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ASSESSMENT OF THE HUMAN RISKS TO PCBs ASSOCIATED WITH THE EXPECTED ENVIRONMENTAL EXPOSURES

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During the past decades, a combination of "open" systems and sloppy or illegal disposal practices have resulted in the release of large quantities of chemicals into the environment. In the late 1960s, when it became apparent that persistent chlorinated hydrocarbon polychlorinated biphenyls (PCBs) were ubiquitous environmental contaminants which took years to biodegrade, attention was focused on their potential to bioaccumulate to what was believed to be toxic levels in animals and humans. As a result, questions arose regarding the chronic side effects caused by long-term exposure to these chemicals. Reflecting public concern, Congress enacted the Toxic Substances Control Act in 1976, which mandated a phaseout of PCB manufacturing and use. At that time, PCBs were considered a highly toxic and dangerous chemical because of their environmental persistence and their potential for causing permanent adverse health effects, such as cancer. In recent years, however, a substantial increase in scientific data has resulted in a better understanding of both the actual effects of human exposure to PCBs and the chemically-induced processes leading to cancer.

While it was appropriate a few years ago to act on the premise that all potentially carcinogenic chemicals represented similar hazards, recent experience has shown that there are important theoretical and practical differences in the actual hazard each "carcinogen" represents to public health. Similarly, there has been a substantial increase in the amount of data reflecting the toxicity of PCBs in animals and humans. Considering the national concern expressed for environmental contaminants, and in particular for PCBs, it seems both appropriate and necessary to reevaluate the hazard and risks posed by PCBs now that we have more information.

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It is the purpose of this paper to provide a framework for identifying the important toxicological considerations used in interpreting the risks inferred by toxicity data, as well as to provide a discussion on the PCB data within this framework so as to arrive at an assessment of the risk to human health.

DEFINITIONS AND BASIC PRINCIPLES OF ASSESSING RISKS

A toxicant is a chemical agent that can produce an adverse effect in a biological system. Such an adverse effect may be an alteration of normal function or destruction of life. This definition is broad since all chemicals are toxic at some dose, i.e., all chemicals are capable of altering some function or producing death in some biological organism. While this statement may seem obvious, it serves to emphasize the basis of risk assessment, i.e., those circumstances and conditions under which an adverse effect can be produced. As Emil Mrak stated years ago, "there are no harmless substances; there are only harmless ways of using substances." A chemical is toxic and produces harm only within prescribed conditions of usage.

Risk is defined as the probability that a substance will produce harm under specified conditions (1); i.e., it is a practical consideration to determine whether or not some harm will be elicited from a specific chemical exposure. Safety is the reciprocal of risk, or the probability that a substance will not produce harm under the specified conditions. Thus, when determining the risk or safety of a chemical, the critical factor is not necessarily the intrinsic toxicity of the chemical per se, but the likelihood that the level of exposure to the chemical is sufficient to express its intrinsic toxicity.

PCB-ARCH-EXT0371949

In general terms, then, the risk is approximated by the equation:

$$R = T \times E$$

where R is risk, T is toxicity, and E is exposure. More accurately, the equation for risk is equal to the toxicity as a function (f) of the exposure, or:

$$R = Tf(E)$$

This better defines the extrapolation, since under certain conditions the risk is not always linear over the entire dose-response curve; and since, depending on how one defines function (f), threshold or nonthreshold dose-response curves may be fitted to this equation. However, regardless of how one chooses to express the risks to chemical exposure, it is clear that: (a) the actual risk is dependent upon both the toxicity (i.e., hazard) and the exposure (i.e., amount of chemical) and (b) to change either alters the risk. Therefore, to make a risk assessment, one must compare the exposure probability with the various dose-response curves for each toxicity to determine whether or not a harmful response is likely to be induced.

In evaluating the risk associated with exposure to PCBs, we will attempt to answer two questions. First, is the level of exposure of a sufficient magnitude such that a hazard exists? Second, if so, what is the hazard or undesirable response expected for that level of exposure. To answer both questions it is necessary to first evaluate the hazards associated with PCBs; i.e., what are the toxic responses and at what levels of exposure will they occur?

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Many aspects must be considered and weighed before the hazards to humans associated with PCB exposure can be evalauted. An evaluation of the human hazard and subsequent risk estimation for any chemical must address the data base utilizing thorough comparative toxicologic assessments. This means that the animal and human data available must be carefully considered in terms of: (a) the breadth and variety of the toxic responses manifested; (b) the degree of species variation or species consistency in the effects monitored; (c) the possible and/or proposed mechanisms of toxicity; (d) the validity of the tests performed and their relevance for extrapolations to man; (e) the dosage used in animal tests versus the expected level of human exposures; and, finally, to the extent that the data are available, (f) the outcomes of serious poisonings and long-term occupational exposures as a guide to the expected human consequences and as a test of the extrapolations made from animal data. Only when a consistent pattern of toxicity in animals coincides with human experiences can accurate and safe guidelines be promulgated.

The following sections of this chapter will discuss the hazard associated with PCB exposure as interpreted from the animal and human data; the choice and use of risk assessment models to define the risk to PCBs from various environmental exposures; the accuracy with which the health risks for a PCB exposure can be estimated at the present time; and the conclusions reached by this study.

EVALUATING THE ACUTE HAZARD ASSOCIATED WITH PCB EXPOSURE FROM ANIMAL DATA

Several reviews of the mammalian toxicity of PCBs have been published within the last decade (2-7). Since much of this

PCB-ARCH-EXT0371951

information has already been given in the previous chapters, a cursory summary rather than an exhaustive review is provided here. This summary presents the types of hazards to be expected and documents the extrapolations one might make to the high exposure human situation based on the animal data. It must first be stated that PCBs have a low order of acute toxicity as measured by the median lethal doses (to 50% of the population) (LD_{50}s) for rodent species. As shown in Table 1, the median lethal doses for various commercial PCB mixtures lie between 1.3 and 19.2 g/kg of body weight. Median lethal doses as high as these classify PCB mixtures, especialy the higher chlorinated mixtures, as only slightly toxic chemicals (1).

PCBs produce a variety of physiologic changes in animals. For example, in the liver, PCBs increase the amount of endoplasmic reticulum, resulting in enlarged hepatocytes and thereby increasing liver size and weight. Higher doses can cause liver damage and necrosis. PCBs applied directly to the skin of rabbits have produced hyperkeratosis, erethyma, blisters, and desquamation. In primates, oral doses of PCBs have led to facial edema, hair loss, and acne-like pustules, as well as prolonged menstrual cycles and increased bleeding in female animals. Additional symptoms reported in various species include gastric hyperplasia, decreases in red and white blood cells, atrophy of the thymus and spleen, and increases in serum levels of phospholipids, triglycerides, and cholesterol.

However, as with lethality, the doses required to cause these acute effects are generally high. The doses required to cause subchronic effects can also be considered high when the slow rate of metabolism, and therefore a tendency to bioaccumulate, is taken into consideration. While a number of effects have been reported for PCBs,

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Table 1

MEDIAN LETHAL DOSES FOR VARIOUS COMMERCIAL PCB MIXTURES

Species	Commercial Brand of PCBs	LD_{50} (mg/kg body weight)
Mouse (oral)	Aroclor 1254	2,000
	Kanechlor	>1,875
Rat (oral)	Aroclor 1221	4,000
	Aroclor 1232	4,500
	Aroclor 1242	8,700
	Aroclor 1248	11,000
	Aroclor 1254	4,000-10,000
	Aroclor 1260	10,000
	Aroclor 1262	11,300
	Aroclor 1268	10,900
	Aroclor 4465	16,000
	Aroclor 5460	19,200
Rabbits (skin)	Aroclor 1221	3,200
	Aroclor 1232	2,000
	Aroclor 1242	1,300
	Aroclor 1248	1,300
	Aroclor 1260	1,300-2,000
	Aroclor 1262	1,300-2,000
	Aroclor 1268	2,500

PCB-ARCH-EXT0371953

those of the liver (i.e., enlargement and necrosis) are the most consistently reported, as are those of the skin (i.e., chloracne or dermatitis). These physiologic responses observed in the liver and skin are fairly predictable effects of many chlorinated compounds.

In assessing the acute and subchronic tests of animals, PCBs do not appear to be remarkably toxic chemicals. The dermal irritation caused by PCBs is not an unusual physiologic response for an organic, solvent-like chemical. The chloracne observed in animals and humans is also a frequently observed effect of other chlorinated chemicals and is reversible in cases where PCBs are the only suspect agent. The observed liver effects (i.e., increased liver weight, proliferation of endoplasmic reticulum, deposition of fat, cell death, and tissue necrosis) are common responses to persistent, chlorinated hydrocarbons, which in general are enzyme inducing agents at lower doses and hepatotoxins at higher doses. Many other chemicals share one or both of these characteristics. While enzyme induction may increase the toxicity of some chemicals and lower the dose producing toxicity, this is not a general phenomenon. In many instances, an increase in metabolism decreases the toxicity of other chemicals. Similarly, inducing agents often increase other routes of biotransformation that detoxify toxic chemicals. In fact, enzyme induction is sometimes used therapeutically. Therefore, induction by itself cannot be considered a toxic response, nor can its consequences be accurately predicted in humans.

In monkeys, PCBs cause a conversion of the gastric epithelium that can be described as a dysplastic growth pattern. This does not constitute a neoplastic transformation (39). While PCBs have been reported as inhibiting the immune system in mammals, this occurs at high doses at which general toxicity leads to a reduced food intake

PCB-ARCH-EXT0371954

and thus a reduced nutritional status. In some test species, PCBs produce changes in reproductive performance, but again usually at high doses. In monkeys, this problem occurs only with the female animals and at doses clearly producing general toxicity and signs and symptoms of intoxication. Reproductive dysfunction during chemical intoxication is not a particularly unusual finding. Therefore, it is concluded that the acute toxicity of PCBs in animals is not particularly remarkable, nor does the chemical represent an unusual acute hazard.

CHRONIC EFFECTS OF PCBs

Mutagenicity

A genotoxic chemical is any compound capable of inducing a permanent, inheritable change in the genetic composition of a cell. Genotoxic effects are divided into three types, depending on the cellular level of the genetic lesion. Mutagenesis refers to mutations or structural changes at the DNA level, called microlesions (1). The other two types of genotoxic effects are: clastogenesis, which refers to structural changes at the chromosomal level, and aneuploidization, which refers to a change in chromosomal number. Both clastogenesis and aneuploidization can alter the amount or expression of genetic material; both types of changes are referred to as macrolesions (1). For the sake of discussion, all genotoxicity tests are referred to in this paper as mutagenicity tests.

The "Ames test," which uses mutant strains of the bacteria Salmonella typhimurium that have lost the ability to synthesize their own histidine, is probably the most popular and best known test for

PCB-ARCH-EXT0371955

mutagenic activity. Since this amino acid is important to protein synthesis, and therefore growth, these cells can grow only if histidine is added to the culture medium. A chemical mutagen can be identified by a mutation in the locus of the histidine defect which reverts the bacteria to the normal state, thus allowing easily identifiable bacterial colonies to grow in a histidine-deficient medium.

Wyndham and co-workers (8), using the Ames assay, tested the several chlorinated biphenyl mixtures and reported that they were weakly mutagenic. A review of their data indicated that 4- chlorobiphenyl had significant activity. Yet, Aroclor 1221, which has a chlorine content of 1.15 chlorine atoms per molecule and is therefore largely a monochlorobiphenyl mixture, showed a greatly reduced activity. This would seem to indicate that either the "heavier" PCB molecules were inhibiting mutagenicity or that the activity is greatest for the 4-chloro-isomer of the monochlorobiphenyl compounds. The test results for the polychlorinated biphenyl compounds 2,2',5,5'-tetrachlorobiphenyl and Aroclor 1268 seem to indicate no substantial mutagenic activity. Subsequent attempts to reproduce the Wyndham et al. results have failed (9-13) (see Table 2). The majority of assays discount any suggestion that PCBs or monochlorobiphenyl are mutagenic in the Ames assay.

Several studies have demonstrated that PCBs lack the ability to damage or alter chromosomes. Green et al. (14) looked for significant chromosomal damage in the bone marrow and sperm cells of rats administered the following dosage regimens: a single dose of Aroclor 1242 at 1250, 2500, and 5000 mg/kg; or 500 mg/kg per day for five days. Even though some of the animals demonstrated definite signs of intoxication, there was no evidence of chromosomal abnormalities. These findings are consistent with the results reported by Dikshith et al.

Table 2

PCBs: TABULATION OF MICROBIAL MUTAGENICITY TESTS

Product \ Tester Strain	S. typhimurium										E. coli	
	C3076	D3052	G46	TA98	TA100	TA1000	TA1535	TA1536	TA1537	TA1538	WP2	WP2uvrA⁻
Aroclor 1268	--	--	--	--	--	--	--	--	--	Neg.	--	--
Aroclor 1254	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	--	Neg.	Pos./ Neg.	Neg.	Neg.
Kanechlor 500	--	--	--	Neg.	Neg.	--	--	--	--	--	Neg.	--
2,2',5-5-tetrachloro-biphenyl	--	--	--	Neg.	Neg.	--	Neg.	--	Neg.	Neg.	--	--
Kanechlor 300	--	--	--	Neg.	Neg.	--	Neg.	Neg.	Neg.	Neg.	Neg.	--
Aroclor 1221	--	--	--	--	--	--	--	--	--	Pos.	--	--
4-chloro-biphenyl	--	--	--	--	--	--	--	--	--	Pos./ Neg.	--	--

Source: reference 13.

PCB-ARCH-EXT0371957

(15) or Garthoff et al. (13) in rats and the study reported by Hoopingarner et al. (16) using cultured human lymphocytes. Heddle and Bruce (11) reported that Aroclor 1254 was negative in the micronucleus test, which measures clastogenic activity (chromosomal breakage) by measuring chromatin bodies in red blood cells. Green et al. (17), using the dominant lethal test, which measures mutagenic events in germ cells by the embryotoxicity it induces, reported that Aroclor 1242 and Aroclor 1254 gave negative results in rats. Keplinger et al. (18) and Calandra (19) also reported a similar lack of mutagenic activity in mice using the dominant lethal test.

Levinskas (13) has recently reviewed the mutagenicity data for PCBs. Besides the above-mentioned tests, Levinskas discusses many additional, though in several cases less often used, procedures. In his review he refers to a study by Odashima in which Kanechlor 300 and 500 were negative in the standard strains of Salmonella typhimurium used in the Ames assay, as well as several additional bacterial strains. However, Kanechlor 300 was reported positive in one or more of four additional strains, while Kanechlor 500 was listed as negative.

On the basis of sedimentation rates, Stadnicki et al. (13) have reported that the epoxide of tetrachlorobiphenyl caused single-stranded chromosomal breaks in the DNA of L-929 cells at concentrations ranging from 1 µg/ml to 100 µg/ml. A mixture of two hydroxy metabolites, and to a lesser extent tetrachlorobiphenyl, caused some damage at 20 µg/ml and significant damage at 100 µg/ml. The significance of this test at these high in vitro concentrations is questionable.

Using Drosophila melanogaster and Bombyx mori as the eukaryote test species, neither the French PCB mixtures, Clophen 30 and Clophen

PCB-ARCH-EXT0371958

50, or the Japanese mixtures, Kanechlor 300 and 500, were mutagenic. Odashima (7, 13) studied chromosomal aberrations in Yoshida sarcoma cells at PCB concentrations causing 50% growth inhibition: Kanechlor 300 gave a positive response and Kanechlor 500 a negative one. Odashima reported cytogenetic analysis of bone marrow cells in mice exposed to PCBs at a near lethal dose. This test gave paradoxical results. Odashima listed exposure to Kanechlor 500 as positive and exposure to Kanechlor 300 as negative (7, 13).

Norback et al. (13) reported that Aroclor 1254 transformed C3H10T11/2 cells to Type III foci after six weeks of continuous exposure to 10 ug/mL of Aroclor 1254, while a concentration of 1 ug/mL was negative. Norback and co-workers suggested that the effects of PCBs in culture include promotion. In contrast to this study, Pienta (13) reported Aroclor 1254 as negative in the Syrian hamster cell transformation test.

Peakall (13) reported chromosomal aberrations in doves fed a 10-ppm diet of PCBs. The frequency changed from 0.8% in controls to 1.8% in treated birds. The average rate of chromosomal aberrations among treated eggs was higher than the highest control value in only 4 of 17 pretreated embryos. In contrast, PCBs injected into white Leghorn eggs up to concentrations of 20 ppm, while toxic, were not clastogenic.

A thorough review of the mutagenicity tests reveals that PCBs gave primarily negative responses. While some positive results were reported, these were largely in vitro tests and for the Kanechlor brands, which gave inconsistent and mixed results for the 300 and 500 brand mixtures. The relevance of some of the in vitro tests that found positive scores only at concentrations of 10 ug/mL or greater

(very high and unlikely in vivo concentrations) is questionable. This interpretation is supported by the fact that in many cases a similar experiment gave correspondingly opposite, i.e., negative, results. According to Levinskas, "considering the large number of tests conducted, it is not surprising that an occasional suspicious positive finding resulted, simply on a statistical basis" (13). A comparison of the number of Ames tests unable to reproduce the results of Wyndham et al. (8) supports his contention.

It is the consensus of this review that PCBs do not represent a significant mutagenic risk to humans; a fact borne out and reinforced by the numerous negative carcinogenic studies of PCBs in animals.

Teratogenicity

A teratogen is an agent that produces congenital defects. Although teratogenic responses are generally identified by definite anatomical defects in the offspring, authorities also regard functional or biochemical changes as evidence of teratogenicity.

An important consideration in evaluating teratogenicity data, sometimes referred to as "Karnofsky's rule," is that "any compound administered at the proper dosage, at the proper stage of development, to embryos of the proper species, will be effective in causing disturbances in embryonic development." What Karnofsky's rule calls attention to is the fact that maternally toxic doses capable of killing the fetus or producing teratogenic effects in the offspring are of much less concern than those chemicals causing the same effects at doses far below a maternally toxic level. If the pregnant female is made sick, then the delicate balance between mother and fetus is likewise affected or disrupted and an adverse fetal effect can be expected.

PCB-ARCH-EXT0371960

Depending on the stage of the fetus, this disruptive pressure can be manifested in many ways. For example, disease, malnutrition, and stress have all been shown to produce changes in the number and quality of offspring produced. Even reversible acute effects on the mother's central nervous system, though of short duration, may disrupt feeding enough to cause undesirable responses in the unborn. Therefore, fetotoxicity is of most concern only when it occurs at doses far below those eliciting toxicity in the mother. In any study, neither death of the fetus (i.e., fetotoxicity) nor a smaller birth size are equated with birth defects (i.e., teratogenicity).

The studies concerned with the teratogenicity of PCBs in mice are contradictory. Toeruek (20) reported that PCBs are not teratogens in mice at dosages up to 500 mg/kg. However, more recent studies have revealed chemically-induced effects in the fetus or in newborns at lower doses. Watanabe and Sugahara (21) injected mice with Kanechlor 500 at dosages approximating 36 to 182 mg/kg/day on days 6 through 15 of gestation. At the higher doses, the pregnancy rate declined to one third of the control values, the number of resorbed fetuses doubled, and the rate of fetal cleft palates reached 5.8%. The authors stated that since there was no change in maternal or fetal weight gain, the PCBs used had a specific teratogenic effect not due to general maternal toxicity. However, their own results do not support this contention. At the higher dosages, the maternal mortality was higher than the rate of cleft palates among the newborn (12% vs. 6%). Also, the authors noted skin lesions, alopecia, and enlarged livers in the dams, indicating significant chemical intoxication.

Marks et al. (22) reported teratogenic effects for the specific chlorinated biphenyl compound 3,3',4,4',5,5'-hexachlorobiphenyl.

PCB-ARCH-EXT0371961

At dosages of 2 to 16 mg/kg/day given on days 6 through 15 of gestation there were significant increases in the percentage of resorptions and fetal malformations. Liver damage occurred in the dams and consisted of single-cell centrolobular necrosis and microabscesses. The fetal livers had even a more pronounced injury, including massive necrosis and the formation of tubule-like pattern of hepatocytes.

Tilson et al. (23) reported that 32 mg/kg/day of the 3,3',4,4'-tetrachlorobiphenyl, when given on days 10 through 16 of gestation, induced signs of neurotoxicity in the offspring. Some of the newborn were labeled "spinners" because of their increased motor activity and episodes of head bobbing and rotational movements. The spinners had decreased forelimb grip strength and all treated animals had difficulty in crossing wire rods. Subsequent studies (24) revealed that this exposure level of tetrachlorobiphenyl significantly altered the dopamine binding sites and the dopamine levels in the corpus striatum of newborn mice.

Contrary to Marks et al. (22), Mattsson et al. (25) reported that doses of approximately 50 mg/kg/day of 2,2',4,4',5,5'-hexachlorobiphenyl did not increase the resorption frequency, and no fetal effects were noted other than enlarged livers. Likewise, Gellert and Wilson (26) reported that no reproductive effects were seen in the offspring of mice exposed to Aroclors 1221, 1242, and 1260 at dosages of 30 mg/kg/day on days 14 through 20 of gestation.

Rats have also been extensively studied using dosages up to 100 mg/kg per day. Although these studies indicate that fetotoxicity increases with dose, no teratogenicity has been reported (18, 19, 27-29).

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Malformations (terata) have been reported in dogs and pigs in an abstract by Earl et al. (30). However, the dosages of PCBs used resulted in a severely reduced food consumption in both the dogs and pigs and the authors reported that there may have been an underlying genetic defect that contributed to the teratogenic response in dogs (39).

Several studies have been published using monkeys as test species (31-34). For six females fed 25 ppm of PCBs for two months, conception was inhibited (31). Of the six, only one was able to give birth; all female animals were clearly intoxicated and one died. A second study (32) tested 18 female animals fed diets of 2.5 or 5.0 ppm of Aroclor 1248. After seven months' exposure, the eight survivors from each dosage level were bred. All animals on the low-dose diet conceived. There were three resorptions and five births. Of those animals given the higher dose diet, one resorption, three abortions, one difficult delivery and subsequent death, and one normal birth occurred. All newborns were small in size and showed hyperpigmentation, but were otherwise normal (32).

In a number of species (e.g., mice, rabbits, rats, and monkeys), PCBs showed no or contradictory teratogenic activity. The study conducted by Earl et al. (30), still unpublished, provides unconvincing data since it is possible that the malformations observed in the offspring were the result of severe maternal malnutrition. This conclusion was substantiated by Hansen et al. (35), who failed to find teratogenic effects in pigs when the mothers were fed a diet of 20 ppm of Aroclor 1242 during gestation and nursing.

PCBs have produced contradictory results in mice. Tests conducted by Marks et al. (22) and Tilson and coworkers (23, 24) indicate that the recorded effects are seen only with symmetrically chlorinated

PCB-ARCH-EXT0371963

biphenyl compounds and that chlorination in the three and four positions is critical. This may explain why Toeruek (20) and others (25, 26) saw no or lesser effects with mixtures containing small amounts of the specific isomers or with other hexachlorobiphenyl isomers at higher doses. However, studies by Biocca et al. (36), like the negative data, greatly lessen the impact of the teratogenic findings in mice. These authors demonstrated that the 28-day LD_{50} for 3,3', 4,4',5,5'-hexachlorobiphenyl is about 19 mg/kg/day (ranging between 11 through 33 mg/kg/day). Moreover, extending the observation interval to 50 days, it was found that the dosage levels 10 times lower caused 100% mortality. Disposition studies revealed that the toxicity of the isomers was related to tissue accumulation and that for the 28-day interval the adipose tissue levels at the LD_{50} dosage were approximately 2,000 ppm. These data reveal that the teratogenic effect seen by Marks et al. (22) occur at doses greater than those that allow for chronic survival. This is consistent with the findings of Watanabe and Sugahara (21) for which the teratogenic effects of PCBs in mice appear at doses of significant maternal toxicity and lethality. In summary, then, the animal data do not indicate that PCBs represent a significant teratogenic risk at doses not causing significant maternal toxicity. Furthermore, the data suggests that preventing subchronic lethality or chronic organ toxicity would prevent teratogenic effects. Thus, the risk to humans is expected to be minimal, considering the much lower doses that humans are generally exposed to in the environmental and the apparent lack of toxicity expected at these doses.

Studies in animals similarly demonstrate that PCBs represent a minimal reproductive and fetotoxic hazard (38, 39). While effects on reproduction or fetotoxicity have been reported, the doses causing such effects are generally high. Rats are fairly resistant, while

PCB-ARCH-EXT0371964

minks seem to be particularly sensitive. Aulerich and Ringer (40) reported that minks fed 2 ppm Aroclor 1254 in their diets had decreased reproductive success. The effect at this level was specific for Aroclor 1254 and was not seen for Aroclors 1016, 1221 or 1242. The reproductive impairment was not permanent and consistently occurred at maternally lethal doses. Orberg (37) has demonstrated an increased metabolism of progesterone, estradiol, and testosterone in animals pretreated with PCBs. It may be proposed, then, that doses that greatly increase the metabolism of important hormones could alter the normal hormone homeostesis and result in reproductive problems.

The series of studies by Allen and co-workers (31-34) have demonstrated that PCBs may disrupt menstrual cycles and significantly alter reproductive success in monkeys. However, the doses used were clearly maternally toxic, fetotoxic, and toxic to the offspring. Studies similar to those in mice indicate that the body burdens in monkeys at the time of death are quite high (41). Since (a) high, maternally toxic or lethal doses were generally required, (b) there are a number of negative studies, (c) the general human environmental exposure is very low, and (d) no reproductive problems in humans have been associated with exposures to PCBs only, PCBs do not appear to represent a significant reproductive risk to humans at the low exposure levels generally occurring via the environment (39).

Carcinogenicity

The carcinogenicity of PCBs has recently been reviewed by several authors (6, 7, 13, 38, 39). The following paragraphs provide a summary of the data. Studies reporting the tumorigenicity of PCBs are

PCB-ARCH-EXT0371965

listed in Table 3. While many investigations have been conducted, rodent studies have inconsistently reported a significant increase in hepatocellular carcinoma. Ito et al. (42) reported hepatocellular carcinoma in mice after 12 months' exposure to a diet of 500 ppm of Kanechlor 500. Kimbrough and co-workers (43) also reported hepatocellular carcinoma in female rats fed 100 ppm of Aroclor 1260 for 21 months.

However, contrary to these findings, many similar studies have shown no ability of PCBs to produce cancer. Kimbrough and Linder (44) found that 300 ppm of Aroclor 1254 failed to produce hepatocellular carcinomas in mice after 11 months. Studies using less chlorinated Kanechlors were similarly unable to produce cancer (13). Likewise, Calandra (19), Levinskas (13), and the National Cancer Institute (NCI) (45) have reported tests on both Aroclor 1254, Aroclor 1260, and HCB in rats at doses up 100 to 200 ppm; none were found to be carcinogenic. Calandra (19) has also reported a two-year study of dogs given doses of 1, 10, and 100 ppm that was negative. Studies of rhesus monkeys were also negative (39, 46).

PCB mixtures present a distinct problem when attempting to estimate the cancer hazard, and therefore the cancer risk, to humans based on data developed in rodent studies. The crux of the problem is the relevance placed on an increase in rodent liver tumors when interpreting the human risk. This dilemma is actually twofold.

First, there has been controversy over the relevance and nomenclature of rodent hepatic lesions. Some of this controversy relates to the criteria used to diagnose cancer. The NCI has recommended a scheme for the classification of hepatocellular tumors and related lesions in rats (47). This recommendation has not been universally accepted, and is used in only some of the reports of PCB carcinogenesis.

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Table 3

TUMORIGENIC EFFECTS OF PCBs

Authors	Year	Species	Compound, Dosage	Effects
Kimbrough et al.	1972	Rats	Aroclors 1248, 1260, and 1254: 100 ppm/52 weeks	Hypertrophy
Nagasaki et al.	1972	Mice	Kanechlors 300, 400, and 500: 500 ppm	Hepatomas induced by Kanechlor 500 only
Allen & Abrahamson	1973	Rats	Aroclors 1248, 1254, and 1262: 0.1%/6 weeks	Hypertrophy; regressive changes
Ito et al.	1973	Mice	Kanechlor 500: 500 ppm/ 32 weeks	Nodular hyperplasia and well differentiated hepatocellular carcinomas in the liver, PCBs increased hepatic neoplasms in mice and increased the tumors induced by BHC
Allen & Norback	1973	Rhesus monkeys	Aroclor 1248: 300 ppm/ 3 months	Hyperplasia and dysplasia of gastric mucosa with invasion of adjacent tissues
Kimura & Baba	1973	Rats	Kanechlor 400	Neoplastic nodules
Borsa et al.	1974	Rats	Aroclors 1242 and 1016: 100 ppm/10 months	Liver cell necrosis
Ito et al.	1974	Rats	Kanechlors 500, 400, and 300: 1000 ppm	Nodular hyperplasia
Kimbrough et al.	1974	Mice	Aroclor 1254: 300 ppm/ 11 months	Hepatomas; adenofibrosis
Makiura et al.	1974	Rats	Kanechlor 500: 0.5% PCBs	Inhibited the induction of liver tumors by several liver carcinogens
Nagasaki et al.	1974	Mice	Kanechlors 500, 400, and 300: 500 ppm/32 weeks	Hepatocellur carcinoma only for Kanechlor 500
Kimbrough et al.	1975	Rats	Aroclor 1260: 100 ppm/ 21 months	Hepatocellular carcinomas 26/184; hyperplastic nodules 146/184; adenofibrosis

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Table 5 (Cont.)

Authors	Year	Species	Compound, Dosage	Effects
Kimura et al.	1976	Rats	PCBs	Anti-promoters in experimental carcinogenesis
Wasserman et al.	1978	Rats	Aroclor 1254: 200 ppm/ 28 months	Hepatocellular adenomas
Levinskas	1981	Rats	Aroclors 1248, 1254, and 1260: 100 ppm/24 months	Nodular hyperplasia; hepatoma

Source: reference 38.

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The NCI classification scheme is extensive and specific in defining neoplastic lesions. It was concluded by NCI that benign hepatic cell tumors (i.e., tumors without the potential for malignant behavior) could not be diagnosed consistently. Therefore, a term such as "adenoma," which refers to a benign tumor, was not recommended. It was also determined that the term "hepatoma," used to denote a benign liver tumor, was imprecise and thus was not recommended to describe any of the lesions under discussion. Contrary to tradition, then, detection of vascular invasion or metastases was not considered by NCI to be essential for the diagnosis of hepatocellular carcinoma. Instead, the use of inclusive cytological criteria describing changes that may or may not have the potential to become the disease process we call cancer, including many responses that will never progress to cancer, was accepted at the expense of the more definitive criteria of malignant or invasive neoplasms. Thus, it seems that the criteria for establishing liver cancer may vary among pathologists.

Only PCBs with a chlorine content of 60% produced cellular morphological changes in rat liver that were classified as hepatocellular carcinoma using NCI guidelines. However, this same PCB mixture was tested in another strain of rat and did not significantly increase the incidence of tumor formation. Several other studies also failed to show any PCB-induced tumors, including a study performed by NCI. Since there is only one report of PCB-induced hepatocellular carcinoma in rats, we must weigh this single report against the majority of tests, which were negative.

As previously stated, the use of inclusive cytological criteria will define as cancer some hepatocellular changes that will never progress to cancer. Furthermore, the liver changes associated with

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PCB exposure were reported to regress after the animal has been removed from the chemical exposure (48). While some investigators have used the inclusive cytological criteria for classifying hepatocellular lesions, other investigators feel this classification scheme lacks sufficient diagnostic discrimination. Thus, the single report of PCB-induced cancer in rats may use a pathological description that differs from the terminology used for describing the benign tumors seen in the other studies.

The second problem stems from the need to determine the mechanism by which a chemical induces cancer. Chemically-induced carcinogenesis is a special aspect of toxicology, since chemical carcinogens may or may not obey traditional toxicologic principles. For example, although carcinogens show dose-response relationships, may undergo biotransformation to active or inactive metabolites, and demonstrate specific structure activity relationships as other toxicants do, they may also be unlike other toxicants: they may not demonstrate thresholds and there may exist a long and indefinite latency period between the critical biochemical effect and any cellular or physiologic expression.

In recent years, the scientific community has concluded that even among chemical carcinogens there are vast differences in the mechanisms by which cancer is induced. Chemical carcinogens can be separated into two groups: one which obeys traditional toxicologic principles and one which does not. Weisburger and Williams, in Casarett and Doulls' Toxicology: The Basic Science of Poisons (1), separate carcinogens as either genotoxic (initiator) or epigenetic (promoter), the distinction being that genotoxic carcinogens induce cancer by initiating a permanent change in DNA. Epigenetic chemicals comprise

those chemicals which alter the manifestation of cancer by other than genetic means and include hormones, immunosuppressants, cocarcinogens, and promoters.

This distinction between types of carcinogens is extremely important (1, 49, 50), since initiating (genotoxic) carcinogens may cause irreversible damage and may not have thresholds. The concept was generally proposed for all carcinogens early in the last decade and was the basis for developing certain nonthreshold risk assessment models for which some risk is present at any level of exposure. On the other hand, chemical carcinogens that promote cells already predisposed to cancer do have demonstrable threshold levels. Therefore, the risk associated with promoters differs from initiators at low doses in that the risk exists only for the duration that the level of the promoter exceeds the threshold.

Rodents used in cancer tests have a high spontaneous incidence for liver tumors. Therefore, if a statistically significant increase is seen after chemical exposure, it is important to determine whether or not this phenomenon represents true initiation or merely promotion of the background incidence. Such is the problem for PCBs. To make the distinction between initiators and promoters, the mutagenicity data and other characteristics of the chemical or the carcinogenic response become critically determinant factors.

Initiators are defined as those agents producing damage to DNA which permit cell survival but predispose the cell for uncontrolled growth. Therefore, initiators must possess significant mutagenic activity. There are several other characteristics separating initiating carcinogens and promoting agents; these are listed in Table 4. The characteristics of PCBs are also listed in Table 4. It can be

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Table 4

CHARACTERISTIC EFFECTS OF CHEMICAL CARCINOGENS UPON TISSUE

Effect	Initiators	Promoters	PCBs
Chemical produces increases of spontaneous tumors at multiple sites.	+	-	-
Chemical increases malignancy.	+	-	-
Chemical produces a tumor capable of transplantation.	+	±	-
Chemical produces a tumor which does not regress once chemical is removed.	+	±	-
Chemical must be mutagenic.	+	-	-
Chemical is effective at nontoxic doses.	+	-	-
Chemical may cause the effect after a single dose.	±	-	-
Chemical should increase the effect of other carcinogens acting on the target organ.	+	±	±
Progression of neoplastic differentiation does not require the continued presence of the chemical.	+	-	-

+ = generally
± = sometimes
- = seldom or never

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seen that the characteristics of PCBs resemble those of a promoting agent and not those of an initiator. In his review of the mutagenic and carcinogenic potential of PCBs, Levinskas (13) likewise cites several authors and experiments supporting the contention that PCBs have promoting activity, including the NCI bioassay (45).

In summary, when assessing the carcinogenic hazard of PCBs, one must decide what weight to give each portion of the data. While one cannot ignore the fact that positive carcinogenic activity has been reported in rodents, one must take into consideration the weakness of this response since it was not reproduced in several subsequent studies. Furthermore, there is a great deal of evidence to suggest that if PCBs induce changes, it is by way of a promotion mechanism. Thus, on the basis of the animal data and considering the inconsistency of the response, PCBs, as weak promoting agents, at low doses would represent a relatively small cancer hazard in man.

Recognizing the problems associated with accurately interpreting the relevance of and risk inferred by animal carcinogenesis bioassays, Robert Squire, former acting director of the Carcinogenesis Testing Program and head of NCI's Tumor Pathology Section, has proposed a ranking scheme for the animal evidence (49). Squire proposes that the basis for determining the strength of a positive test resides in whether the "suspect carcinogen": is positive in a number of species, gives rise to histogenetically different types of neoplasms in one or more species, induces malignant rather than benign tumors, and is consistently positive in an appropriate battery of tests measuring genotoxicity. The dose required to induce tumors as well as the spontaneous incidence of neoplasms in the control animals are also criteria.

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By ranking the test data for each criteria according to a point system developed by Squire, one gets an overall score to assess the strength of the evidence. Squire's approach is appealing because it recognizes several features of an animal bioassay that should be considered when attempting to estimate the likelihood that the human response is similar. Since there are several cancer tests in animals for PCBs, the aggregate score that PCBs would receive depends on the weight assigned to the positive and negative data. However, the total score for PCBs, regardless of the scoring, would probably be about 31 or less. Squire classifies a chemical receiving a score of less than 41 as a class V carcinogen, a class for which he suggests that the regulatory options are many and far less restrictive than for chemicals scoring higher in the ranking scheme. Thus, according to this scheme, even the "positive" evidence for PCBs does not rank them as a human cancer hazard that is as significant as many other chemicals, some of which are still commonly used.

EPIDEMIOLOGY

Acute and Chronic Human Data

In recent studies of occupational exposure, PCBs have not been proven to be a remarkably toxic chemical to persons in the work place, who have probably received the most significant exposure to PCBs. Ouw and co-workers (51) studied 34 workers from a single capacitor plant using Aroclor 1242. Of this group, 31 were exposed for more than one year and 16 for five years or more. Although industrial hygiene at the plant had been generally poor prior to their study (e.g., air

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concentrations were 150% to 222% of the allowable workroom air standard of 1.0 mg/m^3), the clinical tests did not identify any significant health problems. One case of chloracne was reported as well as five cases of an eczematous rash. Even though the average PCB blood levels of the group were over 400 ppb compared to none detected in the control study group, the clinical tests measuring liver function revealed that bilirubin, alkaline phosphatase, serum protein, albumin, SGPT, and immunoglobulins for the group of factory workers were within the normal limits for each test. In addition, bromosulphalein clearance did not correlate well with either PCB blood levels or length of employment.

A more recent study of a far larger group of employees from a capacitor plant reported a similar lack of untoward findings (52). Based on this study of 326 employees, it was possible to separate the employment records into the following categories for years of exposure: 10% had been exposed for 5 years or less; 20.9% 5 to 10 years; 17.5% 10 to 15 years; 11.4% 15 to 20 years; 29.1% 20 to 25 years; and 11% had been exposed for more than 25 years. A summary of the skin complaints revealed that 10.7% of the employees reported rashes and 24.8% reported a burning sensation of the skin. Physical examination further revealed some redness, swelling, dryness, or thickening of the skin in approximately 50% of the individuals, while 2% experienced abnormal secretions from the eyes.

The clinical chemistry of the study was generally unremarkable, and the researchers commented on the "paucity of abnormal results." Of 321 persons examined, the percentage of samples outside of the normal range were: BUN 5.3%; creatinine 1.7%; SGOT 2.2%; SGPT 7.2%; LDH 2.5%; alkaline phosphatase 1.2%; SGGT 1.9%; bilirubin 0.0%;

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cholesterol 17.8%; triglycerides 10.5%; and total lipids 3.4%. These data can be considered indicative of the type of random test results to be expected when 321 persons are tested without simultaneously running a control group to compare against the standardized "normal" values used to indicate an abnormal finding. Likewise, the neurologic examinations failed to produce any prevalence of abnormal findings. There was a decrease in the forced vital capacity of the lungs in 14% of these workers compared to only 5.6% in the normal population (53). While this is an unusual finding, this change was not seen in one group, i.e., the non-smoking women tested. The significance of this finding is unknown at this time and requires verification from other studies.

Maroni et al. (54, 55) have reported an Italian study of employees in a capacitor plant exposed to a foreign PCB mixture similar to Aroclor 1242. The mean age and employment of the 80 employees examined was 37+8 and 12+6 years, respectively. PCB air concentrations ranged from .048 to .275 mg/m^3, and all tested surfaces were heavily contaminated, indicating that employee exposures were both dermal and inhalation. The results showed that PCB blood concentrations ranged from 88 to 1319 ppb. Fourteen workers were found to have skin disorders consisting of dermatitis, folliculitis, or chloracne. Sixteen employees were reported to have abnormal liver effects, consisting of hepatomegaly and sometimes an increase in serum level of liver enzymes. The liver findings did not correlate well with either the duration of employement or the PCB blood levels, and the pattern for hepatic enzyme changes was a random finding inconsistent with hepatotoxic chemicals. It is evident from these data that the clinical changes were unremarkable. Furthermore, control subjects were not

included to determine the normal test variations among unexposed persons of similar ages. Serum bilirubin and alkaline phosphatase levels were within the normal range of variation for all subjects.

Some of the conclusions reached in two recent reviews of the various studies of PCB exposures to date (56, 57) are noteworthy. First, while higher exposures to PCBs tend to mean a higher body burden, there was a general lack of correlation between exposure duration and body burden. Second, although not all studies agree, there was also a suggestion that the higher chlorinated PCBs were more likely to accumulate in adipose tissue, suggesting a slower metabolism rate. Third, the general health of the occupationally exposed group was considered good.

While two of the studies reviewed failed to report clinical findings (other than stating that the workers were in good health), one measured PCB blood levels of up to 1900 ppb in Finnish workers. Of 15 studies reporting clinical measurements, 11 reported dermatologic effects, 9 reported liver function tests, 6 reported lipid measurements, and 5 reported on blood chemistry. Gaffey concluded that while there is no clear correlation between PCB blood levels and chloracne, the studies suggest that when PCB blood levels exceed 150 to 200 ppb, chloracne can occur (56). He also concluded that dermatitis, like chloracne, was a frequently observed effect, and that it may be associated with the higher chlorinated PCB compounds (56).

Of the nine reported studies of liver function, only five found some mild change in liver function tests. No consistent pattern was identified, nor was an association between these changes and PCB blood levels identified. No adverse health effect was associated with PCB exposure in any of the studies. Of the six studies that considered

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lipid metabolism, no consistent pattern associates with PCB exposure; one study, by reporting a decrease in all parameters, contradicted all of the studies reporting an increase. Most studies did associate increased triglycerides with the PCB exposure, but the results for cholesterol were inconsistent. No clinical significance has been attached to these findings. Of the five studies of blood chemistry, none reported any relationship between the tests and PCB blood levels. Of the two studies that measured blood pressure, one found no association, while one reported an association between PCB levels and diastolic blood pressure (56).

In summary, a review of the human data from studies of persons occupationally exposed or whose PCB levels were increased via fish consumption reveals that the combined results of all studies, while demonstrating PCBs caused dermal problems, failed to identify any significant clinical disease associated with electrical grade PCBs. While some physiologic changes were noted, no clinical significance could be attached to any of these, particularly the changes in liver function, which were minimal and generally not compared to an appropriate control group. It has also been noted that PCBs can induce oxidative metabolism in persons occupationally exposed to them (58). Animal studies suggest that inducing agents can increase serum transaminase levels, e.g., SGGT (59, 60) and triglycerides (60). Thus, the random, minimal increases in serum transaminase levels and increased triglycerides found in persons occupationally exposed to PCBs may represent the predictable phenomena of modest enzyme induction. The National Institute of Occupational Safety and Health (NIOSH) study (57) likewise indicates that chronic liver, nervous, or circulatory diseases are not associated with long-term exposure to levels of PCBs

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which were much higher than those encountered in the environment. Therefore, if the environmental exposure to PCBs is insufficient to induce chloracne (the most frequently observed effect), acute, subchronic, or chronic toxicity is probably not to be expected in humans.

Yusho

In 1968 a mass outbreak of chloracne and other symptoms, later termed "Yusho," was caused by the ingestion of cooking oil contaminated by PCBs and other chlorinated compounds. Higuchi (61) and Kuratsune (62) reported that approximately half of the patients complained of a variety of neurologic distresses such as headaches, numbness, hypothesia, and neuralgia. Most of the headaches were transient, but some recurred over a period of months to years. Higuchi (61) concluded that the majority of these headaches probably arose from emotional stress or migraine conditions, and were not related to PCB exposure. Measurements of nerve conduction velocities in Yusho patients revealed, however, that up to 50% of the 20 patients studied had lower than normal sensory nerve conduction velocities, though their motor nerve conduction velocities were normal (61). Female patients, 60%, suffered abnormal menstrual cycles, though the effects varied. Some women suffered prolonged intervals of menstruation, while others had shortened or irregular intervals. Determinations of urinary estrogens revealed a decrease. A possible explanation for this could be an increased degradation of estrogens due to increased liver metabolism (61).

Hematologic examinations of Yusho patients revealed a slight leukocytosis and monocytosis, and serum levels of IgA and IgM were

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generally decreased. Surprisingly, serum indicators of liver damage such as GOT, GPT, and bilirubin were normal. Thus, although PCBs can cause liver injury in experimental animals, as many halogenated hydrocarbons do, the clinical evidence of Yusho indicates that this is not a prominent toxicity in humans (61, 62). Microscopic changes were observed in liver biopsy samples. The major finding, an increase in the smooth endoplasmic reticulum, is interpreted as representive of the induction of the hepatic enzymes for oxidative metabolism, a finding predicted from animal studies and not an indication of toxicity. Analysis of other serum parameters also suggested a disruption of normal lipid metabolism. Serum triglycerides were elevated, while cholesterol was not.

Of 43 affected children examined, 23 boys showed transitory decreases in height and weight gain when compared to unaffected children, while 19 girls did not differ from the control group. Also, some of the infants born to women affected by Yusho were small-for-date. Other symptoms in newborns included dark-brown pigmentation, parchment-like skin, eruption of teeth, and larger than usual fontanelles, indicating transplacental passage of PCBs to the fetus during gestation.

Probably the most common symptoms and the ones largely responsible for the identification of Yusho's disease were eye and skin problems. These consisted of acne-like eruptions, follicular accentuation, swelling of the eyelids with discharge from the eyes, and increased pigmentation of the skin. Unfortunately, even though the chloracne was not a permanent condition, it was a discomforting disfigurement that lasted for a period of months to years.

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Urabe et al. (63) have reported on the cause of the deaths of 31 of the 51 persons who died during the first decade after the Yusho incident. Eleven deaths resulted from various neoplasms; a 35.4% cancer rate, which is higher than the 21.1% rate generally reported for that area of Japan. No conclusion can be drawn from this at present, since the Yusho rate was not age-adjusted and further analysis of the Yusho disease must be done at a later date. Of the reported cancers, the types of neoplasms varied. The numbers of cancer for each tissue were: two stomach, one stomach and liver, two liver, three lung, one breast, and two malignant lymphoma.

While the above effects described in Yusho patients give some idea of the possible consequences of overexposure to PCBs, the exact cause of these symptoms is debatable. The type of PCB mixture contaminating the rice oil, Kanechlor 400, has been discovered to contain polychlorinated dibenzofurans (PCDFs) at concentrations as high as 18 ppm (61, 64). Measurements of the rice oil used by Yusho patients revealed that it contained PCBs ranging from 1 to 3000 ppm, 5 ppm of PCDFs, and approximately 1000 ppm of polychlorinated quaterphenyls (PCQs) (62, 65, 66). Therefore, it is not known which of the Yusho side effects can be attributed solely to PCBs (66, 67) and, if cancer is found in the future to have been significantly increased in this group, the source of cancer induction will remain unknown. (Note: The PCDFs found in the Yusho PCBs are about 1000 times higher than those usually measured in American sources of PCBs). Recently, Kuratsune (66) reviewed the Yusho episode and suggested that the levels of PCBs and contaminants were actually about half of the amount previously reported. He also suggested that since a considerable number of victims did not recover from their symptoms after their levels of

PCB-ARCH-EXT0371981

PCBs had dropped to near normal levels, the high levels of contaminants still present in the victims may be the more likely causal factors of the Yusho problem (66).

Mortality Studies

Reports of high cancer rates among Mobil Oil employees exposed to PCBs (Aroclor 1254) at Mobil's Paulsboro, New Jersey, refinery have been interpreted as indicative of a possible link between PCB exposure and skin (melanoma) or pancreatic cancer (68). The preliminary Mobil study reported eight cancers which developed between 1957 and 1975 among 92 research and development and refinery workers exposed to varying levels of Aroclor 1254 for five or six years in the late 1940s and early 1950s. Of the eight cancers, three were malignant melanomas and two were cancers of the pancreas. According to NIOSH, "This is significantly more skin cancer (melanoma) and pancreatic cancer than would be expected in a population of this size, based on the Third National Cancer Survey." However, it is difficult to draw any conclusions from this study because of the small numbers of individuals exposed and the variety of other chemicals to which they were exposed. In any case, the study was withdrawn for revision and has not yet been re-released (56).

Of the studies reporting the effects of PCBs on the chronic illnesses or the mortality incidence in humans, only two provide large populations of apparently single chemical exposure. Brown and Jones (69) conducted a retrospective cohort mortality study of 2567 employees from two plants where PCBs were used to manufacture electrical capacitors. All workers included in the study were employed for at

least three months in areas of PCB exposure. The vital status of 98% of the population was determined and 39,018 person years were accumulated. The types of PCBs used were Aroclor 1016, 1242, and 1254.

The major causes of death for the 163 persons who had died by the time of the report are separately listed in Table 5. The only statistically significant difference observed was for cancer of the rectum, but only if the female population of plant #2 was considered alone. However, the plants studied are located in an area where mortality from rectal cancer is greater than the United States average (56). As mentioned, this unusual increase stemmed from a high number of deaths in the female population of plant 2; similar findings were not reflected in the female population of plant 1 nor in the male population of either plant. While the liver cancer incidence was higher than expected, it was not significant. There was no relationship between duration of employment involving PCB exposure and the risk of mortality due to cancer or cirhosis of the liver. There was no statistically significant relationship for any cause of death when the total exposed population was considered.

Bertazzi et al. (70) studied 27 deaths in 1310 workers exposed to PCBs for 20,565 person years. Mortality was studied for the 25-year period between 1954 and 1978 for employment between 1946 and 1970. The study group had been employed for at least six months and the exposure was largely to Aroclor 1254. For all cancers, the observed mortality was 14 versus 5.65 expected. This increase, however, was significant only for the male population. Higher than expected incidences in cancer of the digestive organs and in cancer of the lymphatic or hematopoietic systems were also observed, although these were not significant. There were no reports of liver cancer.

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Table 5

MAJOR CAUSES OF DEATH FOR PLANT WORKERS EXPOSED TO PCBs: AROCLOR 1016, 1242, AND 1254

Cause of Death	Observed/Expected	Standard Mortality Rate
	All Causes	
All malignant neoplasms	39/43.79	(89)
Diseases of nervous system	11/12.55	(88)
Diseases of circulatory system	60/62.93	(95)
Accidents	13/18.29	(71)
All other causes	40/44.79	(80)
All causes	163/182.35	(89)
	Malignant Neoplasms	
Cancer of stomach	1/1.66	(60)
Intestine	4/4.03	(99)
Rectum	4/1.19	(336)
Liver	3/1.07	(280)
Pancreas	1/1.90	(53)
Respiratory	7/7.98	(88)
Breast	7/6.84	(102)
Lymphatic	2/4.34	(46)
Other	10/14.78	(68)

Source: Reference 67.

PCB-ARCH-EXT0371984

In assessing the epidemiologic evidence for carcinogenicity, it must be remembered that in any epidemiologic study it may be impossible to eliminate all of the unrelated but confounding variables in the observed populations. Moreover, it is not uncommon to see measurable increases in one type of cancer over what is mathematically expected, since we cannot choose a subpopulation that reflects exactly the baseline cancer rates of the total population. In fact, it is well known that different areas of the United States have different backgrounds for many of the specific types of cancer. All this must be considered carefully, and no conclusions should be made concerning any finding of excess cancer which is not statistically significant, but only above expected values, unless this same excess for that specific type of cancer is repeatedly demonstrated in subsequent studies.

A positive correlation between exposure to a chemical and a resultant adverse health effect relies on the following conditions (69):

- A positive association must be seen in individuals with known exposures;

- The positive association cannot be explained by bias in recording, detection, or experimental design;

- The positive association must be statistically significant;

- The positive association should show both dose and exposure period dependency; and

- The positive association must be observed repeatedly in subsequent studies and cannot be a single, confounding, variable observation.

To date, the mortality studies concerned with PCB exposures present several problems of interpretation, the most obvious and important of which is the different increases in cancer type reported. Taken as a whole, these studies provide no support for assertions that PCBs are a cancer-causing chemical. The variety of tumor sites found to be of most concern within each study largely differs from the animal data and is inconsistent with the selectivity of currently known promoting agents or initiating carcinogens.

In summary, epidemiologic studies have demonstrated that commercial PCBs are not remarkably toxic chemicals after acute exposure and that, when excess exposure does occur, the usual consequences are dermatologic and not of a serious or permanent nature. Data from investigations involving chronic exposures yield similar conclusions. The majority of studies has not identified a clinical disease associated with PCB exposure, nor has it provided persuasive evidence of health impairment. There is no persuasive evidence of an excess in total mortality or in mortality due to cancer, cardiovascular disease, or nervous system disease associated with occupational exposure to PCBs. PCBs have not been linked to any human cancer. Future investigations of occupationally exposed populations will no doubt further clarify this issue as the total mortality within the test group increases with time and yields a larger mortality data base.

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PROCEDURES FOR ASSESSING RISK

In attempting to extrapolate the human risk from chemical exposure using animal toxicity as the basis for the risk extrapolation, there are several models to choose from. The model chosen is primarily determined by the type of health hazard of most concern. However, speaking in general terms, there are only two types used. The first type consists of those methods used for extrapolating the human risk directly from the dose for which there was no observable animal toxicity. This method can be applied to most toxicities (except cancer), since thresholds are assumed for these responses. The second type of model is generally used to assess the risk associated with carcinogens. Since many scientists assume no identifiable threshold for this toxicity, there is some risk attached to any exposure. This concept dictates that mathematical models be used to extrapolate to exposures far below those dosages inducing observable responses in the test animal population.

For noncancer toxicities (i.e., threshold toxicities), the models for extrapolating risk are relatively simple and similar to the Suggested No Adverse Response Level (SNARL) proposed by the National Research Council of the National Academy of Science (72), or the Lowest Observable Effect Limit (LOEL) used by the United States Environmental Protection Agency (EPA) (7). Basically, this type of calculation is computed by assuming that humans are as sensitive as the test species used. Therefore, the amount ingested by the test animal that gives no toxic response is the safe upper limit of exposure for humans, i.e., the human threshold dose.

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The calculation essentially makes the conversion on the basis of the size differential between humans and the test species, usually a body weight comparison rather than surface area. It should also take into consideration those factors that affect a truly comparative dose, e.g., absorption factors if the human exposure differs from the test conditions or if the animal dosage regimen differs from the human exposure interval. The calculation is similar to the following:

$$\text{Safe Human Dose} = \frac{\text{TDo.o(mg/ kg)} \times 70\text{(kg)} \times F \times \text{E.R.} \times t1/2}{\text{S.F.}} = \#\text{mg/day}$$

TDo.o = threshold, or no observable effect dose in the test species;

F = absorption factor, or ratio of animal absorption divided by the human absorption (absorption animal/ absorption human);

E.R. = exposure ratio (dosage regimen animal/exposure regimen human);

t1/2 = ratio of elimination (half-life in animal/ half-life in humans); and

S.F. = safety factor, which depends on the reliability of the data used for extrapolation.

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Typically, the safety factor used varies from 10 to 1000, depending on the extent of animal data available and whether or not there is any human data to substantiate the reliability of the number. Of course, the number calculated should use chronic data where chronic exposures are expected. This type of model calculates one value. Exposure at or below this value is considered safe.

The second type of calculation also has several methods or models from which to choose. However, all differ in their basic assumptions or in the mathematical expression used. Hence, at the low exposures in question, their estimation of risk can vary dramatically (38). Regulatory agencies currently use the multistage model proposed by Crump (7, 73). Using this model, the risk is linearly proportional to the exposure at low doses. While each exposure is considered to carry some risk, the acceptable risk or safe dose is usually suggested as the exposure range for a 10^{-5} to 10^{-7} risk. This means that daily exposure to that dose would increase cancer by 1 person in 100,000 exposed (i.e., 10^{-5}) or 1 in 10,000,000 persons (10^{-7}) with a lifetime exposure.

Risk to PCBs

As stated earlier in this chapter, the determinant factor for assessing the risks associated with chemical exposure is usually the toxicity (acute or chronic) of most concern that can be expected to occur in humans. With PCBs, as for any chemical, determining the toxicity of most concern is extremely important to setting safe exposure limits. Likewise, determining the toxicity of most concern also

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determines the public's perception of the harm of overexposure to PCBs, which in turn affects risk assessment. As demonstrated by the types of analysis used, the difference of whether or not a chemical is carcinogenic can translate into magnitudes of differences in the calculated dose considered to be safe.

PCBs are a good example of this dilemma. As seen in the EPA's ambient water quality criteria for PCBs (7), the safe dose calculated if PCBs are not considered to be carcinogenic is 210 ug/day; if PCBs are considered to be carcinogenic, the 10^{-5} risk dosage is approximated at 160 ng/day. This is greater than a 1000-fold difference in the "safe" exposure based on the chemical's carcinogenic potential. Thus, determining the carcinogenic potential of PCBs accurately has a large impact on its perceived risk.

Even though many arguments may be made regarding the carcinogenic potential of PCBs, the answer to the queston regarding which level may be safe can be found by a simpler, more direct method. While the preceding extrapolations might provide useful guidelines for safe exposures when only animal data are available, they can be and should be tempered by the human experience whenever possible. While human data may not prove that the extrapolations from animal data are correct, they can be utilized in some instances to determine if those extrapolations are incorrect. Such is the case for PCBs.

The model predicting the cancer risk from PCBs based on the data from the Kimbrough et al. study (7) is linear in the dosage range calculated for acceptable risks. Therefore, linear extrapolation to that dose approximating a 100% cancer incidence in humans using the slope for the curve in that portion of the dose response for low risks provides an overestimation of the actual dose required for a high

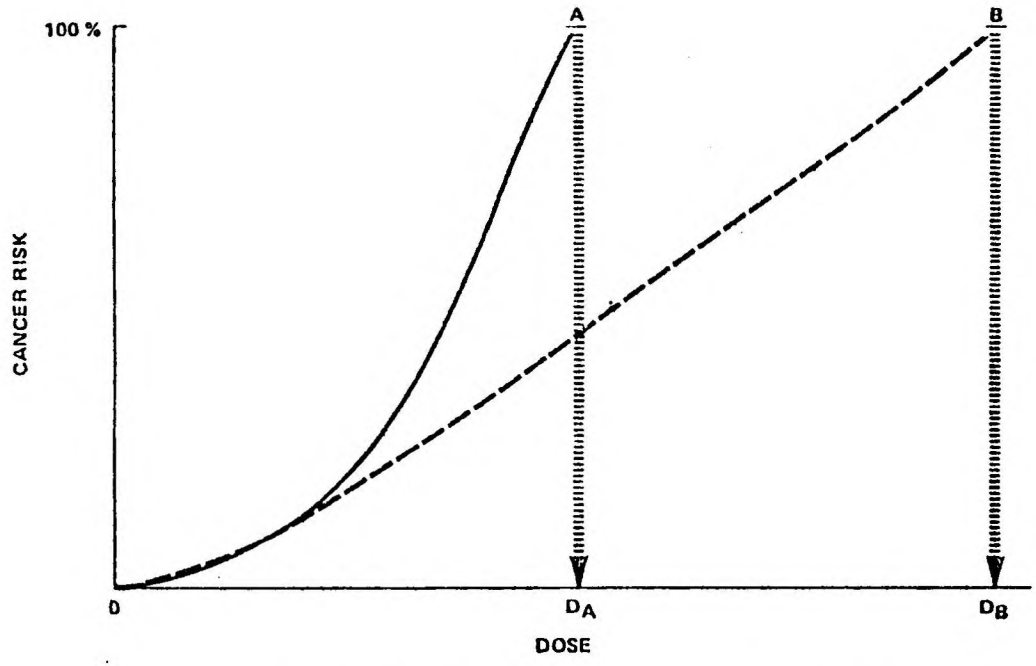

Figure 1 EXTRAPOLATION FROM LOW CANCER RISK EXPOSURE TO HIGH CANCER RISK EXPOSURE

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incidence of cancer (see Figure 1). Performing this extrapolation for PCBs (i.e., 10^{-5} risk is 160 ng/day, so a risk of 1 is 10^5 x 160 ng/day equals 16 mg/day), we should expect a cancer incidence of 100% in the exposed population at about a 16 mg/day-exposure of PCBs if the low exposure perception of the risk is correct.

However, the Occupational Safety and Health Adminstration (OSHA) limit for occupational exposure to PCBs was 0.5 mg/m^3 for Aroclor 1254 and 1.0 mg/m^3 for Aroclor 1242 and other, lower chlorinated biphenyls until PCBs were banned. Assuming that the average volume of air inhaled per workday is approximately 10 m^3, then the allowable workday intake of PCBs could approximate 5 to 10 mg. Granted that perhaps not every worker was exposed daily to these levels, reports such as Ouw et al. (51) or Brown and Jones (69) illustrate that in several instances exposures were higher; therefore, we can assume that the daily exposure approximates of our assumption are a practical consideration. Also, the slope of the extrapolated line would be such that the cancer risk above 1 mg/day of PCB exposure would be easily observable. Since the largest study, by Brown and Jones (69), did not find any statistically increased liver cancer, and could not demonstrate any cancer risk, one must conclude that the cancer risk extrapolated from the animal data for low dose exposure is wrong and by at least two to three orders of magnitude or greater.

By comparing the risk calculated using animal data to that found in 2567 capacitor workers (69), we might conclude that one of three possibilities or a combination of all three exists to explain this error in our calculations: (a) the model is wrong, (b) the animal species used does not represent man, or (c) PCBs are not carcinogenic

PCB-ARCH-EXT0371992

in humans. The first possible explanation may contribute to the problem, but is least likely to be the causal factor for, if reasons 2 and 3 were false, then the occupational cancer would have been measurable. Therefore, one can conclude that either 2 or 3 is the more likely reason for the discrepancy. Regardless of the cause for the discrepancy, it can be demonstrated that, at the very least, the results of the animal tests of Kimbrough et al. (43) do not appear to represent an animal model relevant for assessing the cancer risk in humans using the extrapolation posed by Crump (38). Interestingly, if the data suggesting that PCBs are promoting agents are ignored and if the above model is adapted for the human data (the comparison in Figure 1 demonstrates how the model is excessive by several orders of magnitude at least), we reach an approximate 10-5 risk of cancer that is equivalent to the LOEL calculated by the EPA of 210 ug/day.

It might also be noted that this same test of the 10^{-5} risk based upon animal data for DDT and chlordane shows a large overestimation of the risk for these chemicals as well. Thus, this type of extrapolation seems to be inappropriate for other chlorinated, persistent chemicals which enhance or produce liver tumorigenesis in rodents.

ESTIMATION OF THE HEALTH RISKS ASSOCIATED WITH ENVIRONMENTAL EXPOSURES

Early in this paper it was stated that a thorough evaluation of the hazards associated with PCB exposures must consider and weigh six different characteristics of the data.

The first two factors deal with the breadth and variety of toxic responses produced and the degree of species variation associated with the effects monitored. Many of the PCB-induced adverse effects are

PCB-ARCH-EXT0371993

characteristic of a chlorinated organic compound of the PCB type, or at least these effects are consistently produced by many chlorinated organics. These effects include liver injury, liver enlargement, liver enzyme induction, irritation when applied to the skin, chloracne, and (possibly) a disruption of the estrogenic balance in females due to increased liver metabolism. Although these may indeed be considered adverse effects, all chemicals are capable of altering some physiologic function at a high enough dose. In the more relevant reproductive mutagenic, teratogenic, and carcinogenic tests, tests of chlorinated biphenyls were consistently negative, with only a few exceptions. Some of the exceptions can be discounted because of inadequate study design, disputable interpretations, or use of unusual test methodology. It is unnecessary to display a disproportionately high concern for those few positive studies when their findings cannot be reproduced in a number of subsequent studies conducted under similar or identical conditions.

Third, regarding mechanisms, sufficient evidence exists to indicate that PCBs have the potential to promote cancer rather than initiate tumors. Similarly, the metabolism and elimination of PCBs in primates is far lower than that of rodents, suggesting that man is far less likely to generate toxic metabolites than rodents, i.e., man is probably less susceptible to liver injury and any impact this may have on tumorigenesis.

The fourth factor regards the relevance of the performed test. For the most part, this was not a factor when considering the results of most tests. There are, however, some problems in attaching the

PCB-ARCH-EXT0371994

same significance to all of the mutagenicity tests. The human relevance of single-stranded breaks in DNA at high in vitro PCB concentrations or the applicability of the chromosomal tests in birds is questionable when compared to the more often used and better established tests for mutagenic or clastogenic activity in mammalian and bacterial test systems. Thus, we have concluded that the mutagenic, and therefore initiating, activity of PCBs in humans is minimal, i.e., it is not a significant hazard to humans considering the overwhelmingly negative test responses and the lower human rate of PCB metabolism. The relevance of extrapolating one positive carcinogenesis bioassay without balancing it against numerous negative ones also seems inappropriate considering the likelihood that PCBs are promoters; that the organ response (i.e., liver cancer) has a high background incidence in rodents (74) and is susceptible to promotion by such effects as induction (75, 76) and recurrent liver injury (77-79) (two known effects of PCBs); the strain preference of the positive effect; and the irreproducibility of this effect. Considering the promoting pressures that high, chronic doses of PCBs could exert, it is probably more unusual to find the majority of responses in the rat negative.

The fifth factor deals with the dosages required to produce animal toxicities as compared to the expected human exposure. In animals, PCBs are acutely toxic only at high doses. Similarly, their chronic effects generally occur at relatively high doses or high body burdens. Thus, taking into consideration the expected low environmental exposures to humans, PCBs do not appear to pose a significant risk. If skin disorders are not induced (highly unlikely), other effects seem unrealistic.

PCB-ARCH-EXT0371995

The last factor deals with risks determined by human exposures. The epidemiologic studies have demonstrated that PCBs are not remarkably toxic chemicals after acute exposure and that, when excess exposure does occur, the usual consequences are dermatologic and not of a permanent nature. In spite of over 50 years of use, PCB chronic exposures have added little or no additional adverse effects of note to this picture. The majority of studies has not identified a clinical disease associated with PCB exposure other than chloracne, nor has it provided persuasive evidence of an unusual health impairment. There is no evidence of an excess in total mortality or in mortality due to cancer, cardiovascular disease, or nervous system disease that can be associated with occupational exposure to PCBs. PCBs have not been linked to any human cancer. Therefore, it appears that PCBs are not a remarkable toxicant, but chemicals that require high doses to produce harmful effects.

In evaluating the risk associated with the environmental exposure to PCBs, we should answer two questions. First, is the level of exposure of a sufficient magnitude to constitute a hazard? Second, if so, what is the expected hazard? Jelinek and Corneliussen (80) estimated that the daily PCB intake for a young male adult dropped from approximately 15 ug/day in 1971 to 8.7 ug/day in 1975. This estimate was based on the assumption that most of the intake would come from existing PCB-contaminated fish (an unlikely consideration for most U.S. citizens). The estimate would not be accurate for people who were not eating such fish, or were eating larger amounts of fish, or for those who were exposed to waste sites, contaminated water, or other unusual sources.

PCB-ARCH-EXT0371996

MacLeod (81) more recently reported that indoor air pollution with PCBs is greater than outdoor air pollution, and often ranges from 0.1 ug/m^3 to 0.2 ug/m^3 of air for many of the locations tested. This approximates to a 1.0 to 2.0 ug/day exposure to PCBs from many indoor air sources. This exposure also approximates the currently suggested NIOSH exposure level for industry (82). Thus, it appears that persons within the United States are, in general, environmentally exposed to microgram amounts of PCBs per day in what are probably the higher exposure instances (excluding unusual conditions). This exposure is approximately 1000 times lower than former occupational exposures, which, according to recent evidence, produced no identifiable problems other than chloracne. It would seem that a 1000-fold reduction in exposure would be a sufficient margin of safety for any weak threshold effects that were identified, e.g., skin disorders and induction of liver enzymes. While the NIOSH level is lower than the OSHA standard, it would seem that the old limit reasonably protected the occupationally exposed persons. This bodes well for the rest of us considering our far lower expected exposure from the environment. Furthermore, calculations reveal that PCB exposures of micrograms per day are not likely to significantly alter a person's steady-state tissue concentrations. For example, the average 70-kg man is made up of 15% or greater body fat. In other words, he has at least 10.5 kg of fat in which to store PCBs. Since non-occupationally exposed persons contain 2 ppm or less of PCBs in their body fat, at 2 ppm the average man would contain 21,000 ug or less of PCBs. If one assumed a worst-case estimate without considering metabolism, excretion, other tissues etc., it would take 28.8 years at a daily exposure of 2 ug/day to double his fat levels of PCBs. At 10 ug/day, it would take 5.8 years; at 50 ug/day, it would take 1.2 years; and at 100 ug/day, it would

PCB-ARCH-EXT0371997

take 0.6 years. Since the half-life of PCBs is probably no longer than a month or two, the actual time to double the body burden is much longer than the above calculations and would never be reached for the lower exposures. Thus, the exposure to PCBs faced by the general population, estimated at about 5 ug/day or less for those exposed, is not likely to have much of an impact upon the low body levels of contamination that have been measured in nonoccupationally exposed persons. Since these levels are far lower than the tissue concentrations experienced by capacitor workers, it is unlikely that any untoward consequences can be expected in the general population. The calculations also demonstrate that occasional exposures to much higher levels are not likely to increase a person's adipose levels above the 1 to 2 ppm commonly measured.

From the above discussion, it can be seen that the current daily environmental exposure most likely encountered from the environment is not of a sufficient magnitude to constitute an additional hazard because it is not likely to significantly alter our current body burdens. The animal data has identified certain hazards, but the negative data suggest that these hazards are not consistent or potent responses in every species. While we might speculate that very large doses of PCBs may cause various detrimental effects, the highest exposure group, capacitor workers, appears to have been exposured at levels below those that would cause serious adverse effects in humans. Thus, the current environmental exposures to PCBs, which are much lower than previous occupational exposures, do not appear to be associated with an identifiable hazard, and so the human risk seems to be minimal or insignificant. In order that this paper is not misinterpreted, it is emphasized that this conclusion does not apply to concentrated wastes or chemical waste sites where the exposure may be

PCB-ARCH-EXT0371998

higher or of a different composite nature. It is also emphasized that higher than microgram-per-day exposures to "pure" PCBs do not necessarily carry an added risk. The Federal Drug Administration (FDA) guidelines of 1 ug/kg/day, or a single exposure of 100 ug of PCBs, is still far below the previous OSHA regulation or even the EPA's conservative estimate of the LOEL. Until definitive evidence clearly demonstrates a chronic toxicity in capacitor workers or other exposed persons, environmental exposures to commercial grade PCBs (with low levels of PCDFs), which are far less than the former occupational exposure levels, appear to carry a minimal risk to humans.

PCB-ARCH-EXT0371999

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