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 dreft 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 concantrations 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 Arocior 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 hepatocelluler 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 affect 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.

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	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
...ocinalli	(1954)			5200-6800							
...nagnan	(1972)	Plant	A (PCB Mfg.)	50- 200							
		"	B	100- 500							
		"	D	500- 700		99	370	60- 920			
		"	E	200-1700							
		"	F								
...equenon	(1972)			< 1000		12	440	110-1900	3	360	160-635
...tsuura	(1973)					13	820	320-2100			
...er	(1976)			320-2220	Yes	34	~ 400	Tr.-1200			
...chbein	(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				
...liff	(1981)			As Above		26	L- 83 H- 19	2-1412 1-60	26	L-24 H- 6	2-271 .2-19
...ann	(1981)			24- 393 170-1260							
...ith	(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)

Reference		PCB Concentration In Air ug/m³ Range	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	(1981)		Yes	86	33.4	10-312	36	5.6	1.0-21.6
ocomotive repair)				15	14.2	10- 30	5	1.4	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 times 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.