

Risk Assessment in a Federal Regulatory Agency: An Assessment of Risk Associated with the Human Consumption of Some Species of Fish Contaminated with Polychlorinated Biphenyls (PCBs)

by Frank Cordle,* Raymond Locke,*† and Janet Springer*†

The problem of polychlorinated biphenyls (PCBs) became a national concern in 1971 when several accidental contaminations of foods were reported. Extensive efforts were undertaken by FDA to reduce the residues of PCBs in food. However, the PCB levels in several species of fresh-water fish have raised concern about the PCB residues from environmental contamination, and it is this concern which has prompted a reassessment of the human risk involved from consumption of such fish. The human epidemiology and animal toxicity of PCB exposure are reviewed, as well as risk assessment in general. Specific examples of risk assessment involving extrapolation of animal data to humans, based on several levels of human exposure to PCBs in fish, are presented.

Introduction

Perhaps the most important issue in policy decisions relating to toxic substances in the environment is an assessment of the human risk from exposure to such toxic substances. The best evidence that an agent is toxic to humans or is a human carcinogen with subsequent human risk that can be quantified is provided by adequate epidemiology data backed by confirmatory animal data. However, for practical purposes, most decisions on human toxicity and carcinogenicity are based on animal studies. To a large degree, the problems involving risk to human health from exposure to polychlorinated biphenyls (PCBs) in some species of fish require extrapolation

to humans with all of the uncertainties inherent in such methods.

The term PCBs refers to a complex mixture of different chlorobiphenyls and isomers. Isomers are two compounds which have the same number of chlorine substituents on the biphenyl molecule but at different locations.

PCBs were reportedly first synthesized in 1881 but were not commercially available until 1930 (1). The only domestic producer was the Monsanto Company. The use of PCBs in a wide variety of industrial applications steadily increased from 1930 until 1971, when the manufacturer voluntarily restricted their distribution in the U.S. to closed systems, including electrical transformers, capacitors, and heat transformers.

PCB products manufactured by Monsanto in the U.S. are identified by the trade name Aroclor, and the particular kind of Aroclor is identified by a four-digit number, e.g., Aroclor 1254 or Aroclor 1260. The first two digits refer to the 12 carbon atoms that make up the biphenyl and the second

*Epidemiology and Clinical Toxicology Unit, HFF-108, Bureau of Foods, Food and Drug Administration, 200 C Street, S.W., Washington, D.C. 20204.

†Present address: Environmental Protection Agency, Washington, D.C. 20460.

two digits refer to the approximate content, in weight percentage, of chlorine in the mixture. Under this numbering system, Aroclor 1254 contains 12 carbon atoms and about 54% chlorine, while Aroclor 1260 contains 12 carbon atoms and about 60% chlorine.

PCBs became a national concern in 1971, when several incidents of accidental contamination of foods were reported. In addition, the extent of the environmental contamination and its persistence were not precisely known. Subsequently, various regulatory actions were taken by the agencies involved, and with the cooperation of the only U.S. producer, the situation was felt to be under control.

Then, in 1975, with the reported high levels of PCB contamination in Hudson River fish, national attention was refocused on PCBs. It was soon apparent that the actions and control measures of the early 1970s had not succeeded in totally reducing or even substantially alleviating the problems associated with PCB contamination in the environment.

Despite the many industrial applications of PCBs in the U.S. for 40 years, information on human exposure and on adverse human health effects from such exposure in the U.S. is scant. In this country, sources of minimal human exposure of the population to PCBs are limited to food, air, and water; perhaps the most significant human exposures are limited to sports fishermen consuming fresh-water fish from contaminated streams and lakes, and to occupational exposure in industrial workers. However, the PCB levels in several species of fish have raised concern about the PCB residues from environmental contamination, and these concerns have prompted a reassessment of the PCB action levels. A typical PCB residue from fish resembles the Aroclor 1254 mixture more closely than it does other Aroclors (2, 3).

A review of the data on fish residues gathered by various agencies indicates a serious incompatibility among sampling programs for obtaining data that reliably define trends in PCB levels. The Food and Drug Administration's primary concern is the levels in the edible portion of commercially important fish marketed interstate. Therefore, in most cases, the heads, entrails, skin, and fins are excluded. Furthermore, FDA has not generally sampled fish that are caught and consumed locally, and the sampling usually has dealt with the most important consumption species, which are primarily of marine origin and generally do not contain as high PCB levels as fresh-water species from certain locations. An FDA 1978-1979 survey (unpublished) of PCB residues in fish, including fresh-water species, presented some evidence that fresh-water fish

continue to be the major source of high PCB residues in the food supply.

To determine human exposure to PCBs through dietary fish, one must know the levels of PCB residues in the edible portions of fish, and the amounts of the various kinds of fish consumed by the population at large and by special subgroups of the population. Information has been compiled by the National Marine Fisheries Service-NOAA (4) on the most important types of fish eaten in the U.S. today and the mean daily amount of each type eaten by the subpopulations of actual users. This study included a sample of 25,947 fish eaters selected to represent all fish eaters in the United States.

Information from the survey indicates that some 20 species comprise 95% of all the fish products eaten. Although 98% of the U.S. population (197 million) eat fish, the average annual per capita consumption is small: 15.0 lb/year, with major consumption of a large "unclassified" fish fraction that exists in the U.S. diet, ranking just below tuna in importance. This "unclassified" fraction of fish represents a variety of fish species, each of which, taken separately, would contribute only a minor proportion of the diet. However, when taken as a group, those species represent a major contribution to fish consumption in the U.S. The major portion of many of our most familiar types of seafood is imported, and fresh-water species, led by trout, bass, and catfish, comprise about 9% of our total fish diet.

Table 1 describes the 12 species of interest, i.e., those species of fish found in the FDA 1978-1979 survey to have the highest PCB residue levels as well as the mean PCB levels in these species. Table 2 describes the daily intake of PCBs in these people who ate the 12 species of interest (3939 individuals out of the total of 25,947) at the 50th and 90th percentiles.

Epidemiology of Human Exposure

Considerable scientific interest has centered on the Yusho incident in Japan. In 1968, human intoxication with Kanechlor 400, a PCB manufactured in Japan, was noted when a heat exchanger leaked this PCB into rice oil ("Yusho" oil) that was consumed by Japanese families.

The typical clinical findings included chloracne and increased pigmentation of the skin, increased eye discharge, transient visual disturbances, feeling of weakness, numbness in limbs, headaches and disturbances in liver function. Most of the babies born to affected mothers had skin discoloration

RISK ASSESSMENT OF PCB CONTAMINATION

173

Table 1. Mean PCB levels in FDA 1978-1979 domestic survey by species of interest.*

Species of interest	Assumed tolerance = 0 ^b		Assumed tolerance = 5 ppm		Assumed tolerance = 2 ppm		Assumed tolerance = 1 ppm	
	Mean PCB, ppm	N	Mean PCB, ppm	N	Mean PCB, ppm	N	Mean PCB, ppm	N
Carp	1.10	54	0.90	52	0.88	48	0.54	88
Catfish	1.70	295	1.19	281	0.78	219	0.38	150
Buffalo	0.50	36	0.50	36	0.49	35	0.30	31
Fresh water trout	1.38	87	1.28	85	0.78	58	0.37	40
Sea trout	0.58	10	0.58	10	0.56	10	0.27	8
Bass	1.28	15	1.28	15	0.77	11	0.27	10
Chub	1.14	19	1.14	19	0.86	17	0.58	9
Bluefish	0.58	23	0.58	23	0.44	22	0.37	20
Scup (porgy)	0.72	10	0.72	10	0.72	10	0.58	8
Drum	0.49	12	0.49	12	0.49	12	0.32	10
Mackerel	0.53	21	0.53	21	0.53	21	0.28	17
All others	0.26	206	0.26	206	0.24	204	0.22	201

*Tuna and shellfish were assumed to have 0.0 level of PCB. For assumed tolerance, PCB values below the tolerance were eliminated in calculating the mean.

^bNo tolerance.

Table 2. Intake of PCBs from fish for eaters of species of interest (3989/25,947).*

Assumed tolerance, ppm	Intake at 50th percentile			Intake at 90th percentile		
	µg per day	ppm of diet ^b	µg/kg body weight ^c	µg per day	ppm of diet ^b	µg/kg body weight ^c
0 ^d	8.46	0.0056	0.72	22.1	0.0147	0.32
5	7.57	0.0051	0.11	20.3	0.0135	0.28
2	5.59	0.0037	0.08	14.9	0.0099	0.21
1	3.30	0.0022	0.05	9.22	0.0061	0.13

*For assumed tolerance, PCB values below the tolerance were eliminated.

^bAssumed 1500 g daily intake.

^cAssuming body weight of 70 kg.

^dNo tolerance.

which slowly regressed as the children grew. Adult patients had protracted clinical disease with a slow regression of symptoms and signs, suggesting a slow metabolism and excretion of the PCB in humans, probably due to a long biological half-life.

A review of the literature extant in 1972 revealed the following facts. The average PCB content of the rice oil in the dose-response epidemiologic study was 2500 ppm. In this study, the average cumulative intake of PCBs leading to overt symptomatology was 2000 mg, and the lowest dose leading to overt symptomatology was 500 mg. Originally, rice oil contaminated with a heat exchanger, Kanechlor 400, a polychlorinated biphenyl, was associated with Yusho symptomatology. PCBs were identified in the contaminated rice oil consumed and in the blood and tissues of patients. Therefore, the effects seen were attributed to PCBs.

In the review by Kuratsune et al. (5) a new factor was introduced into the system; namely, the canned rice oil was also contaminated with chlorinated dibenzofurans (PCDFs) to the extent of 5 ppm. In

addition, in this same paper Kuratsune presented data of Nagayama et al. (6) showing polychlorinated dibenzofurans to be present in the liver and adipose tissue of Yusho patients, while none was found in that of a control group. Nagayama et al. (6) reported that the ratios of PCBs to PCDFs in Kanechlor 400, in a Yusho oil of February 5 or 6, 1968, in adipose tissue, and in liver from a patient were 50,000, 200, 144 and 4 to 1, respectively. Thus, relative to Yusho oil, the liver with a PCB/PCDF ratio of 4 to 1 appears to concentrate PCDFs selectively relative to the PCBs. If PCDF is 200 to 500 times more toxic than PCB, the contaminated rice oil would be 2 to 3.5 times more toxic than expected from the PCB content alone. Additional work has indicated that the original estimate of PCBs in the rice oil was in error because the analysis was based on total organic chlorine present, and that the rice oil contained approximately 1000 ppm of chlorinated quaterphenyls in addition to the PCB residues. A discussion of the use of these data in attempting to set so-called safe

levels of PCBs in the diet will be presented in a later section of this report.

The earliest reports of adverse health effects due to exposure of workers to PCBs in this country are probably those of Schwartz (7), who described skin lesions and symptoms of systemic poisoning among workers who were said to have inhaled chlorobiphenyls; their complaints included digestive disturbances, burning of the eyes, impotence and hematuria. Patch tests with the chlorobiphenyls were negative, and Schwartz speculated that mechanical plugging of the follicles of the skin as the fumes solidified on it was responsible for the skin lesions. The chlorine present in the products was thought to then exert an irritating effect on the plugged follicles and to thus cause suppuration. No quantitative data were reported, but a number of preventive practices were recommended.

There have been numerous reports over the ensuing years (1) of cutaneous eruptions and of systemic manifestations as well, among marine electricians, machinists, capacitor and transformer manufacturing workers, and other occupationally exposed to PCBs. However, in many of these reports the exposures are described as having been to mixtures of chlorinated hydrocarbons, quite often of chlorinated naphthalenes and PCBs.

The skin lesions described by Schwartz (7) have come to be designated generally as chloracne. Chloracne can be produced by a number of chemical compounds, including chlorinated dibenzofurans and certain isomers of the chlorinated dibenzodioxins (8). Oily skin and large pores seem to predispose to the disease, while the opposite is the case for smooth, tender skin.

Part of the chloracne lesion resembles adolescent acne, but it is generally more severe, and lesion distribution is inconsistent with adolescent acne although it may be superimposed upon it. It is known that chloracne can be produced by either the systemic absorption of chlorinated biphenyls or the direct application of chloracnegenic compounds to the skin. Systemic effects sometimes result after occupational chloracne has manifested itself; these may include loss of appetite, nausea, edema of the face and hands, abdominal pain, vomiting and burning and soreness of the eyes. No fully satisfactory explanations have been made of the development of chloracne. Chloracne is generally very persistent, and there is no preferred control measure.

As indicated previously, low levels of human exposure to PCBs in the U.S. population may occur from air and water. Samples of ambient air were collected in suburban areas of Miami, Florida; Jackson, Mississippi; and Fort Collins, Colorado. Preliminary results (9) for samples taken in April, May and June of 1975 show that PCBs were present

at all locations. Although the data varied, the average concentrations at each of the three locations was approximately 100 ng/m³. Initial identification of the PCBs indicated that they were most comparable to the Aroclor 1254 standard.

Dennis (10) has also reported that data gathered from monitoring activities of surface waters and bottom sediments of the major drainage basins of the United States indicate the widespread occurrence of PCBs in both surface water and bottom deposits. A preliminary assessment of PCB levels shows mean residue levels in water ranging from 0.01 to 0.05 µg/l. The 0.05 µg/l levels were found in the south Atlantic slope and eastern Gulf of Mexico drainage basin. In general, the lowest PCB residue levels were found in drainage basins west of the Mississippi.

The Great Lakes represent another area of the nation contaminated with PCBs. The Michigan Water Resources Commission (11) reports that many surface water samples contained PCBs at concentrations above the detection limit of 10 parts per trillion. In this study, residues of PCBs were found at 10 locations from rivers and streams discharging into the Great Lakes. Effluents from wastewater treatment plants servicing industrialized communities have been found to be highly contaminated.

Sampling surveys of Great Lakes fish have shown that most species tested contained detectable levels of PCBs and that residue levels were generally proportional to fish size (age) and were highest in the predator species. Except for whitefish, the species of commercial or sport interest (trout and salmon) from Lake Michigan were found to be highly contaminated with PCBs. Data obtained from lake trout collected from various areas of Lake Michigan show mean PCB levels ranging from 3.06 ppm to 11.98 ppm.

The Michigan Department of Public Health has recently completed a study (11) which attempted to assess some of the consequences of human exposure to PCBs from the consumption of sportfish caught in different areas of Lake Michigan. The study included exposed and control subjects from five areas of Michigan bordering on Lake Michigan. Exposed study subjects were those individuals who consumed at least 24 to 26 lb of Great Lakes fish per year. Control subjects were those individuals who consumed less than 6 lb of Great Lakes fish per year.

An assessment of the findings in the study indicates that the most frequently recorded quantity of fish consumed by the study participants was in the 24-25 lb/year range. The highest recorded fish consumption over the two-year period of the study was 180 lb/year and the highest single-season

RISK ASSESSMENT OF PCB CONTAMINATION

175

consumption as 260 lb. Mean PCB levels in whole lake trout are reported as 18.98 ppm in 1978 and 22.91 ppm in 1974, and as 12.17 ppm in Coho salmon in 1973 and 10.45 ppm in 1974. However, comparisons of PCB levels in raw versus cooked fish indicated that actual human exposure to PCBs from fish consumption is less than might be expected from the raw fish data. This is not unexpected, since preparation (trimming away fatty tissue) and cooking have resulted in a decrease in the amount of PCBs actually consumed in fish. For example, the PCB level in cooked lake trout consumed by the study participants ranged from 1.03 to 4.67 ppm; in cooked salmon from 0.48 to 5.88 ppm; and in other cooked fish from 0.96 ppm to 2.06 ppm. These levels are decidedly lower than the level of PCB contamination reported in raw trout and salmon.

PCBs were found in all blood specimens collected from the 182 study participants during the study period, including controls. The values ranged from a low of 0.007 ppm in blood in the control group to a high of 0.386 ppm in the exposed group. Although there was a wide range of blood values for each quantity of fish consumed, there was a positive correlation between the reported quantity of Lake Michigan fish consumed and the concentration of PCB in the blood of study participants. No annual variation in PCB blood levels in humans could be demonstrated. The mean PCB blood values for the control and exposed groups did not appear to change markedly from 1973 to 1974. In addition, abstinence from Lake Michigan fish consumption for a period of 90 days or more did not change the PCB blood levels significantly. PCB blood levels over the abstaining period show variation but no steady decline in PCB. In fact, more subjects showed no change or a rise than showed a decline in PCB blood levels over time.

The calculated quantity of PCBs ingested by eating Lake Michigan fish averaged 46.5 mg/year and ranged from 14.17 to 114.81 mg/year. PCB ingestion for each individual was determined by proportioning his/her reported annual fish consumption by frequency of species eaten and the cooked fish PCB levels for those fish. The community average for cooked fish was used in instances in which cooked fish determination was not available for study participants. Because fish consumption was found to vary from year to year, the average annual consumption for each individual for the two baseline years of study was used in each case.

Results from this study indicate that the calculated mean daily dose received by the exposed group is 1.7 $\mu\text{g}/\text{kg}/\text{day}$ and ranges from 0.09 to 3.94 $\mu\text{g}/\text{kg}/\text{day}$. If the average annual rate of PCB ingestion from fish indicated by these study results were continued over the years, the average sports

fisherman consuming contaminated fish could receive a total PCB dose equal to 200 mg in approximately 4.8 years. Under the same set of assumptions, individuals consuming greater than average amounts of contaminated fish would reach the total dose level sooner. No adverse health effects or groups of symptoms that were clearly related to PCB exposure could be identified in the exposed group. This implies that exposure to PCBs from eating contaminated fish at the levels observed and the presence of PCBs in these exposed persons have not caused any observable adverse health effects similar to those observed in the Yusho population. However, this does not exclude the possibility that effects too subtle for detection are occurring, or the possibility of long-term health effects. Because of the lack of sufficient human data, risk assessments for potential toxic effects of chemicals must of necessity be estimated from animal experiments. In the absence of contradictory kinetic or metabolic data, the animal data are used to estimate potential human risks. Because the numbers of animals used in tests are limited, doses above the human exposure levels are used to increase the probability of detecting potentially toxic chemicals.

Thus, the risks at low doses must be estimated from higher experimental doses. Because of the inability to observe the low end of the dose response curve with precision, the linear (or when necessary one-hit) extrapolation from high to low doses is often used (12-15). Because of the many uncertainties involved in risk estimation, this approach is conservative and errs in favor of public health. Also, linear (one-hit) extrapolation is the limiting case for the multistage model of carcinogenesis at low doses. Since the shapes of dose-response curves at low doses are unknown, it must be remembered that actual estimates of risk are not being obtained. Based upon plausible assumptions, however, it generally is possible to place upper bounds on potential risk by use of linear (one-hit) extrapolation based upon animal data.

Animal Data

Several elements related to risk must be considered in any assessment of animal data: for example, the similarity of exposure in animals compared to humans, e.g., types of Aroclors used in animal experimentations (most human exposure is to Aroclor 1254, and a typical residue from fish resembles the Aroclor 1254 mixture more closely than it does the other Aroclors) (2, 3), and the kinds of outcome that might be comparable to those for humans. Risk assessment—or the estimation of the acceptable daily intake—will be based on general toxicity, carcinogenicity and the effects on reproduction for

which there is little or no previous experience in such risk assessment.

The acute toxicity (oral and dermal) of the PCBs is of relatively low order when the substances are administered as a single dose. In contrast, the subacute toxicity of both the PCBs and individual chlorinated biphenyls appears to be of far greater concern; species sensitivity and cumulative toxic effects appear after continuous exposure at low levels (16-18). The effects of various PCB compounds have been studied in a number of animal species, and the results have been compiled and evaluated in recent reviews (1, 19). In assessing the possible toxicological hazard posed by PCBs for humans, it is preferable to utilize animal feeding studies in which the PCBs are added at low levels to the diet and the treatment is continued essentially throughout the life span of the animals. Few such long-term studies of the toxicity of PCBs are currently available. For assessing the risk posed to humans as a result of exposure to PCBs, three long-term studies have been chosen which are cited and discussed in detail below: the National Cancer Institute's bioassay of Aroclor 1254 for possible carcinogenicity in male and female Fischer 344 rats (20), the study of Kimbrough et al. (21) on the induction of liver tumors in Sherman strain female rats by Aroclor 1260, and the 11-month study by Kimbrough and Linder (18) of the toxic effects of Aroclor 1254 in male BALB/cJ mice. In addition, because of the known extreme sensitivity to PCB-related toxicity of the rhesus monkey compared to rodent species, the short-term study by Allen and Norback (22) of the pathological responses of these primates to PCB exposure as a basis for risk assessment is also described.

In the National Cancer Institute's bioassay of Aroclor 1254 (20), groups of male and female Fischer 344 rats (24 of each sex per group) were administered the test compound in the diet at 25, 50 or 100 ppm levels for a period of 104-105 weeks. Matched controls consisted of groups of 24 untreated rats of each sex. All animals were observed daily for signs of toxicity and palpated for tissue masses at each weighing. Moribund animals were sacrificed and subjected to gross and microscopic pathological examination, as were the animals sacrificed at the end of the experimental period. It was concluded that, under the conditions of the bioassay, Aroclor 1254 was not carcinogenic in Fischer 344 rats; however, it was suggested that the high incidences of hepatocellular proliferative lesions of the gastrointestinal tract in the Aroclor-treated males and females might be associated with the administration of the compound.

In the study by Kimbrough et al. (21), 200 Sherman strain female rats were fed a diet containing

100 ppm of Aroclor 1260 for approximately 21 months, and treatment was discontinued for 6 weeks before the animals were sacrificed at 28 months. A group of 200 untreated female rats served as controls. All animals were observed daily, and moribund animals were sacrificed and subjected to gross and microscopic pathological examination, as were the animals sacrificed at the end of the experimental period. The authors concluded that Aroclor 1260, when fed in the diet, had a hepatocarcinogenic effect in these rats. No significant differences could be observed between experimental and control animals with regard to the incidence of tumors in other organs. In the study by Kimbrough (8), 50 male BALB/cJ mice were fed a diet containing 800 ppm of Aroclor 1254 for a period of 11 months. Another group of 50 male mice received a diet containing 800 ppm of Aroclor 1254 for a period of 6 months and a control rat chow diet for the next 5 months. Control males were fed a plain rat chow diet throughout the 11-month study. Food consumption and body weight were monitored through the study. The animals were sacrificed at the end of 11 months, and the organs were examined grossly for pathology. The liver and any other abnormal-appearing tissues were examined microscopically. Of the 22 surviving animals which had received a diet containing 800 ppm of Aroclor 1254 for 11 months, nine animals exhibited hepatomas. One of the 24 mice which had received a diet containing 800 ppm of Aroclor 1254 for 6 months and the control diet for the next 5 months exhibited a hepatoma. None of the control animals developed hepatomas during the course of the experiment.

Allen and Norback (22) have investigated, among other things, PCB-related reproductive disfunctions in the rhesus monkey, an animal species known to be more susceptible than rodents to the toxic effects of PCBs. In one series of experiments, eight female monkeys were fed a diet containing 2.5 ppm of Aroclor 1248 for 6 months, eight other females were fed a diet containing 5.0 ppm of Aroclor 1248, and 12 females served as controls. At the end of 6 months, all experimental and control animals were bred to control males.

Six of the eight animals receiving the test compound at 5.0 ppm in the diet conceived. The remaining two were bred on five separate occasions without conceiving. Four of the six animals which did conceive experienced abortions early in gestation, and one gave birth to a stillborn infant. Eight females receiving diets containing 2.5 ppm of Aroclor 1248 were able to conceive, but only five females in this group were able to carry their infants to term, while the remaining three animals experienced abortions. The infants born to all experimental mothers receiving the test compound at either 2.5

ppm or 5.0 ppm in the diet were small at birth and exhibited detectable concentrations of PCBs in the skin. All of the 12 control females conceived and had normal births. Each of the three toxicological studies of PCBs described above was used to assess the carcinogenic or reproductive risks posed by these compounds.

Risk Assessment

As indicated previously, the scientific data base needed to support a quantitative estimate of risk to human health as a result of exposure to environmental contaminants is nearly always inadequate to quantify such risk accurately. In a typical case, there are at least four major areas of uncertainty (23): (1) a lack of adequate information about the exposures that occur in human populations at environmental levels of the contaminant; (2) a lack of dose-response data in humans to support projections of the effects of likely levels of exposure; (3) a comparable lack of dose-response data, even in laboratory animals, at the very low levels of exposure that commonly occur in the environment; and (4) a lack of understanding of the interactions and influences that environmental variables and characteristics of the exposed population may have on the effects of the contaminant.

The state of scientific knowledge at present makes it unlikely that these uncertainties can be eliminated. However, it is possible to simplify the analysis by making a number of assumptions (23). One can assume, for instance, that "typical" exposure levels can be calculated from limited data, or can be estimated arbitrarily to encompass what appears to be a reasonable range; that dose-response curves derived from animal studies can be used as analogs to estimate human responses; that the dose-response curve can be extrapolated, using best scientific judgment concerning its probable form, from known responses at high doses to estimated responses at much lower doses; or that for lack of any sounder choice, the influence of confounding variables can simply be left out of the calculations.

Estimates of risk based on such an approach have increasingly been attempted: an example is the recent assessment by the National Research Council of halomethanes in drinking water (24). The results, while crude, have some value in decision-making, if only to place in perspective the hazards of pollutants whose toxic properties are known qualitatively (e.g., mutagenic, carcinogenic). Quantitative assessments of this sort, however, are no stronger than the structure of assumptions on which they rest. Because many of the assumptions are merely pragmatic and are derived from limited information, risk estimates of this type cannot be accepted as

conclusive results. They should instead be viewed as initial attempts that are subject to revision as better information becomes available.

In attempting to estimate risks from exposure to PCBs through the consumption of PCB residues in certain species of fish, several problems are readily apparent. One, there is no measurement of PCBs in the fish actually consumed by individuals. PCB residues are measured in fish from one survey, while fish consumption is measured in another. Second, the risks are computed from a variety of animal studies which include different animal species exposed to a variety of Aroclors and levels of Aroclors in the diet with effects measured in different ways, e.g., general toxicity, carcinogenicity and problems of reproduction.

In the risk assessment described below, the average and an upper limit for PCB intake per day are estimated. The nationwide survey of fish consumption conducted for NMFS-NOAA during 1973-1974 has been used to estimate consumption of fish. This survey included 25,947 persons representative of the U.S. population who recorded their fish and seafood consumption for each family member for a one-month period. Of these 25,947 persons, 8939 ate the species of fish which have levels of PCB above 1 ppm.

Since the effect of instituting a tolerance of PCB levels down to 1 ppm would change the PCB contributed to the diet by fish only in those fish which showed PCB levels above 1 ppm, risks corresponding to tolerances of 5 ppm, 2 ppm, 1 ppm, or 0 were calculated for those 8939 persons who ate the species of interest. Because analytical methods for regulatory purposes are not presently available for levels less than 1 ppm, no risks were calculated for lower levels. The calculated risks could then be extrapolated to that proportion of the total U.S. population which is expected to eat these species, that is, 8939/25,947, or 15.2%.

For these persons, the consumption per day of each type of fish was multiplied by a mean PCB level estimated for each tolerance level to give a total PCB intake from fish per person per day. The 50th and 90th percentiles of PCB intake from fish for those eaters of the species of interest were then used to calculate risks.

The mean PCB level estimated when a given tolerance is in effect is perhaps the most difficult part of the risk estimation. The effect of a tolerance on the distribution of PCB levels depends to a large degree on the actual distribution of PCBs before a tolerance is instituted. The most recent data available on PCB levels in fish were the 1978 and 1979 FDA survey data, consisting of 712 samples for 1978 and 179 samples for 1979 collected from all of the FDA districts. This sampling is not representative or

Table 3. Animal data used for risk extrapolation to humans.

Study	Parameter	Dose of Aroclor fed, ppm						
		0	2.5	5.0	25	50	100	300
Fischer rats fed Aroclor 1254 (20)								
	Total malignancies	5/24			2/24	9/24	12/24	
Males		4/24			13/24	8/24	9/24	
Females		9/48			15/48	17/48	21/48	
Combined								
	Liver carcinoma and adenomas	0/24			0/24	1/24	2/24	
Males		0/24			0/24	1/24	2/24	
Females		0/48			0/48	2/48	4/48	
Combined								
	Hematopoietic system	3/24			2/24	5/24	9/24	
Males		4/24			6/24	8/24	8/24	
Females		7/48			8/48	11/48	15/48	
Combined								
Female Sherman rats fed Aroclor 1260 (21)	Hepatocellular carcinomas	1/178					26/184	
BALB/cJ male mice fed Aroclor 1254 (16)	Hepatoma, neoplastic nodules	0/5						8/22
Female monkeys fed Aroclor 1248 (22)*	Problems of reproduction	0/12	3/8	7/8				

*For the monkeys fed Aroclor 1248, assuming a body weight of 5 kg and daily food consumption of 250 g: 2.5 ppm = 125 µg/kg body weight/day; 5.0 ppm = 250 µg/kg body weight/day.

extensive enough to permit estimation of an underlying nationwide distribution by species. As a rough approximation of the effect of a tolerance on the distribution, the values of PCB above the assumed tolerance were eliminated from the sample distribution and the mean was recalculated for each species. The resulting mean levels are shown in Table 1. It should be noted that assuming a zero tolerance is not equivalent to using all values, inasmuch as the 1975-1979 survey was carried out when a tolerance of 5 ppm was in effect. Thus, the effect of going from zero tolerance to a tolerance of 5 ppm would be greater than shown here. Tuna and shellfish were assumed to have 0.0 mean levels of PCB. The limited data available on tuna show mean levels of less than 0.01 ppm. The values in Table 1 were then multiplied by consumption figures as described above to obtain intake of PCBs per day.

The total intake of PCB per day from fish for eaters at the 50th and 90th percentiles is shown in Table 2. The ppm of the diet is calculated by assuming 1500 g total food intake per person per day.

Data from the NCI bioassay program in which Aroclor 1254 was fed to Fischer rats are presented in Table 3, which shows the numbers for total malignancies, liver carcinomas plus adenomas and malignancies of the hematopoietic system in males, females and males and females combined at various feeding levels. Similar data are also presented in Table 3 for the feeding studies of Kimbrough in which female Sherman rats were fed 100 ppm Aroclor 1260 and BALB female mice were fed 300 ppm Aroclor 1254, and for the Allen reproductive

data in which Aroclor 1248 was fed at 2.5 or 5.0 ppm.

Using the data for Table 3, the upper confidence limits (99%) on lifetime risks for cancer and problems of reproduction in eaters of the 12 fish species of interest at the 50th percentile are presented in Table 4. Upper limits on estimated human risks have been computed from the NCI data for total malignancies for males plus females, liver carcinomas plus adenomas in males plus females and malignancies of the hematopoietic system in males plus females. Risk computed from the Kimbrough data and from the Allen data are also presented in Table 4. The various risks shown are based on PCB values in fish, assuming zero tolerance, or a tolerance of 5, 2 or 1 ppm.

In describing the potential risk to human health from exposure to PCBs it seems appropriate also to review the general scheme of establishing safe regulatory levels based on general toxicity as opposed to carcinogenicity or problems of reproduction. In the Yusho incident, the individuals consumed an average of 15,000 mg/day of the contaminated oil. The oil itself was contaminated at levels of 2000-8000 ppm PCBs and other contaminants (such as polychlorinated quaterphenyls); the average level of the contamination in the oil was 2500 ppm. The levels of contamination of the rice oil were calculated at the time of the incident by comparing the known organic chlorine content of the rice oil with the known organic chlorine content of Kanechlor 400.

Based on the two average levels (consumption of rice oil and residue levels in the rice oil), the

RISK ASSESSMENT OF PCB CONTAMINATION

179

Table 4. Upper confidence limits (99%) on lifetime risks of cancer and problems of reproduction in eaters of fish species of interest.

Study	Basic parameter/species	Lifetime risks per 100,000 ^a							
		50th percentile eaters				90th percentile eaters			
		Assumed no tolerance	Assumed tolerance = 5 ppm ^b	Assumed tolerance = 2 ppm	Assumed tolerance = 1 ppm	Assumed no tolerance	Assumed tolerance = 5 ppm	Assumed tolerance = 2 ppm	Assumed tolerance = 1 ppm
NCI (20)	Total malignancies (male and female rats)	4.1	3.7	2.7	1.6	10.6	9.8	7.2	4.4
NCI (20)	Liver carcinoma and adenomas (male and female rats)	0.9	0.9	0.6	0.4	2.5	2.3	1.7	1.0
NCI (20)	Hematopoietic (male and female rats)	2.7	2.4	1.8	1.1	7.0	6.5	4.7	2.9
Kimbrough (21)	Liver carcinoma	1.8	1.2	0.8	0.5	3.4	3.1	2.2	1.4
Kimbrough (16)	Liver hepatomas (mice)	2.0	1.8	1.2	0.8	5.2	4.8	3.5	2.2
Allen (22)	Female-male reproduction (monkey) ^c	337	307	222	132	888	811	595	367

^aAll risks are lifetime risks computed as rates per 100,000 of the population at risk.^bFor each assumed tolerance, PCB values below the tolerance were eliminated.^cInasmuch as the monkeys were fed Aroclor 1248 for only 6 months, the risk computed for problems of reproduction are not true lifetime risks.

average daily intake of the combination of contaminants was 87.5 mg/day. The average cumulative dose of the contaminants causing an overt effect in the Japanese victims was reported to be 2000 mg. Thus 53 days of exposure was required to consume this amount. The period of exposure no doubt varies around this figure. However, it was estimated that the maximum exposure time was 100 days. It must also be assumed that the adverse health effects result from the combination of contaminants and that these effects are reasonably similar for the levels of PCBs as well as for the levels of chlorinated quaterphenyls or other contaminants.

Humans in the United States have not been exposed to PCBs at the high residue levels that occurred in the Yusho incident. PCB exposure in the United States has been assumed to be sporadic and self-limiting in nature, as far as the general public was concerned. Accordingly, in developing temporary tolerances based on the data from Yusho incident, a time period of 1000 days of exposure was used. As previously stated, this was not an analysis based on lifetime exposure. Rather, it was postulated that PCB levels in food in the U.S. would steadily decrease over the 1000-day time period used in the calculation. This has in fact taken place for most food. Jelinek and Corneliussen (25) reported that from the 1969-1975 period, there were significant decreases in PCB levels in all foods with the exception of fish, where no particular trend had been noted.

In calculating a total allowable exposure from the average overt dose in the Yusho incident, a safety factor of 1 to 10 was used for those effects observed

in the Yusho population, resulting in a total allowable exposure of 200 mg. Because of the sporadic and self-limiting nature of PCB exposure in the United States, the total exposure (200 mg) was spread out over the 1000-day time period, providing a tolerable daily exposure of no more than 200 µg per day. Transforming this figure and using an average body weight of 70 kg for an adult produced a value of 3 µg/kg body weight/day.

Infants and young children may be more susceptible than adults to toxicants such as PCBs. They also consume a greater amount of food per kilogram of body weight and therefore have a proportionately greater exposure to PCBs than adults. Thus, in calculating the temporary tolerances, it seems appropriate to use an additional safety factor for infants and young children. The acceptable daily exposure for children is therefore calculated by using the lowest total dose producing an adverse health effect in the Yusho incident, which was determined to be 500 mg of the contaminants. Using the 1:10 safety factor spread over 1000 days, the tolerable daily exposure is 50 µg/day. Infants and young children should, therefore, not be exposed to PCBs at a level greater than 1 µg/kg body weight/day. An adult who consumes a balanced and varied diet should not be expected to ingest more than the tolerable daily exposure of 200 µg/day. Similarly, infants or young children consuming a balanced and varied diet should not be expected to ingest more than their tolerable daily exposure.

In addition to the human epidemiological data, other data from long-term animal studies (two years) had appeared to establish that the no-effect

level in rats and dogs for PCBs with three levels of chlorination (42, 54 or 60%) was 10 ppm. These animal data have been used with the epidemiological data to estimate allowable daily intake in humans. When data derived from dogs were used, a no-effect level of 2.5 $\mu\text{g/kg}$ body weight/day was estimated. When rat data were used, the estimated no-effect level in man was 8 $\mu\text{g/kg}$ body weight/day or a level similar to the human epidemiological data. Thus, for a 70 kg individual, an allowable level of PCB ingestion would be 175 to 210 $\mu\text{g/day}$. However, more recent analysis of these data has raised serious questions as to the validity of the original interpretation of results. These data appear to offer little help in arriving at an allowable daily intake level of PCBs in humans.

Discussion

There is considerable disparity in reproductive results of monkeys compared to other species. Yet the consuming public tends to consider that monkeys are more like humans than rodents are. Thus it is necessary to consider why such disparities exist. It has been pointed out by McNulty (26) and by Allen et al. (22, 27) that rhesus monkeys are very sensitive to PCBs, not only in the subacute effects, but in problems of reproduction as well. These monkeys received 2.5 ppm or 5.0 ppm in the diet; over a period of 6 months, total intake ranged from 250 to 400 mg.

In contrast, Keplinger et al. (28) reported low mating indices and decreased survival of pups in rodents receiving Aroclor 1242 at 100 ppm. No reproduction effects were found with Aroclor 1242 or 1254 at 1 or 10 ppm although other studies in rodents (29) have demonstrated reproduction effects; e.g., in Sherman rats exposed to Aroclor 1254 or Aroclor 1260, the exposures producing such effects have been at levels considerably higher than the 2.5 or 5.0 ppm used in the monkey studies (20, 100 or 500 ppm).

Additional differences between the monkey and rodent sensitivities to PCBs are illustrated by the fact that the Sherman rats in the Kimbrough study fed 100 ppm of Aroclor 1260 for 23 months apparently exhibited no subacute effects, which is also true of the NCI study in which Fischer rats were fed 25, 50 or 100 ppm for 104-105 weeks. In contrast, the monkeys fed 2.5 or 5.0 ppm in the Allen study displayed some subacute effects similar to Yusho as early as 2 months into the study.

The data upon which the various risk projections of carcinogenicity are made also illustrate the difficulties in such exercises. For example, the data used for projection of risk for Aroclor 1254, the most common Aroclor of human exposure, are

taken from an NCI bioassay project in which the Aroclor 1254 was found under the conditions of the test to be negative for carcinogenicity. In addition, an examination of Table 4 shows that the upper limit of lifetime risk of cancer for the 50th percentile of eaters of the species of interest is generally of the same magnitude in any of the studies shown.

Let us assume that what appear to be increased risks in reproduction from exposure to PCBs based on monkey studies are directly associated with the levels fed, the particular Aroclor fed, and the differences in species sensitivity, i.e., the monkeys are considerably more sensitive to the effect of PCBs than are rodents or humans. It then becomes difficult to explain the differences between the Kimbrough study, which was positive for carcinogenicity in female Sherman rats fed Aroclor 1260 at 100 ppm, and the NCI feeding studies which were negative for Aroclor 1254 fed to Fischer rats at 25, 50 or 100 ppm.

These differences in carcinogenic outcome could be attributed to any of several causes: (a) the Kimbrough study used Sherman rats whereas the NCI study used Fischer rats; (b) three levels of the Aroclor were fed in the NCI study but only one in the Kimbrough study; (c) Kimbrough used 184 test animals at the 100 ppm level, whereas NCI used only 24 animals in each sex group at the 100 ppm level. On the other hand, the difference may be purely statistical in which outcome could be changed in either direction by using comparable protocols and a similar number of animals. Obviously the other elements of unknown quantity in these or any other similar assessments involve the adequacy of the fish consumption data as well as the PCB residue data.

Summary

In any estimates of human risk derived from the extrapolation of animal data, close attention should be given not only to the levels of exposure to the various Aroclors in a variety of animal studies but also to the way in which the exposure relates to human experience. For example, studies in monkeys have reported signs and symptoms similar to those of Yusho after 2 months of exposure to Aroclor 1248 at levels of 2.5 and 5.0 ppm in the diet or 125 and 250 $\mu\text{g/kg}$ body weight/day, respectively. Reproduction problems were reported in these monkey studies at each of these levels after 6 months of exposure.

In contrast, problems of reproduction have been observed in rodents only at considerably higher levels of exposure, e.g., in rats fed 7.2 and 37.0 mg/kg body weight/day of Aroclor 1254 or 100 and 500 ppm in the diet. Rats fed 500 ppm or 35.4 mg/kg

RISK ASSESSMENT OF PCB CONTAMINATION

body weight/day of Aroclor 1260 also exhibited reproduction problems. No problems were observed with Aroclor 1260 at levels of 5 ppm (0.89 mg/kg body weight/day), 20 ppm (1.5 mg/kg body weight/day) or 100 ppm (7.4 mg/kg body weight/day).

In one study, the carcinogenicity of PCBs in rats (Fischer strain) fed Aroclor 1254 at 25 ppm (1.9 mg/kg body weight/day), 50 ppm (3.8 mg/kg body weight/day) or 100 ppm (7.16 mg/kg body weight/day) was reported to be negative under the test conditions. Although some malignancies were observed, there was no statistical difference between test animals and controls. In another study, female Sherman rats fed Aroclor 1260 at 100 ppm (7.4 mg/kg body weight/day) exhibited a statistically significant difference between test animals and controls for hepatocellular carcinomas.

In contrast, there appears to be little evidence of human exposure to these levels in the United States, especially for the consumption of fish. Even in the Yusho experience in Japan, where clinical signs and symptoms were observed, the average level of consumption of PCB residues in the rice oil is estimated to have been 0.75 mg/kg body weight/day.

In the United States, estimates of the daily intake of PCBs for eaters in the 50th percentile are 8.46 $\mu\text{g/day}$ or 0.72 $\mu\text{g/kg body weight/day}$ (based on a 70 kg individual) assuming no PCB tolerance; 7.57 $\mu\text{g/day}$ or 0.11 $\mu\text{g/kg body weight/day}$ assuming a tolerance of 5 ppm, 5.59 $\mu\text{g/day}$ or 0.08 $\mu\text{g/kg body weight/day}$ assuming a tolerance of 2 ppm and 3.30 $\mu\text{g/day}$ or 0.05 $\mu\text{g/kg body weight/day}$ assuming a tolerance of 1 ppm. Estimates of the intake of PCBs for eaters in the 90th percentile are 0.32 $\mu\text{g/kg body weight/day}$ assuming no tolerance and 0.29, 0.21 and 0.13 $\mu\text{g/kg body weight/day}$ assuming a tolerance of 5, 2, and 1 ppm, respectively.

In Michigan sportfishermen, who are presumed to be among the high consumers of fish with PCB residues, the average intake has been reported at 1.7 $\mu\text{g/kg body weight/day}$ with a range of 0.09 to 3.84 $\mu\text{g/kg body weight/day}$.

Problems of interpretations arise in comparing the levels of the various Aroclors which have produced effects in animals, ranging from 125 μg in monkeys to the milligram levels in rodents, with the exposure estimates in humans from fish consumption. For example, estimates of the lifetime human risk of cancer and reproduction problems (Table 4) for exposure in the 90th percentile of fish eaters, i.e., 0.29, 0.21 and 0.13 $\mu\text{g PCB/kg body weight/day}$, indicate risk from exposure well below the average Michigan exposure and certainly well below the levels of exposure in the Yusho incident.

In light of the uncertainties upon which these risk estimates have been made, perhaps an equally

compelling argument could be made for the establishment of either a 2 ppm or a 1 ppm tolerance. As suggested previously, the difference in risk between the two levels decreases only slightly even in the species of interest. From one point of view, this conclusion supports a rationale for proposing the 2 ppm tolerance based on the original calculation of an allowable daily intake resulting from the traditional use of the 1 to 10 safety factor which has been described in the previous section. In this case some similarities exist even in the face of uncertainty. To some, the rationale and logic for establishing 2 ppm can be justified from either the risk approach or the so-called safety approach. To others, nothing short of zero tolerance has any rationale or logic. For these, there may be no answer.

REFERENCES

1. U.S. Department of Health, Education and Welfare. Final Report, DHEW Subcommittee on the Health Effects of Polychlorinated Biphenyls and Polybrominated Biphenyls, Washington, D.C., 1978.
2. Veith, G. D. Baseline concentrations of polychlorinated biphenyls and DDT in Lake Michigan fish, 1971. *Pestic. Monit. J.* 9: 921-928 (1975).
3. Zitko, V., Hutzinger, O., and Chor, P. M. K. Contamination of the Bay of Fundy and Gulf of Marine Area with PCBs, PCTs, and chlorinated DBF and DBD. *Environ. Health Perspect.* 1: 47-50 (1972).
4. National Marine Fisheries Service-NOAA. Seafood consumption study 1978-1974. National Purchase Diary, U.S. Department of Commerce, Washington, D.C., 1976.
5. Kuratsune, M., Masuda, Y., and Nagayama, J. Some of the recent findings concerning Yusho. In: National Conference on Polychlorinated Biphenyls, Chicago, U.S. EPA, Washington, D.C., 1976, EPA Publ. 560/6-75-004.
6. Nagayama, J., Masuda, Y., and Kuratsune, M. Dibenzofurans in Kanechlor. *Japan. J. Hyg.* 30: 126-129 (1975).
7. Schwartz, L. Dermatitis from synthetic resins and waxes. *Int. J. Publ. Health* 26: 586-592 (1986).
8. Kimbrough, R. D. Toxicity of polychlorinated polycyclic compounds and related chemicals. *Crit. Rev. Toxicol.* 2(4): 445-448 (1974).
9. Kutz, F. W., and Yang, H. S. A note on polychlorinated biphenyls in air. In: National Conference on Polychlorinated Biphenyls, Chicago, U.S. EPA, Washington, D.C., 1976, EPA Publ. No. 560/6-75-004.
10. Dennis, D. S. Polychlorinated biphenyls in the surface waters and bottom sediments of the major drainage basins of the United States. In: National Conference on Polychlorinated Biphenyls, Chicago, U.S. EPA, Washington, D.C., 1976, EPA Publ. No. 560/6-75-004.
11. Humphrey, H. E. B., Price, H. A., and Budd, M. L. Evaluation of changes of the level of polychlorinated biphenyls (PCBs) in human tissue. Final Report of FDA Contract No. 223-78-2208, 1976.
12. Brown, J. M. Linearity vs. non-linearity of dose response for radiation carcinogenesis. *Health Phys.* 31: 231-245 (1976).
13. Crump, K. S., Hoel, D. G., Langley, C. H., and Peto, R. Fundamental carcinogenic processes and their implications for low dose risk assessment. *Cancer Res.* 36: 2973-2979 (1976).
14. Gues, H., Crump, K., and Peto, R. Uncertainty estimates for low dose rate extrapolation of animal carcinogenicity data. *Cancer Res.* 37: 8475-8488 (1977).

15. Crump, K. S., Gueass, H. A., and Deal, K. L. Confidence intervals and test of hypotheses concerning dose response relations inferred from animal carcinogenicity data. *Biometrics* 23: 437-451 (1977).
16. Kimbrough, R. D., and Linder, R. E. Induction of adenofibrosis and hepatomas of the liver in BALB c/J mice by chlorinated biphenyls (Aroclor 1254). *J. Natl. Cancer Inst.* 58: 547-552 (1974).
17. McConnell, E. E., Hass, J. R., Altman, N., and Moore, J. A. A spontaneous outbreak of polychlorinated biphenyl (PCB) toxicity in rhesus monkeys (*Macaca mulatta*): toxicopathology. *Lab. Anim. Sci.* 29: 666-673 (1979).
18. Altman, N. H., New, A. E., McConnell, E. E., and Ferrell, T. L. A spontaneous outbreak of polychlorinated biphenyl (PCB) toxicity in rhesus monkeys (*Macaca mulatta*): clinical observations. *Lab. Anim. Sci.* 29: 661-665 (1979).
19. IARC. Polychlorinated Biphenyls and Polybrominated Biphenyls. (Monographs on the Carcinogenic Risk of Chemicals to Humans, Vol. 18). International Agency on Research in Cancer, Lyon, France, 1978.
20. National Cancer Institute. Bioassay of Aroclor 1254 for Possible Carcinogenicity. NCI, Washington, D.C., 1978, DHEW Publ. No. NIH 78-838.
21. Kimbrough, R. D., Squire, R. A., Linder, R. E., Strandbert, J. D., Mondall, R. J., and Bubbe, V. W. Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Aroclor 1260. *J. Natl. Cancer Inst.* 55: 1453-1459 (1975).
22. Allen, J. R., and Norback, D. H. Pathobiological responses of primates to polychlorinated biphenyl exposure. In: National Conference on Polychlorinated Biphenyls, Chicago. EPA, Washington, D.C., 1978, EPA Publ. No. 560/6-75-004.
23. National Research Council. Nitrates. An environmental assessment. Environmental Studies Board Commission on Natural Resources, National Academy of Sciences, Washington, D.C., 1978.
24. National Research Council. Chloroform environmental assessment. Environmental Studies Board, Commission on Natural Resources, National Academy of Sciences, Washington, D.C., 1978.
25. Jellinek, O. F., and Corneliussen, P. E. Levels of PCBs in the U.S. food supply. In: National Conference on Polychlorinated Biphenyls, Chicago, U.S. EPA, Washington, D.C., 1978, EPA Publ. No. 560/6-75-004.
26. McNulty, W. P. Primate study. In: National Conference on Polychlorinated Biphenyls, Chicago, EPA, Washington, D.C., 1978, EPA Publ. No. 560/6-75-004.
27. Allen, J. B., Carstens, L. A., and Barsotti, D. A. Residual effects of short-term, low-level exposure of nonhuman primates to polychlorinated biphenyls. *Arch. Environ. Contam. Toxicol.* 2: 88-95 (1974).
28. Keplinger, M. L., Francher, O. E., and Calandra, J. C. Toxicologic studies with polychlorinated biphenyls. *Toxicol. Appl. Pharmacol.* 18: 204-205 (1971).
29. Linder, R. E., Gaires, T. B., and Kimbrough, R. D. The effects of PCB on rat reproduction. *Food Cosmet. Toxicol.* 12: 63-77 (1974).