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Use of Epidemiology and Clinical Toxicology to Determine Human Risk in Regulating Polychlorinated Biphenyls in the Food Supply

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Polychlorinated biphenyls (PCBs) became a national problem in 1971 when several accidental contaminations of foods were reported. Extensive efforts were successfully undertaken by FDA to reduce the residues of PCBs in food. However, the PCB levels in several species of freshwater fish have raised concern about PCB residues from environmental contamination. This concern prompted a reassessment of the human risk involved in consumption of such fish. The best evidence that a chemical may produce adverse health effects in humans is provided by adequate epidemiologic data confirmed or supplemented by data from valid animal tests. Traditionally, where the regulatory agencies have used results of animal toxicology experiments to evaluate hazard and predict hypothetical safety for humans, "safety factors" such as 1 to 10 or 1 to 100 have been used. The size of the safety factor and the potential exposure to a chemical are established by properly informed scientific judgment. More recent efforts have involved use of a combination of human and animal data and a variety of mathematical models to determine risk. The human epidemiology data and the animal toxicity data of PCB exposure are reviewed, as well as risk assessment in general. Specific examples of risk assessment are presented in which animal data are extrapolated to humans, based on several levels of human exposure to PCBs in fish.

INTRODUCTION

Of the estimated 4.3 million chemicals in existence, some 63,000 are believed to be used in the United States and up to 1000 new ones are introduced each year. Although the discovery and increasing use of new substances have improved the quality of life in the United States in many ways, many of them have proven to be hazardous to man and animals. A major challenge for regulatory agencies such as the U. S. Food and Drug Administration (FDA) is to determine how best to reconcile these potential hazards and potential benefits. This problem is reflected in numerous laws and regulations. Some statutes require that a chemical shown to pose hazards to human and animal health be banned; others require that a chemical be controlled so as to reduce the hazards resulting from its use (Cordle and Kolbye, 1979). 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 them.

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Humans ingest or are exposed to a variety of substances under the regulatory control of FDA, such as foods, food additives, color additives, and to a lesser degree, environmental contaminants such as industrial chemicals, metals, and pesticides. The statutes and regulations used by FDA to control these substances vary with the form of ingestion or exposure and the kind, amount, and length of exposure.

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. Traditionally, the regulatory agencies have used information obtained in animal toxicology experiments to evaluate hazard and predict hypothetical safety in humans by the application of so-called "safety factors," e.g., 1 to 10, or more often 1 to 100. The size of the safety factor and the potential exposure to a chemical are established by properly informed scientific judgment.

More recent efforts involve using a combination of data to provide a reasonable assessment of the risk of a variety of adverse health effects caused by exposure to environmental contaminants (Cordle, 1981; Cordle *et al.*, 1982). To aid in determining the proper action for regulating a toxic chemical in the environment, whether it be a feed additive, industrial pollutant, or natural toxicant, it is helpful to have some knowledge about the background level of the particular adverse health effect that might be expected from exposure to a given substance. This kind of information is usually difficult, if not impossible, to obtain directly from human data. It then becomes necessary to use a combination of data (human epidemiology, animal toxicology, residue, and human exposure) either to set an acceptable level through the use of safety factors based on human exposure to the substance and extrapolation from animal data to human outcome, or to select among a variety of mathematical models to predict risk.

HUMAN DATA

A recent report from the Office of Technology Assessment (OTA, 1981) on improving methods to determine cancer risks indicated that despite the current antiregulatory mood in the U. S., the public dread of cancer is not likely to decrease and Americans still favor regulations that protect public health and the environment. Surveys taken by the Yankelovich, Skelly, and White polling firm show that public support for vigorous food and drug regulation remains extremely high.

The continuing concern about cancer and environmental insults which may increase the risk of cancer are likely to provide impetus for continuing efforts to reduce the incidence and improve the treatment of cancer. Although efforts to improve treatment excite little controversy, efforts to reduce cancer incidence by regulatory intervention generate great debate about whether the expected benefits from the regulations justify their costs. Underlying the problem is the lack of adequate data, both human epidemiological and animal toxicological, to make such determinations, especially in the areas of cancer incidence and mortality, subtle adverse human effects from environmental exposure, and improvements due to regulatory or program intervention.

As an example, the principal data deficiencies for epidemiological assessment of cancer risks, particularly in the regulatory area to determine risk of cancer incidence or mortality, are inadequate information about exposures (to what substances, for

how long, by what method) and lifestyle characteristics such as diet, occupation, and alcohol and tobacco use. Since cancer has a long latency period, relating cancer in the present population to particular exposures might require information from 20 or more years ago. Even when information was collected, records may have been destroyed before they could become useful in cancer epidemiology studies. The following discussion of problems associated with various data sources may be a useful preliminary to a discussion of the present controversy over adverse human health effects resulting from exposure to a wide variety of environmental contaminants, e.g., polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), dioxins, other industrial chemicals and metals, and the debate over animal tests vs epidemiological studies to yield data describing increases or decreases in risks.

Although studies of trends over time in cancer incidence and mortality in defined populations may provide clues to its etiology (provided the data are adequate and valid) unfortunately no national reporting system is available to define the incidence of cancer in the entire United States. As a result, debate continues about the use of incidence data collected by the various National Cancer Institute (NCI) surveys and mortality data collected by the National Center for Health Statistics (NCHS) in the interpretation of cancer trends in the United States.

Three frequently analyzed surveys are the so-called National Cancer Surveys: the first (FNCS), 1937–1939; the second (SNCS), 1947–1948; and the third (TNCS), 1969–1971. Devesa and Silverman (1978) have described in detail the methods used in these surveys. Because these surveys could not be conducted in the same geographical areas, only seven metropolitan areas are common to all three (SCA). For the TNCS, several new areas were added, including two entire states, so that the cancer incidence in rural areas could be described.

Although the population surveyed in each of the three studies was reported to represent 10% samples of the population of the United States at the time of the survey, unfortunately this is not entirely accurate. In fact, no attempt was made to design a valid 10% probability sample of the U. S. for purposes of the studies. The potential problems associated with any inferences directed toward the country as a whole must therefore be recognized. Moreover, when the seven common areas of the three studies are used for comparison, population bases become 5.0, 5.2, and 7.2% of the total U. S. population at the time of each respective survey, rather than the often cited 10%.

NCI started the Surveillance, Epidemiology, and End Results (SEER) program in 1973 to obtain annual cancer incidence and patient survival data on a population base (Devesa and Silverman, 1978). When the SEER program was established in 1973, there were eight geographic participants: Puerto Rico, Detroit, San Francisco, Connecticut, Hawaii, New Mexico, Utah, and Iowa. By 1976 the program included 11 areas: 5 entire states, 5 large metropolitan areas, and the entire Commonwealth of Puerto Rico. The purpose of the SEER program is to measure cancer incidence and patient survival on a continuing basis, so that a new survey does not have to be undertaken every few years to measure cancer incidence. The participating organizations were selected for their demonstrated ability to operate a population-based cancer registry system and for the unique population subgroups that each of them offered.

Unfortunately, the nature of the selection process introduced distortions in population distribution. Thus, although the participants as a whole came from areas that

represented 10% of the total U. S. population (again, not a 10% random sample of the U. S. population), they represented only about 9% of the black population but a larger proportion of other ethnic groups, e.g., 47% of American Japanese, 36% of American Chinese, and 15% of American Indians. With each new study the number of geographic areas that might be compared are reduced; the three NCI surveys comprised seven areas, only four of which were comparable with the SEER program.

Although mortality data by specific cause, age, sex, race, and a variety of demographic variables have been available since 1935, variations in the reporting methods by various states and changes that have gradually occurred in assigning International Classification of Diseases (ICDA) codes to cause of death increase the difficulty of assessing cancer trends over time on the basis of mortality. For example, data on mortality before 1949 are not available for several cancer sites. Trends in mortality from cancer of the uterine cervix and corpus before 1949 are not available for several cancer sites and cannot be evaluated separately because the subsite of the uterus was not coded until the sixth revision of the ICDA. In the fourth and fifth revisions of the ICDA, primary and secondary liver cancers were assigned the same ICDA code, and were not coded separately until 1949.

In addition to the numerous classification changes that have occurred in the past 45 years, the rules for assigning cause of death were substantially revised in 1949, and could introduce artifacts in any observed trends. Perhaps the most important factors affecting error and bias in both mortality and incidence data over time are as follows:

1. improper diagnosis;
2. improvements in case ascertainment;
3. inclusion of prevalent cases;
4. incomplete or incorrect information on death certificates;
5. increased access to medical care;
6. changes in diagnosis over time, among others.

Doll and Peto (1981) have published a thorough discussion of the various strengths and weaknesses, as they see them, of the various data sources that describe the incidence and mortality of cancer in the United States. Besides discussing the difficulties of epidemiological interpretation of data from the NCI surveys and the SEER program to determine cancer incidence and mortality trends over time, Doll and Peto (1981) have also described some general considerations about the current status of the use of epidemiology to determine risk in a variety of settings. They reported that when positive epidemiologic results show an association between exposure or some other variable and cancer, based on a valid study, they tend to dominate any decision to be made on carcinogenicity. However, even risks that will ultimately kill 1% or more of the exposed population may be overlooked or attributed to chance unless a very large-scale investigation is undertaken. In these circumstances, too, when cancer rates among exposed people are only a modest multiple of those among the unexposed, problems of interpretation may become acute, and it may be extremely difficult to disentangle the various contributions of biased information, confounding of two or more factors, and cause and effect. Thus, unless epidemiological studies have been carried out in reasonably large, well-defined groups of people who have been heavily exposed to a particular substance for 2 or 3 decades without apparent effect, they

can offer no guarantee that continued exposure to moderate levels will in the long run be without some increase in risk.

Human evidence can never be totally dispensed with, but the weight that can be given to it varies greatly with the duration and intensity of the exposure experienced by individuals. Positive evidence is always important. Negative human evidence may mean very little, unless it relates to prolonged and heavy exposure; however, it may justify the conclusion that for practical purposes the agent need not be treated as a human carcinogen (Doll and Peto, 1981) if it does relate to human exposure, if it is consistent in a variety of studies (correlation studies over time, cohort studies of exposed individuals, and case-control studies of affected patients), and if the laboratory evidence is also limited in its scope (for instance, to a particular type of tumor in a few species).

Epidemiology has, at present, an undeservedly poor reputation among administrators and regulatory decision makers, who condemn it for failing to achieve ends that it has neither the resources nor data to meet. Epidemiology starts, not with a series of rodents under carefully controlled laboratory conditions over a relatively short lifetime, but with people in an uncontrolled environment and with little possibility of controlling lifetime exposure to a variety of chemical substances. Although epidemiology is more likely than laboratory studies to overlook many small effects of various chemicals, it is much less likely to overlook the potentially large determinants of contemporary cancer rates and trends, especially if these are environmental pollutants or dietary contaminants.

ANIMAL DATA

In discussing the use of animal data in general in risk determination, a fundamental problem with biologic extrapolation is how closely test animals resemble humans. This problem is related to differences in the greater genetic variability of human populations. Populations of test animals are highly inbred and genetically uniform; populations of humans are outbred and include greatly differing genotypes. There is no way to deal with the problem of the human who may differ in sensitivity because there is seldom, if ever, a way to associate sensitivities with the individual. An additional component of the problem concerns poorly understood and unidentified differences in metabolism between test animals and humans.

Although extrapolation techniques are used to estimate the probability of human cancer from test results, opinions differ strongly about the extent to which, and how, extrapolation methods should be used in estimating the amount of human cancer that might be caused by exposure to a carcinogen (OTA, 1981). Various extrapolation models produce estimates of cancer incidence that differ by factors of 1000 or more at levels of human exposure. Given such uncertainty, many individuals refuse to choose one model over another and oppose the use of quantitative extrapolation. Fewer objections are raised against choosing a model to establish priorities for further evaluation of carcinogens as to their likelihood of causing cancer. Regardless of which particular model is chosen, it should produce approximately the same relative ranking as any other.

Proponents of quantitative extrapolation argue that careful attention to the available data is helpful in choosing the correct model and reduces chances for error. There

are now no convincing data to dictate which extrapolation model is best for estimating human cancer incidence or even that one model will be consistently better than all others. However, one particular model for estimating human incidence from animal data (linear, no threshold extrapolation; relating animals and humans on the basis of total lifetime exposure divided by body weight) has been reported to estimate human cancer incidence within a factor of 10 to 100 compared to incidence measured by epidemiological studies. Although this agreement may be gratifying, good data to make these comparisons exist for fewer than 20 substances.

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 generally inadequate to accurately quantify such risk. In a typical case, there are at least four major areas of uncertainty (NRC, 1978a,b):

(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, for instance:

(1) "Typical" exposure levels can be calculated from limited data, or can be estimated arbitrarily to encompass what appears to be a reasonable range.

(2) Dose–response curves derived from animal studies can be used as analogs to estimate human responses.

(3) 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.

(4) 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: for example, see the recent assessment by the National Research Council of halomethanes in drinking water (NRC, 1978b). 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 limited by the assumptions on which they rest, many of which are merely pragmatic and are derived from limited information. Therefore risk estimates of this type cannot be accepted as conclusive results but should be viewed as initial attempts subject to revision as better information becomes available.

In the case study of the regulation of PCBs to be described here, methods which consider the safety factor approach and the mathematical model are used to describe

the problems involved in attempting to determine the risk of adverse human health from exposure to PCBs in some species of fish regulated by FDA.

HISTORY OF EXPOSURE

The term PCBs refers to a complex mixture of different chlorobiphenyls and isomers. PCBs were reportedly first synthesized in 1881 but were not commercially available until 1930 (DHEW, 1976). 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 United States to closed systems, including electrical transformers, capacitors, and heat transformers.

PCB products manufactured by Monsanto in the United States 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 two digits refer to the approximate percentage by weight of chlorine in the mixture. Under this numbering system, Aroclor 1254 contains 12 carbon atoms and about 54% chlorine, and 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, there is scant information on human exposure and its effects on human health in the United States. In this country, sources of minimal human exposure of the population to PCBs are food, air, and water; perhaps the most significant human exposures are limited to sports fishermen consuming freshwater 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 (Veith, 1975; Zitko *et al.*, 1972).

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; sampling usually has been limited to the most important consumption species, which are primarily of marine origin and generally do not contain as high PCB levels as freshwater species from certain locations. An FDA 1978–1979 survey of PCB residues in fish,

including freshwater species, presented some evidence that freshwater 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. The National Marine Fisheries Service (NOAA, 1976) has compiled information on the most important types of fish eaten in the United States 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.

Survey results indicate that some 20 species comprise 95% of all fish products eaten. Although 93% 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 represents a variety of fish species, each of which separately contributes only a minor proportion of the diet. However, when taken as a group, those species represent a major contribution to fish consumption in the United States. The major portion of many of our most familiar types of seafood is imported, and freshwater 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 and mean PCB levels in these species. Table 2 describes the daily intake of PCBs in these people who ate

TABLE 1

MEAN PCB LEVELS IN FDA 1978–1979 DOMESTIC SURVEY BY SPECIES OF INTEREST (CORDLE *et al.*, 1982)

Species of interest[a]	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	0.68	46	0.54	38
Catfish	1.70	295	1.19	281	0.73	219	0.38	150
Buffalo	0.50	36	0.50	36	0.43	35	0.30	31
Fresh water trout	1.36	87	1.28	85	0.76	58	0.37	40
Sea trout	0.56	10	0.56	10	0.56	10	0.27	8
Bass	1.28	15	1.28	15	0.77	11	0.27	10
Chubs	1.14	19	1.14	19	0.96	17	0.58	9
Bluefish	0.53	23	0.53	23	0.44	22	0.37	20
Scup (porgy)	0.72	10	0.72	10	0.72	10	0.53	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

[a] 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.

[b] No tolerance.

TABLE 2

INTAKE OF PCBs FROM FISH FOR EATERS OF SPECIES OF INTEREST (3939/25,947) (CORDLE *et al.*, 1982)

Assumed[a] 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	0.29
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

[a] For assumed tolerance PCB values below the tolerance were eliminated.
[b] Assumed 1500 g daily intake.
[c] Assuming body wt of 70 kg.
[d] No tolerance.

the 12 species of interest (3939 individuals 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 mothers with Yusho had skin discoloration, which slowly regressed as the children grew. Adult Yusho 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: in the dose–response epidemiologic study the average PCB content of the rice oil was 2500 ppm, 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 Yusho patients. Therefore, the effects seen were attributed to PCBs.

In the review by Kuratsune *et al.* (1976) a new factor was introduced, namely, the canned rice oil was also contaminated with chlorinated dibenzofurans (PCDFs) to the extent of 5 ppm. Kuratsune also presented data of Nagayama *et al.* (1975) showing that polychlorinated dibenzofurans were present in the liver and adipose tissue of Yusho patients but not of a control group. Nagayama *et al.* (1975) 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 Yusho 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 compared 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 (1936) 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 thus to cause suppuration. No quantitative data were reported, but a number of preventive practices were recommended.

There have been numerous reports over the ensuing years (Dennis, 1976) of cutaneous eruptions, and systemic manifestations as well, among marine electricians, machinists, capacitor and transformer manufacturing workers, and others occupationally exposed to PCBs. However, in many of these reports the subjects were exposed to mixtures of chlorinated hydrocarbons, quite often of chlorinated naphthalenes and PCBs.

The skin lesions described by Schwartz (1936) 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 (Kimbrough, 1974). Oily skin and large pores seem to predispose to the disease and smooth, tender skin to resist it.

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 (Kutz and Yang, 1976) for samples taken in April, May, and June 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/m^3. Initial identification of the PCBs indicated that they were most comparable to the Aroclor 1254 standard.

Dennis (1976) 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/liter. The 0.05 μg/liter levels were found in the South Atlantic Slope and Eastern Gulf of the Mexico drainage basin. In general, the lowest PCB residue levels were found in drainage basins west of the Mississippi.

The Great Lakes area is also contaminated with PCBs. The Michigan Water Resources Commission (Humphrey *et al.*, 1976) 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 to 11.93 ppm.

The Michigan Department of Public Health has reported the results of a study (Humphrey *et al.*, 1976) which attempted to assess some of the consequences of human exposure to PCBs from the consumption of sportsfish 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 2-year period of the study was 180 lb/per year and the highest single-season consumption was 260 lb. Mean PCB levels in whole lake trout were reported as 18.93 ppm in 1973 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 vs 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 decrease the amount of PCBs in fish actually consumed. 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 5.38 ppm; and in other cooked fish from 0.36 to 2.06 ppm. These levels are decidedly lower than the level of PCB contamination reported in raw trout or 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 0.366 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 consumption of Lake Michigan fish for 90 days or more did not change the PCB blood levels significantly. PCB blood levels during the abstinence showed 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 per year and ranged from 14.17 to 114.31 mg per 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 varied 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 μg/kg/day and ranges from 0.09 to 3.94 μg/kg/day. If the average annual rate of PCB ingestion from fish indicated by these study results continued over the years, the average sports fisherman consuming contaminated fish could receive a total PCB dose equal to 200 mg in approximately 4.3 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.

A recent report describing the residue levels of PCBs in human breast milk by Wickizer *et al.* (1981) illustrates the potential long-term presence of such residues in humans who have been exposed in the past and the need to continue reducing such exposure. Results of the study, which was carried out in the State of Michigan, indicate that of the 1075 breast milk samples collected from 68 of the state's 83 counties, all contained PCB residues ranging from trace amounts to 5 parts per million (ppm) on a fat basis. The mean level was approximately 1.5 ppm; 49.5% of the samples had PCB levels of 1–2 ppm, 17.4% had levels of 2–3 ppm, and 6.14% had levels of 3 ppm or greater. The public health significance of PCB residues in human breast milk and its effects on breast-fed infants are unclear at the present time. Although public health officials and pediatricians have become increasingly concerned about PCB residues in human breast milk and its potential adverse effect on breast-fed infants, given the known benefits of breast feeding authorities have been reluctant to recommend changes in current breast-feeding practices.

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. The numbers of animals used in tests are limited; therefore 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. The linear (or when necessary one-hit) extrapolation from high to low doses is often used (Brown, 1976; Guess *et al.*, 1977; Crump *et al.*, 1976, 1977) because the low end of the dose–response curve cannot be observed with precision. The many uncertainties involved in risk estimation require a conservative approach that 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, 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 (a) the similarity of exposure in animals compared to humans (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) (Veith, 1977; Zitko *et al.*, 1972), and (b) the kinds of outcome that might be comparable to those for humans. In this case 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 (Kimbrough *et al.*, 1975; Kimbrough and Linder, 1974; Altman *et al.*, 1979; McConnell *et al.*, 1979). 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 (DHEW, 1976; IARC, 1978). In assessing the possible toxicological hazard posed by PCBs for humans, it is preferable to use 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. Of the few such long-term studies of the toxicity of PCBs currently available, three long-term studies are discussed in detail below: (a) the National Cancer Institute's bioassay of Aroclor 1254 for possible carcinogenicity in male and female Fischer 344 rats, (b) the study of Kimbrough *et al.* (1975) on the induction of liver tumors in Sherman strain female rats by Aroclor 1260, and (c) the 11-month study by Kimbrough and Linder (1974) 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 (1976) of the pathological responses of rhesus monkeys to PCB exposure is also discussed as a basis for risk assessment.

In the National Cancer Institute's bioassay of Aroclor 1254 (National Cancer Institute, 1978), 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 for 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 Aroclor 1254 administration.

In the study by Kimbrough *et al.* (1975), 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 23 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 in the incidence of tumors in other organs could be observed between experimental and control animals. In the study by Kimbrough and Linder (1974), 50 male BALB/cJ mice were fed a diet containing 300 ppm of Aroclor 1254 for 11 months. Another group of 50 male mice received a diet containing 300 ppm of Aroclor 1254 for 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 300 ppm of Aroclor 1254 for 11 months, nine animals exhibited hepatomas. One of the 24 mice which had received a diet containing 300 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.

PCB mixtures also appear to enhance hepatocarcinogenesis when they are given coincidentally with some chemical carcinogens (Ito *et al.*, 1973) and to inhibit hepatocarcinogenesis when they are given with other chemical carcinogens (Makuira *et al.*, 1974; Hendricks *et al.*, 1977). Preston *et al.* (1981) have reported the promoting effects of Aroclor 1254 and polychlorinated dibenzofuran-free Aroclor 1254 on diethylnitrosamine(DENA)-induced tumors in rats. The rats were treated with DENA in drinking water for 5 weeks and then given a controlled diet or a diet supplemented with either Aroclor 1254 or Aroclor 1254 from which the polychlorinated dibenzofurans (PCDF) were removed. Hepatocellular carcinomas developed in 16% of the rats receiving DENA alone, 64% of the rats treated with DENA followed by the diet containing Aroclor 1254, and 84% of the rats treated with DENA followed by Aroclor 1254 free of PCDF.

Allen and Norback (1976) investigated PCB-related reproductive dysfunctions in the rhesus monkey, a 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 Aroclor 1248 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 aborted 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 in this group were able to carry their infants to term; the remaining three females aborted. The infants born to all mothers receiving Aroclor 1248 at either 2.5 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.

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. First, PCBs are not measured in the fish actually consumed by individuals. PCB residues are measured in fish from one survey; 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 and different ways of measuring effects, 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 1 month. Of these 25,947 persons, 3939 ate the species of fish that contained levels of PCB above 1 ppm.

Since the effect of lowering the tolerance for PCB residues to 1 ppm would change the PCB contributed to the diet by fish only in those fish which contained PCB levels above 1 ppm, risks corresponding to tolerances of 5, 2, 1, or 0 ppm were calculated for those 3939 persons who ate the species of interest. Because no regulatory analytical methods are now 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: 3939/25,947, 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 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.

Estimating the mean PCB level 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 largely on the actual distribution of PCBs before a tolerance is established. The most recent data available on PCB levels in fish were the 1978 and 1979 FDA survey data, consisting of 713 samples for 1978 and 179 samples for 1979 collected from all of the FDA districts. This sampling is not representative or extensive enough to estimate 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 1978–1979 survey was carried out when a tolerance of 5

ppm was in effect. Thus, the effect of going from 0 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 toxicity in general compared 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 2000–3000 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 average daily intake of the combination of contaminants was 37.5 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

TABLE 3

ANIMAL DATA USED FOR RISK EXTRAPOLATION TO HUMANS (CORDLE *et al.*, 1982)

Study	Parameter	Dose of Aroclor fed, ppm						
		0	2.5	5.0	25	50	100	300
Fischer rats fed Aroclor 1254								
Males	Total malignancies	5/24			2/24	9/24	12/24	
Females		4/24			13/24	8/24	9/24	
Combined		9/28			15/48	17/48	21/48	
Males	Liver carcinoma and adenomas	0/24			0/24	1/24	2/24	
Females		0/24			0/24	1/24	2/24	
Combined		0/48			0/48	2/48	4/48	
Males	Hematopoietic system	3/24			2/24	5/24	9/24	
Females		4/24			6/24	6/24	6/24	
Combined		7/48			8/48	11/48	15/48	
Female Sherman rats fed Aroclor 1260	Hepatocellular carcinomas	1/173					26/184	
BALB/cJ male mice fed Aroclor 1254	Hepatomas, neoplastic nodules	0/5						9/22
Female monkeys fed Aroclor 1248[a]	Problems of reproduction	0/12	3/8	7/8				

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

TABLE 4

UPPER CONFIDENCE LIMITS (99%) ON LIFETIME RISKS OF CANCER AND PROBLEMS OF REPRODUCTION IN EATERS OF FISH SPECIES OF INTEREST (CORDLE *et al.*, 1982)

		Lifetime risks per 100,000[a]							
		50th percentile eaters				90th percentile eaters			
Study	Basis parameter/species	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	Total malignancies (male and female rats)	4.1	3.7	2.7	1.6	10.6	9.8	7.2	4.4
NCI	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	Hematopoietic (male and female rats)	2.7	2.4	1.8	1.1	7.0	6.5	4.7	2.9
Kimbrough	Liver carcinoma	1.3	1.2	0.8	0.5	3.4	3.1	2.3	1.4
Kimbrough	Liver hepatomas (mice)	2.0	1.8	1.2	0.8	5.2	4.8	3.5	2.2
Allen	Female-male reproduction (monkey)[c]	337	307	222	132	883	811	595	367

[a] All risks are lifetime risks computed as rates per 100,000 of the population at risk.
[b] For each assumed tolerance, PCB values below the tolerance were eliminated.
[c] Inasmuch as the monkeys were fed Aroclor 1248 for only 6 months, the risk computed for problems of reproduction are not true lifetime risks.

from the 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 (1976) reported that from the 1969–1975 period, PCB levels significantly decreased in all foods except 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 do 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 wt/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 (2 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 μg/kg body wt/day was estimated. When rat data were used, the estimated no-effect level in man was 3 μg/kg body wt/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 μg/day. However, more recent analysis has raised serious questions as to the validity of the original interpretation of results, and these data thus 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 for monkeys compared to other species. McNulty (1976) and Allen *et al.* (1976; 1974) have pointed out 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.* (1971) reported low mating indices and decreased survival

of pups in rodents receiving Aroclor 1242 at 100 ppm. They found no reproduction effects with Aroclor 1242 or 1254 at 1 or 10 ppm although other studies in rodents (Linder *et al.*, 1974) 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).

To illustrate additional differences between the monkey and rodent sensitivities to PCBs, the Sherman rats in the Kimbrough study fed 100 ppm of Aroclor 1260 for 23 months apparently exhibited no subacute effects, nor did the Fischer rats fed 25, 50, or 100 ppm for 104–105 weeks in the NCI study. 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 on which the various risk projections of carcinogenicity are based 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 fish species of interest is generally of the same magnitude in any of the studies.

Let us assume that what appears to be increased risks in reproduction from exposure to PCBs based on monkey studies is directly associated with the levels fed, the particular Aroclor fed, and the greater sensitivity to the effect of PCBs of monkeys than 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 μg/kg body wt/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 con-

siderably higher levels of exposure, e.g., in rats fed 7.2 and 37.0 mg/kg body wt/day of Aroclor 1254 or 100 and 500 ppm in the diet. Rats fed 500 ppm or 35.4 mg/kg body wt/day of Aroclor 1260 also exhibited reproduction problems. No problems were observed with Aroclor 1260 at levels of 5 ppm (0.39 mg/kg body wt/day), 20 ppm (1.5 mg/kg body wt/day), or 100 ppm (7.4 mg/kg body wt/day).

In one study, the carcinogenicity of PCBs in rats (Fischer strain) fed Aroclor 1254 at 25 ppm (1.9 mg/kg body wt/day), 50 ppm (3.8 mg/kg body wt/day) or 100 ppm (7.16 mg/kg body wt/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 wt/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 was estimated at 0.75 mg/kg body wt/day.

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

In Michigan sportsfishermen, who are presumed to be among the highest reported consumers of fish with PCB residues, the average intake has been reported at 1.7 μg/kg body wt/day with a range of 0.09 to 3.94 μg/kg body wt/day.

Thus 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 μg PCB/kg body wt/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 or a 1 ppm tolerance. As suggested previously, the differences 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

ALLEN, J. R., AND NORBACK, D. H. (1976). Pathobiological responses of primates to polychlorinated biphenyl exposure. In *National Conference on Polychlorinated Biphenyls, Chicago.* EPA Pub. No. 560/6-75-004. U. S. Environmental Protection Agency, Washington, D. C.

ALLEN, J. B., CARSTENS, L. A., AND BARSOTTI, D. A. (1974). Residual effects of short-term, low-level exposure of non-human primates to polychlorinated biphenyls. *Arch. Environ. Contam. Toxicol.* 2, 86–95.

ALTMAN, N. H., NEW, A. E., MCCONNELL, E. E., AND FERRELL, T. L. (1979). A spontaneous outbreak of polychlorinated biphenyl (PCB) toxicity in rhesus monkeys (*Macaca mulatta*): Clinical observations. *Lab. Anim. Sci.* 29, 661–665.

BROWN, J. M. (1976). Linearity vs non-linearity of dose response for radiation carcinogenesis. *Health Phys.* 31, 231–245.

CORDLE, F., AND KOLBYE, A. C. (1979). Food safety and public health—Interaction of science and law in the federal regulatory process. *Cancer* 43 (5), 2143–2150.

CORDLE, F. (1981). The use of epidemiology in the regulation of dioxins in the food supply. *Reg. Toxicol. Pharmacol.* 1, 379–387.

CORDLE, F., LOCKE, R., AND SPRINGER, J. (1982). 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). *Environ. Health Perspect.* 45, 171–182.

CRUMP, K. S., HOEL, D. G., LANGLEY, C. H., AND PETO, R. (1976). Fundamental carcinogenic processes and their implications for low dose risk assessment. *Cancer Res.* 36, 2973–2979.

CRUMP, K. S., GUESS, H. A., AND DEAL, K. L. (1977). Confidence intervals and test of hypotheses concerning dose response relations inferred from animal carcinogenicity data. *Biometrics* 33, 437–451.

DENNIS, D. S. (1976). 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,* EPA Pub. No. 560/6-75-004. U. S. Environmental Protection Agency, Washington, D. C.

DEVESA, S. S., AND SILVERMAN, D. T. (1978). Cancer incidences and mortality trends in the United States: 1935–1974. *J. Nat. Cancer Inst.* 60, 545–571.

U. S. Department of Health, Education, and Welfare. (DHEW) (1976). *Final Report. DHEW Subcommittee on the Health Effects of Polychlorinated Biphenyls and Polybrominated Biphenyls.* DHEW, Washington, D. C.

DOLL, R., AND PETO, R. (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in the U. S. today. *J. Nat. Cancer Inst.* 66, 1192–1308.

GUESS, H., CRUMP, K., AND PETO, R. (1977). Uncertainty estimates for low dose rate extrapolation of animal carcinogenicity data. *Cancer Res.* 37, 3475–3483.

HENDRICKS, J. D., PUTNAM, T. P., BILLS, D. D., AND SINNHUBER, R. O. (1977). Inhibiting effect of a polychlorinated biphenyl (Aroclor 1254) on aflatoxin B_1 carcinogenesis in rainbow trout (*Salmo gairdneri*). *J. Nat. Cancer Inst.* 59, 1545–1551.

HUMPHREY, H. E. B., PRICE, H. A., AND BUDD, M. L. (1976). *Evaluation of Changes of the Level of Polychlorinated Biphenyls (PCBs) in Human Tissue.* Final Report of FDA Contract No. 223-73-2209.

International Agency on Research in Cancer. (IARC) (1978). *Monograph on the Carcinogenic Risk of Chemicals to Humans. Vol. 18. Polychlorinated Biphenyls and Polybrominated Biphenyls.* IARC, Lyon, France.

ITO, N., NAGASAKA, H., ARI, M., MAKUIRA, S., SUGIHARA, S., AND HIRO, K. (1973). Histopathologic studies on liver tumorogenesis induced in mice by technical polychlorinated biphenyl and its promoting effect on liver tumors induced by benzene hexachloride. *J. Nat. Cancer Inst.* 51, 1637–1646.

JELINEK, C. F., AND CORNELIUSSEN, P. E. (1976). Levels of PCBs in the U. S. food supply. In *National Conference on Polychlorinated Biphenyls, Chicago.* EPA Pub. No. 560/6-75-004, U. S. Environmental Protection Agency, Washington, D. C.

KEPLINGER, M. L., FRANCHER, O. E., AND CALANDRA, J. C. (1971). Toxicologic studies with polychlorinated biphenyls. *Toxicol. Appl. Pharmacol.* 19, 204–205.

KIMBROUGH, R. D. (1974). Toxicity of polychlorinated polycyclic compounds and related chemicals. *Crit. Rev. Toxicol.* 2(4), 445–448.

KIMBROUGH, R. D., SQUIRE, R. A., LINDER, R. E., STRANDBERT, J. D., MONDALI, R. J., AND BUBSE, V. W. (1975). Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Aroclor 1260. *J. Nat. Cancer Inst.* 55, 1453–1459.

KIMBROUGH, R. D., AND LINDER, R. E. (1974). Induction of adenofibrosis and hepatomas of the liver in BALB/c J mice by chlorinated biphenyls (Aroclor 1254). *J. Nat. Cancer Inst.* 53, 547–552.

KURATSUNE, M., MASUDA, Y., AND NAGAYAMA, J. (1976). Some of the recent findings concerning Yusho. In *National Conference on Polychlorinated Biphenyls, Chicago.* EPA Pub. No. 560/6-75-004. U. S. Environmental Protection Agency, Washington, D. C.

KUTZ, F. W., AND YANG, H. S. (1976). A note on polychlorinated biphenyls in air. In *National Conference on Polychlorinated Biphenyls, Chicago.* EPA Pub. No. 560/6-75-004. U. S. Environmental Protection Agency, Washington, D. C.

LINDER, R. E., GAINES, T. B., AND KIMBROUGH, R. D. (1974). The effects of PCB on rat reproduction. *Food Cosmet. Toxicol.* 12, 63–77.

MAKUIRA, S., AOE, H., SUGIHARA, S., HIRAO, K., ARI, M., AND ITO, N. (1974). Inhibiting effects of polychlorinated biphenyls on liver tumorogenesis in rats treated with 3'-methyl-4-dimethylaminoazobenzene, *n*-2-fluorenylacetamide, and diethylnitrosamine. *J. Nat. Cancer Inst.* 53, 1255–1257.

MCCONNELL, E. E., HASS, J. R., ALTMAN, N., AND MOORE, J. A. (1979). A spontaneous outbreak of polychlorinated biphenyl (PCB) toxicity in rhesus monkeys (*Macaca mulatta*): Toxicopathology. *Lab. Anim. Sci.* 29, 666–673.

MCNULTY, W. P. (1976). Primate study. In *National Conference on Polychlorinated Biphenyls, Chicago.* EPA Pub. No. 560/6-75-004. U. S. Environmental Protection Agency, Washington, D. C.

NAGAYAMA, J., MASUDA, Y., AND KURATSUNE, M. (1975). Dibenzofurans in Kanechlors. *Japan J. Hyg.* 30, 126–129.

National Cancer Institute (1978). *Bioassay of Aroclor 1254 for Possible Carcinogenicity.* DHEW Pub. No. (NIH 78-838), NCI, Washington, D. C.

National Marine Fisheries Service (NOAA) (1976). *Seafood Consumption Study 1973–1974.* National Purchase Diary, U. S. Department of Commerce, Washington, D. C.

National Research Council (NRC) (1978a). *Nitrates: An Environmental Assessment.* Environmental Studies Board, Commission on Natural Resources, National Academy of Sciences, Washington, D. C.

National Research Council (NRC) (1978b). *Chloroform Environmental Assessment.* Environmental Studies Board, Commission on Natural Resources, National Academy of Sciences, Washington, D. C.

Office of Technology Assessment (OTA) (1981). Assessment of Technologies for Determining Cancer Risks from the Environment. OTA, U. S. Government Printing Office, Washington, D. C.

PRESTON, B. D., VAN MILLER, J. P., MOORE, R. W., AND ALLEN, J. R. (1981). Promoting effects of polychlorinated biphenyls (Aroclor 1254) and polychlorinated dibenzofurans-free Aroclor 1254 on diethylnitrosamine-induced tumorogenesis in the rat. *J. Nat. Cancer Inst.* 66 (3), 509–515.

SCHWARTZ, L. (1936). Dermatitis from synthetic resins and waxes. *Int. J. Pub. Health* 26, 586–592.

VEITH, G. D. (1975). Baseline concentrations of polychlorinated biphenyls and DDT in Lake Michigan fish, 1971. *Pestic. Monit. J.* 9, 921–939.

WICKIZER, T. W., BRILLIANT, L. B., COPELAND, R., AND TILDEN, R. (1981). Polychlorinated biphenyl contamination of nursing mothers' milk in Michigan. *Amer. J. Pub. Health* 71 (2), 132–137.

ZITKO, V., HUTZINGER, O., AND CHOR, P. M. K. (1972). Contamination of the Bay of Fundy & Gulf of Marine Area with PCBs, PCTs, and chlorinated DBF and DBD. *Environ. Health Perspect.* 1, 47–50.