarily by the hepatic mixed-function oxidases and is strongly directed by the phenyl rings and the position(s) of chlorination (36). The presence of the biphenyl linkage directs metabolism to the ends of the molecule, so that the major metabolite of biphenyl is 4-hydroxybiphenyl. However, lesser amounts of 2- and 3-hydroxybiphenyl are also detected (37). The 2- and 4-hydroxybiphenyl metabolites are believed to be formed preferentially by mixed-function oxidases utilizing cytochromes P-448 and P-450 respectively, and the formation of each is thought to involve an arene oxide intermediate. However, 3-hydroxybiphenyl is believed to be formed by direct insertion of a hydroxyl group (37). Arene oxides are believed to be the reactive intermediates that account for hepatic toxicity or even carcinogenicity associated with many chemicals (38, 39). Arene oxides are also believed to be involved in covalent binding of PCBs (40). However, arene oxides have not yet been shown to account for PCB hepatotoxicity or carcinogenicity (41).

Chlorination deactivates the carbon atoms of the biphenyl molecule and directs metabolism to the unchlorinated positions. For example, the presence of a single chlorine atom on 4-chlorobiphenyl directs metabolism exclusively to the unchlorinated ring to yield a single major metabolite, 4-hydroxy-4'-chlorobiphenyl, in all species studied (41–45). However, PCB metabolism becomes more complex as the degree of chlorination increases. These compounds are readily metabolized as long as chlorination is restricted to one ring (46, 47), but metabolism may be greatly restricted when both rings are chlorinated (48). Several investigators have provided evidence that the critical factor to PCB metabolism is the availability of adjacent unsubstituted carbon atoms on at least one of the rings, preferably at the 3,4-positions (24, 32, 49). The presence of adjacent unsubstituted carbon atoms facilitates the formation of arene oxide intermediates that subsequently yield the 2- or 4-hydroxylated metabolites. Metabolism by the insertion mechanism at the 3 position proceeds much more slowly and in most cases is not a major factor in PCB metabolism (32, 48).

Biphenyl metabolites are readily conjugated and excreted and with few exceptions are not persistent in tissues. The major exception is the persistence of sulfur-containing metabolites of certain PCBs in the bronchial mucosa (50–53). Recent work indicates that these metabolites are products of glutathione reaction with arene oxide intermediates formed in PCB metabolism.

These glutathione conjugates are excreted in bile, subsequently metabolized by intestinal microbes, reabsorbed from the intestine, and preferentially accumulated in bronchial mucosa (53). The mechanism(s) that account for the affinity of these products for bronchial mucosa and the toxicological significance of this accumulation are as yet unknown, but the amount of the total PCB dose involved is relatively small.

While most studies of PCB metabolism have used the laboratory rat, PCB metabolism has been studied in a number of other species as well. The ability of various types of animals to metabolize PCBs increases in the order of fish < birds < mammals. However, the mechanisms involved appear to be similar in all species studied. That is, the primary metabolites formed by all species are hydroxylated biphenyls most probably formed primarily by hepatic mixed-function oxidases. Therefore, degree and position of chlorination play a major role in the rate of PCB metabolism by all species. The importance of adjacent unsubstituted carbon atoms observed in rats may be even more important in species with less capacity for PCB metabolism. Studies of PCB metabolism by fish indicate a minimal capacity to metabolize these compounds and then only those homologs having adjacent unsubstituted carbon atoms in the 3–4 positions (29, 54, 55). Birds have a greater capacity to metabolize PCBs than fish, but less than most mammalian species (29, 34). Even among mammals the capacity to metabolize PCBs varies greatly with species. Studies of the same PCB homologs in a number of species indicate that dogs metabolize these compounds most rapidly, followed by rats and mice, whereas monkeys metabolize these compounds relatively slowly (57–61). A study of PCB metabolism by human hepatic microsomes indicates that PCB metabolism by humans may be slow relative to other species (62). However, since PCBs are not readily excreted prior to metabolism, it is assumed that humans can metabolize these compounds in vivo because both Jensen (63) and Chen (35) have observed that PCB residues in human tissues are deficient in homologs having adjacent unsubstituted carbon atoms. That is, the more easily metabolized PCB homologs are apparently metabolized and excreted by humans, whereas the others tend to persist.

The net effect of PCB metabolism is the same for all species. Those homologs that can be metabolized will be metabolized to more polar compounds and excreted. Those homologs that can not be readily metabolized will be retained in the body and concentrated in tissues having the highest triglyceride content. The distribution of PCBs to all tissues is proportional to the respective tissue/blood ratios. Therefore, the concentration of a given PCB homolog in any tissue at any time will be determined by the level of exposure, the ability of the given species to metabolize that particular homolog, and time.

Elimination

In the present context, elimination is differentiated from excretion by the fact that excretion implies active processes involving specialized mechanisms located primarily in kidney and liver. Elimination of PCBs by higher animals is passive and coincidental to the passage of other substances from the body. Furthermore, excretion of PCBs is minimal prior to metabolism to more polar compounds, but these compounds are eliminated as unmetabolized parent compounds in association with any substance that may pass from the body. Due to their high lipid solubility, PCBs are most concentrated in substances that have a high lipid content and have been detected in the oils on hair of humans and animals (64). However, the major routes for PCB elimination are substances having the greatest volume and/or lipid content, e.g. milk, eggs, and fetuses, and are thereby restricted to females. Elimination by these routes arouses greater concern because of the possible threat to the young.

Elimination of PCBs in milk varies greatly with the species involved, due to differences in volume and lipid content of the milk produced. However, the basic mechanisms involved are the same for all species. Lipid in milk consists predominantly of triglycerides that originate both from circulating lipids in blood and de novo synthesis in the mammary gland (65). Since PCBs in the body are in dynamic equilibrium with all tissues, the creation of a new lipid depot with the beginning of lactation results in passive movement of PCBs from blood to milk and a corresponding movement of PCBs from all tissues to blood to maintain their respective tissue/blood ratios. A favorable gradient for passive transport of PCBs from blood to milk is maintained by continued synthesis and secretion of milk lipid. Vodicnik & Lech (66–69) have provided excellent examples of the role milk can play in PCB elimination in their comparative studies of PCB elimination in lactating and virgin mice. In these studies, lactating mice transferred most of the body burden to their nursing young in a period of 20 days, whereas the body burden of the virgin animals remained essentially constant. Other studies have demonstrated that PCB elimination in milk by cattle and humans is proportional to the level of exposure, and in the case of cattle accounted for 11–12% of the daily dose consumed (70, 71). In the Yusho incident, at least one infant received a toxic dose of PCBs solely as a result of nursing (72). However, the volume and lipid content of human milk is relatively low compared to that of other species, and there is no evidence that lactation has significantly reduced the PCB body burden of humans.

Eggs, particularly egg yolks, represent another concentration of newly synthesized lipids that may serve as a route for PCB elimination. Unmetabolized PCBs have been detected in the eggs of fish (73), turtles (74), and wild birds (75), as well as in the eggs of domestic fowl used in laboratory studies of

PCB clearance (56). Bush et al (56) studied the fate of Aroclor 1254 in chickens and observed that the concentration of PCBs in egg yolk increased as the body burden increased and decreased when Aroclor administration was discontinued. They also observed that the poorly metabolized PCB homologs were more concentrated in egg yolk than those congeners more readily metabolized and excreted. Steady-state levels have not been predicted in birds, but in a study of the closely related polybrominated biphenyls in chickens, Fries et al (76) demonstrated that elimination in eggs equaled dietary intake in approximately 63 days. In summary, eggs, like milk, represent a depot of newly synthesized lipid that can account for the elimination of significant concentrations of PCBs. Elimination of PCBs in eggs is greatest in domestic fowl, which produce the largest number of eggs. However, wild fowl that produce eggs only once a year may accumulate high body burdens of PCBs and therefore may be more likely to have concentrations in their eggs that would endanger their young.

Polychlorinated biphenyls are relatively small, highly lipophilic molecules that readily cross cell walls; therefore, the placenta offers the fetus little protection from these compounds. However, the fetus, as opposed to milk and eggs, is lean relative to maternal tissues. Therefore, even though an equilibrium is established in which PCBs are partitioned between all tissues, including placenta and blood, PCBs are not concentrated in fetal tissues. Nevertheless, the fetus is exposed (9, 77, 78), and in the case of the Yusho incident children born to mothers who consumed PCB-containing rice oil exhibited signs of intoxication (9). However, Vodicnik et al (66, 68, 69) demonstrated that concentration and elimination of PCBs in the mouse fetus were minimal when compared to those in milk.

PHARMACOKINETIC MODELING

Relatively little work has been conducted on pharmacokinetic modeling of PCBs. Mathematical analyses have for the most part been confined to regression analysis of tissue burdens or excretion rates to characterize their time course in an objective way. These analyses have been primarily descriptive and have provided little insight into the underlying physiologic and biochemical mechanisms involved. We believe that a pharmacokinetic model that places individual physiologic processes and biochemical interactions in quantitative perspective more accurately reflects the mechanisms involved. Therefore, such a model has been used to study several PCBs in the rat (33) and the mouse (58). The present review concentrates on a description of that model.

The pharmacokinetic model is described by the flow diagram in Figure 2, which contains the tissues that account for most of the body burden of PCBs and their metabolites. The mathematical model consists of a set of differential equations that are mass balances on each chemical species in each compart-

ment. These have been described in detail (33), so only two illustrative examples are cited here. For a tissue in which metabolism may occur, such as the liver, the mass balance takes the form

$$\frac{d}{dt}(V_L C_L) = Q_L \left[C_B - \frac{C_L}{R_L} \right] - K_m \frac{C_L}{R_L} \quad 1.$$

where t = time
V = tissue volume or mass
C = concentration
Q = blood flow rate
K_m = metabolic clearance
R = equilibrium tissue-to-blood distribution ratio

and the subscripts L and B refer to liver and blood respectively. For a compartment in which metabolism is neglected, such as adipose tissue, the mass balance takes the form

$$\frac{d}{dt}(V_A C_A) = Q_A \left[C_B - \frac{C_A}{R_A} \right] \quad 2.$$

The product of the tissue volume and the tissue concentration, which equals the amount of PCB in the tissue, has been written in the derivative to allow for the fact that the volume may not be constant on a time scale relevant to the pharmacokinetics of the very slowly cleared PCBs.

An important concept incorporated in Equations 1 and 2 is flow limitation. It is assumed that the PCB in blood leaving any tissue is in equilibrium with the tissue. This assumption has not been explored thoroughly; however, it is known that PCBs leave the blood and enter tissues very rapidly. For example, following intravenous (i.v.) administration, more than half a single dose of 2,4,5,2',5'-pentachlorobiphenyl is removed from blood of rats within two minutes and only 6% can be accounted for in blood at 10 minutes (79). Further, pharmacokinetic simulations based on flow limitation have generally been satisfactory with the important exception of the skin, for which the intercompartment transport parameter had to be reduced by a factor of ten. The limiting factor for skin has not yet been determined.

The blood flow rates and tissue volumes for a 250-gram(g) rat are shown in Table 1; distribution coefficients and kinetic parameters are shown in Table 2 for four PCB congeners: 4-chloro-, 4,4'-dichloro-,2,4,5,2',5'-pentachloro- and 2,4,5,2',4',5'-hexachlorobiphenyl (1-CB, 2-CB, 5-CB, and 6-CB) (33). These two tables illustrate the following important points.

1. The compartment sizes and blood flows are independent of the chemical being modeled. With the exception of effective skin blood flow, all can be

Table 1 Compartment sizes and perfusion rates for a 240-g male Sprague-Dawley rat[a]

Compartment	Volume	Blood flow
	ml	ml/min
Blood	22.5	
Gut lumen	14	
Muscle	125	7.5
Liver	10	16
Skin	40	(0.5)[b]
Adipose tissue	17.5	0.4

[a]Source: Lutz et al (33)
[b]Effective blood flow; see text

measured by methods that do not depend on pharmacokinetic observations. Further, the model can be applied to other animal species by the appropriate choice of tissue sizes and blood flow rates.

2. The tissue-to-blood distribution coefficients show the expected change resulting from metabolism. The parent compounds are lipophilic and tend to concentrate in tissues, while the metabolite (here taken to be a single species

Table 2 Tissue/blood distribution ratios[a]

Compartment	Parent				Metabolite			
	1-CB	2-CB	5-CB	6-CB	1-CB	2-CB	5-CB	6-CB
Blood	1	1	1	1	1	1	1	1
Gut lumen	1	1	1	1	1	1	1	1
Muscle	1	2	1	4	0.14	0.40	0.10	0.30
Liver	1	3	6	12	2	5	2	4
Skin	10	10	7	30	0.25	0.30	0.10	2
Adipose	30	70	70	400	0.40	0.60	0.40	2

	Kinetic Parameters			
Rate constant	1-CB	2-CB	5-CB	6-CB
Metabolic clearance, K_m, ml/min	10.0	2.0	0.39	0.045
Kidney clearance, K_k, ml/min	0.20	0.133	0.033	0.030
Biliary clearance, K_B, ml/min	0.20	0.35	0.30	0.30
Gut reabsorption, K_G, min^{-1}	0.00016	0.00016	0.00016	0.00016
Fecal transport, K_F, min^{-1}	0.0008	0.0008	0.0008	0.0008

[a]Source: Lutz et al (33)

representative of all metabolites) shows a pattern more characteristic of water-soluble materials.

3. There is a great range in the metabolic clearances (K_m). The K_m for 1-CB is 10 ml/min, which represents a significant fraction of the 16 ml/min liver blood flow resulting in a substantial extraction of this compound during a single pass through the liver. The K_m value for 6-CB is only 0.045 ml/min, or less than 1/200 of that for 1-CB. Since the analysis of Lutz et al (33), evidence has suggested that most of the 6-CB cleared by the rat is unchanged material (48, 80, 81). The value of 0.045 ml/min, therefore, represents a total body clearance, most of which may be accounted for by passive transport from blood to intestinal contents (82, 83). The actual metabolic clearance of 6-CB could be an order of magnitude lower than the value shown in Table 2.

Figures 3 and 4 show model simulations resulting from numerical solution of the complete set of differential equations with the parameters chosen for 1-CB and compare these with experimental data of radioactivity derived from 1-CB. These simulations show the important role of skin and fat in mediating the pharmacokinetics of the compound. Parent material enters these tissues with the blood early in the time scale. The tissues serve as reservoirs from which

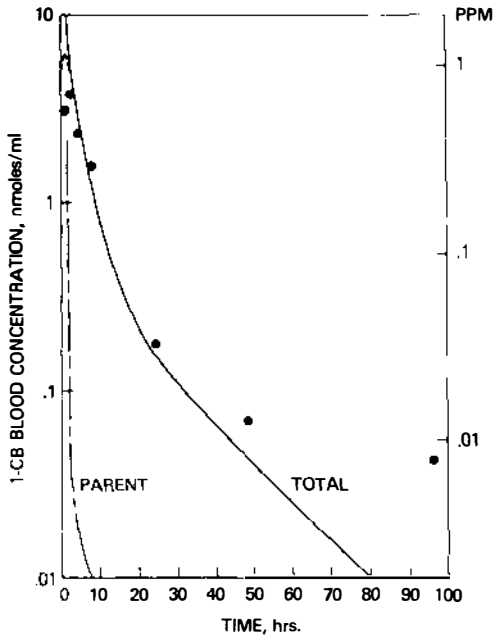

Figure 3 1-CB blood concentration as a function of time after a single i.v. dose of 0.6 mg/kg in the rat. Points represent experimental data for total 1-CB. Simulations are given for total equivalents (——) and parent 1-CB (– – –). Beyond 10 hours, total concentration in blood is composed almost entirely of metabolite. Source: Lutz et al (33)

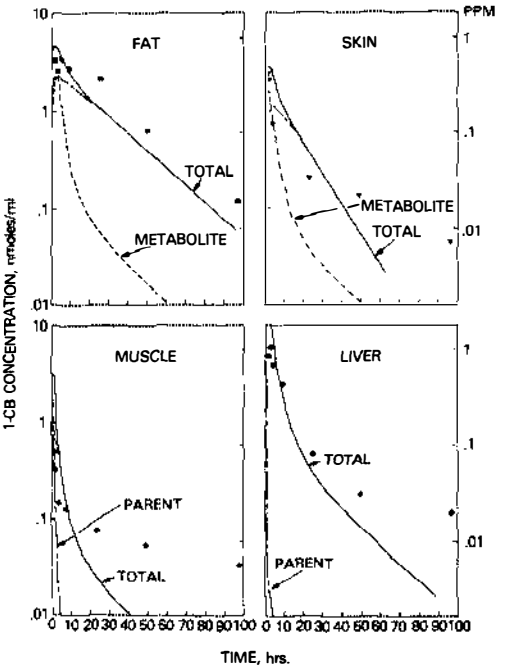

Figure 4 1-CB tissue concentration as a function of time after a single i.v. dose of 0.6 mg/kg in the rat. Points represent experimental data for total 1-CB in the tissues. In each figure, total equivalent concentration (——), metabolite concentration (– – –), and parent concentration (– – –) are shown. Source: Lutz et al (33)

1-CB can reenter the blood and be distributed to the other tissues. Parent material disappears very rapidly from the blood, muscle, and liver. The discrepancy between the model simulations and the data at longer times shows that a small fraction of the radioactivity, typically about 1% of peak concentrations, is behaving kinetically very differently from the mobile metabolite. The nature of this slow component is unknown, but it may reflect covalent binding in these tissues (40).

The pharmacokinetics of the very slowly metabolized 6-CB (Figure 5) show a pattern very different from that of 1-CB. The concentrations in the liver and muscle are able to follow the concentration in the blood quite well after a short redistribution phase, while 6-CB continues to accumulate in skin for about one day and in fat for several days. The transient processes can be assessed without solution of the complete set of differential equations. A characteristic time scale (T) for the movement of a chemical between blood and tissue is seen for constant parameters in Equations 1 and 2 to have the form

$$T = \frac{RV}{Q} \quad 3.$$

or the physiologic volume of distribution of the tissue (RV) divided by the blood flow rate (Q). For 6-CB in the rat, T ranges from (12)(10)/16 = 7.5 minutes in the liver to (400)(17.5)/0.4 = 17,500 min or 12 days in the fat. As noted above, therefore, the 6-CB concentration in liver can follow that in the blood quite closely, while the concentration in fat shows a considerable lag relative to that in blood.

The total physiologic volume of distribution, V_D, of the 250-g rat may be obtained by summing the RV terms for all compartments.

$$V_D = \sum RV \quad 4.$$

Performing the indicated arithmetic for 6-CB yields a value of V_D = 8856 ml or 35 l/kg, of which fat contributes 79% and skin 14%.

The characteristic time scale for elimination from the animal is

$$\frac{V_D}{K_m} = \frac{8856}{0.045} = 196{,}800 \text{ minutes}$$

or 4.5 months.

The long time scale involved in studies of very slowly metabolized PCBs introduces an additional complication, because growth of young experimental animals cannot be ignored. Growth of the rat (33) and swine (31) has been shown to be the major factor responsible for declining adipose tissue concentrations of 6-CB in the absence of a similar decrease in body burden. The relative importance of growth and elimination can be inferred from a one-compartment model of the rat

$$\frac{d}{dt}(V_D C_B) = -K_m C_B \quad 5.$$

Equation 5 may be rearranged to

$$\frac{1}{C_B}\frac{dC_B}{dt} = -\frac{1}{V_D}\frac{dV_D}{dt} - \frac{K_m}{V_D} \quad 6.$$

which states that the relative rate of change in concentration is equal to the negative of the sum of the fractional growth rate of V_D and the total body clearance per unit volume of distribution. If we take the growth rate as 0.017

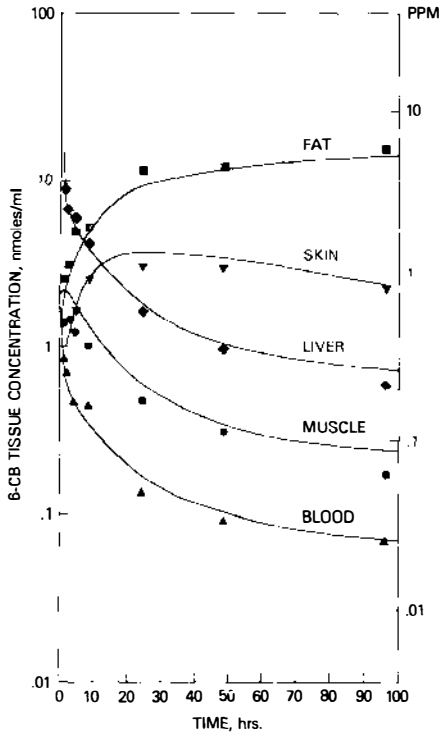

Figure 5 6-CB tissue concentration as a function of time for 96 hours after a single i.v. dose of 0.6 mg/kg in the rat. Source: Lutz et al (33)

day $^{-1}$ (33) and compare this with $K_m/V_D = 0.007$ day $^{-1}$, we see that growth of the 250-g rat is more than twice as important as elimination in reducing adipose tissue concentration. This figure is conservative, because the growing rat substantially increases the fraction of its body mass that is fat relative to lean tissues. For this reason, the rate of growth of 6-CB volume of distribution considerably exceeds the growth rate of the rat.

A consequence of the effect of growth on C_B is a finite total excretion based on extrapolation of excretion rate (% dose/day) curves to infinite time. It has been observed by Matthews & Anderson (24) and confirmed by Muhlebach & Bickel (81) that less than 20% of 6-CB would ever be excreted based on long-term pharmacokinetic studies. This limitation appears to be a consequence of Equation 5. The excretion rate would be

$$K_T = \frac{K_m C_B}{\text{dose}} \qquad 7.$$

or proportional to C_B if K_m is constant. Support for the proportionality between K_f and C_B is provided by the starvation experiments of Wyss et al (80). Since C_B decreases more rapidly than elimination alone would suggest in the growing rat, extrapolation of excretion to infinite time remains less than the dose.

Pharmacokinetic studies of PCB congeners have provided considerable insight into the determinants of their uptake, accumulation, and disposition. Pharmacokinetic modeling of PCB disposition offers the best opportunity to extrapolate knowledge gained with laboratory animals to predict the disposition of these compounds in other species, including humans. Most of the data presented in Tables 1 and 2 are available or could be generated for other laboratory species. However, work with a number of species has demonstrated that one parameter basic to any pharmacokinetic model, metabolic clearance (K_m), varies greatly with species (54–61). Therefore, meaningful extrapolation of laboratory data to other species is dependent on determining the K_m for the species of interest. In the case of man, reliable prediction of PCB disposition will depend on development of an in vitro method for the determination of this parameter.

SUMMARY

The pharmacokinetics of PCBs are complicated by numerous factors, not the least of which is the existence of up to 209 different chlorinated biphenyls. Whereas all PCB congeners are highly lipophilic and most are readily absorbed and rapidly distributed to all tissues, PCBs are cleared from tissues at very different rates, and the same congeners may be cleared at different rates by different species. With the exception of special situations in which PCBs may be passively eliminated in lipid sinks, e.g. milk or eggs, clearance is minimal prior to metabolism to more polar compounds. Rates of PCB metabolism vary greatly with species and with the degree and positions of chlorination. Mammals metabolize these compounds most rapidly, but even among mammalian species rates of metabolism vary greatly. In all species studied, the more readily metabolized chlorinated biphenyls have adjacent unsubstituted carbon atoms in the 3–4 positions. Congeners that do not have adjacent unsubstituted carbon atoms may be metabolized very slowly and are therefore cleared very slowly. Those PCBs not readily cleared concentrate in adipose tissue. A physiologic pharmacokinetic model best illustrates how the concentrations of PCBs in all tissues approach equilibrium with the blood and with one another. Thus, the model illustrates how a depot of PCBs in any tissue, e.g. adipose tissue, will result in exposure of all tissues in proportion to the respective tissue/blood ratios and the body burden. The disposition of a number of PCBs in the rat has been accurately described by a physiologic model, and the model

has been extrapolated to predict the disposition of these same PCBs in the mouse (58). Therefore, the physiologic pharmacokinetic model is believed to offer the best opportunity to extrapolate data obtained with laboratory animals to predict the disposition of PCBs in other species, including man. Most of the parameters of a model of PCB disposition in man are available or could be estimated. The major limitation to the construction of such a model is the absence of accurate estimates of metabolic clearance of individual PCBs by man. Accurate estimates of metabolic clearance depend on development of suitable in vitro methods to accurately predict clearance in vivo.

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