POLYCHLORINATED BIPHENYLS IN GREAT LAKES FISH

Toxicological Justification For Lowering The Acceptable Standard To 2 ppm

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INTRODUCTION

The Toxic Substance Control Commission (TSCC) at its November 19, 1981, meeting recommended that the Michigan standard for polychlorinated biphenyls (PCBs) in fish be set at 2 parts per million.

The text of the motion reads:

> TSCC unanimously recommends that the PCB standard for fish, as regulated by MDA, be established at 2 ppm. TSCC requests MDA to begin the process of setting such a standard for Michigan. The samples of fish should be from skin-on fillets and the chemical analysis should be representative of the total PCB content using the best available technology.

There has been much controversy generated as to whether such a standard is justified. It is recognized that in the process of setting standards, the effect on the economy must be balanced against the benefit to the public that can be expected to acrue from the standard. The available scientific data must be evaluated to ascertain the minimum level to be tolerated as an acceptable public risk. Even for compounds that have been extensively studied, there are usually significant gaps in the available data and some extrapolation is necessary.

This report is intended to present a review of the current scientific literature on PCBs. Justification of the position taken by the Commission is indicated by the data found therein.

PCBs are a class of compounds with the general formula shown in Figure 1. They are normally produced by the chlorination of biphenyl by vaporized anhydrous chlorine with iron filings or ferric chloride catalyst.

Toxicity is dependent upon the number of chlorine atoms located in positions 2 to 6 and/or 2' to 6'. The fact that commercial PCBs are a mixture of compounds necessitates consideration of potential synergistic and antagonistic effects.

The molecular weights vary from 188.7 to 398.5 (Table 1) and there are 209 possible isomers although it has been estimated (1) that approximately 100 should be found in commercial products.

The pure compounds are transparent, crystaline and solid, while the common commercial forms are liquid. Water solubilities range from 0.007 to 5.9 mg/l. Solubilities in most common organic solvents are high. PCBs are thermally and chemically stable, being resistant to oxidation and degradation by other chemical agents.

PCBs are fairly stable to oxidation and hydrolysis under moderate conditions. In contrast PCBs are quite easily photodegraded under various laboratory conditions. The main reaction is a reductive dechlorination, and chlorines in *meta* positions are preferentially lost. The rate of dechlorination is faster in polar solvents like methanol than in hydrocarbon solvents.

Environmental contamination problems are prevalent and disposal is confounded by PCB stability.

Thermal degradation (burning, pyrolysis) seems to be the most feasible method for the destruction of PCBs. This reaction has been studied by several researchers in laboratory experiments and in industrial processes. However, one problem is potential formation of chlorinated dibenzofurans. (Figure 1)

One primary reason for the magnitude of the PCB problem is the massive quantities of the compounds that have been produced since their introduction in the late 1920s by Monsanto Chemical Company. The production peak occurred in the U.S. in 1971 when approximately 85 million pounds of the chemicals were synthesized. Approximately 86% of the total yield was for domestic usage. Production fell until the last year of significant production (1975) when 34.1 million pounds were synthesized of

which approximately 94% was in domestic sales. It is estimated (Brinkman and deKok in (2) that in the period 1930-1975 U.S. cumulative production was 1.4 billion pounds (0.63×10^6 metric tons) with 1.253 being for domestic sales. Imports were relatively light at approximately 3 million pounds. Monsanto ceased PCB production in mid-1977 and the compounds have not been produced in the United States since that time.

The production of PCBs leads to the formation of polychlorinated dibenzofurans (PCDF) (figure 1) and polychlorinated naphthalenes (PCN) (figure 1) as contaminants. Concentrations of up to 33 ppb PCDF have been detected as contaminants of commercial PCBs (Brinkman and deKok in (2),(3-6). The highly toxic 2,3,7,8 tetrachlorodibenzofuran has been found to be one of the contaminants.

PCBs have been used for capacitors and transformers and may be components of inks, plasticizers, lubricants, extenders, adhesives, microscope immersion oils, insulation and a variety of products. PCBs are components of many products currently in use (e.g. transformers, capacitors).

DISTRIBUTION IN THE ENVIRONMENT

One methodology for evaluating the potential persistence of a chemical is the determination of the extent to which it has contaminated the environment. It is estimated that over the period 1930-1975 approximately 150 million pounds of PCBs were exported from the United States. Between 1954 and 1972 Japan produced about 130 million pounds and exported about 11 million pounds. Lesser quantities of PCBs were produced from various sources in Europe (7). The widespread global contamination in many species that has occurred since that time emphasizes the gravity of the situation. Examples of this contamination are cited below (See Table 2).

Australia

Mussels (Mytilus edulis) from Port Philip Bay in Victoria, Australia were found to contain PCBs (8). In the Brisbane River estuary, 6 species of fish, 3 species of crustacea, 1 species of mollusk, mixed species of the polychaetes (marine worms) and 1 species of bird was found to be contaminated with PCBs (9).

Arctic Region

Fat tissues from porpoise contained 6.7 ppm PCB (10).

Northwest Atlantic Ocean, Gulf of Mexico

Gag (Mycteroperca microlepis), black grouper (M bonaci), red grouper (Epinephelus morio), red snapper (Lutjanus campechanus), king mackerel (Scomberomorus cavella) and Spanish mackerel (S. maculatus) were found contaminated (13).

Pacific Region

Ten species of small cetaceans (e.g. porpoise) were examined for PCBs in blubber. The location of the sample ranged from the Eastern Pacific and along the coasts of California, Hawaii, Japan and Uruguay. All species tested were positive. One species (Tursiops truncatus) sampled off the California coast was found to have 2,695 ppm. This is believed to be one of the highest concentrations found in tissues of any population of wild animals (14).

Europe

Sweden

Seasonal variations in PCB levels in perch and roach were noted in waters near a nuclear power plant by Hamnefjarden, Sweden (11). It was also found (12) that PCB contamination existed in a variety of marine organisms off the coast of Sweden.

Finland

In a lake area of eastern Finland, perch, roach, vendace, and rainbow trout were found to be contaminated (15). Seven aquatic bird species found in Lake Paijanne in Finland were also found to contain PCBs (16). Baltic herring (Clupea harengus) and cod (Gaddus morrhua) found in the Gulfs of Bothnia and Finland also showed positive results. On an archipeligo in southwest Finland arctic tern (Sterna paradisaea) showed PCBs in fat of females in concentrations up to 80.1 ppm. PCBs were also found in tern eggs and newly hatched chicks (17).

Italy

A variety of marine animals around the Bay of Naples was shown to be contaminated (18).

England

Livers of grey seals taken off Farne Island showed positive results. The presence in the livers of mother/fetus pairs shows that the compounds can undergo transplacental movement (19).

Spain

Purple herons, spoon ducks, and heron eggs yielded positive results(20).

Japan

Aerial samples of urban areas of large cities such as Tokyo may contain up to 2 ppb PCB (21,22). Tokyo Bay surface water was found to contain up to 320 ppt (23). Other studies too numerous to mention point out the seriousness of the problem in Japan.

United States

Boston, Massachusetts

Air concentrations as great as 7.1 ppt PCB were found (24).

Columbia, South Carolina

Air concentrations as great as 4.4 ppt PCB were found (24).

Texas

Seven species of wintering shorebirds off Corpus Christi were shown to be contaminated with PCBs (25). PCBs at concentrations up to 70 ppt have been found in Galveston Bay (26).

Utah

PCBs were detected in western grebe (Aechmoporus occidentalis) eggs in Bear Valley Migratory Bird Refuge (27).

Midwest and Michigan

As part of the National Pesticide Monitoring Program, it has been noted (28) that highest aerial PCB residues were found in industrialized areas of the northwest and midwest. In a recent study (29) it was found that average aerial PCB concentration over Lake Michigan was 1 ppt while that from surrounding urban areas was 5 ppt. Surficial sediments collected from the Lake in 1975 showed a mean residue of 9.7 ppt PCB (30). Figure 2 shows the distribution of PCBs in the Lake.

The above survey (see Table 2) is not complete. Other studies show PCB concentrations in other species and areas (e.g. 31-33).

BIOACCUMULATION AND METABOLISM

A corollary question to distribution is that of bioaccumulation. This area includes such questions as how much is absorbed, metabolized, excreted, or passes various body barriers? What is the biological half-life for various organs; the body as-a-whole? Unfortunately we do not have a complete pharmacokinetic picture for PCBs. Significant problems arise in interpreting the data avilable. For example, it was found (17) that in arctic terns average concentrations of PCBs in fat for females and males, respectively, were 38.7 and 80.1 ppm. To evaluate the meaning of these results there are a variety of questions that must be answered. For example: Do females have a tendency to bioaccumulate one half as much as males or is some other factor involved? (e.g. Do the females lose PCBs to the eggs and offspring?) Can the figures be extrapolated to the human population? Do females have more body fat thereby diluting the PCBs? Do female terns consume the same diet as males, etc.

There is significant evidence for species differences. For example, different bioaccumulation factors are indicated for perch, roach, vendace and rainbow trout (15). However, in another report (34) on the specific congener, 2,2',5,5' tetrachlorobiphenyl, it was found that whole body elimination was similar for yellow perch (Perca flavescens) and rainbow trout (Salmo gairdneiri). The tissue distribution was quite different, however. In perch the viscera and carcass were the main distribution sites. Skeletal muscle, skin and scales were minor sites. In the trout, skeletal muscle and carcass were major sites while viscera and skin were minor sites. This study points up the need for standard edible portion to be based upon fillet plus skin-on sampling. In another study (35) 3,3',4,4'tetrachlorobiphenyl was examined for excretion rates in rats and rhesus monkeys. Distribution and clearance was similar in male and female rats (contra (17) in terns.) Monkeys clear the compound more slowly.

The difficulty of the problem associated with absorption of different congeners is pointed up by a recent study (36). Six hexachlorobiphenyl congeners were fed to rats, guinea pigs, rabbits, Japanese quail, and trout. Total levels for fat after 29 days were, in descending order found in rat, rabbit, guinea pig, trout and Japanese quail. The results suggest that the extent of ortho substitution affects the level of retention. Rabbits and guinea pigs have greater retention of PCBs with 0, 1 and 2 ortho chloro substituents. Quail retain only the 3,4,5,3',4',5'-isomer while no retention preferences appear to exist for rat and trout. The authors' results are shown in Table 3. Other authors (37) have reported contradictory results (in rats) claiming that absorption efficiencies decreased as the number of chlorines substituted in biphenyls increased. They claim that absorption depends upon molecular size. Others (38) tested absorption of polychlorinated dibenzofurans in monkey and rat livers. They found that livers of both species favored absorption of the 2,3,4,7,8 compound. This is contrary to the previous authors' assertations regarding absorption and molecular size.

Still other authors (39) contrasted elimination of 4,4' dichlorobiphenyl in beagle dogs and cynomolous monkeys (Macaca fascicularis). The elimination rate in the dog is 9 times greater than in the monkey. In anesthetized dogs 33% of the dose was excreted into the bile in 2 hours. In the monkey the amount of excretion is 0.4%.

A better understanding of PCB metabolism should help answer significant questions on health effects of the compounds. Three key questions are of interest:

1. Since routes of metabolism depend upon species, what are the differences in metabolism in species such as dog, rat, monkey and man?

2. What structure-activity relationships exist for metabolism?

3. What congeners are present in man, Lake Michigan fish?

While a thorough discussion of these problems is beyond the scope of this report, several recent findings are presented.

Humans

In a recent study (40) on humans exposed to PCBs, the following was discovered with respect to PCBs found in plasma and adipose tissue.

a) the major congeners had chlorines in the 4 and 4' positions.

b) congeners with chlorines on the 2,4, and 2',4' and/or 3,4 and 3,4' positions were present in higher concentrations than in commercial mixtures.

c) congeners with unsubstituted 3,4 positions were found in lower concentrations.

It should be noted that other authors found that the simplest inducer of cytochrome P-448 was 3,4,3',4' tetrachlorobiphenyl (41, 96). Chlorines at both ortho positions (e.g. 2,4,5,2',4',5'-hexachlorobiphenyl) causes induction of cytochrome P-450. These cytochromes can also be induced by 3,4 substitution on one-ring (42, 92) (e.g. 2,4,5,3',4'-pentachlorobiphenyl). Figures 3 and 4 and Table 4 (from 40) show the differences in an adipose sample of a PCB-exposed worker and a commercial Aroclor. The significance of this work is that man appears to preferentially bioconcentrate PCBs that can induce cytochromes.

Dog

It has been shown (43) that the dog can excrete 70% of administered 2,3,6,2',3',6' hexachlorobiphenyl in 3 days. The study on humans does not show the presence of this congener in plasma or adipose tissue.

Monkey

In this same study it was shown that after 15 days, monkeys were found to have excreted only 61% of 2,3,6,2',3',6' hexachlorobiphenyl. The elimination rate constants for dog were three to four times greater than those obtained for the monkey.

A further discussion of these problems is given in (2). The results of pharmacokinetic and structure activity relationships known to date is summarized in Tables 5 and 6.

The data to date suggest the following conclusions:

1. The literature available is insufficient to define pharmacokinetic parameters either for different species or congeners.
2. Depending upon the species, these parameters may vary for different congeners.
3. The parameters for a given congener may vary for different species.
4. With this paucity of data, a worst-case analysis must be taken.

While the bioaccumulation studies performed to date on animals cannot provide enough information to define the extent of the problem in man,

several studies based upon one incident suggest the need for a "worst case" analysis.

In western Japan in 1968 a mass poisoning occurred due to the ingestion of rice oil contaminated by PCBs that had been a component of heating exchange oil that had leaked into the food. Hayabuchi et al (44) measured blood levels of PCBs 5-8 years after consumption of the oil (Table 7). The authors claim a positive correlation between amount of oil consumed and PCB in the blood. Levels as high as 39 ppb were found and the mean appears to increase as the time from the date of the incident progresses. (e.g. The mean for males and females studied in 1976 is 10.5 ppb as contrasted to a mean in 1973 of 7.1 ppb. This represents an increase of approximately 48%.) Considering the fat:blood ratio of lipid-soluble compounds, one would expect PCB concentrations to be considerably higher in adipose tissue. In another article (45), the authors measured PCBs in Yusho victims, unexposed individuals and a PCB worker. The results are shown in Table 8. Several inferences may be made from examining this data:

1. Using PCB in liver as a measure (since it is the only parameter provided for all patients) there appears to be some positive correlation between the severity of Yusho observed (and probably the amount of exposure to the PCBs) and the PCB tissue level (Figure 5.)

2. So-called unexposed individuals may have PCB concentrations as high as those exposed.

3. No individuals tested were completely free of PCBs. This suggests that the body cannot totally eliminate PCBs or individuals are constantly being exposed from some external source. The data is clearly incomplete and there may be distinct differences in bioaccumulation exposure to high versus low doses. However, the data does prove one point. Since PCB levels were found to be high in patients for as long as nine years after exposure, it is clear that the body is less than 100% efficient in removing the pollutants. This mandates standards minimizing human exposure.

Figure 6 shows the type of metabolites that may be produced by PCBs. It must be emphasized that the type of metabolite(s) produced (if any) depends upon the structure of the given congener and the species tested. Different species can yield different metabolites and there are variations in which congeners can be metabolized. It has been found (46) for various hexachlorobiphenyls that the dog can eliminate the PCBs more rapidly than the mouse, rat or monkey. Species differences have also been shown for 4,4'dichlorobiphenyl (47). Other studies on various congeners emphasize these species differences (48-50). PCBs can undergo hydroxylation, dechlorination, and rearrangements. They can form dihydrodiols, phenols and phenol acetates, methyl ethers and sulfur containing metabolites. Arene oxides are proposed intermediates in the formation of some metabolites and these compounds are potentially electrophilic and they may form covalently-bound substrate macromolecular adducts. Congener binding to DNA and RNA and other macromolecules has been observed (51-61). Various congeners and arene oxides were shown to be capable of causing strand breaks in DNA (62, 63). Structure activity considerations must be examined (64).

METABOLIC EFFECTS OF PCBs

PCBs can affect a variety of normal biochemical pathways. Rats given a single dose of PCBs (190 mg/kg) showed alterations in carbohydrate metabolism two days after the dosing (65). Plasma glucose was decreased while blood lactate, acetoacetate and β-hydroxybutyrate were increased. Multiple dosing at this level (once/week for 5 weeks) showed the above effects and increased serum cholesterol. Other authors have shown that PCBs interfere with carbohydrate and lipid metabolism (66-69). In a recent study, it was found that PCBs increase conversion of acetate or glucose to cholesterol (70). Both in vivo and in vitro studies showed the same trend. In a study on a population accidently exposed to PCBs in sewage sludge (71) it was found that PCBs increased plasma triglyceride levels. In vitro studies of rabbit muscle lactic dehydrogenase showed inhibition by a group of congeners tested. The authors conclude

that inhibition is proportionate to the total number of ring-chlorines (72). Plasma and liver cholesterol as well as urinary ascorbic acid were increased in rats by PCBs(73,74). The significance of these results is yet to be determined.

The role of high and low density lipoproteins and cholesterol on cardiovascular disease is still a matter of controversy. It has been found (75) that PCBs cause increased serum cholesterol and high density lipoprotein in rats. In addition the ratio of low density lipoprotein and very low density lipoprotein to high density lipoprotein has been decreased. Whether PCB can in fact affect the incidence of cardiovascular disease is still an open question. But data such as that presented here emphasizes the need for more research in this area.

PCBs have also been shown to affect other systems. Phospholipid metabolism can be drastically changed (76, 77). PCBs have been found to decrease the activity of choline phosphotransferase and increase the activity of choline kinase (78). The potential effects of these actions has not yet been suggested.

In another human study on the effects of PCBs in the Yusho incident, it was found (79) that porphyrin metabolism can be influenced. An increased urinary excretion of delta-aminolevulinic acid and uroprophyrin was seen.

A recent study (80) details the difficulties inherent in the understanding of the effect of PCBs on metabolic systems. Broiler chicks were fed either fat from PCB-treated swine or untreated PCB in lard. The PCB from swine appeared to be a stronger microsomal enzyme inducer although the untreated PCB was a better inducer of certain specific enzymes.

While specific effects of PCBs on given metabolic pathways remain to be elucidated, the fact that PCBs can affect nucleic acids and carbohydrate, lipid, phospholipid, sterol and porphyrin metabolism suggests that the compounds may exert severe toxicological effects by interference with normal metabolic pathways. This mandates taking a conservative approach to standard setting for PCBs. (Table 9 summarizes known biochemical effects of PCBs.)

PCBs have been shown to be potent inducers of aryl hydrocarbon hydroxylase (AHH), an enzyme involved in carcinogenesis by polycyclic aromatic hydrocarbons (81). PCBs administered in the ppm range to the sheepshead (Archosareus probatoce phalus) caused significant induction of AHH as well as other enzymes (82). PCBs can induce the enzyme in the skin of the neonatal rat (83). They can induce AHH in renal or hepatic but not testicular tissues in the rat (84).

A class of enzymes known as microsomal mixed function oxidases (MFO) are known to play a complex role in the processes of carcinogenicity and mutagenicity. In addition, a complex biochemical mechanism known as the microsomal P-450 linked mono-oxygenase system plays an important role in the conversion of chlorinated hydrocarbons to electrophilic agents which may bind with DNA and proteins. This is suggested as a mechanism of carcinogenic action. The complexity of the problem can be seen by examining a study (85) where the major PCBs identified in human breast milk were prepared as a re-constituted breast milk mixture. This mixture was compared with the commercial PCB mixture, Kanechlor 500. The former was much more efficient in the induction of AHH. The authors claim that the result can be explained by preferential bioconcentration of the most toxic congeners. Even if this assumption is accepted, there is still no known explanation for the body preferentially concentrating the most toxic congneers. It is important to note that PCBs can induce mixed function oxidases, cytochrome P-450 and a variety of enzymes such as demethylases, deethylases, and transferases (see 80,82-98). The mixture can occur in such diverse species as rat, mouse, certain fish, swine and drosophila. The fact that PCBs can induce such a variety of enzymes of which we have limited knowledge with respect to their cellular function and interactions emphasizes the need for a cautious approach in assessing the possible effects of these compounds on man.

TOXICITY

From the previous discussion on metabolism and enzyme induction by PCBs, it would be expected that PCBs could induce a variety of pathological

manifestations. This is, in fact, the case. While many studies have been performed in animals and toxicities vary with species, it appears that monkeys are more sensitive than rats and man is suggested as being the most sensitive species (99). Symptomology is often a valid indicator of the capacity of an agent to produce disease and the Yusho incident provides data on the wide variety of symptoms produced from PCB exposure.

In Japan (1968), rice oil and dark oil were contaminated with PCBs that leaked from a heat exchanger. 400,000 chickens were killed and 2 million were found ill (100). A variety of symptoms were observed in humans (see Table 10 taken from 101). It is clear that PCBs have widely varied systemic effects. The minimum toxic dose was calculated to be 70 mg/kg/day for three months (102). Another study put the figure at an average 0.5 g/120 days (100). Some newborns showed chloracne and skin darkening at birth. It is noted that significant quantities of polychlorinated dibenzofurans were found in the rice oil and hence the effects cannot be attributed to PCBs alone. About 1200 persons were affected (102). While the Yusho incident must be kept in perspective because of the contaminants present, it does suggest the need for careful control of PCBs.

A variety of hepatic effects, including lipid accumulation, enlargement, fatty degeneration and necrosis have been reported from PCB exposure (McConnell in (2) (103-110). In a recent study (111) Macaca fascicularis monkeys fed 5 mg Kanechlor 400 daily for 20 weeks developed enlarged livers and symptoms resembling Yusho patients. In another study (112) rats fed PCBs (75 ppm) were observed to have focal liver necrosis, atypical centrolobular regeneration, accumulation of iron-containing pigment in hepatocytes and kupffer cells and numerous ultrastructural changes observed by electron microscopy. These changes were similar to those observed in rat livers injured by other heptotoxic agents. The study points out the severe and varied hepatotoxic effects that can be produced by PCBs. Hepatotoxic agents present cause for grave concern because of the potential for insidious effects. Keplinger (113) found that Aroclors 1242 and 1254 in concentrations of 100 mg/kg in diet caused, in 18 months, increased liver weight

down to 1.4 mg/kg body weight. These studies point out the gravity of hepatotoxic effects of PCBs. The fact that PCBs have shown hepatotoxicity mandates taking a conservative position in PCB regulation.

PCBs have been shown to induce goiter and hypothyroidism (115). Coho salmon from the Great Lakes show increased incidence of goiter (116-118). Studies on rats suggest that the toxic effects in thyroid is due to a PCB-induced decrease in serum thyroxin (119). PCBs have also been implicated in thyroid enlargement in rats.

PCBs also have a negative effect on the immune systems of the body (Vos, J.G. et al in (2). Reported effects include small spleens in chickens (120), atrophy of lymphoid tissues in chickens (121), thymic and splenic atrophy (122-126), decreased resistance in ducks to hepatitis, lymphopenia (127), decreased numbers of circulating leukocytes and lymphocytes, decrease in antibody titre to tetanus toxoid in guinea pigs (128) and decrease in antibody titre in rabbits (129). Other numerous studies (see Vos, J.G. et al (128), show that PCBs have strong effects on the immune system. In another recent review, a detailed analysis is given on PCB toxicity to lymphocyte function (130). In addition a recent work where a PCB-exposed population in Taiwan was studied (131) showed multiple defects in the immune system caused by PCBs. The fact that there is prima facie evidence of the potential of PCBs to cause varied immune defects (parameters which are difficult to measure in the human population) mandates a conservative approach in standard setting.

There is ample evidence that PCBs may also cause histological alterations in many cells. In a recent study (132) it was shown that PCBs were toxic in mouse spleen lymphocytes. The compounds affected the plasma membrane by inhibiting its 5'nucleotidase and ATPase. The authors suggest a general, rather than a specific mechanism based upon lipid solubility. In another study (133) the interaction of PCBs with cellular phospholipid bilayer membranes was studied by utilization of spin labels and electron paramagnetic resonance (EPR). The compounds were shown to affect the fluidity of the membranes. PCBs in mice can affect splenic

lymphocytes, CB cells, T cells, Null cells, and can cause transient splenic lymphocyte depletion (134). The effects of PCBs on lymphocyte function is reviewed (135). PCBs have also been shown to cause anemia suggested to be related to toxic effects in erythropoesis (135, 136). PCBs can also produce skin lesions including erythema, hyperkeratosis, alopecia, acne, blisters and desquamation (137-139).

Porphyrins are important to a variety of biochemical systems, one of the most important being the cytochromes. Porphyria is a disease where porphyrin metabolism is adversely affected. In chronic hepatic porphyria, excess porphyrins are produced and excreted. PCBs are an etiologic agent for this disease. While there is question whether porphyria can be induced in man, it is common in many species (Strik, J.M. et al in (2) (140).

CARCINOGENESIS

PCBs have been reported to be suspect human carcinogens (3) and possess tumor promoting activity (141). The compounds have been found to cause various liver cancers (142-146). The International Agency for Research on Cancer in evaluating the data on possible carcinogenesis of PCBs concluded as follows:

4. Summary of Data Reported and Evaluation[1]

4.1 Experimental Data

Five polychlorinated biphenyl mixtures have been tested in mice and/or rats only by oral administration. Kanechlor 500 and Aroclor 1254 are carcinogenic in mice, and Aroclor 1260 is carcinogenic in rats; all

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[1] Subsequent to the finalization of this monograph by the Working Group in October 1977, the Secretariat became aware of a study carried out under the NCI Bioassay Programme (NCI, 1978). Groups of 24 male and 24 female Fischer 344 rats were given Archlor 1254 at concentrations of 25, 50 or 100 mg/kg of diet for 104-105 weeks, when surviving animals were killed. No statistically significant differences between tumour incidences in experimental and control animals were seen. However, a few carcinomas and adenocarcinomas of the gastrointestinal tract were observed in treated animals; no such tumours occurred in controls. Hepatocellular hyperplastic nodules were observed in 11/48, 17/46, 29/48 treated animals, compared with none in controls.

induced benign and malignant liver-cell tumours. In an experiment in rats of only one year's duration, Kanechlor 500, 400, and 300 induced liver lesions described in multiple hyperplastic nodules.

4.2 Human data

Human exposure to small amounts of polychlorinated biphenyls is widespread as a result of environmental contamination and the high stability of these compounds. They are commonly found in human tissues. Unusually high levels of exposure to polychlorinated biphenyls have occurred among workers manufacturing or using them and in Japanese who consumed rice oil accidently contaminated with Kanechlor 400. The latter showed acute and chronic toxic effects.

An apparent excess of malignant melanoma has been reported in workers exposed to Aroclor 1254. No melanomas were reported in 9 persons who died from cancer among the 1200 Japanese heavily exposed to Kanechlor 400, but these deaths all occurred within 5½ years of first exposure. Neither the workers exposed occupationally nor the Japanese were exposed solely to polychlorinated biphenyls.

4.3 Evaluation

There is experimental evidence of a carcinogenic effect of some polychlorinated biphenyls in rodents. The epidemiological data provide suggestive evidence of a relationship between exposure to polychlorinated biphenyls and the development of malignant melanoma. Efforts should be made to obtain both confirmatory experimental and epidemiological evidence; in particular, continuing followup of survivors of the Yusho episode is necessary. In the meantime, for practical purposes, polychlorinated biphenyls should be regarded as if they were carcinogenic to humans.

Almost without exception, polychlorinated biphenyls contain various levels of polychlorinated dibenzofurans as contaminants, and the polychlorinated biphenyls responsible for the Yusho episode in Japan were found to contain an unusually high level of polychlorinated dibenzofurans. It is not known if and to what extent polychlorinated dibenzofurans play a role in the observed carcinogenic effects of polychlorinated biphenyls.

It would appear from the data that PCBs have been shown to be carcinogenic in animals. (Table 11 summarizes the work on carcinogenesis of PCBs in animals.) The question as to whether they are carcinogenic in man is still unanswered.

Carcinogenesis is thought to proceed by two processes--initiation and promotion. Initiation is the process whereby an agent provides the stimulus to induce the first step leading to change in the genetic

material. Promotion is the process whereby initiated cells are encouraged or stimulated to evolve into cancer (153). There is significant evidence that PCBs are promotors. It has been found (141) that PCBs administered after the carcinogen 3'-methyl-4 dimethylaminoazobenzene caused a significantly increased incidence of hepatoma. PCBs administered with or before the agent did not induce these tumors. In another study (154) rats treated with the carcinogen diethylnitrosamine were given commercial aroclor 1254 and Aroclor 1254 in which contaminating dibenzofurans were removed. Both PCB mixtures caused increased hepatocellular carcinomas although the former have shown a higher incidence. This study shows that the PCBs alone can act as promoters. Another recent study ((155) showed that polybrominated biphenyls (PBBs) can promote the action of diethylnitrosamine. The similarity in structure between appropriate cogeners of PCBs and PBBs would lend further credence to the evidence that PCBs are promoters.

FETOTOXIC AND TERATOGENIC EFFECTS

PCBs are known to pass the placental barrier. Offspring of pregnant mice treated with PCBs showed an increase in hepatic DMN demethylase. Similar results were obtained for mono-oxygenase activities in fetal livers. PCBs were shown to cause ultrastructural lesions in thyroid follicular cells and a reduction of serum levels of thyroid hormones in neonatal rats exposed to PCB in utero and by milk. In addition, rats fed PCBs showed decreased liver size (156). Viable hatch of flounder was decreased at concentrations of PCBs of 120 ppb (157). This work showed that PCBs in the environment can yield fetotoxic effects.

Low-dose fertility effects have been observed in monkeys and mink (106) and PCBs have been shown to pass the placenta in humans (158). In cows exposed to Aroclor 1254, the concentration in the fetal kidney was greater than that found in the mother (159). This same compound administered to rabbits showed greater concentrations in fetal livers as compared to that of the mother (160).

Pregnant rats fed dichloro and tetrachlorobiphenyls passed these compounds to their offspring. Metabolites were also found in the fetuses (161).

That PCBs may affect male reproduction is evidenced by a work (162) describing effects from feeding cod PCBs at 1, 5, 10, 25 and 50 µg/kg daily for 5.5 months. Testicular abnormalities including disorganization of lobules and spermatogenic elements, inhibition of spermatogenesis, fibrosis of lobule walls, fatty necrosis and in one case, total disintegration of the elements in many lobules was observed. In mink, diets of Aroclor 1242 caused total reproductive failure at concentrations as low as 5 ppm of the diet. Ferrets were found to be more resistant with complete reproductive failure occurring at concentrations as low as 20 ppm of the diet (163).

It is suggested that the immune response of offspring of rabbits fed PCBs may be impaired but only at high concentrations (164). PCBs caused cleft palate and other congenital anomalies in the offspring of treated mice (165). Other authors (166,167) suggested PCBs could induce behavioral abnormalities in offspring.

SYNERGISTIC EFFECTS

PCBs may be contaminated with polychlorinated dibenzofurans (PCDF) and/or polychlorinated naphthalenes (2) (168). While synergistic studies are virtually non-existent, practical experience shows (e.g. see section on Yusho) that a combination of chlorinated hydrocarbons can produce devastating health effects. The toxicity of PCDFs approach those of the dioxins. For example, 2,3,7,8-tetrachlorodibenzofuran has an LD_{50} in guinea pigs of 7 µg/kg (169) and trichlorodibenzofurans in dosages of 0.5 to 1 mg/kg have caused severe and often lethal liver necrosis in rabbits (170). The contaminants originally associated with a given amount of PCB might also be found in the same fish as the PCB. However, the presence of these and toxic dioxins may end up in fish alternatively contaminated with PCBs. In addition, fish may be contaminated with other highly toxic polychlorinated hydrocarbons such as polychlorinated dibenzodioxins such as 2,3,7,8 tetrachlorodibenzo-p-dioxin. In setting a standard, possible additive and synergistic effects must be considered. In an analysis of Great Lakes fish

performed in 1978 (169), 77% were found to contain PCBs, 100% contained DDT, and chlordane and hexachlorobenzene were found respectively in 38% and 65% of the fish tested. Chlorobenzene, chlorostyrenes, chlorophenols, and chlorinated aliphatics were also identified.

As was previously suggested, because PCBs can apparently promote during carcinogenesis, and act as inducers of enzymes involved in metabolism of other carcinogens (e.g. AHH), their presence along with other toxic agents could be expected to have a more severe effect on the population as contrasted to the other agents alone.

In a recent study (127), Kanechlor 400 was tested with and without PCDFs for toxic effects on Macaca fascicularis monkeys. PCBs alone produced loss in body weight, symptomology similar to patients involved in the Yusho incident and enlargement of the liver. The combination produced alterations in the immune system and ultrastructural alterations in the liver, kidney, and skin. PCBs have also been shown (171) to increase the mutagenic effect of other agents in Drosophila.

Since synergistic effects have not adequately been determined, it is recommended that fish be measured for:

a. total organic chlorine and bromine

b. total PCBs and PBBs

c. total chlorinated dibenzofurans

c. total chlorinated dibenzodioxins

Standards must be set based upon which combination of b, c, and d are present. For example, the detection of quantities of c and d even slightly above the limit of detection should either render a decision that the fish are inedible or at least cause the acceptable standard for PCBs to be lowered.

PCBs IN HUMANS

PCBs appear to be present in a large percentage of the human population. It has been found (172) that of 637 human fat samples analyzed at surgery or autopsy, PCB concentrations in 68.9% were less than 1 mg/kg. In 25.9%, the concentration was 1-2 mg/kg and in 5.2%, it was greater than 2 mg/kg. It has also been reported (173) that 43% of blood samples from 723 volunteers showed a mean concentration of PCBs of 0.5 mg/100 ml blood. In setting any standard, the factor of tissue concentration from prior exposure must be considered.

Another recent work has shown PCBs in all samples in the milk of Michigan mothers tested (174). The samples were collected from 68 of the State's 83 counties. The concentrations ranged from trace amounts to 5.1 ppm. Table 12 shows the levels correlated with the percentage of the population tested. The study shows that 73% of the population has PCBs greater than 1 ppm in the milk. The authors suggest breast milk monitoring for PCBs in nursing mothers who have had potentially high exposure to PCBs (175).

By contrast to the situation in Michigan, in milk samples of women analyzed in British Columbia (176), 2% of the samples were >50 ppb, 4% were between 25 and 50 ppb, 29% were between 50-5 ppb and 65% of the sample showed <5 ppb. The fact that the sample size (49) was considerably smaller than that taken in Michigan (1,043) must be considered. However even taking this into account it appears that the situation is significantly more serious in Michigan. Studies in Colorado (177) (8 of 39 women had PCBs ranging from 0.04 to 0.1 ppm) and Japan (108) (concentrations ranged from 0.1 to 0.7 ppm) also suggested a problem of less gravity than in Michigan.

In an EPA study (178) under the National Human Monitoring Program (NHMP) it was found that measurable residue levels of PCBs occur in a large percentage of the general population. The authors found that between 1972 and 1976 there was an increase in the population with > 3 ppm in their adipose tissues. (i.e. From 2.58% to 7.34% for whites and from 7.55% to 16.67% for non-whites.) In addition, for this time period there was an increase in total

population with some detectable level of PCBs. The mean ranged from 84.58% in 1972 to 96.54% in 1976. A representative calculation (Table 13) suggests that a mother with 1.5 ppm in breast milk might be expected to transfer up to 1.5 mg PCB daily to a suckling child. With ingestion of 1 fish containing 5 ppm PCBs, a conservative approach to standard setting is mandated.

EPIDEMIOLOGY

Several recent studies suggest that PCBs may cause various diseases in humans. In a recent work (182), it was found that in a cohort of electrical workers with potential for exposure to PCBs, excess mortality was noted for rectal and liver cancer. Although neither was statistically significant, all cancer mortality was lower than expected. In another study (183), electrical workers were found to have total PCB blood concentrations of 80-1319 ppb. In another study on this group (184), the authors noted significant increases in skin diseases and hepatic involvement (e.g. hepatomegaly with altered concentratons of liver enzymes). It is suggested that the pathological manifestations associated with liver can be associated with blood trichlorobiphenyl but not pentachlorobiphenyl levels. The authors suggest that 20% of cases of abnormal liver injury would be found in those with 200 ppb PCB in blood. Other works (185, 186) suggest a relationship between human melanoma and PCB exposure. It has also been found (187) that in a population exposed to low levels of PCBs in sludge, alterations in liver metabolism occur at levels where no overt symptoms were induced. An epidemiology study (188) on a normal population with moderate PCB blood levels suggested a positive correlation between PCB exposure and hypertension, liver function and blood cholesterol levels. Other reviews (Kimborough, R. (chap. 9) and Kuratsune, M. in (2) outline other epidemiology studies involving PCBs.

While it is difficult to reach conclusions on PCB effects based on the epidemiological evidence available to date, the works discussed above suggest a causal relationship. Until the questions presented are resolved, it is imperative that all measures to limit human exposure be taken.

ANALYTICAL TECHNIQUES

The methodologies available for measuring PCB concentrations are such as to allow accurrate measurements down to the ppt level. For example, a recent study (189) discussed methodologies where PCB levels in waters of the Great Lakes were measured at levels as low as 1 ppt (nanogram/l)(See Table 14). Recent development of methodologies for synthesizing standards (e.g. 190) has made it possible to analyze for specific congeners.

PCBs can be measured by gas chromatography (GC) or combined gas chromatography/mass spectrometry (GC/MS). For total PCB analysis, if only GC is available, perchlorination with antimony pentachloride is advisable (See (191) for review). However, more sophisticated analysis should involve the use of GC/MS (192) although new techniques are continually being developed to improve analysis by both GC and GC/MS (e.g. 193, 194). General methodologies for the use of GC/MS for water samples is well-documented (e.g. Rappe, C. in (2) (195). Specific techniques have been developed for identifying any given isomer (e.g.(196). Specific methodologies have been developed for measurement of PCBs in air (197, 198).

The analysis of PCBS from tissues present special problems that require use of pre-extraction techniques. A recent study (199) describes the techniques available to solve the problem of varying fat content in analysis of PCBs in human milk. Other authors describe cleanup techniques for fatty materials in vegetable samples (200) and in fat samples from steers (201). New techniques involving PCB measurement in both blood and milk is described (202).

The state of the art has progressed to the point where the techniques are available both for the separation of PCBs from other chlorinated hydrocarbons and PCB metabolites and identification of same (203, 204).

It is clear that the methodology exists for accurately measuring PCBs and specific congeners and identifying contaminants and metabolites. Thus the techniques to implement a 2 ppm standard are available.

CONCLUSION

The data available on PCBs is quite detailed. Yet still many unanswered questions remain. However, application of the known information mandates a conservative approach in the setting of PCB standards. It is for this reason that the Toxic Substance Control Commission has recommended a 2 ppm standard. The data presented does not support the maintenance of the current 5 ppm standard.

TABLE 1

GENERAL INFORMATION ON POLYCHLORINATED BIPHENYLS

NAME	EMPIRICAL FORMULA	MOLECULAR WEIGHT	NUMBER OF CHLORINES	NUMBER OF POSSIBLE ISOMERS	PERCENT CHLORINE
Chlorobiphenyl	$C_{12}H_9Cl$	188.7	1	3	18.79
Dichlorobiphenyl	$C_{12}H_8Cl_2$	223.1	2	12	31.77
Trichlorobiphenyl	$C_{12}H_7Cl_3$	257.6	3	24	41.30
Tetrachlorobiphenyl	$C_{12}H_6Cl_4$	292.0	4	42	48.56
Pentachlorobiphenyl	$C_{12}H_5Cl_5$	326.4	5	46	54.30
Hexachlorobiphenyl	$C_{12}H_4Cl_6$	360.9	6	42	58.93
Heptachlorobiphenyl	$C_{12}H_3Cl_7$	395.3	7	24	62.77
Octachlorobiphenyl	$C_{12}H_2Cl_8$	329.7	8	12	65.98
Nonachlorobiphenyl	$C_{12}HCl_9$	364.1	9	3	68.73
Decachlorobiphenyl	$C_{12}Cl_{10}$	398.5	10	1	71.18
				Total:209	

TABLE 2

ENVIRONMENTAL CONTAMINATION BY PCBs

LOCATION	SAMPLE	PCB LEVEL	REFERENCE
Australia	Mussels Fish Crustacea Mollusk Marine Worms	N.A.	(8, 9)
Arctic	Porpoise Fat	6.7	(10)
Northwest Atlantic Ocean Gulf of Mexico	Fish	mean - 0.32 ppm highest - 1.8 ppm	(13)
Eastern Pacific & coasts of California, Hawaii, Japan and Uruguay	Cetaceans (e.g. porpoise)	Maximum - 2,695 ppm	(14)
Sweden	Fish Various marine organisms	N.A.	(11,12)
Finland	Fish Birds Birds	N.A. Maximum - 5 ppm Maximum - 80.1 ppm	(15) (16) (17)
Italy	Marine Animals	N.A.	(18)
England	Seals	N.A.	(19)
Spain	Birds	N.A.	(20)
Japan	Air Tokyo Bay Surface Water	Maximum - 2 ppb Maximum - 320 ppt	(21,22) (23)
United States			
Boston, Massachusetts	Air	Maximum - 7.1 ppt	(24)
Columbia, South Carolina	Air	Maximum - 4.4 ppt	(24)
Corpus Christi, Texas	Birds	Maximum - 6.64 ppm	(25)
Galveston Bay, Texas	Water	N.A.	(26)
Utah	Birds	N.A.	(27)
Northwest, Midwest	Fish	N.A.	(28)
Lake Michigan	Air over lake Air over surrounding urban areas Surficial Sediments	Average - 1 ppt Average - 5 ppt Mean - 9.7 ppt	(29) (29) (30)

N.A. = Information not available to author.

TABLE 3*

HCBP LEVELS IN RABBIT, RAT AND GUINEA PIG ADIPOSE TISSUE, TROUT AND JAPANESE QUAIL CARCASSES 29 DAYS AFTER ADMINISTRATION OF THE ISOMER MIX

ISOMER	TISSUE LEVELS (ppm)				
	Rabbit[a] fat	Rat[b] fat	Guinea pig[c] fat	Japanese quail[d] carcass	Trout[e] Carcass
2,2',4,4',6,6'-HCBP	0.302 ± 0.056	1.253 ± 0.460	0.120 ± 0.020	ND[f]	0.612 ± 0.148
2,2',4,4',5'6-HCBP	0.357 ± 0.077	2.003 ± 0.847	0.074 ± 0.004	ND	0.838 ± 0.174
2,2',4,4',5,5'-HCBP	2.043 ± 0.655	3.053 ± 0.855	0.933 ± 0.004	ND	0.559 ± 0.131
2',3,4,4',5,5'-HCBP	2.103 ± 0.508	1.433 ± 0.681	2.108 ± 0.230	ND	0.462 ± 0.001
3,3',4,4',5,5'-HCBP	2.030 ± 0.495	0.529 ± 0.222	1.500 ± 0.018	0.215 ± 0.018	0.553 ± 0.009

[a]5, [b]4, [c]2, [d]5 and [e]3 species per group.

[f]ND, non-detectable.

NOTE: Numbering System is in error but as reported in original article.

Dosage: 5 mg/kg/29 days.

*From: Sparling, J. et al (36).

ANALYSIS OF PCB CONGENERS IN ADIPOSE TISSUE AND PLASMA
AMONG CAPACITOR MANUFACTURE WORKERS

*From: Wolfe, M.(40).

Peak	Structure Assignment	Concentration in adipose (ug/g) Median	Range	Plasma (ng/ml) Median	Range	Adipose-Plasma Partitic
1A	4,4'-	0.08	0.002-0.2	0.7	0.03-2	90
1	2,4,4'-(2,5,4'-)	9	0.5-183	27	1-850	200
2	2,5,2',5'-	0.5	0.07-3	4	0.5-23	80
3	2,4,2',5'-	0.3	0.06-4	2	0.2-42	90
4	2,4,2',4'-	0.6	0.09-11	3	0.2-24	310
5	2,3,2',5'-	0.5	0.1-5	3	0.4-55	80
5A	(2,3,4,2'-;3,5,3',5'-)	0.3	0.04-3	1	0.2-42	60
6	2,4,5,4'-	7	0.5-36	26	0.7-180	200
7	2,5,3',4'-	0.4	0.1-2	2	0.2-27	70
8	2,4,3',4'-	2	0.2-18	7	0.3-113	160
9	2,3,6,2',5'-	0.2	0.05-2	1	0.3-9	60
10	2,3,5,2',5'-	0.1	0.08-0.3	0.9	0.6-2	
11	2,4,5,2',5'-	0.1	0.07-0.5	0.8	0.4-6	50
12	2,4,5,2',4'-	1	0.07-5	4	0.4-12	240
13	(2,3,4,4',-; 3,4,3',5'-)	0.9	0.03-6	3	0.7-29	190
14	2,3,6,2',3'-					
15	2,3,5,2',3'-					
16	2,4,5,2',3'-					
	p,p'-DDE	2	0.3-8	7	0.6-35	170
17	2,3,4,2',5'-	0.2	0.08-0.5	1	0.6-2	
18	2,3,6,3',4'-(3,4,3',4'-)	0.1	0.07-0.3	0.5	0.3-3	
19	2,3,5,3',4'-	0.1	0.09-0.2	0.6	0.4-1	
20	2,4,5,3',4'-	2	0.09-5	8	0.7-41	180
21	2,3,5,2',4',5'-	0.1	0.05-0.7	0.7	0.2-2	300
22	2,4,5,2',4',5'-	1	0.09-4	5	0.7-12	270
23	2,3,4,3',4'-	1	0.2-4	2	0.6-20	130
24	2,3,4,2',3',5'-	0.1	0.05-0.3	0.4	0.2-2	
25A	(2,3,4,5,3',5'-)	0.3	0.05-1	1	0.4-4	360
25	2,3,4,2',4',5'-	1	0.06-4	4	0.5-17	110
26	2,3,5,6,2',4',5'-	0.2	0.05-0.7	0.6	0.2-2	370
27	2,3,4,6,2',4',5'-	0.1	0.06-0.2	0.3	0.2-0.8	160
28	(2,4,5,3',4',5'-)	0.1	0.05-0.4	0.5	0.2-2	120
29	2,3,4,2',3',4'-	0.07	0.05-0.2	0.8	0.7-0.8	
30	2,3,4,5,2',3',6'-	0.09	0.05-0.2	0.3	0.2-0.3	
31	2,3,5,6,2',3',4'-	0.07	0.05-0.3	0.4	0.2-0.5	
32	2,3,4,5,3',4'-	0.4	0.08-2	2	0.2-5	310
33	2,3,4,5,2',4',5'-	0.6	0.05-3	3	0.6-8	270
34	2,3,5,6,2',3',4',5'-	0.2	0.05-0.5	1	0.2-2	260
35	2,3,4,5,2',3',4'-	0.2	0.08-1	1	0.5-3	360
36	2,3,4,2',3',4',6'-	0.1	0.05-2	0.7	0.2-1	
37	2,3,4,5,2',3',4',5'-		0.1			

Note: Concentrations were calculated from response factors of standards for peaks 1(1); 11(2-20, 23); peak 22 (21,22,24-36). Peaks 14-16 were negligible in fat and plasma. Partit was derived from regression coefficient (slope) of adipose tissue vs plasma levels. Peaks w no partition values had fewer than four cases with detectable values in both adipose and pl or the correlation was not statistically significant (peaks 17,18,24). The number of case with detectable peaks in both adipose and plasma were(peak,n): 1A,14; 1,25; 2,16; 3,9; 4, 1 5A,16; 6,26; 7,7; 8,20; 9,8; 10,3; 11,9; 12,23; 13,17; 20,22; 21,16; 22,23; 23,19; 25A,17; 25,23; 26,16; 27,7; 28,10; 32,19; 33,22, 34,4; 35,11.

TABLE 5

PHARMACOKINETICS OF PCBs

CONGENER	SPECIES	HALF-LIFE OR OTHER PARAMETERS (see notes)	REFERENCE
4,4-	Dog	1 day	(39)
	Monkey	21 days	
2,3,6,2',3',6'-	Dog	1 day	(43)
	Monkey	9 days	
2,4,6,2',4',6'-	Rat	1.253-RR[a]*	(36)
	Trout	0.612(48.8%)RR[a]	
	Rabbit	0.302(24%)RR[a]	
	Guinea Pig	0.120(9.5%)RR[a]	
	Japanese Quail	0.000(0%)RR[a]	
2,4,6,2',4',5'-	Rat	2.003-RR[a]*	(36)
	Trout	0.838(41.87%)RR[a]	
	Rabbit	0.357(17.8%)RR[a]	
	Guinea Pig	0.074(3.7%)RR[a]	
	Japanese Quail	0.000(0%)RR[a]	
2,4,5,2',4',5'-	Rat	3.053-RR[a]*	(36)
	Rabbit	2.043(66.9%)RR[a]	
	Guinea Pig	0.933(30.6%)RR[a]	
	Trout	0.559(18.3%)RR[a]	
	Japanese Quail	0.000(0%)RR[a]	
3,4,5,2',4',5'-	Guinea Pig	2.108-RR[a]*	(36)
	Rabbit	2.103(99.8%)RR[a]	
	Rat	1.433(67.9%)RR[a]	
	Trout	0.462(21.9%)RR[a]	
	Japanese Quail	0.000(0%)RR[a]	
3,4,5,3',4',5'-	Rabbit	2.030-RR[a]*	(36)
	Guinea Pig	1.500(73.4%)RR[a]	
	Trout	0.553(27.2%)RR[a]	
	Rat	0.529(26.1%)RR[a]	
	Japanese Quail	0.215(10.6%)RR[a]	
Decachlorobiphenyl	Cow	0%-Body Retention	(205)
4-	Rat	48.2-ED[b]	(206)
4,4'-	Rat	24.6-ED[b]	
2,4,5,2',5'-	Rat	20.5-ED[b]	
2,4,5,2',4',5'-	Rat	1.3-ED[b]	

(a) Relative retention-the level in ppm is given for the species with the asterisk (this is th highest value reported). The values reported for the other species are those percentages of PCB retained as compared to the reference animal which had the highest retention level (mean values are used).
(b) Excreted dose after 4 hours.

TABLE 6

STRUCTURE-ACTIVITY RELATIONSHIPS FOR PCBs

STRUCTURAL CHARACTERISTIC	SPECIES	EFFECT OBSERVED	REFERENCE
Increased chlorination (1 to 6)	rat	increased body retention	(206)
Availability of unsubstituted adjacent carbon atoms	rat	increased metabolism and excretion	(207-209
Availability of unsubstituted adjacent carbon atoms	mouse	increased metabolism and excretion	(210,211
Chlorines in 4,4' position	man	tendency to bioaccumulate	(40)
Comparison of chlorines in 4,4' position and those in unsubstituted 3,4 positions	man	latter has less tendency to bioaccumulate	
Chlorines in 2,4 and/or 3,4 positions on both rings	man	tendency to bioaccumulate	
Comparison of 2,4 and/or 3,4 positions on both rings and those with unsubstituted 3,4 positions regardless of chlorination.	man	former has greater tendency to bioaccumulate.	
Comparison of 2,4 substitution on both rings and 3,4 substitution on either ring	man	former has greater tendency to bioaccumulate	
2 or more ortho chlorines	mammals	exclusively cytochrome P-450 (not P-448) inducer	(91)
3,3',4,4',5,5' hexachlorobiphenyl	mammals	exclusively cytochrome P-448 (not P-450) inducer	
3,4 or 4,5 positions unsubstituted	mammals	most easily metabolized and eliminated	
2,3 or 5,6 positions unsubstituted, all 3,4 or 4,5 vicinal positions blocked	mammals	slowly metabolized	
No adjacent pairs of unsubstituted positions	mammals	eliminated most slowly	
Substitution at both para positions, 2 ortho positions, at least 2 meta positions and containing 2,3,4 substitution pattern	mammals	mixed microsomal enzyme induction	(88)
3,3',4,4' tetra and 3,3',4,4',5,5' hexa congeners	mammals	mixed microsomal enzyme induction	(212,21

TABLE 7**

MEAN AND RANGE OF AGE, TOTAL AMOUNT OF OIL CONSUMED, THE AMOUNT OF OIL CONSUMED PER KG PER DAY, AND THE BLOOD PCB CONCENTRATION OF YUSHO PATIENTS IN 1973-1976

Year	Sex	No. of Patients	Age (yr)		Oil Consumption				Blood PCB(ppb)	
					Total (ml)		Daily(ug/kg/day)			
			Mean	Range	Mean*	Range	Mean*	Range	Mean*	Range
1973	M	21	35.7	6-74	700	230-3813	207	75-608	6.9	2-29
	F	27	29.3	8-60	784	195-3375	244	68-861	7.2	1-39
	M + F	48	32.1	6-74	746	195-3375	227	68-861	7.1	1-39
1974	M	14	38.9	8-68	748	220-2813	160	32-608	8.6	5-19
	F	24	33.4	9-58	842	212-3375	224	55-861	9.1	2-31
	M + F	38	35.4	8-68	806	212-3375	198	32-861	8.9	2-31
1975	M	13	44.0	10-76	828	216-2813	207	49-351	8.5	3-19
	F	19	32.7	10-59	856	288-3375	236	55-861	8.2	2-37
	M & F	32	37.3	10-76	845	216-3375	224	49-861	8.3	2-37
1976	M	9	50.4	23-77	623	288-1934	196	75-608	9.9	6-14
	F	10	42.2	11-60	888	288-3375	218	55-861	11.5	4-32
	M + F	19	46.1	11-77	751	288-3375	207	55-861	10.5	4-32

* Geometric mean

** From Hayabuchi, M. et al (44).

TABLE 8**

INDIVIDUAL PCB AND PCQ LEVELS IN THE TISSUES OF YUSHO VICTIMS, UNEXPOSED INDIVIDUALS AND IN THE MILK FAT OF A WORKER OCCUPATIONALLY EXPOSED TO PCB

Sample no.	Age	Sex	Date of Death	Severity of Yusho*	Tissue (or fluid)	GC Pattern of PCB+	PCB level (ppb)	PCQ level (ppb)
				Yusho victims				
583	0	M	14.10.68		Intestine	C	29.7	83.6
					Liver	C	50.5	393.0
15868	25	M	9.7.69	4	Adipose Tissue	A	5090.7	2400.0
					Liver	A	225.9	217.5
651	48	F	29,12.70	1	Adipose Tissue	C	270.5	2.2
					Liver	C	7.4	1.2
166.34	46	M	16.5.72	3	Adipose Tissue	A	6091.3	1444.0
					Liver	A	68.5	143.5
8	72	M	30.4.75		Intestine	A	3471.8	1770.0
					Liver	A	114.4	51.7
AN-77-34	59	M	17,3.77	2	Intestine	A	3630.3	1125.0
					Liver	A	68.4	27.0
AN-77-100	69	M	4,9.77	1	Intestine	B	1273.4	24.5
					Liver	C	17.7	1.0
				Unexposed Individuals				
1 unexposed	46	M	19.9.78		Adipose Tissue		1477.8	2.7
					Liver		71.1	0.8
2	70	M	28.9.78		Adipose Tissue		530.1	2.7
					Liver		17.9	0.6
3	54	F	21,9.78		Liver		22.0	0.7
4	35	F	24.9.78		Adipose Tissue		248.0	1.3
				PCB Worker				
	37	F			Mother's Milk Fat		6241.1	0.3

*Grade of Severity of skin lesions; grades increase with increasing severity **Kashimoto, T. et al (46)

+The PCB GC patterns are classified according to Masuda et al (1974). A is peculiar to Yusho patients, B is similar to A &

TABLE 9

BIOCHEMICAL EFFECTS OF PCBs

EFFECT	REFERENCE
Alterations in carbohydrate metabolism	(65)
Alterations in carbohydrate and lipid metabolism	(66-69)
Increased conversion of acetate or glucose to cholesterol	(70)
Increased plasma triglycerides	(71)
Inhibition of lactic dehydrogenase	(72)
Increase in plasma and liver cholesterol and urinary ascorbic acid	(73,74)
Increase in serum cholesterol and high density lipoprotein:Decrease in ratio of low density and very low density lipoprotein to high ensity lipoprotein	(75)
teration in phospholipid metabolism	(76,77)
ease activity of choline phosphotransferase and increase ity of choline kinase	(78)
nce porphyrin metabolism (increase urinary excretion of delta- vulinic acid and uroprophyrin)	(79)
nzyme induction	(80-98)

*Grade of Severity of skin lesions; grades increase according to Masuda et al. [illegible] are classified as [illegible]

+The PCB GC patterns [illegible]

TABLE 10*

PERCENT DISTRIBUTION OF SYMPTOMS OF YUSHO REPORTED BY 189 PATIENTS EXAMINED BEFORE OCTOBER 31, 1968

SYMPTOMS	MALES (N = 89)	FEMALES (N = 100)
Dark brown pigmentation of nails	83.1	75.0
Distinctive hair follicles	64.0	56.0
Increased sweating at palms	50.6	55.0
Acnelike skin eruptions	87.6	82.0
Red plaques on limbs	20.2	16.0
Itching	42.7	52.0
Pigmentation of skin	75.3	72.0
Swelling of limbs	20.2	41.0
Stiffened soles in feet & palms of hands	24.7	29.0
Pigmented mucous membrane	56.2	47.0
Increased eye discharge	88.8	83.0
Hyperemia of conjunctiva	70.8	71.0
Transient visual disturbance	56.2	55.0
Jaundice	11.2	11.0
Swelling of upper eyelids	71.9	74.0
Feeling of weakness	58.4	52.0
Numbness in limbs	32.6	39.0
Fever	16.9	19.0
Hearing difficulties	18.0	19.0
Spasm of limbs	7.9	8.0
Headache	30.3	39.0
Vomiting	23.6	28.0
Diarrea	19.1	17.0

*From: Kuratsune, M. (101)

TABLE 11

STUDIES ON CARCINOGENICITY OF PCBs

SPECIES	TEST SUBSTANCE	ROUTES OF ADMINISTRATION	DOSAGE	INCIDENCE	REFERENCE
TOTAL CARCINOGENESIS TESTING					
dd mice (m)	Kanechlor 300,400,500	oral	500 mg/kg/32 weeks	7/12 - liver nodules 5/12 - hepatocellular carcinoma	(147)
Balb/cs mice (m)	Aroclor 1254	oral	300 mg/kg diet/11 mos	9/22 - hepatoma 22/22 - adenofibrosis	(148)
Sherman rats(f,m)	Arcolor 1260	oral	0, 20, 100, 500 or 1000 mg/kg diet/8 mos	2/10 (m) adenofibrosis 1000 mg/kg 1/10 (f) adenofibrosis 100 mg/kg 1/10 (f) adenofibrosis 500 mg/kg 4/10 (f) adenofibrosis 1000 mg/kg	(149)
	Arcolor 1254	oral	0, 20, 100 or 500 mg/kg diet/8 mos	10/10(m) adenofibrosis 500 mg/kg 9/10 (f) adenofibrosis 500 mg/kg 1/10 (m) adenofibrosis 100 mg/kg 7/10 (f) adenofibrosis 100 mg/kg	(149)
Donryu rats(f,m)	Kanechlor 400	oral	38.5 - 616 mg/kg diet/400 days	6/10 (f) adenomas	(150)
Wistar rats(m)	Kanechlor 300, 400, 500		1000 mg/kg diet " " " 500 mg/kg diet 100 mg/kg diet " "	2/15 - cholangiofibrosis-Kanechlor 300 2/10 - cholangiofibrosis-Kanechlor 400 4/13 - cholangiofibrosis-Kanechlor 500 5/13 - hyperplasia-Kanechlor 500 3/10 - hyperplasia-Kanechlor 400 5/10 - hyperplasia-Kanechlor 500 1/22 - hyperplasia-Kanechlor 300 2/16 - hyperplasia-Kanechlor 400 3/25 - hyperplasia-Kanechlor 500	(151)
Sherman rats(f)	Archlor 1260		100 mg/kg diet 21-22 mos	26/184 - hepatocellular carcinoma 144/184 - neoplastic nodules	(152)

males
females

SPECIES	TEST SUBSTANCE	ROUTES OF ADMINISTRATION	INITIATOR	DOSAGE	INCIDENCE	REF
B. PROMOTION						
Donryu rats	Kanechlor 400	oral	3'-methyl-4 dimethyl aminoazobenzene (3'MeDAB)	600 mg/kg diet/6 mo. 3'MeDAB, then 400 mg/kg diet Kanechlor	9/11 (63.6%)	(141)
Sprague Dawley rats	Aroclor 1254	oral	diethylnitrosamine (DEN)	66 ug/kg diet/5 wk DEN, then 100 mg/kg diet/ 18 wk. Aroclor	21/33(63.6%)[a] 27/32(84.4%)[b]	(154)

[a]PCBs previously treated to remove polychlorinated dibenzofurans.

[b]PCBs untreated; contaminated with polychlorinated dibenzofurans.

TABLE 12*

PCBs IN MOTHERS MILK IN MICHIGAN

LEVEL	PERCENTAGE OF TEST GROUP WITHIN LEVEL
> 3 ppm	6.14
2-3 ppm	17.4
1-2 ppm	49.5
< 1 ppm	26.96

*From Wickizer, T.M. et al (174).

TABLE 13

REPRESENTATIVE CALCULATIONS OF POSSIBLE PCB INGESTION FROM FISH

The calculations in this table are mere approximations only suggested for use in most general terms.

A. Maximum intake at one meal for fish contaminated at 5 ppm PCB

Fish at 5 ppm = 5 mg/1000 gm Fish = 5 mg/2 lb fish

= 2.5 mg/1 lb fish (average serving)

Maximum dosage = 1.25 mg/meal assuming even distribution throughout fish and that ½ lb fish is edible (179).

B. Reproductive effects in monkeys (taken from (102).

Reproductive effects in monkeys seen at dosages of 0.12 mg/kg/day.

110 lb female = 50 kg, thus 0.1 mg/kg/day = total body intake of approximately 5 mg/day.

This is 4 times the average intake expected from ingestion of one fish contaminated at the 5 ppm level.

C. Yusho*

Severe effects were seen in individuals receiving 0.5 g over 120 days. Assuming approximately equal exposure per day, the total dosage per day is 4.16 mg.

This is approximately 3.3 times the dosage expected from ingestion of one fish contaminated at the 5 ppm level.

D. Potential dosage to children

Assume an average Michigan mother has 1-2 ppm (avg. 1.5 ppm) PCB in milk.

Assuming further a six-month baby weighs 7.5 kg (180) and daily milk intake is 500 ml (180) to 1000 ml (181), the total daily PCB intake based upon the Michigan study would be 0.75 to 1.5 mg/day.

With the uncertainty of the burden an infant might receive from the mother who ingested 1.25 mg/day (i.e. eating 1 fish in a given day), the setting of a standard should be based upon a most conservative approach.

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* The fact that the PCB's were contaminated by chlorodibenzofurans must be considered in interpretation of results.

TABLE 14*

POLYCHLORINATED BIPHENYLS IN THE GREAT LAKES

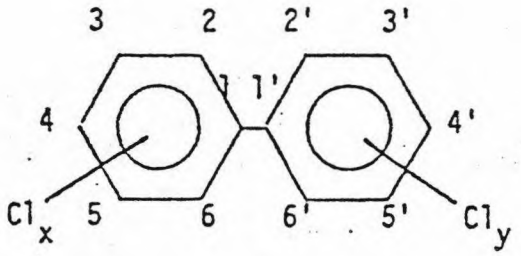
	WATER (ng/l)	Sediments (ng/ml)
Superior	5.0	30
Michigan	31.0	38
Ontario	1 - 3	9 - 33
Huron	5 - 7	75 - 250
Erie	27	43 - 240

*From National Academy of Sciences (189).

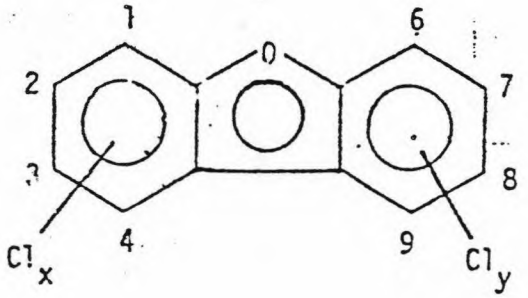
FIGURE 1

STRUCTURES OF RELATED POLYCHLORINED AROMATIC HYDROCARBONS

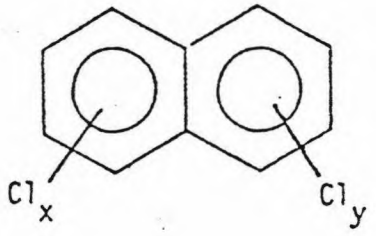
Polychlorinated Biphenyls (PCB)



Polychlorinated Dibenzofurans (PCDF)



Polychlorinated Naphthalenes (PCN)



IN LAKE MICHIGAN SEDIMENTS

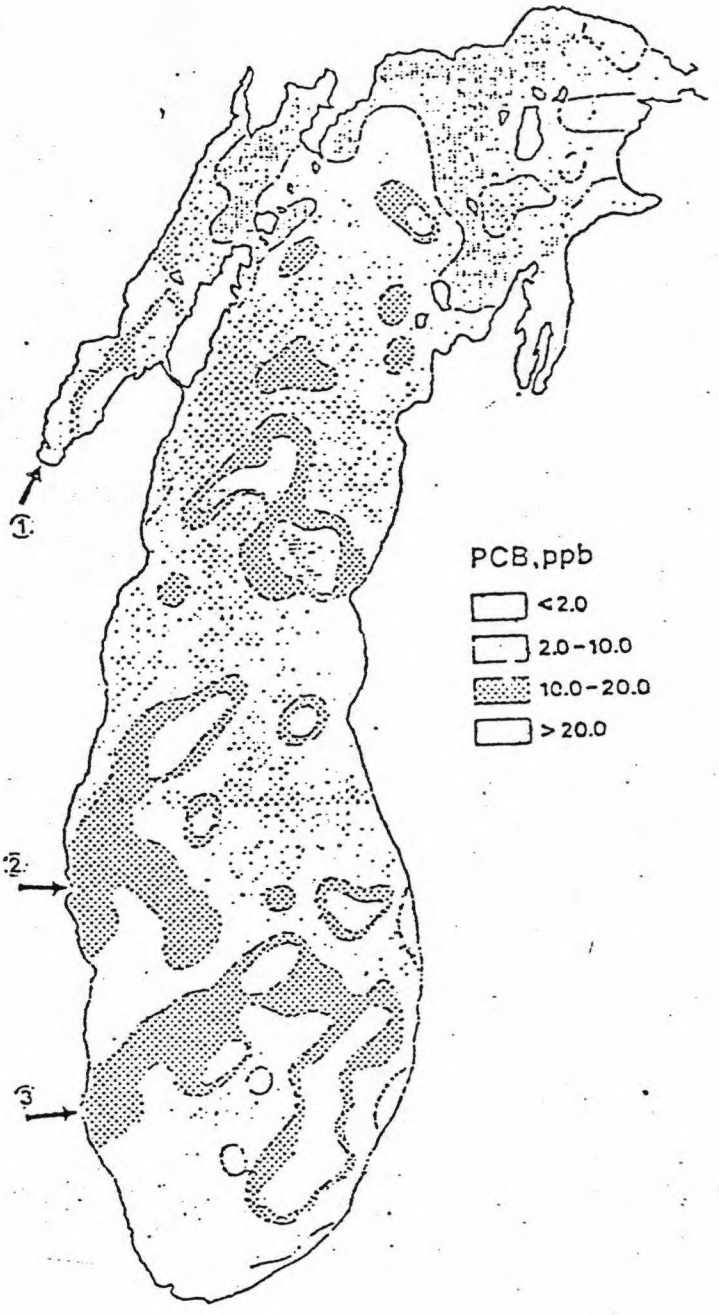


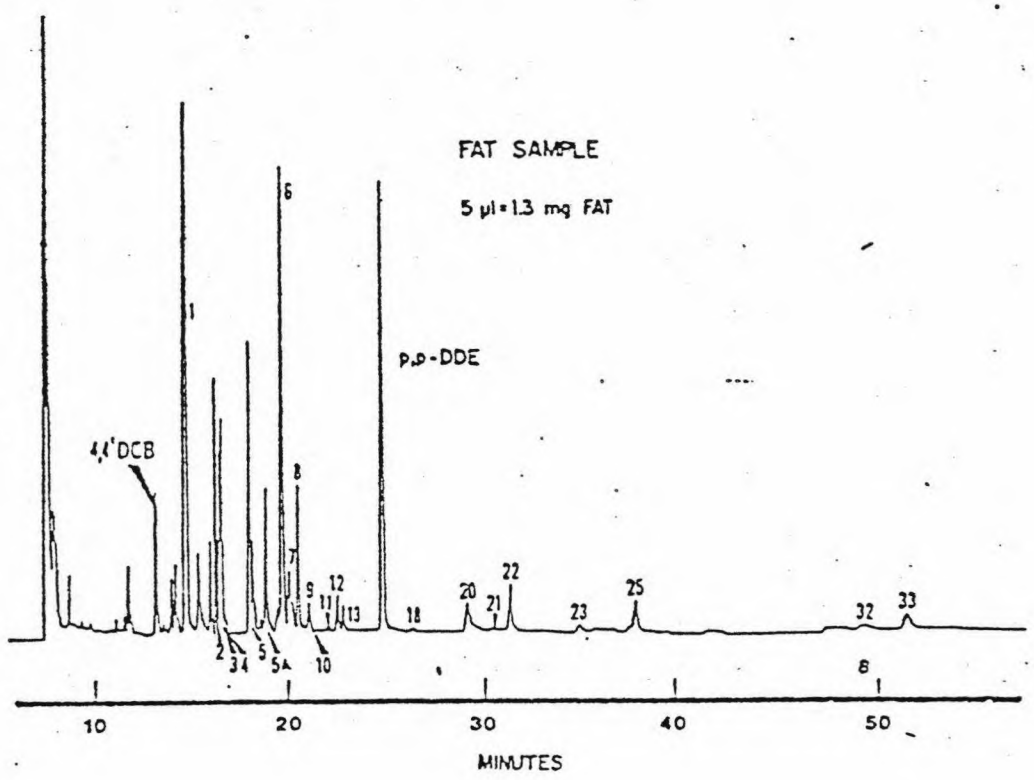
FIGURE 2

Distribution of polychlorinated biphenyls in surficial sediments of Lake Michigan (0-3 cm). Arrows indicate sources and are discussed in text.

From Frank, R. et al. (30).

FIGURE 3*

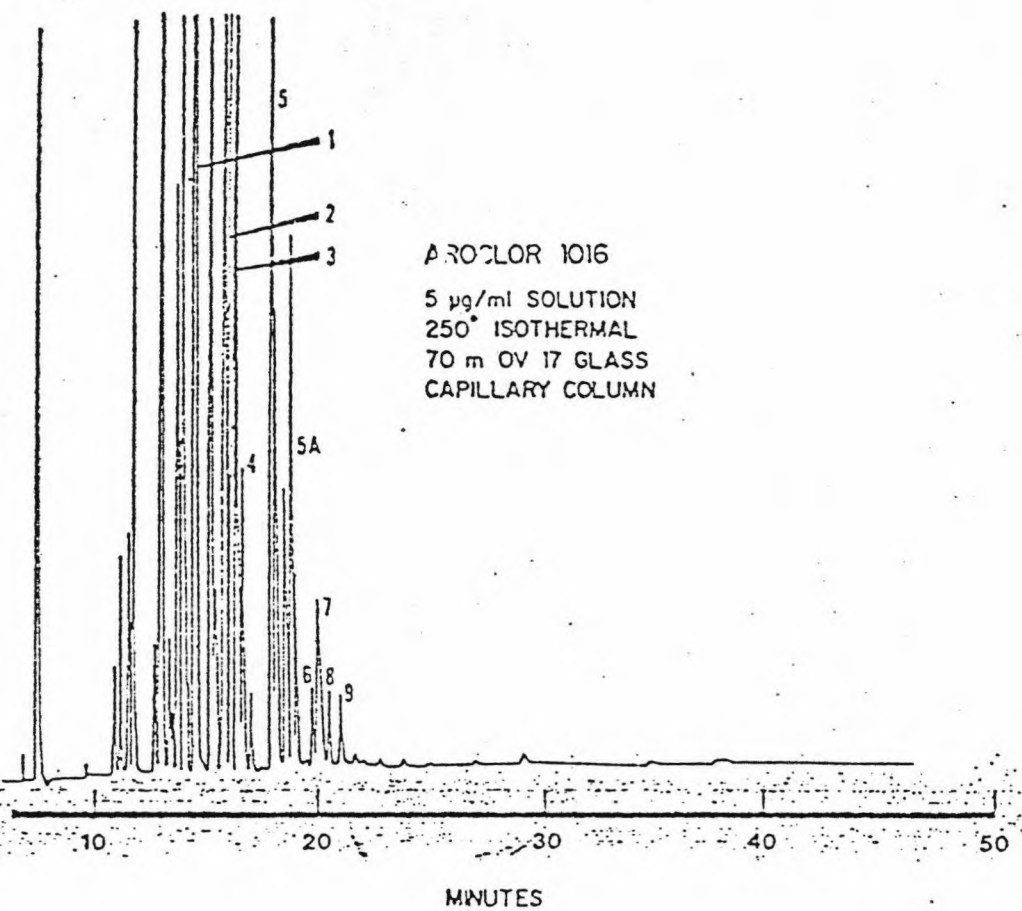
Typical chromatogram from HRGC analysis of adipose sample from a PCB-exposed worker with current high exposure to Aroclor 1016 and with HPCB (peaks 20 to 33) typical of the general population.



* From Wolfe, M. et al (40).

FIGURE 4*

Typical chromatogram from HRGC analysis of standard PCB solution (Aroclor 1016). Peak numbers refer to structure designation in Table 4.



*From Wolfe, M. et al (40).

FIGURE 5.

Correlation between severity of Yusho and PCB Concentration in Liver-extrapolation from Kashimoto, T. et al (45).

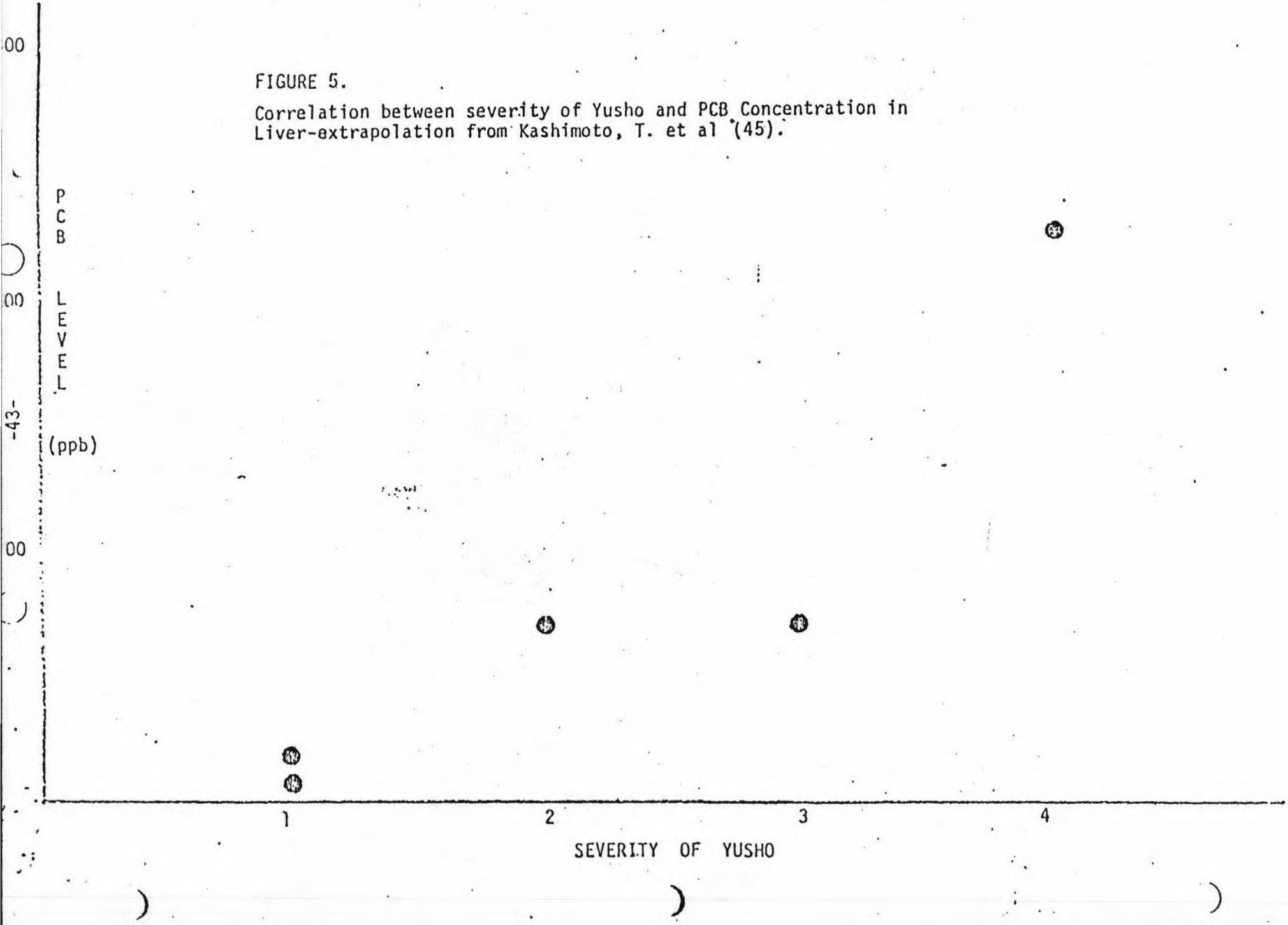
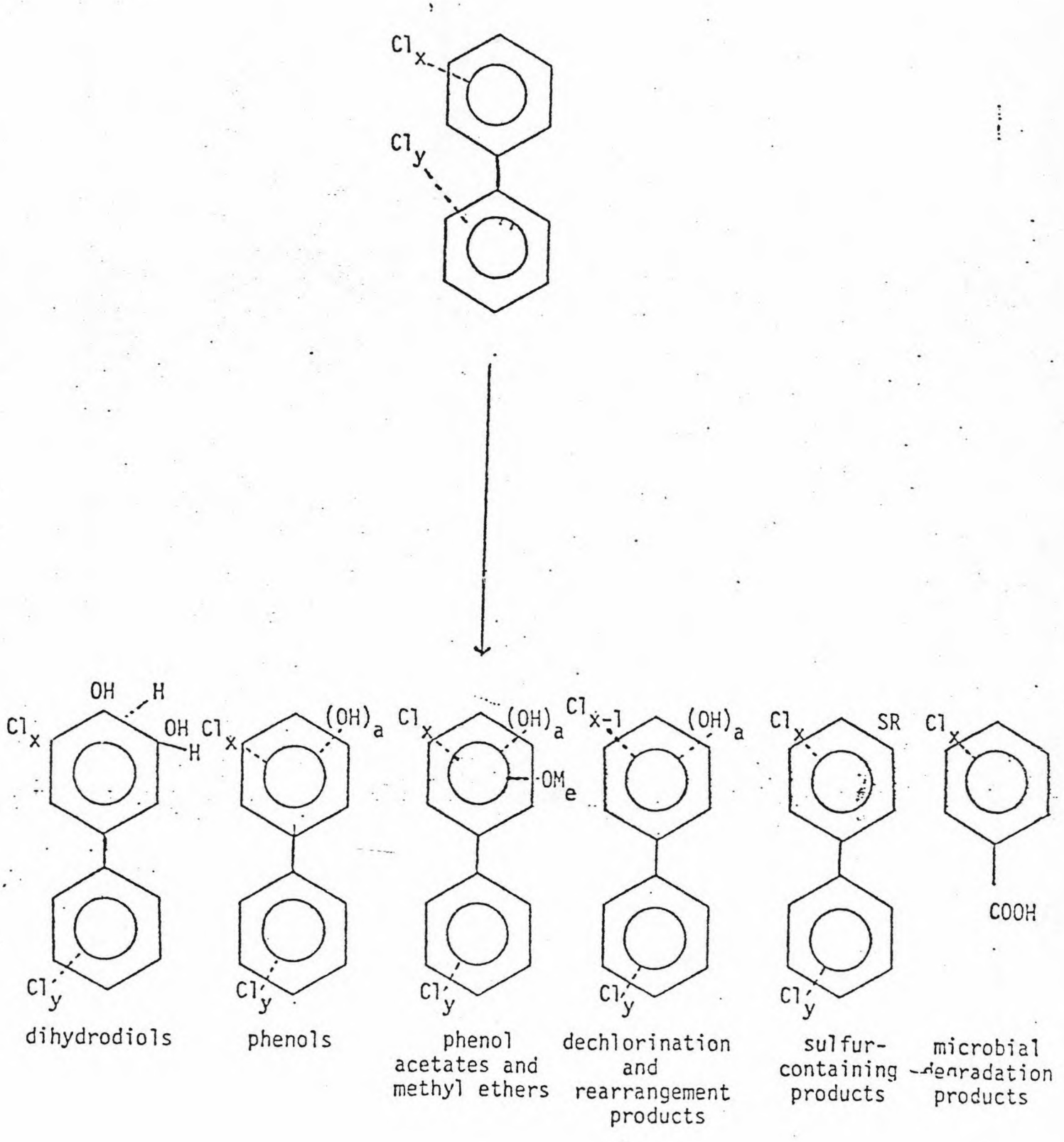


FIGURE 6

A summary of the in vivo PCB metabolites



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