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Health Effects

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Attached is a recent review of the health effects of polychlorinated biphenyls (PCB's).

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Attachment

PLAINTIFF'S EXHIBIT 1402

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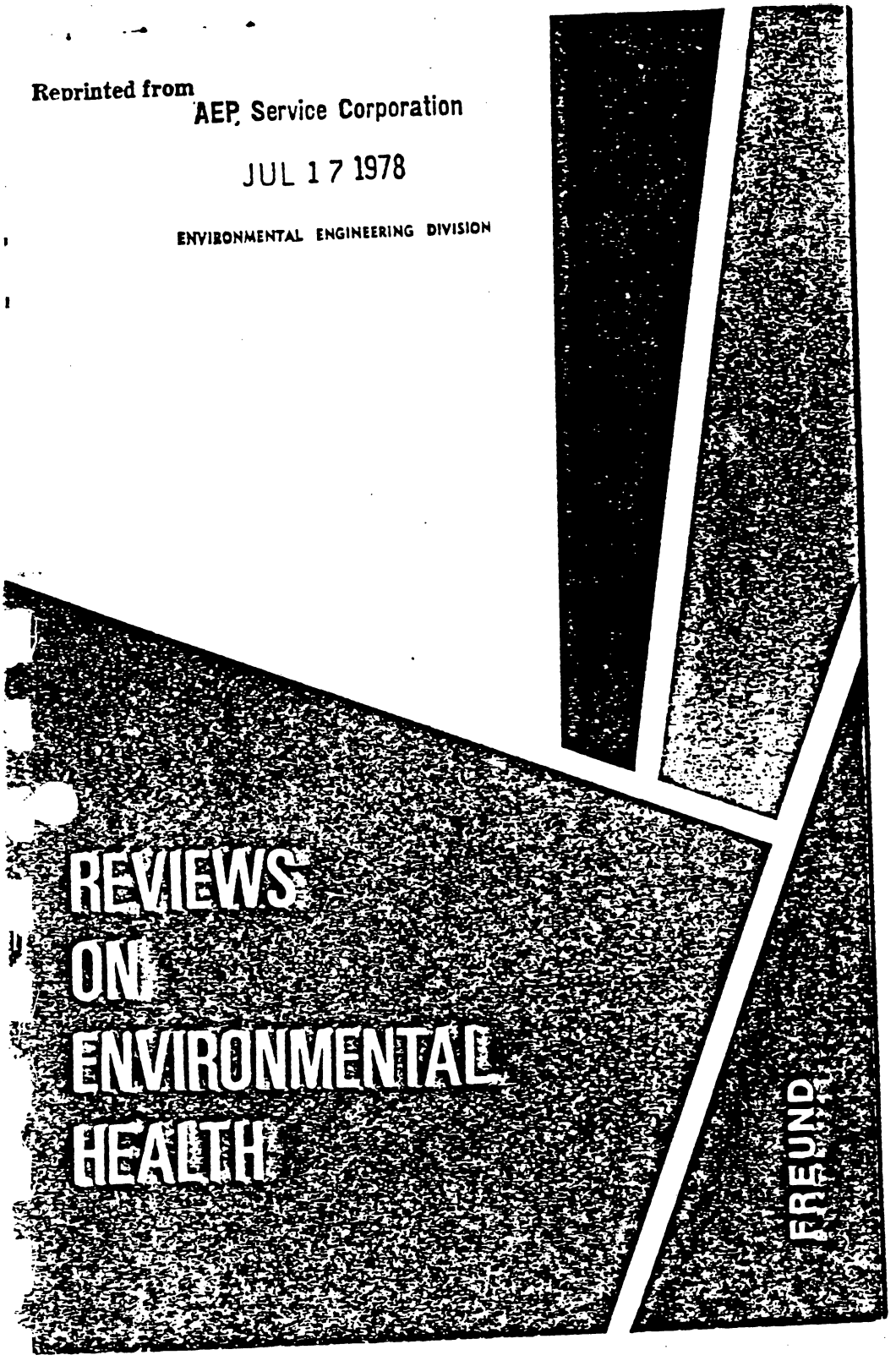

THE HEALTH EFFECTS OF PCBS WITH PARTICULAR EMPHASIS ON HUMAN HIGH RISK GROUPS

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INTRODUCTION

Polychlorinated biphenyls (PCBs) are one member of a class of synthetic chlorinated organic compounds composed of two, six carbon ring structures (phenolic rings) with 10 possible chlorine attachments. These aromatic compounds encompass a complex heterogeneous group of 210 different chlorine-substituted isomers, although the number observed in commercial formulations is much smaller. (Figure 1). The polychlorinated biphenyls have remarkable properties which have prompted their use in numerous industrial products such as hydraulic fluids, plasticizers, adhesives (asphalt and concrete), printing products (carbonless carbon paper) and paper coating. They are still utilized as filling agents on impregnants in electrical transformers and capacitors. Despite their broad industrial applications, PCBs are also highly toxic agents which have been shown to cause harmful effects in numerous animal species, including man. In recognition of their toxic potential, Monsanto Company, the sole U.S. producer, in 1971, voluntarily restricted its sales to only "closed" systems in transformers and capacitors. This has been a significant factor in restricting the accessibility of PCBs to the environment /1,2,3/. However, because of the extreme persistence of PCBs in the environment, human exposure via air, water, and food will continue to be a serious environmental health problem for years to come. It is the intention of this paper to review the health effects of

BIPHENYL

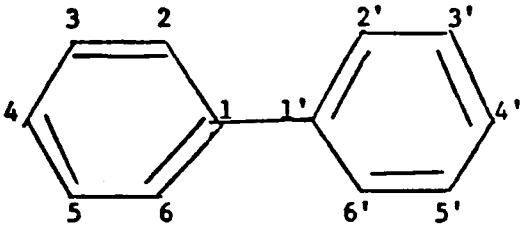

Fig. 1. Biphenyl nucleus showing 10 possible chlorine attachments; positions 2-6 and 2'-6' may be substituted by chlorine. Two hundred and ten different chlorine - substituted biphenyl isomers are possible.

PCBs on animals and man with particular emphasis on human high risk groups.

1. HEALTH EFFECTS OF PCBs: ANIMAL STUDIES

A. *Tissue Storage, Metabolism and Excretion*

Experimental exposure of rats to dietary PCBs has revealed that the isomeric forms are retained to various degrees (as tissue residues) in most body fluids and tissues, with the highest value in adipose (fat) tissue. The adipose tissue often contained more than ten times the concentration of other tissues with the second highest PCB concentration (liver, usually) and more than 100 times the levels in other tissues including the blood, heart, kidney and brain /4,5,6/. Why isomeric forms are retained to various degrees is still not resolved. A possible explanation includes the differential absorption of the isomers through the digestive tract /4/.

The turnover rate of PCBs in tissue will vary with the degree of chlorination. The higher isomers are usually retained the longest in mammals and other vertebrates. It is still uncertain whether PCBs are stored in tissue until a specific point when a steady state is reached and the concentration does not increase further. The given level at which this equilibrium may be reached in adipose tissue could vary with the amount fed to the animals and the type of compound /4,7/.

The urinary excretion of biphenyl and 4-chlorobiphenyl has been studied in rabbits. Biphenylglucosiduronic acid and 4-hydroxybiphenyl were isolated from the urine. The rabbits fed the 4-chlorobiphenyl excreted 4-(p-chlorobiphenyl)-phenol and 4-chlorobiphenyl glucosiduronide. Twice as much 4-chlorobiphenyl as biphenyl was excreted as the glucosiduronic acid derivative. It was suggested that other low chlorinated biphenyls are excreted in a similar manner /8/.

Of dogs injected with 2,4,4'-trichloro-2'-hydroxydiphenyl ether, nearly 100% of the material is recovered as the glucuronide or sulfate in urine and feces over a 5-day period. Humans similarly exposed excrete 65% in urine and 20% in feces after intravenous injection. It is excreted either as free compound or as a glucuronide /7/. Other evidence suggests that some chlorinated biphenyls are hydroxylated by species such as the

rat and pigeon. No evidence of reductive dechlorination was observed in either the trout, rat, or pigeon /9/.

Fish and other aquatic animals accumulate PCBs to levels of the order of 10^4 times higher than those in the ambient water. Predators at the top of the food chain such as birds, seals, and sharks may accumulate PCBs to levels 10^7 or more times the levels in the ambient water /1/.

B. *Toxic Effects of Various Isomeric Mixtures and Possible Contamination of PCB Samples by Other Compounds*

There is no consistent relationship between toxicity and the degree of chlorination which is valid for different species and different routes of exposure. For example, in rats, acute oral toxicity decreases with increasing chlorine content, while in rabbits, acute dermal toxicity appears to be highest for Aroclors of intermediate chlorine content. Also, as will be seen later, most of the data on mammals concerning reproductive effects, demonstrate that toxicity decreases with increasing degrees of chlorination[1].

A study on White Leghorn hens using Aroclors 1221, 1232, 1242, 1248, 1254, 1268, 5442, and BP-6 (at the 20 ppm level; additionally, 1242, 1248 and 1254 were fed at the 2 ppm level) showed that feeding 20 ppm Aroclors 1232, 1242, 1248, and 1254 reduced hatchability and caused teratogenic effects in embryos (edema and unabsorbed yolk). It was determined that adverse effects of the PCBs were not directly related to the degree of chlorination of biphenyls, or the amount of the total residue since Aroclors 1221 and 1268 did not adversely affect the embryonic development /10/. Another study showed that weaning rats were more susceptible to Aroclor 1254 and 1260 than adult rats as determined by acute toxicity studies /7/.

An experiment comparing Aroclors 1254, 1242, and 1221 (respectively 54, 42, and 21% chlorine) was conducted to determine the effect of varying chlorine content on rabbits (oral administration, 300 mg of the PCBs Aroclor 1221, 1242, 1254, once a week, for 14 weeks). The livers of the 1254 and 1242 treated rabbits were significantly enlarged compared to the control animals. The study suggests that the higher chlorine content of Aroclor 1254 causes the most toxicity of these

mixtures. Aroclor 1242 has a lesser, though significant effect on the liver. No significant lessions were found in the 1221-treated rabbits /11/.

Chlorinated dibenzofurans (CDFs) and pentachloronapthalenes have been identified by combined gas chromatography/mass spectrometry in a polychlorinated biphenyl of Japanese manufacture (KC-400). The question of whether chlorinated dibenzofuran in KC-400 may have contributed to the reported "Yusho" incident (see section on Case History of PCB Poisoning Japan) has been raised /12/. Controversy exists on two important factors in relation to the CDFs: 1) whether contamination occurred during manufacture of the PCBs or during the use of the PCB mixture in a heat exchange fluid in the rice oil plant. High temperatures may have led to its formation through the hydroxylation and oxygen ring bridging of chlorinated biphenyl molecules, and 2) there is as yet no direct experimental evidence linking dibenzofuran derivatives with the long-term chronic effects similar to those which have been demonstrated with PCBs /7,13,14/.

Chlorinated dibenzofurans have been detected in several PCB preparations (Clophen A60, Phenoclor DP-6, Aroclors-1248, 1254, 1260) and have been shown to be acutely embryotoxic /13/. Other organochlorine compounds which may be present in food webs include the chlorinated dibenzodioxins in additon to the chlorinated dibenzofurans which are toxic to embryos in amounts less than 1 μg /15,16/.

1. *Effects on the liver and spleen*

The most significant effect of PCBs to the liver for birds and a variety of mammals (e.g. rats, rabbits, dogs) included weight increase, fatty degeneration and necrosis. Increased liver weights are probably caused by the proliferation of smooth endoplasmic reticulum. Along with such structural changes, there are increased activities of some drug metabolizing enzymes such as nitroreductase and aromatic hydroxylase /16/.

In a study testing the effect of PCBs on pentobarbital metabolism and alteration of sleeping time in rats, it was found that Aroclors 1254 and 1260 reduced sleeping time. Such results suggested an acceleration of pentobarbital metabolism caused by liver enzyme induction /17/.

In rats exposed to Aroclor 1242, vitamin A storage in the liver was reduced by as much as 50%, although no toxic or deficiency symptoms

were seen. If only marginal amounts of vitamin A were in the diets of some rats, it has been theorized that avitaminosis could result /18/. This suggests that PCBs may alter lipid metabolism and/or affect preferential absorption from the gastrointestinal tract.

Histopathological effects observed in pheasants fed 210 mg of PCBs daily included loss of appetite, degeneration of liver cord cells and depletion of lymphatic nodules in the spleen /19/.

2. *Carcinogenesis and Tumorigenesis*

Polychlorinated biphenyls when fed chronically to rats caused hepatic adenofibrosis* and biliary epithelial hyperplasia** similar to lesions caused by butter yellow (p-dimethylamino-azobenzene), a known carcinogen. Contamination of PCBs with compounds such as polychlorinated dibenzofurans and chlorinated naphthalenes have been suggested to be causative carcinogenic agents. This controversy is unresolved and needs further investigation /1/.

Studies indicated that when various Kanechlor mixtures were fed to rats, liver weight increased and certain histopathological findings were observed; these included the induction of nodular hyperplasias (increase in hepatic cells, forms nodes), but no hepatocellular carcinomas were observed. The authors suggested that all kinds of Kanechlors have tumorigenic action in the rat liver /20/. Other studies had shown hepatocellular carcinomas were induced in the liver of mice by Kanechlor - 500 which contains a high proportion of chloride groups, but not by Kanechlor - 400 or -300[20]. This study also showed marked cholangiofibrosis (fibrous formations in lobules of the liver) in the *rat* liver. Further investigations are required of the difference in the tumorigenic actions of the PCBs since this was not observed in *mice* treated with PCBs /20/.

* adenofibrosis: glandular formation surrounded by proliferating fibrous tissue; benign, yet difficult to distinguish from cancerous tissue.

** biliary epithelial hyperplasia: an increase in the number of cells in the liver whereby the bulk of the liver is increased.

Evidence exists that some hepatocellular carcinomas may originate from nodular hyperplasias. The histopathological patterns of nodular hyperplasias seen in that study were similar to those induced by known chemical carcinogens such as 3'-methyl-4-(dimethylamino)-azobenzene, N-2-fluororenylacetamide, DL-ethroine, m-toluenediamine, and diethylnitrosamine /20/.

Findings suggested that hepatocellular carcinomas can be induced by administration of Kanechlor -500, -400, -300 for a longer period of time /20/. Increased liver weight, adenofibrosis and hepatomas were induced in mice fed 300 ppm Aroclor 1254 in diet for 11 months /21/. Hepatocellular carcinomas were observed in 26 of 184 rats fed 100 ppm Aroclor 1260 in their diet for 21 months in contrast to 1 of 173 control rats /22/.

3. *Effects on adrenal gland*

Rats receiving 200 ppm Aroclor 1221 in their drinking water for 6 weeks showed morphological alterations in the zona fasciculata of the adrenal gland, as well as increased levels of corticosterone. Such results have been interpreted as possible evidence of the need for a higher level of glucosteroids in defense against the stressor action of Aroclor 1221 /23/.

4. *Effects on the reproductive system (not including primates)*

Rats were exposed to Aroclors 1242, 1254, and 1260 in the diet at levels of 1, 10 and 100 ppm. It was found that Aroclor 1242 did not affect the first generation, but mating indices were decreased in the second generation at 100 ppm. With Aroclor 1254, the number of young delivered and the number surviving to weaning were decreased in both the second and third litters. Aroclor 1260 was found to increase the number of stillbirths at 100 ppm. No effects were seen at concentrations of 1 and 10 ppm /1/.

Studies with chickens indicated decreased egg production at 100 ppm with Aroclors 1242 and 1254, but not with Aroclor 1260. Decreased egg shell thickness occurred at 10 and 100 ppm of Aroclor 1242, but only at 100 ppm with Aroclor 1254; however, such effects were not

seen with Aroclor 1260 even at 100 ppm. Pheasants have also been reported to have their reproductive capacities decreased by PCBs with reduced numbers of eggs laid and reduced developmental success of those that did hatch /1/.

Biochemical studies have indicated that PCBs are capable of inducing the microsomal hydroxylating activity in the liver so as to affect the hydroxylation of both progesterone and testosterone /24/. Such biochemical findings may provide the basis for understanding how PCBs interfere with reproductive processes. Such information may also shed light on the possible effects of PCBs on the depression of secondary sexual characteristics /25/.

5. *Effects on chromosomes*

The effects of Aroclor 1254 (10 ppm in the diet) on dove embryo chromosomes were examined. The experiments studied the largest 8 chromosome pairs occurring in metaphase cells of allantoic sac and limb bud origin with 365 metaphase cells examined per embryo. Parameters observed were aneuploidy, polyploidy and breakage rearrangement. The results, as summarized in Table 1, provide evidence that PCBs may act as clastogenic agents /26/. The studies showed that PCBs may cause chromosomal aberrations *in vivo* in Ring Dove Embryos, but no aberrations as studied in Drosophila.

6. *Synergistic and Additive Effects*

In a study where male rats were orally dosed with carbon tetrachloride (CCl_4) used in conjunction with Aroclor 1254, the Aroclor potentiated the toxicity of CCl_4. This study indicated that the liver is the main site of Aroclor 1254 metabolism and rats with CCl_4 damaged

TABLE 1

The Chromosome Aberration Rate in Dove Embryos Treated with PCBs

	Rate	Range	Total No. Sampled
Control	0.8%	0 - 2%	6
PCB treated	1.8%	0 - 9.4%	17

livers are not able to metabolize this compound as rapidly as rats with normal livers under the conditions of the experiment. The residues in the blood, testes, liver, kidney and heart of CCl_4 treated rats was higher /5/. PCBs given to laying pheasant hens adversely affected egg production, hatchability, and viability of the embryo about the time of hatching but did not affect fertility or eggshell thickness. However, when pheasants were fed 50 mg PCBs along with dieldrin /19/ or DDE /28/, only additive and not synergistic interactions were found.

A study was done to determine the effects of PCBs on neoplastic changes induced by isomers of benzenehexachlorine (BHC) in the livers of the mice fed a diet containing BHC with or without PCBs for 24 weeks. Researchers observed that PCBs promoted the induction of hepatic neoplasms in mice by isomers of BHC /29/.

7. *Immunosuppression*

A reduction in lymphoid tissue and the presence of amyloid or amyloid-like material in the liver of PCB exposed chicks has been reported /30/. (Amyloid formation has been found to be stimulated by certain immunosuppressive drugs). Also, lymphopenia has been reported in rabbits /31/, while in guinea pigs /16/, PCBs decreased the number of antibody-forming cells after stimulation of the humoral lymphoid system with tetanus toxoid. Such immunosuppressive actions by PCBs may help to explain the increase in susceptibility of PCB exposed fish to fungal disease, /32/ PCB exposed ducks to viral hepatitis /33/ and the onset of liver cancer in PCB exposed rats /21,22,34/. (See section on Carcinogenicity).

8. *Primate studies*

Recent studies have indicated that very low levels of PCB exposure are toxic to primates. For example, in one experiment rhesus monkeys which ate food containing 25 ppm of Aroclor 1248 for 2 months developed facial swelling, loss of hair and acne lesions within a month. One monkey died from PCB intoxication 2 months after going off the experimental diet /35/. Another experiment utilized 2 groups of rhesus monkeys which ate food containing 5 and 2.5 ppm of Aroclor 1248.

Within 2 months both groups had lost hair from the face and neck and their skin was of "a sandpaper-like texture". Both groups developed acne, although the 2.5 ppm group developed the lesions later. In 6 months, both groups reached a steady state concentration of PCBs in adipose tissue. Test monkeys were then mated with monkeys which had not been fed PCBs. Six of the 8 female monkeys which had eaten food containing 5 ppm of PCBs became pregnant, in contrast to all 12 monkeys in the control group. In the test group, 4 of the 6 pregnant females aborted or resorbed the fetus, 1 gave birth to a still-born and 1 to a very undersized infant /36/. In the 2.5 ppm group, all females in the test group conceived and of these, 3 resorbed and 5 gave birth to undersized infants /36/.

II. HEALTH EFFECTS OF PCBs: HUMAN EXPOSURE VIA FOOD, AIR AND WATER

A. *Occupational Exposure*

Known toxic effects of PCBs in humans include an acne-like skin eruption called chloracne, pigmentation of the skin and nails, distinctive hair follicles, excessive eye discharge, and swelling of eyelids. Several cases of human toxicity to PCBs in an industrial setting have been reported /37,38/. Exposed workers developed small dermal cysts and comedos (blackheads). These were usually found on the face and ears, although such sores have been reported on numerous other parts of the body. Dermal sores generally persisted for several months after removal from the source and in some instances, lasted four years. Systemic effects have also occurred in several cases. These effects include nausea, lassitude, anorexia, digestive disturbances, impotence and hematuria /1,39/.

A study done on PCB concentration in the plasma of refuse workers found that 32 out of 37 (81%) of the refuse workers had detectable levels as compared to only 11% (6 out of 54) of the controls. Median PCB concentrations for those with detectable amounts were similar in the two groups; refuse workers - 2.6 ppb, controls - 3.7 ppb. The higher frequency of measurable plasma PCB levels in refuse workers (i.e., 81% of refuse workers with detectable levels as opposed to only 11% of

controls with detectable levels) is thought to reflect their increased PCB exposure from incinerated materials /40/.

The American Conference of Governmental Industrial Hygienists has set a TLV of 1 mg/m^3 for occupational exposure to vapors of Aroclor 1242, with lower values for higher Aroclors. Based on an 8-hour exposure, this would result in the inhalation of approximately 5 mg/day. The current Occupational Health and Safety Administration, Department of Labor standards for chlorinated biphenyls are 1 mg/m^3 for 42% chlorine mixtures and 0.5 mg/m^3 for 54% chlorine mixtures, based on the TLVs. Presently, it is not known how much of the inhaled PCBs humans absorb through the lungs /1,2/.

B. *Case History of PCB Poisoning - Japan*

The most well known case of PCB contamination has occurred in Japan, with documented toxic affects in over 1,000 Japanese exposed to rice oil contamination. Kaneuri Rice Oil was polluted with Kanechlor 400, which is equivalent to Aroclor 1248. This contamination incident, which was finally traced to a rice oil shipment in February, 1968, was called "Yusho" and occurred in western Japan in the area of Fukuoka prefecture. The first affected people showed the development of dermal cysts predominantly on the face and ears, but also on most other parts of the body. In severely intoxicated individuals, nausea, lassitude, anorexia, impotence and hematuria were observed. It is apparent that the severity of symptoms are directly related to the amount of PCBs ingested /41/.

It is known that the concentration of Kanechlor 400 in the rice oil was 2,000-3,000 ppm and the average quantity of rice oil consumed by patients in a first epidemiological study (325 cases) was 800 ml. over a period of approximately 8-9 months /42/. Consequently, the average dose of PCB ingested by affected individuals was approximately 2 g. The smallest dose ingested by a patient was estimated to be 0.5 g. /41/.

The children of 13 women (9 of whom consumed between 0.3-2.6 liters of rice oil during pregnancy) were studied for possible teratogenic effects. Eleven children were born alive while 2 were stillborn /41,42/. The infants had a characteristic grayish, dark brown skin pigmentation; 5 had dark nails and gingivae (the gums; the tissues which surround the

necks of the teeth and cover the alveolar processes of the maxilla and mandible) and 9 had increased eye discharge. A detailed study of 4 infants revealed abnormalities which included enlarged frontal sagittal suture. Faces were edematous, and there was an abnormal protrusion of eyeballs /43,44/. As a result of such symptoms, it has been generally concluded that placental transfer of PCBs had occurred affecting the fetus.

The growth of school children afflicted with Yusho has also been studied. Both height and weight gain of boys with Yusho illness were significantly less than a control group, while the girls of Yusho did not differ significantly from the control group /42/.

C. *Consumption Via Food and Drink*

Based on market basket samples of PCB levels in food, an adult is estimated to ingest approximately 5-10 μg PCB/day. This figure was based, in part, on an assumed level of 0.1 ppm in 3% of the food. Such a calculation may lead to an inaccurate representation of the total PCB intake of various consumer groups. It is known that human fish consumption and PCB levels in fish vary considerably /1/. Although the FDA tolerance for PCB residues in fish is 5 ppm, /45/ it is not uncommon to find PCB levels between 10-20 ppm in fish found in the Great Lakes, especially Lake Michigan /46/. Thus, individuals who habitually eat large quantities of fish, especially from such areas as the Great Lakes, will have much higher intakes than the general population. For example, an individual who eats 50 g of fish per day (1.8 oz./day) containing 2 ppm of PCBs will ingest 100 μg/day of PCBs. For a person following the recommended "weight watcher's diet", the levels of PCBs in the diet may be even significantly higher. The "weight watcher diet" suggests 5 fish meals/week, which is approximately 98 g (3.5 oz.) of fish consumed per day /47/. Assuming a contamination of 2 ppm, the "faithful weight watcher" would consume about 200 μg/day of PCB just from fish alone.

In addition to high levels of PCBs in fish, considerable concentrations may also be found in human milk. For example, samples of human milk from two cities in California contained average PCB levels of 60 ppb, while average levels in human milk in Sweden and Germany were

16 ppb and 100 ppb, respectively. Based on a daily milk intake of 150 ml/Kg, breast fed infants in California would ingest about 9 μg/Kg/day of PCB (at least 3 x more than a recommended reasonable dose). Sporadic instances of contamination of other foods such as milk and poultry may also lead to higher intakes for short periods /48/.

A report of measurement of ambient PCB atmospheric levels ranged from 1-50 ng/m^3. This would result in the inhalation of less than 1 μg/day by an adult /1/. The intake from drinking PCB-contaminated water, assuming 10 ppt as the concentration, would also result in less than 1 μg/day by an adult. Lake Michigan levels are usually less than 10 ppt /20/. A range of 1-3 μg/Kg/day (70-210 μg/day for an adult) has been suggested as a "reasonable" level for an Acceptable Daily Intake /1/. One μg/Kg/day has been reported as being 100 times less than the lowest "no-effect level" reported in animal studies /16/.

The Federal Drug Administration established PCB tolerance levels in a number of food products as follows /13,49/ :

Food	Concentration (ppm)
Milk*	2.5
Dairy Products*	2.5
Poultry*	5.0
Fish and Shellfish**	5.0
Eggs	0.5
Infant and Junior Food	0.2
Complete and Finished Animal Feed	0.2
Animal Feed Components	2.0
Paper Food-Packaging Material	10.0

* on fat basis
** on edible portion

However, toxicity data obtained subsequently showing reproductive abnormalities with concentrations of PCBs in primates ranging from 2.5 to 5.0 ppm and the recent demonstration of adenofibrosis and other toxic effects in rats indicate a need for revisions of the present FDA tolerance limitations of PCBs in foods. The FDA is expected to enforce its guidelines more forcefully in the future based on a recent legal decision that allows the FDA to define pesticide residues in foods as an indirect food additive /13/.

Studies have also shown that migration of PCBs from packaging materials does occur /13,50/. In the absence of an effective barrier,

Aroclor 1242 was shown to migrate from paperboard to food in measurable amounts when food was purchased in paperboard containing a significant amount of Aroclor 1242. It is considered an absorption phenomenon dependent primarily on the surface area of the food and secondarily on the fat content of the food. The study suggested that meterials of low gas permeability could be effective barriers to PCB migration /50/.

III. PCB LEVELS IN TISSUE OF HUMANS IN THE UNITED STATES

Adipose samples were collected from tissues withdrawn for therapeutic surgery or from post-mortem exams. Positive samples were obtained from 18 states, including eastern, western and southern states, thus indicating that PCBs are widespread. It was reported that 165 of 637 (25.9%) samples of human adipose tissue contained 1-2 ppm. Thirty-three of the samples (5.2%) contained greater than 2 ppm; 125 (19.6%) contained between a trace and 1.0 ppm; the remaining 314 (49.3%) were negative at the level of ppm identification /51/.

IV. HIGH RISK SEGMENTS OF THE POPULATION

Embryos, fetuses and neonates (2 to 3 months old) often lack the liver microsomal enzyme systems that oxidize various natural and foreign chemicals, including those of a biphenolic nature. The activation of such enzyme systems often facilitate the detoxification and excretion of such substances. Usually by the age of 2 to 3 months, adult levels of the enzyme systems are achieved /52,53/. Unfortunately, this "developmental immaturity" in the unborn and the very young may predispose them to the toxic effects of certain substances since they may be unable to detoxify and excrete them as quickly as necessary. Clinical experience has shown that infants may respond differently to doses of drugs which are easily tolerated by older children and adults. Presumably, this is because older children and adults have fully functioning enzyme detoxification systems while the neonate lacks such development /52,53/.

One such microsomal enzyme system includes the glucuronidation pathway which functions in the detoxification and excretion of a variety of chemicals including alcohols and phenols /52/. Inefficient glucuronidative mechanisms in infants have broad significance since the absence of such mechanisms prevents the prompt elimination of toxic substances from the body. Since some young children have been shown to consume more PCBs per unit of body weight than adults (since PCBs have appreciable concentrations in human milk)/48/, the lack of appropriate detoxification enzyme systems compounds the PCB problem for the very young.

A tragic example of toxicity arising from the inability to form glucuronides has been reported. The drug chloramphenicol, which is known to be metabolized in humans by the action of the glucuronic pathway, caused the death of more than 30 premature babies who had been treated with the antibiotic for infectious diseases /54/. Theoretically, the premature babies were not able to conjugate the drug with glucuronic acid and thus the drug could only be slowly excreted and so tended to accumulate in the body to toxic proportions eventually ling to death.

An additional problem encountered by many neonates is that approximately five per cent of the mothers of normal infants secrete milk which inhibits the activity of glucuronyl transferase (and thus the glucuronidation process) by more than 20% via the action of a steroid present in the breast milk. Inhibition of this glucuronyl transferase has been reported for up to 49 days after birth. Clinically, these children have been reported to develop unusually severe neonatal jaundice. This condition develops because glucuronide formation, which assists in the elimination of bilirubin (breakdown product of hemaglobin), is partially inhibited. Cow's milk does not contain sufficient amounts of this steroid to affect a noticeable inhibition of the glucuronide-conjugation process /55/. Consequently, about 5% of the breast-fed neonates would be expected to have their ability to excrete PCBs impaired. Administration of the antibiotic novobiocin has also been associated with unconjugated hyperbilirubinemia in infants /56/. Novobiocin is a non-competitive inhibitor of glucuronyl transferase activity *in vitro* /57/.

Thus, children receiving concomitant exposure of novobiocin and PCBs would be expected to have their ability to detoxify and excrete PCBs impaired.

After the neonatal period, a broad range of conditions is associated with the improper or incomplete development of the glucuronide conjugation system. The usual physiological problem associated with these conditions is the inadequate detoxification of bilirubin. This spectrum extends from the frequently occurring "mild" condition known as Gilbert's syndrome, to the very rare, but severe and often fatal Crigler and Najjar syndrome /58/.

Since the clinical effects associated with these syndromes are considered to be caused by metabolic disturbances of the glucuronide conjugation scheme, it is expected that PCB elimination in these individuals would be impeded. Gilbert's syndrome has been mentioned as being "encountered relatively often" in a clinical sense, and recently it has been estimated that 6 per cent of the general population may experience this syndrome /59/.

Concomitant exposure to PCBs and other compounds may enhance the toxic effects of PCBs. For example, rats and monkeys given β-diethylaminoethyl-2, 2-diphenylpentanoate (SKF525A, a non-specific inhibitor for many of the microsomal enzyme activities, especially hepatic microsomal enzymes) during the initial 24 hours of exposure to PCB, succumbed rapidly as compared to the control group /35/. Of possible significance is the fact that SKF525A inhibits the proper functioning of the glucuronidation pathway /54/.

Individuals with liver infections may also be at high risk with respect to PCBs. For example, depression of glucuronide synthesis has been observed in humans with infectious hepatitis.

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