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Potential Health Effects in the Human From Exposure to Polychlorinated Biphenyls (PCBs) and Related Impurities

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EXECUTIVE SUMMARY

The present study on the potential health effects in human populations from exposure to commercial polychlorinated biphenyl (PCB) mixtures under occupational or other environmental conditions was conducted by a team of specialists in the medical, toxicological and epidemiological sciences designated as the Category I team. Draft material for the study report was reviewed by a second group of specialists designated as the Category II team, and other scientists, leading to comments and suggestions for improvement which were incorporated into the draft report. The available body of scientific literature on health effects of PCBs in humans and in test animal systems was reviewed and analyzed with emphasis on the relationships linking exposure, dosage to the biological target, and occurrence of specific health effects in the animal or human. Both the toxicological and epidemiological data from acute and chronic animal and human exposures were considered in generating assessments of the probability of occurrence of any specific health effect in humans. The results of these assessments are summarized below, separately itemized under each major health effect. It should be noted that each assessment applies to the potential for development of that effect under the type and level of human exposures actually encountered in the U.S. during the past decades, with the most intensive integrated exposures having occurred in manufacturing operations that were terminated in this country in 1977.

Yusho Disease

Separate consideration was devoted to the Yusho episode recognizing the special character of the human exposures to high concentrations of mixtures of PCBs and their thermal degradation products, polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs). Several conclusions reached by the Category I team are of importance: (a) it is impossible to stipulate whether any of the health effects observed is causally related to PCB exposure, since the other halogenated compounds are also biologically active; (b) the dosage patterns experienced by Yusho patients and U.S. industrial workers (PCB-exposed) are not at all comparable; the latter group experienced low level, long time period exposures primarily via inhalation and skin contact, with only minimal oral ingestion; (c) the similar health effects seen in Yusho patients from the Japanese and Taiwanese episodes of exposure to contaminated cooking oils point to the same type of toxic mixtures resulting from thermal heat exchanger action in the two events; (d) because of points (a)-(c) above, and the fact that at least the PCDFs in the Yusho oils are potentially more toxic than the PCBs on the basis of animal data, it is not possible to extrapolate the Yusho experience to prediction of acute and sub-chronic effects of commercial PCB mixtures in the human; (e) finally, with respect to predictions of human carcinogenesis from the Yusho type of exposure the data are so incomplete that conclusions regarding any types and amounts of excess cancers attributable to those exposures have to await further definitive study.

Body Burdens, Metabolism, and Kinetics

Some general observations derive from consideration of the data on the storage, distribution, metabolism and excretion of commercial PCB mixtures (with associated impurities such as the PCDFs) in mammalian systems. The dynamics of the pathways by which these processes occur in test animal models have been explored intensively and have been fairly well worked out. The variability of PCB effects with species of test animal model has been investigated for a number of important effects, and some general structure vs. activity rules have emerged from these studies. There thus exists a conceptual framework, but not experimental data, for describing such phenomena in humans. Further, important data on the biochemical interactions of PCBs, PCDFs and metabolites with tissues have been obtained that bear directly on interpretation of toxic effects in these tissues.

General Toxicity

From acute, subchronic and chronic studies of PCB effects in test animal models, a general summary of health effects encountered includes: (a) a low order of acute toxicity; (b) skin lesions; (c) effects on liver tissue that are generally reversible at lower doses but that trend toward irreversibility with increased dosing; (d) effects on the gastric mucosa; (e) effects on the menstrual cycle and on reproduction;

(f) porphyria; (g) effects on the kidney; and (h) miscellaneous changes including hematologic alterations, thymic atrophy and lymphatic changes.

There is a considerable range of species susceptibility to biological activity of the PCBs, with one representative comparison of order of decreasing activity being mink, monkey, rat. It is concluded that there is no basis for determining which species most accurately serves as a model for prediction of general subchronic/chronic toxicity in man; rather, the judgment of the most suitable surrogate for man must be made independently for each major health effect. Finally, it is noted that although there is some similarity between acute health effect phenomena produced by PCB exposure in the monkey and human Yusho disease, it would be incorrect to equate Yusho disease with PCB intoxication because of the much more complex mixture of compounds encountered in Yusho oil than in a commercial PCB mixture.

Skin and Other Cutaneous Tissues

Commercial PCBs are capable of producing skin lesions in the monkey model and in exposed humans. Chronic administration of PCBs to the monkey produces chloracne. In humans occupationally exposed to PCBs skin disorders including chloracne have occasionally been observed. These skin disorders have been shown to be reversible in some of the animal and human studies.

Liver Effects

PCB mixtures are capable of generating important effects on liver tissue in animal models. These effects include: (a) increase in liver weights; (b) histopathologic changes in liver including enlarged hepatocytes, deposition of fat droplets in tissue, and tissue necrosis and cell death; (c) enlargement of the liver; (d) the occurrence of adenofibrosis, a benign lesion; and (e) an increase in proliferative lesions of the liver, including increases in hyperplastic foci and nodular hyperplasia. These increases in proliferative lesions appear to increase in severity with increasing degree of chlorination of the PCB mixture, as seen in the greater potency of Aroclor 1260 over Aroclor 1254. The effects on liver tissue are generally reversible at lower doses but trend toward irreversibility with increased dosing.

However, in contrast with the positive findings of PCB effects on liver tissue in animal models, no significant effects on liver function tests have been observed from clinical data on human populations exposed to PCBs in the occupational setting. Further, there has been no epidemiological finding of liver disease in U.S. occupationally-exposed personnel. Also, as noted in the Yusho discussion about persons exposed to contaminated cooking oil with a PCB content of 1000 ppm, there was no finding of liver disease in the categories of either jaundice or hepatocellular injury.

Gastric Lesions

When tested in monkeys and rodents, PCBs show species specificity with respect to a toxic effect on the gastric epithelium, or stomach lining. In the monkey, with Aroclor 1242, there is a mucous conversion of the gastric epithelium that can best be described as a dysplastic growth pattern. This growth pattern does not constitute a neoplastic transformation. In rodents, PCBs do not evoke this effect on the gastric mucosa. In humans occupationally exposed to PCBs there are no clinical findings to date of gastric lesions, and no evidence of stomach cancer due to this exposure.

Carcinogenesis: Experimental and Clinical

A sizeable volume of animal experimental work has been directed toward chronic studies in several species: the mouse, the rat and the dog. There are some areas of interpretation that are still under debate by the investigators concerned, but in the opinion of the Category I team the following represents conclusions that can be drawn from presently available data: (a) the evidence on carcinogenicity is negative for gastrointestinal carcinoma and bladder carcinoma in rats and hepatocellular carcinoma in the dog; (b) some studies have reported an increase in hepatocellular carcinoma in mice and rats exposed to commercial PCBs chronically, whereas other studies have afforded negative results.

With respect to the possibility of cancer linked to exposure of humans to PCBs, epidemiological studies show to date essentially negative results for hepatocellular carcinoma, gastrointestinal carcinoma and all other forms of cancer. There is a single preliminary study that purports to show an increase in melanoma (skin cancer) in occupationally exposed people, but the full data display and analysis have not been made for this study. In contrast, in two larger and more detailed studies, this finding has not been confirmed; no excess incidence of melanoma in exposed personnel has been observed.

Retrospective mortality studies of PCB-exposed human populations have not demonstrated a consistent relationship between extent of exposure and the development of any particular type of cancer. The human studies in hepatocellular carcinoma are not comprehensive, but to the extent that they have been developed the results do not confirm the projection of a risk for liver cancer based on the animal studies. Some findings of increases in lymphatic and hematopoietic malignancies were below the level of statistical significance, and were refuted by observations of changes in the opposite direction in other epidemiological studies. Even findings of statistically significant differences between exposed and control populations with respect to the incidence of rectal cancer in women at one plant have not been confirmed by observations in other studies. The variance in these findings points up the important principle that the Standard Mortality Ratio (SMR) may vary widely in different

studies, and that undue emphasis should not be placed on the SMR found in one study unless it has been confirmed by similar findings in repeat or parallel studies.

Reproductive Effects

Experimental work with commercial PCB mixtures and animal models has been directed to the reproductive process itself, to teratogenesis in the offspring, and to possible fetotoxicity. In most test species, PCBs produce deleterious effects on reproduction at high dosages. In the female monkey at relatively high dosages, difficulties are encountered in conception, in implantation of the fertilized ovum, and in carrying the fetus to term. Similarly dosed, the male monkey does not transmit these difficulties to the reproductive process. In the human, exposed occupationally or otherwise to PCBs, there is in general no evidence for adverse effects on the reproductive process, although there are little data from which to draw conclusions. In the very special case of Yusho exposure to high levels of PCBs and other polychlorinated hydrocarbons, the newborn in significant proportion were pigmented, small, and showed a retarded rate of growth. However, this pigmentation disappeared and the infants caught up with control population infants in total growth.

The potential for PCB-induced teratogenesis, or production of defects in the embryo or fetus, has been investigated in several species of test animals. Most animal tests have yielded negative results when PCBs were administered to pregnant females during the critical periods for organogenesis.

Several possible exceptions to this statement might be noted. In mice, a single congener, 3,4,3',4'-tetrachlorobiphenyl, induced a behavioral defect ("waltzing syndrome") that may be related to an anatomical defect in the inner ear. PCBs in mice may produce some delay in implantation. In rats, no gross teratological changes were observed, but some alterations in thyroid structure or function produced by PCB administration might fall under the definition of terata. In dogs and in swine, no teratological effects were noted at lower PCB doses; however at the highest doses of PCB in the feed, at which the dam suffers marked reduction in food consumption and is therefore nutritionally deficient, there are dose-related teratological effects in the offspring. In monkeys dosed with PCBs, there are no dose-related abnormalities in the offspring, but they are smaller in size. Based on those observations, it is the Category I team's conclusion that commercial PCBs present no appreciable risk of teratogenicity in offspring of human females exposed under occupational conditions.

In test animals, i.e. rats, dogs and rabbits, PCBs are fetotoxic when administered at relatively high doses to the pregnant female. In the human, the only reported epidemiological evidence for fetotoxicity in exposed populations stems from the unique Yusho event, in which causation may not be linked to PCBs.

Mutagenesis

Investigations of possible mutagenesis from acute or chronic exposures to commercial PCBs have shown negative results in a series of in vitro and in vivo test systems. Isolated bacterial test systems (Ames test) and human lymphocytes in culture showed no evidence for PCB-induced mutation or transformation. With in vivo systems in intact animals: (a) cytogenetic tests for alterations of cell structures or for induction of chromosome abnormalities yielded negative results; and (b) both the mouse micronucleus test and the dominant lethal test demonstrated negative results. Incubation of human lymphocytes in culture with PCBs caused an alteration in glucose transport through the cell membranes.

There is no significant evidence that PCBs are mutagenic in test systems, and no reports of such activity in human populations. It is quite unlikely that commercial PCB mixtures would exert mutagenic activity in humans. This conclusion is consistent with the lack of excess cancer incidence observed in PCB-exposed human populations.

Other Health Effects

This grouping includes enzyme induction, immunocompetence and porphyria. PCBs induce mixed function oxidases (MFO) in the liver of test animals. The important issue is whether or not this process includes the specific induction of cytochrome P-448 as a general property of the PCBs, with the added implication that some oxidase system is being induced that

could be involved in chemical carcinogenesis. Several conclusions were reached with respect to this issue: (a) the predominant effect of commercial PCBs is cytochrome P-450 induction, not P-448; (b) commercial PCBs in the U.S. can contain up to about 2 ppm of PCDFs; and (c) the PCDFs can induce cytochrome P-448. From these observations in animal model systems and our judgment, it is concluded that under conditions of U.S. occupational exposure to PCBs, none of the MFO inducing actions of the commercial mixtures will be of toxicological significance over the lifetime of a PCB-exposed person.

With respect to potential PCB effects on immunocompetence in test animal systems, some observations are pertinent to the assessment of probable hazard in the human. It has been observed in chicks that if the PCB dosages are high enough, atrophy of the splenic pulp and necrosis of the lymphoid system can be demonstrated. Similar indicators of change in immunocompetence can also be produced in ducklings, mice, and monkeys as a consequence of severe change in nutritional status. High doses of PCBs leading to marked reduction of food intake and utilization can lead to such changes in nutritional status. These considerations lead to two general conclusions relative to the PCB-exposed humans: (a) as projected from animal studies, if the PCB dosage is high enough to lead to general toxicity in the human (e.g., decreased food intake, fall in body weight, fall in weight gain),

immunosuppression may be demonstrable secondary to malnutrition; and (b) at lower dose levels, there is no likelihood of significant immunosuppression.

Porphyria, or deposition of porphyrin-derived pigments in liver and urine, has been observed in experimental animals such as the rat and rabbit dosed with PCBs. The effect has a delayed onset, and especially in the rat, seems to take place by mechanisms different from those employed by known chemical porphyria-producers in the human. It is concluded that, aside from the unique case of Yusho disease, no evidence has accrued for the occurrence of porphyria in populations exposed to PCBs even under high level occupational exposure conditions.

Epidemiology

This section (XII) of the study presents a separate, independent assessment of the recorded epidemiological literature and data bases on human exposures to commercial PCBs, and on the significance of the health effects attributed to these exposures.

Summary points in this assessment include the following: (a) mortality data, based on very small numbers of deaths, do not confirm a carcinogenic effect of PCBs in man; (b) data on human skin lesions in relation to PCB exposures have shown variability in incidence of this effect with geographical locus and with increasing blood level indicators of exposure; (c) data from studies of liver enzymes and liver function suggest changes in one or more enzymes related to PCB exposure that are not associated

with liver disease and that occur at levels below those at which chloracne occurs; (d) there is frequently a positive correlation between PCB levels and triglyceride levels in blood; and (e) epidemiological data on reproductive effects, hematology and immunology in humans exposed to PCBs do not suggest abnormalities in these systems or processes.

Human Occupational Exposure Levels

Of the various effects noted in animal test systems, only dermatological effects, including some chloracne, have been clearly demonstrated in human populations at the dosage levels associated with occupational exposures. Table 10 summarizes the nature and intensity of some exposures that have occurred to personnel involved occupationally with PCBs and the biological indices that have accompanied these exposures, measured as PCB content in blood and adipose tissue.

Since the risk to human health from even high level occupational exposures has been shown by the studies available to be low, it may be concluded that much lower human exposure levels do not present significant risks.

TABLE 1

INDUSTRIAL OCCUPATIONAL EXPOSURE OF WORKERS TO PCBs
(Capacitor plant workers unless otherwise noted)
Data reported in human epidemiology references

Reference				PCB Concentration in Air Range	PCB Concentration in Air ug/m^3	Dermal Contact Noted?	PCB Level in Blood Plasma Parts per billion** No. Subjects*	Mean	Range	PCB Level in Adipose Tissue Parts per million** No. Sub.*	Mean	Range
Jocinelli	(1954)				5200-6800							
Imagawa	(1972)	Plant	A (PCB Mfg.)		50- 200							
		"	B		100- 500							
		"	D		500- 700		99	370	60- 920			
		"	E		200-1700							
		"	F									
Marquardt	(1972)				< 1000		12	440	110-1900	3	360	160-635
Kitamura	(1973)						13	820	320-2100			
Wu	(1976)				320-2220	Yes	34	~ 400	Tr.-1200			
Fischbein	(1979)		Lo expos.		70- 410		158	L- 73 H- 41				
			Med. "		410- 600		62	L-171 H- 25				
			Hi "		600-1100		43	L-266 H- 82				
Wolff	(1981)				As Above		26	L- 83 H- 19	2-1412 1-60	26	L-24 H- 6	2-271 .2-19
Brown	(1981)				24- 393 170-1260							
Smith	(1981a)				N.D.- 264	Yes	14	L-502 H- 44	210-3330 20- 150			
							12	L-237 H- 51	34-2400 10- 250			
							55	L-149 H- 27	8-1500 7- 130			

TABLE 1 (continued)

ference		PCB Concentration In Air Range ug/m³	Dermal Contact Noted?	PCB Level in Blood Plasma Parts per billion** No. Subjects*	Mean	Range	PCB Level in Adipose Tissue Parts per million** No. Sub.*	Mean	Range
ith	(1981b)	37- 215		14	L- 23 H- 24	5- 52 7- 74			
utility worker ransformer repair groups)				8	L- 16 H- 7	1- 52 4- 19			
				4	L- 36 H- 10	23- 59 7- 17			
				13	L- 24 H- 6	12- 35 1- 18			
				7	L- 11 H- 6	1- 30 4- 10			
		3- 82	Yes	15	L- 22 H- 31	9- 47 11-140			
				10	L- 22 H- 26	12- 48 7-250			
				13	L- 23 H- 8	13- 52 5- 25			
				8	L- 19 H- 6	12- 42 3- 11			
roni	(1981)	48-275	Yes	48 12	377 200	88-1319 41-470			
ase ocomotive repair)	(1981)		Yes	86 15	33.4 14.2	10-312 10- 30	36 5	5.6 1.4	1.0-21.6 1.0- 1.8

*Excluding controls

Note: PCB plasma analyses are expressed in parts per billion (including some ng/ml), while adipose tissue analyses are expressed in parts per million.
"L" PCBs (lower homologs) and "H" PCBs (higher homologs) are defined as species having, respectively, shorter and longer gas chromatographic retention timesas than the DDT metabolite p,p' -DDE.
"L" PCBs include 2-PCBs through 4-PCBs, plus some 5-PCBs; "H" PCBs include 5-PCBs and higher, plus some 4-PCBs.

I. INTRODUCTION

A. Origins and Methodology of the Study

In August, 1981, the firm of consultants in toxicology, Drill, Friess, Hays, Loomis and Shaffer, Inc., Arlington, Virginia (DFHLS) entered into a contract with the Edison Electric Institute (EEI) and the National Electrical Manufacturers' Association (NEMA) whereby DFHLS agreed to examine the toxicological and epidemiological literature on polychlorinated biphenyls (PCBs) and provide EEI and NEMA with DFHLS' independent, professional opinion on the human health effects of PCBs at varying dosages or exposure levels. To this end, the principal scientific studies and data compilations available on toxicological and epidemiological effects of PCBs, as commercial mixtures and as purified single congeners, have been reviewed by a team of scientists designated as the Category I team. Members of the Category I team are Drs. V.A. Drill, S.L. Friess, H.W. Hays, T.A. Loomis, and C.B. Shaffer from DFHLS. Additionally, Dr. G. Matanoski of the Johns Hopkins University has acted as an independent member of the Category I team charged with study of the pertinent epidemiological literature on PCBs and their human health effects, leading to an independent assessment and evaluation of the probability, causality and reality of these effects.

Category I team review of the animal and human data resulted in draft material on the relationships between PCB exposure and specific health effects in test animals and in

exposed human populations. Further, where human data were lacking or incomplete, the Category I team members developed specific projections or opinions as to the probability of occurrence of certain health effects in exposed humans, based on the existing animal/human data bases. Health effect areas scrutinized included: general toxicity; effects on skin and other cutaneous tissues; effects on liver; effects on gastric tissues; carcinogenesis (experimental and clinical observations); reproductive effects including fetotoxicity and teratogenicity; mutagenesis; Yusho disease and occurrence of cancer; and other health effects including enzyme induction, changes in immunocompetence, and porphyria. Dr. Matanoski's treatment of epidemiological observations constituted an independent section of the draft report.

Draft sections from the Category I team were then reviewed for content, conclusions and opinions by the members of a scientific team of pharmacologists and toxicologists designated as the Category II team: Dr. F.G. Standaert (Georgetown University), Dr. A. Alvares (Uniformed Services University of the Health Sciences), Dr. J.A. Thomas (West Virginia University) and Dr. P.E. Enterline (University of Pittsburgh). Dr. Enterline was the prime reviewer of the epidemiological contribution made by Dr. Matanoski.

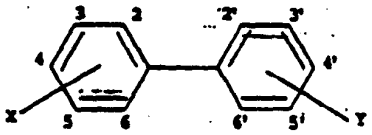
Comments and critique from Category II team members, singly and as a group, were then transmitted to the Category I team for consideration, leading to revisions and amplifications that

are in place in the final draft of this study. Comments and suggestions from scientists representing the sponsors of this study, EEI and NEMA, are also considered.

In the final version of the study, to the extent possible, a section on summary and opinion is appended to each discussion of a potential human health effect attributable to PCB exposure. The primary responsibility for each of these sections is assumed by the Category I team, even though the content may have benefitted from useful contributions by Category II personnel.

B. Commercial PCB Mixtures

Polychlorinated biphenyls (PCBs) are members of a class of non-polar chlorinated hydrocarbons based on the biphenyl nucleus, in which multiple chlorine atoms are substituted on



either or both the primed and unprimed aromatic rings. Certain individual members of the PCB family have been prepared in a relatively pure state, with substitution of ring positions by chlorine ranging from dichloro isomers (symbolized as 2 - CB) up to the nonochloro (9 - CB) and decachloro (10 - CB) derivatives. Commercially, PCBs were marketed in the United States under the trade name of Aroclors. They were also manufactured abroad under the tradenames "Phenoclor" and "Pyralene" (France), "Clophen" (Germany), and Kanechlor (Japan). They are comprised of mixtures of chlorinated biphenyls. The last two digits of the U.S. commercial name denote the percentage of chlorine in each mixture, e.g., Aroclor 1242 contains 42% by weight of Cl corresponding to an average of approximately three chlorines per biphenyl molecule. Likewise, Aroclor 1254, Clophen A50 and Kanechlor 500 all contain 54% chlorine corresponding to five chlorine atoms per molecule on the average.

Commercially useful mixtures of PCBs have been widely distributed over the world in the past few decades, usually in applications that have precluded excessive exposures of user populations. However, because of the great chemical stability of these polychlorinated molecules, their persistence in the environment after accidental release can be lengthy leading to possible exposures of people and biota in the biosphere. The results of these exposures, as well as those of personnel occupationally exposed to PCBs in the course of chemical synthesis

and manufacturing operations, are of great importance from the standpoint of potentially harmful health effects that might occur on an acute or chronic basis.

C. PCB Impurities

Commercial PCB mixtures are truly complex, containing variable numbers and amounts of congeners within a given family of compounds, and traces of impurities, all of which are potentially toxic to humans and animals. Impurities that have been identified in PCBs as manufactured are polychlorinated derivatives of napthalene (PCNs), terphenyls (PCTs), methylbiphenyls, and dibenzofurans (PCDFs).

The occurrence of PCDFs is particularly noteworthy in view of the higher toxicity for certain congeners, relative to PCBs. It is important to note that there are theoretically 135 possible PCDF congeners, a few of which are believed to be highly toxic.

While reviewing PCB toxicological or epidemiological data, a number of factors related to the actual material involved must be considered. The PCDF content of commercial PCBs varies: for Aroclors the reported range is 0-2 ppm of total PCDF congeners. For European and Japanese PCBs, the reported range for PCDF content is 5-20 ppm. The impurity levels can also be affected by exposure to high temperatures and oxygen. For example, Aroclor 1254 is converted to 2-3% PCDFs at 550-600 degrees C. These same conditions result in the formation of polychlorinated quaterphenyls (PCQs).

II. Yusho Episode

In 1968 a mass outbreak of food poisoning occurred in Japan, following ingestion of a cooking oil contaminated with PCBs and other compounds, that aroused worldwide concern over the potential human health effects from exposure to PCBs. However, this poisoning, which became known as Yusho disease, differs significantly in several ways from occupational exposure to PCBs in the United States so that data from the Yusho incident cannot be extrapolated to indicate the effects of PCBs in industrial situations.

Recent studies of the rice oil involved in the Yusho poisoning show that the oil contained relatively large amounts of other chlorinated hydrocarbons such as PCDFs and PCQs (see Kuratsune et al., 1976; and Hayabuchi et al., 1979). The rice oil that caused the disease was found to contain about 1000 ppm of PCBs, 5 ppm of PCDFs, and 1000 ppm of PCQs; the amounts of the latter two classes of chlorinated hydrocarbons in the rice oil are higher than in the Aroclors used in the United States. Hayabuchi reanalysed the intake data for the Yusho patient, and calculated that the average intake for the mean latent period was PCB 466 mg, PCDF 2.5 mg and PCQ 439 mg; the smallest intake by a patient was estimated to be 111, 0.6 and 105 mg respectively.

PCB concentrations in the tissues of Yusho patients were much lower than those of asymptomatic individuals with body

burdens of PCBs resulting from occupational exposure. Further, PCB fractions of blood, tissues, and breast milk of Yusho patients yielded gas chromatographic patterns showing a larger amount of late-eluting peaks than do PCB fractions of tissues of individuals subject to other types of PCB exposure (Koda and Masuda, 1975). These patterns have never been observed in individuals (human or animal) exposed to PCBs in other situations. They are unique to Yusho disease. Also, PCDFs have been found in tissues of Yusho patients.

Further evidence for the uniqueness of the syndrome in humans exposed to the Yusho oil is furnished in two recent studies. Hayabuchi et al. (1981) in follow-up studies on these patients five or more years after the poisoning found significant positive correlations for the years 1973-1976 between blood concentrations of PCBs and the total amount of rice oil consumed, but not with the dosage of rice oil consumed per unit of body weight per day. Kashimoto et al. (1981) found that Yusho is quite different from ordinary PCB toxicity in the sense that, even 12 years after the first outbreak, PCQs have been found in the patients' blood and both PCQs and PCDFs have been found in their tissues and organs.

It is obvious from this brief review that Yusho cannot be considered a model to reflect the possible effects of the PCB exposure in man. Although much can be learned from the Yusho

incident, it would be misleading to attempt to interpret the observations on Yusho patients as valid signs and symptoms of overexposure to PCBs or to attempt to quantify the possible effects of PCB exposure based on Yusho disease.

A. Yusho Disease

Yusho disease is characterized by the ingestion of a mixture of chlorinated hydrocarbons containing PCBs in large amounts over a relatively short period of time (latent period from start of ingestion to onset of the disease averaged 71 days). In contrast, the studies of PCB exposure in workers in the United States have been concerned with the possible effects of chronic exposure to small amounts of PCBs through inhalation or skin contact.

The principal signs of Yusho disease are skin conditions such as acneform eruptions, pigmentation of the skin and nails, and hypersecretion of the Meibomian glands. Chloracne and hypersecretion of the Meibomian glands are believed now to be caused predominantly by PCDFs. Hyperpigmentation of the skin is observed rarely, if ever, in human populations with heavy occupational exposure to primarily PCBs.

The actions of PCDFs appear to differ in several ways from those of the PCBs. Kuratsune et al. (1976) showed, for example, that the liver appears to concentrate PCDFs selectively relative to PCBs. It was also found that relative to PCBs, the concentration of PCDFs was about 250 times higher in the rice oil than in unused Kanechlor-400. Additionally, the PCDFs appear to

be highly toxic, at least in the rabbit; a single oral dose of 0.5-1 mg/kg of the tri- and tetra- chlorodibenzofurans caused severe and often lethal necrosis in the rabbit (Hofmann, 1958; Bauer et al., 1961).

B. Yusho Disease and Liver Function

In view of the effect of PCBs on the liver of the rat and the highly toxic action of PCDFs on the liver of the rabbit, it was anticipated that the Yusho patient would have severe liver damage, but such has not been found.

In their review of Yusho disease, Kuratsune et al. (1972) list "the subjective symptoms of Yusho as stated by 189 patients"; 11% report jaundice. Data to confirm the patients' "subjective symptoms" are not provided, nor is the presence of this "symptom" confirmed by other statements of clinical findings. Prof. Urabe (Chief of the Study Group) did not list jaundice as a sign or symptom of Yusho disease and the diagnostic criteria adopted in 1972 do not make reference to jaundice or the need for a liver function test in these patients (see Kuratsune et al., 1976).

The following two papers on Yusho disease and liver function are in Japanese and the brief summary given below is taken from the report of Kuratsune et al. (1976).

Okumura and Katsuki (1969): They examined 24 patients soon after the onset of the disease;

(i) There were no objective signs of liver disorders; (ii) No patients were jaundiced and only three had palpable livers (in one patient examinations of a liver biopsy showed marked hypertrophy of the smooth endoplasmic reticulum).

Okumara (1972): Liver function tests were performed in 38 Yusho patients with various subjective symptoms. (i) An increase in lactic dehydrogenase (LDH-5) and in thymol turbidity titer was observed in some of the severe cases, "but no definite evidence for liver disorders was obtained."

In a follow-up study of 121 Yusho patients the mean serum bilirubin was 0.48 mg/100 ml compared with 0.87 mg/100 ml in control patients (Hirayama et al., 1974). The difference was statistically significant and the authors suggest that there may be accelerated bilirubin disposal from the blood.

It may be concluded that the Japanese findings do not provide evidence for the development of hepatocellular injury or jaundice in patients with Yusho disease.

C. Yusho Disease and Carcinogenicity

Urabe and co-workers (1979) report that 51 of 737 Yusho patients in the Fukuoka district had died and they list the cause of death for 31 of the patients. There were 11 deaths (35.4%) from neoplasms which they state is substantially higher than the 21.1% rate that is "the mortality rate from neoplasms in the

same prefecture this year." A further analysis is not provided. The following malignant neoplasms were listed as the cause of death for the 11 patients with cancer.

Anatomical Site	No. of Cases
Stomach Cancer	2
Stomach Cancer & Liver Cancer	1
Liver Cancer & Liver Cirrhosis	2*
Lung Cancer	2*
Lung Tumor	1
Breast Cancer	1
Malignant Lymphoma	2
TOTAL:	11

*Autopsied

Information on age and other relevant epidemiological data are not given, and even a tentative conclusion regarding Yusho disease and any malignancy must await further analysis.

III. Body Burdens, Metabolism, and Kinetics

A. Introduction

The degree of chlorination (2 to 10 atoms of Cl per PCB molecule) and the positions of the chlorine substituents on the biphenyl rings both exert a profound influence on how mammalian systems handle any given PCB molecule. The degree and position of chlorination play a major role in determining the pathways for metabolism and elimination of the parent molecules and their metabolites by animal models and the human. These structural factors also bear on lipid solubility of the molecules, and therefore influence to some extent the kinetics of PCB tissue distribution and storage. The following sections deal with the present state of knowlege on these PCB handling mechanisms employed by animal models and the human, recognizing that there is a strong linkage in the dynamic processes beginning with exposure and ending in excretion. These topics will be treated in three groupings: (1) distribution and storage of PCB metabolites in tissues; (2) metabolism and excretion; and (3) kinetics or the dynamics of PCB turnover in animal models and the human. Presently, some generalizations emerge with regard to PCB structure vs. reactivity relationships and mechanisms for handling PCBs in test animal systems that make reasonable extrapolation to potential events in the human organism possible, even when direct evidence for actions of a given compound or PCB mixture in human populations is not available.

Additional attention has been directed to available information on the actions of PCDFs in animal models and the human, and to a variety of biochemical effects recorded for PCBs and their metabolites in mammalian systems. PCDFs may be contaminents of some commercially used PCBs. Although 10-20 ppm of these contaminants have been found in PCBs manufactured in Europe and Japan, only trace amounts on the order of one or two ug of total PCDF congeners per g of PCB have been reported in the American manufactured mixture Aroclor 1254 (Bowes et al., 1975).

B. PCB Distribution and Storage in Tissues

A considerable body of literature exists on studies of the time dependence of the distribution, movement and storage of PCBs and their metabolites in the tissues of experimental animal models and of humans, following exposures to chlorinated biphenyls as pure compounds or mixtures. In test animal models using unlabeled or radiolabeled (1/2 C or 1/2 H) PCBs, controlled exposures were generally by the oral route (stomach tube, or in the feed) or by intravenous injection, followed by study of the changing distribution of the agent and its metabolites in the circulating blood, in tissues, in bile fluid and in excreta as a function of elapsed time after dosing. In the human, exposures with resulting body burdens of PCBs were generally of the subchronic type stemming either from massive poisoning events, as in the Yusho events, from chronic occupational exposures in air and via skin contact, and via PCB contaminants in air, water, food and surface contacts in the ambient. Humans may also have been

exposed to PCBs occupationally in the chemical manufacturing process, in the manufacture of capacitors and in the manufacture and repair of transformers. Until, recently, several microscope immersion oils contained 30-40% PCBs as Aroclor 1254, causing potential exposures of students, pathologists, microscopists, etc; the degree of exposure is low and the penetration through skin from these products may not be as extensive as in large scale manufacturing processes.

In human studies, PCB distribution and storage in readily obtained tissues was generally followed epidemiologically in exposed populations by monitoring levels in blood, sometimes in mother's milk as a function of time and sometimes by measuring PCBs in adipose and other tissue samples obtained clinically and post mortem.

Animal Model Results

The picture of distribution and storage of PCBs and their metabolites in tissues over time has been developed most completely from controlled dose experiments in animal models. Generally, rats and mice were the animals of choice for this work (Burse et al., 1974; Geyer et al., 1980; Guiney et al ., 1978; Mattews and Anderson, 1975; Morales and Matthews, 1979; Albro and Fishbein, 1972; Burse et al., 1976), but the dog, as well as the monkey, has also been used (Hsu et al., 1975a; Milling et al., 1979; Sipes et al., 1980). The dynamics of tissue distribution vary with different isomers and congeners, and depend in large measure on whether or not the specific PCB

molecular structure allows rapid metabolism and excretion of polar metabolites via bile, feces and urine (Milling et al., 1979; Safe et al., 1975; Sipes et al., 1980; Matthews et al., 1978; Guiney et al., 1978; Guzelian, 1979) or slower metabolism with retention of parent compounds and metabolites in tissues. As will be discussed in the following section, metabolic transformation in the liver is particularly facile for those PCBs with lower chlorine content (2 - CB through 4 - CB, i.e. 2-4 chlorines per PCB molecule) and with adjacent ring carbon atoms unsubstituted by chlorine atoms (Matthews and Tuey, 1980; Sundstrom et al., 1976; Kato et al., 1980; Jensen and Sundstrom et al., 1974b; Ghiasuddin et al., 1976; Matthews et al., 1978). For many PCB molecules in which metabolic transformation and excretion is not excessively rapid, the dynamic distribution of parent compounds and metabolites in tissues following dosing has been studied carefully (Mizutani et al., 1980; Safe et al., 1975; Sipes et al., 1980). The following generalizations appear valid in animal models for structures ranging from 1-CB to 6-CB and higher.

First, the PCBs are readily absorbed from the gut following oral administration and appear rapidly in the bloodstream (Albro and Fishbein, 1972; Berlin et al., 1975; Chen and Matthews, 1974). Within minutes to hours, the materials largely clear from the blood and accumulate in the liver and in muscle tissue (Berlin et al., 1975; Burse et al., 1974; Chen and Matthews, 1974). However, traces of PCBs have been found in the

blood of humans, probably by redistribution from other tissues, years after exposure. The liver is the primary locus for metabolism of the PCBs, especially for reactive species, leading to mixtures of parent molecules and metabolites that then either translocate to other tissues or are excreted by both bile/gut, lumen/feces and urinary pathways. As translocation from liver and muscle occurs in the rodent model and other species over time periods ranging from hours to many days, the ultimate depots for major amounts of the non-polar PCBs and their polar metabolites appear to be adipose tissue and skin (Berlin et al., 1975; Hansen, 1979; Guiney et al., 1978; Burse et al., 1974). The general distribution pathway in rodents may therefore be characterized as sequential migration from gut and bloodstream entry points to liver and muscle tissues, in a rapid process, and thence to depot storage in body fat and skin.

When the PCB structure is such as to permit ready metabolism to polar hydroxy, dihydroxy or diol derivatives, the metabolic process may be closely linked in time with excretion of the metabolites (Jensen and Sundstrom, 1974; Lay et al., 1979; Matthews and Tuey, 1980; Matthews et al., 1978; Matthews and Anderson, 1975). Animal studies on urinary and fecal excretion of PCBs (Guselian, 1979; Matthews and Anderson, 1975; Berlin et al., 1975; Lay et al., 1979; Chen et al., 1976; Van Miller et al., 1975), and rates of elimination of PCBs from liver into bile and then into gut/feces, show that the larger

proportion of excretion in rodents is by fecal elimination (Kato et al., 1980; Lay et al., 1979; Chen et al., 1976; Van Miller et al., 1975; Chan and Matthews, 1974) of polar metabolites, mostly glucuronides, eliminated via the bile.

The dynamics of distribution and elimination of PCBs in two monkey species have been studied (Hsu, et al., 1975a; Sipes et al., 1980; Hsu et al., 1975b), and are found to follow a similarly complex pathway, but with wider tissue distribution ultimately than that seen in the rat. In our opinion, this difference may relate in part to the ability to analyze more tissues in larger animals. With fat tissues present in only small proportions in the infant Rhesus monkey, the ultimate depots included bone marrow and the adrenal glands, in addition to skin (Hsu et al., 1975a).

Long-term studies involving chronic administration of PCBs at low dosage levels to animal models for significant fractions of their lifetimes, with determinations of total burdens and tissue distributions achieved over time periods of one to two years of ingestion, are lacking.

Human Body Burden Results from Epidemiological Studies

Experimental data on body burdens and tissue distributions of PCBs in humans as a result of precisely-measured intakes are not available. However, there are several population sectors for which exposures to PCBs can be at least roughly estimated, and from which tissue samples (blood, subcutaneous and other fatty tissue, etc.) have been taken to obtain indices of

body burden. These sectors include: (1) humans occupationally exposed to PCBs during years in which they were employed in manufacturing processes (Karppanen et al., 1972; Hasegawe et al., 1972; Kitamura et al., 1973; Ouw et al., 1976; Fischbein et al., 1979; Wolff et al., 1981; Maroni et al., 1981a, b; Smith et al., 1981a, b; Chase et al., 1981); (2) humans accidentally poisoned by PCBs ingested in contaminated foods, as in the Yusho experience in 1968 and in corresponding ingestions of contaminated rice oil in Taiwan (Chen, 1980; EPA summary, 1980); and (3) humans living in areas in which PCBs have somehow entered the food chain or water supply in measurable amounts, leading to long-term, low-level body burdens in adults that may also be present in the human milk supply for transmission to infants (Humphrey, 1975, 1980; Kuwabara et al., 1979a; Kuwabara et al., 1979b; Mes and Davies, 1979; Watanabe et al., 1980). An additional source of exposure that is more difficult to characterize quantitatively stems from the exposure of families to contaminated clothing of PCB workers. Survey work has been done in all of these population sectors worldwide. The results are sketchy, but tentative qualitative generalizations can be drawn.

Blood or plasma levels of PCBs are most readily followed in potentially exposed population data using highly sensitive analytical techniques such as gas chromatography and mass spectrometry. For occupationally exposed people (NIOSH, 1977; Smith et al., 1980a) values ranging from 10 ppb up to a maximum of 3330 ppb have been observed, with the additional

qualitative finding from Japanese references that the half-life for disappearance of PCBs from blood following cessation of exposure ranges from 3 to 30 months. PCB blood levels were higher with increased duration of exposure. For Yusho victims in Japan, with blood samples taken 5-7 years following exposure to PCBs, in the 1973-1975 time frame (NIOSH, 1977) values in the range 3-33 ppb were observed. Enhancement factors over control group levels (mean, 3 ppb) as great as 10 were calculated, but the observed blood levels were still much lower than levels found in Japanese capacitor workers. It is of interest to note the observation of Humphrey (1975) on the very slow clearance of PCBs from the tissues of humans exposed by eating fish. In general populations, blood plasma or serum levels of PCBs in the range 5-29 ppb have been found (NIOSH, summary p. 36).

A current and well documented study of body burdens of PCBs in persons employed for many years in capacitor manufacturing (Wolff et al., 1981) is of special value from the standpoint of its correlations of tissue concentrations with extent of exposures. With highly chlorinated PCBs (H-PCBs), plasma concentrations of 1-546 ppb in exposed personnel correlated with total accumulated exposure time. For the less highly chlorinated PCBs (L-PCBs), plasma levels in the range 6-2530 ppb correlated better with specific tasks of individuals working with these 2-CB to 4-CB molecules. Also observed in this study was a correlation of levels in plasma with levels in adipose tissue for each class

of PCBs, with H-PCBs and L-PCBs taken as separate classes, and an overall adipose/plasma partition coefficient of 190.

The levels of PCBs and metabolites in subcutaneous fat in humans have also been surveyed in general populations (NIOSH, 1977), in groups such as Yusho patients with high exposures, and in some occupationally exposed individuals. For the general population, levels in fat range from less than 1 ppm to greater than 2 ppm. For Yusho individuals, elevated fat PCB levels in the range 13-75 ppm have been observed, corresponding to peak enhancement factors as high as 30 over the population at large. It should also be noted that the spectrum of compounds in human tissues is not necessarily identical with the spectrum in the mixture to which a given population was exposed (Kuwabara et al., 1971a). Ranges of adipose tissue PCB levels in occupationally exposed individuals have been reported as 160-635 ppm (Karppanen et al., 1972), 1-12.6 ppm (Chase et al., 1981), and 2-271 ppm (Wolff et al., 1981).

Special surveys have been made of PCB levels in the milk of lactating human mothers (Hsu and Davies, 1979; Watenabe et al., 1980; NIOSH summary) and of levels in human embryonic and fetal tissues resulting from in utero transfer from Yusho females (NIOSH, 1977). Human milk samples with values of PCBs in the range 0.008-0.1 ppm have been observed. Clearly, concentrations in milk are higher than those in blood primarily because milk is rich in fat. Organs from the embryonic and fetal tissue displayed PCB levels in the range 0.002-0.750 ppm

for whole tissues, with fat derived from these organs yielding levels in the range 0.04-1.14 ppm.

C. PCB Metabolism and Excretion

Animal experiments involving exposure by feeding, intubation or injection of purified PCB isomers in test animal models have yielded some important generalizations on the mechanisms employed by mammalian species to metabolize PCBs to more polar derivatives, and to excrete both parent compounds and metabolites. Beginning with ready absorption from the gut and transfer to circulating blood, or with direct injection into the bloodstream, a given PCB molecule ultimately reaches the liver where major metabolic actions are initiated. The processes of metabolism and excretion as a result of these actions are complex, and dependent on the molecular structure of the PCB. General features of these processes include the following points:

(1) Variable amounts of PCB metabolites are excreted via the feces after delivery to the gut lumen via the bile flow pathway. Unchanged PCBs can occur and be discharged in milk. Relatively lesser amounts are excreted as polar metabolites in urine than in feces in most animal models (Kato et al., 1980; Lay et al., 1979; Chen et al., 1976; Van Miller et al., 1975; Chen and Matthews, 1974).

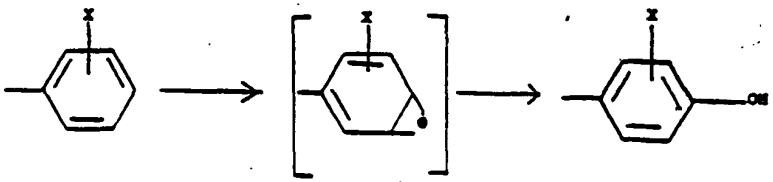
(2) Metabolites are formed in patterns that differ quantitatively or qualitatively among mammalian species. They are generally formed by oxidative processes that are thought

to involve an arene oxide formation that results in monohydroxylation, dihydroxylation, hydroxylation and methylation, or diol formation accompanied by partial reduction of an aromatic ring (Berlin et al., 1975; Lay et al., 1979; Lucier et al., 1978; Milling et al., 1979; Sundstrom et al., 1976; Gardner et al., 1973; Chen et al., 1976; Matthews et al., 1978; Van Miller et al., 1975; Hsu et al., 1975a; Hsu et al., 1975b; Burse et al., 1976). Evidence also exists for dechlorination of a PCB in the process of metabolism (Kato et al., 1980; Hutzinger et al., 1974b). For some PCB structures, the process of oxidative metabolism may be closely followed by excretion via the liver-bile-feces pathway (Chen and Matthews, 1974).

(3) Compounds with lower levels of chlorination (2 - CB to 3 or 4 - CB) generally undergo metabolism more readily, and faster than the more highly chlorinated PCBs. The more highly chlorinated PCBs may persist in tissues for years because they are not metabolized. Indeed, 10 - CB is virtually inert.

(4) In the case of metabolism by oxidative pathways, the most facile process involving formation of hydroxylated products occurs when one or both aromatic rings contains adjacent pairs of ring carbon atoms (called vicinal ring atoms) that are unsubstituted by chlorine atoms. In the absence of unsubstituted vicinal positions, direct hydroxylation can occur in the ring, but with greater difficulty (Geyer et al., 1980; Matthews and Tuey, 1980).

The importance of vicinal unsubstituted positions on PCB rings in facilitating oxidative metabolism in the liver is explained by a mechanism that involves an arene oxide intermediate (Daly et al., 1972). When either or both of the vicinal positions contain chlorine, reaction rates will be lower, but the mechanism is not entirely ruled out. Additional molecular rearrangements, including the so-called NIH (National Institutes of Health) shift of a ring substituent (Daly et al., 1972), may be involved. Less is known about mechanisms of direct enzymatic hydroxylation that do not proceed through an arene oxide intermediate.



Arene Oxide

(5) Hydroxylated metabolites of the PCBs and their conjugates will generally display different orders of toxicity than those shown by the parent molecules.

(6) A general point of interest with respect to PCB metabolites lies in the observation that they are usually more polar than their parent compounds. Conjugation of the hydroxy and dihydroxy metabolites as glucuronides or sulfates can occur, leading to polar conjugates that can readily be excreted. The polar character of metabolites, in contrast with the non-polar

characteristics of the starting PCBs, can lead to differing distribution, storage and excretion patterns for the two classes of chemical compounds. Polar metabolites are not readily partitioned into fat or reabsorbed from the urinary or gastrointestinal tracts. Therefore they are excreted relatively rapidly.

D. PCB Kinetics

Profiles of the dynamic growth and decay of PCB/ metabolite concentrations in each key tissue can be drawn from controlled toxicological experiments. The distribution of a given PCB and its metabolites in the blood, tissues and excreta of test animals is followed as a function of time after administration. Tissues are viewed as body compartments into which materials are delivered from the arterial blood supply, in which some metabolic processes may occur, and from which materials are delivered into the venous drainage systems. A collection of such compartments communicating with the blood supply and controlled by rates of flow through the compartments, with postulated equilibration of any given chemical in a compartment with its venous blood flow, constitutes an appropriate modeling system for correlating PCB distribution, storage, metabolism and excretion kinetics in an animal over time. This multi-compartment model has been employed by Matthews and co-workers and others (Anderson et al., 1977; Bungay et al., 1979; Tuey and Matthews, 1977; Lutz et al., 1977), to sort out the kinetics of specific PCB isomers in rodent models. The PCB administration can be either direct

injection of a PCB into the blood circulation, or its absorption into blood from the gut after feeding or intubation of the compound. Excretory pathways are via the liver/bile/gut route or the blood/kidney/urinary elimination system.

The success of a model equation system in fitting analytical data for a given PCB and predicting the shape of its concentration vs. time curve for each organ or compartment depends in large measure on several factors, including: (1) the assignment of suitable values for distribution coefficients of PCB compounds in each compartment; (2) the differential blood flow to various organs; and (3) the clearance from organs and the body. This fitting process has now been carried out for a number of PCBs for which kinetic data are available (Anderson et al., 1977; Chakraborty, 1978). The goodness of fit of the model to each set of PCB kinetic data available attests to the validity of the assumption that materials partition at equilibrium between blood and tissue according to purely physical properties involving solubility parameters of the chemicals.

E. Miscellaneous Biochemical Effects of PCBs

Studies of the actions of PCBs in animal models and humans exposed to these chemical agents accidentally or in the occupational setting have revealed a variety of biochemical effects on mammalian organisms. Some, such as alteration of drug metabolism by virtue of PCB induction of microsomal mixed function oxidases (MFO), are treated elsewhere in this document.

Other effects appear to be unrelated to MFO actions, and have been detected in the course of acute or chronic toxicological experiments with laboratory animal models or epidemiological surveys of exposed human populations.

In an animal study (Bastomsky et al., 1975) aimed at probing the previous evidence on reduced serum bilirubin levels in Yusho patients, it was found that Aroclor 1254-treated rats showed increased liver microsomal protein, as expected, but with no significant elevation in liver bilirubin UDP-glucuronyl transferase activity that could have accounted for reduced serum levels. Other studies (Grote et al., 1975; Lake et al., 1979) have shown enhanced levels of this transferase activity. At present therefore, the mechanism underlying the hypobilirubinemia in Yusho patients remains speculative.

From epidemiological studies of Yusho patients (Strik, 1979), a rather general biochemical finding has been the observation of porphyrins in urine and porphyrin accumulation in liver, as a result of exposure to chlorinated hydrocarbons including PCBs. Chronic hepatic porphyria is the designated condition, which increases with exposure and can therefore be taken as an indicator of the extent of PCB exposure. Porphyria is discussed elsewhere in this text (section XI).

A biochemical factor that may bear on the toxicity of PCBs in certain sensitive human populations, e.g., fetuses, neonates, enzyme deficient adults, etc., is related to the ability to excrete the toxic phenolic metabolites rapidly and efficiently.

Since a common route of excretion involves preliminary conjugation of the phenolic hydroxyl groups with glucuronic acid in the body, or sulfate conjugation, it has been pointed out (Calabrese, 1977b) that human groups that are biochemically deficient in the ability to conjugate could be predisposed to accumulate PCBs and metabolites because of this deficiency. A more serious consequence of altered liver capability would be a reduced capacity to deal with arene oxide intermediates effectively.

An interesting biochemical defect in human lymphocytes has been studied (Lee and Park, 1980) that can be attributed to direct action of PCBs on these white blood cells. For both human lymphocytes and monocytes, it has been found that incubation of the cells with Aroclor 1254 in culture medium causes a decrease in their ability to take up glucose from the medium. A non-metabolizable analog of glucose, 2-deoxyglucose, was used to detect the biochemical defect, which was attributed to PCB exposure but which may well be more general for any organic chemical that concentrates in the fat of the cell wall. It may entail direct action of PCBs on an active transport process in cell membranes. In this regard, liver glucose-6-phosphatase has been found to be inhibited in rats fed various Aroclor mixtures (Litterest et al., 1972).

The processes by which PCB pretreatment influences rates of protein and nucleic acid (RNA) synthesis and turnover in rat liver tissues have been investigated systematically

(Narbonne, 1979a, b, c, e), using radiolabeled substrates. It is clear that liver tissue, *in vivo* and *in vitro*, responds to PCB treatment (Phenochlor DP6) by increasing the protein synthesis in liver microsomal fractions in a process that is both age and sex dependent. Concomitant increases in liver fat are also seen *in vivo*, as well as changes in levels of RNA synthesis in various liver fractions and increases in liver weights. From the turnover experiments in rats, it is also observed that microsomal membrane protein metabolism is enhanced by ingestion of Phenochlor DP6.

Some further biochemical effects of PCB exposures on the human are seen in workers occupationally exposed to these chemicals for extended periods of time (Smith *et al.*, 1976). The findings, as yet unexplained in terms of requisite dosages or underlying mechanisms, are that: (1) the circulating triglyceride levels in blood plasma are elevated for exposed workers over controls, but are still within normal levels; and (2) the circulating levels of high density lipoprotein are lowered in exposed groups of workers.

Another biochemical effect seen in PCB-treated rats is worthy of note, since it relates to an impairment of excretion of an important drug and its metabolites (Schmoldt *et al.*, 1979). In the Wistar rat pretreated with Aroclor 1248, the drug digitoxin and its metabolites were blocked to a significant degree from excretion via the bile. The results suggest that the

blockage is due at least in part to a PCB-induced impairment of the cleavage of one of the sugars from digitoxin.

Finally, the action of PCBs leading to induction of mixed function oxidases (MFOs) in the liver, with elevation of associated cytochromes P-450 or P-448, has potential consequences. These are discussed elsewhere (section XI).

F. Some Observations on Polychlorinated Dibenzofurans

The PCDFs are of special interest since they are known to be highly toxic in their own right, and the degree to which, as contaminants, they add to the potencies of PCB mixtures in production of adverse health effects in animal models and humans has not been fully evaluated. However, toxicological studies in animals with PCDFs containing 1-4 or more Cl atoms per molecule (Morita and Oishi, 1977; Goldstein et al., 1976; Veerkamp et al., 1981) have shown that the PCDFs are qualitatively quite similar to their structural PCB analogs with respect to properties of tissue distribution, metabolism and excretion. In the mouse, the heavily chlorinated isomers localize in liver, spleen and fat (Morita and Oishi, 1977), with a half-life for clearance from the body of about two weeks. In the rat, metabolism occurs by oxidative pathways leading to mono- and dihydroxylated derivatives (Veerkamp et al., 1981), with a wide variation in ring position by the hydroxy function among the lower chlorinated PCDFs. The octachloro derivative yields no metabolic products in tissues or

excreta (Veerkamp et al., 1981). In the chick (Goldstein et al., 1976), the 2,3,7,8-tetrachlorodibenzofuran (TCDF) has been shown to be relatively poor in enzyme induction. However, Goldstein et al. (1978, 1979a) have shown that 2,3,7,8-TCDF is a potent inducer of cytochrome P-450 and aryl hydrocarbon hydroxylase.

Some important data on PCDF metabolism and excretion in the human were obtained (Rappe et al., 1979) by analysis of liver tissue from two deceased patients in the Yusho disease group in Japan. From the differences in PCDF structural relationships in the contaminated rice oil and in the PCDF fractions isolated from the livers, inferences could be drawn with respect to PCDF structure (all containing 4-6 chlorine atoms per molecule) retained by the liver vs. those that had disappeared from liver by processes of metabolism/elimination. In striking parallelism with PCB disposition in mammalian tissues, it was found that none of the PCDFs retained in liver had two vicinal unsubstituted (by Cl) positions in either aromatic ring. Apparently, all such molecules had been sufficiently susceptible to oxidative metabolism to be hydroxylated and excreted from liver in the bile.

The above observations are not to be taken as all-inclusive with respect to the body of information that must be developed in the toxicology of the PCDFs. This class of compounds, even at low contaminant levels, is an important contributor to the total spectrum of toxic affects from commercial PCB mixtures.

G. Summary and Opinion

Some general reflections and opinions can reasonably be drawn from the previous discussion regarding the use of animal-derived biochemical and kinetic information to predict certain events and hazards in human PCB intoxications.

(1) Pathways of absorption, distribution, metabolism and excretion have been explored fairly extensively in animal models. From the species variability seen, coupled with limited observations in the human, educated guesses and predictions can be made on the occurrence of certain toxic effects and processes in the human.

(2) Mathematical analyses of kinetic data from animal modeling experiments lead to some generalizations (Lutz et al., 1977) that could apply to PCB turnover kinetics in the human: (1) kinetic rate constants for metabolism of PCBs by the liver decrease as the degree of chlorination increases; (2) rate constants for biliary clearance of PCB metabolites from the liver are nearly the same for all PCBs; (3) urinary clearance rates for PCBs decrease as the degree of chlorination of the parent molecules increases; and, (4) for each PCB, the value of the distribution coefficient between fat and blood is greater than that in any other major tissue, indicating that the fat compartment of all tissues may constitute the major PCB depot.

(3) Kinetic models derived from animal data may be useful for prediction of time courses of action in the human once

additional data on metabolism and clearance rates for individual PCBs in human tissues are obtained.

(4) Some general PCB structure vs. activity relationships have emerged from animal studies, particularly rodents, that can have useful predictive power for the human.

(5) There is some relevance of the features of the absorption/distribution/metabolism/clearance processes discussed in this section to the toxicology of PCBs in animals and humans. For example:

(a) The possibility that an arene oxide intermediate can occur in PCB metabolism has special significance in terms of potential reactions with protein, RNA or DNA to cause tissue damage or damage to a cell's nuclear functions.

(b) The retention of PCBs in adipose or other tissue can have major significance by creating reservoirs from which material can be leached over time for reaction at other tissue sites.

(c) There is little evidence in humans for acute cytotoxicity of the kind usually associated with reactive metabolites. Rather, some of the adverse effects of PCBs, e.g., chloracne, could stem from the physical presence of unreacted material in the cells along with oils and/or sebaceous materials of the skin.

IV. General Toxicity

A. General Considerations

Any attempt to undertake a systematic evaluation of the toxicity of PCBs is confounded by a number and variety of factors that complicate the interpretation of the findings and limit their generalization. Therefore, these factors should be recognized at the outset of consideration of the available body of toxicological literature. The more important of these factors are listed as follows:

(a) The multiplicity of commercial products of both U.S. and foreign manufacture;

(b) The multiplicity of isomeric forms of PCBs in commercial products;

(c) Qualitative and quantitative differences in metabolism of different isomers within the same species;

(d) Qualitative and quantitative differences in metabolism of the same isomer between species;

(e) Differences in rates of metabolism of different isomers within the same species;

(f) Differences in rates of metabolism of the same isomer between species;

(g) Differences in the biological half-lives of different isomers within the same species;

(h) Differences in the biological half-life of the same isomer between species;

(i) The presence in commercial products of impurities of much greater toxicity than that of PCBs;

(j) The variability between commercial products of the same type (i.e., same degree of chlorination) in the concentration of impurities of much greater toxicity than that of PCBs;

(k) The variability between commercial products of the different types (i.e., different degrees of chlorination) in the concentrations of impurities of much greater toxicity than that of PCBs; and

(l) Differences between species in susceptibility to the toxic action of (i) individual isomers and their metabolites, and (ii) the impurities that may be present in commercial products.

The preceding factors may underlie the conclusion reached by the Panel of Hazardous Trace Substances (1972) that "[t]here is no consistent relationship between toxicity and degree of chlorination which is valid for different species and different routes of exposure." To this might be added the observation that there is often no consistent relationship between the results of investigations on products of the same degree of chlorination from different manufacturers. These observations constitute caveats that should be borne in mind as individual toxicological experiments and results are evaluated.

B. Impurities in Commercial Products

The work of Voe and his associates (Voe and Koeman, 1970; Voe et al., 1970; Voe and Beems, 1971) led to a recognition

of the significant role played by traces of impurities in commercial PCBs in influencing the apparent toxicity of the latter. In studies involving three commercial PCBs of the same degree of chlorination, these investigators found marked differences in toxicity that were traced to the presence, in two of the products, of small amounts of chlorinated dibenzofurans (PCDFs) and chlorinated naphthalenes. The PCDFs are related closely, both structurally and toxicologically, to the chlorinated dibenzodioxins. The 2,3,7,8-tetrachlorodibenzo-p-dioxin isomer is an extremely potent toxicant in mammals, especially for the fetus. The chlorinated naphthalenes are less toxic than the chlorinated dioxins, but nevertheless cause chloracne and other symptoms in man similar to those produced by PCDFs.

The extent of the contribution made by contaminants to the toxicity of commercial PCBs is uncertain, but the consensus is that it is substantial. There seems little doubt that the skin lesions, including chloracne, are caused by PCDFs. The Panel on Hazardous Trace Substances (1972) states that the PCDFs "are probably the chief if not exclusive cause of chloracne in man." Fishbein (1974), in his review of the toxicity of chlorinated biphenyls, observes that "[l]iver damage and skin lesions are believed to be caused primarily by chlorinated dibenzofuran contaminants and to a minor extent by PCB itself." Furthermore, since the chlorinated dibenzodioxins exhibit pronounced embryotoxicity, it is not unreasonable to expect that the PCDFs share this property and, hence, are largely responsible for the fetal

deaths and resorptions that have been observed experimentally with commercial PCBs.

An appreciation of the role played by contaminants in the toxicity of commercial PCBs is important for two reasons. First, it may explain discrepancies between the results of studies of apparently similar commercial products. Second, it points up the difficulty of attempting to use PCB tissue levels to correlate the results of laboratory studies with observations of occupationally or environmentally exposed populations. For example, some animal populations in the environment appear to be unaffected by PCB tissue levels that are equal to or greater than those associated with adverse effects on comparable species in the laboratory.

C. General Toxicology

1. Acute Toxicity

The Aroclors of the PCB class have a low order of acute toxicity. The acute oral LD50s for rats range from 1-10 g/kg. The LD50s by single application to the skin of rabbits are approximately 1-3 g/kg. Oral and dermal LD50 data have been summarized by Fishbein (1974), Kimbrough et al. (1978), and the Panel on Hazardous Trace Substances (1972).

2. Subchronic and Chronic Toxicity

(a) General

Subchronic and chronic toxicity are grouped together for purposes of this discussion since the effects of chronic

exposure to PCBs are essentially extensions of those observed from repeated exposures of shorter duration.

There are numerous published studies in which commercial PCBs (Aroclors) have been administered by various routes for varying periods of time to most common mammalian species of laboratory animals. Out of this mass of observations, one may identify two principal classes of biological effects of these substances. These classes are (a) alterations in the liver, and (b) skin lesions.

(b) Alterations in the Liver

Enlargement of the liver, both in absolute terms and as a percentage of body weight, has been observed consistently in most species consequent to repeated exposure to PCBs, although it is more pronounced in rodents than in others. This phenomenon has been reported for mice (Kimbrough and Linder, 1974), rats (Bruckner et al., 1973, 1974a, b), guinea pigs (Vos and Van Driel-Grootenhuis, 1972), rabbits (Koller and Zinkl, 1973), dogs (Calandra, 1976), and monkeys (Allan et al., 1973). Early enlargement of the liver is primarily the result of an increase in the size of the hepatocyte associated with an increase in the amount of the smooth endoplasmic reticulum (SER). These developments are associated also with increased enzymatic activity of the liver (Bruckner et al., 1973).

A detailed discussion of the effects of PCBs on liver in test animal systems is given in section VI.

(c) Skin Lesions

Cutaneous effects from repeated exposure to commercial PCBs can be elicited by feeding to monkeys or skin application to rabbits, although the results are somewhat more dramatic in the former. The results of these animal studies are discussed in section V.

(d) Miscellaneous Effects

Hyperplasia and dysplasia of the gastric mucosa have been observed in monkeys fed a diet containing 300 ppm of Aroclor 1248 for three months (Allen and Norback, 1973). Gastrointestinal lesions do not appear to occur in rodents, except at very large single doses by mouth (Kimbrough, 1979). A dietary concentration of 2.5 ppm of Aroclor 1248 produced alterations in the menstrual cycles of adult, female rhesus monkeys (Allen et al., 1979). Menses were prolonged, and there was an increase in menstrual bleeding. Hepatic porphyria has been demonstrated in mice after feeding Aroclor 1254 (Kimbrough and Linder, 1974), in rats after feeding Aroclors 1254 or 1260 (Kimbrough, et al., 1972), and in rabbits after repeated skin application of Aroclor 1260 (Vos and Beems, 1971). Urinary excretion of coproporphyrin was increased in rats fed Aroclor 1242 (Bruckner et al., 1974), and both urinary and fecal excretion of porphyrins was increased in rabbits receiving repeated skin applications of Aroclor 1260 (Vos and Beems, 1971). Other effects reported for one species or another include structural changes in the kidney (Vos and Beems, 1971; Bruckner et al., 1974a, b) hematologic alterations (Bruckner et

al., 1974a, b) and thymic atrophy together with a reduction in the number of germinal centers in the spleen and lymph nodes (Vos and Beems, 1971).

D. Summary and Opinion

Voluminous literature establishes that commercial PCBs are capable of producing a variety of biological effects when administered in large quantities to experimental animals. The majority of these effects can be grouped into two categories, namely, those involving the skin and those involving the liver. A number of miscellaneous effects that have been observed in one species or another can be considered secondary to the action of the substances on the liver. In general, these effects are only elicited by relatively high dosages of the PCBs, reflecting the low order of acute toxicity of the U.S. commercial mixtures.

There is a considerable range of species susceptibility to the biological activity of PCBs as measured by the size of the dosage, the duration of the exposure, and the severity of the effect. Mink appear to be the most susceptible, monkeys somewhat less so, and rodents the most resistant. There is no basis for a judgment as to which species most accurately serves as a model for men. A comparison of the observations on humans in the Yusho incident with those on monkeys fed relatively small amounts of PCBs has led some investigators to conclude that the latter species is an appropriate surrogate for man. Although there are some similarities between Yusho disease and the findings in monkeys, they are not sufficient to justify such a conclusion.

There is evidence throughout the literature that some of the biological effects observed experimentally with commercial PCB mixtures are caused not by PCBs themselves but by other chlorinated aromatic compounds present as impurities, such as the PCDFs. The significance of this finding is that PCB levels resulting from occupational or environmental exposures cannot be interpreted in the same way as those observed in experimental animals. A broader implication of this circumstance is that the results of laboratory studies are not necessarily predictive of what may be expected from incidental exposures since the nature of the exposure may have differed in the two instances.

As is always the case in experimental toxicology, the validity of test results as predictors of hazard to man must await confirmation or denial by observations of exposed human populations. Fortunately, the reports of actual injury to man from PCB exposure are few, although extensive epidemiological surveys have been conducted and others are in progress. An evaluation of the epidemiology of exposure to PCBs is the subject of section XII of this report. Still other sections of the report deal with specific potential health effects in greater detail.

V. Skin and Other Cutaneous Tissues

Epithelial and follicular hyperplasia and hyperkaratosis have been reported to occur following the application of PCBs on the skin of rabbits (Vos and Beems, 1971). Skin lesions have also been observed in rats and guinea pigs from the application of PCBs. Repeated application of Aroclor 1260 to the skin of rabbits caused thickening of the skin as a result of hyperplasia and hyperkeratosis of the epithelium (Vos and Beems, 1971).

Cutaneous effects have been elicited in male rhesus monkeys fed a diet containing 300 ppm Aroclor 1248. Within one month the animals lost considerable hair from the head, neck and back (Allen et al., 1973, 1975). Similar effects have been observed in female rhesus monkeys fed a diet containing 25 ppm Aroclor 1248 for two months (Allen et al., 1974). Within six weeks the animals began to lose hair and developed obvious signs of edema of the lips and eyelids. Small pustules involving hair follicles appeared about the mouth, cheeks and neck. Abraham and Allen (1973) showed that the infant monkey was able to tolerate doses of PCBs that produce extreme morbidity in adult monkeys. They suggested that there may be variations in absorption, distribution, metabolism, storage and excretion in adult and infant monkeys that may account for these differences.

Follicular hyperkeratosis is an important feature of the occupational disease known as acne, which is characterized by the appearance of papules, comedones and cysts. Industrial

dermatosis of the acneform type has been observed among workers exposed to chlorinated hydrocarbons (Jones and Alden, 1936; Mayers and Silverberg, 1938; Maroni et al., 1981). Seven cases of chloracne of the face and head have been reported among 14 chemical operators exposed from 5-19 months intermittently to low concentrations of chlorinated biphenyls (Meigs and Albom, 1954). Puccinelli (1954) and Hofman et el. (1962) report chloracne in several capacitor workers, whereas Smith et al. (1981) noted that none of the capacitor workers examined in this recent survey were found to have acneform lesions suggestive of chloracne.

The acneform eruptions that occur in the skin of both monkeys and rabbits may be caused by a squamous metaplastic change in the epithelium lining the sebaceous glands, which result in a change in the character of the secretion from normal oily to keratinaceous. This condition frequently results in plugging and rupture of the glands with consequent inflammatory reactions (acne). The question of whether a similar condition can occur in man from exposure to PCBs will be dealt with in another section of this report.

It has been suggested that the cutaneous eruptions that occur in both animals and man from exposure to commercial preparations of PCBs may be due to certain impurities. Chemical analysis of the PCBs that contaminated the rice oil that caused the Yusho disease in Japan showed high levels of polychlorinated dibenxofurans (Kuratsune, 1976).

VI. Effect of PCBs on Liver

A. Experimental Data

1. Liver Weight

The administration of PCBs may induce an increase in liver weight (Table 1). The effect is more prominent at the higher dose levels; the lower doses of PCBs do not increase liver weight. The detailed data of Kimbrough et al. (1972) are not included in the table. They found that Aroclor 1260, administered with the diet in doses of 500 and 1000 ppm for eight months, significantly increased liver weight in male and female rats; doses of 20 and 100 ppm were effective only in male rats. Aroclor 1254 increases liver weight in both male and female rats at doses of 20, 100 and 500 ppm.

Although the data in Table 1 illustrate the effect obtained in subchronic and chronic studies, it should be noted that liver weight may also be increased in acute toxicity studies. PCB congeners (penta-, hexa-, and heptachlorobiphenyls) given in a high single dose of 50 mg/kg, can increase liver weight in the rat; in most but not all tests, liver triglycerides, cholesterol and phospholipids were increased (Yoshihara et al., 1979). In the monkey a single oral dose of 1.5 g or 3.0 g/kg of Aroclor 1254 produced slight enlargement of the liver in 4 days (Allen, Norback and Hsu, 1974).

The increase in liver weight is correlated with hepatic cell hypertrophy and an increase in smooth endoplasmic reticulum

Table 1

Effect of PCBs on Liver Weight and Morphology

			Weight Changes +=increase 0=no change	Major Histological findings
Studies in Mice				
Kimbrough & Linder, 1974, Aroclor 1254			+	Pleomorphism, necrosis
Studies in Rats				
Bennett, et al., PCB, 65% Cl	300 mg	6 days	+	Cells swollen, hyaline granules
	250 mg	up to 100 days	+	
Keplinger et al. #247	100 ppm	18 months	+	
Aroclor 1254, 1260	10 ppm	18 months	0	
	1 ppm	18 months	0	
Aroclor 1242	100, 10, 1 ppm	18 months	0	
Litterest et al., 1972	500 mg	4 weeks	+	
Aroclor 1242, 1248	50 mg	4 weeks	+	
1254, 1260	5 mg	4 weeks	0	
	0.5 mg	4 weeks	0	
Allen & Abrahamson, 1973, Aroclor 1248, 1254, 1262	0.1% in diet	8 weeks	+	Fat droplets, areas of necrosis
Bruckner et al., (1973) Aroclor 1242	100 mg/k every 2nd day	3 weeks	+	Sudanophilic vacuolation
Sri ier et al.)1974	25 ppm	2,4,6 months	0	No change with H&E stain, increase lipid with Sudan IV stain
	5 ppm			

CONTINUED

Table 1 (CONTINUED)

Effect of PCBs on Liver Weight and Morphology

			Weight Changes +=increase 0=no change	Major Histological findings
Studies in Rats (Continued)				
Burse et al., Aroclor 1242, 1016	100 ppm	up to 10 months	0	Enlarged hepatocytes, vacuolated cytoplasm characterized as mild changes
Studies in Rabbits				
Vos et al., Aroclor 1260 hexachlorobiphenyl	120 dermal 5 x week	4 weeks	+	Hydropic degeneration, necros
Keller & Sinkl, 1973				
Aroclor 1254	300 mg once/wk	14 weeks	+	Enlarged hepatocytes, necrosis
Aroclor 1242	" "	" "	+	Enlarged hepatocytes, some necrosis
Aroclor 1221	" "	" "	0	No histological change
Studies in the Monkey				
Allen et al., 1973				
Aroclor 1248	300 ppm	90 days	+	Enlarged hepatocytes, no necro
Aroclor 5460	5000 ppm	" "	+	" "

Table 1A

Liver Lesions in Albino Rats Treated with Aroclors for 2 Years*

(Data from Levinskas, 1981)

	Control	Aroclor 1242			Aroclor 1254			Aroclor 1260		
Diet level, ppm	0	1	10	100	1	10	100	1	10	100
No. animals examined	23	32	29	16	30	26	26	26	25	25
Vacuolar change	1	7	8	9	7	9	13	5	7	9
Focal necrosis	1	1	1	0	3	1	1	4	3	6
Focal lymphoid infiltration	1	0	0	0	2	0	1	0	1	0
Focal hypertrophy hepatocytes	0	2	3	8	3	4	14	3	13	9
Nodular hyperplasia	1	1	I	8	0	3	14	0	7	6
Ductal hyperplasia	5	3	3	3	6	3	14	6	7	12
Hepatoma	0	0	0	3	0	0	4	0	1	7
Cholangiohepatoma	0	0	0	1	0	0	2	0	0	4
Hepatocellular carcinoma	0	0	0	0	0	0	0	0	0	0

*The results of this study were presented in a summarized form by Calandra (1975) and were later reanalysed and tabulated by Levinskas (1981).

in the rat, rabbit and monkey (Voe et al., 1972; Allen and Abrahamson, 1973; Bruckner et al., 1974e; Allen, Norback and Hsu, 1974; Allen, Carstens and Barsotti, 1974). Ecobichon and Comeau (1974a, b) found that the effect of PCBs administered intraperitoneally on liver weight and on hepatic enzymes associated with hepatic endoplasmic reticulum was related to the position of the chlorine substitution on the biphenyl nucleus. However, all of the congeners and isomers administered at a dose of 50 mg/kg intraperitoneally for three days produced an increase in smooth endoplasmic, lipid droplets and microbodies, although the quantitative response varied (Hansell and Ecobichon, 1974).

2. General Histology

The administration of PCBs to experimental animals will produce histopathological changes in the liver. The main effects obtained are the production of enlarged hepatocytes, fat droplets and slight degree of necrosis; the occurrence of these changes depend particularly on the dose of the PCB and to some extent on the particular Aroclor (Tables 1 and 1A). Necrosis seems to be more severe in the rabbit than in the rat. In general, the morphological changes observed in the liver of PCB-treated animals are similar to those found after treatment with other chlorinated hydrocarbons.

In a detailed study, Kimbrough et al. (1972) found that Aroclor 1260 (20, 100, 500 and 1000 ppm) and Aroclor 1254 (20, 100 and 500 ppm), given in the diet of rats for eight months, produced

enlarged liver cells and cytoplasmic inclusions. At the higher doses, there was evidence of lipid accumulation, which was associated with a foamy cytoplasm, and pigment accumulation in the Kupffer cells. The pigment gave a positive Prussian-blue reaction, indicating the presence of hemosiderin. Studies of rats four to six months after exposure to different doses of Aroclors 1016 and 1242 indicated that the morphological changes are reversible and disappear gradually after dosing is stopped; the hepatocytes were still larger than controls, but the frequency of vacuolated cytoplasm or inclusions within the cytoplasm had decreased (Burse et al., 1974).

Aroclor 1254 was evaluated by the National Cancer Institute (1978). Fischer rats receiving 25 ppm in the diet for eight weeks had enlarged livers, but without evidence of histological abnormality. The administrations of doses of 25, 50 and 100 ppm for 104-105 weeks did not increase the frequency of liver lesions such as congestion, inflammation, necrosis or angiectasis.

3. Adenofibrosis

Adenofibrosis (synonyms: bile duct proliferation, bile duct adenomatosis, cholangiofibrosis, fibroadenoma) has been observed in some rats receiving PCBs. Adenofibrosis is generally regarded as a benign lesion. In their review of experimental tumors, Stewart and Snell (1957) stated that there is no convincing evidence that adenofibrosis is a precancerous lesion.

It should be noted, however, that Reuber (1968), studying 2-acetamidofluorene and 2-diacetamidofluorene, suggested that adenofibrosis is a precancerous lesion for the development of cholangiocarcinoma.

(i) Studies in mice. Kimbrough and Linder (1974) observed foci of adenofibrosis in the liver of some mice with 300 ppm of Aroclor 1254 in the diet for 11 months. Ito et al. (1974) comment that they did not observe cholangiofibrosis in mice receiving Kanechlor.

(ii) Studies in rats. Kimbrough et al. (1972) observed adenofibrosis in rats treated with Aroclor 1260 and 1254; the effect was observed at the higher dose levels and particularly in animals receiving Aroclor 1254. When the feeding of 500 ppm of Aroclor 1254 was discontinued and the animals studied up to 10 additional months, the fat and liver content of PCB remained high and the adenofibrosis persisted (Kimbrough et al., 1973). In a later paper involving treatment with Aroclor 1260 at 100 ppm for 21 months, mention is only made that a few rats showed areas of adenofibrosis, indicating a low degree of response, but data are not tabulated (Kimbrough et al., 1975). In further studies by the same group adenofibrosis was not observed in rats fed Aroclor 1016 or 1242 (100 ppm) for up to 10 months (Burse et al., 1974).

In a study with three Aroclors, administration of 100 ppm in the diet for 24 months produced a low incidence of

cholangiohepatoma (Table 1A), but concentrations of 1 ppm or 10 ppm were without effect (Calandra, 1976; Levinskas, 1981). Treatment did not significantly affect ductal hyperplasia.

The study of the National Cancer Institute (1978) did not observe adenofibrosis in rats receiving Aroclor 1254 at doses of 25, 50 and 100 ppm for 104-105 weeks.

In studies with various Kanechlors, Ito et al. (1974) administered Kanechlor 500, 400 and 300 in the diet at concentrations of 1000, 500 and 100 ppm. At the concentration of 1000 ppm of the Kanechlors, the incidence of cholangiofibrosis ranged from 13 to 30% in the rats; cholangiofibrosis did not occur at levels of 500 or 100 ppm. Kimura et al. (1976) also reported cholangiofibrosis in rats treated with Kanechlor 400.

4. Hyperplastic Foci and Nodular Hyperplasia in the Liver

Hyperplastic foci or hyperplastic areas represent minimal changes in the hepatocytes. Such foci or areas of hyperplastic changes are uncommon in untreated young rats, but increase with age. The hyperplastic areas or foci may coexist with nodular hyperplasia and/or hepatocellular carcinoma. The significance of hyperplastic foci is that they may be part of a spectrum capable of progressing to a nodule (Squire and Levitt, 1975).

The hyperplastic nodule (nodular hyperplasia, neoplastic nodule, hepatoma) is generally as large or larger than the area of several lobules, and the lesion is sometimes elevated above

the surface of the liver. The lesion is frequently referred to as a neoplastic nodule and some consider it to be a manifestation of a carcinogenic process, the earlier stages of which may be represented by the hyperplastic foci discussed above. The use of these terms in the literature is confusing, as some who use the word "hyperplastic nodule" regard the lesion to be part of the neoplastic process whereas others consider it to be unrelated to neoplasia. Some investigators use the terms adenoma or hepatoma to designate the lesion, implying that it is a benign neoplasm.

Despite the differing terminology, it may be considered that the hyperplastic foci and nodular hyperplasia (neoplastic nodules) occurring in the liver are benign lesions rather than carcinomas. However, such nodules may be part of a sequence of neoplastic changes that eventually progress on to hepatocellular carcinomas. Although the data on hyperplastic foci and nodular hyperplasia are discussed in this section and hepatocarcinogenesis are discussed in section VIII, the experimental data on the incidence of benign and malignant lesions are given in the same table so that the overall biological effect of the treatment can be observed as a unit.

(i) Studies in mice. Ito et al. (1973) observed nodular hyperplasia in mice only at the highest dose level of Kanechlor 500. (Nagasaki et al., 1972, reported the same data.) Whereas Kanechlor 500 produced nodular hyperplasia at 500 ppm, lesser doses were not active and Kanechlor 400 or Kanechlor 300

was inactive at all doses studied (Table 2). There was some evidence that the administration of Kanechlor 500 increased the nodular hyperplastic response induced by α or β isomers of benzene hexachloride.

Kimbrough and Linder (1974) observed adenofibrosis and hepatomas in 9 of 24 mice fed Aroclor 1254 (300 ppm in the diet) for 11 months; in animals fed Aroclor for only six months followed by a five month recovery there was no adenofibrosis and the incidence of hepatoma was only 1/24 mice.

(ii) Studies in rats. Keplinger et al. (1971) did not observe hepatic lesions in rats receiving different Aroclors for 18 months; however, re-evaluation of the slides indicated a significant increase of nodular hyperplasia in the treated animals (see National Cancer Institute, 1978).

Ito et al. (1974) observed nodular hyperplasia in rats receiving 100, 500 or 1000 ppm of Kanechlor 500; a lesser effect was observed with Kanechlor 400 and there was no significant effect of Kanechlor 300.

Kimbrough et al. (1975) reported a significant increase in the incidence of hyperplastic foci or areas and neoplastic nodules in female rats given 100 ppm of Aroclor 1260 mixed with the diet for 21 months (Table 3). In another study, the dietary administration of 100 ppm of Aroclor 1242, 1254 and 1260 for 24 months increased the incidence of nodular hyperplasia (Table 1A); a lesser effect was obtained with 10 ppm, and 1 ppm did not produce

TABLE 2

Incidence of Liver Lesions in Male Mice

Treated with PCBs for 24 Weeks

(Data of Ito et al, 1973)

	ppm in diet	Incidence	
		Nodular Hyperplasia	Hepatocellular Carcinoma
Kanechlor 500	500	7/12	5/12
	250	0	0
	100	0	0
Kanechlor 400	500	0/12	0/12
	250	0	0
	100	0	0
Kanechlor 300	500	0/12	0/12
	250	0	0
	100	0	0
Controls	-	0/6	0/6

)

TABLE 3

Incidence of Liver Lesions in Female Rats

Treated with Aroclor 1260

(Data from Kimbrough et al., 1975)

Lesion	Incidence	
	Controls	Experimental
Hyperplastic foci or areas	28/173	182/184
Neoplastic Nodules	0/173	144/184
Hepatocellular Carcinoma	1/173	26/184

TABLE 4

Incidence of Liver Lesions in Male and Female Rats
Treated with Aroclor 1242, 1254 and 1260
100 ppm in Diet for 24 months
(Data from Calandra, 1975)

	Aroclor		
	1242*	1254**	1260
Nodular hyperplasia	8/20	13/27	7/27
Hepatomas	2/20	4/27	5/27
Hepatocellular carcinoma	0/20	0/27	0/27

*10 males and 10 females
**13 males and 14 females

TABLE 5

Incidence of Liver Lesions in Male and Female Rats Treated with Aroclor 1254

(Data from National Cancer Institute, 1978)

	Males			Females		
	Low Dose	Mid Dose	High Dose	Low Dose	Mid Dose	High Dose
Number of animals necropsied	24	24	24	24	22	24
Hyperplastic foci** or areas	5	8	12	6	9	17
Adenoma, NOS+	0	0	1	0	1	2
Hepatocellular carcinoma	0	1	2	0	0	0

* Hyperplastic foci, hepatocellular adenomas or carcinomas were not diagnosed in the controls.

+ Not otherwise specified

** As defined in report

a positive response (Calandra, 1976; Levinskas, 1981). All three Aroclors produced an increased number of hepatomas at the high dose (Table 4). There was no evidence of metastasis or invasiveness, and the lesions were regarded by the pathologists as benign tumors.

The results of a bioassay of Aroclor 1254 for carcinogenicity, using doses of 25, 50 and 100 ppm in the diet, are summarized in Table 5 (National Cancer Institute, 1978). Their use of terms is confusing, for although they use the words "nodular hyperplasia" in their table, they state in the text that "the areas of nodular hyperplasia appeared to be microscopically similar to what is currently termed 'focal areas of cellular alteration.'" Thus, we have used the term "hyperplastic foci or areas" in Table 5 to describe their results. It is evident from the data in Table 5 that the hyperplastic foci were present in a dose-related frequency. Although the incidence of the hyperplastic foci did not differ significantly from the controls, this incidence appeared to be related to treatment. The biological significance of the increase in "focal areas of cellular alteration" is not clear as relatively few adenomas were found.

Both the above studies (Kimbrough et al., 1975; National Cancer Institute, 1978) demonstrate an increase in proliferative lesions of the liver; the effect is greater with Aroclor 1260 than with Aroclor 1254.

(iii) Studies in dogs. Hepatic nodular hyperplasia did not occur in the dogs receiving dietary levels of 1, 10 or 100

ppm of Aroclor 1242, 1254 or 1260, respectively, for two years (Calandra, 1976). Each treatment group consisted of eight dogs (four female and four male).

5. Summary and Comment

The administration of high doses of PCBs to animals can produce hepatic enlargement and an increase in liver weights, which is associated with an increase in smooth endoplasmic reticulum. Other effects include a slight degree of necrosis and the presence of fat droplets and a vacuolated cytoplasm. These changes, which are similar to those found after treatment with other chlorinated hydrocarbons, are readily induced by high doses of PCBs, but are absent when lower doses of PCBs are given. The response appears to be greater with increased chlorination of the biphenyl nucleus but, depending on dose, even the high chlorinated derivatives may not produce a positive response.

Treatment with PCBs usually increases the occurrence of hyperplastic foci. The nodular hyperplasia, neoplastic nodules or hepatomas have been reported to be increased in some studies, but other evaluations have not confirmed these effects. The effects of PCBs on the occurrence of nodular hyperplasia, neoplastic nodules, hepatomas, or adenofibrosis is highly variable; some studies have reported a positive effect whereas others failed to show an effect of treatment. Again the change in histological response or in frequency of benign hepatic tumors is related to both the dose of PCB administered and the degree of chlorination of the PCB.

Data on hepatocellular carcinoma in PCB-treated animals are discussed in section VIII.

B. Clinical Data

1. Liver Function in PCB-exposed Workers

Based on results in animals, it was expected that if PCBs produced a significant degree of injury in man, it would be to the liver. Such has not been the case, as the clinical studies summarized below have provided little evidence for the occurrence of hepatic dysfunctions in PCB-exposed workers even though the blood level of PCB may be relatively high.

(i) Ouw et al. (1976) studied liver functions in 34 workers exposed to Aroclor 1242 for one month up to 23 years; 31 were exposed for more than one year and 16 for five or more years. Scattered individual abnormal test results were obtained: serum bilirubin was normal and in all 34 subjects, alkaline phosphatase was elevated in 1 of 34 subjects and serum transaminase (SGPT) was increased in five tests.*/ There was no relationship of the results to the blood level of PCB and the mean of each hepatic function test for the whole group was within normal limits. BSP

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*/ The abbreviations used in this section are as follows:

SGOT = serum glutamic oxaloacetic transaminase
SGPT = serum glutamic pyruvic transaminase
SGGT = serum gamma glutamyltranspeptidase
LDG = serum lactic dehydrogenase
AST = aspartate aminotransferase
ALT = serum alanine aminotransferase
SOCT = serum ornithin-carbamoyltransferase
BSP = bromsulfonphthalein

a correlation between diastolic blood pressure and H-PCB but this disappeared when corrected for age. Other investigators have not found this relationship, so the difference may be associated with an unrecognized interrelated variable or a chance association related to the multiplicity of factors that have been examined.

Warshaw et al. suggested that workers in a capacitor manufacturing plant (population of Fischbein et al.) had decreased vital capacity and restrictive impairment of lung function in the absence of signs of radiographic change (Warshaw et al., 1979). They have compared the FVC to that of other worker populations in previous hazardous exposure studies as well as to a non-smoking normal population. The reported percent abnormality of PCB workers is 14% compared to 5.6% cited for non-smoking populations. The comparisons do not indicate that they have been controlled for smoking habits and sex.

Most studies have reported no clinical disease in PCB-exposed populations with the exception of Yusho disease and chloracne (Karppanen et al.; Humphrey, Smith et al.; Chase et al.,; Kreiss et al.). Some have reported symptoms that are difficult to evaluate since most are subjective and could be related to worker bias. Fischbein et al. suggested that neurological symptoms were increased but there is no similar group with which to compare workers and thus make this assessment. Smith et al.

(1981) in the study of the combined work sites found that coughing at work and irritated eyes were related to both L-PCB and H-PCB. Loss of appetite and peripheral "tingling" were associated only with L-PCB. History of skin rash was associated only with H-PCB. Many of these differences were not observed when individual work site data were analyzed separately. The lack of a difference in each site may result because jobs were included as a confounder variable. Most studies have not even reported any symptoms or history of disease (Baker et al. and Kreiss et al.)

In all studies reviewed there was little evidence of clinical disease with the exception of chloracne and this condition seemed to be most frequent under specific conditions of exposure. The other common but not consistent findings were abnormalities of lipid metabolism, especially blood triglyceride levels, and abnormalities of liver enzymes, especially SGOT and GGTP, which were related to levels of PCBs. The lipid and liver changes appeared to occur at lower levels than the skin manifestations and were not associated with clinical disease or symptoms.

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XIV. Glossary of Terms or Abbreviations

AP	alkaline phosphatase
BSP	bromsulfonphthalein liver function test
GGTP	gamma glutamyl transpeptidase
H-PCBs	PCBs with high degrees of chlorination
L-PCBs	PCBs with lower degrees of chlorination
LDH	lactic dehydrogenase
PCBs	polychlorinated biphenyls
PCDFs	polychlorinated dibensofurans
PCNs	polychlorinated naphthalenes
PCQs	polychlorinated quaterphenyls
PCTs	polychlorinated terphenyls
SGOT	serum glutamic oxalic transaminase
SGPT	serum glutamic pyruvic transaminase
SOCT	serum ornithine carbamoyl transferase
Yusho	the disease noted in Japan following human ingestion of cooking oil contaminated with PCBs, PCDFs and PCQs.
Fo	parental test animals
F1a, F1b	litters derived from first generation animals at their first (a) and second (b) matings

tests were also performed on seven workers with relatively high blood PCB; four of the seven tests were slightly above the normal limit of 5% but, as the authors state, since other conditions such as fever may increase BSP retention, these results by themselves could not be taken as proof of hepatic damage. The BSP test results did not show a significant correlation with blood PCB levels or the length of exposure (5 to 23 years) to PCB.

(ii) Fischbein et al. (1979) studied liver function tests in 321 workers exposed to PCBs in an electrical manufacturing plant for less than five years to more than 25 years. The percent of tests that gave an abnormal test result was SGOT 2.2%, SGPT 7.2%, LDH 2.5%, alkaline phosphatase 1.2%, and serum bilirubin 5.3%, and indicated a "very low prevalence of abnormal liver findings." There was no comment or analysis to state that a certain number of the subjects showed a pattern of abnormal liver function tests indicative of hepatic dysfunction. These data can be taken to represent a series of random test results that might be expected in a population of 321 individuals ranging in age from less than 30 years to over 70 years. Control subjects or non-exposed workers were not included for comparison. There was perhaps some indication of a relationship of SGOT levels to plasma levels of PCBs, but the two exposure categories of PCB levels are too broad and require a finer analysis.

(iii) Baker et al. (1980) studied liver function in 148 individuals with various degrees of exposure to PCBs; the

mean PCB serum levels for the four test groups varied from 17.4 ppb to 75.1 ppb. There was no change in liver function tests (SGOT, SGPT, LDH, alkaline phosphatase or serum bilirubin) in relation to PCB blood levels in either drinkers or nondrinkers of alcohol. Serum GGTP (gamma glutamyl transpeptidase) correlated with serum PCB, but a correlation did not exist when alcohol drinkers were removed from the analysis.

(iv) Maroni et al. (1981a, b) studied liver function in 80 workers exposed to PCBs for an average of 12 years and reported that 16 individuals had an abnormal liver finding as judged by clinical examination or by laboratory tests.

Inspection of the data shows relatively few instances of abnormal liver function tests. The most frequently altered laboratory tests were as follows:

8 of 80 subjects with increase of SGGT activity

7 of 80 subjects with increased serum amino-transferase activity (AST or ALT)

6 of 80 subjects with increase of SOCT activity.

It is evident from their data that many of the changes are slight, and as test results from control subjects were not included, we do not know what the normal test variations may be for 80 control subjects of a similar age. Further, examination of the data for the 14 subjects with clinical hepatomegaly shows only one subject with an abnormal test in three types of tests (SGGT, AST/ ALT and SOCT); only two of the subjects gave a positive response in two of

the test types; eight subjects had an abnormality in only one test; three subjects had normal test results. Serum bilirubin and alkaline phosphatase activity were within the normal range in all subjects.

Based on the above review, it is evident that only one of the 80 subjects showed a pattern of test results indicative of abnormal liver function; the other test results reflect only random variations from normal.

Maroni et al. also reported that the mean level of blood PCBs in the 16 workers with abnormal liver findings was significantly higher than that of 64 workers without abnormal liver findings, but the ranges for the two groups show considerable overlapping and the two subjects with the highest blood PCB levels had normal liver function tests. The only control we can use to evaluate the suggested relationship between PCB blood level and liver function are the 10 subjects with chloracne; these 10 individuals had normal liver test results despite the fact that their mean blood PCB concentration was high and not significantly different from the mean blood PCB level found in the 16 workers discussed above. Thus, it cannot be said that this study demonstrates a relationship between a high blood PCB level and abnormal liver function tests, attesting further to the randomness of the liver function test results in the study.

(v) Smith et al. (1981a, b, c) evaluated liver function tests in PCB-exposed employees from an electrical manufacturing plant, a municipal electric utility company and a privately-owned

electric utility company. The data on SGOT and GGPT are difficult to evaluate as the results of the measurements are not given, and therefore may be assumed to be within normal population levels; rather, the authors sought correlations between the log of SGOT and GGTP with the log of the lower serum PCBs and the log of high serum PCBs. Calculations include simple correlations, separate regressions with the confounders as predictors, and squared partial correlation, plus other computations to see if associations existed. Their tables 6, 7 and 8 summarize many of their calculations, and data for transaminases from table 7 are summarized below.

	Correlation With Serum log L-PCB	Serum log H-PCB
Electric equipment Company		
log SGOT	NS	Sig
log GGTP	Sig	Sig
Municipal electric utility company		
log SGOT	NS	NS
log GGPT	NS	NS
Privately-owned utility company		
log SGOT	Sig	NS
log GGTP	NS	NS

Sig = statistically significant
NS = not significant
L-PCB = lower chlorinated biphenyls
H-PCB = higher chlorinated biphenyls

Correlations (associations) were found at the equipment company but the data cannot be examined to determine if the calculated value has any medical significance. Correlations at the publicly-owned utility company were not significant. At the privately-owned utility company, the only positive finding was a positive association of SGOT with serum L-PCB. It is not clear what the change in this one test result means as the serum L-PCBs were not significantly different between the exposed and non-exposed groups.

The test results for total bilirubin, alkaline phosphastase and lactic dehydrogenase are not discussed, and it is presumed that these measurements of liver function were not abnormal.

2. Liver Disease in PCB-Exposed Workers

Medical examination of PCB-exposed workers has not shown the presence of liver disease. In the study of Fischbein et al. (1979), physical examination of 326 individuals (age less than 30 to over 70 years) revealed 4 individuals with abnormal liver size, two of whom had a history of heavy alcohol intake; one of the four had a slight elevation of one liver function test (SGOT of 55).

In another study of 148 individuals with varying degrees of PCB exposure, there was no evidence of liver disease as determined by medical history and physical examinations (Baker et al., 1980). Smith et al. (1981) did not find evidence for live-

disease in their subjects, there being no significant findings on physical examination of workers at an electrical equipment manufacturing plant who were heavily exposed to PCBs, or workers at a municipal utility company or a private utility company who were less heavily exposed.

Deaths from cirrhosis of the liver were not increased by exposure to PCB (Brown and Jones, 1981); six deaths were observed (three of the six consumed alcohol regularly) versus 5.6 expected.

3. Summary and Opinion

The review of clinical data demonstrates that exposure to PCBs does not significantly affect liver function tests. Liver function remains normal in individuals with measurable, and frequently high levels of serum PCB. Also, exposure to PCBs does not result in the production of clinically detectable liver disease. The induction of enzyme systems in the liver and the biological significance of this process, as mediated by PCBs, are discussed in section XI.

VII. Gastric Lesions

The oral administration of PCBs to nonhuman primates has been shown by Allen and co-workers to induce hypertrophy and hyperplasia of the gastric mucosa. Mucosal cysts may be present within the epithelium of the stomach, but in the mucosal lining and the submucosa, there may be edema of the submucosa of the stomach. In addition, there is frequently invasion of the underlying mucosa by isolated glandular elements of the mucosal epithelium. General effects of this nature have been produced in the monkey by:

i) A single oral dose of 1.5 g or 3 g of Aroclor 1248 (Allen, Norback and Hsu, 1974).

ii) Aroclor 1248, 300 ppm and Aroclor 5460 (a polychlorinated triphenyl), 5000 ppm in the diet for 90 days (Allen, Abrahamson and Norback, 1973; Allen and Norback, 1973).

iii) Aroclor 1248, 25 ppm in the diet for 2 months (Allen, Carstens and Barsotti, 1974).

iv) Aroclor 1248, 100 ppm in the diet for 2-3 months (Allen, 1975).

v) Aroclor 1248, 2.5 ppm and 5.0 ppm in the diet for up to one year (Barsotti and Allen, 1975). (Gastric changes were not listed for these doses in Allen's review.)

vi) The hyperplastic gastritis may persist for over one year following discontinuance of PCB exposure (Allen, 1975).

A mixture of low chlorinated biphenyl (Clophen A-30) was not observed to produce gastric lesions in the monkey (Iatropoulos et al., 1977).

The findings of Allen et al. were recently confirmed and extended by Becker et al. (1979). Their study involved six monkeys, one untreated and one each receiving a diet containing 3, 30, or 300 mg/kg of PCB (Aroclor 1242); two monkeys received a diet containing 10 mg/kg. Monthly biopsies taken from the greater curvature of the stomach showed a dramatic decrease in the number of parietal cells with a concomitant increase in the number of mucous neck cells. The zymogenic (chief) cells were also reduced in number. This was followed in all treated animals by a mucous conversion of the gastric epithelium, with down-growth of the gastric glands into the submucosa and the eventual formation of cysts. It is noteworthy that the lesions were confined to the stomach; no changes were found in other regions of the gastrointestinal tract.

The gastric changes can be described as a dysplastic growth pattern, but there is no neoplastic transformation (Allen and Norback, 1973). However, the authors speculate that they are "suggestive" of an eventual neoplastic transformation.

Analysis of the results obtained in the monkey indicates that the PCB-induced morphologic changes in the gastric mucosa

may be specific to this species and not predictive of possible effects in man.

(i) Even within the monkey a specificity of action is present, as the lesion induced by PCBs is found only along the greater curvature of the stomach; neither the cardiac nor pyloric portions were affected (Becker et al., 1979).

(ii) Hypertrophy and hyperplasia of the gastric mucosa have not been reported in the rodent (Allen and Abrahamson, 1973), rabbit (Voe, 1972) or in other species (Voe and Koerman, 1970).

Clinical findings to date have not suggested or indicated that exposure to PCBs increases the occurrence of cancer of the stomach in the human (see also section VIII, relating to carcinogenicity).

VIII. Carcinogenesis: Experimental and Clinical

A. Experimental Studies

All authors do not use the words tumorigenesis and neoplasia to indicate the same type of response. Tumorigenesis is a general term that refers to both benign growths and malignant growths; compounds may affect the occurrence of benign tumors without inducing cancer. Neoplasia means simply a new growth. The term "neoplasia" can refer to a benign or malignant growth. Oftentimes authors may combine data relative to benign and malignant growths so that when the terms tumorigenesis or neoplasia are used, they must be carefully defined.

1. Hepatocellular Carcinoma

(i) Studies in mice. Ito et al. (1973) observed hepatocellular carcinomas in mice only in the high dose group given Kanechlor 500; lower doses of Kanechlor 500 or the other Kanechlors did not produce a carcinogenic response (Table 2). The administration of 300 ppm of Aroclor 1254 in the diet for 11 months did not induce hepatocellular carcinomas in mice (Kimbrough & Linder, 1974).

(ii) Studies in rats. The administration of Kanechlor 400 for 400 days did not induce hepatocelluler carcinoma (Kimura & Baba, 1973), but the period of treatment may have been too brief to detect a carcinogenic effect. In a further study Kimura et al. (1976) administered Kanechlor to rats for six months but due to body weight changes a variable dosage schedule was employed. Following the cessation of treatment, the rats were

fed on a normal diet for 270-410 days; autopsy, after a total experimental period of 450-590 days, did not reveal hepatocellular carcinoma in any of 12 rats.

Ito et al. (1974) treated rats with different doses of Kanechlor 500, 400, and 300 for periods up to 52 weeks; hepatocellular carcinomas were not observed, but the duration of treatment was probably too short to rule out the possibility of a positive response.

The three major studies pertaining to PCBs and hepatic carcinoma in the rat are those of Kimbrough et al. (1975), Calandra (1975) and the National Cancer Institute (1978). Kimbrough and co-workers, using the Sherman strain of rat, found that 100 ppm of Aroclor 1260 in the diet for 21 months produced a significant increase in the incidence of hepatocellular carcinoma in female rats (Section VI, Table 3). Male rats were not studied.

The administration of three different Aroclors at a dose of 100 ppm to rats for 24 months (Table 4) did not induce hepatocellular carcinoma (Calandra, 1975). The author states that this negative finding was based on evaluation of the liver sections by 3 pathologists, who read the slides independently and separately. He states further that Professor P. Pour re-evaluated the Kimbrough slides and did not agree with the reported findings (see also section VI, Table 1A).

The results of the National Cancer Institute (1978) bioassay of Aroclor 1254 for possible carcinogenicity are shown in section VI, Table 5. Fischer 344 rats were used and the PCB

mixture was administered at three dose levels (25, 50 and 100 ppm) in the diet for 104-105 weeks. The effect of the treatment on body weight and mortality at the higher dose levels demonstrated that maximum tolerated doses were used, thus providing a satisfactory test of carcinogenic potential. A sufficient number of rats of both sexes was available for meaningful statistical analyses of the incidence of late-developing tumors. Treatment was associated with only three hepatocellular carcinomas in male rats, which was not significantly different from the controls, and it was concluded that Aroclor 1254 was not carcinogenic in the bioassay.

(iii) Studies in dogs. Hepatocellular carcinoma did not occur in dogs (four male and four female per group) receiving 1, 10 or 100 ppm of Aroclor 1242, 1254, and 1260, respectively, in their diets for two years (Calandra, 1975).

(iv) Discussion. Data from the mouse provide only limited and restricted evidence for a carcinogenic effect of the Japanese compound Kanechlor 500 (Table 2). Studies on the rat give conflicting results on hepatic carcinoma. (Section VI deals with the benign hepatic proliferative lesions found in the treated rats, which may or may not indicate carcinogenic potential.) Kimbrough et al. (1975) reported an increase of hepatocellular carcinomas in female rats receiving Aroclor 1260, whereas the studies of Calandra (1975) and the National Cancer Institute (1978) did not observe a significant increase in hepatocellular carcinomas in rats receiving different Aroclors. Whether the

divergent results are related to the different strains of rats that were used, represent differences in the effect of the two Aroclors, or are due to other factors is not known. It is obvious, however, that in view of the differing results obtained it is not possible to extrapolate or project possible effects in man. Hepatocellular carcinomas did not develop in dogs treated with Aroclor for two years.

2. Bladder Cancer

Kimbrough (1972) observed bladder cancers in two rats fed 100 ppm of Aroclor 1260 for eight months. In a later study with 200 rats receiving 100 ppm of Aroclor 1260 for 21 months the only bladder tumor observed (a transitional cell papilloma) was in a control animal, and it was concluded that "the occurrence of the bladder tumor in the previous experiment was apparently unrelated to the ingestion of Aroclor 1260" (Kimbrough et al., 1979). This type of variation demonstrates the unreliability of attaching significance to small changes in tumor incidence in a given experiment, particularly when the incidence does not show a statistically significant difference from a control group.

Benign or malignant bladder tumors did not occur in rats treated with Aroclors 1254 (25, 50 and 100 ppm) for 104-105 weeks (National Cancer Institute, 1978).

The above studies do not demonstrate that administration of Aroclor 1254 or Aroclor 1260 induces bladder cancer in the rat.

3. Stomach, Intestinal Tract Cancer

Treatment of female rats with Aroclor 1260 (100 ppm in diet) for 21 months did not induce tumors in the gastrointestinal tract (Kimbrough et al., 1975).

Treatment of rats with Aroclor 1254 (25, 50 and 100 ppm in the diet) for 104-105 weeks did not induce gastrointestinal carcinomas (National Cancer Institute, 1978). Tumors occurred in random manner as illustrated in Table 6.

4. Carcinogenesis - Other Organs

Studies with PCBs in relation to cancer of the liver, gastrointestinal tract, and urinary bladder have been discussed separately above. In the studies with PCBs other organs have been evaluated in detail without finding any effect of chronic administration of Aroclors on the incidence of benign or malignant neoplasms. The following appraisals refer to tumors of these other organs.

Kimbrough et al. (1975) found that the chronic administration of Aroclor 1260 to rats did not affect the incidence of benign tumors or carcinomas of the thyroid gland, adrenal gland, uterus, lung and other organs. Frequently investigators look only for increases in tumor incidence, when in fact decreases are often obtained. It is worth noting that mammary adenocarcinoma occurred in 5/173 control animals versus an incidence of 1/184 in treated animals. If the incidence had been reversed, some authors may have commented or suggested that PCBs may increase the occurrence of mammary cancer, but such would not have been

Table 6

Incidence of Gastrointestinal Carcinomas
in Rats Treated with Aroclor 1254
(Data from National Cancer Institute, 1978)

	Number of Carcinomas			
	Control	Low Dose	Med. Dose	High Dose
Males				
Stomach, adenocarcinoma	0	0	1	0
Jejunum, carcinoma	0	0	0	1
Cecum, adenocarcinoma	0	0	1	0
Females				
Stomach, adenocarcinoma	0	1	1	0

the case as the number of mammary adenocarcinomas in control groups can vary significantly from study to study. If the incidence of spontaneous tumors can vary, then the number of malignancies in the treated group will vary with each experiment independent of the treatment given. An additional illustration of tumor variability is the incidence of ovarian granulosa theca cell tumors which was 5/149 in controls versus 0/163 in the treated animals.

In the National Cancer Institute (1978) study, the chronic administrations of Aroclor 1254 was without effect on the development of benign or malignant neoplasms in the various body organs of the rat (the liver, gastrointestinal tract and urinary bladder were discussed separately above). In the study, interstitial cell tumors of the testes were present in nearly all control and treated animals, there being no effect of treatment. Leukemias, which were the second most common neoplasms, were found in 13% of control males and 17% of control females. A statistically significant dose-related trend for leukemia was present in the treated males but not in the female rats. However, direct dose comparisons between each treatment group (male or female) and the control group were not statistically significant, so that an effect in males could not be clearly related to the administration of Aroclor 1254. Adding the few lymphomas to the leukemias for the analysis did not change the

conclusion. Kimbrough et al. (1975) also did not find a significant effect of Aroclor 1260 on leukemia incidence (1/173 in controls vs. 0/184 in treated animals).

It may be concluded from these studies that the chronic oral administration of high doses of Aroclors 1260 or 1254 does not induce benign or malignant tumors of the thyroid gland, adrenal gland, uterus, lung, hematopoietic system, pituitary gland, thymus, kidney and other organs in rats.

5. Summary and Opinion

Animal studies do not provide convincing evidence that PCBs induce liver cancer. Of the major studies in the rat, one has been judged positive and 2 have been negative. Hepatic carcinoma was not produced in the dog. Chronic administration of Aroclors in the rat did not induce bladder cancer, gastrointestinal carcinomas or cancer of the thyroid gland, pituitary gland, adrenal gland, uterus, lung, hematopoietic system or other organs.

B. Clinical Studies

The studies of Brown and Jones (1981) and Bertazzi and co-workers (1981) have evaluated the relationship between exposure to PCBs and the subsequent development of cancer. Both analyses are retrospective mortality studies of workers to determine the cause of the death and, for malignancies, the specific type of cancer causing the death; the deaths are designated as "observed cases." The person-years of exposure of the workers to

PCB were determined and combined into calendar time periods and five-year age groups to calculate from mortality statistics the number of "expected" deaths. The number of observed versus expected deaths was than compared. Background data relative to these studies are summarized briefly, as follows:

(i) Brown and Jones (1981). The authors analyzed 163 known deaths occurring among 2,567 workers exposed to PCBs for 39,018 person-years. Exposure to PCBs ranged from three months to over 20 years. The type of PCBs used at the plants were Aroclor 1254, 1242, and 1016.

(ii) Bertazzi et al. (1981). The authors analyzed 27 deaths occurring in 1,310 workers exposed to PCBs for 20,565 person-years, determining "observed" versus "expected" rates for malignancies. Mortality was studied for a 25-year period (1954-1978). Exposure up to 1964 was mainly to Aroclor 1254 and Pyraline 1476; starting in 1965 mixtures with 42% chlorine were used (mainly Pyraline 3010 and 3011).

(iii) Bahn et al. (1976, 1977). These authors report 2 cases of malignant melanoma in 31 men exposed to Aroclor 1254. It is not clear from their studies if they are discussing morbidity or mortality; Brown and Jones (1981) interpret the report as mortality.

Pertinent data on the mortality from malignancies are summarized in Table 7 and are discussed below.

All Malignancies. Brown and Jones reported 39 observed cases of cancer versus 43.8 expected cases, whereas Bertazzi et al. found a statistically significant increase in males, but not in female workers (Table 7). There was no increase in the risk of mortality from all malignancies with length of exposure or with the number of years of employment (Brown and Jones, 1981).

Rectum. The only statistically significant difference observed in the study of Brown and Jones was for rectal cancer in females from Plant 2 (Table 7). There was no significant finding for females in Plant 1, males in Plant 1 or 2, or for the combined data for males and females. The incidence of rectal cancer showed a slight, but statistically insignificant, increase with increase in latency; no direct relationship with increased length of exposure is apparent.

Bertazzi et al. (1981) did not report a case of rectal cancer in PCB exposed individuals.

Stomach, Pancreas. The studies did not demonstrate an increased risk for stomach or pancreatic cancer (Table 7).

Hepatocellular Carcinoma. Three cases of liver cancer were observed in the study of Brown and Jones (1981), but the difference from the control rate was not reported to be statistically significant (Table 7). Bertazzi and co-workers did not mention observing any case of hepatic cancer. Examination of the data for latency effect or for length of exposure to PCBs did not show any relationship to development of liver cancer (Brown and Jones, 1981).

Table 7

Deaths From Specific Types of Cancer

Comparison of Observed Deaths in PCB Workers With Expected Deaths

Reference	Malignancy	Sex	Number of Cases: Observed	Expect	SMR	Statistical Significance
1	All	M,F	39	43.79	89	NS
2	"	M	8	3.32	241	P=0.04
2	"	F	6	2.33	258	NS
1	Rectum	M	1	0.51		NS
1	"	F(plant 1)	0	0.18		NS
	"	F(plant 2)	3	0.50		P<0.05
1	"	M,F	4	1.19	336	NS
1	Stomach	M,F	1	1.66	60	NS
1	Pancreas	M,F	1	1.90	53	NS
2	Digestive Organs	M	3	0.88	340	NS
	(stomach, pancreas, biliary tract)	F	0	-	-	NS
1	Hepatic Carcinoma	M,F	3	1.07	280	NS
1	Lymphatic & Hematopoietic	M,F	2	4.34	46	NS
2	"	M	2	0.46	435	NS
2	"	F	2	0.45	444	NS
3	Melanoma	M	2	0.04		P=0.001
1	"	M,F	0	-	-	NS
2	"	M,F	0	-	-	NS

Ref 1, Brown and Jones, 1981
Ref 2, Bertazzi et al., 1981
Ref 3, Bahn et al., 1976, 1977
SMR, Standardized mortality ratio (observed deaths/expected deaths x 100)
NS, Not significant

Lymphatic and Hematopoietic Cancer. The two studies show diametrically opposite risk values, although neither is statistically significant (Table 7).

Melanoma. Bahn et al. (1976, 1977) reported two cases of malignant melanoma occurring among 31 men who had been exposed to Aroclor 1254. Based on the Third National Cancer Survey incidence rates, Bahn et al. calculate for a person-year analysis that only 0.04 malignant melanomas would be expected, the difference being statistically significant (P=0.001). The extensive studies of Brown and Jones and of Bertazzi et al. fail to confirm the increased risk of mortality for malignant melanoma reported by Bahn and co-workers (Table 7), raising doubts about the significance of the Bahn studies. Even an association with the low P value of 0.001 has not been confirmed.

Summary. The clinical evaluation of PCBs relative to cancer is currently based on a limited amount of data, and any conclusion regarding their effects must be regarded as tentative. Nevertheless, some detailed analyses are available and conclusions based on them, as listed below, are of some significance.

1. Retrospective mortality studies have not demonstrated a consistent relationship between exposure to PCBs and the development of a particular type of cancer.

2. The clinical findings on hepatocellular carcinoma are of great interest as some experimental studies report an

increase in liver cancer in rodents receiving PCBs. Although Brown and Jones (1981) observed three cases versus 1.07 expected cases, the difference is not statistically significant. Their analysis of PCB exposure and risk of mortality from liver cancer is also noteworthy since it did not demonstrate an effect of latency (number of years from date first employed) or a relationship to increased duration of employment in jobs involving PCB exposure. These latter observations are, however, based on small numbers. Bertazzi et al. (1981) did not report any significant relationship between PCB exposure and liver cancer. Taken together these studies do not confirm the projection of a risk for liver cancer in humans based on the animal studies.

3. The SMR (Standard Mortality Ratio) may vary widely in different studies, and emphasis should not be placed on an increase in the SMR found in one study unless a significant change in SMR can be confirmed in several repeat studies. For example, Brown and Jones found the SMR for lymphatic and hematopoietic malignancy to be decreased while Bertazzi et al. reported an increase, although neither result was statistically significant (Table 7).

4. Brown and Jones observed a statistically significant increase in SMR for rectal cancer in women at one plant, but not in a different plant, and no significant effect in male workers at either plant was observed. Bertazzi et al.

did not report any rectal cancer (Table 7). Overall, therefore, a convincing demonstration of rectal cancer as a result of extended exposure to PCBs has not been made.

IX. Reproductive Effects

A. Reproduction

Numerous reports have appeared in the literature on the effects of polychlorinated biphenyls on reproduction in animals. Gellert and Wilson (1979) showed that female Sprague-Dawley rats given 30 mg/kg Aroclor 1221, 1242 and 1260 by gavage during days 14 through 20 of pregnancy had no effect on the reproductive function of the offspring as judged by (a) normal estrus cycles, (b) normal appearance of ovaries and uteri, and (c) fertility of males. Feeding 550 ppm of Aroclor 1254 for 67 days to Sherman rats resulted in fewer litters, smaller litter size and 100% mortality by day three of the $F1_a$ pups. At 100 ppm survival of both $F1_a$ and $F1_b$ offspring was reduced. The pups were smaller than controls but appeared normal at weaning. Aroclor 1260 fed at a dietary level of 500 ppm (35.4 mg/kg) for 67 days prior to mating markedly reduced litter size and survival-to-weaning in the $F1_a$ and $F1_b$ generation. Dietary levels of 5 ppm Aroclor 1254 and 100 ppm Aroclor 1260 had no effect on reproduction in rats exposed through two generations (Linder et al., 1974). A dietary concentration of 2.5 ppm of Aroclor 1248 produced alteration in the menstrual cycle of adult female rhesus monkeys. Menses were prolonged and menstrual bleeding was increased (Allen et al., 1979).

Keplinger et al. (1971) fed rats and dogs Aroclor 1242, 1254 and 1260 at doses of 1.0, 10.0 and 100 ppm. No adverse

effect on reproduction was observed in rats given 1.0 and 10 ppm Aroclor 1242, but there was a decrease in survival of pups at 100 ppm of Aroclor 1242, 1254 and 1260 as well as a decrease in mating indices. The effect of PCBs on reproduction in beagle dogs and swine has been studied by Earl at al. (1974). Aroclor 1254 interfered significantly with reproduction in dogs at doses above 2.5 mg/kg/day while in swine 10.0 mg/kg/day lowered fertility and survivability of neonates. The reproductive effects in dogs are questionable because of unexplained changes in the reproduction pattern among controls.

B. Teratogenicity

1. Introduction

Teratogenicity is that property of an agent whereby it is capable of inducing congenital defects in the developing embryo. Such agents that are chemical substances are known as "teratogens" and the defects they induce are known as "terata". Although teratogenicity is considered generally to involve only anatomical defects, some authorities regard functional or biochemical changes as manifestations of teratogenicity.

A distinction must be made between teratogenicity and fetotoxicity, i.e., toxicity to the fetus. The finding of dead or resorbing fetuses in the uterus of an experimental animal is not evidence of a teratogenic action of the test substance. Similarly, a smaller size of the newborn is indicative of fetotoxicity rather than teratogenicity.

A substance may appear to be teratogenic if it produces severe toxic effects on the pregnant female. Maternal disease and malnutrition affect the number and quality of the offspring. Defects in the offspring that are secondary to toxic effects of the substance on the mother are not considered teratá.

Teratogens produce their harmful effects during the period of formation of cells, tissues, and organs. Hence, once development of the fetus has been completed, a teratogenic event can no longer occur. Chemical substances administered to the mother can be transmitted, together with their metabolites, via the milk to the suckling young, and may produce toxic effects in the latter. However, such effects are not indications of teratogenicity.

Conventional tests for the detection of teratogenicity involve administration of the test substance to pregnant females at repeated intervals throughout the period of organogenesis, e.g., days 6 through 15 of the gestation in the rat. The treated females are sacrificed on the day prior to parturition, and the fetuses removed from the uterus surgically for examination. Alternatively, the test substance may be administered over relatively long periods of time, and the animals allowed to breed normally as in the usual one- to three-generation reproduction studies. The appearance of malformed offspring among the succeeding generations would be evidence of teratogenicity.

In order for a chemical substance to which the mother is exposed to exert a direct action on the conceptus, it or one

or more of its metabolites must be able to cross the placental barrier. Transplacental passage of PCBs has been demonstrated in several animal species (Allen et al., 1980; Curley et al., 1973; Couvillion et al., 1974; Grant et al., 1971), and is known to occur in the human (Funatsu et al., 1972).

2. Mice

PCBs were not teratogenic in mice at dosages up to 500 mg/kg given on days 1 through 6 or days 7 through 11 of gestation (Tuerk, 1973). However, a recent study (Marks et al., 1981) with the hexachlorocongener 3,3',4,4'5,5'-hexachlorobiphenyl in mice at dosages in the range of 0.1-16 mg/kg/day during days 6 through 15 of gestation produced a significant increase in fetal malformation, a significant decrease in average fetal weight, and an increase in the percentage resorptions.

Torok (1976) reported that oral administration of 375 mg/kg or 750 mg/kg of 2,2'-dichlorobiphenyl to mice on days one through three of gestation resulted in prolongation of the interval between breeding and parturition. He attributed this observation to delayed implantation. Although the treated animals had fewer litters and lesser mean litter sizes, there was no indication of teratogenicity.

Some mice exposed to 3,4,3'4'-tetrachlorobiphenyl were reported to exhibit a "waltzing syndrome" (Davis et al., 1979; Tilson et al., 1979). The dosage was 32 mg/kg administered by gavage to the mothers on days 10 through 16 of gestation. The

syndrome consisted of increased motor activity, hyperreflexia, and episodes of head bobbing and rotational movements that were present up to at least eight months of age. Not all exposed mice were affected similarly, but even those that did not exhibit the syndrome showed diminished performance in various neurobehavioral tests. Tilson et al. (1979) refer to these observations as the "behavioral teratology" of 4-CB.

3. Rats

There are a plethora of studies in which the reproductive effects of feeding various Aroclors to rats have been investigated (Calandra, 1976; Gellert and Wilson, 1979; Keplinger et al., 1971; Keplinger et al., 1972; Linder et al., 1974; Villeneuve et al., 1971a). Collectively, these studies reported fetotoxicity as the dosage was increased, but no teratogenicity was demonstrated. It may be useful to note the order of magnitude of the dosages involved. Villeneuve et al. (1971a) found no effect from the administration of dosages of up to 100 mg/kg per day orally to pregnant females from the sixth through the fifteenth day of gestation.

Ultrastructural lesions in thyroid follicular cells and a reduction in serum thyroid hormones have been reported in neonatal and weanling rats whose mothers had been fed a diet containing 50 ppm or 500 ppm of Aroclor 1254 throughout the period of gestation (Collins and Capen, 1980). The authors suggest that alterations in thyroid structure and function in the fetus or neonate may be related to subsequent disturbances in growth or development.

4. Dogs

In the study conducted by Earl et al. (1974), pregnant bitches were given dosages of 0.25, 1.0, or 5.0 mg/kg of Aroclor 1254 from the day of breeding to the day on which they were necropsied. At 5.0 mg/kg, there was an increase in the percentage of resorptions, a decrease in the number of live pups per litter at birth, and a reduction in the percentage of those surviving to two weeks. The terata observed consisted of enlarged fontanelles, cleft palates, and superfluous phalanges. This dosage was said to limit diet consumption severely. The authors state that one litter of the controls "may have had a genetic defect that caused an unusually high incidence of terata."

5. Swine

Earl et al. (1974) included miniature swine (Hormel strain) in the investigation described immediately above. Pregnant sows were given daily oral doseges of 1 mg/kg, 10 mg/kg, or 30 mg/kg of Aroclor 1254. Dosing began 21 days before breeding and was continued until the day of necropsy. The authors concluded that dose-related effects were seen at all treatment levels as evidenced by decreases in the number of pregnancies, number of live pigs farrowed per litter, and percentage of live offspring after two weeks of age. Syndactyly and cleft palates were observed in the young of sows receiving 10 mg/kg, and patent fontanelles and cleft palates in the offspring of those receiving 30 mg/kg. As in the case of the dogs, the higher dosages caused a marked reduction in food consumption.

6. Monkeys

In a study reported by Allen et al. (1974), six adult, female rhesus monkeys were fed a diet containing 25 ppm of Aroclor 1248 for two months. During this period, all animals developed characteristic signs of toxicity, although they maintained a regular menstrual cycle. One animal died. At the beginning of the fifth month, or three months after discontinuance of exposure to the test substance, an attempt was made to breed the survivors. Three animals appeared to conceive, but only one succeeded in carrying her fetue to term. Although this infant was well developed, its body weight was considerably lower than that of the average rhesus infant. Examination of the tissues showed no gross or microscopic lesions.

In a second study by the Wisconsin group (Barsotti et al., 1976) involving 18 adult, female rhesus monkeys, nine were fed a diet containing 2.5 ppm, and nine were fed a diet containing 5 ppm of Aroclor 1248. After seven months on these diets, the eight surviving animals from the 2.5 ppm group and eight from the 5 ppm group were mated with control males. All animals in the 2.5 ppm group became pregnant, but three of these resorbed their embryos; the remaining five gave birth to live infants. In the 5 ppm group six animals became pregnant. These impregnations resulted in three abortions, one resorption, one stillbirth (suffocation during difficult delivery), and one uncomplicated birth. At birth, the six infants were small; however, other than their small stature and focal areas of dermal

hyperpigmentation, their general appearance, hemograms, and osseous development as evaluated radiographically were normal.

The adult, female rhesus monkeys that were the original subjects in the study discussed above were fed the diets containing 2.5 ppm or 5 ppm of Aroclor 1248 for six months prior to breeding, throughout gestation, and for three months after delivery for a total of about 18 months (Allen et al., 1980). Only 16 females were bred, inasmuch as one had died and another was dropped from the study for some reason not explained. About one year after discontinuance of the Aroclor-containing diets, the animals were bred again to control males. All of the seven survivors in the 5 ppm group conceived, but only four gave birth to live infants. In the 2.5 ppm group, one animal had an abortion and the remaining seven had uncomplicated deliveries. Apart from their somewhat smaller size compared to the young of the control animals, the infants appeared normal. Analyses of adipose tissue from two stillborn infants of mothers in the 5 ppm group showed the presence of PCBs, but histological evaluation of adipose and other tissues showned no abnormalities.

7. Clinical Data

Funatsu et al. (1972) studied in detail four babies born to mothers who had ingested rice oil contaminated with a heat-exchange fluid containing PCBs, PCDFs and PCQs. The mothers were among the population exposed in the "Yusho" episode. Three of the four babies exhibited some evidence of intrauterine malnutrition or retardation of growth, and all four had dark brown

pigmentation of the skin that was most pronounced at the genitalia, axillae, and near the fingernails. The same pigmentation was noted on the lips, gums, and palate. While one or more of the infants displayed other clinical signs, no neurological or cardiovascular abnormalities, nor any malformations were observed. The pigmentation of the skin and mucous membranes disappeared within two to five months of age in all cases.

8. Summary and Opinion

(a) In a variety of tests, commercial PCB mixtures (Aroclors) showed no teratogenic activity in mice, rats, rabbits, and monkeys.

(b) Earl et al. (1974) have not demonstrated convincingly a teratogenic action of Aroclor 1254 in dogs or swine. An evaluation of their work suffers from a paucity of information and the possible presence of a genetic defect in the dog colony. The published abstract tends to be misleading. Examination of the unpublished manuscript shows that the authors did not regard the two lower dosages as teratogenic for either species. The highest dose is said to limit food consumption severely in both species. Therefore, it is likely that the defects observed in the offspring were the result of severe maternal malnutrition. Hansen et al. (1975) failed to find teratogenic effects in swine when the mothers were fed a diet containing some 20 ppm of Aroclor 1242 throughout gestation and nursing.

(c) The observations of Collins and Capen (1980) on ultrastructural alterations in the thyroid glands of perinatal

rats whose mothers were exposed to Aroclor 1254 are indicative of functional changes rather than of teratogenicity.

(d) The occurrence of a "waltzing syndrome" in mice exposed prenatally to 3,4,3',4'-tetrachlorobiphenyl might represent a true teratogenic effect (Davis et al., 1979). This phenomenon usually results from a structural or functional defect of the middle ear. The dosage used to produce the syndrome is relatively high. While the exposed animals were not uniformly effected insofar as the overt signs are concerned, Tilson et al. (1979) presented evidence to show a wider prevalence of more subtle neuro-behavioral effects. It is not known whether this condition could be induced by a commercial PCB mixture.

(e) The scientific literature presently supports the conclusion that PCBs present no appreciable risk of teratogenicity for humans, in our opinion, in view of the essentially negative test results in four test species and the questionable positive findings in the dog and in swine.

C. Fetotoxicity

Rabbits given 1.0 mg/kg of Aroclor 1254 daily for 28 days of gestation had no effect on the developing fetus but doses of 12.5 to 50 mg/kg were fetotoxic. Rats appear to be more resistant than rabbits, as doses up to 100 mg/kg do not cause fetal deaths or malformations (Villaneuve et al., 1971a). Embryotoxic effects of Kanechlor 300 and 500 were produced in

Sprague-Dawley JCL rats when fed at levels of 500 ppm in the diet throughout gestation (Shiota, 1976b). Diets containing 5.0 ppm of Aroclor 1248 were fetotoxic to rhesus monkeys.

Fetuses and neonates of mothers with Yusho disease have developed some of the characteristic signs of disease as a result of transfer of PCBs to the fetus and infant through the placenta and breast feeding (Yamashite, 1977; Matsuda, et al., 1978; Yakushijji et al., 1978). Studies in mice on the transfer of PCBs to fetuses and offspring indicate that the amount transferred depends upon the chemical structure of the individual compounds and the position of the chlorine atoms within the chemical structure (Matsuda et al., 1978, 1979).

Aroclors 1242 and 1254 are potent inducers of hepatic microsomal enzymes. A single intraperitoneal injection of 100 mg/kg of Aroclor 1242 to rats increased liver weight, total microsomal activity, as measured by hydroxylation of acetanilide and N-demethylation of aminopyrene, and hepatic cytochrome P-450 (Bruckner et al., 1973). The breakdown of endogenous substances such as progesterone, estradiol and testosterone has been shown to be increased in animals pretreated with chlorinated biphenyls (Orberg, 1978). It is possible that alterations in the metabolism of the endogenous substances by PCBs may upset the normal balance that is essential for implantation of the fertilized ova in the uterus (Smith, 1968). Feeding a PCB mixture containing 60% chlorine significantly increased the uterine weight of guinea pigs (Vos, 1972).

Yamashita (1977) studied the clinical features of PCB, PCDF and PCQ induced fetopathy in four babies born from mothers poisoned by contaminated rice oil. There was intrauterine retardation of growth, dark brown pigmentation on the skin and mucous membranes, edematous face and exopthalmus. In some cases the retardation persisted for many months but the infants eventually gained their weight for the age group.

Although over 100 nursing mothers residing in Michigan during 1977-1978 had residues of PCBs in breast milk ranging from 1.0 ppm to over 3 ppm, there have been no reports of serious adverse effects on reproduction or infant mortality (Wickizer, 1981).

Summary and Opinion

1. It is apparent from studies on humans and animals that certain classes of polychlorinated biphenyls are more toxic than others and that the degree of chlorination is one of the determinant factors in their toxicity. But, as stated previously under cutaneous toxicity, the presence of contaminants may be responsible for the adverse effects on reproduction. Oishi et al. (1978, 1980) compared the activities of PCBs and dibenzofurans in rats and found that dibenzofurans markedly depressed body weight, decreased weights of the thymus, ventral prostrate and seminal vesicles and reduced hemoglobin and hematocrit values, while PCBs had little or no effect.

2. On the question of fetotoxicity in PCB-exposed females, positive results are seen in certain test animals (rats, dogs, rabbits) when the PCBs are administered at relatively high doses (greater than 10 mg/kg) to pregnant animals. In the human, the only reported evidence for fetotoxicity in exposed populations stems from the unique Yusho event, in which causation may not be linked to PCBs. No such reports have been made on other exposed human populations, suggesting the absence of this effect in the human under occupational exposure conditions.

X. Mutagenesis

A. General

The term "mutagenesis" refers to any process that induces a permanent change (mutation) in the genetic composition of a cell, thereby causing that cell to differ in a consistent way from its parent. If a mutation occurs in a germ cell, the offspring resulting from the union of that cell with another will have an altered genetic composition that will persist in the germ line unless the alteration is lethal. Mutations occur spontaneously through unknown mechanisms, but they also may be caused by radiation or chemical substances (mutagens). While in a strict sense the term "mutation" applies only to changes in the DNA at the molecular level, it is considered broadly to include alterations in the number and structure of chromosomes.

Mutagenicity is the property of an agent, chemical or physical, to induce mutations. Chemical substances may be tested for mutagenicity by a variety of methods, among which are those that employ (a) bacterial test systems, (b) cytogenetic analysis *in vivo*, (c) cytogenetic analysis *in vitro* and (d) dominant lethality in a rodent.

B. Bacterial Test Systems

The "Ames test" is the most popular test of mutagenesis employing a bacterial test system. It is a so-called "backward" mutation system that uses a series of mutant strains of *salmonella typhimurium* that have lost the ability to synthesize the amino

acid histidine. Hence, they can grow only if exogenous histidine is supplied. A mutation has occurred if, after exposure to the chemical substance, the organisms regain the ability to grow in the absence of histidine.

Aroclors 1221, 1254, and 1260 showed little mutagenic activity in the Ames test (Wyndham et al., 1976) with indications that Aroclors with lower chlorine contents are weakly positive in the Salmonella test systems. However, these results must be discounted since they could not be replicated (McMahon et al., 1979; Safe, 1980). As a general finding, Heddle and Bruce (1977), McMahon et al. (1979), Schoeny et al. (1979), and Safe (1980) were unable to find evidence of mutagenicity of PCBs in bacterial test systems.

C. Cytogenetic Analysis in Vivo

In this procedure, the experimental animal is treated with the test substance and, after a suitable period of time, sacrificed for examination of rapidly dividing tissues. Bone marrow and the seminiferous tubules are generally the most frequently used tissues for this purpose. It is customary to inject the animals with colchicine several hours before sacrifice in order to promote the accumulation of cells in the metaphase stage of division. In this stage, the chromosome can be examined more readily for abnormalities.

In two investigations, PCBs were judged not to have produced chromosomal abnormalities. Dikshith et al. (1975)

examined seminiferous tubules of rats at different intervals after daily dosages of 50 mg/kg of Aroclor 1254. Green et al. (1975a) examined both bone marrow and spermatogonial cells of rats after either a single dose of 5000 mg/kg of Aroclor 1242, or four daily doses of 500 mg/kg. In all cases, it was concluded that no significant chromosomal damage had occurred.

The micronucleus test is a test for agents that tend to break chromosomes (clastogens). A micronucleus is a fragment of chromatin that has broken away from a chromosome during cell division and has failed to be included in either of the daughter nuclei. The phenomenon can be observed best in newly formed erythrocytes since these stain differently from the mature erythrocytes in that they exhibit polychromasia for a period of 24 hours or so. Furthermore, the nucleus has been extruded at the last maturation division so that the micronuclei, which remain behind, are readily visible in an otherwise chromatin-free cell. Micronuclei occur in a small fraction of normal red cells, but their incidence is increased by the action of clastogens. The test is carried out by administering the agent to the test animal, and examining the polychromatic erythrocytes in bone marrow smears after some interval of time has been allowed for micronuclei to form.

Heddle and Bruce (1977) reported Aroclor 1254 as negative in a micronucleus test.

D. Cytogenetic Analysis in Vitro

Hoopingarner et al. (1972) activated cultured human lymphocytes with phytohemagglutinin and treated them with 100 ppm of Aroclor 1254 at various stages of a division cycle. The cells then were examined for chromosomal aberrations for the different stage treatments. Aroclor 1254 had no apparent effect on chromosomal integrity as measured by cytological evidence.

E. Dominant Lethality in Rodents

A dominant lethal mutation is one that occurs in a germ cell. While it does not impair the function of that cell, it kills the fertilized ovum or the developing embryo. Mice and rats are the preferred experimental species. In its simplest form, the test consists of treating males with the suspected mutagen, mating them with normal females, and counting the number of viable offspring. The test could be used to detect dominant lethal mutations in females, but it would be difficult to rule out adverse effects on the embryo that might be secondary to non-genetic effects on the mother.

Green et al. (1975b) concluded that Aroclors 1242 and 1254 were not mutagenic since they failed to induce dominant lethal mutations in rats. In similar studies reported both by Keplinger et al. (1972) and Calandra (1976), Aroclors 1242, 1254, and 1260 were administered to male, albino mice in a single intraperitoneal dosage of either 500 mg/kg or 1000 mg/kg. Subsequent matings of these animals to control females showed no effect of

treatment on the number of implantation or resorption sites, number of viable embryos, or preimplantation loss.

F. Summary and Opinion

There is no evidence from in vivo test systems that any commercial PCB mixture is mutagenic. The same observation holds true for the bulk of the investigations employing in vitro techniques. In our opinion, therefore, it is quite unlikely that the PCBs as a class evoke mutagenic activity in the human, either acutely or chronically. Since chemical mutagenesis and carcinogenesis often correlate for a given active chemical, this opinion is reinforced by the essentially negative findings on carcinogenesis in populations occupationally exposed to PCBs (sections VIII and XII).

XI. Other Health Effects

A. Enzyme Induction

1. Introduction

Most chemicals that are allowed to enter the body are converted by the body to a variety of different chemical entities. In this manner, food becomes transformed into energy. Chemicals, other than food or those that are naturally present in the body, that are introduced into the body are generally called "xenobiotics," and they also are frequently converted by the body to derivatives of the original compounds. The conversion processes are regulated by the enzymatic systems generally termed biotransformation systems. Although there are a multitude of xenobiotic substances to which humans are exposed, there are only a few different enzyme systems involved. The body basically biotransforms chemicals by oxidizing, reducing, hydrolysing or combining (conjugating) the agent with other chemicals. Although each of these systems is important, of particular interest here are those systems that result in conversion of the original compound to the oxidized derivatives.

It is not uncommon for the body to react to some xenobiotic compounds that it normally biotransforms by increasing its ability to perform the biotransformation function by producing an increase in the amount of enzymes available. This process, which is called "induction" of the enzyme system, effectively makes the body more capable of biotransforming not only the compound that initiated the induction but also all other compounds

that are oxidized by the same enzymatic system. In this manner it is feasible for a given xenobiotic agent to induce a biotransformation system that affects the ability of the body to biotransform not only the original compound but also a large number of other xenobiotics as well as some naturally existing chemicals within the body. Shortly, it will be shown that the PCBs in general have been described as being effective, that is, potent inducers of major oxidative biotransformation systems in experimental animals and in the human. Via induction of enzymes, the concentration of various normally occurring chemicals may be altered. The scientific evidence associated with these subjects will be evaluated in terms of the available current literature.

The major oxidative biotransformation system in the body, as far as xenobiotics are concerned, is present in greatest activity in the liver and is present in lesser activity in most other tissues. In experimental studies, the liver generally serves as a monitor of drug or chemical effect on the oxidizing enzymes. The enzymes are located in the "microsomal" fraction of the liver cells. This is a fraction of the cell that can be obtained by proper ultracentrifugation techniques. The biotransformation system of interest is known as the "microsomal mixed function oxidase system (MFO)". Functionally this system operates to incorporate oxygen into the xenobiotic agent via a series of enzymatic actions. The system does this by making an "active" oxygen atom available via a hemeprotein enzyme. This hemeprotein is in fact a family of proteins collectively identified as

"cytochrome P-450." The ability of the enzyme to operate as an oxidative system is dependent on the existence of several naturally occurring substances and, in particular, on the existence and quantity of available cytochrome P-450 in the microsomal fraction of the liver.

Microsomal P-450 can be measured directly or indirectly using various substrates. Direct measurement of P-450 is based on measurement of the protein system from which these enzymes obtained their name, that is, when the enzymes are reduced and combined with carbon monoxide they exhibit, in a spectrophotometer, maximal absorption of light energy at the wavelengths of 450 nanometers, hence the name cytochrome P-450 system. The P-450 system can also be measured in terms of its activity on specific substrates such as ethylmorphine and antipyrine. Induction of this system is measured in terms of an increase in P-450 and/or its activity (based on units of protein per sample of microsomes). Investigations of enzyme induction have separated the P-450 enzymes into two groups, identified as P-450 and P-448 groups, on the basis that various components of the P-450 group of enzymes are "induced" to different degrees by different xenobiotic agents. The P-450 enzymes are those that are mainly induced by the barbiturates, whereas the P-448 enzymes are mainly induced by 3-methylcholanthrene and show maximal absorption at 448 nanometers. The literature includes studies that suggest that the P-448 enzymes as well as the P-450 enzymes are induced

by certain PCBs although there appears to be some species and tissue specificity in their inductive properties.

Investigations of the effects of PCBs on cytochrome P-450s have centered on two areas of interest. One involved the induction mechanism via the use of either a commercially available sample of a single PCB congener (such as 2,4,5,2',4',5'-hexachlorobiphenyl) that was synthetically prepared and could be tagged with a radioactive atom to facilitate analytical work. Generally, a group of experimental animals (rats) was administered the PCB. Samples were then obtained at various levels. Livers were then examined directly for the quantity of cytochrome P-450 or indirectly for P-450 and P-448 activity via its enzymatic action on various substrates. The liver may also be examined histologically and for evidence of the state of protein synthesis. Induction of the P-450 enzymes in the human is estimated by measuring the plasma elimination rate (plasma half life) of antipyrine in controls as compared to exposed subjects. Antipyrine is a drug that is completely absorbed when given orally and completely metabolized by the liver P-450 microsomal system.

The second area of interest concerned the ability of the liver microsomal system to biotransform PCB. Of particular interest was the nature of the intermediate and final products of the biotransformation process. This subject is important in understanding the toxicology of the PCBs because of the following hypotheses:

(a) Certain PCBs induce the microsomal mixed function oxidation systems thereby influencing not only their own metabolism but also the metabolism and time course of action of available endogenous hormones as well as other xenobiotics (including drugs) administered to humans.

(b) Certain PCBs or contaminants of commercial preparations of PCBs may lead to the formation of intermediate epoxide type derivatives, and these derivatives can covalently bind to macromolecules in the liver thereby leading to hepatic toxicity.

2. Induction of Liver Enzymes

Various studies have reported on the effect of short term exposure of rats to mixtures of chlorinated biphenyls. One such study by Ecobichon et al. (1974) used the Aroclors identified as Aroclor 1016, 1221, 1242, and 1254, and another study by a French investigator, Narbonne (1980), used a French preparation known as Phenoclor DP6. In both studies the sample material consisted of a mixture of congeners of the chlorinated biphenyls. These studies showed that when rats were administered 10 ppm of the PCBs in their diet for only one day, the livers from the animals showed induction of P-450, aniline hydroxylase, and aminopyrine-N-demethylase. The induction of these enzymes was maximum in about five days. If the rats were given 10 ppm of the PCBs in the diet for 8 consecutive days, induction occurred in three to five days and to a lesser extent over the remaining

8 day interval. In the Ecobichon study, intraperitoneal injection of the Aroclors in doses of 50 mg/kg was made for three consecutive days. Animals were sacrificed 96 hours later. Mixed function oxidative enzymes were found to be induced in the liver. The greatest induction was seen with the more highly chlorinated Aroclors. The conjugation enzyme induction occurred rapidly on exposure to the Aroclors, and particularly to those Aroclors that are more highly chlorinated. The PCBs used in these studies were commercial grade.

In order to better understand which of the P-450 cytochromes are induced by the PCBs, Ryan et al. (1979) treated groups of rats with Aroclor 1254, phenobarbital or 3-methylcholanthrene. The livers were used to prepare three different P-450 fractions on the basis of differing molecular weights and they identified the three fractions as $P\text{-}450_a$, $P\text{-}450_b$ and $P\text{-}450_c$. All three of the P-450s were obtained from the PCB treated animals. $P\text{-}450_a$ and $P\text{-}450_b$ were obtained from the phenobarbital treated rats and $P\text{-}450_a$ and $P\text{-}450_c$ were isolated from the 3-methylcholanthrene treated rats. ($P\text{-}450_c$ is probably equivalent to P-448). Therefore, this study showed that the Aroclor induced at least three identified cytochromes including the type induced by phenobarbital and the type induced by 3-methylcholanthrene.

In 1980 Parkinson et al. investigated the validity of the concepts that were current at that time regarding the structure-activity relationship between specific PCB congeners and hepatic

enzyme induction. The study was designed to yield the structure vs. activity data. Basically, they conducted experiments in rats using 8 synthetic PCB congeners plus phenobarbital and methylcholanthrene as enzyme inducers. They concluded that in order for a PCB to induce a methylcholanthrene-type or a mixed-type liver enzyme system, the PCB would have to contain chlorine substituted at specific positions on the phenyl rings, whereas the PCB inducers of the phenobarbital type had multiple diverse structures that could not readily be defined.

Whether PCBs are administered for as short a time as 1 to 3 days or whether they are administered daily for up to a year, various liver enzymes appear to be induced, but the phenomenon of induction does not seem to be specifically very harmful to the animals. Allen and Abrahamson (1979) fed rats diets containing 100 ppb of Aroclor 1248, 1254, and 1260 for 13, 26 and 52 weeks. The growth rate of these rats was comparable to the controls but the test animals did show liver hypertrophy, some focal cellular degeneration and an increase in serum lipids. In general, the effects were no greater in those animals that received the diet for a year than in those that received the diet for 13 weeks.

Alvares et al. (1973) published results from experiments that involved treatment of rats with Aroclor 1254. Intraperitoneal administration of 25 mg/kg/day for 6 days

produced a tripling of cytochrome P-448 content of the livers and a 10-fold increase in the enzyme activity involving benzo(a)-pyrene hydroxylation (which is a typical 3-methylcholanthrene type of induction), as well as an increase in ethylmorphine-N-demethylation (a typical phenobarbital type of induction). They therefore concluded that Aroclor 1254 induced a mixture of both P-448 and P-450. In 1977, Alvares and Kappas described some additional work that showed the ability of Aroclor 1254 to cross the placental barrier of the rat, to be transmitted to the neonatal rat through the mother's milk, and to cause increases in biotransformation enzymes in the fetus and newborn.

Goldstein et al. (1978, 1979) attempted to resolve the question of whether pure PCB congeners had enzyme inducing properties that were different from those produced by commercial preparations of the single congeners or the PCB commercial mixtures (such as Aroclor 1254). These authors synthesized a "pure" sample of 2,4,5,2',4',5'-hexachlorobiphenyl and showed that it had different enzyme induction properties than did the same commercially obtainable, specially prepared, congener that was reported to be "99% pure". The difference in the induction capability of the two preparations was primarily in regard to the induction of P-448 cytochromes in which the synthetically pure isomer, at doses of 250 mg/kg administered to female rats, induced aryl hydrocarbon hydroxylase (AHH: a P-448 enzyme system) only 5-fold; whereas the commercial isomer at a dose of 50mg/kg produced a 30-fold increase of AHH. Also, a GC-MS analysis

of the two preparations of hexachlorobiphenyl showed that the commercial preparation contained 4 contaminants that were not present in the pure congener. Two of these contaminants were identified as a tri and a tetra chlorodibenzofuran (TCDF). TCDF was then shown to be a potent inducer of AHH and cytochrome P-448. The ED (effective dose, 50% of test animals) for TCDF re: enzyme induction was found to be 0.5 micrograms/kg for three days. Therefore, the conclusion was that even a 99% pure congener that was commercially obtainable can contain sufficient dibenzofuran to alter the enzyme induction action.

In one report, Alvares et al. (1977) had studied alterations in drug metabolism in both rats and humans. In the rat study Aroclor 1016 elicited a barbiturate type of induction of hepatic enzymes. That Aroclor did not induce cytochrome P-448; however: Aroclor 1254 did induce cytochrome P-448. The human study involved 5 workers in a capacitor manufacturing plant who handled primarily Aroclor 1016. These exposed workers showed a low half-life (10.8 hrs) of antipyrine as compared to control non-exposed subjects (who showed a half-life of 15.6 hrs). The volume of distribution of the drug in the two qroups was not different, so the comparison of the half-lives of the drug in the two groups is valid. Thus, enzyme induction occurs in the human in response to occupational exposure to Aroclor 1016 and the induction

as measured by antipyrine metabolism is a P-450 type of induction.

In 1975 Sickers at al. reported on the effects on liver enzymes associated with topical administration of immersion oils (as used in microscopy). These immersion oils were known to contain approximately 30% PCBs. One to ten microliters of the oils were applied daily for six days to the shaved backs of rats and the animals were sacrificed on the 7th day. The authors found that both skin and liver enzymes were induced. In a second experiment 10 microliters of the oil was topically administered on one occasion only, and the animals were sacrificed at various intervals following application of the oil. P-450 and liver monooxygenases were induced (including benzo-a-pyrene hydroxylase, a P-448 enzyme system) showing maximal effect in 2 days with a slow return to normal by 28 days. In this study there must have been very large differences between individuals in the control group because their data show very large differences between groups with only a 95% significance. The immersion oils currently marketed in the USA do not contain PCBs.

3. Metabolites of PCBs

Shimada and Sato (1980) studied the reactive metabolites of PCB metabolism. Their work involved the use of isotope-labeled PCB congeners. This work suggests that PCB epoxides may be the activated forms that covalently bind the macromolecules in the livar cells. A hexachlorobiphenyl congener

(2,4,5,2',4',5'-hexachlorobiphenyl) that has no adjacent unchlorinated atoms in the biphenyl ring and that cannot be converted to the epoxide was found not to be covalently bound although accumulation of this PCB in the liver was found to occur. Other PCBs show covalent binding that is principally with microsomal proteins rather than the ribosomal RNA; a conclusion based on the finding that various proteases would solubilize the radioactivity of the labeled atom. Treatment of the animals with phenobarbital produced livers that showed good covalent binding to the PCB, but treatment of the animals with methylcholanthrene produced livers with poor PCB binding capability. The authors concluded that PCB epoxides were formed by the monooxygenase system and these epoxides were responsible for the binding of the compound to microsomal proteins. Their conclusions are based on indirect findings.

4. Interactions Based on the Induction of Enzymes by PCBs

One report (Murphy et al., 1979) described studies that the authors claimed indicated the existence of a drug interaction in the form of potentiated lethality of fluroxene in Aroclor pretreated animals. The authors did show that the Aroclors induced hepatic enzymes. Their method of measuring enzyme induction was to measure the metabolism of warfarin by livers of the Aroclor-treated animals according to a procedure that they had developed and that they claimed could differentiate between induction of P-450 as compared to P-448. They found that Aroclor 1254 in rats mainly induced cytochrome P-448 whereas Aroclor 1260 induced mainly

cytochrome P-450. The authors then indicated that both Aroclors caused animals to show increased lethality on subsequent administration of fluroxene. We have difficulty interpreting this article. We do not believe that the conclusions are supported by the data that are given. In one case involving Aroclor 1260 the data are not given in the table and in the other case the data obtained following administration of fluroxene do not appear to be different from the control data.

5. Enzymes Other than Cytochromes Affected by PCBs

Two additional reports deal with an action of the Aroclors on ATPase activity. One of these reports (Lee and Park, 1979) used cultured human lymphocytes and showed a dose-response relation for Aroclor 1254 and inhibition of mitochondrial respiration. From this effect they indicated that there may be a decrease in adenosine triphosphate (ATP) concentration. We can see no way to evaluate what this report means since the concentrations of the Aroclor used are not correlated with concentrations that might be involved in intact biological systems. The other report (LaRocca and Carlson, 1979) indicated that the Aroclors produced *in vitro* inhibition of rat magnesium ATPase activity at a concentration of 30 parts per million. A weak correlation was found between increasing inhibition and increasing chlorination. A strong correlation was found between PCB-induced inhibition of the ATPases and decreasing aqueous solubility. We don't know what these results signify other than that they seem seem to be incidental findings -- many other chlorinated hydrocarbons do the same thing.

6. Summary and Opinion

The available data from experimental studies on animals and man indicate that the commercially available preparations of the PCBs (Aroclors) as well as some highly purified PCB congeners act to induce some of the hepatic enzymes. Considerable effort has been devoted to determine which of the microsomal enzymes are induced by the Aroclors. There are some data that indicate that the predominant induction occurs for the P-450 type of cytochromes (identified as a phenobarbital-type of induction). When experiments are conducted with the "more pure" congeners there is very little evidence for induction of any enzyme systems other than the P-450 cytochromes. In general, induction is greatest with the most highly chlorinated derivatives, but the least chlorinated derivatives also induce the P-450 cytochromes.

The subject of whether the "pure" congeners of the PCBs have less action on the cytochrome systems than the commercial materials may be only of academic interest, since the preparations that are available to industry and the public are the commercial preparations such as the Aroclors. It should be recognized that authors tend to describe effects due to PCBs whereas they are usually referring to effects of Aroclors (such as Aroclor 1254), which are mixtures of PCBs plus various trace contaminants.

The commercially available preparetions of the PCBs are capable of inducing certain hepatic enzymes in the rat and there is one report suggesting that occupational exposure to

commercial PCBs may induce an hepatic enzyme. There are no data suggesting that the overall health of the animals or man is influenced as a consequence of PCB-induced microsomal enzymes. Although it is suggested by some people that changing the metabolic transformation capability is inherently detrimental to the animal, there is no real evidence to support such an hypothesis. When enzymes are induced and they are then involved in the bioactivation of xenobiotic agents, such enzyme induction could be harmful depending on the dosage sequence and the inherent toxicologic properties of any specific agent. On the other hand, if the enzymes that are induced are involved in bioinactivation of xenobiotic compounds, then induction may be beneficial to the animal again depending on the dosage sequence and inherent toxicologic properties of any specific agent. There is no good experimental or clinical evidence that PCBs may act through their enzyme induction capability to affect "hormone" levels and result in harmful effects on the body.

8. PCB Effects on Immunocompetence

A few reports appeared prior to 1970 that suggested indirectly that PCBs may influence immunocompetence. In 1970, Vos and Koeman showed that when chicks were fed 400 ppm PCB for 60 days they showed atrophy of the splenic pulp and lymphoid necrosis. (Chicks at higher doses all died during the test.) The chicks also showed porphyria and liver necrosis. In 1971, Vos and Beems reported that commercial PCB samples applied to

the skin of rabbits daily five times weekly for 38 weeks (27 applications each containing 188 mg PCB) produced histologic atrophy of the cortex of the thymus and a reduction in the number of germinal centers in the spleen. At this time the animals showed marked chloracne of the skin, increased fecal coproporphyrin and protoporphyrin as well as liver and kidney damage. The authors stated that these effects were strong indicators of an immunosuppressive action of the PCBs.

In 1977, Loose and co-workers fed Aroclor 1242 to mice for six weeks. The animals were then immunogenically stimulated with sheep red blood cells as an antigen and the antibody response was measured. The method of measuring antibody activity involved plaque-cell estimation in the spleen and the measurement of the plasma immunoproteins. Positive findings were obtained as compared to controls and the authors particularly remarked about the reduced IgA levels found in the PCB-treated animals. It was also noted that clinically subtoxic levels of Aroclor 1242 were profoundly immunosuppressive. These authors also cite the work of Koller and Thigpen (immunosuppression by a PCB to pseudorabies virus in rabbits), Vos and van Driel-Grootenhuis (immunosupression by PCB in guinea pigs) and Friend and Trainer (increased mortality in ducklings that had been previously exposed to Aroclor 1254 and then inoculated with duck hepatitis virus).

In 1978, Loose and co-workers studied the effects of PCBs on host resistance systems. Mice that were fed diets containing 167 ppm Aroclor 1242 for three weeks and for six weeks exhibited increased sensitivity to salmonella endotoxin and a decreased survival time to inoculation with malaria. Thus they concluded that host resistance was impaired by prior treatment with PCBs.

Also in 1978, Thomas and Hindsdill reported on studies in which they fed monkeys 2.5 to 5.0 ppm PCB (Aroclor 1248). After six months the monkeys developed chloracne, alopecia and facial edema. After 11 months control and treated monkeys were tested with antigens (sheep red blood cells and tetanus toxoid). The only positive finding was in the 5.0 ppm monkeys who showed significantly lower antisheep red cell antibodies as compared to controls. No effect was obtained regarding the antibody response to tetanus toxoid. These authors also fed mice up to 1000 ppm of the PCB for three to five weeks without evidence of overt toxicity, but these animals did show a higher mortality when challenged with the pathogen salmonella typhimurium as compared to the controls.

In 1980, Oishi and Hiraga reported on their studies in which they had given mice PCBs (commercial product) by oral intubation once weekly for four weeks. Other groups of mice were fed CDF (chlorinated dibensofuran) or CDD (chlorinated dibenzo-p-dioxin). Only the groups of animals that had received 10 or 100

micrograms/kg CDF showed decreased thymus weights. All groups were challenged with endotoxin and again only the CDF-pretreated animals showed increased lethality compared with the controls. It is noteworthy that the authors found no deaths in their control animals given endotoxin, a finding that raises doubt about their experimental design. In this study the PCB pretreated animals did not show increased susceptibility to endotoxin. In the same year (1980) Imanishi et al. showed that mice fed PCBs for 21 days at 100, 200, or 400 micrograms/gm were significantly more susceptible to herpes simplex virus and electromelia virus than were animals fed a PCB-free diet.

In 1981, Cheng et al. reported on the immunologic evaluation of patients from Taiwan who developed an acne-like skin disease, termed Yu-Cheng disease, that was related to the consumption of rice-bran oil contaminated with PCBs, PCDFs and PCQs (in an accident very similar to Yusho). The authors had 30 such patients who showed average whole blood PCB levels of 45 ppb, with a range of 15 to 98 ppb, plus an additional control group of 23 healthy persons matched according to age and sex who showed no detectable levels of PCB in their blood. The patients had decreased concentrations of IgA and IgM immune globulin but not IgG. Their study of subpopulations of lymphocytes showed that the percentage of B cells was not affected by the disease but the percentage of some species of T cells was decreased as compared to the controls.

Environmental chemical effects on immunocompetence have been extensively reviewed by Faith, Luster and Vos (1980). A number of studies cited by them found PCBs to be immunosuppressive in various species (from ducklings and chicks to mice and monkeys), in some cases at dose levels that produce little effect other than hepatocyte hypertrophy. Only one study (Street and Sharma, 1975), which involved feeding low levels (0.18 to 6.5 mg/kg/day) of Aroclor 1254 to rabbits, showed no significant effect on humoral or cell mediated response. Our review of the Street and Sharma report indicated that there was a dose-related trend toward immunosuppression in their animals and at the higher doses (2.1 and 6.5 mg/kg/day) for four to eight weeks the animals showed significant increase in liver weight. The Faith, Luster and Vos review lists several general factors (nutritional status, hormonal levels and amounts of immunoregulatory proteins such as alpha-fetoprotein) that influence immune function. Therefore those studies in which immune function was studied following exposure to levels of the PCBs that resulted in overt toxicity are meaningless from an immunotoxicologic viewpoint. In contrast, immunosuppression at dosage levels that do not produce general toxicity would be significant.

Summary and Opinion

The overall conclusion that can be reached in regard to the studies on the effects of PCBs on immunocompetence is:

(1) with exposure conditions that lead to general toxicity, immunosuppression may be demonstrable, but it may be indirectly induced; (2) with experimental conditions wherein only subclinical toxicity is observed, such as hepatocyte hypertrophy, there is the possibility that immunosuppression is also produced; and (3) under still lower PCB exposure conditions it is impossible that immunosuppression is involved. Perhaps the best study to estimate a no-effect dose for exposure to PCBs would be the Thomas and Hindsdill (1978) study which suggests that six months' exposure to between 2.5 and 5 ppm of PCBs in the daily diet of monkeys is a threshold for effects on the immune system. Unfortunately, there are few data directly concerned with the dose-response relationship for effects of the PCBs on the immune system in animal models or the human.

C. Porphyria

The administration of PCBs to rats will produce a delayed type of porphyria, i.e., deposition of porphyrins and their degradation products in tissues and excreta. Although the mechanism of action of the PCBs is unknown, it apparently differs from that of other porphyrogenic compounds such as hexachlorobenzene or isopropylacetamide. It has been thought that the effect of PCBs in animals may indicate that these compounds can induce conditions such as porphyria cutanea tarda in man, but clinical data have not shown this to occur in PCB-exposed workers.

(i) Experimental Data. The fecal content of coproporphyrin and protoporphyrin of rabbits was increased by Aroclor 1260

and by hexachlorobiphenyl, but the difference was statistically significant only for coproporphyrin (Voe et al., 1972b). Bruckner et al. (1974) observed an increased excretion of urinary coproporphyrin in rats given Aroclor 1242, 5 or 25 ppm for two, four, and six months.

Goldstein et al. (1974) emphasized the delayed onset of the PCB-induced porphyria; rats fed 100 ppm of Aroclor 1254 became porphyric after two or seven months of treatment. Although the excretion of coproporphyrin and other porphyrins was increased, the largest elevation was in the uroporphyrin fraction. There was also a marked accumulation of uroporphyrin in the liver. The studies of Goldstein et al. suggest that PCBs may effect uroporphyrin formation or utilization. The induction of delta-aminolevulinic synthetase (ALA synthetase, a rate-limiting enzyme in heme synthesis) does not appear to be the mechanism by which porphyria is induced by PCB, as it is for many porphyrogenic chemicals. In their studies the increase in ALA synthetase activity was probably secondary to the porphyria. Also, Aroclor acts to increase liver cytochrome P-450 rather than to decrease it.

Hexachlorobenzene is known to induce a delayed type of hepatic porphyria similar to that produced by Aroclor 1254. However, the two responses apparently differ significantly as Goldstein et al. reported that the rats fed PCBs did not exhibit the nervous or cutaneous signs associated with hexachlorobenzene poisoning.

(ii) Clinical Studies. Some of the Yusho patients ingesting rice oil contaminated with PCBs reported pigmentation of the skin and nails, but there were no studies to evaluate a possible relationship of the reported symptoms to any change in porphyrin metabolism (Kuratsune, 1972).

Smith et al. (1981 a,b,c) determined urinary coproporphyrin, uroporphyrin and porphobilinogen in PCB-exposed workers; they did not find a correlation between the urinary porphyrins and the serum level of the lower chlorinated PCBs or the higher chlorinated PCBs. The subjects did not have any recognizable dysfunction and there was no clinically apparent illness with high levels of PCB exposure or with high serum PCB.

Other investigations evaluating the health effects of PCB exposure have not reported cases of porphyrin-related disease or cases of porphyria cutanea tarda (Fischbein et al. 1979; Maroni et al. 1981).

The observation that PCBs increase ALA synthetase in animals raises the possibility that PCBs can cause an attack of porphyria in patients suffering from acute, intermittent porphyria. However, a case of this type has not been reported in the medical literature. As noted above in studies on the rat, the action of PCBs appears to differ from that of other porphyric agents.

XII. Epidemiology

Although case reports of toxic effects, especially skin lesions related to exposure to chlorinated organic chemicals, have been recorded almost from the beginning of their use (Jones and Alden, 1936), few epidemiological studies appeared until the accidental exposure of a large Japanese population to PCBs, PCDFs and PCQs from the contamination of rice oil. Since that time, numerous studies have been undertaken to determine the health effects related to exposure to PCBs in the workplace and general environment. It must be remembered that there were problems in these studies in assessing the effects because some of the environmental exposures may have involved PCBs that had been altered by processing at high temperatures (Brown, J.F., Jr. et al., 1981). The numbers of individuals exposed occupationally are relatively small, although some may represent the heaviest and most protracted exposures of any reported, and their added burden of PCBs from the workplace must be compared to the background levels that are currently present in all populations. Many of the commonest changes noted in biochemical and other medical measurements obtained in screening surveys have not yet been associated with any subsequent development of disease.

In order to evaluate the epidemiological studies that assessed the effects of PCBs, we will discuss the results of mortality data, morbidity data, and screening surveys separately even though many studies include data on several outcomes.

A. Mortality Studies

In 1968, an unknown number of persons in the western part of Japan ingested rice oil containing Kanechlor 400 that was contaminated with polychlorinated dibenzofurans (PCDFs) in amounts 250 times more than the usual levels in Japanese PCBs (IARC, 1978) and more than 1000 times the usual levels in U.S. Aroclors. By 1977, 1665 cases of "Yusho" had been recognized based on symptoms of ocular disturbances, skin lesions, primarily subjective neurological symptoms and blood PCB levels (Urabe, 1979). Fifty-one deaths have occurred in these patients and the causes have been reported to include liver cancers and lymphomas. However, there have been no reports on the numbers of expected deaths by specific causes based on the usual death rates in similar Japanese populations. The distribution of causes may simply represent the usual distribution of deaths found in the age groups characteristic of Yusho patients, and so it is impossible to assess the mortality patterns of these cases at the present time.

Bertazzi et al. (1981) have reported a study of 1,310 workers, predominantly women, who, beginning in 1946, initially were exposed to Aroclor 1254 and Pyralene 1476 and subsequently were exposed to mixtures with 42% chlorine content. Mortality data were collected on all individuals with six months or more of employment over a 25-year period ending in 1978. The total number of deaths (27) was small but there was an excess of mortality in

female workers compared to the general population, which is unusual for any working group. This study demonstrates a significant excess for all neoplasms for the combined sexes and an excess specifically of lymphomas. It is difficult to interpret these data since the type of cancer incriminated seems to differ from that of other studies. Further, the data of Brown and Jones (1981) (see below, and also the compilation in Table 7, section VIII) on workers in two manufacturing plants do not confirm a finding of excess malignancies in PCB-exposed personnel. The unusual two-fold excess in mortality of female workers in the Bertazzi et al. study deserves further attention.

A retrospective cohort mortality study of 2,567 workers in two electrical capacitor manufacturing plants that had used PCBs for over 30 years, identified 163 deaths (Brown and Jones, 1981). The type of PCBs used over the years had varied and include Aroclors 1254, 1242 and 1016. The overall mortality and total cancer mortality were low, but there were three-fold excesses of cancers of both the rectum and the liver (with a total of 7 deaths) although the results were not statistically significant. The only significant excess was that of the subset of rectal cancers in females in plant 2. The standardized mortality ratios (SMRs) for rectal cancer, liver cancer or cirrhosis did not increase with increasing latency or duration of employment. Unless one can demonstrate that the risk of cancer increases in association with increasing duration of employment, which serves

as a proxy measure of dose, it is difficult to suggest that the agent is possibly causative for the disease.

Although this study has devoted strict attention to details such as the completeness of identification of workers and ascertainment of outcome it has not verified the diagnosis of cases nor investigated the presence of confounding variables. Rectal cancers are often misclassified by location in the intestinal tract. The classification "liver cancers" may include cancers of the gall bladder and biliary system as well as metastatic lesions to the liver from cancers at other sites. Therefore when one has an excess of liver cancers, verification of specific site within the liver system as well as identification of primary liver lesions is extremely important, especially since the number of deaths from this cause is small. The investigators have not verified the diagnosis of either liver or rectal cancers. Since alcohol is considered a frequent etiological agent for cirrhosis of the liver and possibly for liver cancer, some information on consumption would be relevant as a confounding variable. No data on possible confounding variables have been reported in the paper.

The mortality data from the occupational groups and the Yusho patients are based on very small numbers of deaths and at present do not confirm a carcinogenic effect in man. The observation of excess liver cancer deaths in workers occupationally exposed to PCBs is of major interest since the liver was a target

site for changes in animals and since man has demonstrated evidence of subclinical alterations in liver function. If liver cancers are to be evaluated, the diagnosis of primary cancers of the hepatic cells must be confirmed in the mortality studies since the number of cancers in the group will be very small. The available data demonstrate no consistency in the cancer mortality patterns in the studies and no data on a possible relationship of cancers to dose of PCBs.

B. Morbidity or Incidence Data

Skin

Skin lesions have been reported in association with exposure to chlorinated aromatic compounds since the early 1900's (Jones and Alden, 1936). Taylor has emphasized that acneform eruptions are more frequent with the chloronaphthalenes and the dibenzofurans and that the variation in the quantity of these substances that may be present as contaminants in PCBs may account for differences in reporting of skin eruptions with exposures. Taylor has also reported that the acnegenic capacity of various compounds changed according to their form (fumes, liquid or solid) and the degree of chlorination (Taylor, 1979). These factors may also influence the presence of reported skin disorders in studies.

Not only the frequency but the characteristics of skin lesions have differed in the various studies. Jones and Alden's early description of the lesions they associated with chlorinated biphenyls included "blackheads" or "carbon-colored" comedones

sometimes distributed in unusual areas of the body and often associated with cystic areas and yellow pus (Jones and Alden, 1936). Taylor noted that the cystic swelling and hypersecretion of the meibomian glands are important characteristics of the chloracnegenic effect of PCBs compared to other similar chemicals. These were the typical lesions reported by Meigs et al. in 7 of 14 workers exposed to a PCB vapor leak from a heat exchanger in a plant in Connecticut (Meigs et al., 1954). The exposure to vapors was intermittent but of extended duration. Liver function tests were normal in most of these workers and no PCB levels in individuals were obtained, although an air sample prior to the onset of skin disease was 100 ug per m^3, which was within the accepted standards.

The patients who were initially described with Yusho disease had lesions similar to that described above in about 33% and a brownish pigmentation of the skin and nails in 10% of patients. These frequencies were increased subsequently to include about 70 to 85% of patients because of new definitions of characteristics of disease or delayed development of the signs. The eyes were also involved, exhibiting swelling of the upper lids, hyperemia of the conjunctiva and eye discharge (Kuratsune, 1972). Pigmentation of the skin and eye discharges also occurred in newborns of affected mothers. No comparison groups have been included in these studies of Yusho patients. Where the lesions are pathognomic of PCB-related disease this may not be necessary

but when the lesions are more general, comparison groups are essential. There were histopathological changes in five patients autopsied that seem to be associated with contaminated rice oil ingestion. These changes included hyperkeratosis of hair follicles and increased melanin pigment in the basal layer of the epidermis (IARC, 1978). Three out of the five cases also had proliferation of ductal epithelium of esophageal glands. It would have been helpful if these pathological assessments had been made blindly so that qualitative judgments such as "increased melanin" could have been compared in exposed and non-exposed groups. Correlating these pathological findings with changing levels of PCBs, PCDFs and PCQs would also have been helpful but there are no reported data relating to these issues in the papers available. It is known that the amount of used Kanechlor in the rice oil consumed by the patients was between 0.5 and 2.0 g, which would indicate a PCB exposure similar to levels in occupational settings.

Hara et al. in two separate papers (1974, 1975) have described the skin lesions in workers in a capacitor factory where Kanechlor had been used. The serum PCBs of all workers ranged from 7 to 300 ppb but it is not known how these values correlated with the presence of skin lesions (Hara et al., 1974; Hara et al., 1975). Discontinuance of the exposure not only decreased the overall PCB level to 75% of the original value but the skin lesions disappeared to "vestigial markings on a few individuals." The summary of the report does not indicate

the correlation of the blood PCB and skin lesions although there are data in this paper on the half-life of PCBs in relation to duration of exposure.

Hasegawa has reviewed the health of workers in five plants whose industrial process included exposure to Kanechlor (Hasagawa et al., 1972). The industries included capacitor manufacture, PCB manufacture, and biphenyl recovery. The vapor concentrations ranged from 13 to 965 ug/m^3. Skin lesions were reported to be unrelated to blood PCBs but generally related to direct skin contact. The average blood PCB level was 370 ppb. The principal dermal findings included brown chromodermatosis of the dorsal joints of hands, fingers and nail beds and acne. There were no further descriptions of the latter lesions so that the presence of chloracne could not be confirmed, but the brown skin discoloration certainly is typical of the Japanese worker reports.

Kitamura et al. described 13 workers from an electrical capacitor manufacturing plant (Kitamura et al., 1973). The lesions in 10 of the workers described in this group are even more vague. They did not include the typical coloration of nails; chloracne was not directly diagnosed; and the follicular lesions did not occur at points of contact with PCBs. From the description of the study it is not clear that the author's conclusions that the skin lesions were due to PCBs was justified without further information on the usual frequency of similar types of skin lesions in normal populations or a description of typical chloracne. The blood PCB level in this group was 820 ppb average.

Inoue et al. studied the health of workers who were exposed to Kanechlor 500 in a thread-glossing factory (Inoue et al., 1975). The frequency of skin lesions was low. The blood PCBs were over 50 ppb in 7 out of 54 individuals studied. One person had representative chloracne with blood PCBs of 190-210 ppb.

Ouw et al. described one case of chloracne among 34 workers exposed to Aroclor 1242 in capacitor manufacture (Ouw et al., 1976). The average blood PCB was 400 ppb. In addition five workers complained of eczematous rash but there was no description of lesions. Seven out of 15 process workers and 6 out of 19 impregnation room workers complained of burning and irritation of the eyes, face and skin. It is difficult to reconcile these complaints with level of exposure since it should have been higher in the latter group of workers than the former. However, Aroclor concentrations in air as high as 2220 ug/m^3 were measured. The investigators indicated that the "dermatological complaints" occur more often among workers with higher "blood Aroclor levels" but they also indicate there is no clear correlation. It is difficult to be sure of the true meaning of dermatitis as elicited by history when the answers can be biased and the authors do not indicate which cases are related to physical findings only.

As part of a health hazard evaluation at a facility that manufactured electrical distribution equipment, NIOSH studied the

health of eight workers and found no symptoms or physical signs of chloracne (NIOSH, 1977). There were several subjects who reported skin rashes but not those typical of PCB exposure. The mean PCB level in blood was 98 ppb with the highest value being 286 ppb.

Another health hazard evaluation was done after an accidental spill of PCBs (NIOSH, 1980). In this situation there were no signs of chloracne. However, the mean blood PCB level of exposed workers was only 6.4 ppb; this was below the mean for unexposed workers. Humphrey studied the PCB level of individuals on the basis of fish consumption (Humphrey, 1979). He found that the PCB level was correlated with fish consumption with mean blood levels ranging from 46 ppb to 82 ppb and a maximum individual level of 366 ppb. There were no skin lesions or other health problems associated with PCBs.

A medical and biochemical survey was made of 120 male workers exposed to PCBs in the maintenance of railroad cars and locomotives (Chase et al., 1981). Among the exposed group of 86 workers the "medical histories and physical findings" revealed "several cases of chloracne" -- "with none being found in the other groups." No further details are given as to whether the conditions were currently active, nor was there a description of the lesions. It would be of interest to confirm these cases as true chloracne since the current mean plasma PCB level in the exposed group is only 13.4 ppb (range 10-312 ppb), a very low level of PCBs to be associated with chloracne.

Fischbein et al. (1979) completed a medical survey of capacitor manufacturing workers who were self-selected for physical and bio-chemical examinations. A high proportion (45-55%) of both male and female workers complained of skin disorders with 11% giving a history of acne beginning after the onset of exposure. "Dermatologic findings" were present on physical examination in 38 to 41% of female and male workers, respectively. However, these lesions included "erythema, swelling, dryness, and thickening," which would not be lesions characteristic of PCB exposure. Five percent of the study population had acneform eruptions. There is no mention of whether these were typical of chloracne or were the usual acne lesions found in any medical survey. Since skin lesions are common in the general population and since the population was self-selected initially it is difficult to evaluate these findings. The average lower PCB homologues in plasma were 124 ppb and of higher PCBs, 48 ppb. The authors report that the skin findings were correlated with plasma H-PCBs. Unfortunately, if the examinations were done with the observer knowing the job held by the participant, all results can be biased, since reporting might be related to the job held and the PCB levels were related to job. There was no note of skin hyperpigmentation but 15% of workers had eye abnormalities including "injected conjunctiva and palpebral hyperpigmentation and edema." Again, it is not clear how frequently these lesions would have been reported in normal subjects had examinations been done without knowledge of exposure categories.

Maroni et al. (1981) recently reported on two groups of workers who were exposed to PCBs in the manufacture of capacitors. One group (A) had been exposed to both 54% and 42% chlorinated biphenyls. Although the levels of the trichlorinated chemical were similar in current employees in the two plants (128 ppb (A) and 137 ppb (B)), the levels of pentachlorinated agent differed (249 ppb (A) and 68 ppb (B)). It is of interest that 10 cases of acne and folliculitis appeared in the two plants and at least four were entirely typical of the condition. All four typical cases occurred in nine employees who had worked in a high power capacitor impregnation area of plant A where levels of pentachlorinated biphenyls were high. Their mean blood PCB was 450 ppb, a value not different from that of the five unaffected workers but certainly higher than the overall levels in the two plants. Maroni et al. also noted two cases of bleeding hemangiomas, but one had existed from birth and the only difference in his condition was that bleeding had taken place after the job started and the lesion was excised. The other patient had bleeding from the tongue and a cavernous hemangioma was discovered as well as chronic myelocytic leukemia. Case reports such as this and particularly the unusual circumstances surrounding multiple conditions in one patient in the second case make such findings difficult to interpret. The reports of chloracne appear valid and suggest a problem.

Baker et al. examined sludge users, workers in a capacitor plant, workers' families and community non-sludge users

(Baker et al., 1980). Since the sludge contained PCBs, it was felt that its use as fertilizer might seriously affect the PCB level in the blood. The level of Aroclor 1242 ranged from 7.2 to 48.6 ppb and for Aroclor 1254 from 10.1 to 26.5 ppb, with the lowest levels being found in sludge users and the highest levels in workers. No cases of chloracne or other symptoms of toxicity were noted but only two PCB values were above 200 ppb.

Smith et al. examined workers involved in the maintenance, repair and overhaul of electrical transformers and measured levels of PCBs by job (Smith et al., 1981). The mean serum levels of L-PCBs in the municipal utility workers were 11 to 36 ppb with a maximum of 59 ppb, and of H-PCBs of 6 to 24 ppb with a maximum of 74 ppb. In the privately-owned facility workers had similar values with L-PCB levels between 19 to 22 ppb with a maximum of 52 ppb, and H-PCB levels between 6 and 31 ppb with a maximum of 250 ppb. There was no significant difference in either place in the frequency of skin lesions between those with less than 10 ppb and those with greater than 10 ppb H-PCBs. There was a significant excess of symptoms of eye irritation in one and a history of bronchitis and loss of smell in the other among those with serum levels of H-PCBs greater than or equal to 10 ppb compared to less than 10 ppb. However, since these are subjective measures of disease and since workers may have been influenced to report subjective symptoms differently depending on job it is impossible to evaluate the importance of these observations.

Smith et al. reported on the physical findings and symptoms in 197 workers who manufactured electrical equipment. The serum levels of L-PCBs in the workers varied by job, with the geometric means ranging from 89 to 502 ppb, the highest levels (2400 to 3330 ppb) being found in the department where capacitors were processed, finished, and tested, and in a department that had assigned work throughout the plant. The geometric mean level of H-PCBs ranged from 22 to 91 ppb, with the highest values (150 to 250 ppb) in these departments. This plant had always used 42% chlorinated biphenyls, both Aroclor 1242 and 1016. Although there were some symptoms of skin and eye lesions (darkening of skin and nails, skin rash, and irritated eyes) that appeared to be different between the groups with L-PCB 200 ppb greater than or equal to 200 ppb compared to those with lower values, these differences disappeared when the comparisons were corrected for age and job. Thus one can conclude that symptoms were primarily related to age and job with the latter association being either real or biased. The symptoms were not related to the body burden of PCBs independent of job. No evidence of skin lesions suggestive of chloracne was found on physical examination, in spite of some extraordinarily high PCB blood levels.

In a preliminary report, Bahn (1976) indicated the incidence of cancer in 64 employees exposed to Aroclor 1254 in a research and development laboratory and 65 refinery workers

with a similar exposure from the same area. The investigator reported a significant excess in the incidence of melanoma of the skin as well as pancreatic cancer based on expected cancer rates from the Third National Cancer Survey. In a subsequent letter to the New England Journal of Medicine, Bahn et al. have reported only on the excess of melanoma (Bahn et al., 1976). When Lawrence criticized the study on the basis of the fact that individuals could have been exposed to multiple chemicals in the laboratory environment (Lawrence, 1977), Bahn and colleagues suggested that the reason for emphasizing the melanoma risk was the biological plausibility of such an association whereas an excess risk of pancreatic cancers could have indicated an association with multiple chemicals (Bahn et al., 1977).

The investigators themselves have discussed several of the flaws of this study. Information on true exposure is limited and perhaps more importantly one-fourth of the exposed workers had to be omitted. The author has also suggested that she underestimated the death ratio by including individuals during their early years of employment when there had not been a sufficiently long latency from the time of first exposure of PCB to the expected time of cancer development.

There are other problems with this study related to the identification of cases in the exposed population and the comparability of case ascertainment in the Third National Cancer Survey data. Apparently the investigators identified cases

without attempting to validate the accuracy of diagnosis. Pancreatic cancer is very difficult to recognize and diagnose. The diagnoses of the two cases need to be validated from hospital records in order to make them comparable to data from the survey. Skin cancers such as melanomas may be diagnosed in doctors' offices. Thus, the lesions could be missed in the cancer survey data where records were obtained primarily from hospitals but identified in populations with routine medical care. It would be necessary to validate the cases in this study through the use of hospital and pathology records and then to compare these cases to a comparable group of employed individuals who have had active medical surveillance by physicians.

In summary, the data on skin lesions in relation to PCB exposures have indicated a remarkable consistency. Individuals who have a body burden indicated by a blood level of 200 or more ppb PCBs have an increased risk of chloracne. There is little evidence of risk below this level and those studies that do suggest a risk at lower levels usually do not have a comparison group or they have not collected the data in a manner such that bias might be avoided. The data also suggest that typical skin lesions may occur more frequently in workers exposed to PCBs that have been heated and to PCBs that have 54% or more chlorination. Since the skin lesions occur more frequently after heating, it is possible that chloracne is actually due

to some alteration or contamination of the PCBs with more acnegenic materials such as dibenzofurans, as found in the Yusho incident. Symptoms of chloracne are reported frequently among those who use Kanechlor; this could be related to level of exposure or its high level of PCDFs relative to PCBs. Such a possibility could not be evaluated with the information in these papers. The relationship to direct skin exposure could also not be evaluated.

C. Biochemical Changes and Liver Function

Extensive studies of liver function have been included among the recent papers on PCBs. Some of these are summarized in Table 8. The early study of Meigs et al. involving a PCB leak from a heat exchanger indicated that there were no abnormalities in seven workers with chloracne except for some transient changes in liver function tests in one worker (Meigs et al., 1954). These changes could not be definitely attributed to PCBs.

The study of Hasegawa et al. of 99 workers in six industrial plants in Japan indicated that increases could occur in enzymes such as SGOT, SGPT and decreases in blood cholinesterase (Hasegawa et al., 1972). The authors regarded the changes in liver function as mild and not clinically significant. Kitamura et al. (1973) indicated that in the 13 capacitor workers the hepatic function tests were normal.

Table 8

Biochemical Studies of Enzymes and Liver Function

Study	No. Subjects		Average Dose ppb	Correlation or elevation with dose SGOT	SGPT	GGTP	AK	LDH	Bilirubin	Notes
Hasegawa et al., 1972	99	Tot.	320	+	+	N.T.	N.T.	N.T.	N.T.	cholinesterase
Kitamura et al., 1973	13	Tot.	820	hepatic function tests normal						
Guo et al., 1976	7	Tot.	>500	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	BSP abnormal in 57 percent
NIOSH 1977	7	Tot.	98.4	Norm.	Norm.	N.T.	Norm.	N.T.	Norm.	
Fischbein et al., 1979	321	Lo	124	Reported % above normal						No comparison group. No correction confounding variables
		Hi	48	2.2%	7.2%	1.9%	1.2%	2.5%	0%	
Baker et al., 1980	89 Sludge users	Tot.	Hi 17.4 (10.)	Correlations with PCB						Analyzed with non-drinkers
	18 workers		75.1 (26.5)	None	None	None	None	None	None	No other variable controlled
	19 worker fam.		33.6 (14.8)			after correction alcohol				Hi-PCB used in analysis
	22 Community		24.4 (12.8)							
Maroni et al., 1981	80	Lo	216							Hepatomegaly 80%
	Liver abnorm. 16	Hi	308	?	?	50% elev.	Norm.	?	Norm.	Significantly higher PCBs in liver cases
		Tot.	524	Positive association abnormal liver findings and PCBs ?						
	Liver norm. 64	Lo	92							
		Hi	176							
		Tot.	296							

TABLE 8 (continued)
Biochemical Studies of Enzymes and Liver Function (continued)

Study	No. Subjects	Average Dose ppb	Correlation or elevation with dose: SGOT	SGPT	GGTP	AK	LDH	Bilirubin	Notes
Chase et al., 1981	120	Tot. 33.44 Exposed (10-312) Non- T 12.0 exposed (10-27)	Pos.	None	None				Corrected for age Not other risk factor as alcohol.
Smith et al., 1981a	244	Lo 89-502 ng/ml (approx ppb)	None	None	None	None	None		Correlation include corrections
		Hi 22-51	Pos.	None	Pos.	None	None	None	
Smith et al., 1981b	47 Pub.	Lo 11-36 ng/ml	None	None	None	None	None	None	
		Hi 6-24	None	None	None	None	None	None	
	46 Priv.	Lo 19-23 ng/ml	Pos.	None	None	None	None	None	
		Hi 6-31	None	None	None	None	None	None	
Reanalysis Smith et al., 1 & 2 above	224	Lo	None	None	Pos.	None	None	None	Analysis each PCB independent
		Hi	Pos.	None	Pos.	None	None	None	
Smith et al., 1981c	47 Pub.	Lo	None	None	None	None	None	None	of other
		Hi	None	None	None	None	None	None	
	46 Priv.	Lo	Pos.	None	None	None	None	None	
		Hi	None	None	None	None	None	None	
Kreiss et al.,	458	17.2 microg./L (3.2-167.9)	N.T.	None	Pos.	N.T.	N.T.	None	

Ouw et al. tested the liver function of capacitor workers through the use of biochemical markers and found the overall test data for the group to be normal (Ouw et al., 1976). The BSP liver function test was conducted only on individuals with blood PCBs above 500 ppb; four out of seven workers were above normal levels, but it is not clear whether these values were above the range of error of the test or whether there were other factors that might have influenced the results. It is indicated that the blood PCB level and the BSP test do not correlate.

NIOSH (1977) evaluated the liver function of seven of eight workers exposed to PCBs in the manufacture of electrical equipment. The levels of SGOT, SGPT, alkaline phosphatase, and total bilirubin were normal in a group of seven workers with a mean PCB level of 98 ppb.

Fischbein et al. (1979) examined a group of 321 workers from two capacitor manufacturing plants. The workers had mean levels of L-PCBs of 124 ppb and H-PCBs of 48 ppb. A small proportion of the workers had abnormalities in the biochemical tests. Two percent had abnormally high levels of SGOT, 7% high levels of SGPT, 2% high levels of GGTP, 1% high levels of alkaline phosphatase and 3% high levels of LDH. However, there were no abnormally high levels of bilirubin. The results of this study have not been corrected for important confounding variables such

as age, alcohol intake and other diseases currently or in the past (e.g. hepatitis) that may influence these findings. There is no unexposed group for comparison. The investigators have not presented data correlating increasing enzyme levels to increasing PCB levels, which would be an appropriate method of presenting the relationship between two variables that are continuous. The study does include a comparison of the data dichotomized by two levels of SGOT, less than 50 and greater than 50 i.u. and two levels of both lower and higher homologues of PCBs. These data indicated significant differences between the proportion of individuals with high and normal SGOT levels for H-PCBs greater than 75 ppb compared to lower levels and for L-PCBs greater than 200 ppb compared to lower levels. It is not clear whether these PCB levels were selected after examining the data, in which case the conclusions would be questionable.

The 16 individuals involved in a PCB spill (NIOSH, 1980) had normal liver function tests that included total bilirubin, transaminase, alkaline phosphatase, and lactic dehydrogenase. The triglyceride changes could not be evaluated by the investigators because of inappropriate test procedures. Cholesterol levels were normal. This group had very low blood PCB levels of 6.4 ppb as a mean value, a level lower than that of non-exposed groups.

Baker et al. (1980) studied PCB levels in users of PCB-contaminated sludge as a fertilizer compared to workers in

a PCB-using facility, their families and non-sludge users in the community. The PCB level varied from 17.4 to 75.1 ppb in the four groups with the lowest level being found in the sludge users. There were no signs of changing levels of SGOT, SGPT, alkaline phosphatase, LDH or bilirubin in relation to blood PCBs in drinkers and non-drinkers of alcohol. The GGTP level correlated with PCB level in the total population but, when alcohol consumers were removed, the correlation disappeared.

Maroni et al. (1981) studied liver abnormalities in 80 workers from a capacitor manufacturing and testing plant. Sixteen workers (20%) had asymptomatic liver abnormalities. Over 80% of these had enlarged livers. Among this group the most frequent enzyme elevations were the gamma glutamyl transpeptidase (GGTP) in half the cases, the transaminases in 44% and the ornithin-carbamoyl-transferase (SOCT) in 38% of cases with enlarged livers. The mean L-PCB level was significantly higher in workers with abnormal liver findings compared to controls (215 to 92 ppb), mean H-PCB level was significantly higher (308 to 176 ppb) and total mean PCB level was significantly higher (524 to 296 ppb). The levels of PCBs in these workers are high compared to values from many of the exposures recently reported. It is interesting that the authors report that although there is an association between liver disease and PCBs there was no such association for chloracne, but the number of cases was smaller for the latter parameter.

Chase et al. (1981) examined the serum PCB levels and the biochemical markers of liver and lipid activity in 120 maintenance workers who had had varying exposures to PCBs in their work. Plasma PCBs were correlated with SGOT and, after adjusting for age, the correlation between these two variables is still significant. There is no significant correlation between plasma PCBs and GGTP or SGPT. If this correlation is correct it has occurred with levels of PCBs in the blood of exposed workers (33.4 ppb) that are lower than those found in other studies relating subclinical changes in liver function with PCBs (NIOSH, 1977). However, without corrections for other potentially confounding variables such as alcohol intake and the history of other diseases such as hepatitis, it is difficult to assess the finding.

Recently, NIOSH has completed three studies representing cross-sectional medical surveys in two groups, individuals working in capacitor manufacturing (Smith et al., 1981a) and individuals working in maintenance and repair of electrical transformers (Smith et al., 1981b). The third study combined the data from each study in an overall analysis.

In the capacitor manufacturing group there were 224 participants for whom L-PCBs and H-PCBs were determined, as well as biochemical studies. Several simple correlations were calculated and, for all those that were significant, multiple regression equations were developed using all other predictor

variables for which information was available. This included drug intake, smoking history, other biochemical markers, age, sex and others. Serum H-PCB was significantly correlated with SGOT and GGTP. There were, however, no clinical findings suggestive of liver disease and no indication that the levels of these enzymes were abnormally high. Exposures in this plant were high with plasma PCB levels being 8 to 50 times the level found in the community.

Smith et al. (1981b) have reported in the survey information on 93 individuals who were about equally distributed between a municipal electric system and a privately-owned electric utility company. The levels of H-PCBs and L-PCBs are similar in the two facilities. There were very few enzyme tests related to liver function that were significantly correlated with PCB levels. The only significant correlation was a positive relationship between L-PCBs and SGOT for the private company.

Smith et al. (1981) subsequently reanalyzed the data for the three sites presenting partial correlations for L-PCBs and H-PCBs independently without correcting the level for alternate homologues since they were closely interrelated. Under these circumstances, there is not only a positive correlation between H-PCBs and SGOT and GGTP at the manufacturing plant but also a correlation with L-PCB and GGTP. The positive correlation between L-PCB and SGOT still remained after corrections for the private utility company. Combining the data for all sites it is

noted that log SGOT and log GGTP demonstrate both significant and homogeneous trends in relation to log L-PCB level. Only log SGOT is related to log H-PCB and in this case the trend for all sites is homogeneous but not significant. In these analyses, the only confounding variables considered were age and sex for one study site whereas the analyses in the previous papers controlled multiple variables such as smoking and other diseases. Reducing the number of variables and increasing the number of subjects available for study may have accounted for the changes in the relationship with biochemical markers and symptoms to the levels of PCBs. Because of the many changes in relationship, it is difficult to indicate precisely the association between specific liver enzymes and specific homologues of PCBs. It does appear that in these studies one or more enzyme levels within normal ranges may be related to one or more types of PCBs in the blood.

In order to identify the enzyme system that is induced by the various chlorinated forms of biphenyls, Alvares et al. (1977) tested the induction of liver cytochrome P-450 and P-448 by Aroclor 1016 in rats and in workers occupationally exposed to the agent. In rats, the lower chlorinated PCB elicited a barbiturate type of effect on the oxidative enzyme system inducing cytochrome P-450, ethylmorphine-N-demethylase, and microsomal protein. Unlike Aroclor 1254, which induces both P-450 and P-448, the rats with Aroclor 1016 showed little effect on benzo(a)pyrene

hydroxylase activity, which suggests little induction of P-448 by the chemical. The tests in exposed workers were conducted by determining the half-life of the antipyrine whose metabolism is stimulated by the barbiturate class of inducing substances. The workers had a significantly shorter metabolic half-life of the drug than the controls suggesting that the Aroclor 1016 had induced cytochrome P-450.

In a study of 458 community residents in a town that had high levels of PCBs in fish, Kreiss et al. (1981) found a correlation between PCBs as measured against Aroclor 1260 and GGTP. There were no correlations with other liver enzymes. Corrections were made for several other variables such as age, sex, fish and alcohol consumption, and obesity.

In summary, the data from the studies of liver enzymes and function suggest that the populations exposed to PCBs usually do not have clinical liver disease, although in one study there was asymptomatic hepatomegaly (see Table 8). Few of the early studies allow us to separate the various homologues of PCBs in order to correlate enzyme response to level of chlorination of PCBs. Recent studies suggest that SGOT and/or GGTP are the most sensitive markers of change in the liver enzyme systems related to PCB exposure. In the studies that included extensive testing of all enzyme systems as well as characterization of the PCBs, the data have inconsistencies that do not allow us to judge clearly the level or the specific type of

PCB that is related to increased levels of specific liver enzymes. Many of the studies have not corrected for other confounding variables such as alcohol consumption. The data are suggestive that there are changes in one or more liver enzymes related to PCB exposure that are not associated with disease and may occur at levels below those at which chloracne occur.

D. Lipid Metabolism

The long-term studies of patients with Yusho disease have revealed several other abnormalities, among which were elevated blood triglycerides (Urabe et al., 1979). In recent reports of individuals exposed to PCBs, assessment of lipid metabolism has indicated some abnormalities, but in general no clinical manifestations of these abnormalities such as increased risks of cardiovascular disease have been noted. Some of these studies are summarized in Table 9.

Table 9

Lipid Studies

Study	Number Subjects	Average Dose	ppb	Correlation or elevation of lipids: Triglycerides	Cholesterol	H-Chol.	L-Chol. LDL-	Notes
Hasegawa et al., 1972	99	Tot.	3703	Decr.	Decr.	N.T.	Decr.	
Nara et al., 1973	118	Tot.	7-300	Incr.	N.T.	N.T.	N.T.	
Baumgarner et al., 1973	37	Tot.	4	N.T.	Normal	N.T.	N.T.	
Fischbein et al., 1979	321	Lo Hi	124 48	Reported as % above normal 10.5%	17.8%			No comparison with control. No correction for confounding variables
Baker et al., 1980	89 sludge users 18 workers 19 worker fam. 22 community	Tot. 17.4 75.1 33.6 24.4	Hi (10.1) (26.5) (14.8) (12.8)	Pos.	None	sl. neg. (NS)	N.T.	Compared for H-PCB only. Analyzed only on non-alcohol drinkers. No other variables controlled.
Smith et al., 1981a	224	Lo Hi	50-502 ng/ml 22-51	Neg. Pos.	None Pos.	None None	None None	Corrected for other variables

TABLE 9 (continued)
Lipid Studies

Study	Number Subjects		Average Dose ppb	Correlation or elevation of lipids: Triglycerides	Cholesterol	H-Chol. HDL-	L-Chol. LDL-	Notes
Smith et al., 1981b	47 Pub.	Lo	11-36 ng/ml	None	None	None	None	Positive correlations corrected for other variables.
		Hi	6-24	Pos.	None	).	None	
	46 Priv.	Lo	19-23	Pos.	Pos.	None	None	
		Hi	6-31	Neg.	None	None	None	
Smith et al., 1981c (Reanalyses of papers above)	Capaci-tor	Lo		None	None	None	None	Included fewer confounding variables
		Hi		Pos.	Pos.	None	None	
	Pub. ut.	Lo		None	None	None	None	
		Hi		Pos.	Pos.	Neg.	None	
	Priv. ut.	Lo		None	Pos.	None	None	
		Hi		None	None	None	None	
Kreiss et al.,	458		17.2 microg/L. (3.2-157.9)	None	Pos.	None	None	

Hasegawa et al. (1972) had noted changes in lipid metabolism of Yusho patients as manifested by decreases in the blood levels of cholesterol, triglycerides, phospholipids and beta-lipoproteins. Other studies such as that of Hara et al. (1973) on Yusho patients had noted elevated triglycerides in 55% of subjects who had blood PCBs above 50 ppb. The latter data were not corrected for any risk factors such as age or weight. Bumgarner et al. (1973) indicated normal cholesterol levels in 37 refuse workers who had a mean PCB level of 4 ppb.

Fischbein et al. (1979) has examined lipid metabolism in 321 capacitor workers. Cholesterol levels of 300 or more mg/100 ml were found in 17.8% of workers and triglyceride levels of 200 or more mg/100 ml were reported in 10.5% of the population. The total lipids were elevated (above 1 g/100 ml) in 3.4% of the population. These metabolic parameters, however, are influenced by age, personal habits, and the presence of other diseases; it is therefore essential that the data be compared to a population with similar age and sex distribution and that confounding variables be controlled before one can assess the role of PCBs in these observed changes. Since these comparisons were not made, no conclusions can be drawn from these observations.

In the study of Baker et al. (1980) in which PCB-contaminated sludge users were compared to exposed workers, their families and community controls, there was a highly significant

positive correlation of plasma triglycerides and serum H-PCB. This correlation was strengthened when alcohol consumers were removed. There was a negative corralation of HDL cholesterol with H-PCBs that was not statistically significant. The investigators suggested that the mean level of serum PCB in fasting subjects with hypertriglyceridemia was only 25.0 ppb which is lower than the levels at which this abnormality was noted in previous studies (50-200 ppb, NIOSH document). It is not clear, however, whether the other studies with higher levels have used total PCBs, whereas this study used only H-PCBs in the correlation analyses. The H-PCBs constitute 35 to 99% of the total mean PCBs in the groups. Personal characteristics may influence triglyceride levels, and many factors were apparently considered by these investigators including age, sex and drinking habits. These lipid abnormalities may be occurring at the lower PCB limits, or even below those limits reported previously.

Chase et al. (1981) in their study of maintenance workers exposed to PCBs found that levels of plasma PCBs were significantly correlated with triglycerides but not with cholesterol. Adjusting for age or length of employment does not change the significance of this correlation. The triglycerides are not significantly correlated with fat PCB levels. As mentioned previously the levels of plasma PCBs in this group of workers is low (33.4 ppb).

Smith et al. (1981a), in the study of 224 workers from a capacitor manufacturing plant, found that serum PCBs were correlated with measures of lipid metabolism. Corrections were made for relevant variables such as smoking, history of diabetes and heart disease, drug use, and others. The partial correlations indicated a significant correlation between serum H-PCB level and total cholesterol and triglycerides and a significant negative correlation of plasma triglycerides with serum L-PCB levels. When the levels of H-PCB and L-PCB were combined the correlation was positive as seen in other studies where total PCBs have been examined. There were no signs of clinical disease in relation to the elevated lipids. It was noted that several of the lipid measurements were correlated with GGTP level. As the authors suggested, this may indicate that PCBs induce hepatic microsomal enzymes, as has been found in laboratory animals and man, and these in turn may increase synthesis of specific lipids.

Smith et al. (1981b) in a health study of 93 workers divided between a public and private utility plant found correlations of lipid metabolites with PCB levels that conflicted with data from the previous study. Triglycerides were positively correlated with H-PCBs in one facility and negatively correlated with H-PCBs in the other. Both correlations were significant even after correction for multiple variables. Both triglycerides and cholesterol were positively associated with L-PCBs in only

one facility even though the levels of the biphenyls in the blood were similar in the two populations. High density lipoproteins were negatively correlated with H-PCBs in only one establishment. In this case, the other facility also demonstrated a similar negative relationship but the level of the correlation was much lower.

Smith et al. (1981c) have combined the data from these two studies and corrected the results for only age, sex and study site. Under these circumstances there were less conflicting data in the correlations. Only one significant correlation with L-PCB was noted and that was a positive correlation with cholesterol at the private utility. Both cholesterol and log triglyceride were associated with H-PCBs at the equipment manufacturing site. Triglycerides and H-PCB were positively correlated and HDL-cholesterol and H-PCB negatively correlated at the municipal utility site. Combining the data from all study sites indicated that log triglyceride was significantly associated with both L-PCB and H-PCB but the trend for all sites was homogeneous only with L-PCB. Log HDL-cholesterol was significantly and negatively associated with H-PCBs and this trend was consistent across all sites. There was no significant relationship of PCBs with total cholesterol.

Kreiss et al. (1981) have studied a community where high levels of PCBs and DDT were founds in fish. Among the 458 participants, there was a positive correlation between cholesterol

and PCBs measured as Aroclor 1260. There was no additional contribution by serum triglyceride or HDL-cholesterol to the prediction of serum PCB in multiple regression analysis.

In summary, the studies in man suggest that there is frequently a positive correlation between PCBs in blood and triglyceride levels, although there are many studies that demonstrate no relationship. The correlation is often to the higher homologues of PCBs and occurs in some cases with blood levels of H-PCB at 25 ppb or below. The data associating HDL-cholesterol and H-PCBs are not as often significantly correlated, but when they are, the relationship is negative. Lower levels of HDL-cholesterol may be an important risk factor for coronary heart disease but there is no evidence of a relationship of these lipid findings to clinical disease in these studies. The variation in the presence of lipid abnormalities in relation to PCBs in the studies and the variation in the specific lipid changes observed would suggest that there may be a confounding variable that has been ignored and that is influencing these relationships. A positive correlation of blood lipids with plasma PCB levels could in part be a consequence of the tendency of PCBs to distribute equally among all lipid pools in the body.

E. Reproductive Effects

Very few papers have addressed the problems of human reproductive effects related to PCB ingestion. The early paper

by Kuratsune (1972) on the Yusho patients had indicated that out of 11 women patients and two of the wives of patients who were exposed at any time during pregnancy, there were 10 live born and two stillborn infants and three of the live born were small for their age. The authors do not provide comparison figures on reproductive outcomes for that area of Japan so that it is impossible to assess the meaning of these figures. It is clear, however, that for all babies whose records were reviewed, skin staining and eye discharge were usually present. Kreise et al. (1981) simply indicated that there was no association of miscarriage, still birth or infant death rate independent of age effects in a study of a community with high PCB levels. In general, the data on reproductive effects from exposure to PCBs are limited.

F. Hematology and Immunology

Most of the studies of hematological effects have found no abnormalities and these observations have been made in simple statements. The studies of Kitamura et al. (1973), Bumgarner et al. (1973), Karppanen and Kolho (1973), Fischbein et al. (1979), Baker et al. (1980), and Maroni et al. (1981) have not revealed any abnormalities of hemoglobin or leukocytes. Ouw et al. (1976) reported several protein and globulin tests on exposed workers that were higher or lower than the reported normal. However, the overall levels of globulins were not different in two groups of workers with high and low exposures. In the initial abstract

relating to the Baker et al. (1980) study, the authors reported increased hematocrit and hemoglobin in relation to PCB levels controlled for age. The second complete report corrects for several other variables that may account for the difference in results. In the three reported studies of Smith et al. (1981), the investigators looked at red cell count, white cell count, hemoglobin and hematocrit and found no significant correlation with either L-PCB or H-PCB when corrected for confounding variables. In the latter studies they have also examined the correlation of total protein, albumin and the various globulin fractions and found no significant correlations after correcting for other factors.

In general, there are no recent studies that suggest abnormalities of the heme system in man related to levels of PCBs. In addition, the Smith et al. (1981b) study of workers in electrical utilities showed no significant variation in PCBs related to urinary porphyrins, porphobilinogen or 17-ketosteroids or 17-hydroxysteroids.

G. Other Factors

Kreiss et al. (1981) in the study of a PCB-exposed community found increased diastolic blood pressure to be correlated with PCB levels even after the correction for other variables. No comparison data for a control group were given. The study of workers in the equipment manufacturing plant also demonstrated