PCBs: HUMAN AND ENVIRONMENTAL HAZARDS

Edited by

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and
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PREFACE

Polychlorinated biphenyls (PCBs) have been used for industrial purposes for over 50 years. Nonetheless, except for the occupational exposure first reported in the early 1940s, concern about the ecological and human health impact did not become an environmental issue until 1966 when S. Jensen published "Report of a New Chemical Hazard" in the *New Scientist* (Volume 32, page 612). Research since then has offered insights into major aspects of the problem, and this volume presents the reader with varied viewpoints, the latest research findings, and an overview of the steps that are being taken to solve these problems, particularly in the Great Lakes region.

The material in this book is based on papers given at an International Symposium on PCBs in the Great Lakes held at Michigan State University March 17-19, 1982. At that time, scientists and other concerned citizens presented and evaluated data regarding PCBs to help develop a basis for regulations to protect human health.

The book is divided into five parts. Chapters 1 through 8 present background, scientific, social, and political information that is important to understand the PCB contamination problem. Chapters 9 through 12 describe the current state of the art with respect to chemical analyses and monitoring. Chapters 13 through 19 summarized the information on the metabolism, biotransformation, toxicology, and persistence of PCBs. Chapters 20 through 22 present the data on the effects of PCBs on human health. Chapters 23 through 30 address the roles of federal and state agencies in the regulation of PCBs.

While much remains to be learned about the effects of chronic low levels of PCB exposure on human beings and animals, it is hoped that the information presented in this volume will stimulate further research and encourage the readers to formulate conclusions about the essential issues and the necessary related actions.

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ACKNOWLEDGMENTS

The success of the International Symposium on PCBs in the Great Lakes, presented by the Michigan State University Center for Environmental Toxicology, was due to the interest and dedication of the many individuals and organizations involved, and it is our pleasure to acknowledge as many of them as possible First, a grateful acknowledgment is extended to Jerry B Hook, Director of the Center for Environmental Toxicology, for his early conceptualization of the plan for this symposium and subsequent contributions to its implementation. Second, we would like to give special thanks to the members of the symposium planning committee John Hesse and Harold E.B Humphrey of the Michigan Department of Public Health, William E. McCracken of the Michigan Department of Natural Resources, and Burton D Cardwell of the Michigan Department of Agriculture. Third, our special appreciation is extended to all of the authors whose written presentations made this book possible Every attempt was made to reproduce their manuscripts accurately, however, the editors accept responsibility for any errors Fourth, we would like to thank the Michigan State University Agricultural Experiment Station and Cooperative Extension Service, which actively supported this meeting. We would also like to express our appreciation for the support provided by the Michigan State University Institute of Water Research; the Michigan Departments of Agriculture, Natural Resources, and Public Health the Michigan Toxic Substance Control Commission, and the Michigan Sea Grant College Program Finally, we would like to acknowledge and thank Terry Waters, Mary Robinson, and Carole Abel for their expert secretarial and typing skills; and Donna Taxon for her editorial assistance

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PART I

SCIENTIFIC, SOCIAL, AND POLITICAL OVERVIEW

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CHAPTER 1

INTRODUCTION

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Historically, two factors have greatly affected the cost of illness and disease. One is the personal health care provided by hospitals and private physicians; the other is environmental health services, including traditional public health work. The diseases that tend to generate the greatest cost are the complex ones and the basic knowledge of their etiology or causes is sometimes lacking. The cause and effect relationships between communicable diseases are fairly easy to identify, but when we are dealing with the effects on health of chemicals, and of environmental impurities, these are very, very poorly understood. As one chemical effect on health comes to be understood, others are used in an even wider spiral.

In public health, we try to stress prevention from three different approaches. The first, by one's own personal behavior; that is, we can smoke less or not at all. We can drink less alcohol or not at all. Secondly, by some institutional means, when our personal behaviors are inadequate for the problems we face. In this case, the state, in the broadest sense, can supply safe water and help insure the adequate disposal of wastes. The third approach is none of the above. For example, neither industry nor government, or we as individuals, can do much about some of these social pressures that tend to increase susceptibility to disease. Finally, there seems to be a genetic component of susceptibility, but we know that our ancestors are very hard to change.

The complexity of the polychlorinated biphenyl (PCB) issues argues that some institutional action is necessary; and if history is to be believed, it is likely to be the most effective means for preventing PCB induced illnesses. As a

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regulatory agency, I think we know that the regulation and control of PCBs and other toxic chemicals are fraught with many difficulties. Human epidemiological data are often unavailable, and conclusions from them are uncertain because of population limitations. Animal tests, as many of you well know, are extremely costly; and even then they only provide information at high dosages in one or two species. Short-term tests are useful but they are not necessarily definitive.

Now, against that background, I think it is also recognized that decision-making at all levels of government presupposes the availability of a body of information on the basis of which the relative merits of alternative policies can be analyzed and considered. If this information, or the data base, is constrained or invalid, resulting decisions must also be constrained or invalid, and sometimes this threatens the whole fabric of democratic government. So we would hope that the discussions here for the next few days would clarify many of the issues on the health effects as well as the ecotoxicological effects of PCBs and, at the same time, reduce some of the constraints on data generation as well as on data interpretation. We know that widely different opinions have been expressed on several of the topics which will be discussed here in the next three days. In such instances, the organizers of this Symposium have tried to select speakers who are most qualified to explain each of two or more different points of view. Finally, a glance at the contents of this Symposium gives us some idea about the broad spectrum of topics which specify the extent of the PCB issue. While these three days are rather full and comprehensive, this Symposium, as you well know, is not all inclusive but it is certain to contribute to a new perspective on PCBs and thus engender a renewed vigilance about other chemicals which are pervasive in our biosphere.

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CHAPTER 2

THE PCB PROBLEM: AN OVERVIEW

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This International Symposium on Polychlorinated Biphenyls (PCBs) in the Great Lakes addresses a class of problem that is not much older than many of us gray-beards in the audience. However, chemical contamination of man's environment by his technology is almost as old as civilized man (e.g., there is skeletal evidence of probable lead poisoning in sites of very ancient mining and smelting activity). But global contamination with toxic organics began with the burgeoning of industrial chemistry between World Wars I and II and picked up substantially both in the diversity of hazardous materials and in the tonages that were released into the earth's hydrosphere, atmosphere, lithosphere, and biosphere after World War II.

Global contamination by hazardous materials came into sharp focus as atmospheric testing of nuclear weapons by the United States and the U.S.S.R. reached high levels prior to the 1963 Limited Nuclear Test Ban Treaty. International research by a wide range of disciplines established that testing presented risks to man of cancer, birth defects, and genetic change from radionuclides contained in fallout. Other scientists assembled data on global circulation, atmospheric residence times, fallout patterns, deposition on land and water surfaces, and movement of radionuclides through natural and human ecosystems and into man and his tissues.

The 1963 Limited Nuclear Test Ban Treaty was an early triumph of environmental sanity even though it has been honored by only the major testing nations.

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The halogenated hydrocarbons were manufactured for various kinds of industrial uses from pesticides to paints and inks, from cutting oils to heat exchange fluids, among many other uses. It wasn't long after these compounds entered uses which resulted in widespread releases to the atmosphere and to surface waters that they began to appear in fish, birds, food animals, and indeed, in man himself. DDT and its related persistent halogenated pesticides received much attention as contamination was demonstrated to be virtually world wide and that body burdens were carried by most living organisms including man. The scientific data on presence, accumulation, and effects began to appear in the scientific literature in the 1950s; but Rachel Carson's dramatic book, "Silent Spring," published in 1962, drew public attention to this global contaminant.

Similar global and ecosystem quantification approaches to those for nuclear fallout were used to assess the transport, fate, and effects of these broad spectrum pesticides on non-target organisms and to assess the potential risk to man's ecosystems and his health. Unlike the case with atmospheric testing of nuclear weapons, DDT and related pesticides had high utility in food production and infectious disease suppression. The debate and political and judicial processes that eventually led to the 1972 ban on the use of DDT in the United States was provided with a broad array of research data. Up to and even following the Environmental Protection Agency's (EPA) decision to ban the use of DDT after December 31, 1972, in the United States, scientists continued to debate the interpretations of the research cited as the basis of the decision. Indeed, the late Phil Handler, former President of the National Academy of Sciences and a respected biochemist, argued to his last year that the human health data cited for that decision would not stand careful bias-free scrutiny.

In a somewhat different category of global contamination, we note that the very light weight chlorofluoroalkanes have been said to be associated with damage to the earth's stratospheric ozone layer (NAS, 1976). Here the hazard to man would be indirect, coming from reduced screening of ultra violet radiation and a possible increase in skin cancer for man, as well as potential biological and climatic effects. The atmospheric transport, upper atmospheric and stratospheric physics, and photochemistry, the sampling problems and modeling are difficult and costly. In the most recent reassessments (Norman, 1981), there continues to be ambiguity about the relationship between releases of chlorofluoroalkanes and changes in the ozone layer. Nevertheless, in 1979 the United States placed a ban on uses of these chemicals which result in significant release to the atmosphere.

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In the case of the polybrominated biphenyls (PBBs) we have an array of compounds that were widely used in ant control and as fire retardants, but they are not in the same class as DDT and the PCBs as global contaminants. The PBBs did seriously contaminate several areas of the United States, including Michigan's food animal industry through the now famous error in mixing Firemaster rather than a chemical food additive into animal feeds.

The gathering and use of research data in making various regulatory agency and legislative decisions in Michigan's PBB episode again demonstrate that the setting of specific standards, establishing disposal specifications, and many other aspects are made in contexts where the scientific data could equally support other standards and other specifications.

The story of PCBs is one of major global contamination by a group of highly useful chemicals which now appear in the tissues of most living creatures as well as in the air, water, soils, and sediments over most of the earth. The Great Lakes have been a particularly interesting contamination area with substantial food-chain concentration of these highly fat soluble chlorinated hydrocarbons.

While the manufacture of PCBs is now prohibited in the United States, the size of the environmental burden in waters, sediments, soils, disposal sites, and in deployed transformers and other containers of PCBs is very large, having been estimated by the National Academy of Science (1979) study to be 82 million kg.

The reduction of the DDT body burdens of animals and man following its 1972 banning by EPA gives some encouragement that the PCBs will also eventually decrease to trivial levels in systems such as the Great Lakes. However, PCBs exhibit differences in mobility, biodegradability, waste storage, continuing uses, and other characteristics that suggest we are likely to have to cope with this hazardous pollutant for some time to come (NAS, 1979).

As we look at the challenge of continuing to live with an environment and food chain that is contaminated with PCBs, we need to refine our assessments of the risk it poses for man; and where those risks are significant, seek options for mitigating them. The economic and political aspects of these alternatives will continue to be significant issues in the Great Lakes region for some time to come.

Much of the program of this symposium addresses research pertinent to these questions by highly capable scientists in a

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broad array of disciplines. I would like to make some observations about decision making in these complex areas where the research is pressed to the limits of our current knowledge, and where the political and economic ramifications of the decisions are substantial. These observations come from over 20 yr of participation in environmental research and various, mostly federal, scientific advisory bodies and professional organizations.

First, research results that bear on urgent decisions rarely have the luxury of science's normal process of rigorous peer review prior to publication with the journal articles then subjected to broad international scrutiny and commonly replicated by others and the resulting confirmation or refutation published.

Under the very best of these urgent decision conditions, we find highly competent scientists doing first class research; and almost as soon as it is available, it is provided to decision makers for use in the decision process. Under less satisfactory conditions we may find over-worked, in-house researchers performing rushed, last-minute, poorly conceived research or contracting with readily available, marginally capable individuals who generate scientifically questionable results which are added to the decision pool with no, or inadequate, review. Under the least desirable circumstances, we may have studies set up "to prove" a previously arrived at conclusion; and inadequate care allows such bias to shape experimental design and the results, often without overt dishonesty, but certainly reflecting poorly on the role of science in decision making.

Secondly, my long exposure to the process has given me the impression that decision makers in developmental agencies or regulatory agencies often have the unenviable problem of being subject to very strong public or not-so-public pressures, predominantly from one side or the other in arriving at their decisions. In spite of the popular mythology, we get rather stout-hearted and honest people in these roles in our state and federal agencies. However, their decisions can (as we would assume) reflect the people they feel they represent. Regulatory agencies, all else being equal, tend to make decisions that are "fail safe" while developmental agencies would tend to make decisions that protect large prior investments by major sectors of the economy.

When the body of scientific data is equivocal, it is occasionally the case that such decisions cite data that do not represent what the scientific community--given its normal slow

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processes--would agree to constitute unequivocal support of the decision.

By these over-simplifications of an exceedingly difficult societal process, I'm not sketching a good guys-bad guys picture. Rather, developmental agencies tend to draw their scientific data from a group of scientists who come at questions differently from those chosen by regulatory agencies. If there is plenty of time and if both groups publish their studies in high quality, broadly read journals, these perspective biases tend to be worked out and a balanced picture emerges. In today's fast paced world,this is not always the case with environmental decision making.

A third observation. On occasion one agency holds both developmental and regulatory responsiblities and we find scientists of one section taking issue with scientists of the other. Many of us will remember the early Atomic Energy Commission (AEC) in this connection. Internally in our better chemical manufacturing companies, the toxicology section researchers may on occasion take issue with product development researchers. I personally remember participating in an environmental issue and providing opposing testimony to colleagues in other departments here at the University.

Experienced scientists are not surprised that perspectives do influence research programs, but they are frequently surprised that a decision may be made by a public official in spite of the absence of convincing specific data. However, we need to appreciate that the political processes in representative governments reflect the perceptions of the constituencies who impact government. When a wide spectrum of a population is frightened and believes they are at great risk, regulatory agencies find it very difficult to be in the position of trying to convince them the risk is small or negligible. Thus, regulatory agencies--whether of executive, legislative, or judical bodies--will tend to take a "fail safe" posture under conditions they perceive to reflect high public apprehension.

I trust that these over-simplified observations based on long exposure to these processes are not interpreted as reflecting a cynical perspective. I intend these remarks simply to underline the role that I believe the scientific community must play in these complex societal processes. This is an important, indeed an essential role. The collective product of the scientific enterprise must be the gathering of data, the evaluation of that data, and the rendering of judgments supported by the data, with clearly identified assessments of the confidence with which the data, the evaluation, and the judgment may be taken. Most of us have conducted experiments.

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the results of which we were later unable to repeat or confirm. Most of us have also conducted experiments which failed to control or even to take cognizance of a particular variable which later proved to be highly significant. Science moves ahead by this process of improvement, correcting errors, and international discourse over results.

Environmental decision making which considers both scientific data and the perceptions of citizens about risk also moves in ways that aren't precisely straight lines or point events. While connected, scientific research and political decision making are far from one and the same process. As scientists, we must provide high quality research as our product; and even when it is unpopular to do so, we must question poor research, recognizing always that the agency's decision is a very different product than those of research.

I wish you well in this very interesting symposium on PCBs in the Great Lakes. The complexity of the science questions that bear on the important regulatory and developmental issues insures that this is no open-and-shut issue. As citizens of the Great Lakes basin we are affected by the recreational, economic, and health questions its PCB burdens pose. But, as scientists, our obligation is to provide the highest quality science as expeditiously as good science will permit so as to better understand the various questions. We can be thankful we aren't also burdened with responsibility for making the key decisions that have and will be made.

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CHAPTER 3

AN OVERVIEW OF THE SCIENTIFIC BASIS FOR CONCERN WITH POLYCHLORINATED BIPHENYLS IN THE GREAT LAKES

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The ubiquitous distribution of residue forming xenobiotic substances, particularly organochlorine compounds, is rapidly becoming apparent. Widespread dissemination is suggested by a variety of studies of areas presumably remote from the direct industrial and/or cultural influences attributable to man, including melting snow in the Antarctic (Peterle, 1969; Peel, 1975), mammals of the Arctic (Bowes and Jonkel, 1975; Clausen et al., 1974); in the surface waters and atmosphere above the Sargasso Sea (Bidleman and Olney, 1974); the waters of the Gulf of Mexico (Giam et al., 1973); remote island sites (Swain, 1978); rainfall over the Hawaiian Islands (Benvenue et al., 1972); and the sediments of Siberian Lake Baikal (Swain, 1980). Although a number of these compounds have been banned outright, or had their utilization severely restricted in the 1969 to 1971 time period, they still are routinely reported in the Great Lakes Basin (International Joint Commission, 1977, 1978). Strachan and Huneault (1979) note three principal reasons for this continued occurrence:

(1) the widespread geographic occurrence of organochlorine substances;
(2) their persistence and relatively long biological half-lives; and
(3) the demonstration of long range atmospheric transport of these substances.

The persistence of many of the xenobiotic compounds of concern is measured in years or decades (International Joint Commission, 1975). This fact, combined with hydraulic detention times of the order of centuries for the sequentially coupled

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St. Lawrence Great Lakes (Rainey, 1967), yields a potential for bioaccumulation and bioconcentration virtually unparalleled elsewhere in North America. When one considers that the Great Lakes represent 20 percent of the world's freshwater and 95 percent by volume of the freshwater of the adjacent United States (McGrath, 1980), the problem is of even greater interest.

Current estimates suggest that more than 30,000 chemicals of commercial and/or industrial significance are used in the Great Lakes Basin, and in excess of 1,000 new compounds are developed each year (Maugh, 1978; Ames, 1979; Costle, 1980). Even if only a small proportion of these compounds are toxic in nature (<1.0%), and if a similarly small percentage enters the Great Lakes ecosystem, the magnitude of the problem is readily apparent.

It is not surprising, then, that contamination by toxic organic substances of anthropogenic origin have been suggested as the major environmental concern confronting both the scientific community and the management structure associated with the Great Lakes (Sonzogni and Swain, 1980).

Because of the complexity of the issue; the multiplicity of substances and their metabolities, daughter compounds, and degradation products; the size and scope of the ecosystem in both spatial and temporal scales; and the intricacy and interdependence of the trophic system in the Great Lakes, it has been reasoned that an ecosystem approach to the problem was the method of choice for examining the relationships and proportions of these interdependent entities (Swain, 1981). The use of such a conceptual framework related to toxic substances has been previously suggested (Gillett et al., 1974; Metcalf et al., 1975; Thomann, 1978, 1980; Bierman and Swain, 1978; and Weininger, 1978). However, few of these approaches have considered man as an integral part of the environmental structure, and none have regarded him as both an interactive and reciprocal part of the ecosystem. The intent of this overview is to use an ecosystem approach to address the basis of scientific concern surrounding polychlorinated biphenyls (PCBs) and their impact on environmental quality and human health in the Great Lakes Basin.

Polychlorinated biphenyls are a group of chlorinated hydrocarbons manufactured by the controlled chlorine substitution of the biphenyl molecule. More than two hundred arrangements of components are theoretically possible, but in actual practice, slightly more than 100 formulations have been used. PCBs have been manufactured and used on a worldwide basis. In the United States, PCBs were produced under the trade name Aroclor. The Japanese produced not only Aroclors, but also

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Sanotherm and Kaneclor; in Germany the trade name Clophen was used, as was Pyralene and Phenoclor in France, Fenclor and Phenoclor in Italy, Sovol in the USSR, and Delor in Czechoslovakia.

The chemistry, properties, and characteristics have been previously described in detail (Hutzinger et al., 1974; Brinkman and De Kok, 1980) and need not be reiterated here.

In general, however, PCBs were first synthesized in 1881, but did not see industrial application in the United States until 1929. For nearly 50 yrs until cessation of production in 1977, U.S. industry manufactured and used PCBs because of their high dielectric constant, their chemical and thermal stability, their non-flammability, and their low cost.

Their uses included insulating fluids in electrical transformers and capacitors in the power industry, heat transfer substances, cutting oils, hydraulic fluids, lubricating oils, and plasticizers for making brittle plastic pliable. Application was also found for these compounds in paints, printing inks, carbonless copy paper, sealants, adhesives, and the like.

Regrettably, the identical characteristics which made the PCBs industrially desirable, also make them persistent and accumulatible in the environment. The chemical stability of the PCB compounds is unique. They are resistant to acid-base reactions, hydrolysis, chemical oxidation, photodegradation, thermal changes, and most chemical agents. As a result of this stability, they are generally poorly metabolized by biologic systems. PCB solubility in water is very low, and appears to decrease with increasing chlorination (Hutzinger et al., 1974). They have relatively low vapor pressures, but in general, the lower the chlorine content, the more likely the compound is to volatilize.

PCBs tend to bond tightly to particulate matter, notably soils and sediments. Thus, surface waters with low particulate loads may have barely detectable levels of PCB in the water mass, but high concentrations in the bottom sediments. Of further concern is the effective half-life of these substances. Present estimates of PCB half-life fall into a range of 8 to 15 yrs in environmental samples.

Since PCBs are poorly soluble in water and extremely soluble in oils and fats, they tend to partition out of the aquatic ecosystem into biologic tissue. Because of their persistence and the fact that they are poorly metabolized, these substances bioaccumulate in the food chain, often increasing

several orders of magnitude in concentration at each succeeding trophic level.

Because PCBs bioaccumulate so successfully through the food chain, and because the components of the Great Lakes ecosystem are inexorably linked and interrelated, it is possible, at least in theory, if not in actual fact, to trace the PCBs added to the atmosphere as a result of burning waste oil to heat a building through the Great Lakes ecosystem to exposure of man and his progeny. To accomplish this end, an ecosystem approach to the problem provides a means of organizing the massive amount of existing information (Figure 1).

The upper lakes--Superior, Michigan, and Huron--are the most susceptible. This increased susceptibility is a function of:

(1) large surface areas,
(2) extreme depth,
(3) low suspended sediment loads per unit volume,
(4) low autochthonous production of particulates,
(5) highly sensitive biota, and
(6) extreme hydraulic detention times (Sonzogni and Swain, 1980).

Of the upper lakes, Lake Michigan currently has the largest mass of PCB residue contained within its basin. The principal sources of PCB to this ecosystem are three:

(1) atmospheric inputs,
(2) tributary loads, and
(3) direct discharges.

The preponderance of scientific evidence suggests that the atmosphere can be a major source of PCBs to the Great Lakes. While there is currently scientific controversy over the exact magnitude and the extent of atmospheric deposition, all estimates suggest that it is the principal source. Murphy and Rzeszutko (1977) estimated that 80 percent of the PCBs contributed to Lake Michigan were from atmospheric sources, and Eisenreich et al. (1981), using more recent data, estimate a value approaching 60 percent. Regardless of the exact percentage, it is clear that the bulk of the contributions of PCBs to the upper lakes is derived from atmospheric sources.

Earlier estimates (Swain, 1981) suggested that these loadings drive the water mass concentrations to the extent of 2-10 ng/l (ppt). Recent measurements for open Lake Huron, however, indicate values nearly an order of magnitude below these levels; in a range of from 0.2-1.0 ng/l (Swain et al.,

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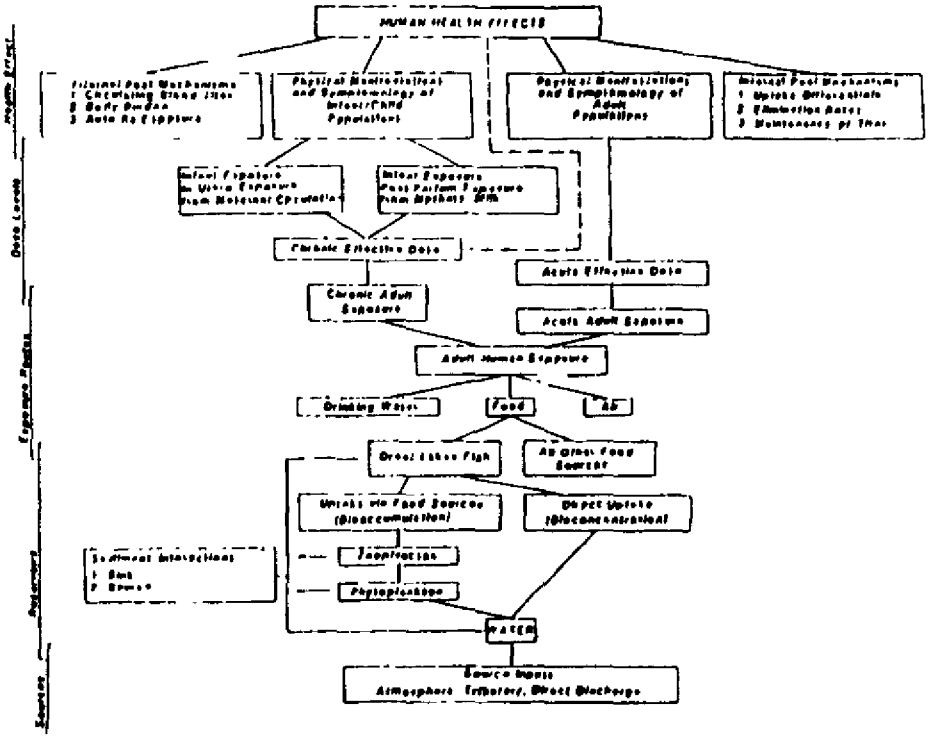

Figure 1. A conceptual framework for toxic substances in the Great Lakes ecosystem.

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1982). While the samples taken from the rest of the Great Lakes yet await analysis, similar declines in observed PCB levels in these bodies of water may reasonably be anticipated.

Planktonic constituents living in the surrounding milieu tend to biomagnify the level of PCB to the order of 20 to 200 ng/g (ppb). Glooschenko et al. (1976), working on Superior, observed PCBs in 7 of 15 seston samples in concentrations ranging from 0.5 to 1.3 mg/kg. Of the eight remaining samples, three had levels that were below the threshold of detection, while the remaining five were detectable, but below the level of quantification. Veith et al. (1977) report from 0.05 to 0.12 mg/kg PCB, and 0.04 to 0.05 mg/kg of DDT residues and 2.0 ug/kg of dieldrin in the samples of the opossum shrimp Mysis relicta taken from the Minnesota north shore of western Lake Superior during 1973-1974.

While the sediments act alternately as both a sink and a source of pollutant materials depending on a variety of naturally occurring processes--adsorption, desorption, sinking rates, wind driven resuspension, and the like--the planktonic constituents of the second trophic level, in turn, fall prey to the consumers of the next trophic level, the Great Lakes fish.

Because of their widespread availability throughout the Great Lakes ecosystem, their persistence, their lipophilicity, and the long hydraulic detention times of the coupled system, polychlorinated biphenyl compounds tend to biomagnify in Great Lakes biota; either through food chain transfer (bioaccumulation) or as a function of direct uptake across gill or other surface membranes (bioconcentration). While there is some question as to the exact magnitude of contribution of each of these phenomena to the body burden of Great Lakes fish--Weininger (1978) estimates approximately 95 percent food chain transfer and 5 percent direct uptake; Thomann (1978) calculates 75 percent bioaccumulation and 25 percent bioconcentration--there is no argument that the higher trophic levels show substantially increased levels of PCBs as compared with the water masses, the primary producers, and the primary consumers.

As a result of these phenomena, and because of the relative ease of quantifying organochlorine compounds at the mg/kg level, as compared with levels in the ug/kg or ng/kg range, Great Lakes fish have been extensively utilized as both monitoring and indicator organisms. While an exhaustive analysis of extant data is beyond the scope of this effort, a synopsis of historic studies is provided in Table 1 and summarized in Table 2.

The fish of particular concern, the sports species can be expected to achieve levels in an approximate range of 2 to 20

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TABLE I

Polychlorinated Biphenyls Observed in Fish of the Great Lakes

Location	Species	Date	Quantity in mg/kg	Reference
Lake Superior				
Nearshore, Ontario	Lake Trout	1974	0.387-1.796	Upper Lakes Ref. Group, 1977
	Walleye	1974	0.243-3.635	Upper Lakes Ref. Group, 1977
	Whitefish	1974	0.125-3.635	Upper Lakes Ref. Group, 1977
	Herring	1974	0.193-0.757	Upper Lakes Ref. Group, 1977
Nearshore, Minnesota	Mottled Sculpin	1974	0.035-0.600	Upper Lakes Ref. Group, 1977
Nearshore, Michigan	Lake Trout	1974	N.D.-0.46	Upper Lakes Ref. Group, 1977
	Siscowet Trout	1974	1.95-8.37	Upper Lakes Ref. Group, 1977
	Whitefish	1974	0.27-0.89	Upper Lakes Ref. Group, 1977
	Herring	1974	0.22-1.03	Upper Lakes Ref. Group, 1977

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Table 1 (cont.)

Location	Species	Date	Quantity in mg/kg	Reference
	Mottled Sculpin	1974	N.D.-0.46	Upper Lakes Ref. Group, 1977
Nearshore, Wisconsin	Bullhead	1974	0.017-0.050	Upper Lakes Ref. Group, 1977
	Northern Pike	1974	0.020-0.030	Upper Lakes Ref. Group, 1977
	Walleye	1974	0.080-0.218	Upper Lakes Ref. Group, 1977
	Yellow Perch	1974	0.046-0.05	Upper Lakes Ref. Group, 1977
	White Sucker	1974	0.024	Upper Lakes Ref. Group, 1977
	Rainbow Smelt	1974	0.202-0.263	Upper Lakes Ref. Group, 1977
	Brown Trout	1974	0.145	Upper Lakes Ref. Group, 1977
	Rainbow Trout	1974	0.065-0.110	Upper Lakes Ref. Group, 1977
Open Lake	Slimy Sculpin	1974	0.16-0.36	Upper Lakes Ref. Group, 1977
	Burbot	1974	1.40-1.59	Upper Lakes Ref. Group, 1977

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Table 1 (cont.)

Location	Species	Date	Quantity in mg/kg	Reference
	Lake Trout	1974	0.80-4.32	Upper Lakes Ref. Group, 1977
Nearshore, Apostle Islands	Lake Trout (Fillets-Whole Fish)	1974	1.68-1.80	Upper Lakes Ref. Group, 1977
Nearshore, Wisconsin	Rainbow Smelt	1974-1976	0.250-0.270	IJC, 1978
	Rainbow Trout	1974-1976	0.40-0.110	IJC, 1978
	Brown Trout	1974-1976	0.130-0.235	IJC, 1978
	Perch	1974-1976	0.02-0.450	IJC, 1978
	Northern Pike	1974-1976	0.03-0.65	IJC, 1978
	Bullhead	1974-1976	0.003-0.03	IJC, 1978
	Carp	1974-1976	0.19-1.34	IJC, 1978
Isle Royale Area	Siscowet Trout	1975	2.06-6.90	IJC, 1978
	Whitefish	1974	0.72-3.77	IJC, 1978
Nearshore, Michigan	Lake Trout	1975	0.62-2.58	IJC, 1978
	Siscowet Trout	1975	2.06-31.20	IJC, 1978
	Herring	1974	0.22-1.03	IJC, 1978
	Chubs	1974	0.62-0.69	IJC, 1978

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Table 1 (cont.)

Location	Species	Date	Quantity in mg/kg	Reference
Nearshore, Wisconsin	Lake Trout	1974	2.7	U.S. Fish & Wildlife Ser., 1974
	Lake Whitefish	1974	0.7	U.S. Fish & Wildlife Ser., 1974
	Bloater	1974	1.2-2.7	U.S. Fish & Wildlife Ser., 1974
Nearshore, Michigan	Lake Trout	1974	3.7-4.5	U.S. Fish & Wildlife Ser., 1974
	Herring	1974	1.1	U.S. Fish & Wildlife Ser., 1974
	Bloater	1974	0.61-0.79	U.S. Fish & Wildlife Ser., 1974
Isle Royale	Lake Trout	1974-1976	0.3-1.72	Swain, 1978
	Siscowet Trout	1974-1977	5.4-8.4	Swain, 1978
	Whitefish	1974-1976	0.37	Swain, 1978
Lake Michigan				
	Bloater	1972	3.12-8.17	Willford et al., 1976
	Bloater	1973	4.20-6.33	Willford et al., 1976
	Bloater	1974	4.83-6.22	Willford et al., 1976
	Coho Salmon	1972	4.93-15.4	Willford et al., 1976

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Table 1 (cont.)

Location	Species	Date	Quantity in mg/kg	Reference
	Coho Salmon	1973	8.24-16.6	Willford et al., 1976
	Coho Salmon	1974	6.99-16.3	Willford et al., 1976
	Lake Trout	1972	3.53-25.3	Willford et al., 1976
	Lake Trout	1973	9.36-30.6	Willford et al., 1976
	Lake Trout	1974	7.05-47.4	Willford et al., 1976
Vicinity Saugatuck & East-Central Lake Area (annual mean values)	Bloater	1972	5.66	U.S. Fish & Wildlife Ser. in IJC, 1978
	Bloater	1973	5.24	U.S. Fish & Wildlife Ser. in IJC, 1978
	Bloater	1974	5.57	U.S. Fish & Wildlife Ser. in IJC, 1978
	Bloater	1975	4.54	U.S. Fish & Wildlife Ser. in IJC, 1978
	Bloater	1976	4.11	U.S. Fish & Wildlife Ser. in IJC, 1978
	Coho Salmon	1972	10.93	U.S. Fish & Wildlife Ser. in IJC, 1978
	Coho Salmon	1973	12.17	U.S. Fish & Wildlife Ser. in IJC, 1978
	Coho Salmon	1974	10.45	U.S. Fish & Wildlife Ser. in IJC, 1978

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Table 1 (cont.)

Location	Species	Date	Quantity in mg/kg	Reference
	Coho Salmon	1975	10.77	U.S. Fish & Wildlife Ser. in IJC, 1978
	Coho Salmon	1976	9.21	U.S. Fish & Wildlife Ser. in IJC, 1978
	Lake Trout	1972	12.86	U.S. Fish & Wildlife Ser. in IJC, 1978
	Lake Trout	1973	18.93	U S. Fish & Wildlife Ser. in IJC, 1978
	Lake Trout	1974	22.91	U.S. Fish & Wildlife Ser. in IJC, 1978
	Lake Trout	1975	22.28	U.S. Fish & Wildlife Ser. in IJC, 1978
	Lake Trout	1976	18.68	U.S. Fish & Wildlife Ser. in IJC, 1978
Nearshore, Michigan	Salmon	1974	0.22-1.64	Mich. Dept. Agr. in IJC, 1978
	Lake Trout	1974-1975	0.99-27.80	Mich. Dept. Agr. in IJC, 1978
	Chub	1974	2.87-3.74	Mich. Dept. Agr. in IJC, 1978

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Table 1 (cont.)

Location	Species	Date	Quantity in mg/kg	Reference
Nearshore, Wisconsin	Carp	1976	16.3	Kleinert, 1976
	Lake Trout	1976	2.9-33.8	Kleinert, 1976
Lake Huron				
Vicinity of Bay Port, Michigan	Yellow Perch	1974	2.2-3.9	U.S. Fish & Wildlife Ser. in IJC, 1978
	Carp	1971	3.0-4.7	U.S. Fish & Wildlife Ser. in IJC, 1978
Vicinity of Alpena, Michigan	Yellow Perch	1974	0.65-0.94	U.S. Fish & Wildlife Ser. in IJC, 1978
	White Sucker	1974	0.73	U.S. Fish & Wildlife Ser. in IJC, 1978
	Whitefish	1974	0.46	U.S. Fish & Wildlife Ser. in IJC, 1978
Nearshore, Michigan	Brown Trout	1974	0.35-1.93	Mich. Dept. Agr. in IJC, 1978
	Carp	1974	1.06-4.30	Mich. Dept. Agr. in IJC, 1978
	Chinook Salmon	1974	1.29-2.97	Mich. Dept. Agr. in IJC, 1978
	Yellow Perch	1974	0.02-0.23	Mich. Dept. Agr. in IJC, 1978

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Table 1 (cont.)

Location	Species	Date	Quantity in mg/kg	Reference
	Brown Trout	1975	0.64-1.70	Mich. Dept. Agr. in IJC, 1978
	Carp	1975	0.92-2.75	Mich. Dept. Agr. in IJC, 1978
	Lake Trout	1975	0.99-5.7	Mich. Dept. Agr. in IJC, 1978
	Rainbow Smelt	1975	0.69-0.80	Mich. Dept. Agr. in IJC, 1978
	Whitefish	1975	0.20-0.43	Mich. Dept. Agr. in IJC, 1978
Nearshore, Michigan	Brown Trout	1974-1975	1.1-1.3	Upper Lakes Ref. Group, 1977
	Perch	1974-1975	N.D.-0.20	Upper Lakes Ref. Group, 1977
	Rainbow Trout	1974-1975	0.94	Upper Lakes Ref. Group, 1977
	Whitefish	1974-1975	N.D.-0.34	Upper Lakes Ref. Group, 1977
	Chinook	1974-1975	2.31	Upper Lakes Ref. Group, 1977
Nearshore, Ontario	Perch	1974-1975	0.003-0.40	Upper Lakes Ref. Group, 1977

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Table 1 (cont.)

Location	Species	Date	Quantity in mg/kg	Reference
	White Sucker	1974-1975	0.125-1.53	Upper Lakes Ref. Group, 1977
	Rainbow Trout	1974-1975	0.09-2.17	Upper Lakes Ref. Group, 1977
	Walleye	1974-1975	0.258-0.827	Upper Lakes Ref. Group, 1977
	Northern Pike	1974-1975	0.024-0.085	Upper Lakes Ref. Group, 1977
[illegible] Lake	Burbot	1974-1975	0.77-2.35	Upper Lakes Ref. Group, 1977
	Bloater Chubs	1974-1975	0.89-361	Upper Lakes Ref. Group, 1977
	Slimy Sculpins	1974-1975	0.52-0.77	Upper Lakes Ref. Group, 1977
Lake Erie				
Nearshore	Shad	1977	0.69-1.72	Herdendorf et al., 1978
	Perch	1977	0.35-1.34	Herdendorf et al., 1978
	Catfish	1977	3.4-3.85	Herdendorf et al., 1978
	Drum	1977	0.26-0.36	Herdendorf et al., 1978
Nearshore, Michigan	Carp	1974	3.7-3.9	Mich. DNR in IJC, 1978
	Catfish	1974	2.97-3.0	Mich. DNR in IJC, 1978
	Drum	1974	0.52	Mich. DNR in IJC, 1978

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Table 1 (cont.)

Location	Species	Date	Quantity in mg/kg	Reference
	Yellow Perch	1974	0.03	Mich. DNR in IJC, 1978
	Walleye	1974	0.22	Mich. DNR in IJC, 1978
	White Bass	1974	2.19	Mich. DNR in IJC, 1978
	Carp	1975	3.17-3.9	Mich. DNR in IJC, 1978
	Catfish	1975	3.29-5.65	Mich. DNR in IJC, 1978
	Drum	1975	0.11	Mich. DNR in IJC, 1978
	Salmon	1975	0.38	Mich. DNR in IJC, 1978
	Walleye	1975	0.34	Mich. DNR in IJC, 1978
	White Bass	1975	0.55-1.78	Mich. DNR in IJC, 1978
	Rainbow Trout	1975	0.70	Mich. DNR in IJC, 1978
	Chinook Salmon	1975	0.25	Mich. DNR in IJC, 1978
Lake Ontario Nearshore	American Eel	1976	0.12-14.77	IJC, 1977
	Largemouth Bass	1976	0.09-2.92	IJC, 1977
	Smallmouth Bass	1976	0.45-10.93	IJC, 1977
	White Bass	1976	0.83-5.17	IJC, 1977
	Black Crappie	1977	0.51-0.89	IJC, 1977
	Brown Bullhead	1977	0.30-2.81	IJC, 1977
	Channel Catfish	1977	1.93-4.05	IJC, 1977
	Northern Pike	1977	0.58-4.17	IJC, 1977
	Yellow Perch	1977	0.22-1.72	IJC, 1977
	White Perch	1977	0.86-9.70	IJC, 1977

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Table 1 (cont.)

Location	Species	Date	Quantity in mg/kg	Reference
	Coho Salmon	1977	1.60-10.27	IJC, 1977
	Chinook Salmon	1977	2.36-13.47	IJC, 1977
	Brown Trout	1977	1.31-15.14	IJC, 1977
	Lake Trout	1977	1.38-18.30	IJC, 1977
	Rainbow/Steelhead	1977	10.64	IJC, 1977
	Walleye	1977	0.08-1.21	IJC, 1977
St. Lawrence River (edible portions of fish)	Smallmouth Bass	1976	0.25-16.17	IJC, 1977
	Northern Pike	1976	1.18-3.93	IJC, 1977
	Yellow Perch	1976	0.46-4.26	IJC, 1977
	White Perch	1976	0.66-11.80	IJC, 1977
	Walleye	1976	1.41-6.52	IJC, 1977
Eastern Nearshore Area (edible portions of fish)	Catfish	1976	7.9-12.42	IJC, 1977
	Pike	1976	0.22-0.89	IJC, 1977
	Coho Salmon	1976	2.0-5.38	IJC, 1977
	Sucker	1976	0.96-1.15	IJC, 1977
	Carp	1976	1.3-3.29	IJC, 1977
	White Perch	1976	0.82-2.8	IJC, 1977
	American Eel	1976	4.4-8.5	IJC, 1977
	Yellow Perch	1976	0.28-0.52	IJC, 1977
	Bullhead	1976	0.21-0.41	IJC, 1977
	Rainbow Smelt	1976	1.12-1.22	IJC, 1977

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Table 1 (cont.)

Location	Species	Date	Quantity in mg/kg	Reference
	Sheepshead	1976	0.89-6.6	IJC, 1977
	Rock Bass	1976	0.11-5.21	IJC, 1977
Adjacent to Credit River	Coho Salmon	1975	2.1-22.5	IJC, 1977
Various Nearshore Areas	Alewife	1975	0.14-381	Haile et al., 1975
	Smelt	1975	1.40-3.49	Haile et al., 1975
	Slimy Sculpin	1975	1.58-9.17	Haile et al., 1975
	Rock Bass	1976	N.D.-2.60	IJC, 1978
	White Perch	1976	4.5-6.4	IJC, 1978
	Yellow Perch	1975	1.7-3.3	IJC, 1978
	Rock Bass	1975	2.0-2.4	IJC, 1978

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TABLE 2

Representative Mean Contaminant Ranges Summarized From Literature Values in Selected Great Lakes Fish

Lake	Species of Fish	DDT (mg/kg)	PCB (mg/kg)
Superior	Lake Trout	0.5-1.0	2.0-4.0
	Siscowet Trout	5.0-10.0	8.0-15.0
	Yellow Perch	0.01-0.05	0.02-0.05
Michigan	Lake Trout	5.0-10.0	18.0-20.0
	Coho Salmon	3.0-10.0	7.0-17.0
	Yellow Perch	--	0.5-1.0
Huron	Lake Trout	2.0-4.0	3.0-5.0
	Yellow Perch	0.04-0.4	0.04-0.4
Erie	Coho Salmon	0.3-0.5	0.5-1.5
	Yellow Perch	0.1-0.5	0.03-0.1
Ontario	Lake Trout	2.0-4.0	6.0-8.0
	Coho Salmon	1.0-2.0	6.0-8.0
	Yellow Perch	0.03-0.1	0.5-3.0

mg/kg. For the first time in 50 yrs of science on the Great Lakes, it has become necessary to consider man as a truly reciprocal and interactive part of the Great Lakes ecosystem. Up to now, man has had the luxury of regarding himself as simply contributing to "source inputs" in the ecosystem equation. Suddenly, it is becoming painfully evident that as "top predators" in the Great Lakes food web, mankind has collectively become a 'reservoir" or "sink" term in the ecosystem toxic substances mass conservation expression.

Public exposure to orally ingested PCBs is rather effectively controlled through the United States Food and Drug Administration's tolerance levels set for these substances. Established in 1973, the FDA levels restrict fish, shellfish, and th fat portions of poultry above 5.0 mg/kg; require levels no greater than 2.5 mg/kg (fat portion) in milk and dairy products; 0.5 mg/kg in eggs; 0.2 mg/kg in infant and junior foods; and limit PCBs in packaging materials to 10 mg/kg. At

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the time of the preparation of this summary, FDA has undertaken steps to reduce the tolerance levels/permissible amounts to 2.0 mg/kg in fish and shellfish; 1.5 mg/kg in milk and milk products; 0.3 mg/kg in eggs; and 3.0 mg/kg in poultry. Establishment of these reductions in acceptable values has been delayed in part by action enjoining the activities of the agency. The lower levels for eggs, milk and dairy products, and poultry went into effect on August 28, 1979, but the National Fisheries Institute filed objections to the proposed standards for fish and requested a hearing. Hence, the implementation of this guideline has not occurred.

The theoretical effects of adopting and implementing regulatory standards of this sort are two:

(1) reduction of the absolute magnitude of exposure per unit of time, and hence measurable levels of body burdens among the general population, and

(2) a tendency toward a leveling effect in exposure potentials throughout the population-at-large, leading to a more nearly uniform exposure experience across a population.

While exposure among the general population via food sources has been demonstrated, particularly prior to the 1973 limitations imposed by the Food and Drug Administration (Kolbye, 1972; Biros et al., 1970; Finklea et al., 1972), there appears to be no data from "market basket" studies supporting substantial differences in current levels of exposure from food sources between one area of the country and another. Jelinek and Corneliussen (1976) report that "the occurrence of PCBs has narrowed to the point where freshwater fish are now the primary source of PCBs in our diet." They further note that "the daily intake of PCB for the average citizen is low, since his consumption of freshwater fish is low." They also add, however, "PCB intake could be quite different for those people whose diets include substantial quantities of sports fish." Thus, if the exposure potential from food sources for the general population can be assumed to be approaching a uniform level, and that, as a result of FDA limitation, that level is at least an order of magnitude below the exposure potential for consumption of Great Lakes fish, an argument for consideration of the health consequences of Great Lakes Basin residents is raised.

As was previously noted, public consumption of Great Lakes fish heavily contaminated with PCBs is regulated through the embargo of commercial catches in the United States by the

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counties of the State of Michigan that border on and abut lake Michigan, there are presently well over a third of a million licensed sports fishermen. As a group, these sports fishermen and their families consume more than three times the national average of fish per year. Preliminary studies by the Michigan Department of Public Health (Humphrey, 1976; Humphrey, 1983) have demonstrated what appears to be a direct, nearly linear relationship between the total amount of Great Lakes fish consumed and the absolute circulating titer of PCBs in the blood of these individuals.

For humans, as well as Great Lakes biota, there are two major routes of toxic action--acute toxicity and chronic toxicity. The acutely toxic activity is dose/time dependent. A very high exposure over a very short period of time to exceed the "critical dose" or "effective dose level" is sufficient to produce physical manifestations and symptomology in adult human populations.

The effects of long-term chronic exposure are less well known. Such phenomena can be assumed to be dose/time dependent, and to involve a very long lag phase. Typically, with organic toxicants, this period may be in excess of 25 to 35 yrs.

Of present critical concern, however, is the potential for serious and significant impacts upon selected "high risk" populations. A mother, belonging to the group of consumers who eat large quantities of Lake Michigan sports species of fish, selectively increases her own circulating blood titer of PCBs as a result of additional exposure to fish.

Transplacental passage of the PCB molecule has been repeatedly demonstrated (Kodama and Ota, 1980; Masuda et al., 1978; Polishuk et al., 1977; Funatsu et al., 1972; and Jacobson et al., 1983). As a result, the mother's unborn child is also exposed to PCB as a result of maternal circulation. Literature values and early Great Lakes experimental efforts suggest that, for the period of 9 months of gestation, the unborn infant may be exposed to a significant level of his mother's blood burden (Kuwabara et al., 1978; Jacobson et al., 1983). This exposure comes at a time of unprecendented growth and development, and critical maturation of tissues.

At birth, the child may be exposed to an additional source of PCB as a result of nursing. A recent nationwide survey of 1,038 nursing mothers in the United States (summarized in Ames, 1979) demonstrated that approximately a third (30%) of the women had PCB in measurable amounts in their breast milk. A more recent study of 1,057 Michigan mothers reported PCB in breast

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milk of all participants (Wichizer et al., 1981). In this latter survey, an average level of 2.3 mg/kg was found.

Among individuals consuming Lake Michigan fish who participated in the early phase of the Michigan blood level PCB study, a single analysis of breast milk was made (Humphrey, 1976). The sample was received from a mother in the low exposure class who had consumed 12.73 kg of Lake Michigan fish during a two year period (1973-74), approximately one-half of the maximum recommended by the Michigan Department of Public Health.

This woman had a circulating blood titer of 0.053 ug/kg PCB. A breast milk sample collected the same month as the blood sample contained 4.0 ug/kg PCB on a fat basis (2% fat content), equivalent to 80.0 ug/kg PCB on a whole milk basis. This value is substantially above the level reported in the literature for the general population, and for that portion of Michigan residents unexposed to large quantities of Lake Michigan fish. On the basis of present work, the value reported for this sample is not unusual for breast milk from women exposed to substantial quantities of Lake Michigan fish (Humphrey, 1981, personal communication).

It can be reasonably assumed that a nursing infant will consume 1 kg of breast milk per day. At a level of 80 ug/kg, the child could be exposed to 80 ug of PCB each day.

Dose, as contrasted with exposure, is calculated upon mass of compound per mass of body weight per unit of time. To carry the analogy of exposure to dose, it is necessary to make only one further assumption; i.e., that a reasonable birth weight is 3-4 kg (approximately 6-8 pounds). Thus, the dose rate for a child of these proportions would be between 20 and 26.6 ng/kg/day, some 20 to 25 times the maximum daily dose rate of 1 ug/kg/day PCB recommended by the U.S. Food and Drug Administration for adult intake.

Internal pool mechanisms may be very important in the long view; however, at present their effects are unknown. It is known, however, that as the child undergoes natural growth and developmental cycles, he is repeatedly subjected to intensive spurts of growth in which most of the available fatty materials are drawn into circulation and metabolized to aid in the provision of energy for the tremendous anabolic activites that are going on. Since PCBs are lipophylic in nature, it is to be expected that the stored contaminant will be mobilized with the body fat, potentially producing a selective form of autore-exposure.

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The effect of this activity is unknown. It is known, however, that much of the mobilization would occur at the times when the myelin sheathes surrounding the central nervous system are being laid down. Myelin, of course, is an insulating substance and is composed largely of lipid materials. Thus, it may be reasonably expected that some impact on the body's centers of higher integration will result (Fein et al., 1982; Jacobson et al., 1983).

It has also been suggested from recent studies that PCBs and their congeners have a major impact on reduction of sperm production and motility in males (Dougherty et al., 1980).

The problem is inordinately complex. It is not currently possible to project or calculate the absolute risks associated with exposure to PCBs and their congeners. However, it is possible to estimate a relative risk of exposure for those individuals who consume Great Lakes fish, as compared with those who do not.

It appears that the major source of PCB for Lake Michigan Basin resident populations is derived from Great Lakes sports species of fish. To place this contaminant burden in perspective, it is necessary to examine the relative contribution of other kinds of sources. For PCBs and their congeners, among non-occupationally exposed individuals, the sources are two: respired ambient air and potable drinking water.

Estimates of the average annual intake from orally ingested drinking water suggest very minimal exposure levels, even assuming that mean raw water values at approximately 4 ng/l are used (Table 3). Finished drinking water levels are at least an order of magnitude below that of raw water values; hence, the 4 ng/l estimates represent a very conservative upper mean.

TABLE 3

Estimated Oral Exposure to PCB From Great Lakes Drinking Water

Average Raw Water PCB Content	4 ng/l
Average Daily Water Intake Per Person	2 l
Maximum Daily Oral Exposure	8 ng/day
Maximum Annual Oral Exposure	2.9 ug/yr

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When one examines the potential for respiratory exposure, similar relationships are observed. Assuming complete and instantaneous sorption and selective uptake of PCBs at the alveolar surface of the lung, based on an average tidal volume of approximately half a liter, the annual uptake of PCBs through the respiratory route is only on the order of 5 to 10 ug annually (Table 4).

In terms of exposure potential using maximum exposure values, it is possible to breathe the air in the Lake Michigan Basin (outside of the metropolitan centers) and drink its polished drinking water for a very long time before you would achieve the same effective exposure from eating a single one-pound fish meal of Lake Michigan lake trout. The length of time required for equivalent exposure, of course, is a function of the concentration of contaminants in the fish (Table 5). If 12 mg/kg may be taken as a reasonable mean for Lake Michigan lake trout currently, more than 500 yrs would be required for an equivalent exposure from air and water. If the contaminant level in fish is reduced to 5 mg/kg, the currently applicable tolerance limit for interstate sales, a 200 yr equivalent exposure is received from each 0.45 kg of fish. At the current Canadian standard, and the guideline proposed for the U.S., 2

TABLE 4

Estimated PCB Exposure from the Atmosphere

Level of PCB in the Atmosphere[1]	1.5 ng/m^3
Average Rate of Respiration	20 respirations/min 1,200 respirations/hr 28,800 respirations/day
Mean Tidal Volume of the Lungs	500 ml
Total Daily Air Volume Respired	14,400 l/day 14.4 m^3/day
Average Daily Respiratory Exposure	14.4 m^3/day x 1.5 ng/m^3 = 21.6 ng/day
Annual Exposure	7.8 ug/yr

[1]Eisenreich, S. (1981)

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TABLE 5

Relative Exposure to PCB from Great Lakes Fish Compared With Irreducible Sources

A. Relative exposure to PCB from consumption of Lake Michigan lake trout:

Scenario No. 1: 12 ppm PCB in lake trout flesh

12 ppm = 12 mg/kg; since 1 lb = 0.45359 kg, 12 mg/kg x 0.45359 kg/lb = 5.443 mg/lb. Thus, lake trout at 12 ppm PCB contain 5,443 ug PCB per pound of fish.

Scenario No. 2: 5 ppm PCB in lake trout flesh

5 ppm = 5 mg/kg; 5 mg/kg x 0.45359 kg/lb = 2.267 mg/lb. Thus, lake trout at 5 ppm PCB contain 2,267 ug PCB per pound of fish.

Scenario No. 3: 2 ppm PCB in lake trout flesh

2 ppm = 2 mg/kg; 2 mg/kg x 0.45359 kg/lb = 0.907 mg/lb. Thus, lake trout at 2 ppm PCB contain 907 ug PCB per pound of fish.

B. Total estimated mean ambient exposure to PCB from drinking water and respired air:

Estimated total annual exposure = 2.92 ug/yr (water) + 7.88 ug/yr (air) = 10.8 ug/yr

C. Estimated time required for equivalent exposure from ambient sources as from consumption of one pound of fish:

Estimated time for equivalent exposure = $\frac{\text{Quantity of PCB in one pound of fish (ug)}}{\text{Estimated total annual ambient exposure (ug/yr)}}$

From Scenario No. 1:

Estimated time for equivalent exposure = $\frac{5,443 \text{ ug}}{10.8 \text{ ug/yr}}$ = 503.9 yr

From Scenario No. 2:

Estimated time for equivalent exposure = $\frac{2,267 \text{ ug}}{10.8 \text{ ug/yr}}$ = 209.9 yr

From Scenario No. 3:

Estimated time for equivalent exposure = $\frac{907 \text{ ug}}{10.8 \text{ ug/yr}}$ = 83.98 yr

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mg/kg, an equivalent exposure of more than 80 yrs is acquired per 0.45 kg of fish.

Yet another perspective is gained by taking the same contaminant values and comparing them against recommended PCB intake rates for full grown adults. As was noted earlier, the Federal Food and Drug Administration has recommended a maximum daily dose rate of 1 ug/kg/day PCB for adult intake. If this daily value can be assumed to be an annual average, then a 70 kg adult may ingest no more than 25,550 ug of PCB annually (Table 6).

Assuming that the average lake trout from scenario number 1 contains 12 mg/kg PCB, the sports fishermen may consume approximately four and one-half 0.45 kg meals per year, or nine 0.23 kg meals per annum, and not violate the maximum recommended dose rate. Similarly, at 5.0 mg/kg PCB in lake trout, eleven 0.45 kg or twenty-two 0.23 kg fish meals may be consumed, and at 2.0 mg/kg, twenty-eight 0.45 kg meals or a net amount of a single 0.23 kg fish meal per week may be eaten and not exceed the guidelines.

TABLE 6

Total Consumption of Great Lakes Fish at Varying Concentrations of PCB Permissible Within Established Guidelines

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Federal Food and Drug Administration recommended maximum adult intake of PCB
1 ug/kg/day
Average annual exposure limits for a 70 kg adult
25,550 ug/annum (1 ug x 70 kg x 365 day/yr)
From Scenario No. 1, lake trout at 12 mg/kg PCB:
Allowable consumption = $\frac{25,550 \text{ ug/yr}}{11,975 \text{ ug/kg}}$ = 2.13 kg/yr,
or approximately 9 meals containing 0.45 kg of fish.
From Scenario No. 2, lake trout at 5 mg/kg PCB:
Allowable consumption = $\frac{25,550 \text{ ug/yr}}{4,987 \text{ ug/kg}}$ = 5.12 kg/yr,
or approximately 22 meals containing 0.45 kg of fish.
From Scenario No. 3, lake trout at 2 mg/kg PCB:
Allowable consumption = $\frac{25,550 \text{ ug/yr}}{1,995 \text{ ug/kg}}$ = 12.81 kg/yr,
or approximately 56 meals containing 0.45 kg of fish.

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Because of calculations of this sort, the Michigan Department of Public Health established a Public Health Advisory related to fish consumption. This Advisory recommends limitation of the absolute amount of fish consumed per year, and recommends against consumption by children, women who expect to bear children, pregnant women, and nursing mothers.

A major question facing the scientific/regulatory/managerial community is the length of time that this problem will persist. The final answer is, at present, unknown. At best, only estimates can be made. The accuracy of the estimate is directly proportional to the quality of the initial data being utilized. The limiting data in this case are the loading values of PCB to the lakes, the initial concentrations in the water, the lake-wide mean water column concentrations of PCB, and internal loss velocities. The available fish data can be assumed to be more accurate.

The most remarkable data set in existence for Great Lakes fish is the information contained in the U.S Fish and Wildlife Service's Contaminant Monitoring Program (Willford, 1982). These data represent the only historical time sequence information on toxic contaminants in the Great Lakes by species of fish, for which sampling, analytical methodologies, and data handling have been carefully controlled to represent an accurate trend.

The data on corregonid fishes, in this case bloater chubs, shows a relatively continuous downward trend after 1974 (Figure 2). It was reasoned that these fish with their relatively short life cycle, as compared with lake trout for example, ought to reasonably reflect levels of PCB in the water column at the time the sample was taken. The rationale for this judgment is presented in Bierman and Swain (1982). Because of the lack of historically reliable time-sequence measurements of water column concentrations, it is necessary to infer concentrations from available fish data. Figure 3 suggests that concentrations in lake trout also seem to be declining, as do the PCBs in coho salmon shown in Figure 4.

When the body burden of individual species in the Fish and Wildlife Service data set are internally normalized (Figure 5), the apparent trends become clearer. It appears that for the salmonid fishes--the lake trout and coho salmon--real decreases have begun, but they appear to lag the corregonid fish by a substantial margin, perhaps 1 to 3 yrs. The decrease in all three species of fish suggest an overall reduction in the loads of PCB applied to Lake Michigan.

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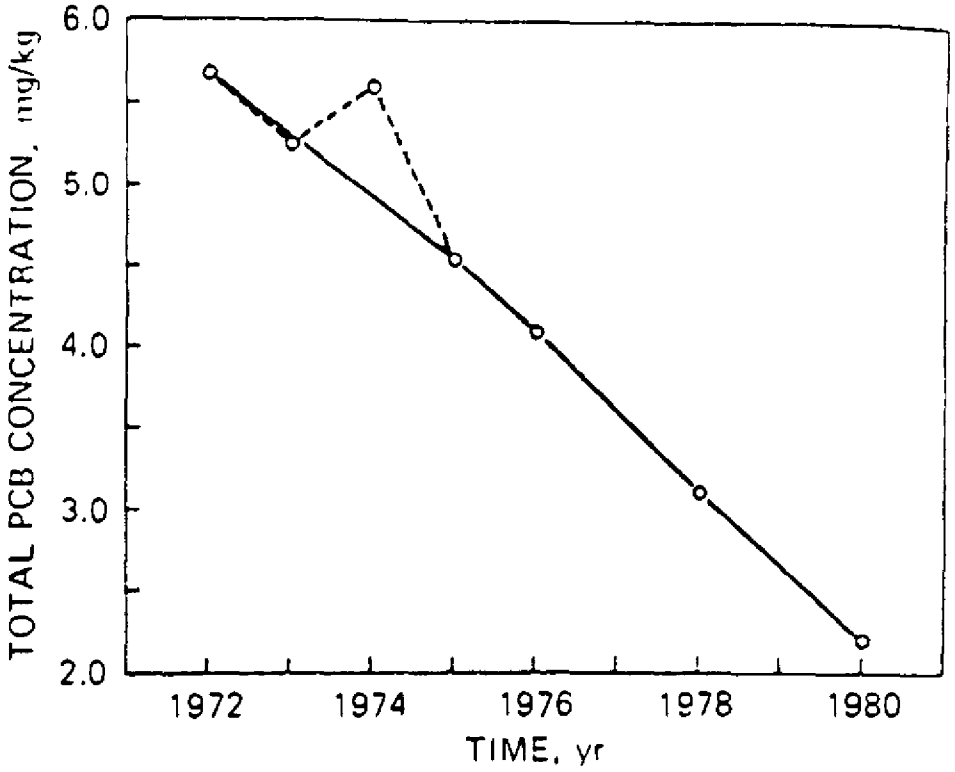

Figure 2. PCB concentrations in Lake Michigan bloater chubs.

If numerical simulation is then used, applying a least-squares fit to determine the net loadings of PCB to Lake Michigan necessary to produce each of the historic data points in the bloater chub curve (Figure 2), the sequential reductions in historical total loadings can be estimated. Extrapolating these reductions into the future, it is possible to estimate the loss rate for PCBs in each species of fish (Figure 6).

The calculation suggests that under the scenario projecting continuously decreasing loadings similar to those that have apparently occurred historically, coho salmon consistent with those in the data set would have reached the 5.0 mg/kg level in 1980, and lake trout with size and age characteristics similar to those previously collected will achieve 5.0 mg/kg by 1984 (Table 7). The projected times to 2.0 mg/kg are 1986 and 1989 for coho and lake trout, respectively.

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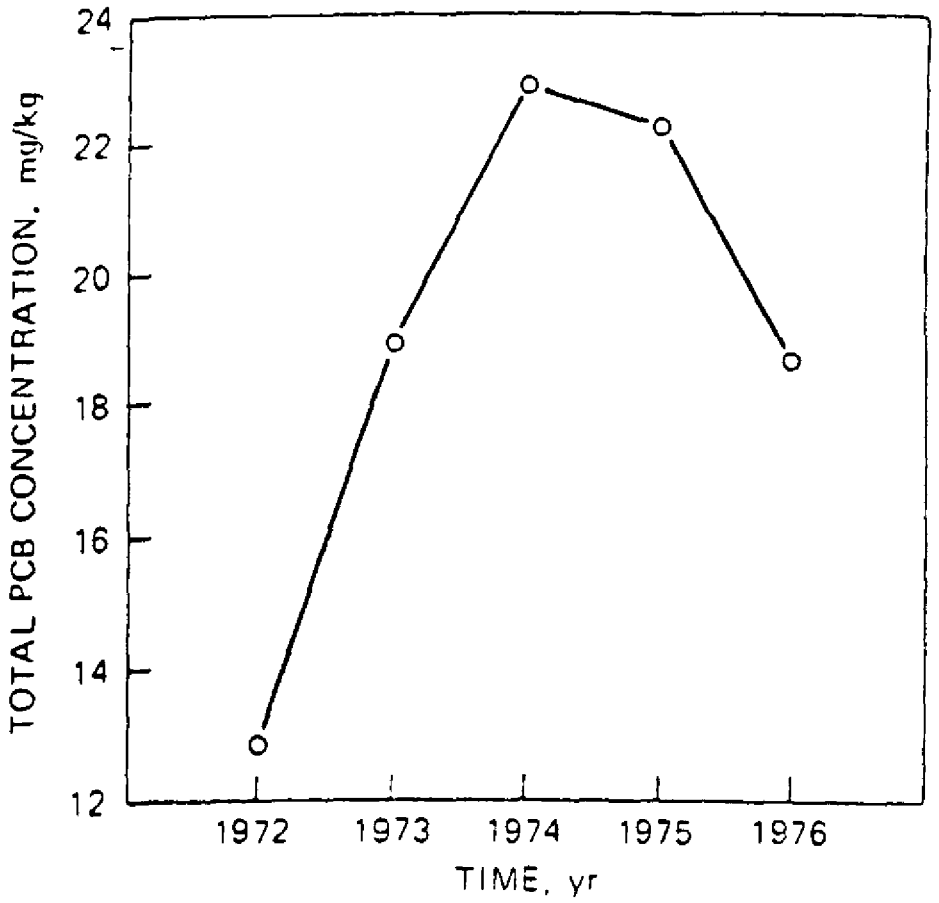

Figure 3. PCB concentrations in Lake Michigan lake trout.

However, if the loading of PCB is not continuously reduced incrementally, and instead of a continuous decrease, the load estimated for 1980 of slightly less than two and one-half metric tons per year is maintained, it appears that lake trout would not achieve the 5.0 mg/kg level until 1998, and coho and lake trout would not achieve 2.0 mg/kg until 1998 and 2006, respectively (Table 8).

If PCBs in Lake Michigan fish are truly declining at the rates the data would seem to indicate, why is there a continued concern over this compound? There are several reasons. Probably the most important involves human consumption. If humans consuming fish from Lake Michigan follow similar loss patterns for PCB, the human loss curve can be reasonably

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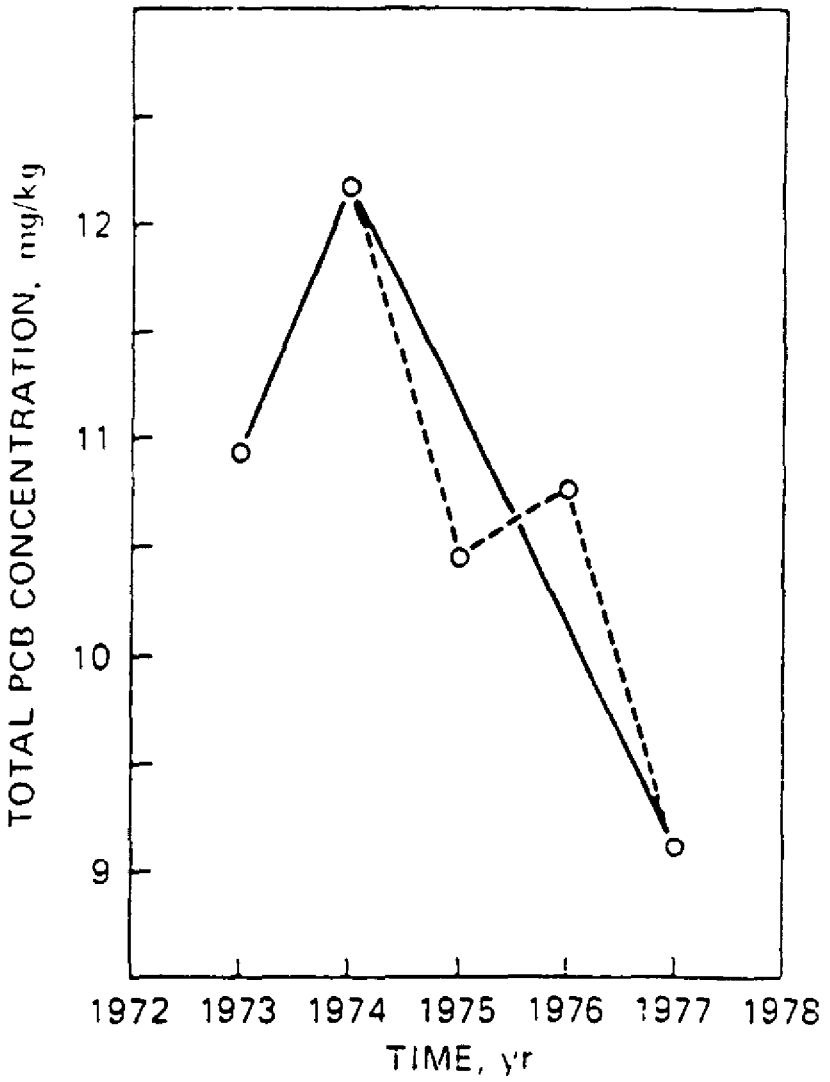

Figure 4. PCB concentrations in Lake Michigan coho salmon.

expected to lag the curve for lake trout by some 5 to 15 yrs--a decade being a reasonable approximation--since the human life cycle is four to five times longer than that of the lake trout, and it appears that PCBs are as poorly metabolized in humans as they are in fish. Given the longer human life cycle, the retention probably increases proportionately.

Thus, even with the projected declines in the aquatic environment, we are faced with the possibility of PCB persisting in the human population from this source for as long as 5 to 8

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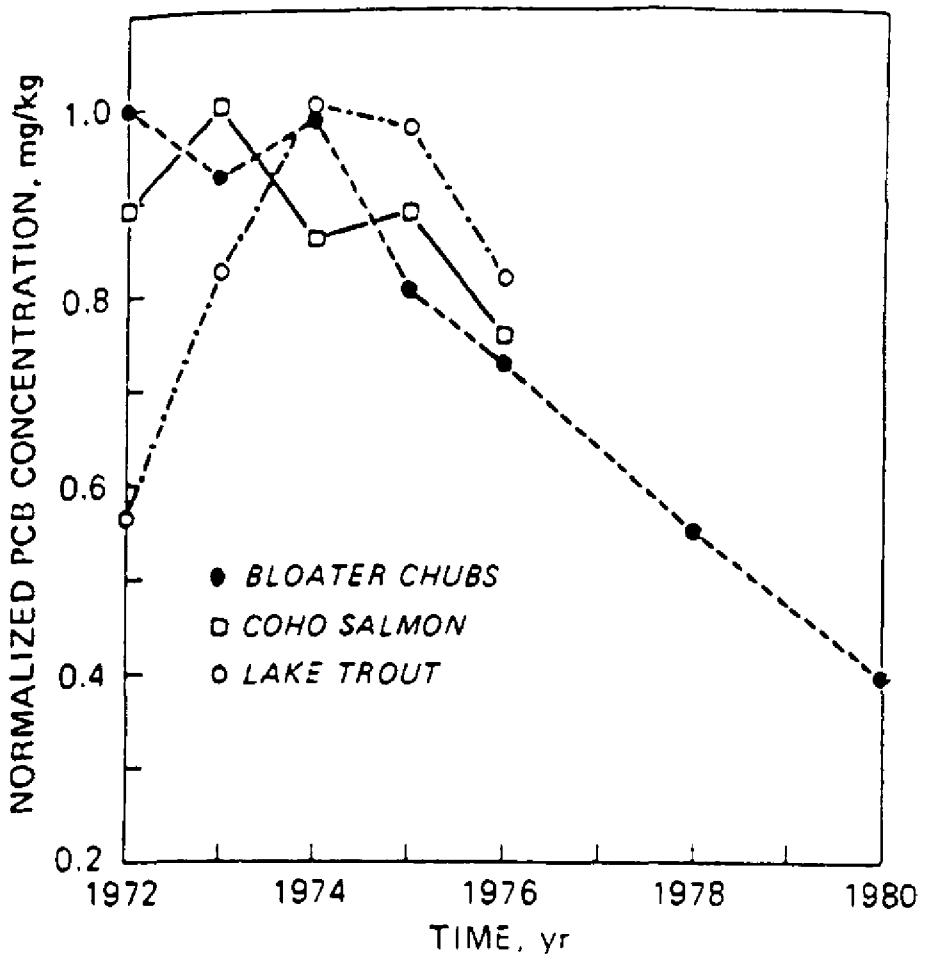

Figure 5. Normalized PCB body burdens in Lake Michigan fish.

generations into the future. Any consideration of the toxicological impacts of this compound should be set against the incredible persistence of this substance in the environment, and in human tissue.

Beyond this issue, it is necessary to remember that it has been estimated that only about one-third of all the PCB manufactured has reached the environment to date. It is to be hoped that the rest has been successfully contained. In addition, recent information suggests that some of the compounds being proposed as PCB substitutes may not differ markedly from the original compound. All of this information suggests that the PCB problem is likely to continue at least into the foreseeable future.

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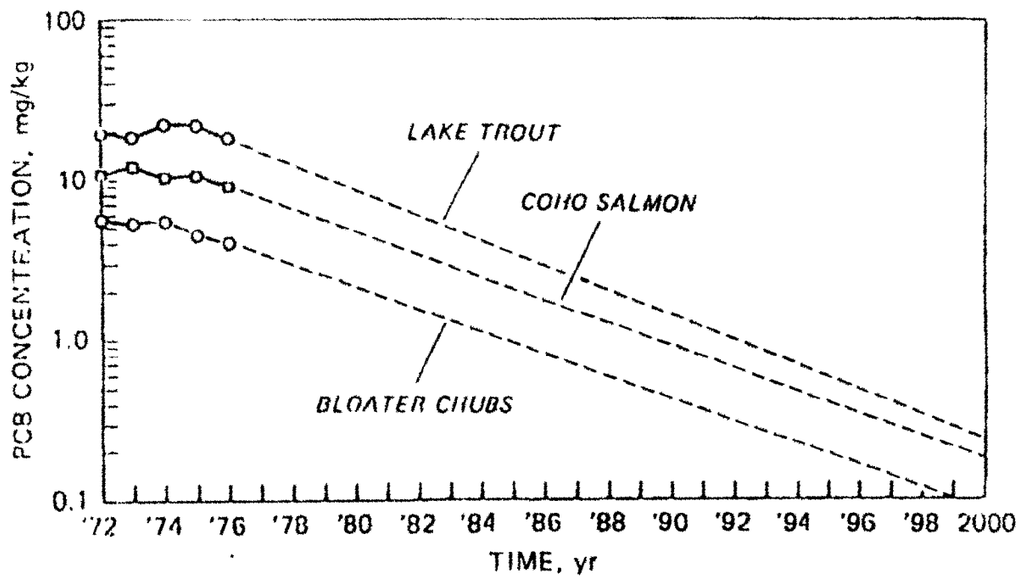

Figure 6. Estimated loss rates for PCB in Lake Michigan fish.

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TABLE 7

Estimated Year When Various Guideline Values of PCB Will be Achieved in Lake Michigan Fish, Based on Continuous Load Reductions

Guideline Value Achieved mg/kg	Species of Fish		
	Bloater Chubs	Coho Salmon	Lake Trout
15.0	--	--	1977-1978
10.0	--	--	1979-1980
5.0	--	1979-1980	1983-1984
2.0	1980-1981	1985-1986	1988-1989
1.0	1984-1985	1989-1990	1992-1993
0.5	1989-1990	1994-1995	1997-1998

TABLE 8

Estimated Year When Various Guideline Values of PCB Will Be Achieved in Lake Michigan Fish, Under a Steady-State Load of 2.4 Metric Tons Per Year After 1980

Guideline Value Achieved mg/kg	Species of Fish		
	Bloater Chubs	Coho Salmon	Lake Trout
5.0	--	1981	1998
2.0	1981	1998	2006

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CHAPTER 4

PCBs IN THE GREAT LAKES: SOURCES, SINKS, BURDENS

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INTRODUCTION

Polychlorinated biphenyls (PCBs), as a class of synthetic, chlorinated organic chemicals, are ubiquitous in the marine and freshwater environments of our planet (NAS, 1979; Nisbet and Sarofim, 1972; Ballschmiter and Zell, 1980). The global distribution of PCBs is demonstrated by their occurrence in fish and fish products from as dissimilar environments as the Antarctic Ocean, the North Atlantic Ocean, North Sea, and Alpine Lakes (Zell and Ballschmiter, 1980; Ballschmiter and Zell, 1980; Ballschmiter et al., 1981). Since 1929, approximately 2×10^9 kg of PCBs have been commercially produced, and about 2×10^8 kg remain in mobile environmental reservoirs (31%) and in landfills or equipment dumps (58%) (NAS, 1979). The voluntary and projected legislative bans instituted since 1971 by the Monsanto Chemical Company to restrict production, sale, and use of PCBs to closed systems suggests that the tropospheric and hydrospheric burdens should be decreasing. Indeed, decreasing concentrations in certain fishes from the Great Lakes (Hartig, 1981), sediment (Eisenreich et al., 1980), and atmosphere (Eisenreich, 1982a; 1982b) support this hypothesis. However, PCBs are refractory compounds resisting chemical and biological degradation and will remain active for decades to come (Ballschmiter et al., 1978).

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The National Academy of Sciences (1979) issued a report on PCBs in which estimates of the environmental load for the U.S. and Atlantic Ocean were made (Table 1). The major environmental reservoirs for PCBs in the northern hemisphere were concluded to be marine sediments and water and freshwater sediments, especially those of the Great Lakes. The data indicate that the North Atlantic Ocean is the ultimate sink for PCBs emitted in North America, and atmospheric transport/deposition is the major input mode. Similar information on the sources, sinks, and burdens in the Great Lakes is only now becoming available and is summarized in this chapter, although considerable uncertainty still exists in estimating fluxes at air/water and sediment/water interfaces.

MASS BALANCE APPROACH

One approach to viewing the "PCB status" of the Great Lakes is to construct a model describing the inputs, outputs, and compartmental burdens. A mass balance model provides an understanding of the transport and distribution of PCBs in the lakes and an estimate of the residence time that the pollutant remains in the ecosystem or in any compartment. The mass balance

TABLE 1

Environmental PCB Load Estimates for the United States and Atlantic Ocean (NAS, 1979)

Environmental Compartment	PCB Loading (10^6 kg)
Atmosphere	0.013
Hydrosphere	
Freshwater	0.012-0.035
Freshwater Sediments	1.4-7.1
Freshwater Biota	0.03
Marine Water	6.0-66
Marine Sediment	0.66-27
Marine Biota	0.03
Lithosphere	0.14-2.8

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approach has been applied to the cycling of PCBs in Lake Michigan (Weininger and Armstrong, 1981) and Lake Superior (Eisenreich et al., 1980, 1981b).

Figure 1 schematically describes the mass balance model of pollutant cycling in a Great Lake ecosystem and will be used as a paradigm for discussing PCB transport and distribution. The time-dependent change in the PCB concentration in a lake may be given by:

$$d(C_tV)/dt = \Sigma Q_iC_i - Q_oC_t - V_sC_dK_p/h - k_dC_d - k_vC_d$$

where:

C_t = total PCB concentration in water (mass/volume)
Q_i = inflow volume (volume) at influent concentration, C_i (mass/volume)
V = lake volume (volume)
Q = outflow volume (volume/time)
V_s = apparent net settling velocity for particles (length/time)
C_p = particulate PCB concentration (mass/volume)
h = lake depth (length)
k_d = first-order rate constant for PCB degradation ($time^{-1}$)
C_d = dissolved PCB concentration (mass/volume)
k_v = PCB volatilization rate (length/time)
K_p = PCB partition coefficient (volume/mass)

The ΣQ_iC_i signifies the summation of all inputs of PCBs. The sources of PCBs to the Great Lakes are atmospheric deposition, tributary inputs, municipal/industrial discharges, and sediment resuspension/pore water advection. Available data and theory do not presently permit an estimation of sediment resuspension and pore-water advection although Rogers (1982) and Chambers and Eadie (1981) have addressed the former while Eadie (personal communication, GLERL, NOAA, 1982) is addressing the latter. The outputs of PCBs are tributary outflow (Q_oC_t), sedimentation ($V_sC_dK_p/h$), biological degradation (k_dC_d), and volatilization (k_dC_d). PCB burdens in the Great Lakes are expressed as mass accumulated in the atmosphere, water, sediment, and biota.

PCB Concentrations and Burdens

Atmosphere

The atmosphere does not represent a significant reservoir of PCBs for the Great Lakes but is a major input pathway. The

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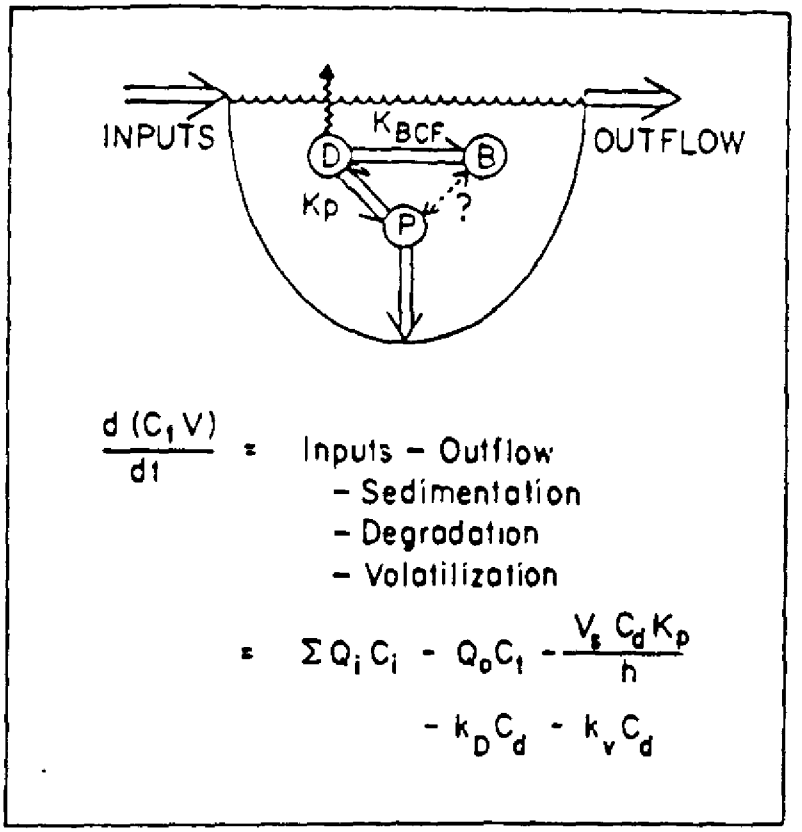

$$\frac{d(C_t V)}{dt} = \text{Inputs} - \text{Outflow} - \text{Sedimentation} - \text{Degradation} - \text{Volatilization}$$

$$= \Sigma Q_i C_i - Q_o C_t - \frac{V_s C_d K_p}{h} - k_D C_d - k_v C_d$$

Figure 1. Mass balance model of pollutant cycling. See text for definition of symbols.

concentrations of PCBs in air have been summarized by Eisenreich et al. (1981b) and updated in MacKay et al. (1982). Airborne PCBs have been primarily measured in Lakes Superior and Michigan by Eisenreich et al. (1981a), Eisenreich et al. (1982b), Doskey and Andren (1981a), Rice et al. (1981a), and Murphy and Rzeszutko (1977). Doskey and Andren (1981a) have reported that the mean PCB concentration in the atmosphere over Lake Michigan during 1977-78 was approximately 1 ng/m^3 with a range of 0.5-1.5 ng/m^3. Rice et al. (1982) have reported higher PCB concentrations in 1979-80 ranging from 1.0 to 5.4 ng/m^3. Airborne PCB concentrations over Lake Superior were approximately 1.5 ng/m^3 in 1978 (Eisenreich et al., 1981; Hollod et al., 1982) but have apparently decreased to a mean of about 0.3 ng/m^3 in 1981 (S.J. Eisenreich, unpublished data). Airborne PCBs occur at concentrations of 0.3 to 2 ng/m^3 in the Great Lakes (Table 2), occur primarily in the vapor phase (up to 100%), and are dominated by the lower chlorinated isomers such as Aroclor 1242

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TABLE 2

PCB Concentrations in the Air, Rain, Water, and Sediments in the Great Lakes Basin

Environmental Compartment	Lake Superior		Lake Michigan		Lake Huron		Lake Erie		Lake Ontario	
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
Air (ng/m^3)	0.3	--	1.0	--	--	0.5-1.0	2.0	--	2.0	--
Rain (ng/l)	--	10-30	--	20-50	--	10-50	--	10-50	--	20-50
Water (ng/l)	--	1-2	--	1-5	--	1-3	--	2-10	--	2-6
Sediments (ng/g)[a]	3.7±5.7	2.2-57	9.7±15.7	2-190	13±10[b]	3-90	95±114	4-800	57±56	5-280

[a]From Frank et al., 1977; 1979a; 1979b; 1980; 1981.
[b]PCB concentration in sediment of Georgian Bay is 11±11 ng/g.

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(approximately 60-80%). Reasonable atmospheric fluxes (Mackay et al., 1983) and observed atmospheric burdens lead to the conclusion that atmospheric residence time over an individual lake is approximately 1 to 5 days.

Even less is known about PCB concentrations in precipitation (Table 2). Although levels in urban/industrial-impacted areas such as southern Lake Michigan may exhibit rain concentrations up to approximately 100 ng/l (Murphy and Rzeszutko, 1977), present day values over the whole basin probably average about 10 to 50 ng/l. Support for this is provided by field data (Davis, 1980; Swain, 1978; Strachan and Huneault, 1979; Murphy et al., 1981). Frank and Braun (1981) found PCB concentrations in rain during 1975 in 6 agricultural watersheds in southern Ontario to be 20 to 100 ng/l, similar to the concentrations found in stream water. PCB concentrations in air and rain should be highest close to and downwind of populated areas, but in fact, are rather well dispersed over the whole basin implicating atmospheric transport as a principal distribution process.

Hydrosphere

Few data are available on PCB concentrations in the waters of the Great Lakes. Konasewich et al. (1978) summarized the literature prior to 1978 and found wide discrepancies in the reported concentrations. Little attention has been paid to the hydrospheric burden of PCBs, even though the dissolved species supports the elevated biotic burdens often reported. For example, total PCB concentrations in Lake Superior over the last ten years have been reported from 0.8 to about 110 ng/l in the open waters, and perhaps up to 200 ng/l in nearshore waters and harbors (Swain, 1978; Reinert, 1970; Konasewich et al., 1978; Veith et al., 1977). By comparison, the concentrations of PCBs in Lake Michigan have been reported to range from 1 ng/l to as high as 200 ng/l in open waters, and higher in harbors and embayments. PCB concentrations in the contaminated Waukegan Harbor of southern Lake Michigan ranged from 20 to 1000 ng/l in 1979, while 0.5 km offshore, 1 to 10 ng/l values were found (Thomann and Koutaxis, 1981). The present day concentration in Lake Michigan is probably much closer to 1 to 5 ng/l, while Lake Superior has PCB levels of 1 to 2 ng/l. Tables 2 and 3 show the measured and estimated concentrations of total PCBs in the Great Lakes on a whole-lake average. The entire range of mean values is 1 to 10 ng/l, with locally higher concentrations likely near point sources.

Eisenreich et al. (1983a) have found that PCB concentrations in Lake Superior averaged 1.3 ± 1.3 ng/l in 1978 (n =

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TABLE 3

PCB Concentrations in Water

Watercourse	Concentration (ng/l) Median	Range
Great Lakes		
1. Superior	1-2	0.2-8.4
Michigan	1-5	0.5-10
Huron	1-3	0.5-10
Erie	2-10	5-20
Ontario	2-6	1-20
2. Open Waters	-	0.5-5
Embayments	-	1-10
Harbors	-	5-50
Marine	0.1-1.0	0.1-5.0
Rivers		
Undisturbed	1	1-5
Disturbed	-	10-200

30), 3.6 ± 1.8 ng/l in 1979 (n = 25), and 0.9 ± 0.4 ng/l in 1980 (n = 62). Concentrations in Lake Michigan have tentatively been assessed at about 2 ng/l (Armstrong, 1982, personal communication) and 2 to 5 ng/l (Rice et al., 1982). The distribution of isomeric mixtures is about 50 ± 20 percent Aroclor 1242 (1016) with 60 to 80 percent operationally existing in the dissolved phase. Although hydrophobic pollutants such as PCBs are known to partition into suspended matter (Steen et al., 1978; Paris et al., 1978; Karickhoff et al., 1979; O'Connor and Connolly, 1980), partitioning favors the dissolved phase in waters of low suspended concentrations (SS) even though K_p may be 10^5 to 10^6 l/kg.

The relatively uniform PCB concentrations in the open waters of the Great Lakes are attributed to the interaction of

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varying concentrations of suspended solids with dissolved PCBs, with subsequent particle loss to the sediments. In Lake Erie where PCB loadings are likely elevated, high sedimentation rates remove a greater mass to the sediment. In Lake Superior, lower PCB loadings are balanced by inefficient removal processes because suspended solids concentrations are low and sedimentation rates are slow. The net effect of variable PCB loadings, suspended solids and sedimentation rates is low, and relatively uniform water-column concentrations. In all cases, the fraction in the particle phase (i.e., CdK_p/C_t) is that portion of the PCB burden influenced by loss to the sediments.

Sediments

Sediments represent the ultimate sink for PCBs and other hydrophobic pollutants in the Great Lakes. As a result, numerous studies on the distribution of PCBs in the surficial sediments have been conducted, primarily to assess the extent of environmental degradation and insult. The most ambitious and wide-ranging study to date was conducted in 1968 to 1971 by the Ontario government in which more than 1200 surficial sediment samples (upper 3 cm) were collected and analyzed for PCBs and organochlorine insecticides. The intent of the study was to establish baseline levels and identify sources to enable future trends to be assessed. The surficial sediment concentration of PCBs were reported for Lake Erie (Frank et al., 1977), Lake Ontario (Frank et al., 1979a), Lake Huron (Frank et al., 1979b), Lake Superior (Frank et al., 1980), and Lake Michigan (Frank et al., 1981). Table 2 depicts the mean, standard deviation, and range of PCB concentrations observed in the 0 to 3 cm surficial sediments. The lower lakes, especially Erie and Ontario, have the highest mean and range of concentrations averaging 50 to 60 ng/g. The Upper Great Lakes exhibit surficial sediment concentrations of 3 to 10 ng/g. Eisenreich et al. (1979; 1980) have observed concentrations 10 to 20 times greater in the upper 0.5 cm of Lake Superior sediments. There is evidence to suggest that actual surficial concentrations in areas of low sedimentation may be substantially higher than those given in Table 2. However, overall sediment burden may be calculated using these data, and certainly the sedimentary and lake-to-lake trends may be evaluated. Table 4 lists the PCB concentrations observed in surficial sediments of the Great Lakes by several authors. PCB concentrations are higher in depositional vs. non-depositional zones within the same lake, and the Upper Lakes exhibit lower concentrations than the Lower Lakes, presumably due to proximity to sources.

The historical input of PCBs to the sediments of the Great Lakes has not been generally reported, but is presently being

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TABLE 4

PCBs in Great Lakes' Sediments

Watercourse	Whole Lake (ng/g)	Non-Deposition Zones (ng/g)	Deposition Zones (ng/g)	Range (ng/g)	Reference
Superior	4.8	3.9		<2.5-57	Frank et al., 1980
	(5.5)	(2.1)			
	130	40	180	5-290	Eisenreich et al., 1979, 1980
	(110)	(40)	(110)		Veith et al., 1977
	7.0			5-1300	Glooschenko et al., 1976
Michigan	9.7	6.3	17.3	<2-190	Frank et al., 1981
	(15.7)	(8.1)	(23.9)		
				3.7-133	Schacht, 1974
				5-200	Weininger and Armstrong, 1981
				2-7	Simmons et al., 1980
Huron	13	11	15	<3-90	Frank et al., 1979a, 1979b
	(10)	(7)	(13)		
Georgian Bay-North Channel	11	11	11	<3-43	Frank et al., 1979a, 1979b
	(11)	(13)	(8)		

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Table 4 (continued)

Watercourse	Whole Lake (ng/g)	Non-Deposition Zones (ng/g)	Deposition Zones (ng/g)	Range (ng/g)	Reference
Erie	95 (114)	64 (105)	115 (114)	4-800	Frank et al., 1977
Lake St. Clair	10 (6)	--	--	ND-28	Frank et al., 1977
Ontario	57 (56)	31 (40)	85 (57)	5-280	Frank et al., 1979a, 1979b
Bay of Quinte	48 (43)	41 (45)		<2-260	Frank et al., 1980

Numbers in parentheses indicate one standard deviation.

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constructed by this author for the Great Lakes, and D.E. Armstrong for Lake Michigan. PCB accumulation in sediments over time can only be determined by carefully examining detailed cores. Figure 2 shows the depth profile of four sediment cores taken in Lake Superior with a box corer and carefully fractionated into approximately 0.25 cm segments in the uppermost sediments. The right vertical axis shows the dates of specific depth segments as determined by ^{210}Pb geochronology (Evans et al., 1981). The profiles are typified by high surficial concentrations (0-0.5 cm) followed by a rapid decrease with depth, such that no detectable values were observed at depths greater than 1 to 5 cm depending on the core. In general, PCB concentrations appeared in the sediment profile in 1940 to 1950. However, careful examination of sediment cores least disturbed by bioturbation indicate that the PCBs entered the Lake Superior system about 1950. All cores exhibit 20 to 100 percent lower PCB concentrations in the upper 0 to 0.25 cm than in the 0.25

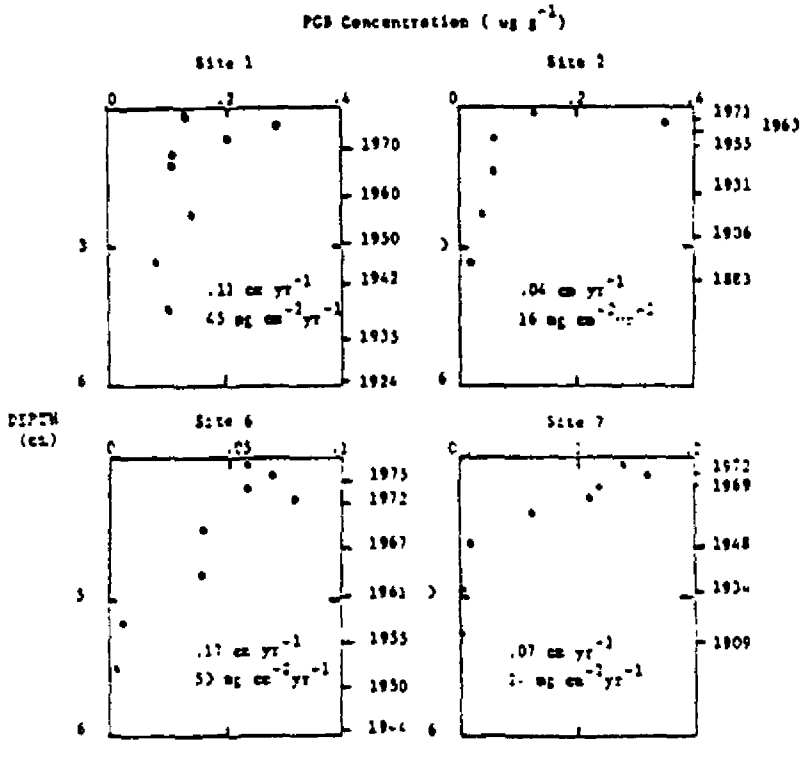

Figure 2. PCB concentration profiles (ug/g) in sediment cores from Lake Superior in areas with sedimentation rates $\geq$ 0.04 cm/yr.

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to 0.5 cm segment. This behavior implicates a mechanical loss of the most flocculant sediment during sampling or provides evidence for a recent decrease in sedimentary PCB flux in response to decreased loadings. Both possibilities are being carefully examined using sediment cores in zones of more rapid deposition.

Environmental PCB Burdens

The PCBs accumulated or stored in the major environmental reservoirs of the Great Lakes may be estimated from concentrations in the atmosphere, lake water, and sediments. The biotic compartment contributes no more than a few percent at most to the whole lake burden. Table 5 lists the physical characteristics of the Great Lakes needed, in part, to estimate compartmental burdens of PCBs for each of the Great Lakes shown in Table 6. The sediment burden for each of the lakes was estimated from the sediment concentrations in the upper 0 to 3 cm provided by Frank et al. (1977; 1979a; 1979b; 1980; 1981), assuming that all PCBs resided in that depth increment, and the density was 2.5 g/cm^3. Studies of depth profiles in cores of the Upper Lakes suggest that most of the PCB burden is contained in the 0 to 3 cm segment, while PCBs extend to greater depths in the high sediment flux areas of the Lower Lakes. Therefore, sediment burdens listed in Table 6 likely underestimate actual values. The water burden of PCBs was calculated from mean lake concentrations and lake volume. Atmospheric burdens assumed a constant air concentration to a 1 km mixing height over the lake surface area. A conservative estimate of the total mass of PCBs in the Great Lakes is 473 x 10^3 kg of which 88 percent

TABLE 5

Physical Characteristics of the Great Lakes

	Volume (10^{12} m^3)	Area (10^{10} m^2)	Mean Depth (m)	Annual Discharge (10^{10} m^3/yr)	RT_{H_2O} (yr)
Superior	12.1	8.21	147	6.72	179
Michigan	4.92	5.78	85	3.60	137
Huron	3.54	5.96	59	16.1	22
Erie	.484	3.56	19	18.2	2.7
Ontario	1.64	77	83	21.2	7.7

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TABLE 6

PCB Burden in the Great Lakes

Lake	Sediments		Water		Atmosphere	
	Concentration ng/g	Burden 10^3 kg	Concentration ng/l	Burden 10^3 kg	Concentration ng/m^3	Burden 10^3 kg
Superior	3.3±5.7	20	1-2	12-24	0.3	0.025
Michigan	9.7±15.7	82	1-5	4.9-25	1.0	0.058
Huron	13±10	58	1-5	3.5-18	0.5	0.030
Erie	9±11	182	2-10	1-9.7	2.0	0.051
Ontario	57±56	115	2-6	3.3-9.8	2.0	0.039
TOTAL	--	457	--	25-87	--	0.20

Total PCB Burden: 442 to 504 MT

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is contained in the top 3 cm of sediment. It is unlikely that this estimate is inaccurate by more than a factor of 2. Inclusion of the PCB burden contained in the sediments of Waukegan Harbor and North Ditch, southwestern Lake Michigan, would more than double the Great Lakes burden. If the PCB burden had been deposited in the lake at a constant rate over the last 30 yrs, a long-term average net input of 1300 kg/yr would be added to Lake Superior to 6200 kg/yr for Lake Erie. Note that the mass of PCB in Lakes Erie and Ontario exceed that in the remaining lakes by more than 100 percent. The sedimentary PCB burden in the Lower Lakes may be much higher. There is no doubt that even conservative estimates show that lakes near urban/industrial centers suffer a massive environmental insult due to the input of anthropogenic organic chemicals such as PCBs.

Detailed estimates of the PCB burden have been made for Lake Michigan (Weininger and Armstrong, 1981) and Lake Superior (Eisenreich et al., 1982)(Table 7). The total PCB burden of Lake Superior was estimated as 39,000 kg, fortuitously close to the value listed in Figure 3. The total PCB burden of Lake Michigan was estimated as approximately 70,000 kg, about 20 percent higher than estimated before. About 60 and 86 percent of the PCB mass has accumulated in the sediments of Lake Superior and Lake Michigan, respectively.

PCB SOURCES AND SINKS

The principal sources of PCBs to the Great Lakes are atmospheric deposition, tributary input, and municipal/industrial discharges. Atmospheric transport and deposition of PCBs has been implicated as a primary input pathway to freshwater and marine ecosystems as a result of its presence in marine (Harvey and Steinhauer, 1974; Bidleman and Olney, 1974; Glam et al., 1980; Atlas and Giam, 1981) and Great Lakes' atmospheres (Doskey and Andren, 1981; Eisenreich et al., 1981; 1982b). For example, the North Atlantic Ocean (water + sediments) is the principal sink for PCBs produced in North America from 1930 to 1976 (NAS, 1979; Table 1). A second major sink is freshwater sediment, primarily in the Laurentian Great Lakes, where atmospheric inputs may be partially responsible for sedimentary accumulation. Eisenreich et al. (1979) concluded that atmospheric inputs could support their accumulation in surficial sediments.

Early studies of PCBs in precipitation by Murphy and Rzeszutko (1979) in the Lake Michigan Basin clearly showed that atmospheric deposition was an important pathway. Later studies

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TABLE 7

PCB Burdens in Lakes Superior and Michigan, 1980

	Lake Burdens	
	Superior[1]	Michigan[2]
Lake Water (kg)		
PCB_T	1 ng/l	2 ng/l
Dissolved (approx. 80%)	9,600	8,200
Particulate (approx. 20%)	2,400	1,600
	12,000 kg	9,600 kg
Sediments (kg)		
Approx. 0.1 ug/g	15,300 kg (0-.5 cm)	30,000 kg (0-2 cm)
Approx. 0.025 ug/g	11,600 kg (.5-2 cm)	30,000 kg (2-5 cm)
	26,900 kg	60,000 kg
Atmosphere (kg)		
Approx. 1 ng/m^3 1 km hm	82 kg	58 kg
Biota (kg)	Approx. 5-10 kg	Approx. 10 kg
TOTAL	Approx. 39,000 kg	Approx. 70,000 kg

[1]Eisenreich et al. (1981b)
[2]Weininger and Armstrong (1981)

by Murphy et al. (1981) and Doskey and Andren (1981b) also showed that wet and dry deposition were important. The magnitude of the PCB problem is properly viewed in the context of recently published input-output models for PCBs in Lake Superior (Eisenreich et al., 1981a, 1981b) and Lake Michigan (Weininger and Armstrong, 1981). For both systems, atmospheric deposition is the dominant input pathway and sedimentation is the dominant

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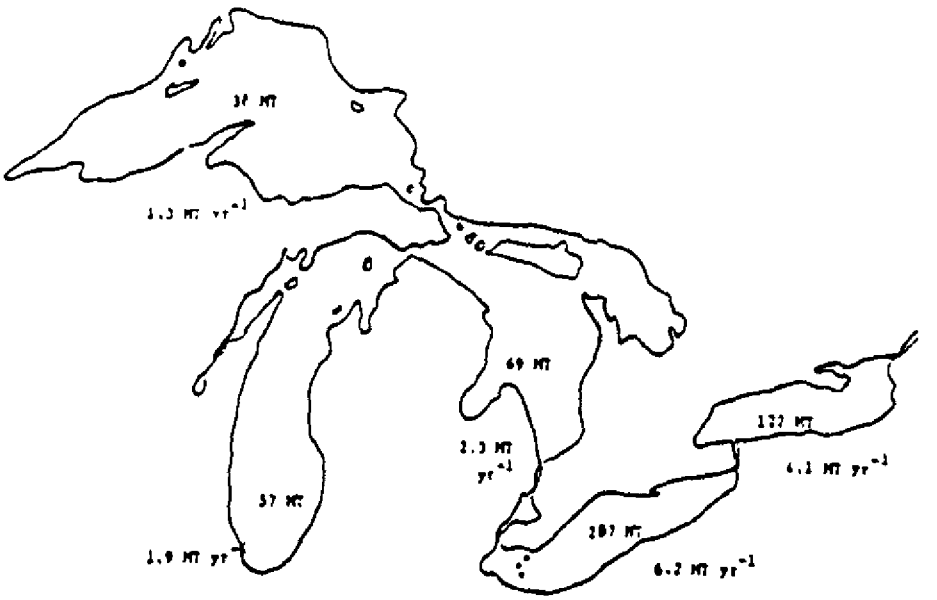

Figure 3. PCB burden (10^3kg) and mean annual input rate over 30 years to the Great Lakes (10^3kg/yr)

loss pathway. The input-output values require that the net annual accumulation of PCBs is 6300 to 8600 kg and 3950 kg for Lake Superior and Lake Michigan, respectively, corresponding to increases in water-column concentrations of approximately 0.5 to 0.7 ng/l/yr and approximately 0.8 ng/l/yr. Since fish, sediment, and atmospheric PCB concentrations seem to be slowly decreasing, then either atmospheric inputs are too high or other loss mechanisms have not been considered. A brief discussion of the problem follows.

Atmospheric deposition can be derived from the scavenging of particulate or gaseous PCB in the atmosphere by precipitation and the dry flux of particulate and gaseous PCB. The wet inputs have been measured in the field by collecting and analyzing rain and snow. As shown in Table 2, PCB concentrations in precipitation on a volume-weighted basis range from 10 to 50 ng/l. Thus, wet deposition may be estimated by:

$$F_W = C_{rain} \cdot J = C_{air} \cdot J \cdot W$$

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where:
F_W = wet flux (mass area^{-1} time^{-1})
C_{rain} = PCB concentration in air (mass volume^{-1})
J = precipitation intensity (length time^{-1})
W = scavenging coefficient (dimensionless)

For the Upper Great Lakes, 10 to 30 ng/l PCB in rain and 74 cm/yr annual precipitation yield wet fluxes of 7.5 to 23 ug/m^2/yr. For the Lower Great Lakes, 20 to 50 ng/l PCB in rain and 85 cm/yr annual precipitation yield wet fluxes of 17 to 43 ug/m^2/yr.

Interestingly, the PCB flux to the sediments of Lake Superior and Lake Michigan is approximately 10 to 19 ug/m^2/yr and approximately 45 ug/m^2/yr, respectively. Note that the wet flux of PCBs to Lake Superior is close to the sediment flux, while additional sources are evident for Lake Michigan.

Estimation of the dry flux of particles and gases to the Great Lakes, however, is not nearly so manageable a task. Recall that 80 to 100 percent of the airborne PCBs occur in the vapor phase, although this may be an overestimate since PCBs trapped on a back-up solid absorbent (e.g., XAD-2, polyurethane foam) may collect vapor desorbed from particles retained upstream on a filter. As a result, both particle flux and vapor-phase exchange across the air/water interface need be considered. A detailed examination of the particle and gas-flux questions is beyond the scope of this paper, but the reader may consult excellent discussions of these topics in Doskey and Andren (1981), Slinn and Slinn (1981), MacKay and Yuen (1981), and Eisenreich et al. (1981). Recently, Andren (1983) addressed the dry flux of PCB-laden particles to water surfaces in some detail and will not be considered here. The gas-phase flux of PCB vapor across the air-water interface is given by:

$$F_{D_1} = K_{oL} (C - P/H),$$

$$1/K_{oL} = 1/K_L + RT/HK_g$$

where:
F_D = dry vapor flux
K_{oL}, K_L, K_g = mass transfer coefficients (m/hr)
C = aqueous PCB concentration (mol/m^3)
P = atmospheric partial pressure of PCB (atm)
H = Henry's Law Constant = P/C at saturation (atm m^3/mol)
RT = 0.0245 at 25°C (mole·atm/m^3)

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MacKay et al. (1979) have shown that resistance lies 95 percent in the gas phase if $H \geq 5 \times 10^{-3}$ atm m^3/mol, lies 95 percent in the liquid phase if $H \leq 5 \times 10^{-6}$ atm m^3/mol, and occurs in both phases between these values. Gas-phase control implies air-to-water transfer, and liquid-phase control implies the opposite. Considerable confusion as to the value of Henry's Law Constant existed until recently. The Henry's Law Constant for PCBs is approximately 10^{-3} to 10^{-4} atm m^3/mol and varies little between isomers (Murphy et al., 1983). However, laboratory (Doskey and Andren, 1981a, 1981b) and field data suggest that H = 10^{-6} to 10^{-7} atm m^3/mol in natural aquatic systems. What is the source of the conflict? Recently, Eisenreich et al. (1983a) reported total PCB and isomeric depth profiles in the water column of Lake Superior. They concluded that although surface profiles supported atmospheric transfer as a source, calculations showed that air and surface water PCBs were in near equilibrium with H = 10^{-3} to 10^{-4} atm m^3/mol. Briefly, this suggests that (1) atmospheric inputs are primarily a result of precipitation inputs; (2) net vapor-phase transfer is presently negligible; (3) atmospheric PCB concentrations are buffered by air/water exchange; and (4) volatilization is only a minor loss mechanism. A modified tentative PCB mass balance for Lake Superior (Table 8) shows that inputs only slightly exceed outputs, which could easily be balanced by low biodegradation and/or volatilization rates. Similar models for the other lakes require better estimates of tributary, municipal, and industrial inputs.

Since the major loss of PCBs from the lakes is sedimentation, accurate estimates of sediment fluxes are critical. The PCB flux to the sediments of Lake Superior and Lake Michigan determined from analysis of sediment cores are approximately 1000 to 1600 and 2600 kg/yr, respectively. An alternate method of estimating sediment fluxes is given by:

$$F_{sed} = V_s C_d K_p A_s$$

where:

F_{sed} = PCB sediment flux (mass/time)
V_s = net apparent particle settling velocity (length/time)
C_d = dissolved PCB concentration (mass/volume)
K_p = PCB partition coefficient (volume/mass)
A_s = lake surface area ($length^2$)

The V_s values were obtained from Bierman and Dadswell (1982). Calculated sediment fluxes from above agree reasonably well

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TABLE 8

Tentative Mass Balance of PCBs in Lake Superior

Input (kg/yr)			Output (kg/yr)	
Tributary			Tributary	
1300			140	
Municipal			Biodegradation	
66			100	
Industrial			Volatilization	
2			0	
Atmospheric			Sedimentation	
Wet	620-1850		1000-1600	measured
Dry	200-1000	particle	1600-200	calculated (v_s)
	0	vapor		
Total	820-2850			
TOTAL INPUT			TOTAL OUTPUT	
2200-4200			1840	

with measured PCB fluxes to the sediments (Table 9). Another method of estimating PCB losses to the sediments is to examine the decrease in concentration in certain fish (and therefore burden) over recent years. Hartig (1981) has provided the concentrations of total PCBs in Lake Michigan bloater chubs from 1972 and 1980. Figure 4 clearly shows that PCB values in this short-lived species decreased linearly over the 8 yrs of study, supposedly in response to decreasing inputs and water concentrations. Assuming the total PCB concentration in water was between 1 and 3 ng/l, then bioconcentration factors (BCF) are approximately 2.2×10^6 to 7.3×10^5. Since fish concentration ought to be linearly related to water concentration, the PCB concentration in Lake Michigan water was back calculated as between 2.5 and 6.4 ng/l in 1972. Assuming that the decreasing fish concentration represented an annual loss to the sediments, 900 to 2000 kg/yr PCBs were sedimented out, closely matching previous estimates (Weininger and Armstrong,

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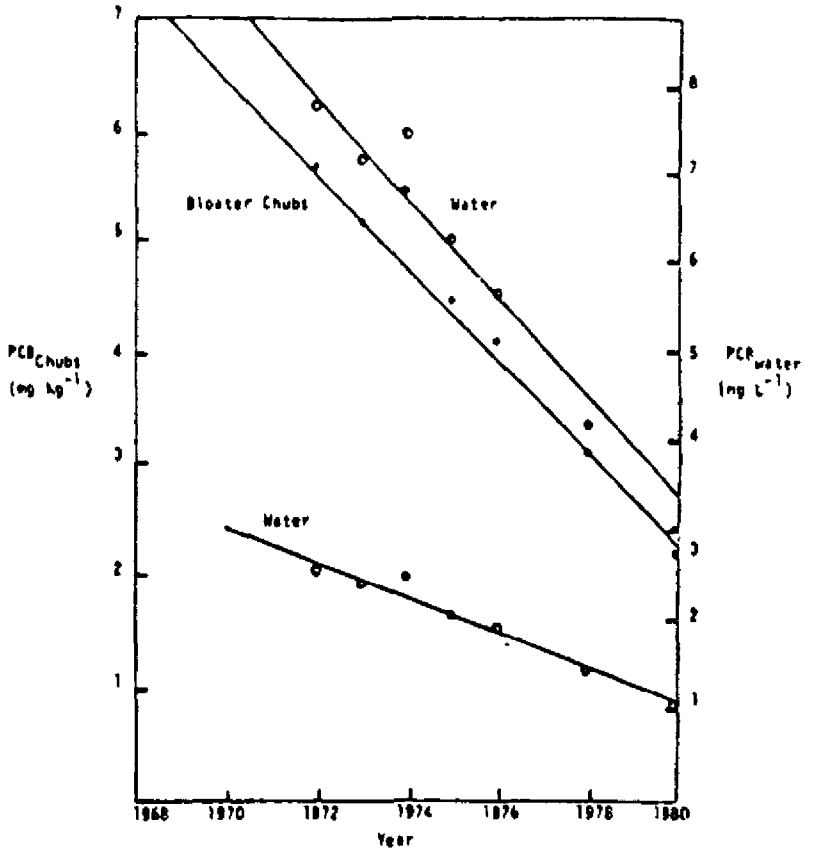

Figure 4. Estimation of historical PCB concentrations in water and sediment losses from trends of PCB levels in Lake Michigan bloater chubs, 1972-1980.

1981). If correct, this analysis shows that the PCB water burden is decreasing. There is no reason to suspect that this is not occurring for Lake Superior as well.

One measure of the response time of a lake to changing inputs/outputs of contaminants, and lifetime of chemicals is to consider residence times. Table 10 shows four different methods of estimating the PCB residence time in Lakes Superior and Michigan. The conventional calculation is to divide the water burden by the input or output rate. If the system is at steady-state, the residence times calculated by either method are equal because inputs equal outputs. The estimated residence time for PCBs in Lake Superior is between 2 and 7 yrs, while similar values for Lake Michigan are between 1.5 and 4 yrs. The residence time estimated by Eisenman and Swain (1982) for

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TABLE 9

Estimating PCB Fluxes to the Sediments

Parameters	Lake Superior	Lake Michigan
V_s (m/yr)	120-150[a]	69-84[a]
C_{ss} (mg/l)	0.2	1.0
$C_{PCB,T}$ (ng/l)	1.0	2.0
K_p	10^6	2.5×10^5
A_s ($10^{10} m^2$)	8.2	5.8
$F_{PCB} = V_s C_d K_p A_s$		
Calculated F_{PCB} (kg/yr)[b]	1600-2000	1600-2000
Measured F_{PCB} (kg/yr)	1000-1600	2600[c]

[a]Bierman and Swain (1982)
[b]$F_{PCB} = V_s C_d K_p A_s$
[c]Weininger and Armstrong (1981)

DDT in Lake Michgian of about 1.7 yrs, and the 2.2 yrs estimated from data on bloater chubs given here agrees very well with the mass balance calculations. The PCB residence times of a few years are in sharp contrast to the water residence times of 100 (Lake Michigan) and 172 yrs (Lake Superior). The lakes apparently respond quite quickly to inputs of toxic, hydrophobic pollutants by removing them to the sediment. However, re-mobilization from sediments may maintain elevated concentrations in the biota for many decades.

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TABLE 10

Residence Time of PCBs in Lakes Superior and Michigan

Environmental Compartment	Residence Time	
	Lake Superior (yr)	Lake Michigan (yr)
Water Burden Input Rate	2.9-5.5	1.5[a]
Water Burden Output Rate	6.9	3.6[a]
DDT Decrease in Fish	2.0	1.7[b]
PCB Decrease in Chubs	--	2.2[c]
Water Volume Water Output	172	100

[a]Weininger and Armstrong (1981)
[b]Bierman and Swain (1982)
[c]Eisenreich et al. (1982a, 1982b)

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CHAPTER 5

REGULATORY CONSIDERATIONS REGARDING LIMITING HUMAN EXPOSURES TO PCBs

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INTRODUCTION

Back in 1969, I was associated with the Mrak Commission on Pesticides and Their Relationship to Environmental Health (HEW, 1969); and, of course, the focus there was on the chlorinated hydrocarbons that were being used as pesticides, mainly DDT. At the time, we were facing some very serious questions about the benefits of chemicals in the service of man as compared to the deleterious effects of chemicals on the environment. As many of you know who waded through some or all of the Mrak Commission report, the main emphasis and degree of concern with those chemicals was not really the health of man. The main emphasis was on protecting the ecology against the various effects that these biopersistent compounds could have. Well, about that time, when we were focusing on DDT, we began to hear the term, or at least I began to hear the term, polychlorinated biphenyls (PCBs), and I wondered what they were. There was a stray report here or there in 1969 and there was a beginning awareness of an accident in Japan. As I left the Mrak Commission and joined the Food and Drug Administration (FDA) in February of 1970, it became evident that we were going to have to familiarize ourselves with whatever these chemicals were that were called PCBs, because the more we looked in foods the more residues we found. I think most of us are familiar with the history and the purpose of these compounds, so I won't dwell on these in great detail, except to say that by the time the federal agencies had a beginning awareness of the nature

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appreciate that we were starting "behind the curve". It's questionable in a situation like this whether you can catch up fast enough so that you can get on top of the curve and start controlling human exposure. Now I won't necessarily say that I am happy to be back in Michigan because there were many tensions and frustrations directed at the FDA on several problems, not the least of which was polybrominated biphenyls. Again, we were behind the curve on that problem, not because the FDA was slow, but because a chemical got loose in the environment and contaminated the food supply. Staying with PCBs, the main problem that we found was similar to the problem in Japan: besides all of the open ended uses of the compounds, the stuff was being used in heat exchangers used for food processing. And that, of course, was the cause of the Yusho incident.

EPIDEMIOLOGY: YUSHO

I would like to briefly describe the information that became available to us in the early 1970s as we dealt with Yusho to give you a feel for the kinds of information that were available and an appreciation of some of the considerations; and then I will gradually lead you into the regulatory perspective. First, the information concerning these contaminants in the rice oil was pretty iffy. From our calculations, the oil contained about 2,000 mg/kg of PCB compounds. We knew that it was a mess because there were other things in there: chlorinated napnthalene derivatives and, as was later appreciated, also chlorinated dibenzofurans. In addition, there were other chlorinated complex structures that later were identified as quaterphenyls. But initially, all we could really get a handle on was the chlorinated biphenyl series of compounds. On reviewing the exposure in Yusho, you could make a few simplifications in order to deal with the problem a little bit further. You would estimate that the duration of exposure that led to chronically obvious illness in the Yusho incident was about 100 days. Based on this, you calculate that it took about 2,000 mg in adults before the appearance of the disease. With regard to, I think it was about an 8 yr old boy, we figured that it took about 500 mg exposure before the appearance of overt disease. We didn't know what a no-effect level was because as we looked at the data provided by the Japanese, we found the data were not of the quality of a good classical, prospective epidemiological study. The data were from a retrospective study, "catch as catch can," and the Japanese did the best they could.

TOXICOLOGICAL DATA

Looking at animal data, we attempted to determine the pattern of what happened in animals exposed to various PCBs and we attempted to find levels that were associated with no adverse effects. I suppose it is important to repeat and to keep clear in our mind that every compound is toxic at some level. And with few exceptions, the converse should be true: that every compound is not toxic at some level. But the kinds of problems posed by PCBs have turned out over the years to be a little more extraordinary than we thought they were at the time. In terms of the animal data, one could see fairly obvious effects in rodents at 100 mg/kg in the diet. At around the 10 mg/kg level in the diet, according to the information we had then, was the no-adverse effect level. In between these two levels, you had an increase in probability of picking up metabolic disturbances due to the enzyme induction and inhibition powers, if you will, of these chemicals. And if we did some calculations based on a no-adverse effect of 10 mg/kg using the more classical rules for dealing with food additive and 100-fold safety, we came up with an acceptable daily intake roughly of 150 ug/person/day for an adult.

TOLERABLE DAILY INTAKE

As we looked at the Yusho data, coming back to the humans, we thought we had every reason to believe that this stuff has a long biological half-life, but we did not know how long. And we did not know what a no-effect level was in humans. We wondered if there were some way that we could approximate a 100-fold safety rule to see where we would come out. When you are dealing with a situation of widespread environmental contamination by a biopersistent compound, you have to think down the road a little bit because nobody has a magical wand to wave so that these residues immediately disappear from the food supply. In contradistinction to a food additive (where your recourse is simply not to permit the intentional or negligent addition of a compound into food while it is being processed), when you are dealing with an environmental contaminant in many food products, your only recourse is not to permit the ingestion of particular products as food. Looking at the Yusho data, we thought, what happens if we take one-tenth of the level that is associated with overt disease in adults and spread that over a ten times greater time period to provide some coverage for the unknown biopersistence of this compound. A tenth of the 2,000 mg is 200 mg; and if you spread that over 1,000 days, which is about 3 yrs, you come up with a 200 ug/adult/day type of exposure. That wasn't very far from the 150 ug/adult that was calculated from the more or less

classical approaches using rodent data. In effect, that's what we did.

REGULATORY PERSPECTIVE

Back in those days we were besieged, bothered, and bewildered because every place we looked we were bumping up against these residues. Just to refresh your memory, they were found in paper used as food packaging. They were found in fish, of course. They were found in fish meal that was being used for poultry feed. There was leakage from heat exchangers that had been using PCBs, and so we had several major incidents involving contamination of poultry and eggs. Then we began to look in milk and milk products and we found that the PCBs had been used as silo coatings and that they would flake off in the silage and contaminate dairy products. In reality, we did our best to try to prevent human consumption of as much of these contaminated food products as we felt we reasonably could. We could not turn off the food supply. We had to come to a level based on a particular food commodity, a level where we would decide that we were going to get tough. So what we did in the early 1970s was to set up a series of what we tried to clearly state as temporary action levels, or guidelines, or whatever you want to call them. The resources of the FDA were expended nationwide and internationally going after food, doing a lot of sampling, and taking food products off the market if they were above our action level and also in interstate commerce.

FACTORS REGARDING HUMAN EXPOSURE

The problem that anybody concerned with protecting public health from chemicals in food faces boils down to several questions. What levels of the residues are actually occurring in a food commodity? The answer is going to be a frequency distribution of data, because all food is not equally contaminated. Then comes the question of what is a typical serving size of that food. Again you are up against a frequency distribution curve. The third question is how frequently people eat that volume of product contaminated with X level of residue. So you are dealing with another probability curve. Believe me, that gets very complex. You have to look at your data, and all other available data, and then you have to make a decision which you may have a little difficulty defining as the right decision. The decision is difficult because you are dealing with a spectrum of considerations; and if you go too high on the spectrum, you may over react to the problem. So in terms of interstate commerce, we made some assumptions and set out action levels as I indicated earlier, and we enforced them.

SPORADIC VERSUS SYSTEMATIC EXPOSURES

If one looks at the United States from the viewpoint of the FDA, one looks at a variety of regional and ethnic eating habits; but one usually can count on most people getting food from a store of some kind. Much of the food that they buy in the store comes from various parts of the country at various times so the probability of a systematic human exposure is usually limited, unless a particular purchaser has a brand preference and that particular brand of product is always made from certain sources. However, if one talks about sport fishing people who go to a particular lake or stream, and consistently fish that particular area, and those fish are consistently contaminated, and they eat those fish frequently, quite obviously they are getting a very systematic exposure. So from one extreme of the nationwide probability that you are not getting a systematic exposure, you go to the other extreme of the sport fishing family frequently ingesting a highly contaminated product. In between there are certain considerations which deal with intrastate commerce, for which the state authorities have the authority and for which we in FDA only try to render advice when it is appropriate; we try to do that also if asked with respect to the problems associated with sport fishing people.

As I look back on the approach that was taken by FDA in the early 1970s, I've been reasonably well satisfied with the rather substantial decrease in PCB residues in most foods. That part of it is a success story; not perfect, but very substantial progress was made. The fish situation over the past decade has, of course, not been ameliorated nearly as much. We have had in some localities systemtic human exposure progressing over time. I guess it was around 1974 when I heard people in a sister agency criticizing me because they felt I was too tough on PCBs; then I found out that they were permitting pollution of receiving bodies of water by PCBs leading to levels of up to 5 mg/kg in the edible portion of the fish. I couldn't believe it. That sister agency changed its attitude and started turning off the faucet a little bit more aggressively with respect to PCBs as effluents in the receiving bodies of water such as the Great Lakes. That was a surprise which I am not sure many of you are fully cognizant of and I am not assigning blame to anybody, but it did happen. Because the efforts to cut off the PCB effluents were not as aggressive as they should have been, the data that you saw earlier today on fish might have looked even brighter, had these efforts been undertaken earlier in time. Just as it is difficult sometimes for the various agencies within a state to get their act together, it happens in Washington, D.C., too.

CHEMICAL AND BIOLOGICAL CONSIDERATIONS

We know that many PCBs have a long biological half-life, especially the higher chlorinated isomers. Conversely, we know that the lower chlorinated isomers have far greater acute toxicity. We know that many compounds will inhibit or induce enzymes, including many natural substances in our diet; but the difference is that most of those natural substances in our diet have relatively short biological half-lives.

In dealing with PCBs, it is important to get a good approximation of which PCB isomers humans are actually getting exposed to. For example, it doesn't make much sense to study Arochlor 1248 if the residue pattern that is occurring in fish is an approximation of a mixture of Arochlor 1254 and 1260. The reason is that 1248 has a tremendously high percentage of the lower chlorinated isomers as compared to 1254 or 1260 and so you are dealing with substantially different spectrums of toxicity than what the humans of concern are ingesting. Probably none of us has a very accurate idea of what really did cause Yusho because we had a "glop" there, if I may use that term, a real mess. We had the chlorinated naphthalenes; we had the PCBs; the quaterphenyls; the dibenzofurans; and for all I know, some other stuff. This type of incident, unfortunately, has been repeated from time to time with similar effects, notably in Taiwan. But in this country I haven't heard of any appreciable presence of quaterphenyls in foods and I haven't heard of any appreciable presence of dibenzofurans in fish, per se, that I would call a substantial problem. A lot also depends on which dibenzofurans we are talking about, as it depends, in similar fashion, on which dioxin we are talking about if the subject of this meeting was dioxins.

The reproductive work that was done by Jim Allen using Arochlor 1248 on rhesus monkeys that caused such a tremendous national uproar, where people were politicking to ban all breast feeding of babies, was something that I felt was inappropriate and not fully relevant to the human situation. I would ask any of you who are dealing with monkeys, or are considering data from non-human primates, to remember that there is a very substantial difference between the rhesus monkey and certain other monkeys like the chimp; some of these differences deal with the fundamental sensitivity and feedback of the pituitary circuit and estrogen, estradiol, etc. It will take additional research using different monkeys using a mixture of 1254 and 1260 to get a better handle on what's really happening with pregnant monkeys. If you want to find out what's really happening with the fetus, expose the mother monkey but don't intoxicate the mother monkey; don't poison her, because if you poison any pregnant animal, you're going to have problems with

the offspring. The real clue is to approach this study with what I call a sub-toxic approach in the maternal animals.

That ends this part of the talk. You'll notice that I have not yet spoken about the cancer risk factors. What I don't want us to lose sight of, aside from the human considerations, is that we have some real concerns with the ecology and with some very fundamental aspects of the biology of reproduction, not only with humans, but with just about all other forms of animal life.

FUNDAMENTALS OF CHEMICAL CARCINOGENESIS

I'd like to go back to some fundamentals. This formula, I equals V/R (or a function of V/R), reflects a very simple fundamental: that the incidence of a disease is a reflection of both the challenge (V) to and the biological resistance (R) of that human, or any animal, to the disease. The same is true for cancer. There can be an increase in the incidence of a disease, either by an absolute increase in V or by a decrease in R, or both. In my judgment, very few people really think about this relationship.

Table 1 gives a shorthand version of classical carcinogenesis theory: if there are initiated cells, those cells have to be promoted by some process if cancer is going to result. The process of tumor promotion, and I am using the term somewhat broadly, can be effected by classical tumor promoters or by other forms of toxicity which approximate the adverse biological effects associated with tumor promoters. The process involves a selective pressure on cell reproduction over a considerable period of time in order to complete the promotion phase. And, it usually requires substantial dosing that is performed consistently. Said differently, if you interrupt the substantial dosing before the critical effect of promotion actually is attained, there is either an arrest or, in many cases, a substantial degree of reversibility of the so-called promotion process.

The term potentiator in Table 2 is used in almost a mathematical sense to reflect enhancement of the I in the I equals V/R relationship. If you have a compound which increases the activation of electrophiles, and those electrophiles are carcinogenic initiators, you will enhance the risk of cancer. Classical promoters under certain circumstances enhance the risk for cancer by a different mechanism. If you chop out part of the liver of an experimental animal, you will have an effect similar to tumor promotion. If you intoxicate that liver, you will also have an effect similar to promotion. Suc

TABLE 1

Shorthand Version of Classical Carcinogenesis Theory

NORMAL MODE		
DNR in Normal Cell	Normal Replication - - - - - - - - - - - Normal Repair	Replicated DNA Replicated Normal Cells
CARCINOGENESIS		
Critically Damage DNA (Genotoxicity)	Abnormal Replication - - - - - - - - - - - Abnormal Repair	Initiated Cells (Potential for Malignant Transformation)
Initiated Cells	Promotion or → → → → → → → → → → → Toxic Hyperplasia Selective Pressure Through Succeeding Generations of Cell Line	Cancer (Malignant Characteristics)

intoxication can occur by poisoning various defense mechanisms or it can occur by a hyperplastic-like process, or by both. Under certain conditions, many other factors, including hormones, can enhance the risk of cancer. Nutritional aberrations, such as a deficiency of vitamin A, can have a powerful ultimate effect on risk, as can a very high level of unsaturated fatty acids in the diet. I am just trying to give you some perspective here.

Table 3 shows some of the changes that have been associated with classical promoters, and what I want you to take home is that there are many forms of toxicity that can be caused by a variety of compounds, some of which do not fulfill all the criteria for classical promoters. Figure 1 is just a different way of looking at this, but I want to draw your attention to the histones because they act to protect mammalian DNA, along

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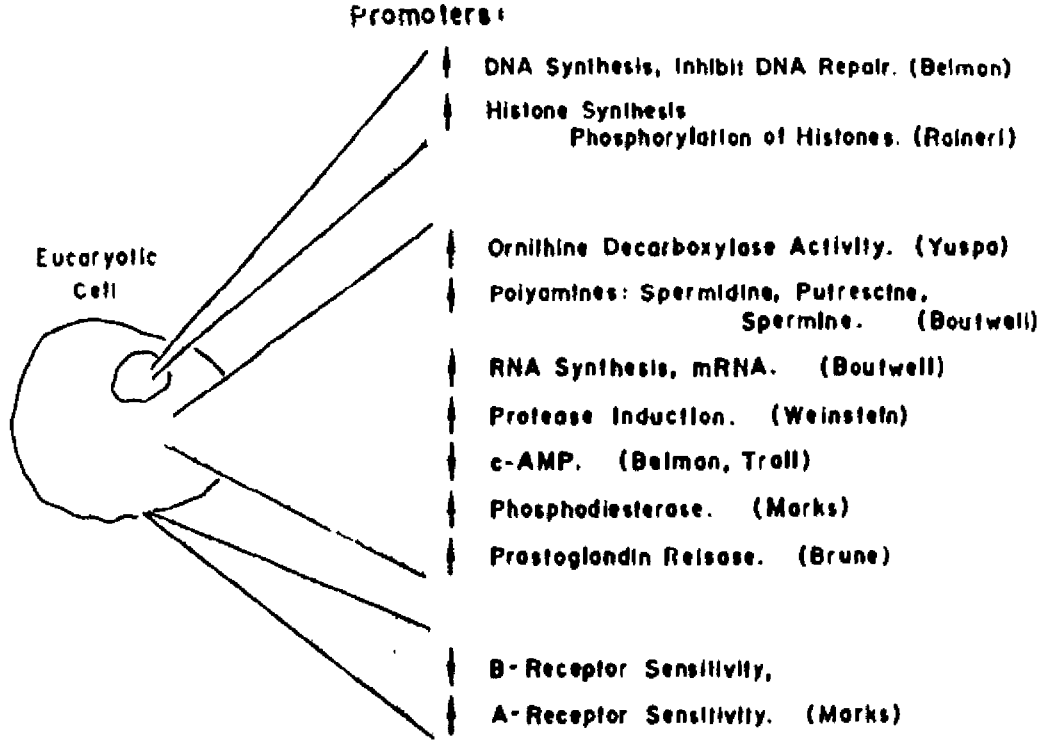

Figure 1. Factors influencing and/or influended by promotion.

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TABLE 2

Carcinogenic Sequence

Chemical Precursor	Activation → → → → → → → → →	Electrophilic Carcinogen
Electrpohile and DNR	– – – – – – – – –	Damaged DNR
DNA Damage	Normal Repair and Replication → → → → → → → → →	None or Some Initiated Cells
DNA Damage	Abnormal Repair and Replication → → → → → → → → →	More Initiated Cells
Initiated Cells	Abnormal Replica-Through Many Cells Cycles → → → → → → → → →	Malignant Cells
	Repetitive Exposure to Promoters or Agents Which Cause Toxic Hyperplasia	

with other nucleoproteins. The list of promoters on Table 4 is not perfect and I should have labeled it indirect carcinogens, but the word promoter in the broad sense will do. I include PCBs more in a category of a promoting-like compound than an initiating-type of carcinogen. As you study the effects in liver when you apply promoters (and please remember that the liver is an organ that has cells initiated independently, probably from many sources, not the least of which may be endogenous nitrosamines from the intestinal tract), you can follow the progression of critical lesions by looking for enzyme-altered foci. If human beings showed such effects, then they would be entering what I would call a substantial zone of risk; but in order to get this kind of a risk, you need that

TABLE 3

Promoter Induced Cellular Changes

Altered Surface Tension	↑Deacylation of Cellular Lipids
↓Lipid Microviscosity	↑Prostaglandins
↓In Cell Surface Charge	↑m-RNA Activity
Loss of Contact Inhibition	↑Protease
↓Chalone Responsiveness	↑Polymorphonuclear Leukocyte Degranulation
↓B - Receptors	Stimulates T-Cell
Inhibits Binding of Epidermal Growth Factor	↑Ornithine Decarboxylase
↓Na^+ ·K^+ ATPase	↑Putrescine Levels
↓Mg^{++} ·Ca^{++} ATPase	↑Protein Production
↑Phosphodiesterase Synthesis	γ - Glutamyl Transpeptidase
↓c - AMP	↑DNA Synthesis
↑c - GMP	↑Histone Phosphorylation and Synthesis
↑Uptake of Hypoxanthine	Stimulates Synthesis of 2 New Proteins
↑Uptake of Choline	↑5' Nucleotidase
↓Glucose-6-Phosphate	Inhibition of DNA at Endonuclease Step
↑Phospholipids	↑Levels of Sister Chromatid Exchange
↑Arachidonic Acid Metabolism	↓Histidase

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TABLE 4

General List of Promoters

Deoxycholate	Lithocholic Acid
Sodium Chloride	Glucose
Ethanol	Cholesterol
Saccharin	Tryptophan
Sodium Oleates	Fatty Acid Esters:
Citrus Oil	Oleic Acid
Sodium Cyclamate	Lauric Acid
Vitamine A-Palmitate	Retinyl Acetate
Caffeine	High Fat Diet
High Meat Diet	Catechols
BHT	Surface Agents
Sulphur Dioxide	Tweens
Paraffin	Spans
Glass	Carbon Tetrachloride (CCl_4)
Iodoacetic Acid	Anthralin 2-Naphthylamine
DDT	(Trichloro-2 Propene Oxide)
Hydroquinones	TCPO
Asbestos	($ChCl_3$) Methyl Chloride
Dieldrin	Thioacetamide
Thiourea	3-Aminotriazole
Linear Alkanes (10,12,14-C)	PVP
Iron Dextran	Phenobarbital
Chloroform	Phorbol Esters:
Diterpenes:	Croton Oil
Tigliane	TPA
Ingenane	PMA
Daphnane	Sodium Laurel Sulfate
Aluminum Hydroxide	Cholestyramine
PCB	Prolactin
Pyrilamine Maleate	Hormones
Injury	

which I mentioned: substantial, consistent, and repetitive dosing.

CONCLUSIONS

What I am trying to say is that the ordinary human in the United States is probably in pretty good shape. For low exposure, and for infrequent or inconsistent exposures to PCBs,

I don't think that there is any need to get excited or to have any fear. At the other end of the spectrum, there are people who may be getting very substantial repeated exposures to PCBs; here I am again talking about sport fishing people. An action level doesn't apply to them in the legal sense. To the best of my knowledge, some of the people who have had substantial, repetitive exposures to PCBs do show some changes in enzymes like the gamma-glutamyltranspeptidase, which can also be influenced by many other factors such as alcohol intake. I think people who are getting high, repeated exposures to PCBs should have some sort of medical follow-up. If their serum enzyme levels indicate problems, I think somebody ought to tell them to live a little differently (i.e., reduce exposure to PCBs and alcohol, etc.), because there may be a secondary promotional-like process underway. I do not think that PCBs should be treated like primary carcinogens.

CHAPTER 6

RESPONDING TO PUBLIC CONCERN OVER ENVIRONMENTAL POLLUTION HAZARDS

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Many in this audience probably remember a phase in our recent history when scarcely a week went by without a news report of a laboratory discovery somewhere that another product or substance might cause cancer or some other human affliction. The theme became so repetitive we began to hear it said, half-seriously, "Everything causes cancer." As in the story of the boy who cried "Wolf!" once too often. I fear the dismal warnings we were then hearing began to lose some of their urgency. Not because the wolf wasn't there, but because people came to fear there were so many wolves lurking around us that there was really no chance of escape. Our environment and our food supply, so it seemed, were laced with a great variety of alien substances which could imperil our health and more of these hazards were being identified with alarming frequency.

The steady flow of these reports of ominous laboratory findings portending an adverse impact, immediate or potential, on human health appear to have occasioned misunderstanding and confusion in the public mind about the exact meaning and significance of the findings. With so many potential health perils reportedly threatening us, it is readily understandable why some people may have concluded they have stumbled into an environmental trap from which they cannot break loose. We hear them say: Why get excited? Why worry?

Perhaps, if you are a research specialist or a government administrator working day by day on matters involving pollution of the environment, you may have occasionally experienced a sense of dismay because the public doesn't seem to take your

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work or your warnings seriously. If you happen to feel that way, that would be understandable, too. But perhaps an obvious reminder is in order: Because the experts know, it doesn't follow that everyone knows the danger or appreciates the extent of a particular type of contamination or exposure.

It may also be well to remember that all of us are continually buffeted by a variety of relentless pressures and demands competing for our attention and our concern. Is it realistic to expect each individual to become intensely alarmed about every threat to his health and every assault on the environment that he hears about? If so, I fear we would soon become prime candidates for psychiatric attention. And if not, then each of us must devise a personal scale of priorities for our individual concerns and fears.

But let us not forget a basic rule of behavioral psychology--the one that says a squeaking wheel gets the grease. Popular attention can and will be focused on whatever topics are dominant at the time in the news media. In fact, the degree of media attention a given topic may arouse can be a powerful factor in shaping our own reaction and determining where that particular subject fits in our personal scale of priorities.

PCB POLLUTION OF THE GREAT LAKES

We are concerned at this symposium with environmental pollution hazards associated with polychlorinated biphenyls (PCBs) in the Great Lakes. Are most of the people residing in Michigan and in other Great Lakes states and provinces concerned? I would like to think the answer is, "Yes, to some extent--some more so than others, of course." But are they deeply worried at this time about PCBs in the Great Lakes? I doubt it. Should they be? I don't know. Others at this symposium may be able to tell us whether we should be mildly concerned or greatly alarmed, or something in between.

But if the public should be genuinely disturbed, or perhaps even fearful, then the public is entitled to straight talk on the issue from responsible and reliable sources. A well-informed people given reliable information can be expected to react positively and responsibly in their own best interest to the efforts of official agencies to bring a serious environmental hazard under control.

I will not go into the techniques for mobilizing that kind of public response at this time because this is not the appropriate forum for that discussion. But the agencies of govern-

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ment, as well as the universities and others in the arena of social and political action, know there are ways of developing public support for goals which are broadly perceived as worthwhile and desirable.

PUBLIC CONCERN OVER PCBs IN THE GREAT LAKES BASIN

To the people from regulatory agencies and to the scientists and researchers in our midst who may feel frustrated by what appears to be a low level of public awareness or concern about PCBs in the Great Lakes basin, may I suggest let's pause for a moment to review the situation. If you believe there is inadequate public recognition and support for your work, is anything to be gained by blaming other people for being confused or indifferent, given the bewildering array of warnings, demands, restrictions, and requirements all of us face?

What <u>is</u> needed, I suggest, is a carefully drawn definition of the problem as the experts see it and reflecting their consensus and a clearcut statement of needed remedial or protective action. In the course of taking those two steps, it can be reasonably determined what types and levels of public involvement are advisable and the means of generating popular support.

The initiative should come, as I see it, from the appropriate official agencies. But if for some reason they cannot or do not act, it is likely that aroused citizen groups will assert leadership at least until government finally accepts responsibility. Supportive resources will be found in educational institutions, in social and political action organizations, and in the field of communications.

I am convinced the public will listen when you have something to say that needs to be said; and when it is said clearly enough, to be readily understood.

PCB CONTAMINATION OF GREAT LAKES FISHES

In 1969, we are told, PCB contamination was found in Great Lakes fish; more so in Lake Michigan than in any of the other Great Lakes, and more so in the southern part of Lake Michigan than in the upper part (Humphrey, 1975; NRC, 1975). The latter observation regarding contamination in southern Lake Michigan cannot be said to be surprising considering the heavily industrialized and urbanized regions of Michigan, Indiana, Illinois, and Wisconsin adjoining the southern portion of that lake.

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After discovery of the contamination, the official agencies recognized a possible threat to health among those people, sports fishermen and their families in particular, who were eating trout and salmon and some of the other species of fish taken from Lake Michigan (MDPH, 1971). If the health of sports fishermen alone were the only concern, it would be cause enough for responsive government action. But isn't there more to be considered?

What assurance can be offered about the quality and purity of water taken from the Great Lakes, and from Lake Michigan especially, when that water is used for community water supplies, for agricultural irrigation, for domestic and commercial food processing and canning, and for other types of industrial processing?

What is the impact, now and for the future, of PCB contamination on the commercial fishing industry in the Great Lakes region and on the workers and their families who rely on that industry for their livelihood?

Are we concerned about the possibility of an adverse impact on the tourist industry of the Great Lakes region?

And what may be the effect eventually on government resources and government costs in providing health protection, health care services, pure food protection, and the regulatory controls and mechanisms for monitoring or preventing environmental hazards (McCracken, 1982; MDA, 1981; Walker, 1981)?

As these questions come to mind, responding to them on the basis of information shared with the public up to this point may lead us to feel there is no cause for great alarm. If for some reason PCBs in Great Lakes waters are seen as a serious menace in the future, however, they may easily become a highly disturbing factor in the lives of countless people throughout the Great Lakes basin.

RESPONDING TO PUBLIC CONCERN

In responding to public concern about the hazards of environmental pollution, it would seem almost axiomatic that we must know, more or less specifically, what the public is concerned about. Similarly, if we are dealing with a situation in which, to our dismay, the public appears to be apathetic and unconcerned, we may want to know why.

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In either case, the answer, in oversimplified terms, is two-fold: ask and listen.

To discover the degree of public awareness about an issue or the tone of public reaction to that issue, a good approach is to ask. There are numerous techniques available for doing so, including questionaires and neighborhood canvassing. If no other means are at hand, or as a supplemental device, you might try a public opinion survey conducted by a qualified and reputable polling organization.

Or, you might wish to develop a system for listening to what the public is saying about a given topic. How? By routinely noting the essence of complaints, questions, or suggestions reaching your agency in letters and telephone calls relating to the topic under consideration; or by observing the frequency and content of news media attention to the subject; or by noting the points of view expressed in published editorials and letters to the editor; or by noting attitudes expressed and positions taken by citizen groups, adversary organizations, and political leaders. Regional and district field offices of government departments could be asked for periodic summaries of their perception of citizen interest and attitudes in their area as an indication of public awareness and concern about the given topic.

I am not suggesting for a moment that anyone in a position of official responsibility should react spontaneously to every straw fluttering in the wind. I do suggest that a responsible administrator should have the full benefit of his agency's observations and perceptions of public attitude and concern when evaluating alternative courses of action, and perhaps also when he is considering the possibility of altering a plan or compromising on a procedural approach to avoid counter-productive controversy.

May I point out, too, that if some of the comments and complaints voiced by the public reveal their authors are poorly informed or arriving at ill-advised judgments, no benefit results from dismissing these points of view out of hand. Rather, it could be productive to interpret them as an indication of the educational challenge which needs to be faced and of the communications job which has to be done. This is all the more important, I believe, when government agencies are about to impose restrictions or prohibitions and need broad acceptance and compliance to achieve effective results.

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PBB OPINION RESEARCH

A few years ago, in the midst of the polybrominated biphenyl (PBB) exposure incident we were then experiencing in Michigan, I was associated with the Michigan Department of Public Health (MDPH) for several months as a communications consultant. The department was then preparing to undertake a statewide study to determine the extent and degree of exposure to PBB among Michigan residents and to search for demonstrable links between exposure and its effect on human health. As organized by the MDPH with federal and state funding, one of the major components of the study was to be conducted by medical researchers from Mt. Sinai School of Medicine in New York and another by the School of Public Health, with the assistance of the Survey Research Center of the University of Michigan. Results of the work of both groups were to be monitored by the Wayne State University School of Medicine.

Before proceeding with a study of that magnitude and cost, the MDPH wished to be certain that a sufficient number of people in all parts of the state would willingly participate in it if asked. It so happened that Market Opinion Research (MOR), a Detroit polling organization, was about to conduct one of its quarterly surveys of Michigan residents. Arrangements were made to have 10 questions relating to the PBB situation included in the MOR survey. The responses were reassuring and yet in some respects surprising. MOR's survey report indicated that it had indeed been worthwhile to ask people what they knew or thought about the matter (MOR, 1978).

The MOR cross sectional statewide survey was conducted over a two week period in December of 1977 by telephone interviewers who questioned 800 adult respondents selected by the polling organization to provide a statistically valid sampling of the Michigan population. The reported results were said by MOR to be subject to possible error of plus-or-minus three percentage points. Here are some of the results of that survey:

To the first question: How concerned would you say you are about food additives, preservatives, or contaminants in your food?

--47 percent said they were very concerned;
--28 percent said they were somewhat concerned;
--25 percent said they weren't concerned at all or didn't know.

Note that 75 percent of the respondents were sufficiently aware of the matter to express concern, and nearly half were "very concerned". Moreover, younger people showed greater

concern about the matter than older people. Of the respondents in the 18 to 24 age group, 86 percent expressed concern compared to 70 percent or less in older age brackets.

Among the respondents expressing concern, 44 percent mentioned food additives, 32 percent mentioned PBB, and 2 percent mentioned PCB (identified in the MOR report as PCP). Both PBB and health perils associated with food additives had been prominently in the news shortly before the MOR survey was taken; PCB had not. Even so, we can see some awareness of PCBs indicated in that sampling despite the absence of current news media emphasis. Interestingly, too, the greatest awareness of PCBs was evidenced in the age group of 25 to 44, although the percentage was small (4%).

Responding to another question, some 35 percent of those interviewed (or more than a third) feared that food additives, preservatives, and contaminants can cause cancer, while 27 percent feared they could cause other health problems.

Among all the persons contacted and questioned in the survey, 48 percent thought they had some of these substances in their bodies, including 29 percent who thought they had PBB. It may be pertinent at this point to note that at the conclusion of the General Population Study, the Mt. Sinai School of Medicine researchers reported that 70 percent of Michigan's population had levels of PBB of more than 0.3 ug/kg in their blood, including 11 percent with more than 3 ug/kg (Selikoff and Anderson, 1979). In other words, the breadth of exposure was much greater than most Michigan residents had thought.

And finally, nearly 52 percent of those who were questioned said that if selected as part of a random sample of Michigan residents to study the effects of PBB on the general population, they would be willing to participate. Interestingly, among the respondents who felt they had PBB in their bodies, 93 percent said they were willing to participate in a general population health study.

Subsequently, the PBB General Population Study was conducted with adequate numbers of Michigan residents willingly taking part--7,711 questioned in two random sample telephone surveys conducted by the University of Michigan School of Public Health, and 1,738 individuals examined by the Mt. Sinai medical research team at six clinics throughout the state (UMSPH, 1979; Selikoff and Anderson, 1979). I mention the PBB polling survey by way of indicating what can be learned about public attitudes and reactions when using that technique.

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CONCLUSION

If anyone at this symposium is interested at this time in involving the public to a greater extent in dealing with the matter of PCBs in the Great Lakes, I would suggest as one approach that you first try to determine what the public may already know about the subject and what concerns there may be in the popular mind, if any at all, about PCBs. Then, having asked and listened, you may be better prepared to proceed with your plans. And if there is still a question in your mind about what the public can do, or what you might wish people would do, go public with the story and tell all of us what needs to be done.

ACKNOWLEDGMENT

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CHAPTER 7

THE ENVIRONMENTALIST'S VIEW OF THE PCBs PROBLEM IN THE GREAT LAKES

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INTRODUCTION

It is my pleasure to address you as part of this International Symposium on PCBs in the Great Lakes. I bring to this program the non-scientific perspective of a layman and the concerns of the people I represent through the Michigan United Conservation Clubs (MUCC)--the sports anglers and their families of Michigan.

We welcome this symposium. It is my hope that the questions I bring you today will be answered through this meeting or through new initiatives which come out of these deliberations. We are rapidly coming to the realization that the future of quality recreational fishing rests on our ability to safely manage chemical discharges to air and waters of the Great Lakes Basin.

MUCC AND PCBs

The interest of our organization in water quality problems actually dates back to our founding in 1937. MUCC now represents over 100,000 members and 400 affiliated organizations. Nearly all our members (95%) are anglers and half fish the Great Lakes. Since we know there is a direct relationship between the quantity of Great Lakes fish eaten and the polychlorinated biphenyl (PCB) levels found in human blood (Humphrey, n.d.), our interest is obvious.

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Let me mention to you a few of the recent actions of MUCC regarding PCBs. In 1976, we prompted the Michigan Department of Natural Resoruces (MDNR) to include the first "Public Health Advisory" regarding consumption of contaminated fish on the 1977 Michigan Fishing Guide, a brochure distributed with all sports fishing licenses. That same year MUCC was instrumental in passage of the nation's first ban on PCBs through a state law (Act 60 of 1976). In 1977, we blew the whistle on one of the most flagrant cases of PCB pollution in the Great Lakes Basin at Cast Forge on the South Branch of the Shiawassee River. Record PCB levels of 345 mg/kg in biota and 530 mg/kg in sediments a mile below the plant were known by the state but not publicized. The river is still closed to fishing, but a $1 million clean-up plan is now underway, the first such restoration effort we know of.

In 1978, we helped force the closing of a toxic liquid waste incinerator on the Saginaw Bay (Hartley & Hartley at Kawkawlin, Michigan) operated by SCA Services, Inc. This company operated its liquid disposal business in the 1960s by storing the waste liquids in open ponds in the Tobico Marsh and periodically setting them on fire. Then in 1971, the state licensed an uncontrolled incinerator at the site. SCA's advertising was revealing:

> Now you can get rid of your troublesome chemical wastes EASILY, CONVENIENTLY, ECONOMICALLY, SCIENTIFICALLY . . . Ship us your waste or we will pick it up and we will process it in accordance with federal, state, and local regulations, relieving you of liability as well as relieving you of a burdensome task. We will process such chemical wastes as: PCBs, cyanides, pesticides, chlorinated solvents . . . carcinogens, heavy metal wastes, . . . mercury sludges . . . and so on.

This was a <u>legal</u> operation; no one was ever prosecuted for this environmental travesty. No wonder the Great Lakes have toxic chemical problems; no wonder no one trusts government regarding toxic chemical management.

I should also note that MUCC has been active in seeking solutions to the PCB problem. We have bucked local opposition and vocally supported proposed PCB incineration at the Peerless Cement kiln in Detroit and at the General Motors Chevrolet plant in Bay City. We have supported various PCB treatment technologies in the region. And we have been active in virtually all phases of hazardous chemical management and regulation in our state.

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I mention these examples only by way of background to demonstrate how seriously MUCC takes PCB contamination of the Great Lakes. Our membership has demonstrated its commitment to toxic chemical control over and over with money and energy. And this public support is consistently underestimated by public agencies and politicians.

GREAT LAKES PCBs AND MICHIGAN ANGLERS

PCBs in the Great Lakes are particularly important for the state of Michigan and our anglers. We own title to 40 percent of the area of the Great Lakes. Michigan has a higher ratio of our area covered by freshwater compared to land than any other state or country--two square miles of Great Lakes surface water for every three of land.

Tourism and travel, much of it related directly to the Great Lakes, is over a $9 billion annual industry in Michigan. The Great Lakes sports fishery is a $350 million annual business in our state alone. This fishery is one of the best and most exciting in the world. Michigan has 1.5 million licensed anglers, not including the many children and spouses who don't need licenses to fish.

The salmon fishery continues to expand. For example, Lake Michigan salmon (and steelhead) now run up the Grand River to the state capitol and may eventually be caught on this campus of Michigan State University. Those fish are being caught and eaten in huge quantities. Many families catch and can hundreds (some thousands) of pounds of salmon every year and eat those fish all year long.

In the midst of this expanding recreational fishery, sports anglers are faced with this ironic note of warning on their fishing law digest:

> Certain Great Lakes fish should not be eaten--by children, women who are pregnant, nursing, or expect to bear children. Limit consumption by all others to no more than one meal per week.

Incidentally, this warning includes those salmon and steelhead I mentioned now migrating to Michigan State University.

What does this warning mean to the sports anglers and their families of Michigan? This very distinct population in Michigan is at very distinct risk from long-term exposure to PCBs. I can assure you that many anglers do not take seriously the warnings about limiting consumption of Great Lakes fish. You've

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heard the rationale: "Everything causes cancer. I'm not a white rat. Remember the cranberry scare. Everyone's got to die from something." Perhaps most pathetic of all: "I've been eating these fish all my life and it never hurt me." One outdoor writer in the region is spreading the good word to sportsmen that concern over PCBs is a "fright scene orchestrated by environmental extremists and their kneejerk media handmaidens" and that PCBs and table salt "may well be about equally toxic" (Spiers, 1981). It makes good copy and this kind of nonsense is just the excuse many sportsmen need to justify what they want to believe that nothing bad has been proven about PCBs.

The public, and especially the majority of the sports fishing public, is crying for information and answers to questions. It is my conclusion that government and public unversities have failed miserably in providing information and answers to questions of vital public concern.

FISH MONITORING DATA

If you want an exasperating experience, try to find basic information on what fish species and what size classes from what waters have or do not have various contaminants. The cursory information provided in Michigan's Public Health Advisory is better than nothing, and that is about the best you can say for it.

There is, however, no comprehensive document available to the public summarizing all available data on fish contaminants in Michigan. I suspect other states are no better off. In fact, we finally were forced to compile all the data we could find ourselves for publication in our magazine, Michigan Out-of-Doors (Schmidt, 1981).

Why hasn't the MDNR, and until recently the Michigan Department of Public Health (MDPH), shown any interest in publicizing data on contaminants? No one wants to be the bearer of bad news about poisoned fish. But the public is demanding better information about environmental contaminants from its public servants. It is deplorable how little we know about fish contaminants, not only in Great Lakes fish but from fish in inland waters as well. It is inexcusable how poorly the limited data we have has been made available to the public.

For example, the 1982 Public Health Advisory states that musky from Lake St. Clair should not be eaten. From this you would assume that all other species in any size class from Lake St. Clair are safe. Yet we know from Ontario data that this sanguine conclusion is dead wrong. Doesn't anyone from Michigan

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agencies talk to anyone in Ontario agencies? As another example, all Lake Huron trout and salmon are lumped in a single advisory. Aren't any of the small fish safe?

The Ontario program for monitoring and publicizing fish contaminants is the best model we can point to. It is an honest attempt by the provincial government to point out to the public exactly what we do and do not know about fish contaminants. Michigan can claim that we can't afford the program. I suggest that until state governmental agencies first demonstrate concern and recognize the importance of collecting and publicizing such monitoring data, the money will never be available. It may also be time for sports anglers to begin thinking about using fishing license money to partially fund such programs.

PUBLIC HEALTH AND PCBs

The public is demanding answers to complex questions on public health impacts from long-term exposure to PCBs. We recognize that Michigan has done some of the only research in this area, but it is pitifully inadequate. And there are some basic questions for which answers may already be available that are not being translated into plain English.

What do we know about the effects of PCBs on animals? What do the studies already completed demonstrate? If people are reminded what happens to mink fed Lake Michigan salmon, it has an impact on their attitudes. Somehow results of animal studies seldom get translated into reports average people can relate to and understand.

If I interpret the data correctly, I read that a woman eating only 6.4 kg of Lake Michigan fish/yr could typically expect to have 4 mg/kg PCBs in her breast milk (Swain, 1981). Further, her nursing infant would then be exposed to 20 to 25 times the maximum daily dose rate recommended by the U.S. Food and Drug Administration (FDA) for adult intake. This is shocking. Why isn't this type of common sense information widely publicized? Women want to know. I have seen other data concluding that nursing infants of heavy fish eaters could receive a total body burden of PCBs from nursing of up to 3.44 mg/kg (Harger, 1980). Women are looking for honesty from state government, no matter how incomplete the information may be or how unpalatable it may sound.

Again, I have to point to Ontario for the best model for public information on this issue. Their publication, "Health Implications of Contaminants in Fish" (OMOE, 1978) is the best

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summary on this question we know of. To my knowledge, no comparable publication is available from any of the Great Lakes states.

The other frightening question we raise concerns our ignorance on possible additive or synergistic effects of Great Lakes contaminants. Virtually everyone in Michigan already carries a body burden of PCBs and polybrominated biphenyls (PBBs). And PCBs in fish are not often a single pollutant but can be found in combination with mercury, DDT, PBB, chlorinated dioxins, dibenzofurans, chlorinated benzenes, and/or various other chemicals. The International Joint Commission has now identified 468 chemical contaminants in the Great Lakes system. PCBs cannot be treated as a single contaminant in an otherwise sterile environmental laboratory. How does this stuff all add up? We can't even get our MDPH to set a safe limit for dioxins in fish (Walker, 1981), let alone tell us what these exotic combinations may mean for the public health of our state.

REDUCING PCBs IN FISH

I recognize that some questions I raise may be beyond the limits of epidemiology to answer today. So let me try some simpler ones. If a salmon steak is canned with the skin on, eaten six months later with the skin off, how much are PCBs reduced or increased in the meat? If a salmon is smoked, what happens to PCBs in the skin and fat? If a salmon is broiled in butter with the skin on, what happens to the PCB level in the meat? It is hard to believe, with all the great minds concerned about public health implications of PCBs that no one has even cooked up a few salmon in different ways to answer these and related questions.

IMPACTS OF PCBs ON FISH AND WILDLIFE

We are also greatly concerned about direct impacts of PCBs on fish and wildlife, as well as public health. Research such as is being conducted by the U.S. Fish and Wildlife Service Great Lakes Fish Laboratory in Ann Arbor on lake trout reproduction is of great interest to sportsmen. But like so much research, it is communicated poorly, if at all, to the general public. Then when the budget ax falls, no one is sure what we would be losing if all the Great Lakes research facilities were closed. That is exactly what is happening today on the Great Lakes and I suggest these labs are themselves in part to blame for their political problems due to their dismal public relations with their constituency.

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But what do PCBs in the environment mean to native fur bearers? If reproduction in commercial mink are affected by diets of Lake Michigan salmon, what of the native populations feasting on spent salmon every fall? What of other predatory species in waters affected by PCBs, such as snapping turtles? What of fish eating birds (see, for example, Haseltine et al., 1981)? I suspect there is more information available than we see, but what good is it buried in a research volume?

POLITICS

I will conclude with one comment on the politics of toxic substances in the Great Lakes. Most of my questions have dealt with the need for public information and public accountability for government programs. We are making progress in Michigan. The single biggest factor in this progress towards honesty and public accountability has been the over-sight functions provided by the Michigan Toxic Substance Control Commission (TSCC). It has made numerous contributions to resolving toxic substance problems in Michigan, raising issues no one else will confront (see, for example, Holcomb, 1981). But its most important contributions have been two intangible ones:

(1) Independent over-sight of the politics and priorities of state agencies regulating PCBs and other hazardous chemicals.

(2) Providing a forum--the only one available--for the public to voice the concerns such as I have raised today.

The TSCC has been a force for positive change in this state.

Yet there are powers within the executive and legislative branches of state government today with the avowed objective of eliminating the TSCC. This objective is totally contrary to the public interest and the public's broad support for the continuation of the TSCC. It is terribly frustrating to be fighting these petty factional squabbles while the real questions of public health and environmental quality go begging for attention.

SUMMARY

Let me summarize with just two statements:

(1) The public, especially the sport fishing public, is crying for more information on PCBs and other

environmental contaminants. There is a need for a vastly improved information base on PCBs and other contaminants in the Great Lakes environment and a vastly improved delivery system to get that information to the general public.

(2) People want honesty from their government. They want government to level with them in language they can understand about what we know and what we don't know about PCBs. If you aren't straight forward with people, no one trusts anyone.

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CHAPTER 8

THE COMMERCIAL FISHERMEN'S VIEW OF THE PCBs PROBLEM IN THE GREAT LAKES

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It is a pleasure to talk to you about the effects that polychlorinated biphenyls (PCBs) have upon our commercial fisheries. First of all, I want to emphasize that the industry does not want to produce a product that will adversely affect human health, and that we applaud all efforts to reduce contaminants in the lakes. Having said that, I want to point out that it is the commercial fishing industry that has probably suffered the most from contaminants in their products. They have seldom, if ever, had any direct role in causing the contaminant pollution, yet in only a few cases have they been compensated for their losses. When contaminants occur in fish, and these contaminants cause disease, the public knowledge of this may reduce the attractiveness and price of these products in the market. Any time there is mention of the PCB problem in the news media, sales in the retail fish markets and supermarkets go down. The public is so sensitive that I am sure that even the publicity associated with this symposium will cause some people to think again about the fish they are eating and forego fish for at least a period of time.

A government, motivated either by known or feared consequences of eating contaminated fish, may take a number of different steps. It may determine the maximum sizes that may be taken, as occured in Muskegon last year. The fishermen there were advised that whitefish weighing more than 1.8 kg (4 lb) could not be sold. This year, because the levels have come down, fishermen will be permitted to take whitefish up to 2.7 kg (6 lb). A government may legally close certain fisheries, as has been done in western Michigan. The area from approximately Montague south to the Indiana line is closed for chub fishing because of high levels of dieldrin. Another step a

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government can take is to set action levels and ban the sale of fish which exceed this level. Alewives, the predominant species in Lake Michigan, can't be harvested because of high levels of PCBs. It is estimated that at least 455,000 kg of these fish, which could be used as sardines, could be harvested out of just the Wisconsin ports on Lake Michigan. A government may issue advisories that the more contaminated species should not be eaten, except occasionally. This is the way that the sports fisheries have been handled. Sports fishermen are warned against eating highly contaminated fish too often or in too large amounts.

This different treatment of sports and commercial fishermen has been bothersome for some time. Let's look at a situation that is repeated daily when commercial fishermen and sports fishermen are on the same fishing grounds. A lake trout is brought aboard a commercial vessel as the fisherman lifts his net that was set for a different species of fish. He is not permitted in the state of Michigan to have this incidental catch. He must throw it back in the lake because, under the Food and Drug Administration (FDA) standard, the fish is not fit for human consumption. Now, let's assume that an hour later this same fish is caught by a sport fisherman and is declared legally acceptable as human food in the state of Michigan. There is something wrong with this situation. The fish is either fit to be eaten regardless by whom it is taken or it is not safe to be eaten. If the current concern over PCBs indicates that fish with certain levels of contamination are not fit to be eaten, then no one should be eating them.

When I was first asked to participate in this symposium, I wondered why Michigan was concerned over the present situation. PCB levels have been declining faster than anyone has expected them to. A few years ago, when PCB levels ranged in the high teens and low twenties, individuals who caught their own fish, and consumed their catch, were merely warned not to eat fish too often. From what we known, a lot of fish were eaten. I ate my share. Now that PCB levels, in many species and in many places, are as low as 5 mg/kg, there is an expressed concern over the effects of PCBs in humans. Perhaps there is new evidence that will be presented in the next two days that will tell us why there is new concern.

I also wonder why this symposium is being convened, and why Michigan is considering unilateral action to establish a lower guideline for PCB in fish, when this same issue is being considered in Washington. For the past 15 months, the FDA, various environmental groups, the National Conservation Council, the National Fisheries Institute, the National Marine Fisheries Service, and other associated commercial fishery

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interests have been arguing the case before Administrative Law Judge Daniel J. Davidson (FDA Hearing Examiner). At first, a decision was expected on January 11, 1982, but there was so much evidence presented that he postponed his decision and it is now expected around the first of May.

At these hearings, consideration has been given not only to the level at which human beings can be adequately protected, but also the required level that can be established without causing economic disruption to an industry. The law judge has made a determination that in deciding whether to drop the guidelines for PCBs from 5 mg/kg to a new legal level of 4, 3, or 2 mg/kg, there must also be a consideration of the economic loss to industry. Judge Davidson also ruled that you cannot take the dockside value of the fish and use this to represent the economic loss. Instead, the dockside value must be multiplied by 6 to determine the economic loss to the industry on a national level. This multiplier takes into account that the fish doesn't stay on the dock, but instead moves through transportation to wholesalers, processors, and canners to the ultimate consumer, whether it be through a restaurant, a club, a fast-food outlet, or in your own dining room.

The factor of 6 might be a little high considering the total economic loss to the industry in Michigan because, obviously, we do not have canneries as they do on both the East and West coasts. Also, there may be another process or step eliminated but it would be fair to say that a multiplier of 4 to 5 is a reasonable figure to use. William McCracken, chairman of the Fish Contaminants Advisory Committee, has made a study to determine the economic impact of lowering the allowable level of PCB in commercial fish harvested in Michigan from 5 to 2 mg/kg. He said that the effect on the commercial market would be $4.2 million. He did not take into consideration a million pounds of chubs that could be produced were it not for dieldrin. They are currently selling for a dollar a pound on the dock. So if we take the $4 million, and another million to it, and multiply by 4.5, we are up to about $22 million. Mr. McCracken had another interesting figure and that was the increased regulatory cost to the state of Michigan of policing a 2 mg/kg level if it were not also adopted by the neighboring states. This cost would be high because much of the fish sold in Michigan comes from other states. He estimates that the cost to the state would be $500,000.

Additional economic losses may occur if contaminants reduce the biological productivity of fish stocks. Some years ago our chub fishery in Lake Michigan began to decline and there was a great deal of concern about this. Was the fishery being overfished? The problem, however, was not overfishing but a

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lack of recruitment over a period of years. The fishermen were reducing the standing stock and there was no recruitment of young coming up to offset that. It was determined that the presence of DDT was either making the eggs infertile or killing off the little fish with the yolk sacs still attached. When the DDT levels came down, the recruitment of stocks went up. This incident provided dramatic evidence that contaminants in fish could materially affect their ability to reproduce.

We hope that out of this symposium may come a closer surveillance of the uses of PCBs. We know that some of it is still being used. We hope that the state would determine where this PCB is getting into the lakes and the fish. I am sure a lot of good can come from this symposium.

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PART II

PCBs: ANALYSIS AND MONITORING

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CHAPTER 9

MONITORING FOR PCBs IN FISH: THE HUMAN HEALTH PERSPECTIVE

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INTRODUCTION

I have always been impressed with the opening quotation provided by Dr. David B. Peakall of the Canadian Wildlife Service in a presentation that concerned monitoring in the aquatic environment (Peakall et al., 1980). He walked to the podium with a bible tucked under his arm and read the following excerpt from Deuteronomy (Chapter 14:11-17):

> Of all clean birds ye shall eat. But these are they of which ye shall not eat: the eagle, the ossifrage. and the osprey, . . . and the pelican, and the gier eagle, and the cormorant.

The audience was left rather quiet, some fidgeted. Dr. Peakall continued with his talk. He made no further mention of the bible passage, but its relevance to his presentation of the Herring Gull monitoring program in the Great Lakes was suitably clear.

I am sure that the authors of Deuteronomy did not have access to gas chromatographs, high pressure liquid chromatographs, or mass spectrometers; however, they may have sensed a danger associated with the consumption by the public of these fish-eating birds. It is remarkable that all of these birds are currently under the strictest of protection in North America although the rationale for their protection is conservation of the species rather than concern for public health.

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This paper is not about fish-eating birds; rather, it concerns fish-eating people. Specifically, this paper provides the perspective of the human health evaluator on the need for polychlorinated biphenyls (PCBs) monitoring data in Great Lakes fish and also the benefits for man of the application of results of surveillance and monitoring programs.

ENVIRONMENTAL SURVEILLANCE AND MONITORING

Despite large resource expenditures for surveillance and monitoring, there remains considerable confusion over the definitions of these two activities (Berlin, 1979; Holdgate, 1979). Surveillance is usually defined as "the repeated measurement of a variable in order that a trend may be detected." Monitoring, on the other hand, is more action oriented and "designed to tell us how well our regulations are working and how far standards are being met." The line between these two activities is not always distinct. A preliminary survey of contaminant levels, or their effects, in the environment at one point in time may be repeated (surveillance) to identify trends. These trends may indicate control actions are required and the surveillance program is continued as monitoring to determine the impact of the control actions on environmental levels of the contaminant(s) and to assess compliance with regulations. For the purposes of this paper I have used the above definitions of surveillance and monitoring. The identification of new, previously unrecognized contaminants I have put as part of the surveillance activity; determining levels of PCBs in fish, now that PCB use is carefully controlled in North America, I have considered monitoring.

Man's interest in monitoring has largely been self-serving. In the past, the canary was carried down the mine shaft by generations of miners to warn of the presence of toxic gases. Today there are a variety of rationales for surveillance and monitoring programs (Gray, 1980; Nielsen et al., 1980). Furthermore, we have adopted more sophisticated terminology (Hytteborn, 1979). For example, surveillance and monitoring programs with biota are now described in terms of the use of active species (i.e., those species put in place in the zone of contamination and subsequently sampled) and passive species (i.e., those species that are residents of the zone of contamination and are subsequently sampled). Some species have extensive ranges, are long lived, and accumulate pollutants that are found over large areas; these species are "integrators" of pollutants that are "widespread". Other species are restricted in their habitat and range and serve as indicators of "point-source" or "local" contamination. Still other species

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can more adequately provide data on the effects of pollutants as opposed to the levels (Gilman, 1983).

Only sometimes does the rationale for surveillance and monitoring pertain to human health concerns. Currently, federal, state, and provincial programs in the Great Lakes basin are partially coordinated through the International Joint Commission (IJC)(Anon., 1978). The programs are primarily passive, they identify both local and widespread pollution problems, they ascertain contaminant levels, and, to a lesser extent, their effects on biota. To provide the data necessary for evaluation of human health risks from environmental contaminants, it is vital that specialists in health assessment contribute to the modification of existing programs and the design of future programs.

SELECTION OF FISH FOR PCB MONITORING

The strongest rationale for monitoring fish for levels of PCBs is also the most simple rationale: PCBs are toxic, they accumulate in fish, and people eat fish. Monitoring programs that are to provide useful data for health risk evaluation must meet the following four basic criteria:

Criterion 1. Monitoring programs must sample fish species that are consumed by the public.

PCBs from the Great Lakes basin will be ingested by sport fishermen, commercial fishermen, and the public through consumption of Great Lakes fish. To assess the health impact for man of PCBs in Great Lakes fish, it is essential to have information on the species of fish consumed, the amounts consumed, the frequency of consumption, and the preferences of "special groups" for certain species. These special groups include various ethnic, religious, socio-economic, and native sub-populations. Application of this knowledge to the selection of fish species for monitoring and in the calculation of average annual intake of PCBs will enhance the relevance of monitoring programs for public health.

Criterion 2. Fish species to be sampled must be collected at the same time of year and location that they are commonly caught for consumption.

The PCB content of fish can vary significantly because their body lipid levels can fluctuate (seasonal and sex related), their diets can vary, and their migratory patterns can expose them to varying concentrations of PCBs at

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specific times of year. Hence, assessments of public exposure to PCB must be based on data obtained from fish that have been sampled when and where these species are caught for consumption by the public. The usefulness of sampling data forthcoming from monitoring programs carried out at arbitrary times of the year is diminished because of the need to estimate levels of PCB at the time of public exposure.

Criterion 3. Monitoring programs must sample and analyze enough fish to ensure that raliable PCB concentrations can be calculated for the species and size classes consumed.

Suitable sample size is dictated by the amount of variation between the individual analyses. Currently, a sample size of 20 fish of any one size class (each fish analyzed individually) from any one location is adequate to detect a 10 to 20 percent change in PCB concentration from one year to the next (Anon., 1978). When standardization of size class is not possible, then statistical comparisons of concentration cannot be based on mean PCB concentration per size class. Instead, levels of PCB in individual fish must be plotted against the size class for that fish. When the analytical and measurement data for a large number of fish have been plotted, it is possible to compare PCB concentrations between years via linear regression analysis.

Criterion 4. Analysis of fish for PCB must be carried out on the consumed portion of the fish.

There is unanimous agreement between the Great Lakes jurisdictions of the need to analyze "edible portions" of fish when addressing public health concerns. However, definition of edible portion has become a contentious issue within and between analytical groups and between jurisdictions. Debates over skin-on and skin-off fillets, dorsal or whole fillets, belly-fat-on or belly-fat-off fillets, etc., continue. Detailed discussion of this complex issue appears in this volume (McCracken, 1983). The significance of consistent analyses of similar portions of fish between programs cannot be overstated from the perspective of health risk evaluation. Without agreement between the jurisdictions on a standard edible portion, comparisons of data collected from Great Lakes fish are almost impossible.

Application of these four criteria in the development of monitoring programs tailored to health concerns and addressing

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PCBs in fish must be tempered by several practical considerations.

Consideration 1. Cost of sampling.

Monitoring programs are expensive. When considering species capable of reflecting human exposure to PCB, it is necessary to examine existing programs. Do these programs sample for species that might be capable of providing data useful to public health officials? What is the ease and cost of sampling for the selected species (e.g., Rainbow Smelt, Osmerus mordax, are far cheaper to sample than Lake Trout, Salvelinus namaycush)?

Consideration 2. Availability of species.

Historical data and trends in PCB levels are significant when assessing impact on human health. Is there the potential for multi-year sampling or is the fish stock dwindling?

Consideration 3. Biological data base for species.

The best monitoring species are those with well known life cycles, feeding habits, population dynamics, migratory patterns, etc. Knowledge of PCB uptake and depuration rates, sex differences, and the relationship between size and level of contamination is useful. Also, is the selected species amenable to laboratory studies?

The need to integrate monitoring criteria and practical considerations underscores the importance of interagency and interdisciplinary consultation. The fisheries biologist, analytical chemist, health risk evaluator, and monitoring coordinator must be willing to cooperate and compromise to prepare a program that will produce meaningful data on exposure of man to PCBs. Furthermore, the data must be available in a format that can be used by health biometricians (i.e., the levels of PCB by species, size class, location, and season must be provided).

BENEFITS OF MONITORING AND SURVEILLANCE PROGRAMS

Do the benefits of contaminant surveillance and monitoring programs justify their costs? From the human health perspective, no quantitative answer is possible unless a value is assigned to "good health". Nevertheless, in qualitative terms and in full recognition of the desire to optimize public health, these programs are a bargain; some specific benefits from Great

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Lakes monitoring have been thoughtfully described by Swain (1981).

Data resulting from monitoring programs designed to determine PCB levels in fish enable us to:

--assess exposure of the public (especially critical sub-populations) to PCBs in fish;

--inform the public whether or not the current PCB guidelines are being met;

--identify previously undetected or new PCB sources;

--determine the effectiveness of abatement programs and the need to modify pollution control schemes to meet changing conditions.

Multi-contaminant monitoring and surveillance programs for both levels and effects provide the above advantages for other contaminants and also enable us to:

--identify "new" or previously unrecognized contaminants in media or food of direct importance to man;

--identify population effects in biota that may provide an early warning of the cumulative impact of environmental contaminants on living tissue;

--direct limited resources toward contaminants of highest priority and optimize the output of research, data gathering, and assessment activities.

As monitoring programs shift toward providing data that meet the needs of health risk evaluators, the task of making good use of the data comes into sharp focus. The end point in contaminant levels monitoring is not a listing of hundreds of mean contaminant levels in media and biota; rather, it is the determination of the effects of these levels of contaminants in man. Other papers in this proceedings address the impact of multi-media exposure to contaminants, contaminant interactions, and the assessment and regulatory processes.

CONCLUSIONS

Thoughtfully considered and carefully conducted monitoring and surveillance programs that provide suitable data for human health risk evaluations are urgently needed. Most important is the development of an agreement between the jurisdic-

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tions to analyze similar edible portions of fish to facilitate comparisons of data collected throughout the Great Lakes basin. The ultimate outcome of these programs will be better risk evaluations and enhanced utilization of environmental resources by North Americans.

The IJC has recently published a report of a Roundtable meating on the detailed requirements for data adequate for health risk assessment (Anon., 1982). This document will, hopefully, stimulate the production of more useful data for the assessment of human health risks from environmental PCB and other chemicals in the Great Lakes basin.

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CHAPTER 10

EDIBLE TISSUE SAMPLING FOR FISH CONTAMINANT ANALYSIS

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INTRODUCTION

There has been disagreement for years about how fish should be prepared for contaminant analyses. Whole fish, skin-on fillets, and skin-off fillets are three of the many types of sample portions which have been recommended and hotly debated as tha "proper" methods of sample preparation. The State of Michigan has looked into this issue in some depth and is proposing a rationale for selecting the portion to use in the analysis when the investigator desires to characterize the edible portion of fish. This paper presents Michigan's reasoning on this issue.

FISH CONTAMINANT MONITORING IN MICHIGAN

Michigan has three state agencies involved in fish contaminant monitoring. The Michigan Department of Agriculture is the state agency responsible for regulating the state's food supply. The Michigan Department of Agriculture coordinates its work with the U.S. Food and Drug Administration (FDA) which has the corresponding federal responsibility. Under their joint authority, regulation of fish and fish products in the food supply has been carried out for a number of years. Sampling by these agencies includes commercial catches of fish, fish and fish products as sold in wholesale and retail outlets, and fish served by restaurants.

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The Michigan Department of Natural Resources (DNR) is the state agency responsible for management of environmental protection programs and for management of the state fishery for commercial and sport fishing. Sampling includes fish from lakes and streams.

The Michigan Department of Public Health (DPH) is the state agency responsible for evaluating human health effects of eating contaminated fish and issuing health advisories as needed. The Michigan DPH does not have fish sampling responsibilities, but uses data from the Departments of Agriculture and Natural Resources and other sources in evaluating potential health effects.

Michigan carried out the Great Lakes Environmental Contamination Survey (GLECS) for about 9 yrs during the 1970s. GLECS was a cooperative program involving the Michigan Departments of Natural Resources, Public Health, and Agriculture, the U.S. FDA, and the U.S Fish and Wildlife Service. GLECS was hampered by the lack of a consistent funding source. This ultimately caused it to be discontinued in 1980.

The state established a Fish Contaminant Advisory Committee (FCAC) in January, 1981, to ensure that the fish contaminant monitoring efforts of the Michigan Departments of Agriculture, Natural Resources, and Public Health are coordinated. Among other things, the FCAC was charged with developing and maintaining a fish contaminant monitoring plan to guide the state's efforts in this area, and to resolve any technical issues relating to fish contaminant monitoring. The FCAC completed the fish contaminant monitoring plan in January, 1982. Most of the plan cannot now be carried out because funding is not available. However, it will serve as the state's blueprint for fish contaminant monitoring if and when the resources become available. The most difficult technical problem which faced the FCAC in developing the plan was how fish should be prepared for analysis, particularly when attempting to characterize the edible portion.

FISH CONTAMINANT MONITORING OBJECTIVES

The type of fish sample to be taken for contaminant analysis depends on the objective of the study. The importance of the objectives cannot be over-emphasized. The principal objectives that the Michigan fish contaminant monitoring plan is designed to achieve are:

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(1) To provide information for assessing potential human exposure to toxic materials due to consumption of commercial and sport fish.

(2) To determine chronological trends in fish contaminants.

(3) To identify new or previously unrecognized contaminant residues in fish.

(4) To communicate results to appropriate government agencies for regulation of commercial food supplies, for determination of human exposure and public health advisories, and for determination of the need for new remedial measures or the success of completed remedial measures. Also, to communicate any resulting public health advisories to the general public.

The first objective is to determine amounts of consumable contaminants present in fish. Therefore, it makes sense for the edible portion of fish to be used for contaminant analysis when carrying out this objective.

The second objective is to determine chronological trends in fish contaminants. Again, the FCAC decided the edible portion should be used for carrying out this objective because the trends in edible portions are of most interest in Michigan.

The third objective is to identify new or previously unrecognized contaminant residues in fish. In this case the FCAC decided that the whole fish would be most appropriate because, when looking for "hot spots" or areas of previously unrecognized contaminant residues, the sample would include parts of the fish that may contain those residues even if these are not the edible parts of the fish.

The fourth objective is simply to communicate results from studies carried out to achieve the first three objectives.

JURISDICTIONAL INCONSISTENCY IN EDIBLE PORTION SAMPLING

A survey of other jurisdictions in the Great Lakes region indicates there is much inconsistency in what portions of fish are sampled for contaminants analysis. Sampling done by the other jurisdictions is summarized below. The persons from the various jurisdictions who provided information for the survey are listed following the jurisdiction in parentheses and are listed as references at the end of the paper:

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Illinois

The Illinois Department of Conservation, in conjunction with other federal and state agencies, has established a fish contaminant monitoring program with the following objectives:

(1) To assess fish toxicity and public health implications due to the build-up of contaminants in fish.

(2) To determine the impact on fish species diversity and abundance.

(3) To locate sources of contaminant discharges and evaluate the long-term effects of environmental controls and land use changes.

Composites of scales-off, skin-on, boneless fillets are used for analysis; however, catfish are prepared as skinless, boneless fillets. Whole fish samples are also required from specified contaminant sites in addition to the fillets. The whole fish are analyzed by the U.S. Environmental Protection Agency (EPA) for a broad range of contaminants (Mick, 1982).

Indiana

The Indiana DNR and the State Board of Health monitor contaminants in Lake Michigan salmonids and other commercial species to determine the suitability for human consumption and to evaluate trends in contaminant levels. Composites of skin-on, one-inch thick, cross-sectional steaks are used for salmonid analysis, while individual whole fish of other commercial species are utilized.

The State Board of Health also sampled nineteen stream stations as part of the U.S. EPA Basic Water Monitoring Program. Composites of whole fish are analyzed. However, an "edible portion", which is usually a skin-off fillet, may also be analyzed when whole fish are found to contain contaminants above FDA action levels (James, 1982; Bridges, 1982).

Minnesota

The Minnesota Departments of Natural Resources and Public Health and the Minnesota Pollution Control Agency have developed a cooperative effort for fish contaminant monitoring. The short-term objectives of the monitoring program include: defining locations, species, and size of fish which contain residues exceeding safe consumption levels; assessing the environmental

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integrity of the state's fish populations; and locating discharges of priority pollutants. Long-term objectives include the assessment of pollution abatement programs and compilation of a tissue data bank.

"Edible portions", which are usually skin-off fillets, are used to assess human health impacts; while whole fish are analyzed to address the environmental integrity of the fishery. In certain cases, specific organs (liver, kidney) may be analyzed to monitor pollutants known to selectively accumulate (Helwig, 1982).

New York

The New York Department of Environmental Conservation has a diverse fish contaminant monitoring program. Some current program objectives include heavy metal, pesticide and industrial organic contaminant trend analyses, and tracking of sources of polychlorinated biphenyl (PCB) and mercury contamination in marine and fresh-water species.

A standard fillet, defined as a boneless, skin-on, scales-off portion is used for all analysis. The standard fillet is used to supply a baseline reference from which judgments on human fish consumption can be made (Skinner, 1982).

Ohio

The Ohio DNR annually samples coho salmon from the Grand and Huron Rivers in connection with the Great Lakes International Surveillance Plan (GLISP). These fish are supplied to the U.S. EPA for analysis. These samples are skin-on fillets and provide information for evaluating the hazard that toxic substances pose to the fish-consuming public (Atgear, 1982).

Ontario

The Ontario Ministries of Natural Resources, Environment, and Labour sample and analyze approximately 15,000 fish/yr. Skinless, lean dorsal muscle is used for analysis. The data are used to develop lake-by-lake, species-specific tables listing consumption recommendations which are designed to protect public health.

In a separate program, the Ontario Ministry of the Environment samples whole fish to provide contaminant trend information

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and to identify any additional potentially hazardous contaminants (Johnson, 1982).

Pennsylvania

The Pennsylvania Department of Environmental Resources and the Erie County Health Department are involved in a cooperative effort to provide fish samples for the U.S. EPA Basic Water Monitoring Program and the GLISP. Composites of whole fish of both bottom feeders and perch are used to determine trends in contaminant levels.

The same whole-fish composites of perch also provide information for assessing human health impacts. Also, under the GLISP, skin-on fillets of coho salmon are used to provide information for evaluating the hazard that toxic substances pose to the fish-consuming public (Frey, 1982; Wellington, 1982).

Wisconsin

The Wisconsin DNR monitors contaminants in fish from the Great Lakes and their tributaries and inland lakes and rivers. Program objectives include the review and update of the fish contaminant advisory, identification and elimination of point sources of contaminants, and evaluation of commercial fish stocks. Both skin-on boneless fillets and whole fish are utilized.

The Wisconsin Department of Agriculture and Consumer Protection routinely monitors PCB concentrations in smoked fish and PCB and chlorinated pesticide concentrations in chubs taken from markets and commercial fisheries. A skinless, boneless fillet is used for analysis (Sheffy, 1982; Mendel, 1982).

U.S. EPA - Region V (Chicago)

The U.S. EPA fish contaminant monitoring program consists of four elements. This effort is part of the GLISP, and a cooperative plan with Great Lakes jurisdictions. Several references to the plan are noted above. The first element involves open lake fish monitoring to define contaminant trends and identify new contaminants. Whole fish are homogenized for analysis. The second element includes analysis of skin-on fillets from game fish to evaluate potential human health hazards. The third element involves detection of new problem areas and contaminants in Great Lakes tributaries and embayments. Composites of whole

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fish are scanned for a broad range of organic and metal contaminants. The fourth element is designed to follow-up on data gathered for element three. Contaminant concentrations found to be significantly above background levels or FDA action levels in the whole fish composites will then also be monitored in skin-on fillets of game fish from these problem sites (DeVault, 1982).

U.S. FDA (Detroit)

The U.S. FDA is currently sampling commercial and potentially commercial species from 48 Great Lakes locations. At present, the FDA lab manual provides the following guidance for sampling raw fish for contaminant analysis: "Use the edible portion." The "edible portion" is defined to mean skin-on fillets in general, but allows for judgment to be used and often cross-sectional steaks or skin-off fillets are allowed. However, in reality, most samples prior to 1981 were prepared as skin-off fillets (Schneider, 1982).

Based on the above information, the jurisdictional sampling methods have been grouped under two general classes of objectives, shown in Table 1 (Sections A and B). Section A shows the sample types used when the objective is to determine the condition of the environment with respect to toxic materials. Section B shows the sample types used when the objective is to determine amounts of contaminants consumed when eating fish.

Most jurisidictions agree that whole fish should be analyzed when the objective is to determine the condition of the environment (Section A). However, there are many inconsistencies in the sample portion used to determine amounts consumed (Section B). Most jurisdictions use, at one time or another, skin-on fillets or skin-off fillets. There are also other types of samples. Skinless dorsal muscle is used in Ontario. This is the sample portion which would contain a minimum of fat and which would, therefore, contain the least fat-soluble contaminants, such as PCBs and other non-polar organics. It can be considered a "best case" sample portion. On the other hand, some jurisdictions use the "worst case" sample portion. Indiana uses whole fish and cross-sectional steaks which would contain a maximum of fat and fat-soluble contaminants. So, indeed there is much variation.

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TABLE 1

Jurisdictional Methods of Fish Sampling

Jurisdiction	Type of Sample				
	Whole Fish	Cross-Sectional Steak	Skin-On Fillet	Skin-Off Fillet	Skinless Dorsal Muscle
A. Objective: Environmental Monitoring for Toxic Materials					
Illinois	X				
Indiana	X				
Michigan	X				
Minnesota	X				
New York			X		
Ohio			X		
Ontario	X				
Pennsylvania	X				
Wisconsin	X		X		
U.S. EPA (Chicago)	X				
B. Objective: Assessing Human Exposure; Determining if Fish Are Safe to Eat					
Illinois			X	X	
Indiana	X	X		X	
Michigan			X	X	
Minnesota				X	

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Table 1 (cont.)

Jurisdiction	Type of Sample				
	Whole Fish	Cross-Sectional Steak	Skin-On Fillet	Skin-Off Fillet	Skinless Dorsal Muscle
B. (continued)					
New York			X		
Ohio			X		
Ontario					X
Pennsylvania	X		X		
Wisconsin	X		X	X	
U.S. EPA (Chicago)			X		
U.S. FDA (Detroit)				X	

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THE NEED FOR STANDARDIZATION

There are several reasons why standardization of edible tissue sampling is needed. The first is simply because of the differences among the jurisdictions as indicated above. Michigan salmon data show that the skin-on fillet contains from 2 to 4 times as much DDT and PCB as the skin-off fillet (Rohrer et al., 1981). Thus, assuming that the action levels (contaminant concentrations used to determine if fish are safe to eat) do not vary among the jurisdictions, fish may pass in one jurisdiction and fail in another.

As discussed above, the U.S. FDA's guidance for sampling raw fish is to "use the edible portion", but is somewhat vague as to exactly what this means. In those jurisdictions and those programs where this is the only guidance for preparing samples, differences may occur among laboratories, and perhaps even among analysts at a single lab when they interpret what the "edible portion" is.

The same sample portion should be used for determining the commercial salability of fresh fish as for determining when warnings should be issued to sport anglers. This is because it is likely that persons purchasing fresh fish would prepare and eat the fish much as they would if they caught the fish themselves. However, sampling for these two purposes has often not been done consistently in the past.

One of the reasons that there are so many differences among the jurisdictions may be that no single portion serves to characterize contaminants in the edible portions of all species. For example, smelt are normally eaten as headless, gutted whole fish. Catfish are usually eaten as skin-off fillets. Therefore, the Michigan PCAC reached the conclusion that a species-specific standard edible portion is needed.

Although this seemed to be a sensible approach, the controversy was not over. Some fish are cooked with the skin on, but the skin is not eaten. Three examples of this are salmon, large trout, and whitefish. Since cooking prior to sampling is not practical, and since the information on precisely what happens to fat soluble contaminants during various cooking methods is incomplete, the debate has continued on what should be the edible portion. The debate has centered on two main points: should the "worst case" be used in order to be most protective, or should the "most likely case" be used to be credible with the most people? When sampling raw fish, the "worst case" is where the skin-on, high-fat portion which is to be cooked is used in order to obtain the highest concentration of fat-soluble contaminants. The "most likely case" is where

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the portion which would be eaten, after cooking, is used. This portion would contain lower concentrations of fat-soluble contaminants.

THE STANDARD EDIBLE PORTION PROPOSAL

To resolve these dilemmas, Michigan proposes that:

(1) there should be a standard edible portion which is specific for each species; and

(2) the "most likely case" should be used, that is, the portion of the raw fish which would actually be eaten after cooking.

In order to determine just how certain fish are prepared, cooked, and eaten, Michigan is making a survey of fish eaters. The survey will request information on those species for which there is the greatest difference of opinion regarding these questions. Included are Great Lakes salmon, whitefish, and catfish, and trout from both Great Lakes and inland waters. Figure 1 shows that form which is being used in the survey. It has been mailed to a 1 percent sample of those holding Michigan fishing licenses. Several thousand responses are expected. The results will be used to determine the official species-specific standard edible portion for these species.

In the meantime, a preliminary listing of standard edible portions has been prepared, based on the best judgments of the FCAC. It is shown in Table 2. The three types of standard edible portions are skin-on fillet, skin-off fillet, and headless, gutted whole fish. Only three kinds of sample portions are included in order to keep it relatively simple. The only fish in the category of headless, gutted whole fish is smelt. However, for skin-on fillets, there are a number of different kinds of fish including perch, walleye, bass, and the panfish group including bluegills and sunfish. The skin-off fillet group includes catfish, northern pike, whitefish, trout, salmon, and carp. The belly flap, which contains much of the fat, will be left on for skin-on fillets and will be taken off for skin-off fillets. The scales can be either left on or taken off because they should not have a significant effect on contaminant concentration.

There are several major advantages to this concept:

(1) It provides standardization among laboratories and jurisdictions. Of course, this advantage will occur regardless of whether the concept is "best case,"

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1. PREPARATION

Do you trim away the dorsal and belly fat areas?

	FISH FROM THE GREAT LAKES				Trout From Other Waters
	Trout	Salmon	Whitefish	Catfish	
ALWAYS					
USUALLY					
SOMETIMES					
RARELY					
NEVER					

2. COOKING METHODS

a. Indicate how you cook each species of fish. Check a method only if you use it at least 20% (1/5) of the time.

	FISH FROM THE GREAT LAKES				Trout From Other Waters
	Trout	Salmon	Whitefish	Catfish	
PAN FRIED					
BROILED					
STEAMED					
DEEP FRIED					
CANNED					
SMOKED					
OTHER					

b. Do you cook the fish with the skin on?

	FISH FROM THE GREAT LAKES				Trout From Other Waters
	Trout	Salmon	Whitefish	Catfish	
ALWAYS					
USUALLY					
SOMETIMES					
RARELY					
NEVER					

3. CONSUMPTION

Do you eat the fish skin along with the fish flesh?

	FISH FROM THE GREAT LAKES				Trout From Other Waters
	Trout	Salmon	Whitefish	Catfish	
ALWAYS					
USUALLY					
SOMETIMES					
RARELY					
NEVER					
DO NOT EAT					

Figure 1. The Michigan Fish Eaters Survey Form.

"most likely case," etc., as long as it is standardized.

(2) The "most likely case" is believed to provide a more realistic measurement of the contaminants which would actually be consumed when eating the fish. Although the actual information on the effect of cooking is somewhat incomplete and sketchy at this time, studies have shown (see list of references) that many methods of cooking do reduce contaminants to some extent because fat will drip off or otherwise escape from the fish.

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TABLE 2

Standard Edible Portions of Michigan Fishes

Standard Edible Portion	Common Name	Scientific Name
Skin-on Fillet	Yellow Perch	Perca flavescens
	Walleye	Stizostedion vitreum
	Sauger	Stizostedion canadense
	Largemouth Bass	Micropterus salmoides
	Smallmouth Bass	Micropterus dolomieui
	Bluegill	Lepomis macrochirus
	Pumpkinseed	Lepomis gibbosus
	Rock Bass	Ambloplites rupestris
	White Bass	Morone americana
	Black Crappie	Pomoxis nigromaculatus
	White Crappie	Pomoxis annularis
	Green Sunfish	Lepomis cyanellus
	Longear Sunfish	Lepomis megalotis
	Warmouth	Lepomis gulosus
	Sucker Family	Catastomidae
Skin-off Fillet	Black Bullhead	Ictalurus melas
	Brown Bullhead	Ictalurus nebulosus
	Yellow Bullhead	Ictalurus natalis
	Channel Catfish	Ictalurus punctatus
	Muskellung	Esox masquinongy
	Northern Pike	Esox lucius
	Lake Whitefish	Coregonus clupeaformis
	Round Whitefish (Menominee)	Prosopium cylindraceum
	Lake Herring	Coregonus artedii
	Chubs	Coregonus hoyi
	Lake Trout (lean & siscowet)	Salvelinus namaycush
	Steelhead	Salmo gairdneri
	Brown Trout	Salmo trutta
	Brook Trout	Salvelinus fontinalis
	Splake	Salvelinus fontinalis X Salvelinus namaycush
	Atlantic Salmon	Salmo salar
	Coho Salmon	Oncorhynchus kisutch
	Chinook Salmon	Oncorhynchus tshawytscha
	Pink Salmon	Oncorhynchus gorbuscha
	Carp	Cyprinus carpio
	Sheepshead	Aplodinotus grunniens

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Table 2 (cont.)

Standard Edible Portion	Common Name	Scientific Name
	Buffalo	Ictiobus cyprinellus
	Burbot	Lota lota
	Quillback	Carpiodes cyprinus
	Sturgeon	Acipenser fulvescens
Headless, Gutted Whole Fish	Rainbow Smelt	Osmerus mordax

(3) The "most likely case" is understandable and credible to fish eaters. It is understandable because the edible portion is simply the portion eaten, rather than the portion cooked. This should help prevent people from ignoring advisories which are based on how fish are cooked. For example, a person might say, "Why should I pay attention to a warning based on a skin-on portion when I don't ever eat the skin"

(4) The "most likely case" corresponds with fish preparation recommendations from the state. Michigan advises people to avoid eating or even cooking contaminated fish with the skin on.

There is one disadvantage to the concept. In certain instances it may underestimate contaminants contained in the portion of fish that is eaten. However, in general, the difference in contaminant concentrations between skin-on and skin-off fillets are small in relation to the uncertainty of knowledge about human health effects. Thus, the disadvantage to this concept is minimal. Michigan believes that it is important to standardize so that everyone will be able to understand what is meant by a contaminant concentration from an edible portion, and not have to wonder what portion of the fish was used in the analysis.

The standard edible portion will be most advantageous if it is adopted by all the jurisdictions in the Great Lakes region. In order to pursue this, Michigan's first step will be to

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petition the U.S. FDA to establish the concept in its national lab manual. Also, Michigan will be recommending it to the U.S. EPA, to working groups under the direction of the International Joint Commission, and to the other jurisdictions.

In conclusion, Michigan believes that the "most likely case" standard edible portion is a good common-sense approach to fish contaminant sampling when the objective is to determine amounts of consumable contaminants present in fish.

ACKNOWLEDGMENTS

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CHAPTER 11

THE PHOTOCHEMISTRY OF PCBs

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Within the last few years, a sudden interest has developed in a hitherto relatively unknown class of industrial organochlorine compounds: the polychlorinated biphenyls (PCBs). Figure 1 give the structures of some selected symmetrical and unsymmetrical PCBs.

Traces of these compounds have been reported in environmental samples since 1966 (Anon., 1966). In the following years, PCB contamination was found to be almost universal (Risebrough et al., 1968; Gustafson, 1970; Peakall and Lincer, 1970; Veith and Lee, 1970; Richardson et al., 1971; Edwards, 1971) including human milk (Acker and Schulte, 1970), human adipose tissue (Biros et al., 1970), and brain tissue of infants (Hutzinger et al., 1972). Little is known about the toxic effects of PCB after long-term exposures, as observed in the endemic poisoning resulting from PCB contaminated rice oil (Kuratsune et al., 1971).

Polychlorobiphenyls are prepared commercially from the iron catalyzed chlorination of biphenyl. The product is a complex mixture containing at least sixty different PCB isomers with varying chlorine content. Table 1 lists some glc retention times of some selected PCBs.

The characteristic properties of PCBs which make them desirable for industrial use are their high dielectric constant and their thermochemical stability up to 900°C. Their stability, coupled with the ease with which they are taken up by living organisms and accumulated at higher levels of the food web, has resulted in environmental problems.

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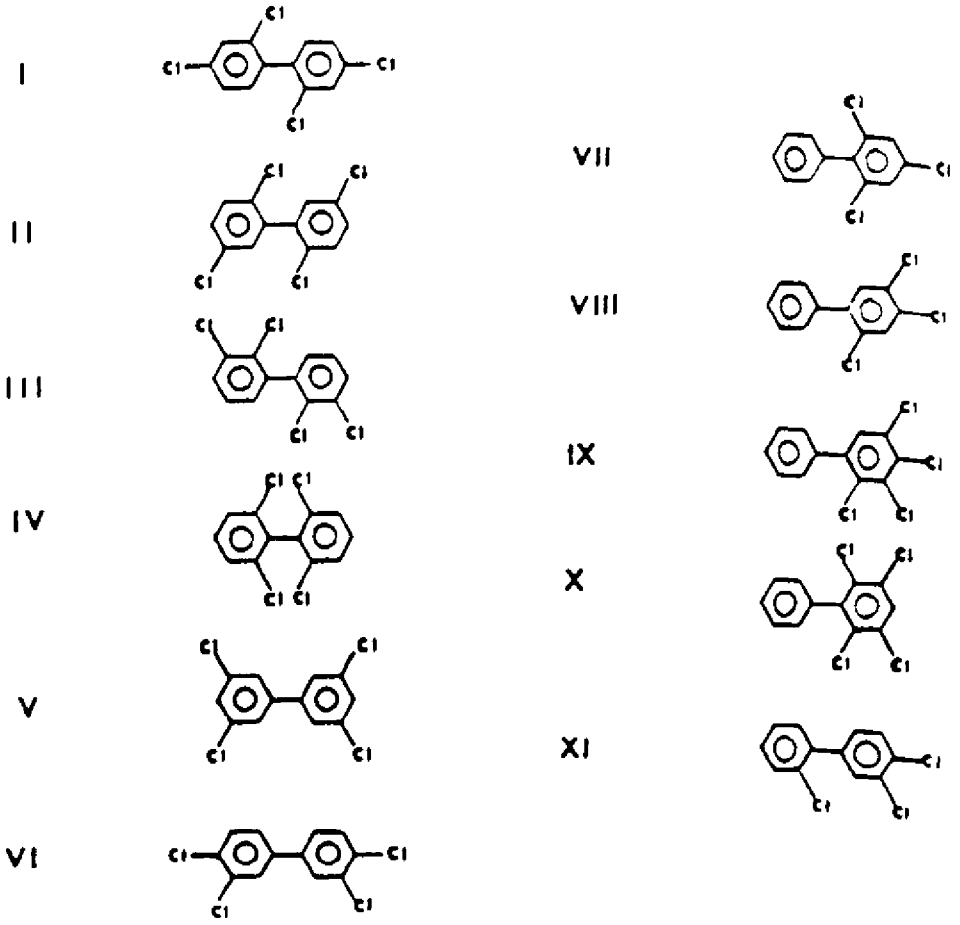

Figure 1. Structures of symmetrically substituted tetrachlorobiphenyls (I-VI) and unsymmetrical tri- and tetrachlorobiphenyls (VII-XI).

They were used as dieletric fluids in capacitors and transformers; as industrial fluids in hydraulic systems, gas turbines, and vacuum pumps; as plasticisers in adhesives; in textiles, surface coatings, sealants, and copy paper; as heat transfer agents, fire retardants, and fruit preservers. With such a variety of uses, it is not surprising that industrial leaks are largely responsible for the presence of PCB in the ecosystem.

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TABLE 1

Gas Chromatographic Retention Times of Polychlorinated Biphenyls in Cyclohexane[a]

PCB	R_t	PCB	R_t	Designation
Monochloro		Trichloro		
2-	0.60	2,4,6-	1.55	(VII)
3-	0.82	2,2',6-	1.65	
4-	0.85	2,2'5-	1.85	
Dichloro		2,4,5-	2.20	(VIII)
2,6-	0.92	2,3',5-	2.45	
2,2'-	1.00	2,4'-	2.60	
2,5-	1.15	3,4,2'-	2.75	(XI)
2,4-	1.25	3,4,5-	3.60	
2,3-	1.40	3,3',4-	4.30	
3,5-	1.50	Tetrachloro		
3,3'-	1.75	2,2',4,4'-	3.70	(I)
3,4-	1.80	2,2',5,5'-	3.65	(II)
4,4'-	1.95	2,2',3,3'-	4.80	(III)
		2,2',6,6'-	2.30	(IV)
		3,3',5,5'-	5.70	(V)
		3,3',4,4'-	8.90	(VI)
Methoxylated PCB		2,3,4,5-	4.80	(IX)
2,4,4'-Trichloro-2'-		2,3,5,6-	3.35	(X)
methoxy	5.05			
4,4'-Dichloro-2,2'				
dimethoxy	6.30			

[a] R_t relative to cyclohexane

There is evidence that PCBs are metabolized slowly in some organisms to their hydroxy derivatives (Block and Cornish, 1959). However, little is known about the efficiency of uptake and excretion and it is considered probable that a steady-state situation exists in some areas.

Even though all the available commercial PCB mixtures are toxic to some extent, those containing four or less chlorine substitutents have the highest toxicity, as reported in a study of their interaction with tissue culture cells (Hoopingarner et al., 1972).

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The uv spectra of the PCBs I-XI were obtained in cyclohexane solution. Scanning was carried out in the 220-320 nm region. Typically, PCB solutions were 0.1-1.0 x 10^{-4}M except in cases where higher concentrations had to be used in order to obtain the molar absorptivity (ε) in 280-300 nm region. The values of ε were calculated at 290 nm and at the maximum wavelength of the conjugaton band (240-270 nm). In cases where this band disappeared, the extinction coefficient was calculated at 255 nm.

Since PCB absorption in the uv conformed to Beer's Law, ε was calculated using equation 1.

$$\log I_0/I = A = \varepsilon bM \qquad (1)$$

Those PCB-containing <u>para</u> and no <u>ortho</u> chlorines exhibited a band in the 240-270 nm region of greater intensity than that of biphenyl itself. PCB containing <u>ortho</u> chlorines showed decreased intensity relative to that of unsubstituted biphenyl. When only <u>meta</u> chlorines were present, the intensity of absortion was similar to biphenyl. Extinction coefficients are listed in Table 2.

In 1971, the first study of PCB photochemistry appeared in the literature (Safe and Hutzinger, 1971). Dechlorination of 2,2',4,4',5,5'-hexachlorobiphenyl at wavelengths greater than 300 nm in hexane yielded more than ten products containing two to five chlorines per molecule. The individual isomers were not identified beyond establishing their parent peaks from the mass spectra.

Our studies of the photolysis of 2,2',4,4'-tetrachlorobiphenyl showed stepwise dechlorination to be the only reaction undergone by this compound in hexane (Ruzo <u>et al.</u>, 1972). At about the same time, 2,2',5,5'-tetrachlorobiphenyl was photolysed in dioxane-water and hydroxy substitution was obtained in addition to small amounts of condensation and reductive dechlorination products. 2,2',5,5'-, 3,3',4,4'-, and 2,2',6,6'-tetrachlorobiphenyls were found to decompose at about the same rate in non-degassed solutions. However, no accurate kinetic values were obtained and no pnotoproducts were identified beyond their molecular weight.

The photolysis of 2,2',4,4',6,6'-hexachlorobiphenyl in oxygen saturated methanol solution has been found to yield oxygenated, methoxylated, and dechlorinated products (A,B,C) (Anderson <u>et al.</u>, 1973) in small amounts. These compounds arise from cleavage of <u>ortho</u> chlorines and subsequent radical reactions with oxygen. None of them are observed in degassed solutions.

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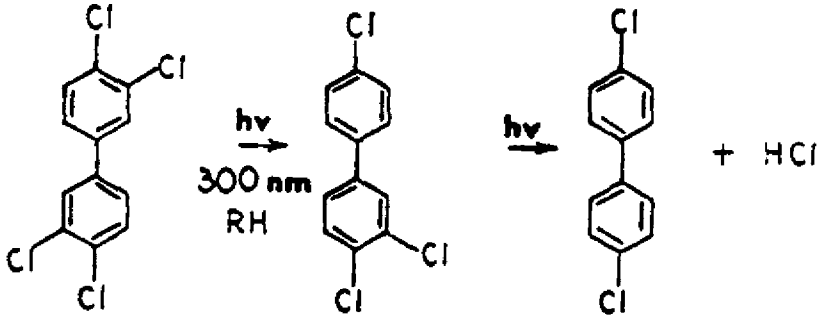
TABLE 2

Molar Extinction Coefficients of PCB in Cyclohexane Solution

PCB	ε(290 nm)	ε(240-270 nm)	λ_{max}
I	320	10,000	253
II	300	1,200	(255)
III	170	1,500	(255)
IV	50	300	(255)
V	950	18,000	252
VI	6,000	22,000	262
VII	85	4,800	(255)
VIII	1,200	11,800	260
IX	1,100	19,200	260
X	390	2,800	(255)
XI	730	13,100	252
Biphenyl	900	15,000	249



All these results point to the intermediacy of biphenyl-free radicals, either abstracting hydrogen from the solvent, or combining with triplet oxygen to give peroxides and subsequently ethers.

The methoxylated or hydroxylated products observed may be formed in a manner similar to that of several haloaromatic systems studied (Barltrop et al., 1967; Kharasch, 1967).

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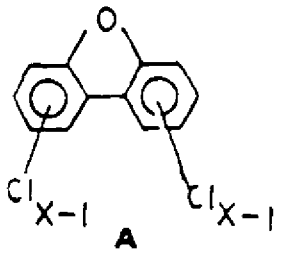

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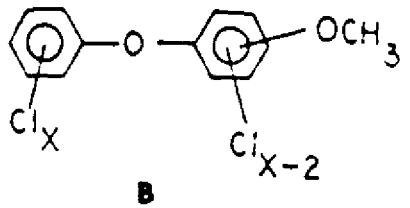

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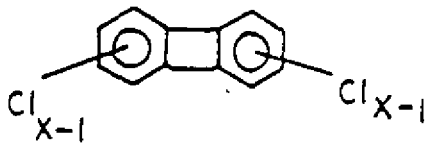
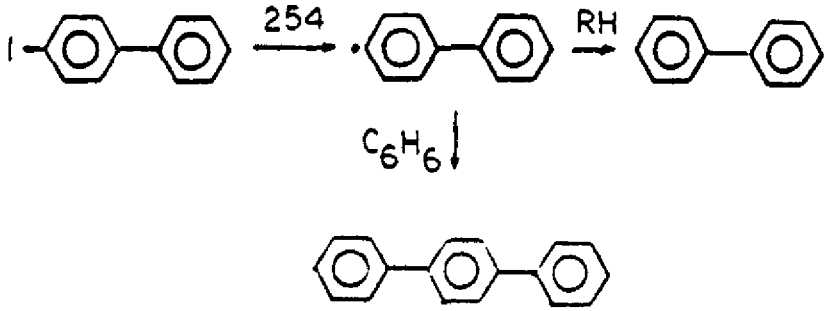


C

At the beginning of our research (1970), no reports existed in the literature concerning the photochemical behavior of PCB. Several chloroaromatics had been studied; and in every case, either chlorine cleavage with subsequent free radical hydrogen abstraction (Forbes and Dearden, 1959; Latowska and Latowski, 1966; Majer and Simmons, 1964; Henderson and Zweigh, 1967) or nucleophilic displacement of chlorine (Barltrop et al., 1967; Crosby and Yu-Li, 1966; Havinga and Kronenberg, 1968) occurred.

The photochemistry of iodobiphenyls at 254 nm in benzene and hydrocarbon solvents was reported in 1968 (Kharasch and Sharma, 1968). Kharasch found that iodine cleavage resulted in the formation of a biphenyl radical which could then either attack the solvent to yield terphenyl or abstract hydrogen and form biphenyl.



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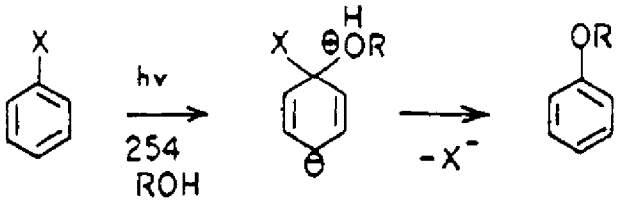
In the presence of oxygen, the recombination reaction becomes negligible and p-hydroxybiphenyl is obtained. Further proof of the intermediacy of free radicals is obtained when the reaction is run in the presence of nitric oxide (NO), a known radical scavenger which can inhibit the back reaction; thus the quantum yield of iodobiphenyl reaction increases.

The photolysis of iodobenzene in fluorocarbon solvents at 77° K has been studied by ESR. The results also suggest the formation of free phenyl radicals upon photolysis (Ingalls et al., 1964).



R = CH_3, H X = Cl, Br, I

The ionic intermediate can be stabilized by electron withdrawing groups ortho or para to X. The reaction usually has a low quantum yield (≈0.1), and the preferred course is elimination of X before nucleophilic attack takes place. Tables 3-9 give the photoproducts of some selected biphenyls.

Haloterphenyls have also been found to dechlorinate photochemically with subsequent formation of terphenyls and cyclization products (Sato et al., 1969).

In 1933, Adams showed that those derivatives of biphenyl which had substituents above a certain limiting size in the ortho position could be resolved into stereoisomers (Adams and Yuan, 1933). This phenomenon was explained as a result of restricted rotation of the two benzene rings by interference from the substituent groups.

The ultraviolet absorption spectra of several 2,2'-disubstituted biphenyls showed unexpected differences with their benzene analogs (Pickett et al., 1936). The band maxima in the benzene derivatives corresponded to similar ones in the

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TABLE 3

Photoproducts of 2,2',4,4'-Tetrachlorobiphenyl (I) in Cyclohexane and Methanol Solutions

Products (Cyclohexane)	m/e	Products (Methanol)[a]	m/e
2,4,4'-Trichlorobiphenyl	256	2,4,4'-Trichlorobiphenyl	256
4,4'-Dichlorobiphenyl	222	4,4'-Dichlorobiphenyl	222
4-Chlorobiphenyl[b]	188	4-Chlorobiphenyl[b]	188
		$C_{12}H_6Cl_3(OCH_3)$	256
		$C_{12}H_6Cl_2(OCH_3)_2$	282
		$C_{12}H_7Cl_2(OCH_3)$[b]	252

[a]Combined methoxylated products constitute <5% of total product formation.
[b]Product constitutes <1% of total product formation.

TABLE 4

Photoproducts of 2,2',5,5'-Tetrachlorobiphenyl (II) in Cyclohexane and Methanol Solutions

Products (Cyclohexane)	m/e	Products (Methanol)[a]	m/e
2,3',5-Trichlorobiphenyl	256	2,3',5-Trichlorobiphenyl	256
3,3'-Dichlorobiphenyl	222	3,3'-Dichlorobiphenyl	222
3-Chlorobiphenyl[b]		$C_{12}H_6Cl_3(OCH_3)$	256
		$C_{12}H_6Cl_2(OCH_3)_2$[b]	282

[a]Combined methoxylated products constitute <3% of total product formation.
[b]Product consitutes <1% of total product formation.

biphenyl compounds which are displaced toward lower energies. Absorption was nearly additive for the two rings. With 4,4'-dichlorobiphenyl, the red snift was greater and the band intensity showed a 10^3-fold increase compared to that of

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TABLE 5

Photoproducts of 2,2',3,3'-Tetrachlorobiphenyl (III) in Cyclohexane and Methanol Solutions

Products (Cyclohexane)	m/e	Products (Methanol)[a]	m/e
2,2'3'-Trichlorobiphenyl[b]	256		
2,3,3'-Trichlorobiphenyl	256	2,3,3'-Trichlorobiphenyl	256
3,3'-Dichlorobiphenyl	222	3,3'-Dichlorobiphenyl	222
3-Chlorobiphenyl[b]	188		
		$C_{12}H_6Cl_3(OCH_3)$	286
		$C_{12}H_6Cl_2(OCH_3)_2$	282

[a]Combined methoxylated products constitute <3% of total product formation.
[b]Product constitutes <1% of total product formation.

TABLE 6

Photoproducts of 2,2',6,6'-Tetrachlorobiphenyl (IV) in Cyclohexane and Methanol Solutions

Products (Cyclohexane)	m/e	Products (Methanol)[a]	m/e
2,2',6-Trichlorobiphenyl	256	2,2',6-Trichlorobiphenyl	256
2,2'-Dichlorobiphenyl	222	2,2'-Dichlorobiphenyl	222
		$C_{12}H_6Cl_3(OCH_3)$[a]	286

[a]Product constitutes < 1% of total product formation.

2,2'-dichlorobiphenyl. At the time (1936), no explanation was offered for this phenomenon.

In 1938, the geometry of biphenyl derivatives was studied on the basis of their dipole moments (LeFevre and Vine, 1938). the carbons 4-1-1'-4' were found to be colinear in a large majority of the compounds studied. X-ray studies confirmed these findings (Pickett, 1936).

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TABLE 7

Photoproducts of 3,3',5,5'-Tetrachlorobiphenyl (V) in Cyclohexane and Methanol Solutions

Products (Cyclohexane)	m/e	Products (Methanol)[a]	m/e
3,3',5-Trichlorobiphenyl	256	3,3',5'-Trichlorobiphenyl	256
		3,3'-Dichlorobiphenyl	222

[a]Product constitutes < 1% of total product formation.

TABLE 8

Photoproducts of 3,3',4,4'-Tetrachlorobiphenyl (VI) in Cyclohexane and Methanol Solutions

Products (Cyclohexane)	m/e	Products (Methanol)[a]	m/e
3,4,4'-Trichlorobiphenyl	256	3,4,4'-Trichlorobiphenyl	256
3,3',4'-Trichlorobiphenyl	256		
4,4'-Dichlorobiphenyl	222	4,4'-Dichlorobiphenyl	222
4-Chlorobiphenyl[a]	188	4-Chlorobiphenyl[a]	188
		$C_{12}H_6Cl_3(OCH_3)$[a]	286

[a]Product constitutes <1% of total product formation.

The earliest observations with regard to the actual excited state of biphenyls were given by Lewis and Kasha in 1944. The triplet energy (E_t) of several haloaromatics was calculated from their phosphorescence spectra. E_t values were lowest for 4,4'-disubstituted biphenyls (< 66 kcal) and highest for the ortho substituted PCB (>70 kcal).

The solution spectrum of biphenyl shows a single structureless band with λ_{max} around 250 nm and ϵ_{max} of 18,000. Presumably, this band represents the 208 nm transition of benzene, which is shifted by conjugation with the chromophoric phenyl substituent. The forbidden benzene transition at 25[illegible]

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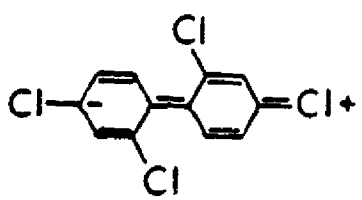
TABLE 9

Photoproducts of Unsymmetrical PCB (VII-XI)
in Cyclohexane Solution

PCB	Products	m/e
VII	2,4-Dichlorobiphenyl	222
	4-Chlorobiphenyl	188
VIII	3,4-Dichlorobiphenyl	222
	4-Chlorobiphenyl	188
IX	3,4,5-Trichlorobiphenyl	256
	3,4-Dichlorobiphenyl	222
X	2,3,5-Trichlorobiphenyl	256
	3,5-Dichlorobiphenyl	222
XI	3,4-Dichlorobiphenyl	222

nm is probably hidden below the main biphenyl band. The additional weak band displayed at 270-290 nm by some halobiphenyls is probably the result of interactions between the substituent's free electrons in the π system (Beaven and Hall, 1956;. The electron distribution in the excited state can be represented by 1 or 2:



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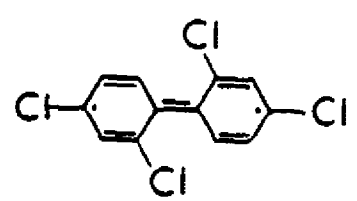

2

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Thus, if the excited state of PCB is a dipolar or diradical species with coplanar rings and a C-C linkage of essentially complete double bond character, then the short wave shift in the conjugaton band of an ortho chlorinated PCB would arise from an increase in the transition energy resulting from the raising of the triplet energy. The excited triplet is thus shown to be more sensitive to steric effects than the ground state.

On this basis, a correlation may exist between the steric requirements of the triplet and the photochemical lability of the ortho chlorines, relative to that of those in the meta or para positions.

Studies of deuterium isotope effects have been carried out (Bartell, 1961). A molecule such as biphenyl d_{10} would be expected to be closer to planarity than normal biphenyl h_{10} owing to the shorter length of the C-D bond compared to the C-H bond. The extinction coefficient of biphenyl d_{10} reflects the increase in resonance between the rings, in hexane solution a ratio of $\varepsilon_H/\varepsilon_D \approx 0.96$ has been obtained (Leffek, 1967).

In 1967, Wagner (1967) reported the actual triplet energy of biphenyl. He found that there was a 10 kcal difference between the highest energy phosphoresoence band at 65.5 kcal and the lowest energy absorpton band at 75.5 kcal. This case of non-overlapping emission and absorption spectra is a direct result of the Franck-Condon principle (Pringheim, 1949). Quenching experiments relative to benzophenone would indicate an E_t value of 69.5 kcal.

The most stable conformation of ground state biphenyl depends strongly on the medium. The dihedral angle between the rings is 40-50° in the gas phase (Bastiansen, 1949), 20-25° in solution (Suzuki, 1959), and 0° in the crystalline state (Trotter, 1961; Hirota, 1966). Since ortho substituents increase this angle, better quenching could be expected if the excited state was non-planar, and worse quenching if planar. Wagner found that the quenching efficiency of substituted biphenyls was less than expected when quenching a series of ketones.

One advantage liquid-phase photochemistry has over the gas phase is that several kinetic simplifications can be made. Absorption of light by a PCB can produce several excited singlets with many corresponding vibrational levels. In solution, decay to the lowest excited singlet occurs almost instantaneously (10^{-12} sec)(Wilkinson and Dubosis, 1963). Thus, it may be assumed that all singlet processes happen from the lowest singlet (S_1).

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Experiments using mono- and di-chlorobiphenyls show that inter-system crossing quantum yields (Φ_{isc}) increase with increasing number of chlorine substituents (Wagner and Scheeve, unpublished results). Though small, chlorine has a measurable heavy atom effect (HAE). With iodine and bromine, HAE values are greater (McGlynn et al., 1963; Medinger and Wilkinson, 1965). Such effects on S-T transitions are quite general and are probably the result of spin orbit coupling which causes mixing of singlet and triplet states (Robinson and Frosch, 1963). The singlet then acquires a small amount of triplet character and the triplet some singlet character, so the transition loses some of its forbidden character. HA effects are responsible for large phosphorescence/fluorescence ratios obtained with haloaromatics (Dewar and Gleicher, 1965). It has also been pointed out that HAE involving $\pi - \pi^*$ excited state are quite pronounced since normally negligible amounts of spin orbit coupling are present in symmetrical aromatics (El-Sayed, 1964).

For kinetic calculations in solution, the rate of phosphorescence can usually be ignored since it is much slower than the rates of other triplet processes. The following mechanistic scheme can be written for the photochemical processes of PCB (A) in solvent (SH), with quencher (Q).

SCHEME 1

Process	Rate	
$A_0 + h\nu \rightarrow A_1^* \xrightarrow{isc} A_3^*$	a (if $\Phi_{isc} = 1$)	(1)
$A_3^* \rightarrow A_0$	$K_d\ (A_3^*)$	(2)
$A_3^* \rightarrow A^\cdot + Cl^\cdot$	$K_r\ (A_3^*)$	(3)
$A^\cdot + SH \rightarrow A-H + S^\cdot$		(4)
$S^\cdot + S^\cdot \rightarrow S-S$		(5)
$A^\cdot + A^\cdot \rightarrow A-A$		(6)
$Cl^\cdot + SH \rightarrow H-Cl + S^\cdot$		(7)
$Cl^\cdot + A^\cdot \rightarrow A_0$		(8)
$A^\cdot + S^\cdot \rightarrow A-S$		(9)
$A_3^* + Q \rightarrow A_0 + Q_3^*$	$K_q\ (Q)(A_3^*)$	(10)

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Under steady-state conditions, $dA^{*3}/dt = 0$ and the only directly measurable parameter is the quantum yield of reaction. Using the definition of Wagner (1971), the quantum yield for a particular photoprocess is given by:

$$\Phi_i = \Phi_{ES}\,\Phi_R\,P_i. \tag{11}$$

Assuming $\Phi_{isc} = 1$ for PCB containing three or more chlorines:

$$\Phi_i = P_i\,\frac{K_r}{K_r + K_d} \tag{12}$$

so that Φ_i becomes the quantum yield of reaction.

When a triplet quencher is used, equation 12 becomes:

$$\Phi_i = P_i\,\frac{K_r}{K_r + K_d + K_q(Q)} \tag{13}$$

Dividing equation 12 by equation 13, the familiar Stern-Volmer relationship is obtained:

$$\frac{\Phi}{\Phi_Q} = 1 + K_q t(Q) \tag{14}$$

Where Φ_Q represents the quantum yield of reaction in the presence of quencher (Q). The lifetime of the triplet (t) is the reciprocal of the sum of the rates of all the reactions undergone by the triplet.

$$t = (K_r + K_d)^{-1} \tag{15}$$

A plot of the relative quantum yield versus quencher concentration is linear with a slope equal to the product $K_q t$ and an intercept of 1, if only one excited state is reacting and being quenched.

The photoreactions of PCB were found to be zero order when >99 percent of the incident light was absorbed. The following equation gives the rate constant for a zero order reaction (k):

$$(PCB)^0 - (PCB)^t = k\,t \tag{16}$$

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where t is the time of irradiation and (PCB) is the substrate concentration at 0 and t times. Plots for I-VI are shown in in Figures 13 through 15. The k values are given in Table 10.

For compounds VII-XI, one point rate constants were determined (Table 11). The k values obtained in cyclohexane were found to be slightly lower than those in methanol solution.

The largest k values were obtained for PCBs containing ortho-para chlorination (I, VII-IX, XI). Compounds with ortho-meta chlorination showed intermediate k values (II-IV, X), and those with meta-para substitution (V-VI), the lowest.

TABLE 10

Reaction Rate Constants (k) and Quantum Yields (Φ_r) for PCB in Cyclohexane

PCB	k, 10^{-9}M sec^{-1}	Φ_r
I	74.5	0.100
II	7.4	0.010
III	5.0	0.007
IV	3.8	0.006
V	1.2	0.002
VI	2.8	0.005

TABLE 11

One Point Reaction Rate Constants (k) for Unsymmetrically Substituted PCB in Cyclohexane Solution

PCB	k, 10^{-9}M sec^{-1}	Φ_r
VII	14.0	0.02
VIII	42.4	0.05
IX	29.3	0.04
X	6.0	0.01
XI	12.0	0.02

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Absolute quantum yields of reaction (Φ_r) were determined for I-XI. Degassed cyclohexane solutions of PCBs containing an internal standard were irradiated in parallel with actinometer solutions at 300 ± 10 nm. Values for Φ_r are given in Tables 10 and 11.

The quantum yields obtained correlated well with the rate constants. The extremely low values of Φ_r found for V and VI by necessity must contain a relatively large error and were calculated basically for comparison purposes.

In order to determine the lifetime of the excited state of I-VI, quenching of the dechlorination reaction was carried out. 1,3-Cyclohexadiene (E_t = 50 kcal/mole) was found to be an appropriate quencher for the systems under study.

Vpc analysis of PCB reacted permitted the calculation of relative quantum yields, Φ^0/Φ. The Stern-Volmer plots obtained were linear with unity intercepts. The slopes are equal to $k_q t$. The diffusion rate constants in cyclohexane and methanol are known (Wagner and Kochevar, 1968); however, some change is expected in their value at 30°C, according to the Debye (1942) equation.

Using these values, the excited state lifetimes were calculated (Table 12). The t values were the same in both solvents within experimental error.

TABLE 12

Lifetimes of the Triplet Excited States of Polychlorinated Biphenyls

PCB	Solvent	$k_q t$	$t, 10^{-8}$ sec
I	Methanol	101.4	0.78
I	Cyclohexane	68.8	0.85
II	Methanol	87.1	0.67
III	Methanol	100.1	0.77
IV	Methanol	91.0	0.70
IV	Cyclohexane	76.9	0.95
V	Methanol	248.3	1.91
V	Methanol	286.0	2.20

MONS 222371

The sensitized isomerization of cis → trans piperylene was used to determine isc for several PCB. Reproducible results were only obtained for 3,3',4,4'-tetrachlorobiphenyl (VI) indicating a-value of unity by comparison with benzophenone. The sensitized phosphorescence of biacetyl gave better results allowing the calculation of isc for I, III, V, and VI.

Benzene solutions of PCB and biacetyl were degassed and their phosphorescence emission at 521 nm compared with that of benzene solutions of benzophenone/biacetyl. In all cases, $\Phi_{isc} = 1$ (Table 13).

With the exception of most fluoroaromatics, the primary process in haloaromatics involves cleavage of the C-X bond to yield radicals. In some of the early experiments, the presence of free halogen atoms was observed from transient spectra due to formation of ClO, BrO, IO, following the flash photolysis of the halogenated compound (Majer and Simmons, 1964).

The formation of dechlorinated PCB in hydrogen donating solvents such as cyclohexane and methanol points to the presence of a free radical species capable of hydrogen abstraction. Cleavage of the C-Cl (83 kcal/mole) in the triplet yields a phenyl radical in a primary rate determining step. Formation of HCl is detected during irradiation in keeping with such a mechanism.

It is preferentially the ortho chlorines that cleave. Some meta cleavage was also observed (III), but could be considered negligible compared to ortho dechlorination. In the absence of ortho substituents, meta dechlorination occurs preferen-

TABLE 13

Intersystem Crossing Quantum Yields of Selected Polychlorobiphenyls

PCB	Φ_{isc}
I	1.00 ± 0.01
III	0.97 ± 0.03
V	0.99 ± 0.02
VI	0.99 ± 0.00

MONS 222372

tially (VI, VIII, IX). These results point to the importance of steric and resonance effects in determining the course of the reaction.

Dechlorination in I-VI was in a stepwise manner, chlorine cleaving first on one ring, then in the same position in the other ring. In none of the cases studied was one ring dechlorinated preferentially over the other.

The methoxylated products obtained in methanol solution most likely arise from nucleophilic attack of the solvent with intermediacy of an ionic species stablized by charge delocalization over the biphenyl system.

Since no methoxylation occurs at the para position, it must be concluded that bond weakening of the ortho chlorine plays an important part in this process. Attack of the nucleophile can be visualized as occurring on an already partially ionized C-Cl bond, where carbon has developed a partial positive and chlorine a partial negative charge. This weakening of the bond would not occur at the para carbon-chlorine position since it does not destabilize the excited state.

The linearity of the Stern-Volmer plots (Wagner, 1971) and the absence of fluoreacence from tetrachlorobiphenyls indicate the existence of only one reactive excited state, a triplet.

Quantum yields give a more dramatic demonstration of the substituent effects as shown in Tables 10 and 11. The value of Φ_r for 2,2',4,4'-tetrachlorobiphenyl (0.100) is greater by a factor of 10-50 than those obtained for II-VI. The unsymmetrical PCB VII-IX and XI also show larger values. The lowest values obtained are for those compounds containing no ortho chlorines (V and VI). It is clear that the reactivity of PCB could at least partially be explained on the basis of the "ortho" effect; however, the large difference between the 2,4 and 2,3 substituted PCB could not be explained without calculation of the k_d and k_r values. The ratios of decay/reaction for six PCB triplets are listed below:

PCB	k_d/k_r
I	9
II	100
III	120
IV	150
V	520
VI	200

MONS 222373

In all cases decay is preferred to reaction; however, this tendency grows more pronounced in the order 2,4, 2,3, 3,4, and 3,5 substitution. In compounds having 2,4 substitution, the reaction becomes a competitive path to reversion to the ground state.

Transannular effects are shown to be present in the reaction of 3,4,2'-trichlorobiphenyl (XI) to yield, 3,4-dichlorobiphenyl (Φ_r = 0.02). This quantum yield is the smallest of those obtained for 2,4 PCB; but still greater than those of the rest, the highest of which is 0.01 (II). It can be concluded that the driving force for the reacting is greatest when both the ortho and para chlorines are on the same ring and that the rates increase when the effects arise from both rings.

Since PCBs are thermally and biologically non-degradable, their presence in the environment, either by misuse or accidenal leakage, constitutes a long-term problem. Photochemical degradation is shown to be a major, if not the only, degradation pathway since solar radiation of the wavelength required is present.

The prevalent substitution patterns of tetrachlorobiphenyls found in Arochlor 1242 and 1248 (42 and 48% chlorine, respectively) are 2,5; 2,3; 2,4; and 3,4 (Hutzinger et al., 1972). Of these, the only ones that can be degraded with relative ease are the 2,4 substituted isomers.

The photochemical introduction of biological "handles", which make metabolic degradation possible, is shown to take place in methanol and in water. Methoxy and hydroxy groups are introduced rather slowly; this detracts from their environmental significance. Furthermore, since PCB introduction in the aquatic environment usually takes place in the presence of other hydrophobic substances (oils), contact with the potential nucleophile, water, would be minimized.

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CHAPTER 12

ANALYSIS OF PCBs USING SPECIFIC ISOMER HIGH RESOLUTION CAPILLARY GAS CHROMATOGRAPHY

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HALOGENATED AROMATICS

Polychlorinated biphenyls (PCBs) are one of a number of groups of chemical compounds referred to as halogenated aromatics. These groups of compounds include the polychlorinated naphthalenes (PCNs), polychlorinated benzenes (PEs), polychlorinated terphenyls (PCTs), polybrominated biphenyls (PBBs), polychlorinated dibenzofurans (PCDFs), and polychlorinated dibenzo-p-dioxins (PCDDs). The difficult problems associated with the toxicology and analytical chemistry of these compounds are due to the large numbers of theoretically possible isomers of each group (Table 1). For example, the commercial PCB formulations are complex mixtures of PCB isomers that have not yet been completely identified (Hutzinger et al., 1974; Sissons and Welti, 1971; Ballschmiter and Zell, 1980; Jensen and Sundstrom, 1974). In addition, the variable partitioning of the isomers between different trophic levels in the environment and within different members of the same trophic levels, in conjunction with preferential biological degradation of certain isomers, makes the composition of PCBs in these samples quite different from the commercial mixtures (Jensen and Sundstrom, 1974;

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TABLE 1

Multiplicity of Isomers in the Halogenated Aromatics

Halogenated aromatic	PCB	PBB	PCN	PCDD	PCDF
Number of isomers	209	209	135	75	135

Yakushiji et al., 1978; Kuroki and Masuda, 1977; Safe, 1980). Compared to the commercial PCB formulations, precipitation samples are almost void of the early eluting isomers as are lake trout from the Great Lakes. Human blood samples also evince a lack of the early eluting isomers and, in addition, contain fewer isomers than the lake trout implying a more rigorous degradation and/or elimination of selected PCB isomers from humans than from fish. The toxicity of PCBs is a function of the structure of the individual isomer. Therefore, it is not sufficient to quantify the total amount of PCBs present in an environmental sample, but the concentrations of the isomers which are potentially more toxic must also be determined.

TOXICOLOGY OF PCB ISOMERS

Recent toxicology studies on PCBs have concentrated on the use of these compounds to induce a microsomal cytochrome P-448 dependent monooxygenase enzyme designated aryl hydrocarbon hydroxylase (AHH)(Parkinson and Safe, 1981; Goldstein, 1979; Poland et al., 1979; Poland and Glover, 1977). An evaluation of the structure-activity relationship among halogenated aromatics indicates a correlation between those compounds which induce AHH activity and their structure. Table 2 indicates all the PCB isomers which are known AHH inducers (Parkinson and Safe, 1981; Poland and Glover, 1977; Goldsetin et al., 1977; Parkinson et al., 1980a; 1980b; 1981a; 1981b; 1981c). The toxicity of the following isomers have been confirmed: 3,3'4,4'-tetra-; 3,3',4,4',5-penta-; 2,3,3',4,4'-penta-; 2,3,4,4',5-penta; 3,3',4,4',5,5'-hexa-; and 2,3,3',4,4',5-hexachlorobiphenyls (Parkinson and Safe, 1982; Yoshimura et al., 1979; Goldstein, 1979; Poland et al., 1979; Yamamoto et al., 1976; Ax and Hansen, 1975; Poland and Glover, 1977; Goldstein et al., 1977; Parkinson et al., 1980a; Yoshihara et al., 1979; Stonard and Greig, 1976). The isomers listed in Table 2 should be of concern to environmental toxicologists, analytical chemists,

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TABLE 2

A Summary of PCB Isomers Which Induce AHH Activity

Number of Chlorine Substituents							
1		2		3		4	
Peak Number	Structure	Peak Number	Structure	Peak Number	Structure	Peak Number	Structure
077	3,3'4,4'	126	3,3',4,4',5	169	3,3',4,4',5,5'	189	2,3,3',4,4',5,5'
081	3,4,4',5	105	2,3,3',4,4'	156	2,3,3',4,4',5	170	2,2',3,3',4,4',5
		118	2,3',4,4',5	157	2,3,3',4,4',5'		
		114	2,3,4,4',5	166	2,3,4,4',5,6		
		123	2',3,4,4',5	158	2,3,3',4,4',6		
				128	2,2',3,3',4,4'		

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and others who are concerned with the contamination of the environment by anthropogenic materials.

LOW VS. HIGH RESOLUTION GAS CHROMATOGRAPHIC ANALYSIS OF PCBs

The majority of laboratories analyzing environmental samples for PCBs are using some form of packed column gas chromatography coupled with either an electron capture detector (ECD) or a mass spectrometer (MS) and are indicated in Table 3 as low or medium resolution techniques. The results from these techniques are quantified by comparison with commercial PCB formulations (Hutzinger et al., 1974; Cairns and Siegmund, 1981; Sawyer, 1978) and provide semi-quantitative concentrations. However, low and medium resolution PCB analyses have several disadvantages: the lack of sufficient resolution masks some of the subtle changes in the distribution of PCBs within an ecosystem; the difficulties in making an accurate quantitative estimate of the PCB concentration when the PCB composition in the sample has been subjected to extensive degradation; the inability to provide quantitative data on individual isomers; and the lack of quantitative data on the potentially toxic PCB isomers.

High resolution specific isomer capillary gas chromatograph PCB analysis (Ballschmiter and Zell, 1980; Ballschmiter et al., 1978; Albro and Parker, 1979; Mullin and Filkins, 1981;

TABLE 3

Resolution Characteristics of Various Instrument Combinations

Column Type	Detector	Quantitation Method	Resolution
Packed column	EC	Peak matching or pattern matching	Low
	MS	Peak matching or pattern matching	Medium
Capillary column	EC	Isomer response	High
	MS	Isomer response	High

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Albro et al., 1981; Mullin et al., 1981) is now a viable analytical technique which utilizes a high resolution fused silica capillary column as the medium of separation, couples it with either an electron capture detector or a mass spectrometer and requires all 209 PCB isomers as reference standards for initial instrument calibration (Table 3). The synthesis of all of the PCB isomers is an awesome task and a great deal of progress has been made in achieving this goal (Mullin et al., 1981). Of the 209 possible isomers, 182 have been synthesized using the Cadogan coupling (Cadogan et al., 1962) of a chlorinated aniline with a chlorinated benzene (in excess) in the presence of amyl nitrite. Proton magnetic resonance (PMR) and mass spectrometry (Mullin et al., 1981) are used on the purified products to characterize the isomers synthesized.

The proposed numbering scheme (Ballschmiter and Zell, 1980) is used to more easily discuss the individual PCB isomer by relating them to an integer from 1 to 209. The relative retention times (RRTs) and relative molar response factors have been determined for most of the PCB isomers available using octachloronapthalene (OCN) as an internal standard.

ANALYSIS OF SAMPLES USING HIGH RESOLUTION CAPILLARY GAS CHROMATOGRAPHY

A number of commercial formulations and environmental samples have been analyzed and quantified for PCBs by using the individual PCB isomers as reference standards. The following analytical conditions were used on a Varian model 3700 gas chromatograph[1] equipped with an electron capture detector

Column - 50 meter narrow bore fused silica capillary coated with SE-54 (Hewlett-Packard)

Injector Temperature - 270°C

Detector Temperature - 330°C

Oven Temperature - 100°C to 240°C (280°C with 32 minute final hold for precipitation samples) at 1°C per minute with a 2 minute final hold

Sample Volume - 6 ul injected vented from 0.75 to 1.75 minutes at a ratio of 10:1

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[1]The use of trade names does not constitute an endorsement by the U.S. Environmental Protection Agency of these products.

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Carrier Gas - Hydrogen at a constant pressure to yield a linear velocity of 45 cm/second at 100°C oven temperature

The high resolution capillary gas chromatographic separation of a mixture of Aroclor® 1016 plus 1254 plus 1260 (5:3:2 by weight), a composite human blood sample, a composite precipitation sample from the Great Lakes shoreline and a lake trout sample from the Great Lakes are shown in Figures 1, 2, 3, and 4, respectively. Using the isomeric PCB standards to calibrate the mixture of Aroclors as a reference standard, the relative retention times of the above samples were compared to the RRTs of the standard enabling the identification of many of the peaks in the samples as specific PCB isomers. Figure 4 illustrates the more complex chromatogram obtained from the lake trout which the high resolution capillary technique is able to resolve sufficiently to qualitatively identify many of the peaks and quantify those identified peaks; this would not have been possible using the low or medium resolution techniques.

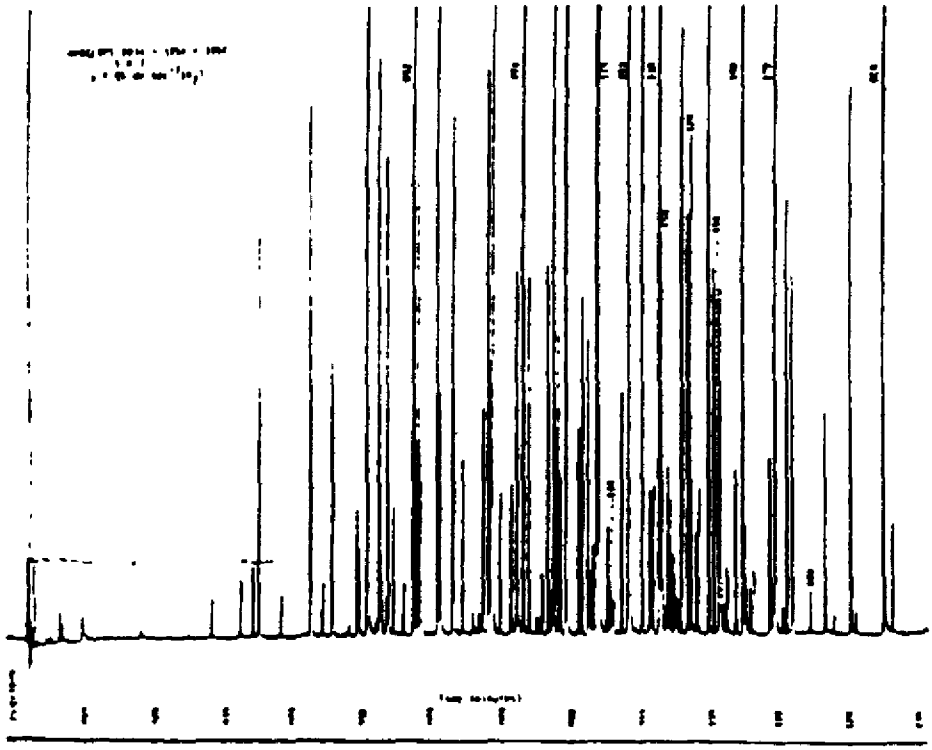

Figure 1. High resolution capillary gas chromatographic separation of a mixture of Aroclors 1016 plus 1254 plus 1260.

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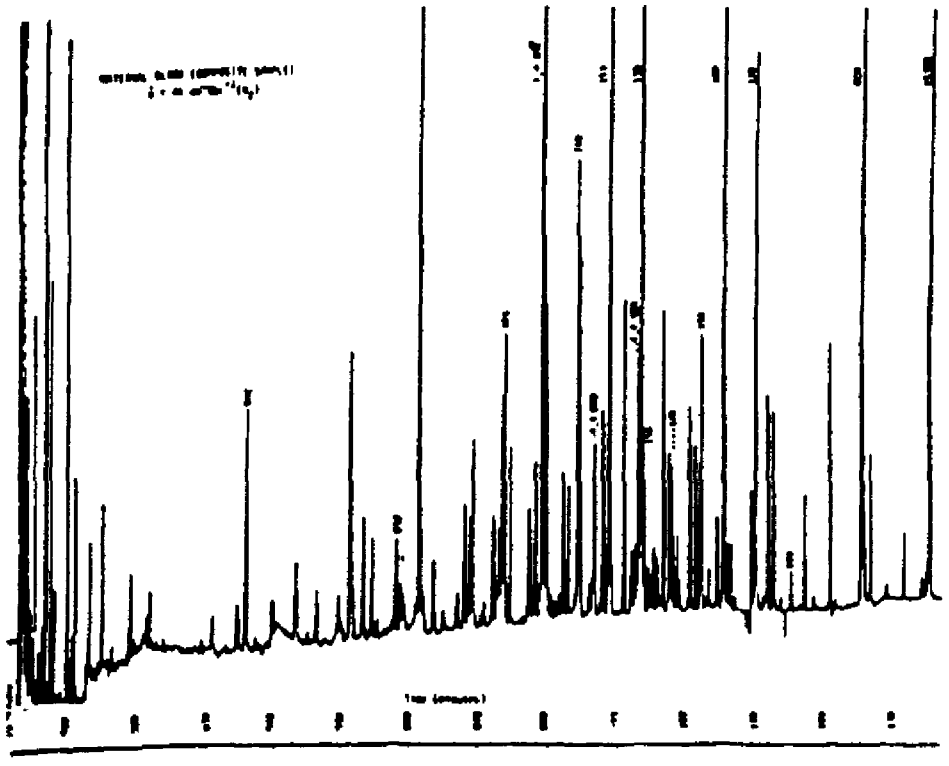

Figure 2. High resolutions capillary gas chromatographic separation of chlorinated hydrocarbons in a composite human maternal blood sample.

CONCLUSION

The use of high resolution capillary gas chromatography, in conjunction with the use of PCB isomers as reference analytical standards, presently is a viable analytical technique for the analysis of commercial PCB formulations and environmental samples from many different matrices. Future efforts will address the application of this technique to a greater variety of samples to determine the effects of PCB structures on the dynamics of PCB persistence in the environment.

ACKNOWLEDGMENTS

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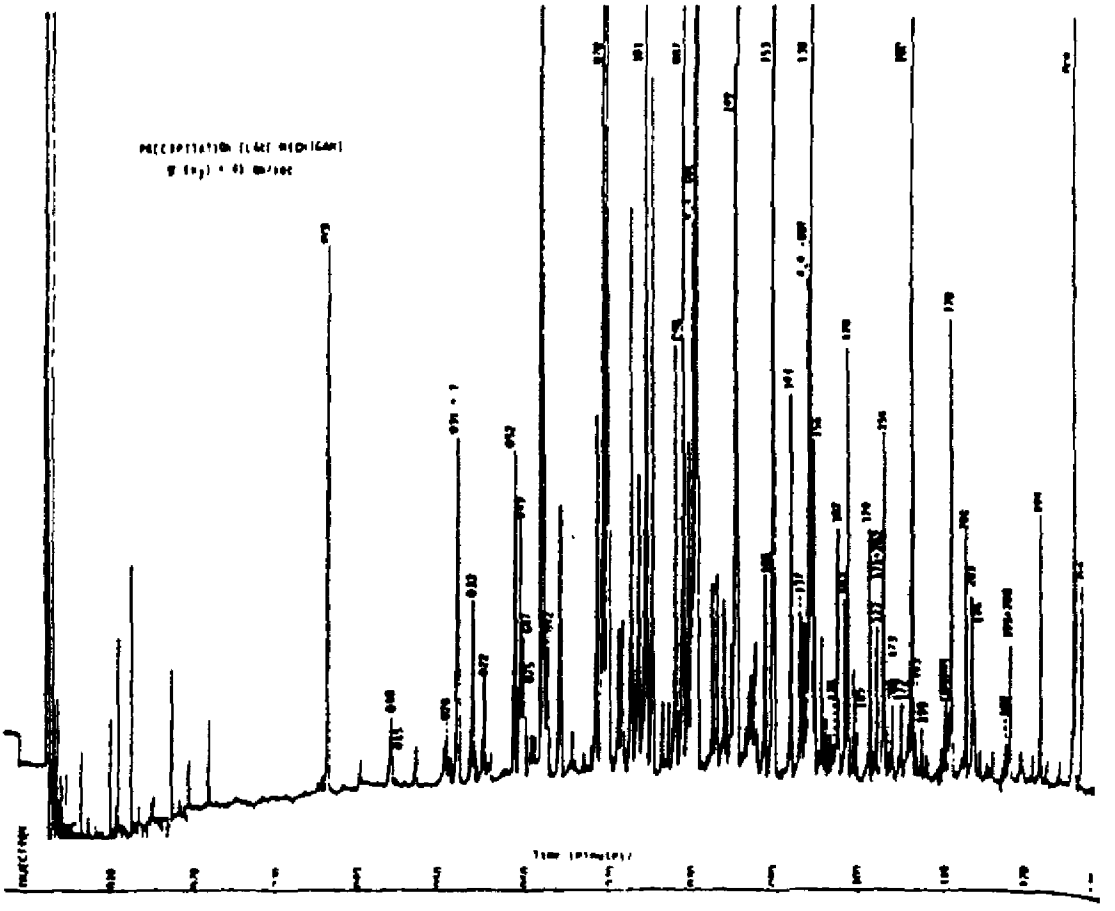

Figure 3. The high resolution capillary gas chromatographic separation of a composite precipitation sample from Lake Michigan.

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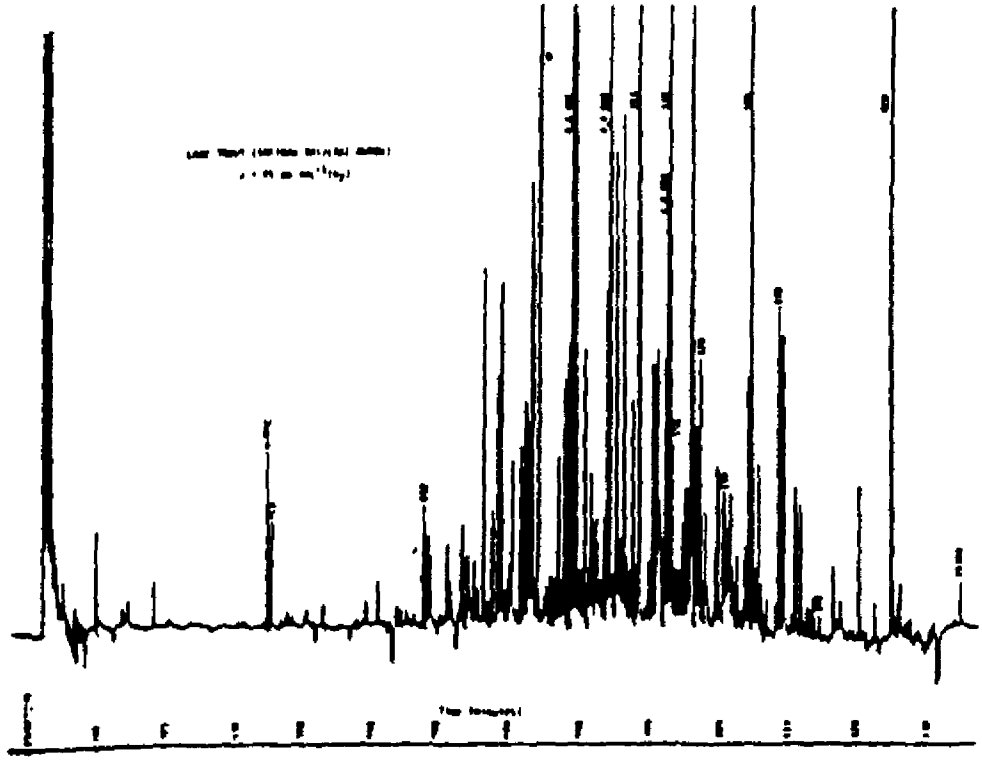

Figure 4. High resolution capillary gas chromatographic separation of chlorinated hydrocarbons in a lake trout from Saginaw Bay/Lake Huron.

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PART III

METABOLISM AND TOXICOLOGY OF PCBs

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CHAPTER 13

CONCEPTS IN TOXICOLOGY AND CARCINOGENESIS: A BASIS FOR DISCUSSING THE POTENTIAL ENVIRONMENTAL HAZARD POSED BY PCBs

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All of us who are attending this conference have an interest in addressing the question of what is a "safe" level of an environmental chemical. We are concerned with a rational approach towards setting acceptable levels of environmental pollutants. Scientific input is just one of several avenues feeding into this decision-making process. The deliberations involved in the establishment of acceptable levels for a chemical in the environment must take into account political considerations, social considerations, economic considerations, and scientific considerations.

While we can be proud of our scientific accomplishments in the area of toxicology it is also important, if we wish to maintain our credibility, to put our limitations up front. The science of toxicology is an exciting and dynamic field. We have made some very significant strides towards understanding the mechanisms of action of toxic chemicals and using this information to try to arrive at rational decisions relative to the establishment of acceptable levels for environmental chemicals. However, we are far from our ideal goal. While we are reasonably good at making qualitative predictions, we have quite a ways to go when it comes to quantitative predictions.

I would like to develop for you some basic concepts in traditional toxicology and compare and contrast this with problems that we face in modern aspects of toxicology specifically related to carcinogenesis. I shall then discuss some current concepts in chemical carcinogensis and show you how this impacts

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on the question of deciding what is and what is not a "safe" or "acceptable" level of a particular chemical.

The basic concepts upon which traditional toxicology is based were derived from classical pharmacological studies. In clasical pharmacology we picture a drug (or in our case toxic chemical) interacting with a receptor located on the target cell membrane or within target cells, giving us a drug receptor complex which causes an effect. The magnitude of the effect is often thought to be directly related to the amount of drug receptor complex that is formed (Gilman et al., 1980). We can use this paradigm to try to explain dose-response type data. In classical pharmacological or toxicological studies as we increase dose we observe increased intensity of effects. In pharamcological studies we would be talking about a therapeutic effect, in toxicology an adverse effect. When one looks at a classical type dose effect relationship, taking a sedative hypnotic drug as an example, we see that if we focus on sedation as the therapeutic effect, as one increases dose an increased percent of individuals in the treated population respond to the therapeutic effect. We eventually arrive at a dose where 50 percent of the population responds to the therapeutic effect and we call this the "effective dose$_{50}$", the ED_{50}. If we continue to increase the dose, we produce toxicity, in this case death. Eventually we reach a point where 50 percent of the population will die. We refer to this later dose as the LD_{50} or lethal dose for 50 percent. A measure of safety called the "therapeutic index" is obtained on dividing the LD_{50} by the ED_{50}. This represents a ratio of the dose required for the beneficial effect vs. harmful effect in the average of the individuals comprising the test population. These principles of pharmacology have led to the basic concepts in "traditional" principles of toxicology (Saffiotti, 1977). In traditional toxicology we are primarily concerned with terminal toxic effects; LD_{50}, for example. These toxic effects have the following characteristics. First, they appear early--dose your animals, inspect them a few hours later, perhaps a couple of days later, and ascertain whether or not they are alive. Second, the intensity of the induced pathology can be directly correlated with the intensity of toxic exposure. Third, manifestations of toxicity are due to altered functional products, degenerative changes, or death of target cells. Let us contrast this with the situation that we face when dealing with the cancer problem. This is one area, along with mutagenesis and teratogenesis, which can be considered among the "modern" aspects of toxicology. We can think of these as self-replicating toxic effects as opposed to terminal toxic effects (Saffiotti, 1977). The general characteristics of carcinogenic effects are the following:

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(1) their appearance is delayed. Delayed by months to years in animals, delayed by perhaps decades in the human;
(2) the frequency of the expression of injury (i.e., tumor incidence) in the exposed population is directly correlated with the intensity of exposure. However, the intensity of the induced pathology is independent of the intensity of exposure to the carcinogenic substance. That is, once the cancer is formed in a specific individual, it makes little difference whether it took a high dose to do it, a medium size dose, or a low dose, the ability of that tumor to spread, to metastasize, to express its malignant potential is independent of the dose of the chemical that it took to start the process in the first place;
(3) the manifestations of toxicity are due to proliferation of a new cell population.

There are many chemicals which are recognized as carcinogens. Today it is known that many of these are not cancer causing in and of themselves but must be metabolized to a reactive, electrophilic, form which is then capable of initiating the cancer process (Miller and Miller, 1981). These chemicals are mutagenic. It is also quite possible to metabolize these chemicals to inactive metabolites. The relative ability to metabolically activate vs. inactivate can at least in part explain some of the selectivity that we see in terms of species/sex susceptibility, and probably some of the reasons for organ selectivity of different carcinogenic chemicals.

Carcinogenesis appears to be a multi-stage phenomenon (Boutwell, 1974). The hypothesis that carcinogenesis can be divided into a stage of initiation and a promotion stage has gained a high degree of credibility. The basic studies began with Berenblum and Shubik (1947) in the 1940s. They reported that they could apply coal tar, one application, to the skin of mice and skin cancer would arise. They then decreased the dose of coal tar used down to a level at which one application did not result in skin tumors being formed. So far, this fits nicely with the classical toxicology concept of a "no effect" level. They then asked, "what would happen if we took this low, 'safe dose', of coal tar and added a second chemical to the system." The "low" dose of coal tar was applied to the skin of mice and followed by repeated applications to the skin of an irritant, croton oil. They observed that this low dose of carcinogen, the initiating dose, when followed by the croton oil treatment results in the production of tumors. Berenblum and Shubik termed the low dose of carcinogen the "initiator" and the croton oil the "promoter". The next question asked was "how reversible is this process?" What happens if after

applying the initiator one waited a few months before promoter application? When this experiment was performed, tumors arose. This was the first indication that initiation of carcinogenesis is probably a "permanent" and perhaps heritable event. Next, the question as to the reversibility of the effects of promoter treatment was investigated. Is this reversible or is each dose analogous to a turn of a ratchet wrench. That is, does it require multiple applications but never "slips" back? If, after initiation a few doses of promoter are applied and one waits a month or so prior to completing the process (i.e., the same total number of doses but spread out), no tumors are formed. Therefore, while the initiation process appears to be heritable, the promotion process, at least in part, is reversible. The initiation-promotion hypothesis appears to be widely accepted due to a considerable amount of scientific evidence supporting it (Boutwell, 1974; Miller and Miller, 1981). We now do not simply think of "chemical carcinogens". We think of them in terms of initiators and promoters of carcinogenesis. Some chemicals are capable of acting as a complete carcinogens (i.e., capable of carrying out both the initiation and promotion steps). In "low" doses a complete carcinogen may serve as an initiator. Promoters do not appear to be mutagenic. These compounds are capable of altering gene expression and might, therefore, act through an epigenetic mechanism (Weinstein, 1981). How good are we at discerning carcinogens, and specifically, how good are we at discerning carcinogens which are effective in man? Today the basic approach is the National Cancer Institute/National Toxicology Program Rodent Bioassay (Page, 1977). This assay involves exposing two species of rodents (usually rats and mice), male and female of each, to the test compound for most of their life. The question asked in this assay is are these chemicals carcinogenic or not? This is aqualitative test. How good are these tests as predictors of human carcinogens? Let us consider carcinogenicity data compiled by the International Agency for Research on Cancer (IARC)(IARC, 1979). Based upon epidemiology studies, industrial exposure accidents and medical exposure, there is reasonable evidence indicating that those chemicals listed below are carcinogenic to man:

Aflatoxins
4-Aminobiphenyl
Arsenic compounds
Asbestos
Auramine (manufacture of)
Benzene
Benzidine
N,N-bis(2-chloroethyl)-2-naphthylamine
Bis(chloromethyl) ether
Cadmium oxide
Chloramphenicol (strong suspicion)

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Chromium(chromate-producing industries)
Cyclophosphamide
Diethylstilboestrol
Haematite (mining)
Isopropyl oil
Melphalan
Mustard gas
2-Naphthylamine
Nickel (refining)
Oxymetholone (strong suspicion)
Phenacetin
Soot, tars, and oils (polycyclic aromatic hydrocarbons)
Vinyl chloride

With the exception of arsenic compounds and benzene, all of the chemicals listed above are carcinogenic in at least one laboratory animal species. In addition, for five of these chemicals, aflatoxins, 4-aminobiphenyl, diethylstilboestrol, melphalan and mustard gas, and vinyl chloride, evidence of carcinogenicity in experimental animals preceded evidence of carcinogenicity in man (Rall, 1979). From these data we can conclude that there are clear historical examples which show that if there is strong evidence that a chemical is carcinogenic in appropriate laboratory animal test systems, it must be treated as if it were carcinogenic in man. What about the question of organ specificity? There appears to be solid data for 109 chemicals which are carcinogenic in both rats and mice; and out of these, 70 have at least one common target organ (Purchase, 1980). Put another way, approximately one-third of them attack totally different target organs.

At this point it would be appropriate, within the context of this conference, to consider the definitions of some basic terms in toxicology. When employing the word toxicity, the toxicologist talks about the capacity of a chemical to produce injury. The term hazard refers to the probability that injury will result from a chemical under specific conditions of exposure. The toxicologist uses the term safety to connote the reciprocal of risk, that is the probability that harm will not occur under specific conditions of exposure. The toxicologist is able to make some reasonable judgments about hazard or safety under specific conditions of exposure (i.e., dose, sex, age, what chemicals has the animal previously been or currently being exposed to). It is important to keep the above discussion in mind when contemplating the question of whether or not a chemical is going to be carcinogenic. We picture the initiator of carcinogensis as transforming normal cells into initiated cells probably by virtue of causing a mutation. A rather prolonged treatment with promoter is then required for expression of malignancy, to transform the initated cells into frank cancers.

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There are many places in this scheme when a second chemical can interact with the carcinogen. For example, what if an animal is treated such that its capacity for oxidative metabolism is enhanced. Do we increase the ability to metabolize precarcinogens to initiators? Do we increase the ability to form inactive metabolites? Pretreatment of animals with a microsomal enzyme inducer or the combined administration of the inducer and a carcinogen usually inhibits the tumorigenic effect of the chemical administered (Conney, 1982). Let us look, for example, at a selected group of chemicals which can inhibit carcinogenesis. Prior administration of phenobarbital (Peraino et al., 1971), butylated hydroxytoluene (Ulland et al., 1973), butylated hydroxyanisol (Wattenberg, 1973), 3-methylcholanthrene (Miller et al., 1958), polybrominated biphenyls (Schwartz et al., 1981), and polychlorinated biphenyls (PCBs) (Hendricks et al., 1977; Nishizumi, 1976; Makiura et al., 1974) have a protective effect on chemically-induced carcinogenesis. These agents are effective in a wide variety of carcinogens including azodyes (Makiura et al., 1974; Miller et al., 1958), aromatic amines (Makiura et al., 1974; Miller et al., 1958; Schwartz et al., 1981; Ulland et al., 1973; Peraino et al., 1971), alkylating agents (Nishizumi, 1976; Wattenberg, 1973), and aflatoxins (Hendricks et al., 1977). We must keep in mind the fact that several inducers of microsomal enzymes have been shown to be capable of promoting carcinogenesis if they are administered after initiation has taken place (Conney, 1982). In this situation the induction of microsomal enzymes and tumor promotion might not be causally related.

What is the usual carcinogenicity data which we derive in laboratory animal studies? Generally, we are dealing with something between 50 and 100 percent tumor incidence. In some of the best laboratory studies we are dealing with 10 percent tumor incidence as our low value. When we try to extrapolate from this observed 10 percent incidence down to zero tumor incidence, we encounter a large mathematical error. In addition, there is the question as to whether or not it is justifiable to draw a straight line through the origin in the first place. We are really making a guess, albeit an educated guess, with some very significant errors. The conclusion one can draw from this is that we must not lose sight of the fact that in toxicity testing we use the animals as surrogates for humans and that attempts to quantify responses beyond the realm of scientific or biological certainty are open to some very serious questions.

What we will try to do for you in the next series of presentations is to give you a feel for selected aspects of the toxicology of PCBs and an indication of what levels we are at in regard to assessing the toxicological potential of these compounds.

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CHAPTER 14

BIOTRANSFORMATION AND PERSISTENCE OF POLYCHLORINATED BIPHENYLS (PCBs) IN FISH

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INTRODUCTION

In addition to the workplace, important routes of exposure of the human population to chemicals are by way of the atmosphere and the diet. Consumption of chemically contaminated aquatic species, such as fish, is probably one of the major routes of dietary exposure in the human population since fish and many other aquatic species which dwell in aquatic environments are ultimately the final common destiny for many chemicals. Due to several unique features, the polychlorinated biphenyls (PCBs) are taken up from lower members of the food chain in the water and are found in concentrations in consumable fish species which far exceed levels which can be measured in the water itself (Norstrom et al., 1978).

While it is now known that not all of the over 200 PCB congeners behave in the same manner in different biological systems, the general properties of high lipid solubility and lack of biotransformation of certain PCB congeners has led to the bioaccumulation and persistence of this class of compounds. The relative composition of PCB mixtures is based on the degree and position of chlorination (Hutzinger et al., 1974). While, in general, the higher chlorinated congeners of the PCBs are more persistent, the actual structure of a specific congener is more important in determining persistence and toxicity than

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is the absolute numbes of chlorine atoms in the molecule (Kato et al., 1980). It was not until specific chemical structures of the chlorinated biphenyl components of these complex mixtures became known that details of the toxicity, biotransformation, and bioaccumulation of these compounds could be investigated (Fishbein, 1972).

BIOACCUMULATION

The information presented in Figure 1 illustrates the time-dependency and magnitude of bioaccumulation of Aroclor 1254 and 1248 by channel catfish exposed to these mixtures in water (Mayer et al., 1977). It can be seen that even after 77 days of exposure the concen'ration of PCBs in fish had not reached the steady state, even though bioaccumulation had proceeded to over 60,000 times the concentration of these mixtures in the exposure water. Based upon first order kinetic theory, an approximation of the time to reach the steady state would be five times the half-life for each Aroclor component.

It is important to note that data concerning bioaccumulation of chemicals, including the PCBs, can be expressed on an absolute amount of chemical in the body at any given time, or the concentration, that is, mg/kg, ug/g, or ppm. This is an important concept since in long-term exposure studies the fish are growing, and one must deal with the combination of constant intake of chemicals and the tendency toward dilution of the concentration in the animal by growth (Lieb et al., 1974). This is illustrated in Figure 2 in which A represents the PCB concentration in fish in mg/kg, B represents the total PCB content of the fish in ug, and C illustrates the body weight measured over the exposure period. It is clear that while the concentration in the fish begins to level off at approximately 2[illegible] weeks of dietary exposure, the absolute amount of PCBs in the animals continued to increase. This data illustrates that although a steady state may be reached in terms of concentration in the animal during the exposure, total PCB content in absolute ug/animal may continue to increase. The concentration in the animal may not increase since the body weight continues to increase and reduces the concentration by dilution. The information presented in Figure 3 further illustrates this point. When trout were fed a diet containing 15 mg/kg of Aroclor 1254 for 16 weeks, and then were switched to a control diet, the fish which continued to receive PCBs in the diet continued to accumulate PCBs (A), but the trout removed from the PCB-containing diet had no further increase in PCB content (B). It is important to recognize that the absolute amount of PCBs expressed as ug/fish did not change significantly from the 16-32 weeks while on the control diet. This data dramatically

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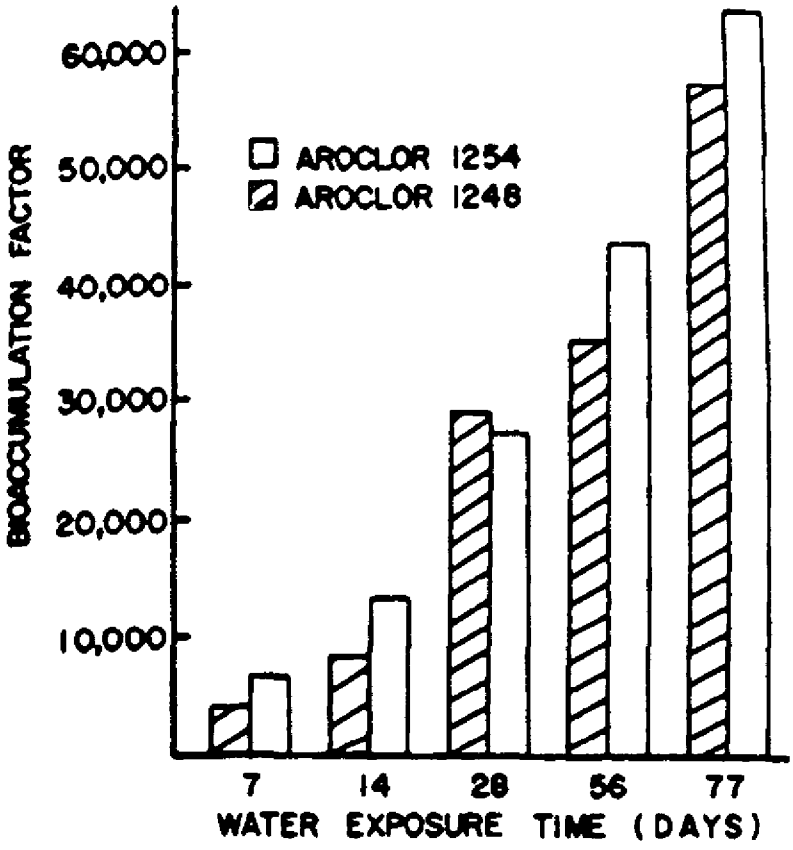

Figure 1. Bioaccumulation of Aroclor 1248 and 1254 by channel catfish during chronic water exposure. The concentration of Aroclor 1248 and 1254 in the water was 5.8 and 2.5 ug/l, respectively. The bioaccumulation factor was defined as the PCB concentration in the whole fish divided by the PCB concentration in the water. This figure was adapted from Mayer et al., 1977.

illustrates the lack of elimination of Aroclor 1254, even when animals were fed a control diet. However, if the data are expressed as concentration, that is mg/kg, the situation is quite different. This is illustrated in Figure 4 in which PCB concentration in lipid is plotted against the average fish weight and the time in weeks after removal from the PCB-containing diet. These data show that the PCB concentration decreased over time after removal of the fish from the PCB-containing diet, and this decrease in concentration can be

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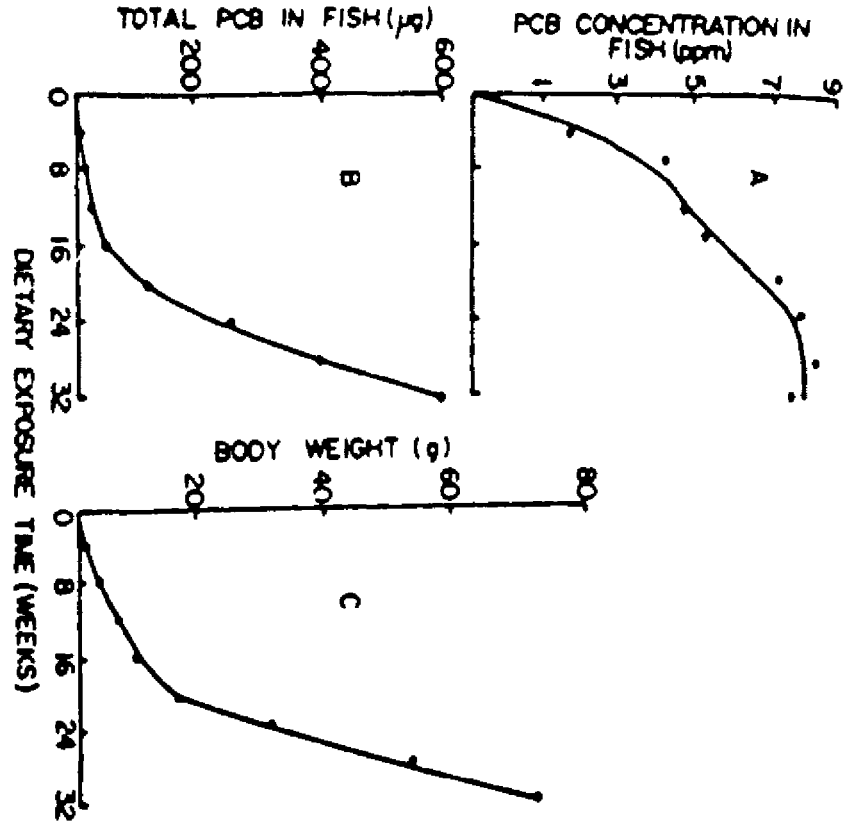

Figure 2. Bioaccumulation of Aroclor 1254 by rainbow trout during chronic dietary exposure. The fish were exposed to 15 mg/kg of Aroclor 1254 in the diet for 32 weeks. This figure was adapted from Lieb et al., 1974.

accounted for almost entirely on the basis of dilution through the weight gain of the fish. These experiments indicate that when rainbow trout are removed from a diet containing Aroclor 1254, there is essentially no excretion of PCBs, but the concentration in the animal decreases by dilution because of weight gain.

In general, the tendency of PCBs to accumulate in fish is greater when animals are fed PCB mixtures containing higher chlorinated congeners (Mayer et al., 1977), and this is illustrated in Figure 5. It should be noted, however, that this data illustrates total PCB levels and does not indicate which congeners are present. Much of the work on bioaccumulation of

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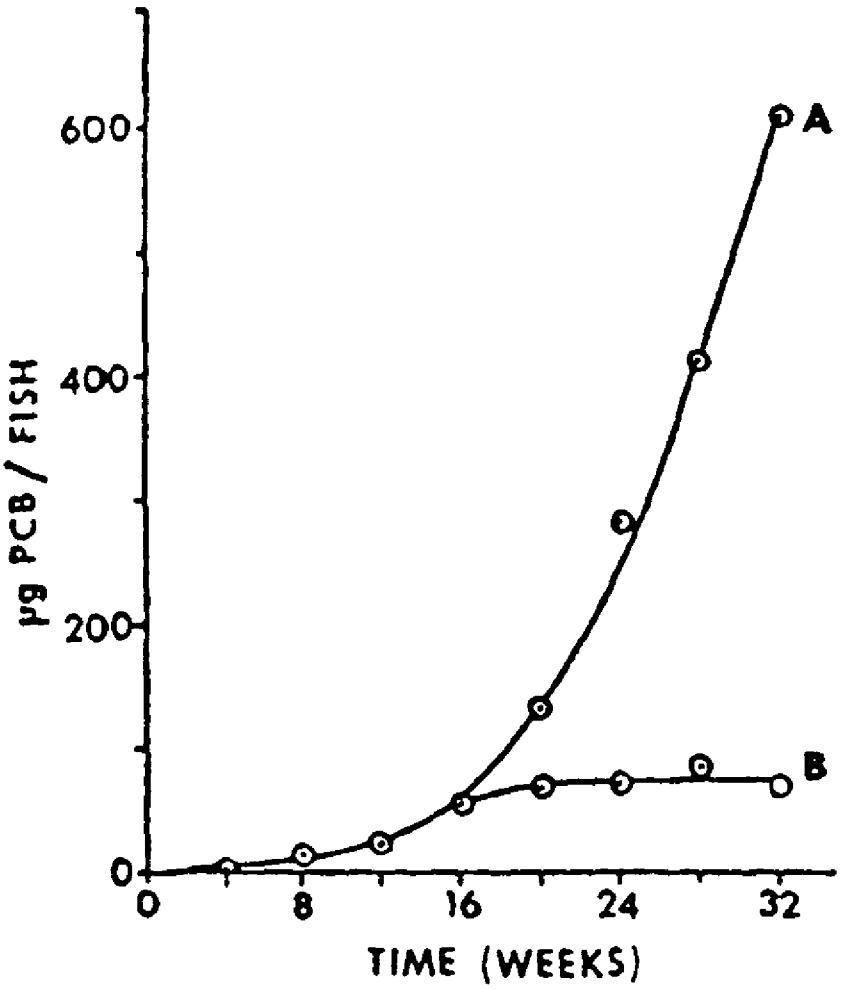

Figure 3. Persistence of Aroclor 1254 in rainbow trout after stopping chronic dietary exposure. This figure was adapted from Lieb et al., 1974.

PCB mixtures had been done in parallel when other studies were pursuing the molecular structure of specific PCB components in these complex mixtures. It is apparent from work that has been carried out over the past several years that there is a great deal of species differences in the biotransformation of PCB congeners to more readily excreted chemical forms. Since a major driving force in the elimination of any specific PCB congener is its rate of metabolism to a form which may be excreted in the urine or bile, the process of biotransformation

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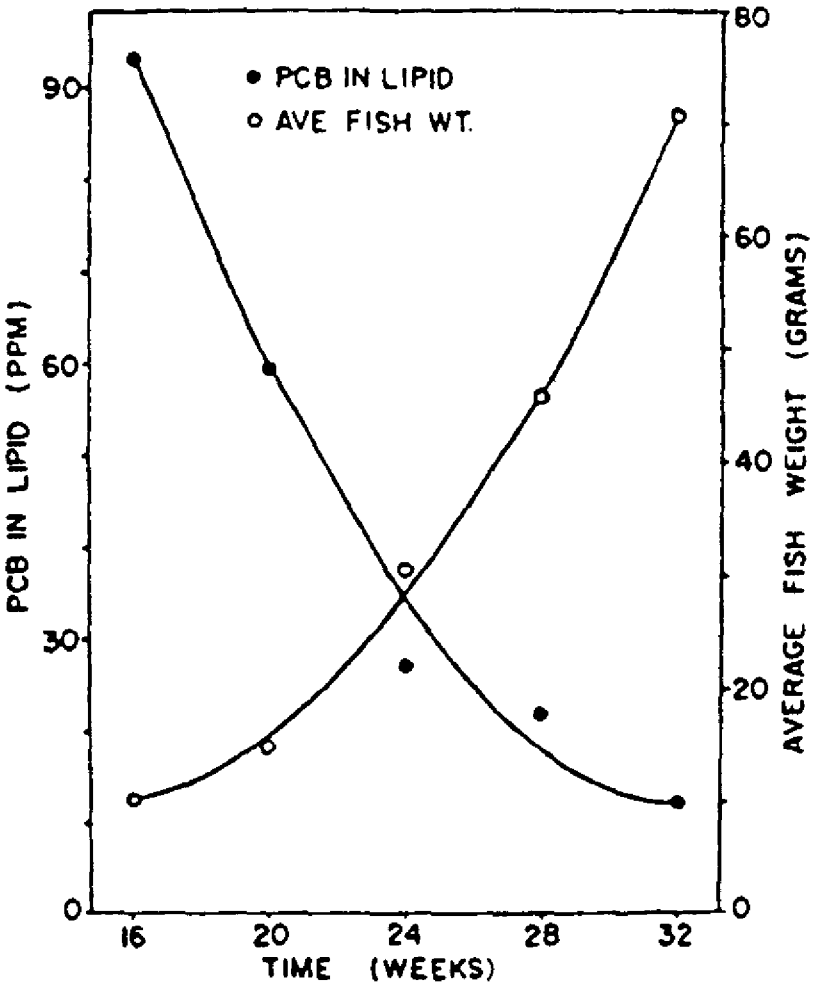

Figure 4. Dilution of the PCB concentration in lipid by the growth of rainbow trout after chronic dietary exposure to Aroclor 1254 was stopped. This figure was adapted from Lieb et al., 1974.

is extremely important in determining the persistence of various congeners in different biological systems (Kato et al., 1980).

BIOTRANSFORMATION AND PERSISTENCE

Only a limited amount of information is available concerning the biotransformation of specific PCB congeners in aquatic species, but it is clear from what is known that, as opposed

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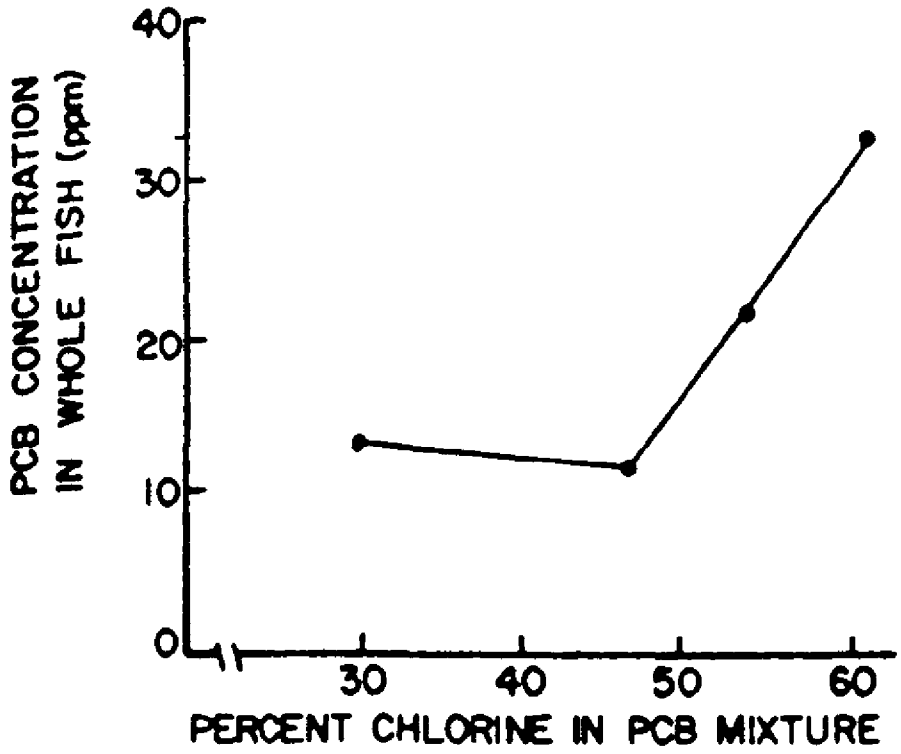

Figure 5. PCB concentration in channel catfish after chronic dietary exposure to PCB mixtures containing higher chlorinated congeners. All of the fish were continuously exposed to either Aroclor 1232, 1248, 1254, or 1260 at a concentration in the diet of 24 mg/kg for 193 days. This figure was adapted from Mayer et al., 1977.

to mammals, those species of fish studied have only a limited ability to metabolize PCBs containing a higher number of chlorine atoms (Hutzinger et al., 1972; Melancon and Lech, 1976; Hinz and Matsumura, 1977). For example, it has been found that when sunfish were exposed to three PCB congeners, they were able to efficiently metabolize 2,5,2'-trichlorobiphenyl to polar metabolites but not 2,5,2',5'-tetrachlorobiphenyl or 2,4,5,2',5'-pentachlorobiphenyl (Sanborn et al., 1975). In general, it would appear that while mono-, di-, and trichlorobiphenyl congeners can be metabolized by several species of fish, congeners with higher amounts of chlorination, regardless of chlorination position, are slowly metabolized. Although there is a variation among fish species in their ability to biotransform the lower chlorinated PCB congeners, there appears to be

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general agreement that fish biotransform most PCB congeners at considerably slower rates than their mammalian counterparts. The overall result of this reduced capacity to biotransform many PCB congeners contributes to the persistence of PCB congeners in fish which are not persistent in mammals.

It is often observed that PCB residue patterns obtained from fish more closely resemble the patterns of congeners seen in the mixture to which the fish were exposed. In several studies in which Aroclors were fed to mammals, including the goat and the swine, the Aroclor residue pattern differed from the pattern of the Aroclors fed experimentally, particularly with respect to the lower chlorinated congeners (Hansen et al., 1977). This is illustrated in Figure 6 which shows an electron capture gas chromatographic analysis of a standard of Aroclor 1242 and extracts of channel catfish fat and liver after exposure to this PCB mixture (Hansen et al., 1976). It can be seen that the pattern in fat and liver closely resembled that of the standard. In comparable mammalian studies, the residue pattern from tissues is often different from that of the Aroclor fed to the animal. These experimental results agree with the observation that lower chlorinated congeners, such as 2,5,2',5'-tetrachlorobiphenyl tend to bioaccumulate and persist in fish but seem to be more transient in most mammalian species.

At present there is much information available concerning the metabolism of specific PCB congeners in mammals and its relationship to the propensity of a specific congener to be persistent in mammals (Kato et al., 1980) but information concerning biotransformation of specific PCB congeners in fish is sparse. Since in vitro and in vivo biotransformation studies indicated that 2,5,2',5'-tetrachlorobiphenyl (4-CB) is both slowly metabolized by fish and found in fish sampled from the wild, the disposition of 4-CB has been extensively studied in rainbow trout. Rainbow trout were exposed to ^{14}C-labeled 4-CB in a single exposure and subsequently were transferred to a raceway and were fed and maintained according to normal hatchery standards for over a year. After an initial equilibrium period in which some of the radioactive label was lost immediately after the transfer to freshwater, there was very little excretion of this compound by the experimental animals (Guiney et al., 1979). The data in Figure 7 dramatically illustrates the persistence of this compound. The calculated half-life from regression analysis of the elimination curve was approximately 1.76 yr. Note that the y axis in this curve represents the amount of 4-CB in tissues as a percent of total body burden and not concentration. It is obvious that over this period of time, the concentration would decrease because there was no input, and the animals grew to approximately three times their initial body weight. However, it should be noted that after the initial

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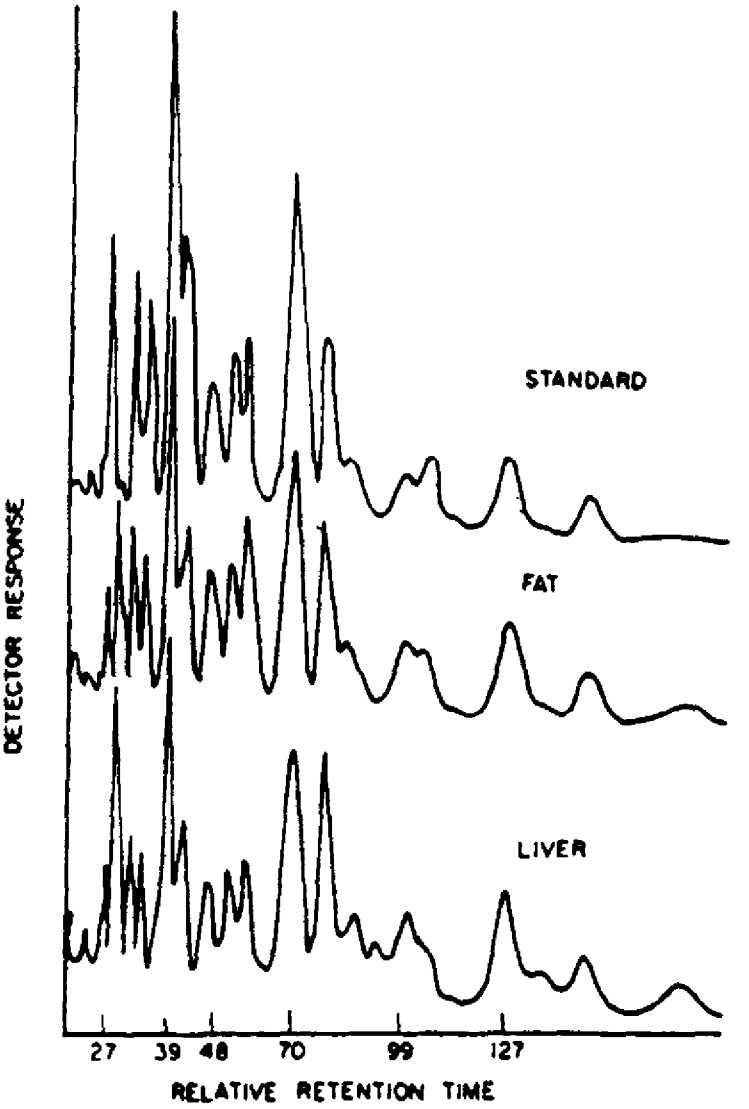

Figure 6. Electron capture gas-liquid chromatographs of an Aroclor 1242 standard and extracts of catfish fat and liver. The extracts were diluted to give a detector response comparable to the standard. This figure was adapted from Hansen et al., 1976.

equilibration period, very little of the total body burden was eliminated, even with this lower chlorinated PCB congener. In mammals, similar types of studies have indicated that the half-life of this lower molecular weight PCB congener is much

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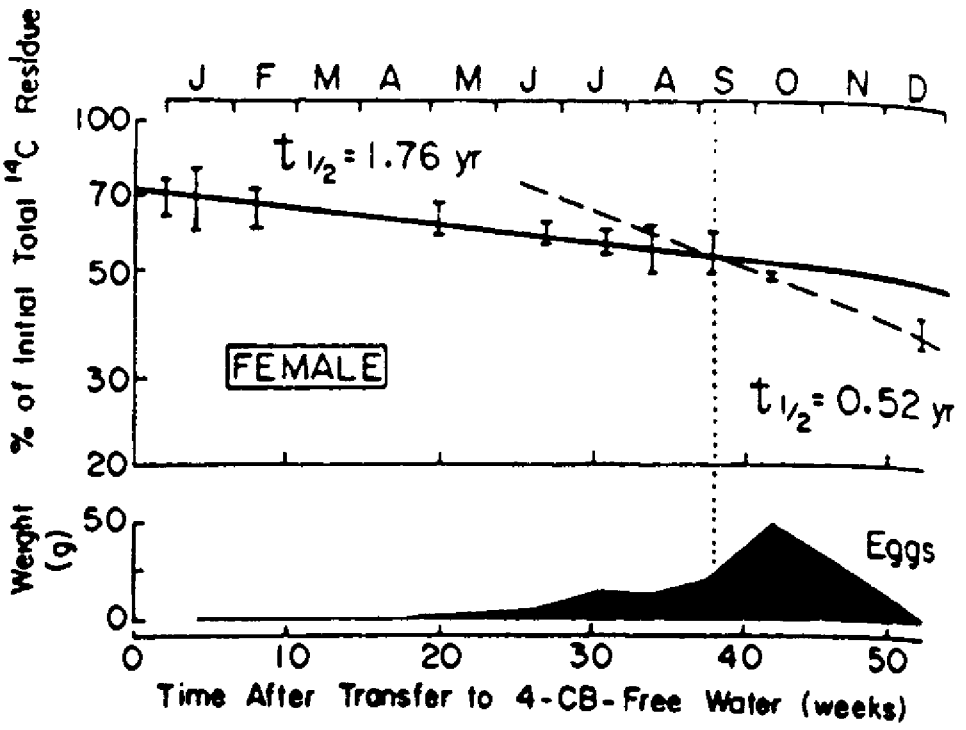

Figure 7. The enhancing effect of spawning on whole body elimination of 2,5,2',5'-tetrachlorobiphenyl (4-CB) residues from female rainbow trout. The top panel shows the rate of elimination of radioactive 4-CB residues from the whole fish. The bottom panel shows wet weight of the eggs in the fish. The months of the year after the fish were transferred to 4-CB free water are shown across the top of the figure. This figure was adapted from Guiney et al., 1979.

shorter. When this study was extended through the spawning season, the slope of the elimination curve increased sharply in both males and females at the time of spawning. Data shown in Figure 7 indicate that elimination of 4-CB was increased at the time of formation of eggs. In this figure, the y axis expresses the percent of the initial body burden of 4-CB. This change in slope which indicates an actual loss of 4-CB from the fish is in agreement with the observation that a corresponding amount of 4-CB was lost from fat and was recovered in the eggs expelled during spawning (Figure 8).

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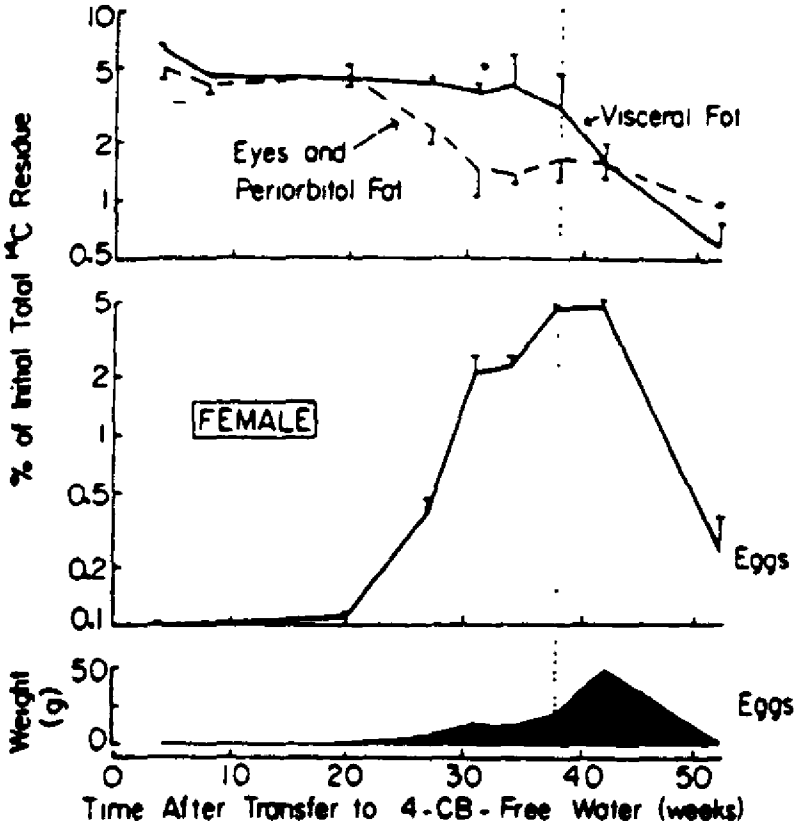

Figure 8. Illustration of the redistribution of 2,5,2',5'-tetrachlorobiphenyl (4-CB) residues that occurs between body fat depots and eggs during the spawning in female rainbow trout. This figure was adapted from Guiney et al., 1979.

The results of these latter experiments indicate that even some of the lower chlorinated PCB congeners may persist for a long period of time in a species such as trout which does not readily biotransform these congeners. These results also illustrate that the total body burden of such congeners may be reduced via the spawning mechanism; but under normal circumstances, elimination of this compound is slow when compared to mammals.

Most data indicate that 2,5,2',5'-tetrachlorobiphenyl (4-CB) as well as other PCB isomers may be extremely persistent in fish, and that dilution of residues by growth rather than

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actual elimination is the basis for the reduction of tissue concentrations over long periods of time. However, more recent work (Guiney et al., 1980) has demonstrated that actual eliminaton of 4-CB can occur during the fry-stage of rainbow trout development, but the mechanism concerned with the observed reduction in body burden at this time is poorly understood. When fertilized rainbow trout eggs were exposed to water-born ^{14}C-labeled 4-CB for 24 hr and transferred to an incubator supplied with flowing 4-CB free water, the burden of this isomer in the eggs and sac fry remained constant throughout these stages of development (Figure 9). This virtual cessation of elimination lasted for almost 2 months and the calculated half-life was 231 days. However, when the developing trout entered the fry stage, a rapid phase of 4-CB elimination was observed over the next 2 months. The calculated half-life of elimination during the fry stage was 14.6 days. This latter finding

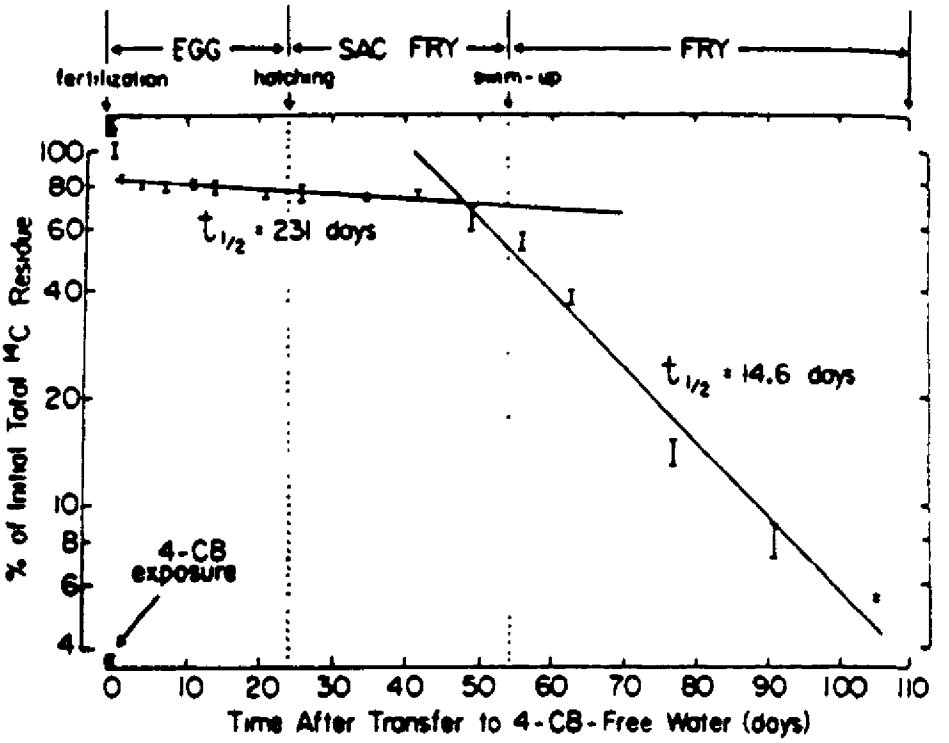

Figure 9. Elimination of 2,5,2',5'-tetrachlorobiphenyl (4-CB) residues during early development in rainbow trout. The time course of development is given at the top and the duration of 4-CB exposure at the lower left. This figure was adapted from Guiney et al., 1980.

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indicates that although 4-CB concentration in the fry was decreased because of dilution by growth, there was also actual, true elimination of the compound. More explicitly, the initial 4-CB body burden decreased from approximately 70 percent at the end of the sac fry stage to approximately 5 percent at the end of the fry stage (Figure 9). The underlying reason for this enhanced rate of elimination, that is uniquely confined to the fry stage of development, is not known. It is possible that it may be related to the low fat content of the fry as opposed to the adult or a high rate of biotransformation at this stage of the life cycle. Alternatively, it may be that lipids or lipoproteins absorbed from the yolk sac or synthesized in the liver bind 4-CB. The resulting 4-CB lipoprotein complex may then be more rapidly elimination in feces than the unbound form of 4-CB.

SUMMARY

Information gathered over the past several years in a variety of laboratories indicate that most fish species biotransform the lower chlorinated PCB congeners at slower rates than mammals. Although there is variation in this among fish species, it would appear that the overall residue patterns in fish resemble the patterns found in the exposure source, and there is less biotransformation and elimination of congeners which are readily excretable after metabolism in mammals. Current information also indicates that the degree of bioaccumulaton of PCBs in fish may be directly related to the fat content of the species in question and that the major mechanism for reducing PCB concentrations in fish is by dilution by growth, rather than by true elimination of a portion of the total body burden.

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CHAPTER 15

METABOLISM OF PCBs IN MAMMALS: ROUTES OF ENTRY, STORAGE, AND EXCRETION

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INTRODUCTION

The presence of toxic chemicals in the environment is not a recent occurrence. The presence of toxic chemicals pre-dates life itself and each class of chemicals has presented its own set of problems. The polychlorinated biphenyls (PCBs) are certainly no exception. Most of the effects of toxic chemicals can be tolerated if certain limits of exposure are not exceeded and exposure to most chemicals can be limited by removing the source. Because of their persistence in the environment and bioaccumultion in the food chain, removal of the source of exposure to PCBs has proved particularly difficult. Given the inevitability of past and future human exposure to PCBs, work in our laboratory has been directed to understanding the fate of these compounds in mammals. The following is a general overview of what we feel are the determining factors for the fate of PCBs in higher animals.

ADSORPTION AND DISTRIBUTION

With the exception of the laboratory situation, PCBs are always found as a mixture of many chlorinated biphenyls. Depending upon the degree and position of chlorination, there may be 209 different chlorinated biphenyls. Since it would be impractical to study the metabolism and disposition of all PCBs, we chose to study a series of carefully selected representative chlorinated biphenyls in an effort to learn the basic rules which determine why this group of chemicals tends to accumulate

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in the bodies of higher animals. To facilitate the study, we used compounds which were labeled with carbon-14.

One of our first efforts was to study the absorption, tissue distribution, metabolism, and excretion of four chlorinated biphenyls. The chemicals studied were 4-chloro-(1-CB), 4,4'-dichloro-(2-CB), 2,4,5,2',5'-pentachloro-(5-CB), and 2,4,5,2',4',5'-hexachlorobiphenyl (6-CB)(Matthews and Anderson, 1975)(Figure 1). These biphenyls represent a range of chlorination from 10 to 60 percent. Our studies of the disposition of these biphenyls in the rat demonstrated that following ingestion each was readily absorbed from the gastrointestinal tract and distributed to all the tissues. The highest initial concentrations were observed in liver, but within a fews days the concentration in liver was reduced by 90 percent. The less chlorinated 1-CB and 2-CB were apparently cleared from the liver more rapidly than were the more highly chlorinated 5-CB and 6-CB. The rates of whole body clearance by excretion in urine and feces varied greatly. Greater than 90 percent of 1-CB was excreted in approximately two days, whereas approximately 4 to 10 days were required to excrete 90 percent of 2-CB and 5-CB, respectively. The 6-CB was excreted extremely slowly and the data indicated that the rat would never excrete 90 percent of the dose.

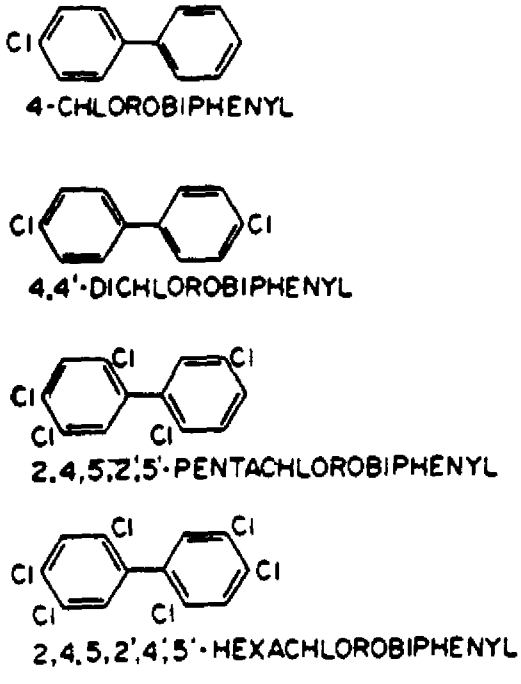

Figure 1. Structural formulas for four chlorobiphenyls.

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An examination of additional tissues made it obvious that 6-CB, and to a lesser extent 5-CB, was being cleared from liver and other lean tissues by redistribution to adipose tissue and skin. Once a PCB was sequestered in adipose tissue, the rate of clearance from the body by excretion in urine and feces was greatly reduced.

EFFECT OF POLARITY ON DISTRIBUTION

Investigations to determine the factors which account for clearance of PCBs from tissues showed that in each case the PCB derived radioactivity excreted was in the form of PCB metabolites. Very little parent compound was excreted. On the other hand, the material retained in the tissues was primarily unmetabolized PCB. Isolation and identification of PCB metabolites from several species in a number of laboratories have showed that the metabolites are always more polar than the parent compound (Gardner et al., 1973; Goto et al., 1974; Safe et al., 1975; Hasa et al., 1977; Kato et al., 1980). The polarity of PCB metabolites facilitates their excretion in the aqueous mediums of urine and bile. Unmetabolized PCBs are not soluble in water and, therefore, even when they are present in liver and kidney they have a greater affinity for the tissues than urine and bile and are not excreted. The net result is that those PCBs which can be readily metabolized are readily excreted, whereas those PCBs which are not readily metabolized are stored in lipid-rich tissues such as adipose tissue.

The effect of lipid solubility on the affinity of PCBs for various tissues as measured by the tissue/blood ratios is illustrated in Table 1. In this table, it is seen that as the number of chlorines on the biphenyl rings increase from one to six the tissue/blood ratio tends to increase. Furthermore, the increase is proportional to the amount of lipid in the tissue, so that the most highly chlorinated PCB studied, 6-CB, is 400 times as soluble in adipose tissue as in blood. On the other hand, the metabolites of these PCBs are approximately equally soluble in blood and tissues and the effect of chlorination is much less. Adipose tissue has little or no capacity to metabolize PCBs to more polar compounds. Enzymes responsible for PCB metabolism are located primarily in liver. Therefore, the lipid solubility of PCBs also acts to increase their persistence by isolating them from the enzymes which can convert them to metabolites which can be excreted.

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TABLE 1

Tissue/Blood Distribution Ratios for Selected PCBs and Respective Metabolites

	Parent PCB				PCB Metabolites			
Compartment	1-CB	2-CB	5-CB	6-CB	1-CB	2-CB	5-CB	6-CB
Blood	1	1	1	1	1	1	1	1
Gut Lumen	1	1	1	1	1	1	1	1
Muscle	1	2	1	4	0.14	0.40	0.10	0.30
Liver	3	6	12	2	5	2	4	
Skin	10	10	7	30	0.25	0.30	0.10	2
Adipose	30	50	70	400	0.40	0.60	0.40	2

PCB METABOLISM

An examination of the molecular structures of the four PCBs described above revealed two major differences between those which were readily metabolized and excreted and the one which was not. The most obvious difference was that 6-CB, the more persistant PCB, was more highly chlorinated than the others. However, 5-CB, which had almost as many chlorines as 6-CB, was metabolized and excreted much more rapidly. The second major difference between 6-CB and the other chlorinated biphenyls is that 6-CB does not have adjacent unsubstituted carbon atoms.

Work done in the fifties indicated that the presence of adjacent unsubstituted carbon atoms facilitates the metabolism of chlorinated benzenes (Jondorf et al., 1955; Jondorf et al., 1958). More recent studies of the metabolism of unchlorinated biphenyl indicate that the preferred route of biphenyl metabolism involves the formation of an arene oxide between the number 3 and 4 carbons of one biphenyl ring (Billings and McMahon, 1978). This arene oxide is degraded both spontaneously and enzymatically to yield a variety of hydroxylated metabolites. Hydroxylated metabolites of PCBs are much more polar than the parent compound; and possibly more important, they are readily conjugated with glucuronic acid to form water soluble conjugates which are readily excreted.

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We have studied the metabolism of a number of chlorinated biphenyls in our laboratory. A simplified metabolic scheme for 5-CB involving the arene oxide between the number 3 and 4 carbons of one ring is presented in Figure 2 (Chen et al., 1976). The arene oxide shown in Figure 1 is formed between the only two adjacent unsubstituted carbon atoms found in this PCB and all of the 5-CB metabolites detected were hydroxylated in the 3 or 4 positions.

In order to demonstrate that the reduced metabolism of 6-CB is due to the absence of adjacent unsubstituted carbon atoms and not simply a higher degree of chlorination, we studied the metabolism and disposition of three additional hexachlorobiphenyls (Kato et al., 1980; Matthews and Tuey, 1980). Two of these compounds, 2,4,6,2',4',6'-hexachlorobiphenyl and 2,3,5,2',3',5'-hexachlorobiphenyl, do not have adjacent unsubstituted carbon atoms. The third compound, 2,3,6,2',3',6'-hexachlorobiphenyl, is equally chlorinated but has adjacent unsubstituted carbon atoms in each ring (Figure 3). In this study, we observed that 2,3,6,2',3',6'-hexachlorobiphenyl was metabolized and excreted as rapidly as the dichlorobiphenyl described earlier. Approximately 90 percent of the dose of 2,3,6,2',

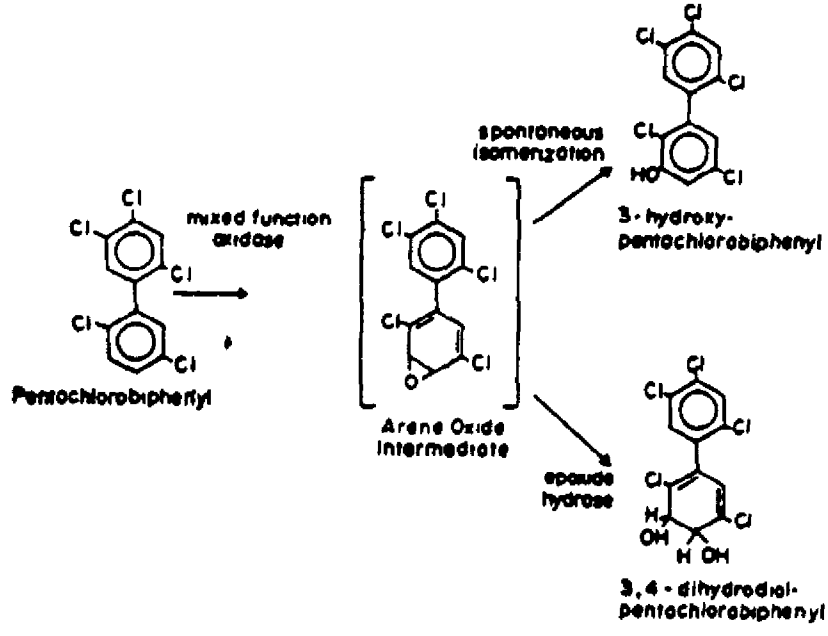

Figure 2. Metabolic scheme for 2,4,5,2',5'-pentachlorobiphenyl (5-CB).

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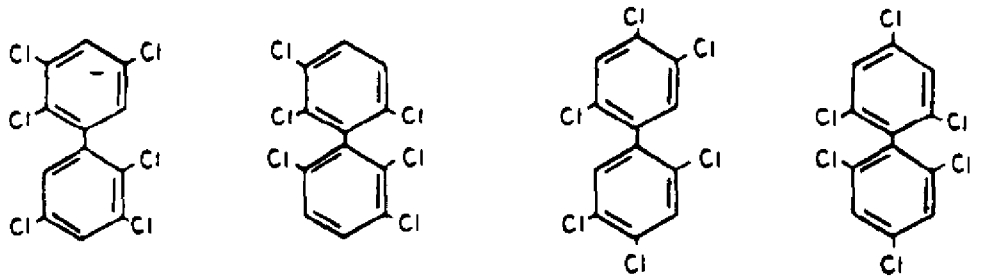

Figure 3. Structural formulas for four hexachlorobiphenyls.

3',6'-hexachlorobiphenyl was excreted in 4 to 6 days. On the other hand, those hexachlorobiphenyls which do not have adjacent unsubstituted carbon atoms were metabolized and excreted at a rate more comparable to that previously observed for 6-CB. A rat would not be expected to live long enough to excrete 90 percent of the dose of these compounds. Also, as observed with 6-CB, most of the dose of these PCBs were stored in adipose tissue.

The absence of adjacent unsubstituted carbon items is thought to inhibit the metabolism of PCBs in two ways. The presence of the relatively large chlorine atom sterically hinders the approach of the enzyme to the biphenyl molecule and chlorination deactivates the respective carbon atom and hinders the formation of an arene oxide involving that carbon atom. The net result is that the position of chlorination may be as important a determinant of PCB persistence as the degree of chlorination.

OTHER SPECIES

Most of the work discussed above describes metabolism and disposition of PCBs by laboratory rats. That is because rats have been most frequently used in toxicology studies because they are one of the most convenient and economical species to work with. However, the metabolism and disposition of PCBs have also been studied in a number of other species and some interesting species variations have been observed. Among the mammals studied, dogs appear to have the greatest capacity to metabolize PCBs (Sipes et al., 1979). Laboratory rats and mice are about equal and have an intermediate ability to metabolize PCBs (Tuey and Matthews, 1980) and monkeys metabolize and

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excrete PCBs relatively slowly (Abdel-Hamid et al., 1981). PCB metabolism has also been studied in both birds (Hutzinger et al., 1972) and fish (Lech and Peterson, 1983) and each has some capacity to metabolize PCBs, but very limited capacity to metabolize those which are more slowly metabolized by mammals. In all species the mechanisms for PCB metabolism, as well as the distribution and excretion of the respective parent compounds and metabolites, appear to be similar. The net result being that those species which metabolize PCBs most slowly have the greatest potential to accumulate higher concentrations of these compounds in their tissues.

EQUILIBRATION OF PCBs AMONG TISSUES

It should be pointed out that even though PCBs and similar lipid soluble compounds are concentrated in adipose tissue they are not isolated there. Following exposure to PCBs, an equilibrium is reached in which the concentration in each tissue is dependent upon the concentration in all the other tissues. This equilibration among the tissues is illustrated by the model in Figure 4. As discussed earlier, PCBs are readily absorbed from the gastrointestinal tract. As shown in the model, these compounds are transported by blood to all tissues. Initial tissue distribution is proportional to the rate of blood flow to the tissue and tissue volume. Therefore, the highest initial concentrations are observed in highly perfused tissues such as liver and a significant portion of the dose is in muscle because it accounts for more than twice the volume of any other tissue. Within a few hours to a few days after exposure the PCB concentrations in each of the tissues reach an equilibrium. At equilibrium, the concentration in each tissue is determined primarily by the lipid content of that tissue. Thus, we see high concentrations of PCBs in adipose tissue and much lower concentrations in relatively lean tissues such as muscle, blood, and even liver.

The equilibrium between the tissues is maintained by their common intermediate, the blood. The tissue/blood ratio shown in Table 1 is determined by the partition of the respective PCB between the two mediums and is a constant for each PCB. Therefore, any change in the concentration of PCB in either blood or tissue will cause a net movement of PCB in the appropriate direction to reestablish the equilibrium (Lutz et al., 1977). Therefore, when the PCB concentration in liver is reduced by metabolism and excretion, more PCB will partition from blood to liver to reestablish the tissue/blood ratio. If the PCB concentration of blood is reduced by partition into liver, then additional PCB will partition from all other tissues into blood to reestablish the respective tissue/blood ratios.

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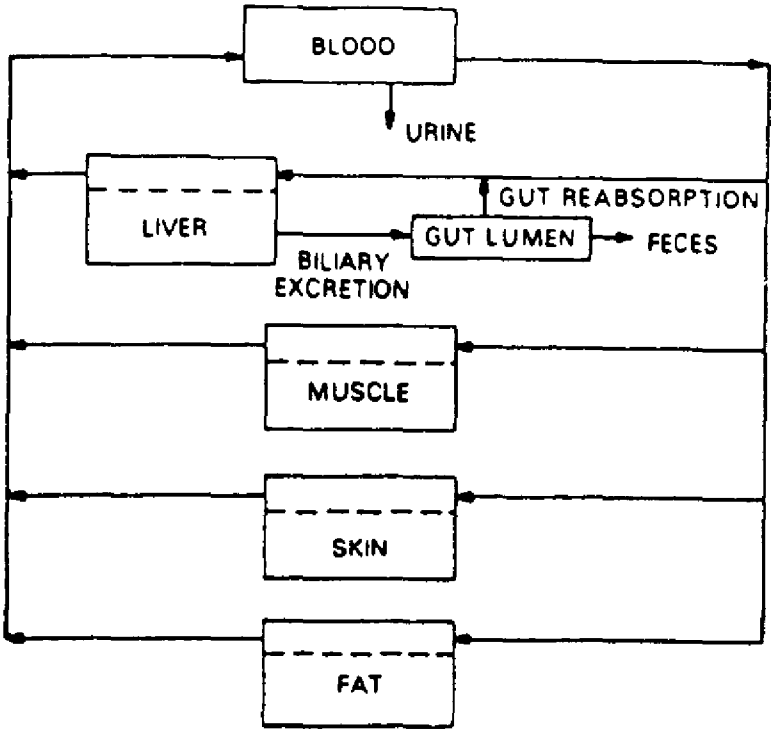

Figure 4. Schematic model of PCB absorption, equilibration in tissues, and excretion (Lutz et al., 1977).

It is in this way that those PCBs which can be cleared from the liver by metabolism and excretion are cleared from all the other tissues as well. Conversely, those PCBs which are not readily metabolized may be concentrated in adipose tissue, but all tissues are assured of a finite exposure by this same dynamic equilibrium. Therefore, even though adipose tissue is most probably not a site of toxic action for PCBs, a reservoir of PCB in adipose tissue assures chronic exposure of the site(s) of toxic action wherever they may be.

SUMMARY

The results presented here are a brief overview of a series of studies of carefully selected PCBs. The PCBs studied are selected as representatives of the 209 PCBs possible and were chosen to permit studies of the effect of degree and position of chlorination on PCB metabolism and disposition by mammals.

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The results of these studies indicate that PCBs are readily absorbed from the gastrointestinal tract. Following absorption, PCBs are transported by the blood primarily to those tissues having the greatest blood flow or tissue volume, such as liver and muscle. Those PCBs which can be readily metabolized are metabolized to more polar compounds and excreted. Those PCBs which are not metabolized are not readily excreted and tend to concentrate in lipid-rich tissues such as adipose tissue. Studies of PCB metabolism indicate that the presence of adjacent unsubstituted carbon atoms facilitate the metabolism of these compounds. PCBs which do not have adjacent unsubstituted carbon atoms are metabolized much more slowly than those which do and are consequently much more persistent in tissues.

The persistence of PCBs in the tissues of animals and man is of particular concern, because these compounds are not isolated in any one tissue but are carried throughout the body to all tissues by the blood. The persistence of PCBs in the environment and in the tissues of higher animals assures continued exposure for years to come, and to date there is no known method whereby PCBs may be safely removed from human tissues.

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CHAPTER 16

PATHOLOGIC EFFECTS OF PCBs IN MAMMALS

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INTRODUCTION

The toxicologic effects of polychlorinated biphenyls (PCBs) have been the subject of several reviews (Fishbein, 1974; Kimbrough, 1974; Kimbrough et al., 1978; Vos, 1972). Kimbrough (1976) described pathologic findings associated with long term administration of commercial mixtures of PCBs to rodents and primates. Her brief review stressed hepatotoxicity and described the lesions seen in the liver of rats and mice. She also described the tumorigenic response associated with the long term exposure of rodents to PCBs.

This review will describe major clinical signs associated with PCB toxicosis in mammals and emphasize the effects on the liver including hepatocarcinogenesis. It will also discuss typical lesions seen in the thyroid, skin, stomach, and lymphoid organs. Similarities with and differences between the effects seen with other polyhalogenated aromatic hydrocarbons will be pointed out as deemed appropriate.

CLINICAL SIGNS

Oral administration of high doses of Aroclor 1242 (4.25 g/kg) to rats resulted in a wasting disease characterized by diarrhea, chromodacryorrhea, loss of body weight, and terminal ataxia (Bruckner et al., 1973). In Vos review (1972) he cited several references in which death resulted after high doses of PCBs were given to rats, mice, and rabbits. Guinea pigs were killed by lower doses.

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Accidental exposure of a colony of rhesus monkeys to PCBs in a concrete sealant produced a disease characterized by slow and continuous weight loss, alopecia, acne, facial edema, and diarrhea (Altman et al., 1979). A high incidence of abortions and stillbirths was recorded. Allen (1975) described nearly identical signs in rhesus monkeys in experiments in which diets contained 100 or 300 mg/kg of Aroclor 1248. Long term administration of doses as low as 2.5 mg/kg caused periorbital edema, alopecia, erythema, and acneform lesions on the face and neck.

Miniats et al. (1978) reported that oral doses of 25 mg of Aroclor 1254/kg of body weight when given to germ free pigs caused inappetance, hemorrhagic diarrhea, retarded growth, incoordination, coma, and death.

Signs of a wasting disease have also been described after oral administration of commercial mixtures of polybrominated biphenyls (PBB) (Firemaster) to rats (Gupta and Moore, 1979). Guinea pigs react similarly but a lower dose of Firemaster (FM) is required to cause toxicosis (Sleight and Sanger, 1976). Collins et al. (1982) found that hamsters survived oral doses of 3.2 g/kg of FM; whereas, a single dose of 0.4 g/kg killed guinea pigs within 14 days. Generalized debilitation and weight loss are also seen after administration of chlorinated dibenzo-p-dioxins to rats (Gasiewicz et al., 1980) and mice (McConnell et al., 1978a). Again guinea pigs and rhesus monkeys are highly susceptible to the toxic effects of these compounds (McConnell et al., 1978a, 1978b).

Chemical structure of the PCB and PBB congeners affects toxicity. For example, 2,4,5,2',4',5'-hexachlorobiphenyl (HCB) and 2,4,5,2',4',5'-hexabromobiphenyl (HBB) are relatively nontoxic (Akoso et al., 1982a; Biocca et al., 1976; Moore et al., 1978). These congeners are classified as phenobarbital (PB)-type inducers of hepatic drug metabolizing enzymes. Congeners such as 3,4,5,3',4',5'-HCB and 3,4,5,3',4',5'-HBB are much more toxic and each is a 3-methylcholanthrene (MC)-type inducer. Poland and Glover (1977) stressed the structure/activity relationships for PCB congeners and emphasized that those which induce aryl hydrocarbon hydroxylase activity (MC-type) should be considered as toxic. Since the commercial mixtures of PCBs contain many congeners, the toxicity of a mixture will certainly be affected by the proportion of the various congeners in the mixture. Work with purified congeners of PBBs indicates that the major portion of the toxicity of FM is associated with 4 congeners, each of which is classified as a mixed-type inducer; that is, it can induce MC- and PB-type induction. Nearly 75 percent of the commercial mixture of PBB is comprised of congeners with only PB-type

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activity and these congeners are relatively nontoxic (Dannan et al., 1982).

LIVER

The gross lesions and histologic findings associated with administration of PCBs to animals were well summarized by Vos (1972) and by Kimbrough et al. (1972). Hepatomegaly is a commonly reported effect of PCB administration to animals. Hypertrophy of hepatocytes is seen and individual cells may appear foamy and contain sudanophilic vacuoles. Necrosis of hepatocytes can occur especially at high doses. Location of lesions may be discrete but often is centrilobular. Hyperplasia and increased mitotic activity is also seen in some animals. Kasza et al. (1978) compared the toxicity of PCBs and PBBs as to the effects on the rat liver. Similar lesions were caused by each of the mixtures. Fatty metamorphosis and necrosis was much more evident in mice given 3,4,5,3',4',5'-HCB than those given 2,4,5,2',4',5'-HCB (Biocca et al., 1976). Work with analogous PBB congeners in rats has also shown that hepatic lesions are much more severe with 3,4,5,3',4',5'-HBB than with 2,4,5,2',4',5'-HBB (Akoso et al., 1982a; Render et al., 1982).

Ultrastructural changes in hepatocytes of animals given commercial mixtures of PCBs have been described by several researchers (Kimbrough, 1974; Nishizume, 1970; Norback and Allen, 1972). Increases in smooth endoplasmic reticulum is a consistent feature and in part accounts for hypertrophy of hepatocytes. Mitochondria were described as atypical and concentric membrane arrays which sometimes surrounded lipid vacuoles were also reported. Kasza et al. (1978) compared the ultrastructural changes caused by PCBs or PBBs in rats. They found that changes were similar. They described decreased numbers of mitochondria, increased liposomes, and a decreased number of Golgi condensing vesicles in addition to the changes previously mentioned. Our work with congeners of PBB in rats indicates that MC-type inducers such as 3,4,5,3',4',5'-HBB produce many more concentric membrane arrays than seen with the PB-type inducers such as 2,4,5,2',4',5'-HBB. In addition, the rough endoplasmic reticulum is markedly disrupted by the MC-type inducer (Akoso et al., 1982a; Render et al., 1982).

The role of PCBs in hepatocarcinogenesis has attracted considerable public health and research interest. Commercial PCB mixtures have induced hepatic tumors in rats (Ito et al., 1974; Kimbrough et al., 1972, 1975; Kimura and Baba, 1973) and in mice (Ito et al., 1973; Kimbrough and Linder, 1974; Nagasaki, 1972). Hepatocellular carcinomas were described in each species; and in addition, what are classified as neoplastic

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nodules and foci of cellular alteration were described (Squire and Levitt, 1975). More recent studies have been done to determine if PCBs serve as promoters of carcinogenesis. When the PCBs were given after a known tumor initiator such as diethylnitrosamine (Preston et al., 1981; Pereira et al., 1982), there was convincing evidence that they act as tumor promoters. An earlier study by Kimura et al. (1976) in which female rats were given PCB after they had been given 3'-methyl-4-dimethyl aminoazobenzene also indicated a tumor promoting effect in the liver.

PBBs apparently also may act as tumor promoters (Jensen et al., 1982; Trosko et al., 1981). A relatively nontoxic PBB congener, 2,4,5,2',4',5'-HBB, is apparently a relatively potent promoter of hepatocarcinogenesis in the rat (Jensen et al., 1982). Results of this study indicate that toxicity and carcinogenicity may not necessarily be related with compounds such as PBBs or PCBs. Although research is clearly demonstrating that PCBs and PBBs can act as promoters of hepatocarcinogenesis in animal test systems, it remains difficult to assess the potential hazard of these compounds as carcinogens in man.

Hepatic porphyria can be induced by PCBs in the female rat (Bruckner et al., 1974; Goldstein et al., 1974; Strik, 1973). Porphyria has also been seen in mice and 3,4,5,3',4',5'-HCB was much more potent than 2,4,5,2',4,'5'-HCB in causing porphyria (Biocca et al., 1976). Gupta et al. (1981) described porphyria in female rats and mice given FM, but they did not observe porphyria when rats or mice were given 2,4,5,2',4',5'-HBB. We have found that porphyria occurs when female rats are given FM or a combination of 2,4,5,2',4',5'-HBB and 3,4,5,3',4',5'-HBB. Porphyria is seen only rarely when either congener is given alone.

THYROID GLAND

There is considerable evidence that PCBs affect the metabolism of thyroid hormones. Bastomsky and co-workers reported that administration of PCBs to rats increased ^{131}I uptake by thyroid follicular cells, lowered serum thyroxine concentrations, and reduced protein-binding of thyroid hormones. Increased conjugation of thyroxine and increased excretion of thyroxine glucuronide in the bile were also found (Bastomsky, 1974; Bastomsky and Murthy, 1976; Bastomsky and Wyse, 1975; Bastomsky et al., 1976).

Collins et al. (1977) evaluated the histopathologic, histochemical, and ultrastructural changes in thyroid follicular cells after administration of 50 or 500 mg/kg of

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PCBs to rats for 4 to 12 weeks. They also attempted to correlate the structural changes in follicular cells to changes in serum thyroxine concentration. Hypertrophy and hyperplasia of follicular cells with projections into the lumen were prominent histologic features. Cells were more columnar than in controls. By 4 weeks, ultrastructural examination revealed that there was an accumulation of lysosomal bodies and colloid droplets and abnormalities of the luminal surface of follicular cells. Lesions became more pronounced by 12 weeks. Follicular cells were greatly distended and large lysosomal bodies with strong acid phosphatase activity were present. Mitochondria were vacuolated. The ultrastructural changes were associated with significant reductions of serum thyroxine at both doses of PCBs. Lesions persisted for 12 weeks after cessation of feeding PCBs, but by 35 weeks the thyroid follicular cells were similar to controls. Serum thyroxine levels had returned to normal by this time.

The PBBs apparently produce similar thyroidal alterations in rats (Akoso et al., 1982b). Feeding of FM or 3,4,5,3',4',5'-HBB to rats produced histologic and ultrastructural changes nearly identical to those described by Collins et al. (1977) with PCBs. However, ultrastructural changes were much less pronounced as a result of feeding diets containing 2,4,5,2',4',5'-HBB. Thyroxine concentrations were markedly reduced by FM and 3,4,5,3',4',5'-HBB, but were only slightly affected by 2,4,5,2',4',5'-HBB.

SKIN AND ASSOCIATED STRUCTURES

Persistent skin lesions such as increased pigmentation and chloracne are well documented as a result of human exposure to PCBs (Kuratsune et al., 1972). Similar if not identical changes occur in rhesus monkeys exposed to PCBs. Allen and co-workers have characterized the gross and histologic skin lesions associated with feeding PCBs (Allen, 1975; Allen and Norback, 1976). Grossly, hair loss from the face, head, and neck occurred within one month after exposure to diets containing 100 mg/kg of Aroclor 1248. The eyelids and the region around the mouth became edematous and there was a loss of eyelashes. Excessive lacrimation and congestion of the conjunctiva were apparent and small comedones were obvious around the face and neck. Excessive secretion of meibomian glands was a consistent feature. Histologically, large intrafollicular keratin cysts and epithelial hyperplasia of hair follicles were evident in the skin of the face. Tissues surrounding these cysts were edematous and contained inflammatory cells. Carstens et al. (1979) described hypertrophy, squamous metaplasia and keratinization of the meibomian glands and eyelids of infant

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rhesus monkeys from dams given PCB. McConnell et al. (1979) described similar gross lesions and histologic appearance in rhesus monkeys accidentally exposed to PCBs. In addition, they described thickened and tortuous meibomian glands upon eversion of the eyelids. They also described onychogryphosis with rhexia in animals with severe alopecia. These lesions were more apparent in the nails of the feet.

Dermal applications of PCBs to the skin of rabbits caused hyperplasia and hyperkeratosis of the epidermal and follicular epithelium (Vos and Beems, 1971). Application of Aroclor 1260 caused earlier and more severe lesions than those caused by repeated applications of 2,4,5,2',4',5'-HCB (Vos and Notenboom-Ram, 1972).

STOMACH

Allen et al. (1974) described gastritis in adult rhesus monkeys fed diets containing PCBs. The gastric mucosa was greatly thickened and contained numerous cysts filled with mucin and lined by epithelium. The muscularis mucosa had penetrated into the underlying submucosa. Large cysts were abundant in the submucosa. Ulceration was also a feature. The gastric lesions were considered as highly debilitating and persisted for at least one year after exposure to PCBs. Carstens et al. (1979) described gastric mucosal hyperplasia in infant rhesus monkeys from dams given PCBs. Some of the glandular elements had penetrated the muscularis mucosa. Th submucosa was edematous and contained inflammatory cells. The PBBs apparently cause similar gastric lesions in rhesus monkeys (Lambrecht et al., 1978).

Morgan et al. (1981) recently reported an increased incidence of focal lesions in the glandular portions of the stomachs of male and female F344 rats fed diets containing 25, 50, or 100 mg/kg of Aroclor 1254 for two years. Histologically, the lesions were identified as intestinal metaplasia. Adenocarcinomas were diagnosed in the stomachs of 6 of 144 rats fed PCBs; whereas, no neoplasms were found in 47 control rats.

LYMPHOID ORGANS

Vos and Beems (1971) described cortical atrophy of the thymus, lymphopenia, and depletion of germinal centers of lymph nodes and spleen in rabbits given repeated applications of PCBs. Severely atrophied thymuses and small lymph nodes and spleens were seen in infant rhesus monkeys from dams fed PCBs (Aroclor

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1248) at a concentration of 2.5 mg/kg in the diet for 18 months (Carstens et al., 1979). Thymocytes were described as nonexistent and germinal centers were inapparent in the lymph nodes and spleen. Bone marrow was hypocellular.

Marked thymic involution and moderate depletion of lymphocytes in the spleen were described in mice fed diets containing 10 or 30 mg/kg 3,4,5,3',4',5'-HCB; whereas, 300 mg/kg of 2,4,5,2',4',5'-HCB caused only slight thymic involution and no splenic changes (Biocca, 1976). Studies with analogous PBB congeners in rats have given similar results (Akoso et al., 1982a; Render et al., 1982). Thymic atrophy typified by depletion of cortical lymphocytes was seen in rats fed diets containing 10 or 100 mg/kg of 3,4,5,3',4',5'-HBB for 10 and 30 days; whereas, rats given 100 mg/kg 2,4,5,2',4',5'-HBB had normal appearing thymuses. Lymphocytic depletion also occurred in the spleen and lymph nodes of rats given 3,4,5,3',4',5'-HBB.

Reproductive effects of PCBs including mutagenicity and teratology are not included in this review. Those interested in these areas are referred to the review of Kimbrough et al. (1978).

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CHAPTER 17

TOXICOLOGY OF PCBs IN MINK AND FERRETS

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INTRODUCTION

The first indication that the incorporation of Great Lakes fish into the diet of mink was creating reproductive problems was expressed by commercial ranchers in the early to mid 1960s (Hartsough, 1965). Ongoing investigations within our laboratory supported these contentions (Aulerich et al., 1970). In these studies, alewife-fed mink failed to produce any offspring. In 1968, Lake Michigan coho salmon were made available as mink food. Rations that contained these fish caused reproductive complications and mortality in mink that appeared to be dependent upon the percentage of coho salmon fed as well as the duration of feeding. Breeding and parturition were reported as normal or near normal, but newborn mortality was excessive and many still-born offspring were observed. Mortality of newborn was reported by the commercial ranchers to be as high as 80 percent. A direct relationship between the extent of reproductive failure by the mink and the chlorinated hydrocarbon pesticide content of the fish (DDT plus its metabolites and dieldrin) was demonstrated (Aulerich et al., 1971); however, no clinical signs of chlorinated hydrocarbon pesticide poisoning were evident. The feeding of these pesticides far in excess of the fish content of these pesticides prompted us to dismiss these compounds as being implicated (Aulerich and Ringer, 1970). Over the past 10 yrs (Ringer et al., 1981; Aulerich et al., 1973) we have clearly demonstrated that PCB residues within the Great Lakes fish were responsible for the reproductive complications of the mink and that mink were particularly sensitive to the polychlorinated biphenyl (PCB) mixtures used in capacitors, closed-system heat exchangers,

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hydraulic fluid, as plasticizers, and for many other uses. This paper discusses our current knowledge on this sensitivity in mink (Mustela vison) and relates it to another carnivore that is closely related, the ferret (Mustela putorius furo).

ACUTE AND CHRONIC TOXICITY

PCBs are not very toxic when given as a single dose to mammals or birds. The oral LD_{50} of Aroclor 1254 and 1260 in rats is in the range of 4 to 10 g/kg body weight (Kimbrough et al., 1978). The acute oral toxicity decreases in rats with increasing percentage of chlorine content (Kimbrough et al., 1978). In the mink, the acute oral toxicities of Aroclors 1221, 1242, and 1254 are approximately 1, 3, and 4 g/kg body weight, respectively (Aulerich and Ringer, 1977). Thus, as in the rat, the acute toxicity decreases with increased chlorine content and these PCBs would be classified as only slightly toxic based on acute oral toxicity.

In a series of experiments, Aroclor 1254 was fed to mink in graded dosages, for 4 or 9 months prior to whelping (parturition) and the chronic effects on reproduction were assessed (Table 1). The results clearly demonstrated that 2 mg/kg or more Aroclor 1254 fed continuously were detrimental to reproduction. Using the assumption that mink consume approximately 150 g of food per day, the total intake of PCB at 2 mg/kg and 9 months feeding prior to whelping would have been 81 mg. This level of intake is about the same as the intake on 5 mg/kg fed for 4 months (90 mg). Both treatments were equally detrimental to reproduction.

Not all Aroclors are as chronically toxic to reproduction as is Aroclor 1254. As can be seen by the data in Table 2, Aroclor 1016, 1221, and 1242 did not cause adverse reproductive effects when fed at 2 mg/kg in the diet for 9 months prior to whelping. However, as shown in Table 3, the feeding of 5 mg/kg of Aroclor 1242 is detrimental to reproduction. Aroclor 1016 at concentrations as high as 20 mg/kg does not lower the number of young (kits) born per female.

When concentrations higher than those that affect reproduction are chronically fed to mink, adult mortality results (Table 3). It can be readily seen from these data that for both Aroclor 1242 and 1254 feeding a level of between 5 and 10 mg/kg in the diet will kill 50 percent of the adult animals in about 9 months. An estimated LC_{50} (dietary concentration) calculated from these data yielded values of 6.65 mg/kg for Aroclor 1254 and 8.60 mg/kg for Aroclor 1242 (Ringer et al., 1981). Male mink survive longer than female mink when fed these

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TABLE 1

Summary of the Effect of Aroclor 1254 on Mink Reproduction

Treatment Level	Period Fed	Reproduction Offspring/ Female
15 mg/kg	January-May	0
10 mg/kg	August-June	0
10 mg/kg + 10 mg/kg DDT	January-May	0
10 mg/kg + 0.5 mg/kg dieldrin	January-May	0
5 mg/kg	August-June	0
5 kg/mg	January-May	0.8
5 mg/kg + 6 mg/kg DDT	January-May	1.0[a]
5 mg/kg + 6 mg/kg DDT + 0.2 mg/kg dieldrin	January-May	2.0[a]
2 mg/kg	August-June	0.3
1 mg/kg	January-May	4.3
0 mg/kg		4.1
0 mg/kg		5.0
0 mg/kg		6.0

[a]All died before 4 weeks of age

lower levels of PCBs (Platonow and Karstad, 1973; Bleavins et al., 1980).

The question is often asked whether this sensitivity to PCBs by mink is an anomaly. However, our laboratory has demonstrated (Tables 4 and 5) that mink are sensitive to polybrominated biphenyl (PBB) toxicity (Aulerich and Ringer, 1979) and more recently, hexachlorobenzene (unpublished data). The estimated LC_{50} for PBBs is 3.95 mg/kg when fed for 313 days.

CLINICAL SIGNS AND LESIONS

Clinical signs and lesions in mink from PCB feeding and PBB feeding are fairly non-specific. These include anorexia, loss of weight, fatty infiltration of the liver, general unthrifty appearance, and lethargy. Often seen prior to death is the appearance of dark fecal stools indicative of the presence of blood from the upper intestinal tract. Necropsy reveals the presence of gastric ulcers of varying severity.

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TABLE 2

Reproductive Performance and Mortality of Female Mink Fed a Control Ration or Experimental Diets Containing 2 mg/kg Supplemental PCB (August 8, 1972, to June 1, 1973, or Until the Kits Were 4 Weeks of Age)

	Adult Females			Kits				
Dietary Treatment	Percent Mortality	Number Mated	Number Whelped	Number Born Alive	Number Born Dead	Whelped/ Female Mated	Alive at 4 Weeks	Average Weight (g ± S.E.) at Birth
Control	0	8	8	28	5	4.1	18	9.9 ± 0.32
2 mg/kg PCB Aroclor 1016	0	8	8	28	8	4.5	16	9.2 ± 0.33
2 mg/kg PCB Aroclor 1221	12	7	7	43	1	6.3	37	9.6 ± 0.22
2 mg/kg PCB Aroclor 1242	12	7	7	35	4	5.6	32	9.3 ± 0.27
2 mg/kg PCB Aroclor 1254	17	7	2	1	1	0.3	0	5.4

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TABLE 3

Adult Breeder Mortality and Reproduction in Mink Fed Various Levels of Aroclors 1254, 1242, and 1016

Treatment Level (mg/kg)	Period Fed (days)	Adult Mortality Number Dead/ Number Total	Mortality (%)	Reproduction (Kits/ Female)
Aroclor 1254[a]				
0	280	1/ 7	14	5.0
0	297	0/ 8	0	4.1
0	297	1/ 8	12	0.3
5	280	2/ 7	29	0.0
10	280	5/ 7	71	0.0
Aroclor 1242[b]				
0	247	3/30	10	4.9
2[a]	297	1/ 8	12	5.6
5	247	1/15	7	0.0
10	247	10/15	67	0.0
20	192[c]	15/15	100	0.0
40	138[d]	15/15	100	0.0
Aroclor 1016[b]				
0	247	3/30	10	4.9
2[a]	297	0/ 8	0	4.5
20	247	3/15	20	6.3

[a]Data from Aulerich and Ringer, 1977
[b]Data from Bleavins et al., 1980
[c]All mink died within 192 days on diet
[d]All mink died within 138 days on diet

TABLE 4

Mortality and Reproduction in Mink Fed Various Levels of PBB

Treatment Level (mg/kg)	Period Fed (days)	Adult Mortality Number Dead/ Number Total	Reproduction Offspring/Female
PBB (FireMaster FF-1)[a]			
0	313	0/10	3.5
1.0	313	0/10	2.6
2.5	313	1/10	2.6
6.25	313	9/10	0.0
15.625	93[b]	10/10	-

[a]Data from Aulerich and Ringer, 1979
[b]All mink died by this period; no females survived to whelping

liver weight and kidney weight relative to body weight are increased over that found in control animals.

COMPARISON TO THE FERRET

The European ferret, also a carnivore from the Mustelid family, shows reproductive complications when PCBs are fed at a slightly higher concentration in the diet. The feeding of 20 mg/kg of Aroclor 1242 for nearly 9 months prior to parturition is not lethal to the adult breeder (Table 6), yet results in total reproductive failure of these breeders (Ringer et al., 1981; Bleavins et al., 1980). As with the mink, 20 mg/kg of Aroclor 1016 does not alter the number of young born per breeding female. In our early studies, it was shown that the ferret was able to consume Great Lakes fish when fed at 30 percent of the diet without reproductive complications, whereas the same diet caused total failure in mink. The somewhat greater resistance of the ferret was what accounted for this difference.

PLACENTAL AND MAMMARY TRANSFER

Placental transfer of PCBs to the fetus from the mother has been demonstrated in rats (Takagi et al., 1976; Ando, 1978), mice (Masuda et al., 1979), rabbits (Grant et al., 1971), cattle

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TABLE 5

Reproductive Performance of Mink Fed PBB Diets and the Weight and Survival of Their Offspring (Kits)

PBB Dietary Level (mg/kg)	Number Females Whelped/ Number Mated	Number Kits Whelped		Average Number Kits Whelped/Female		Percent Kit Mortality (Birth to 4 Weeks)	Average Kit Weight (g ± S.E.)	
		Alive	Dead	Whelped	Mated		At Birth	At 4 Weeks
0	5/8	22	6	5.6 ± 0.03	3.5 ± 1.07	23	9.1 ± 0.30	128 ± 7.0
1	5/8	17	4	4.2 ± 0.92	2.6 ± 0.95	47	7.5 ± 0.30[a]	87 ± 2.3[a]
2.5	6/8	15	6	3.5 ± 0.72	2.6 ± 0.78	47	8.6 ± 0.61	132 ± 16.0
6.25	0/1	--	--	--	--	--	--	--
15.625	0.0	--	--	--	--	--	--	--

[a]Significantly different from controls ($P < 0.01$) by t-test

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TABLE 6

Adult Mortality of Mink and Ferrets Fed Aroclor 1242 or 1016 for 247 Days

Treatment Level and Aroclor Fed (mg/kg)	Adult Mortality	
	Died/Total	Percent
Mink		
0 PCB	3/30	10
5 Aroclor 1242	1/15	7
10 Aroclor 1242	10/15	67
20 Aroclor 1242	15/15	100
40 Aroclor 1242	15/15	100
20 Aroclor 1016	3/15	20
Ferret		
0 PCB	0/15	0
20 Aroclor 1242	0/15	0
20 Aroclor 1016	1/15	7[a]

[a]Died during whelping due to breech presentation

(Platonow and Chen, 1973), rhesus monkeys (Allen and Barsotti, 1976), and humans (Masuda et al., 1979). Our studies have shown that placental transfer of PCBs also occurs in the mink and ferret (Bleavins et al., 1981) and gives rise to the embryotoxicity demonstrated by these species. PCBs appear to cross the placenta more readily (Table 7) in the mink than in the ferret (Bleavins et al., 1981). The placenta in the two species differs in anatomical structure, with the mink having a greater area for diffusion. The greater placental surface area between the mother and fetus may contribute to the greater transplacental exchange and undoubtedly contributes to the greater PCB embryotoxicity in the mink than ferret.

In experiments using radiolabeled PCBs (Table 8), our laboratory has shown that a significantly greater quantity of PCBs entered the growing offspring through mammary transfer than through placental transfer (Bleavins et al., 1981). This greater transfer to the offspring by milk has been shown in

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TABLE 7

Fetal Tissue Concentrations[1] of ^{14}C in Mink and Ferrets 2 Hours Following Maternal Intravenous Injection

		Whole Kit		Tissue				
Animal	n	Last Trimester	n	Adipose	Kidney	Liver	Brain	Intestine
Mink	4	0.019 ± 0.0017[a2]	2	0.037 ± 0.0181[a]	0.028 ± 0.0027[a]	0.095 ± 0.0543[a]	0.011 ± 0.0007[a]	0.021 ± 0.0045[a]
Ferret	4	0.012 ± 0.0004[b]	4	0.020 ± 0.0019[a]	0.022 ± 0.0011[a]	0.018 ± 0.0023[a]	0.012 ± 0.0012[a]	0.013 ± 0.0021[a]

[1]Concentration is expressed as a percentage of the initial maternal dose per gram of tissue
[2]Means with the same superscript are not significantly different ($P > 0.05$) within columns

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TABLE 8

PCB Concentrations[a] at Birth and 2 Weeks of Age in Kits Born to Female Mink Intraperitoneally Dosed With ^{14}C Aroclor 1242

Animal Number	Gestation (Days)	Time Between Dosing and Whelping (Days)	Biphenyl Concentration[b]				
			Newborn Kits		2 Week Old Kits		
			Per Gram	Per Kit	Per Gram	Per Kit	Milk
E-2030	57	26	0.012	0.095	0.026	1.863	0.029
F-262[c]	54	28	0.009	0.079	--	--	--
F-754	56	30	0.008	0.083	0.018	0.745	0.023
F-1312[c]	60	35	0.015	0.125	--	--	--
F-1650	61	35	0.007	0.064	0.018	1.085	0.023
Mean ± S.E.[d]	56 ± 2.5	31 ± 1.8	0.010 ± 0.0015	0.089 ± 0.0102	0.019 ± 0.0035	1.231 ± 0.2831	0.025 ± 0.0020

[a]Concentration is expressed as a percentage of the initial maternal dose per gram of tissue
[b]Value is the average PCB concentration based on two kits per female
[c]No kits surviving to 2 weeks of age
[d]S.E. = standard error

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other mammals (Takagi et al., 1976; Masuda et al., 1979; Allen and Barsotti, 1976) and in man (Masuda et al., 1978). This PCB transfer by the lactating mink probably resulted in the high offspring mortality observed when Great Lakes fish were fed to commercial ranch mink in the late 1960s.

METABOLIZED PCBs

A recent study from our group has shown that considerably fewer PCBs are required to cause reproductive failure in mink, based on analysis, when metabolized by another species first and then fed to mink. Platonow and Karstad (1973) reported that levels of PCBs as low as 0.64 mg/kg caused reproductive complications in mink when fed meat from a cow that had been given Aroclor 1254. This level of effect is below that observed when the PCB mixture is added directly to the diet as discussed earlier. In our most recent study (Hornshaw, 1981), 30 percent Great Lakes fish were fed to mink and reproduction recorded (Table 9). Carp-fed mink failed to reproduce. Based on a calculated intake, over 250 days of feeding, and analyses of the fish against an Aroclor 1254 standard, these mink consumed approximately 56 mg of PCBs. Growth of the offspring was subnormal on several groups fed various fish at even lower levels of PCB intake. This toxicity, at dietary levels below Aroclor 1254 toxicity amounts, can probably be explained by the fact that tissues retain more of the highly chlorinated congeners of the PCB mixture once they have been metabolized. A similar response has been reported for meat taken from a cow fed PBB and then administered to mink (Aulerich and Ringer, 1979). Lethality of adults was somewhat greater on the metabolized form.

SUMMARY

Mink are among the more sensitive species or are the most sensitive mammalian species to PCB toxicity. Dietary administration of Aroclor 1254 at 2 mg/kg adversely affects reproduction. Meat containing PCB contamination when fed to this carnivore affects reproduction at even lower levels. PCBs are embryotoxic to the developing embryo. Spermatogenesis, oogenesis, and implantation are unaffected.

Placental transfer of PCB occurs but mammary transfer from the lactating dam is a more pronounced means of offspring contamination.

TABLE 9

Reproductive Performance and Calculated PCB Intake[a] of Mink Fed Great Lakes Fish Diets - 1981

Diet	Females Whelped/ Mated	Kits Born		Average Live Kits/ Female Mated	4 Weeks Kit Weight (g)	Calculated Total Intake, (mg)
		Alive	Dead			
Control (Marine Fish)	9/10	38	11	3.8	123	3.4
Carp	3/11	0	9	0	-	56.2
Sucker	9/10	25	14	2.5	111	23.6
Perch Scraps	9/11	33	12	3.0	98	25.9
Whitefish Necks	8/10	32	7	3.2	107	18.0
Alewife Fish Meal	10/12	53	9	4.2	124	7.9

[a]Based on an assumed food intake of 150 g/day

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CHAPTER 18

INHIBITION OF INTERCELLULAR COMMUNICATION BY VARIOUS CONGENERS OF POLYBROMINATED BIPHENYL AND POLYCHLORINATED BIPHENYL

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INTRODUCTION

The widespread use, distribution, and accidental contamination of polybrominated biphenyls (PBBs) and polychlorinated biphenyls (PCBs) have prompted a large variety of studies designed to ascertain if they might have biological consequences on human health.

Although there are no conclusive data indicating that either the PCBs (Green et al., 1975a, 1975b; Wyndham et al., 1976; Hoopingarner et al., 1972; Nilsson and Ramel, 1974) or PBBs (Wertz and Ficsor, 1978; Rubinstein et al., in preparation) are mutagenic, there have been reports on animals linking exposure to these chemicals to teratogenic consequences (Watanabe and Sugahara, 1981; Beaudoin, 1977; Beaudoin and Fisher, 1981) and to carcinogenesis (Nobuyuki et al., 1973; Kimbrough et al., 1975, 1981; Preston et al., 1981; Jensen et al., 1982). Recently, it has been postulated that certain chemicals which inhibit intercellular communication mechanisms might play a role in teratogenesis (Trosko et al., 1982a) and carcinogenesis (Trosko et al., 1982b).

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Based on the concept that carcinogenesis consists of initiation of a single cell, possibly by a mutagenic event (Trosko et al., 1981), and the subsequent promotion of that single cell into a clonal critical mass of dysfunctional cells, possibly by the inhibition of intercelluar communication (Trosko et al., 1980), several recent reports have implicated specific congeners of PBB with the tumor promotion process (Trosko et al., 1981; Tsushimoto et al., 1982). In addition, it is fairly well established that a variety of intercellular communication mechanisms play important roles in the developmental processes, as well as in the control of cellular proliferation and differentiation in multicellular organisms (Loewenstein, 1982; Gilula, 1980; Cline and Golde, 1979; Potter, 1980; Blumberg et al., 1982). Therefore, inhibition of these important intercellular communication mechanisms might be predicted to play a role in teratogenesis when occurring during organogenesis (Trosko et al., 1982a) and in tumor promotion of initiated differentiated tissue (Trosko et al., 1982b).

Recently, Yotti et al. (1979) and others (Murray and Fitzgerald, 1979; Fitzgerald and Murray, 1979; Umeda et al., 1980; Williams, 1981; Newbold and Amos, 1981; Kinsella et al., 1981; Warren et al., 1982) have shown that several known tumor promoters (and teratogens) have the ability to block one form of cell-cell communication i.e., metabolic cooperation, presumably by making gap junction mediated cell transfer non-functional (Enomoto et al., 1981; Yancey, 1982) . In addition, Trosko et al. (1981) and Tsushimoto et al. (1982) have shown 2,4,5,2',4',5'-hexabromobiphenyl (HBB), but not 3,4,5,3',4',5'-HBB, inhibits intercellular communication at non-cytotoxic doses in Chinese hamster cells. Based on the assumption that inhibition of intercellular communication at non-cytotoxic doses could lead to tumor promotion, Jenson et al. (1982) have shown the 2,4,5,2',4',5'-HBB was a powerful liver tumor promoter in rats. Since it has already been shown that the PCBs are rat liver tumor promoters (Nobuyuki et al., 1973; Preston et al., 1981), we designed the following experiments to test if specific purified congeners of PCBs would inhibit intercellular communication in a manner similar to specific congeners of PBB.

METHODS

Cell Culture

A Chinese hamster cell line (V79), derived originally from lung tissue (Ford and Yerganian, 1958), was used for the assay. Cells were grown in modified Eagle's medium (Eagle, 1959) (Eagle's balanced salt solution with 50% increase of vitamins and essential amino acids except glutamine), supplemented

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with non-essential amino acids (100% increase), 1 mM sodium pyruvate and 5 percent fetal calf serum. Under the incubation condition with 5 percent CO_2 in humidified air at 37°C, cells not contact-inhibited have a generation time of about 12 hours.

Cytotoxicity

The effect of different concentrations of PBBs and PCBs on the colony-forming ability of Chinese hamster cells was tested. Initially, 300 to 2000 cells were plated in each of four 9 cm dishes. After about 4 hours when cells attached on the surface of the dish, the chemicals were added. 2,4,5,2',4',5'-HBB and 2,4,5,2',4',5'-hexachlorobiphenyl (HCB) were dissolved in dimethylsulfoxide (DMSO), while 3,4,5,3',4',5'-HBB and 3,4,5,3',4',5'-HCB were dissolved in a 1:1 acetone-DMSO mixture. The final concentration of the solution in the medium was kept lower than 1 percent. This concentration of DMSO had no effect on cell survival. The chemicals were removed from dishes after 3 days and growth was continued for 1 week, until colonies had grown to sufficient size to score. Colonies were rinsed with 0.85 percent saline, fixed with 95 percent ethanol, and stained with Giemsa. The resulting colonies were scored visually.

Tumor Promoter Assay

Inhibition of metabolic cooperation, which is one of the properties of tumor promoters (Yotti et al., 1979), was measured in Chinese hamster V79 cells. Initially, wild type Chinese hamster V79 cells ($6TG^S$, HG-PRT$^+$) were seeded in 6 cm dishes at a cell density of 4×10^5 cells per dish. In each treatment group 12 dishes were used. Immediately after the plating of wild type cells, 100 6-thioguanine resistant ($6\text{-}TG^r$) cells (presumptive HG-PRT$^-$) were seeded in the same plate. After about 4 hours, the test chemical was added into a series of plates. As a positive control, 12-O-tetradecanoyl phorbol-13-acetate (TPA)(0.1 ug/ml) was added to another series of plates. Then, $6\text{-}TG^r$ (10 ug/ml) was added immediately after treatment with the chemicals. The cells were cultured with test chemicals and TPA for 3 days. After removal of the chemicals, cultures were grown in the selective medium for 4 additional days. The medium was decanted, survival colonies were fixed and stained. For each treatment group, there were 6 control dishes, each of which contained 100 $6TG^r$ cells to monitor the cytotoxicity of chemicals.

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Chemicals

Pure 2,4,5,2',4',5'-HCB and 3,4,5,3',4',5'-HCB were kindly given by Dr. James D. McKinney of the National Institute of Environmental Health Science (NIEHS) (NIEHS, Research Triangle Park, NC). Dr. Steven Aust (Michigan State University, East Lansing, MI) kindly provided purified samples of 2,4,5,2',4',5'-HBB and 3,4,5,3',4',5'-HBB. As a positive control from the promoter assay, TPA was obtained from Chemical Cancer Research Chemicals, Inc. (Brewster, NY), and dimethylsulfoxide was obtained from Fischer Scientific Co. (Fairlawn, NY).

RESULTS AND DISCUSSION

The ability of different concentrations of two purified congeners of PBB and PCB to affect the colony-forming ability of Chinese hamster V79 cells and to inhibit metabolic cooperation was measured. In Figure 1, the data clearly indicate that 3,4,5,3',4',5'-HCB is far more cytotoxic than 2,4,5,2',4',5'-HCB. This is similar to the analogous congeners of HBB (Tsushimoto et al., 1982).

In Figure 2, it is obvious that the 2,4,5,2',4',5'-HCB is able to rescue 6-TG^r cells at non-cytotoxic levels; whereas, the 3,4,5,3',4',5'-HCB is unable to do so. Again, these results with the two purified PCB congeners are similar to the analogous PBB congeners (Tsushimoto et al., 1982). It is also important to note that there seems to be a real, "no effect" or threshold level below which the 2,4,5,2', 4',5'-HCB does not inhibit intercellular communication, and above which there seems to be a quantitative dose response over the dose range tested.

To test, under identical experimental conditions, the similar effects of the 2,4,5,2',4',5'-HBB and 2,4,5,2',4',5'-HCB congeners on metabolic cooperation, the experiment in Figure 3 was performed. It can be seen that the 2,4,5,2',4',5'-HCB congener is only slightly more cytotoxic than the 2,4,5,2',4',5'-HBB congener over the dose range tested (Panel A). In Panel B, it is clear that both 2,4,5,2',4',5'-HBB and 2,4,5,2',4',5'-HCB can rescue 6-TG^r cells by inhibiting intercellular communication, confirming earlier results. Altnough the relative recovery of 6-TG^r cells for the control, TPA-treated positive control and experimental treated cells differ from experiment to experiment (possibly due to physiological differences in cells and different growth factors found in serum from experiment to experiment), the pattern is reproducible.

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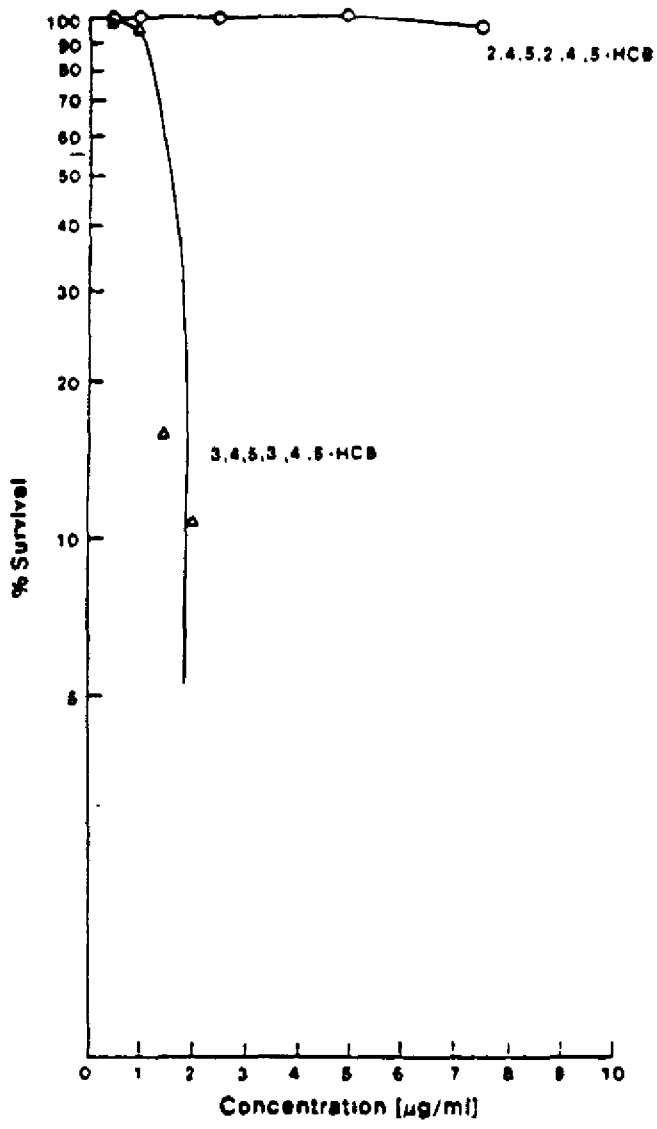

Figure 1. Dose-responsive curve for 2,4,5,2',4',5'-HCB and 3,4,5,3',4',5'-HCB on the colony-forming ability (percent survival) of Chinese hamster V79 cells.

These results, taken together with the reports in the literature, indicate that the ability of specific congeners of PCB, like those of PBB, to inhibit intercellular communication might be responsible, in part, for both their teratogenic and

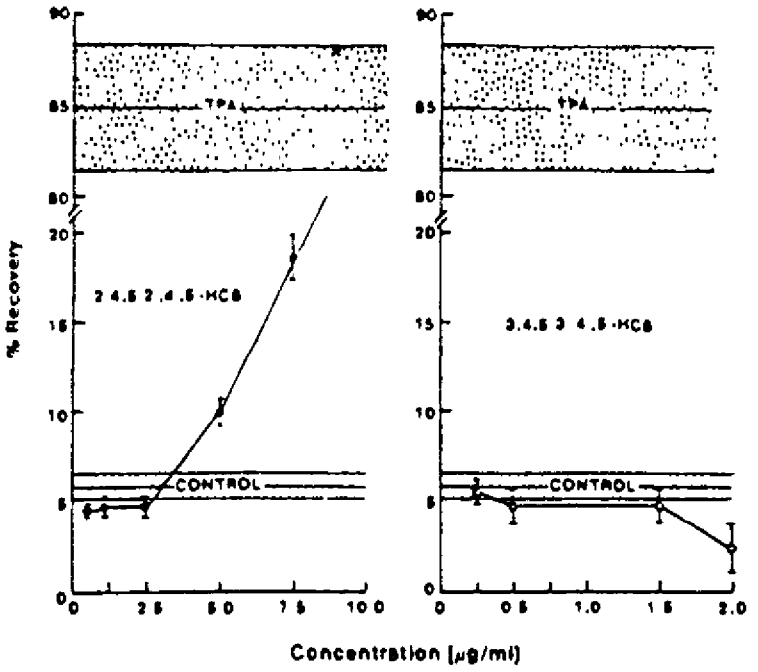

Figure 2. Dose-responsive curve for 2,4,5,2',4',5'-HCB (left panel) and 3,4,5,3',4',5'-HCB (right panel) on the inhibition of metabolic cooperation (rescue of 6-TG^r cells). Stipled area and striped areas represent negative and positive controls (solvent; TPA-treated, respectively) by their standard error of the mean (SEM).

tumor promoting activities. In the case of PCBs' ability to act as a tumor promoter, it can be speculated that by elimination of cell-cell communication at non-cytotoxic doses, the normalizing influence, suppressing the initiated cell's phenotype, is blocked. Consequently, the initiated cell might gain a selective growth advantage, allowing the clonal expansion of initiated cells, during which time additional genetic changes could occur (Yotti et al., 1979; Trosko and Chang, 1980). Once a stabilizing genetic change occurs, the cell might then be promoter-independent and have metastatic properties. The fact that certain congeners do not inhibit intercellular communication (i.e., 3,4,5,3',4',5'-HBB and 3,4,5,3',4',5'-HCB) does not necessarily rule out their potential as a tumor promoter or teratogen, since their cytotoxic natures might contribute to compensatory hyperplasia, which is correlated

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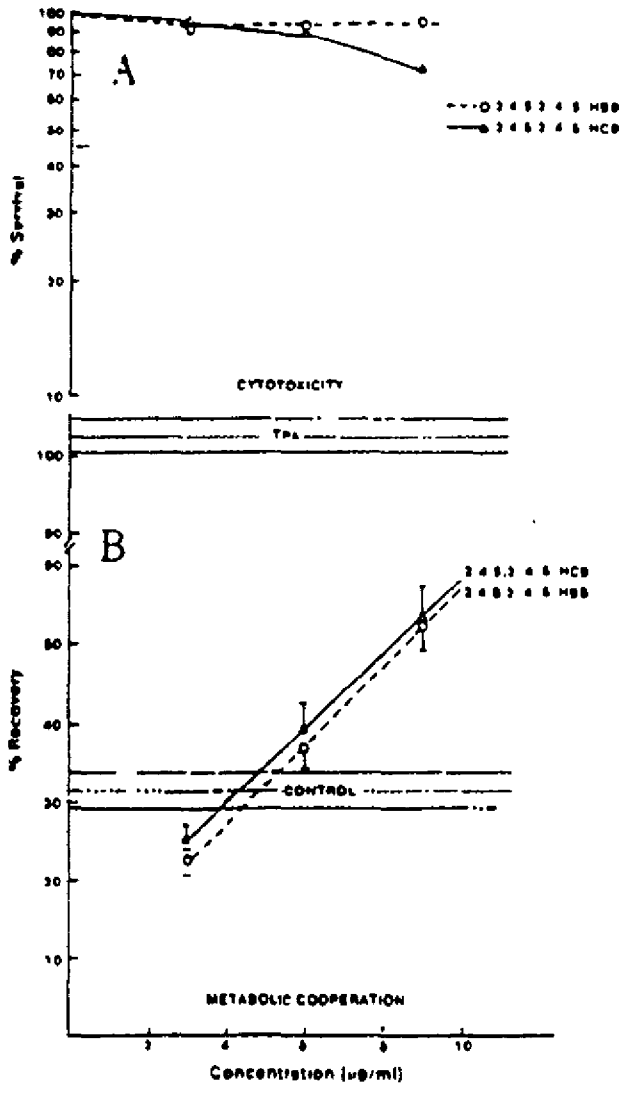

Figure 3. Dose-responsive curve for 2,4,5,2',4',5'-HBB and 2,4,5,2',4',5'-HCB on the inhibition of metabolic cooperation. Stipled area and striped areas are as described in Figure 2.

with tumor promoters (Frei, 1976; Trosko and Chang, 1980), and to the elimination of critical stem cells needed for development (Wilson, 1977), respectively.

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CHAPTER 19

EFFECTS OF POLYCHLORINATED BIPHENYLS ON THE EXPRESSION OF EMBRYOTOXICITY CAUSED BY MODEL TERATOGENS

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INTRODUCTION

Although polychlorinated biphenyls (PCBs) were produced in large quantities ever since the 1930s, it was not until a major accident of human poisoning occurred in Japan in 1968 (Yusho disease) that substantial interest in their toxicity was aroused. There were a number of accidental food contaminations discovered and reported in the United States in 1971. Thus, PCBs also became very much a national concern. The rapid generation of new information concerning the chemistry and toxicology of these compounds is witnessed by the large number of scientific publications and comprehensive review articles published during the 1970s (see, for example, Fishbein, 1974; Kimbrough et al., 1976; Matthews et al., 1976; Report, 1976).

In spite of the total production ban in this country, the persistence of PCBs in the environment and their concentration in the biological food chain has caused much concern and indeed is the stimulus for this gathering and scientific discussion on the issue of PCBs in the Great Lakes Region of North America and the toxicological importance of the contamination.

The acute mammalian toxicity of PCBs can be classified as slightly toxic to practically nontoxic (Kimbrough et al., 1978).

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Remarkable species differences are well documented. Much more important than the acute effects are the subacute and chronic toxicities of PCBs. In this mode of exposure, the species sensitivities differ drastically. Notable are the high susceptibilities of mink (Aulerich et al., 1973) and of subhuman primates (Barsotti et al., 1976; McConnell et al., 1979). The visible symptoms in monkeys corresponded to the typical signs of PCB intoxication which have also been reported in accidental human exposure such as the Yusho incident or mishaps in industrial production plants. However, the issue of high primate sensitivity is confounded by the fact that Aroclor 1248 and 1254 were involved, and that PCBs with lower degrees of chlorination have different and higher toxicity than those with higher degrees of chlorination.

The PCBs have been investigated thoroughly in a variety of species in order to assess their reproductive and prenatal toxicology. Many of these studies used the commercial PCB mixtures which cause our environmental contamination problems. Most prominently the chromatographic pattern of samples collected from man and his environment resembles closest the chromatograms obtained with authentic Aroclor 1254 (Report, 1976). Typically, embryotoxicity studies followed the standard protocols for teratology screening. Most of these evaluations led to the conclusion that PCBs have low potential to cause gross deviation in morphologic development (=terata), yet dysmorphogenesis has been reported (e.g., Watanabe and Sugahara, 1981) with mixtures and pure congeners (Lucier et al., 1978; Marks et al., 1981). In the modern terminology of research in prenatal toxicology, teratogenicity is only one very obvious form of the manifestation of embryotoxicity. Experimental designs to unmask much more subtle effects brought about by prenatal exposure to PCBs have already revealed definitive subtle neurotoxic sequelae which were unmasked by behavioral testing (Tilson et al., 1979). Furthermore, immunotoxic consequences have been reported (Loose et al., 1979).

The intent of the experiments which will be described in this contribution to the symposium was not to reassess the teratogenicity of PCBs. Rather the concept to be tested in the first phase of a study that is much more comprehensive was that of embryotoxic interactions between PCBs as the primary chemical insult to embryonal tissues followed by a well established model teratogen as the secondary chemical insult. The measurements pursue the hypothesis advanced by a number of investigators that in the large category (65-70%) of human embryopathies of unknown etiology many cases may eventually become explainable as being due to interactions and combinations of two or more factors. There is considerable concern over the potential relationship between chemical exposure at low levels from multiple

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sources and the effects that this may have on the manifestation of embryotoxicity.

Among the objectives of the experimental design was to deliberately select PCB exposure levels which were or were not expected to be sufficient to induce the metabolism of endogenous and exogenous chemicals. The induction or lack thereof was then to be correlated with the outcome of a second embryotoxic insult inflicted by either one of two model teratogens which differ fundamentally in their need for and mode of bioactivation to unfold their embryotoxic effects.

MATERIALS AND METHODS

We selected 1, 10, and 100 mg/kg[1] of Aroclor 1254 as an additive to ground mouse chow fed ad libitum to female ICR Swiss mice HAP: Swiss (ICR) Br; Harlan Industries, Indianapolis, Indiana . The batch of Aroclor 1254 had been thoroughly analyzed in the Pesticide Research Center of Michigan State University by GC/MS and was found to be free of contaminants such as dibenzofurans and dibenzo-p-dioxins which have often confounded previous PCB related research. Compared to other studies involving laboratory rodents, the exposure levels chosen may be considered low to moderate. When calculated on the basis of estimated daily food consumption, the dosage would be no higher than 15 to 20 mg PCB/kg at the highest 100 mg/kg diet level.

The treatment scheme differentiated between acute PCB ingestion which was started on day 6 of gestation (vaginal plug day = day 0) and chronic PCB intake. In the latter design, 30 day old female mice were put on the PCB diets for 90 days prior to mating. The PCB exposure was maintained throughout gestation in both situations. The two modes of PCB treatment were chosen with the desire to separate the effects of enzyme induction and the resultant metabolic consequences from more direct effects that PCBs might have on rapidly differentiating embryonal tissues. In the acutely exposed pregnant mice, significant liver enzyme induction by 1 and 10 mg/kg PCB was not expected after 5 days of ingestion when the exposure to the second chemical insult occurred. Common to both acute and chronic PCB ingestion was that on day 11 of gestation (260-265 hr after successful mating) the animals received a single intraperitoneal injection of the model teratogen. One of the drugs is

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[1]mg/kg in the animal's diet is not equivalent to mg/kg in the animal.

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cyclophosphamide (CPA) and the other 5-fluorodeoxyuridine (FUdR). These compounds were chosen because CPA in mice and other typical laboratory animal models relies exclusively on bioactivation in the maternal liver by a cytochrome P-450 mediated reaction to 4-hydroxycylophosphamide (4-OH-CPA). Further conversion occurs to a stable alkylating phosphoramide mustard (Mirkes et al., 1981). This metabolite is stable enough that it can be transferred across the placenta and exert its effect on the embryo, which cannot perform cytochrome P-450 dependent drug oxidation reactions. By contrast, FUdR can be readily activated in the embryo. These distinctive features of the model drugs are witnessed by the fact that CPA is inactive in vitro in both whole embryo (Fantel et al., 1979) as well as limb bud cultures (Manson and Smith, 1977; Barrach et al., 1978), but causes teratogenic effects similar to those induced at comparable stages of development in vivo when a bioactivation system is added to the culture (Fantel et al., 1979; Mirkes et al., 1981) or when 4-OH-CPA is used directly in limb bud cultures (Barrach et al., 1978). The pyrimidine analogue FUdR, on the other hand, is converted by embryonal tissues to 5-fluorodeoxyuridine monophosphate (FdUMP) which blocks thymidilate synthetase and thus DNA synthesis (Myers, 1981). A characteristic of both drugs is also that many of the teratogenic effects are expressed in deviant development of the limbs and the paw (Gibson and Becker, 1968a; Knudsen and Kochhar, 1981). This appeared to be advantageous as regards the ease of evaluation of the drug's effects and for later in vitro correlations with cultured limb buds. Since both enhancement or attenuation of teratogenicity were among the possible interactions between PCBs and the model compounds, we had to first define two doses of each drug that would cause (a) an effect clearly distinguishable from background events in untreated controls and (b) a teratogenic response in most of the positive control animals with a minimum degree of embryotoxicity or embryolethality.

The data obtained during the course of the investigation were analyzed by Dunnett's t-test and by one-way analysis of variance.

RESULTS AND DISCUSSION

First, the observations with CPA will be discussed. In teratogenesis research this compound has received considerable attention over the past two decades, but only recently has a clearer picture emerged linking CPA bioactivation to teratogenesis (see above citations) and mutagenesis as well as teratogenesis (Hales, 1981a, 1981b). Throughout the course of this

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study repeat blocks of control animals were used concomitantly with the particular single drug or drug combination group. At different times the various control group fetuses had differing weights on day 18. In order not to complicate the comprehensive tabular presentation of the results, these differences were not reported in the tables, but they were accounted for only in the statistical evaluations. While none of the PCBs alone either in the acute or in the chronic exposure mode caused any signs of dysmorphogenesis compared to control fetuses (Table 1), 10 mg CPA/kg caused visible malformations in 21.6 percent of the live fetuses. There was no increase in embryonal losses at this dose and only a modest reduction in body weights on day 18 of fetal development. The second and higher dose of 16 mg CPA/kg did not increase embryolethality, but drastically raised the percentage of malformed surviving fetuses to 93.4 percent, while at the same time reducing the fetal weights significantly. This was a clear sign of general embryotoxicity for which fetal weight is a very sensitive indicator.

The emphasis in the morphologic evaluation was put on an assessment of limb and paw development. Bone length measurements were performed on about two-thirds of the live fetuses since bone development has previously been shown to be very sensitive to the effects of CPA (Gibson and Becker, 1968a). Combination of PCBs with CPA brought about a variety of alterations in the expression of embryotoxicity. The fetal weights were reduced by all combinations of 10 mg CPA with PCBs compared to either chemical alone. However, the percentage of malformed live fetuses was attenuated at 1 and 10 mg/kg PCBs, while it remained unchanged at 20.6 percent with 100 mg/kg (Table 1). When paw development was assessed in particular, a strikingly similar effect was observed (Table 2). At both 10 mg CPA/1 mg/kg PCBs and 10 mg CPA/10 mg/kg PCBs, the incidence of paw malformations was reduced, while there was no sigificant change at 10 mg CPA/100 mg/kg PCBs with 16.5 percent occurrence compared to 21.6 percent observed at 10 mg CPA/10 mg/kg PCBs.

In the higher CPA dose group of the acutely PCBs exposed animals, there was a peculiar effect in the combination of 16 mg CPA/10 mg/kg PCBs which was also encountered with the higher FUdR dose (see below). This combination led to the most severe weight reductions among the day 18 fetuses. Coincident with this expression of embryotoxicity was that the 16 mg CPA/10 mg/kg PCBs acute fetuses were almost all malformed (94.8%; Table 1) just as in the positive control of 16 mg CPA where the incidence frequency was 93.4 percent. By contrast, fetal weights of 16 mg CPA/1 mg/kg PCBs and 16 mg CPA/100 mg/kg PCBs under the acute PCB ingestion design were indistinguishable from each other and somewhat higher than those observed after

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TABLE 1

Effects of Acute PCB Ingestion on the Response of Mouse Embryos Treated on Day 11 With Cyclophosphamide (CPA)

Treatment			Dead or Resorbed		Malformed		
CPA (mg/kg)	PCBs (mg/kg)	Number of Litters	Total Number	Percent	Total Number	Percent	Fetal Wt. (g) Mean±S.E.M.
0	0	14	5/173	2.9	0/168	0	1.31±0.02
0	1	8	0/81	0	0/81	0	1.19±0.03
0	10	3	1/33	3.0	0/32	0	1.17±0.03
0	100	4	1/40	2.5	0/39	0	1.19±0.03
10	0	11	6/140	4.3	29/134	21.6	1.15±0.01
10	1	10	9/116	7.8	6/107	5.6	1.11±0.01
10	10	6	10/84	11.9	6/74	8.1	1.02±0.02
10	100	9	2/100	2.0	20/97	20.6	1.05±0.02
16	0	19	12/223	5.4	197/211	93.4	0.89±0.02
16	1	8	11/98	11.2	37/87	42.5	0.93±0.02
16	10	6	8/85	9.4	73/77	94.8	0.85±0.01
16	100	10	3/115	2.6	64/112	57.1	0.97±0.01

Pregnant animals consumed a diet containing the amount of PCBs indicated beginning from day 6 of gestation. On day 11 the mice received an intraperitoneal injection of CPA. Fetuses were obtained on day 18.

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TABLE 2

Effects of Acute PCB Ingestion on Paw Development of Mouse Embryos Treated on Day 11 With Cyclophosphamide (CPA)

Treatment				Percent of Fetuses Affected						
				Malformed	Paw Development		Syndactyly		Ectrodactyly	
CPA (mg/kg)	PCBs (mg/kg)	Number of Litters	Live	Percent	Total Number	Percent	Fore	Hind	Fore	Hind
0	0	14	168	0	0/168	0	0	0	0	0
10	0	11	134	21.6	29/134	21.6	9.7	6.0	3.7	9.7
10	1	10	107	5.6	3/107	2.8	0	0.9	0	0
10	10	6	74	8.1	5/74	6.8	1.4	0	0	0
10	100	9	97	20.6	16/97	16.5	8.2	9.3	1.0	2.1
16	0	19	211	87.2	192/211	91.0	64.9	50.7	2.8	16.1
16	1	8	87	42.5	37/87	42.5	10.3	11.5	20.7	16.1
16	10	6	77	94.8	76/77	98.7	23.4	46.8	15.6	66.2
16	100	10	112	57.1	64/112	57.1	8.0	28.6	25.0	39.3

Pregnant animals consumed a diet containing the amount of PCBs indicated beginning from day 6 of gestation. On day 11 the mice received a single intraperitoneal injection of CPA. Fetuses were obtained on day 18.

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16 mg CPA alone. This trend was particularly noticeable at 16 mg CPA/100 mg/kg PCBs (0.97 g vs. 0.89 g; Table 1). At the same time, the CPA combination with both 1 and 100 mg/kg PCBs reduced the percentage of malformed fetuses (Table 1) and the rate of incidence of paw malformations (Table 2).

Upon closer analysis of the paws, there were numerous alterations detectable in the manifestation of teratogenic effects brought about by CPA/acute PCBs. For example, the frequency of occurrence of syndactyly of the forelimb was reduced at 10 mg CPA/1 mg/kg PCBs as well as 10 mg/kg PCBs and at all three PCB levels at 16 mg CPA (Table 2). Ectrodactyly of the forelimb and hindlimb were markedly increased at 16 mg CPA and all PCB levels in the forelimbs as well as at 10 and 100 mg/kg PCBs in the hindlimbs.

In the chronic PCB animals, the percentage of malformed fetuses was lower at all three PCB exposure levels when 10 mg CPA/kg was given. However, at 16 mg/kg there was attenuation by PCBs only at the 100 mg/kg dose (Table 3). This effect was also reflected in the significantly higher mean fetal body weight determined among the 16 mg CPA/100 mg/kg PCB fetuses.

The examination of paw development reflected these interactions very clearly (Table 4). Syndactyly incidence was reduced in both forepaws and hindpaws at 10 mg CPA and all PCB levels. Notable was again the interaction between the higher CPA dose of 16 mg/kg and 10 mg/kg PCBs which enhanced the frequency of syndactyly and ectrodactyly in forelimbs (Table 4).

As regards the measurements of bone lengths, some of the results could be anticipated on the basis of fetal weights. Thus, while 10 mg CPA alone caused little decrease in the fetal weights (Table 1) and was without significant effect on humerus, radius, ulna, femur, tibia, and fibula length, the higher dose of 16 mg CPA caused a substantial fetal weight reduction and concomitantly a significant reduction in length of all these long bones in the forelimbs and hindlimbs (Figure 1). Upon combination with various PCB levels, the 10 mg CPA dose both in acute (data not shown) and chronic animals (Figures 2 and 3) brought about bone length reductions in all long bones at all PCB levels. However, in the combined exposure the correlation of fetal weights to bone lengths was not as obvious as with CPA alone (compare Table 1 and Figure 1). In the forelimbs of acute PCB animals, the combination of 16 mg CPA with 10 mg/kg PCBs caused the largest reductions in all long bones of both forelimbs and hindlimbs, while this effect was attenuated at 100 mg/kg PCBs. Very similar observations were made in the off-spring of mice that were on the chronic PCB regimen (Figures 2 and 3). Overall, there appeared to be a

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TABLE 3

Effects of Chronic PCB Ingestion on the Response of Mouse Embryos Treated on Day 11 With Cyclophosphamide (CPA)

Treatment			Dead or Resorbed		Malformed		
CPA (mg/kg)	PCBs (mg/kg)	Number of Litters	Total Number	Percent	Total Number	Percent	Fetal Wt. (g) Mean±S.E.M.
0	0	13	8/153	5.2	0/145	0	1.29±0.02
0	1	4	0/41	0	0/41	0	1.19±0.01
0	10	3	1/33	3.0	0/32	0	1.17±0.03
0	100	4	1/40	2.5	0/39	0	1.19±0.03
10	0	11	6/140	4.3	29/134	21.6	1.15±0.01
10	1	8	11/94	11.7	7/83	8.4	1.07±0.10
10	10	8	4/91	4.3	9/87	10.3	1.06±0.13
10	100	11	8/120	6.6	10/112	8.9	0.99±0.14
16	0	19	12/223	5.4	197/211	93.4	0.89±0.02
16	1	9	10/90	11.1	79/80	98.8	0.83±0.14
16	10	8	15/99	15.1	84/84	100.0	0.84±0.10
16	100	9	6/98	6.1	49/92	53.3	0.97±0.13

Mice had consumed 0, 1, 10, and 100 mg/kg PCBs in their diet for at least 90 days prior to breeding and continuing throughout gestation. On day 11 of pregnancy, CPA was injected intraperitoneally and fetuses were obtained on day 18.

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TABLE 4

Effects of Chronic PCB Ingestion on Paw Development of Mouse Embryos Treated on Day 11 With Cyclophosphamide (CPA)

Treatment				Percent of Fetuses Affected						
				Malformed	Paw Development		Syndactyly		Ectrodactyly	
CPA (mg/kg)	PCBs (mg/kg)	Number of Litters	Live	Percent	Total Number	Percent	Fore	Hind	Fore	Hind
0	0	13	145	0	0/145	0	0	0	0	0
10	0	11	134	21.6	29/134	21.6	9.7	6.0	3.7	9.7
10	1	19	83	7.1	192/211	91.0	1.2	0	0	0
10	10	8	87	10.3	7/83	8.4	3.4	3.4	1.1	1.1
10	100	8	112	8.9	6/87	6.9	3.6	0.9	0	0
16	0	11	211	87.2	8/112	7.1	64.9	50.7	2.8	16.1
16	1	9	80	98.8	79/80	98.8	11.3	45.0	36.3	80.0
16	10	6	84	100.0	84/84	100.0	49.2	56.0	72.6	90.5
16	100	9	92	53.3	48/92	52.2	16.3	25.0	22.8	22.8

Mice had consumed a diet containing the amounts of PCBs specified for 90 days prior to breeding and continuing throughout gestation. On day 11 of pregnancy, the animals received a single intraperitoneal injection of CPA. Fetuses were obtained on day 18.

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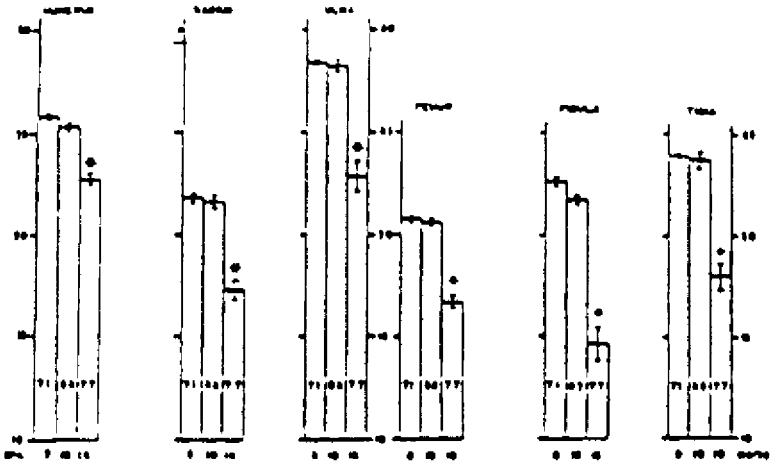

Figure 1. Effects of cyclophosphamide (CPA) on bone length of fetal limbs in mice. On day 11 of gestation, animals received a single intraperitoneal injection of CPA at the dose specified. Fetuses were obtained on day 18. The results on the ordinate are recorded in reticle units, and one unit corresponds to 0.1 mm. Values shown represent mean ± S.E. derived from examining the number of fetuses indicated in the bars. Asterisks denote significant differences from control ($p < 0.05$).

tandency that chronic PCB exposure caused slightly more bone length reduction than the acute PCB intake did.

The results obtained in our present experiments have some resemblance to those obtained by Gibson and Becker (1968b) in the Swiss-Webster strain of mice. They used phenobarbital as a pure inducer of cytochrome P-450 and enzyme reactions coupled to this hemoprotein although the effects of the drug were not quantitated. We have correlated our observations to measurements of cytochrome P-450 content and selected xenobiotic metabolizing enzymes in microsomes prepared from livers of the pregnant mice. The cytochrome content was significantly elevated only at the 100 mg/kg PCB exposure level, both acute and chronic. Aminopyrine demathylation was used as a prototype reaction coupled to P-450 as the terminal oxidase. The reaction was significantly enhanced at 10 mg/kg PCB chronic as well as at 100 mg/kg acute and chronic. Arylhydrocarbon hydroxylase

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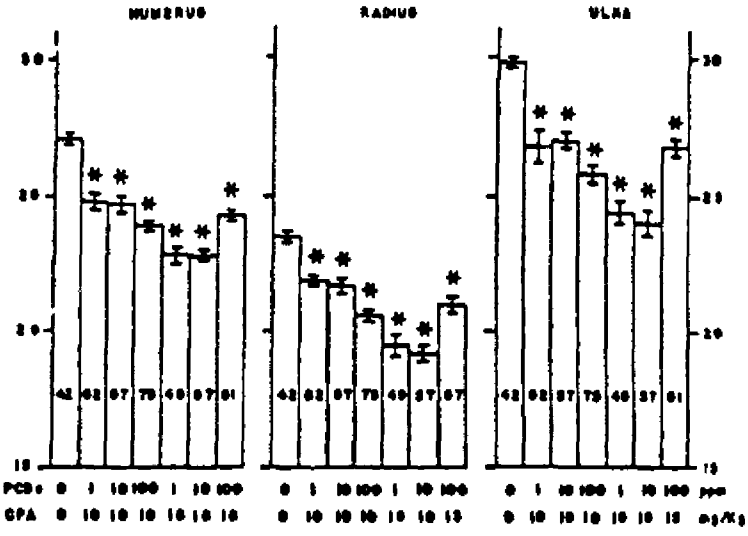

Figure 2. Effects of chronic PCBs in combination with cyclophosphamide (CPA) on bone length of fetal forelimbs in mice. Animals had consumed the doses of PCBs indicated on the abscissa in their diet for at least 90 days prior to breeding and continuing throughout gestation. On day 11 of pregnancy, mice received a single intraperitoneal injection of CPA. Other details as in Figure 1.

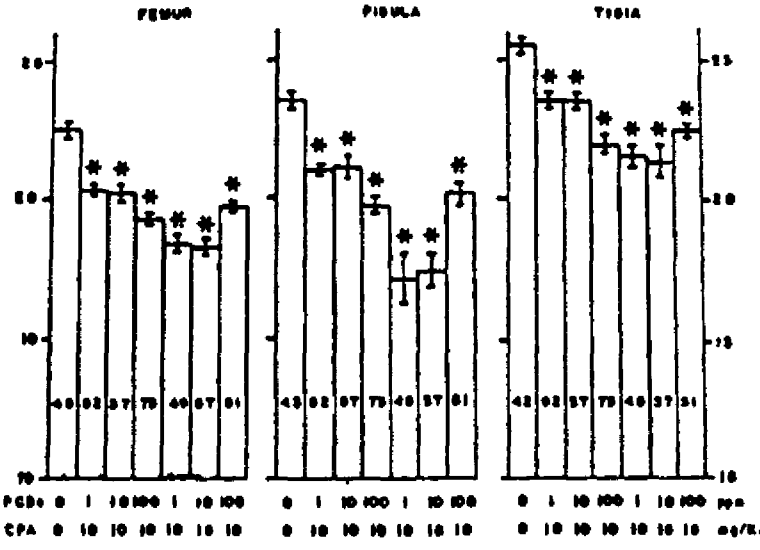

Figure 3. Effects of chronic PCBs in combination with cyclophosphamide (CPA) on bone length of fetal hindlimbs in mice. Experimental details are as in Figures 1 and 2.

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and ethoxyresorufin-o-deethylase activity were also measured. Although both reactions are coupled to cytochrome P-450 and thus probably not relevant to CPA bioactivation, these enzyme activities were measured to obtain a more complete picture of the induction pattern brought about by the PCBs. At 100 mg/kg PCB which caused significant induction of aminopyrine demethylation after acute and chronic ingestion, the teratogenicity of the 16 mg CPA dose was markedly reduced in the present observations. This conclusion agrees with the findings of Gibson and Becker (1968b), who described reduced teratogenicity caused by 20 mg CPA/kg after induction of the pregnant mice with phenobarbital. These investigators correlated their measurements with the appearance of alkylating activity in the plasma of mice which was elevated as judged by more alkylation of the indicator dye nitrobenzyl pyridine. The outcome of experiments similar in design performed in the rat were entirely different as the recent publications by Hales (1981a, 1981b) have shown. In that species it was demonstrated quite convincingly that phenobarbital pretreatment led to enhanced activation of CPA to mutagenic molecular forms and that the *in vivo* teratogenic effect of CPA was markedly increased. If more alkylating metabolites are formed by the stimulation of P-450 coupled monooxygenase activity which hydroxylates CPA to 4-OH-CPA, and if the accumulated evidence unequivocally shows that this reaction is the prerequisite for biological activity (Mirkes *et al.*, 1981), then it is not unreasonable to anticipate that teratogenicity should be increased. The observations revealing that the opposite was happening in the mouse led Becker and his associates about a decade ago (when much less was known about CPA metabolism than now) to study the binding of radioactive CPA and its then still unidentified metabolites to macromolecules of the maternal liver and of the mouse embryo (Murthy *et al.*, 1973). It was found that pretreatment with phenobarbital decreased binding to embryonal DNA without affecting RNA or embryonal protein binding. On the other hand, more radioactivity derived from CPA was associated with maternal liver proteins.

In the meantime, the bioactivation of CPA has been elucidated in much more detail. We have initiated experiments which are aimed at defining the basis for the interactions between PCBs and CPA regarding embryotoxicity of CPA. The approach involves an examination of the pharmacokinetics of ^{14}C-CPA, binding to maternal and embryonal macromolecules as well as an *in vivo-in vitro* correlation. For the latter experiments, limb buds from embryos exposed to PCBs *in utero* will be used in organ culture. The activated metabolite 4-OH-CPA at accurately defined concentrations can then be added for very specific exposure times to the explants.

The second model teratogen, FUdR, whose interactions with PCBs were examined has not attracted anywhere as much attention by investigators in teratogenesis as it has in carcinogenesis. The malformations caused by this important therapeutic agent which is used as an antimetabolite in cancer chemotherapy (Myers, 1981) are also clearly reflected in deviant paw and limb development (Knudsen and Kochhar, 1981). After a dose of 7.5 mg FUdR/kg 49 percent of the live fetuses had visible malformations, while this dose caused no embryolethality or significant fetal weight reduction on day 18 of gestation (Table 5). The higher dose of 20 mg FUdR/kg increased the percentage of live, malformed fetuses to 99 percent, while at the same time producing only a very modest increase in embryolethality (Table 5). Combination of 7.5 mg FUdR with each of the 3 PCB acute dietary exposure levels almost doubled the percentage of malformed fetuses, but had no such clear-cut effect in chronic PCB mice (data not shown). This increase was reflected almost exclusively by a rise in the frequency of paw malformations (Table 6). When the development of the phalanges was examined more closely, a number of changes was noted in the expression of malformations by FUdR alone or in combination with the PCBs. Examples are that snydactyly in hindlimbs of all live fetuses was increased from 7.7 percent at 7.5 mg FUdR alone to 44.4 percent at 7.5 mg FUdR/100 mg/kg PCBs acute, but not chronic (data not shown). Also, ectrodactyly occurrence in forelimbs of acute PCBs fetuses was markedly increased from the positive control level where it was 6.2 percent at the 7.5 mg FUdR/kg dose. At both doses of FUdR, polydactyly in the hindlimb occurred more frequently among those embryos/fetuses that had been acutely exposed to PCBs.

TABLE 5

The measurements of bone length revealed a number of interactive effects with PCBs and showed the most noteworthy differences between acute and chronic PCB ingestion that were observed in the entire study of bone development. The model teratogen alone caused small, but significant, reductions at both 7.5 and 20 mg FUdR/kg in the length of humerus, radius, and ulna, while in the hindlimb only the higher dose led to shortened long bones including femur, fibula, and tibia (Figure 4). The magnitude of this effect in the hindlimb appeared to be unrelated to the rather modest weight reduction observed in the fetuses of this dose group (Table 5). When the pregnant mice were acutely exposed to PCBs, then the most conspicuous effect was noted in the combination of 20 mg FUdR with 10 mg/kg PCBs (Figure 5). It was pointed out during the description of the effects of CPA that there was a particularly pronounced effect by combining 16 mg CPA with 10 mg/kg PCBs on an acute basis. Here a similar phenomenon occurred with FUdR. The fetal weights in this group were reduced further than those measured

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TABLE 5

Effects of Acute PCB Ingestion on the Response of Fetuses Treated on Day 11 With 5-Fluorodeoxyuridine (FUdR)

Treatment		Number of Litters	Dead or Resorbed		Malformed		Fetal Wt. (g) Mean±S.E.M.
FUdR (mg/kg)	PCBs (mg/kg)		Total Number	Percent	Total Number	Percent	
0	0	9	3/104	2.9	0/104	0	1.21±0.03
0	1	4	0/41	0	0/41	0	1.19±0.03
0	10	3	1/32	3.1	0/32	0	1.17±0.03
0	100	4	1/39	2.6	0/39	0	1.19±0.03
7.5	0	5	1/65	1.5	31/64	49.2	1.16±0.03
7.5	1	5	4/52	7.7	43/48	89.6	1.14±0.02
7.5	10	5	8/65	12.3	51/59	86.4	1.04±0.02
7.5	100	5	3/57	5.3	45/54	83.3	1.12±0.03
20.0	0	6	5/72	6.9	66/67	98.6	1.15±0.03
20.0	1	6	5/77	6.5	71/72	98.6	0.99±0.01
20.0	10	6	5/84	6.0	75/79	94.9	0.86±0.01
20.0	100	8	12/83	14.5	69/71	97.2	0.99±0.02

Pregnant animals consumed a diet containing the amount of PCB indicated beginning from day 6 of gestation. On day 11 the mice received an intraperitoneal injection of FUdR. Fetuses were obtained onday 18.

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TABLE 6

Effects of 5-Fluorodeoxyuridine (FUdR) Alone and of FUdR Plus Acute PCBs on Paw Development in Mouse Fetuses

Treatment				Percent of Fetuses Affected								
				Malformed	Paw Development		Syndactyly		Ectrodactyly		Polydactyly	
FUdR (mg/kg)	PCBs (mg/kg)	Number of Litters	Live	Percent	Total Number	Percent	Fore	Hind	Fore	Hind	Fore	Hind
0	0	9	33	0	0/104	0	0	0	0	0	0	0
7.5	0	5	65	49.2	32/65	49.2	12.3	7.7	6.2	33.8	1.5	1.5
7.5	1	5	73	98.6	71/72	98.6	18.0	13.1	82.0	34.4	1.6	6.6
7.5	10	5	48	89.6	42/48	87.5	37.2	16.3	39.5	58.1	0	14.0
7.5	100	5	54	83.3	51/59	86.4	26.7	44.4	53.3	42.2	4.4	11.1
20.0	0	6	67	98.5	45/54	83.3	48.6	38.9	29.2	61.1	1.3	18.1
20.0	1	6	72	98.6	71/72	98.6	40.8	46.5	57.8	47.9	1.4	39.4
20.0	10	6	79	94.6	75/79	94.6	50.7	40.0	48.0	3.3	1.3	44.0
20.0	100	8	71	97.2	69/71	97.2	44.9	47.8	31.9	49.3	1.5	36.2

Pregnant animals consumed a diet containing the amount of PCBs indicated beginning from day 6 of gestation. On day 11 the mice received a single intraperitoneal injection of FUdR. Fetuses were obtained on day 18.

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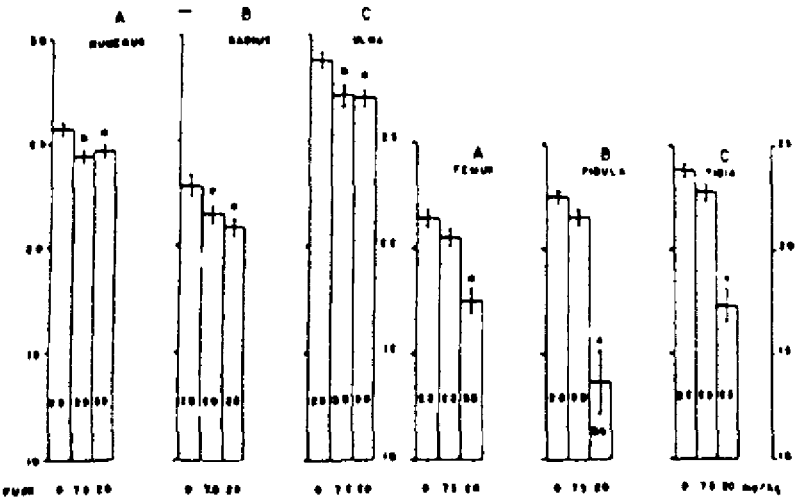

Figure 4. Effects of 5-fluorodeoxyuridine (FUdR) on bone length of fetal limbs in mice. All details are as in Figure 1, except that pregnant mice received a single intraperitoneal injection of FUdR.

in 1 or 100 mg/kg PCB exposed fetuses (Table 5). This observation was reflected in the reduction of bone length not only in the forelimb but also in hindlimbs (Figure 6). Furthermore, in hindlimbs of acutely PCB exposed fetuses, the reduction of femur, fibula, and tibia length resulting from 7.5 mg FUdR/kg became significant when PCBs were ingested acutely at 10 and 100 mg/kg (Figure 6).

In striking contrast were the observations made when PCB intake was chronic. The effects of both 7.5 and 20 mg FUdR on radius and ulna were completely reversed while they persisted in the humerus (Figure 7). Similar results were obtained in hindlimbs (Figure 8). The drastic reductions in length caused by 20 mg FUdR in femur, fibula, and tibia were attenuated to control fetus length by the combination with chronic PCBs at each of the 3 dietary intake levels (Figure 8). Thus, the differences between acute and chronic PCBs in the results obtained with the two model teratogens regarding bone development is remarkable. Among the CPA treated mouse fetuses, chronic PCBs did not affect the bone length reductions, while many of the effects of FUdR were completely eliminated by PCBs.

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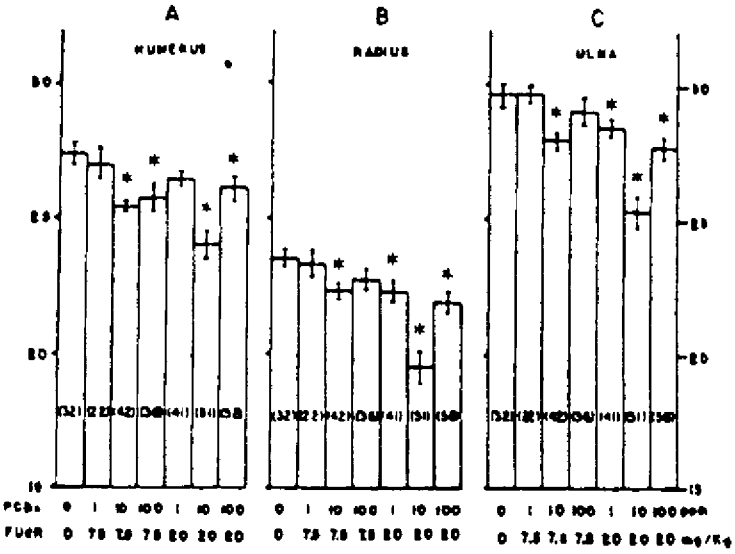

Figure 5. Effects of acute PCBs in combination with 5-fluorodeoxyuridine (FUdR) on bone length of fetal forelimbs in mice. Animals consumed a diet containing the amount of PCBs indicated on the abscissa beginning from day 6 of gestation. On day 11, the mice received a single intraperitoneal injecton of FUdR. Fetus procurement and examination details are as in Figure 1.

There is no plausible explanation yet for the multitude of interactions described in this communication between CPA or FUdR and PCBs. We have established that CPA as the prototype of a drug dependent exclusively on maternal liver activation in the mouse by a cytochrome P-450 dependent monooxygenase reaction shows markedly altered teratogenicity when combined with PCBs. However, it appears that bioactivation cannot be the only explanation for the observations presented. This conclusion is based on the fact that the bioactivation of FUdR by thymidine kinase to FdUMP is not coupled to cytochrome P-450 or P-448. We have just embarked on experiments to study the pharmacokinetics and placental transfer of ^{3}H-FUdR in control and PCB exposed mice. Part of these measurements will include ion exchange chromatography to differentiate between ^{3}H-FUdR and ^{3}H-FdUMP in mouse embryos. One may then become able to estimate whether PCBs alter the distribution ratio between parent compound FUdR and the bioactive inhibitor of thymidilate synthetase. Another approach in the desire to elucidate the basis for the alteration in expression of teratogenicity of FUdR by

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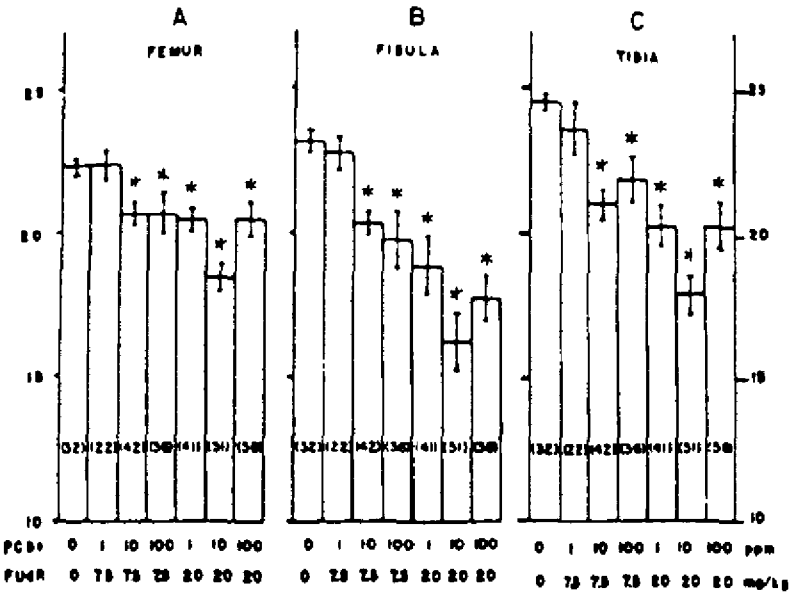

Figure 6. Effects of acute PCBs in combination with 5-fluorodeoxyuridine (FUdR) on bone length of fetal hindlimbs in mice. Other details as in Figure 5.

the PCBs will involve limb bud culture. Limb buds from PCB exposed embryos are to be exposed to FUdR in vitro in order to measure whether PCBs have altered the embryonal tissue responsiveness to FUdR. We hope that by a combination of the in vivo results described here with the in vitro studies to be performed on isolated, PCB pretreated embryonal tissues a better understanding will be obtained for why the observed in vivo changes occurred.

ACKNOWLEDGMENTS

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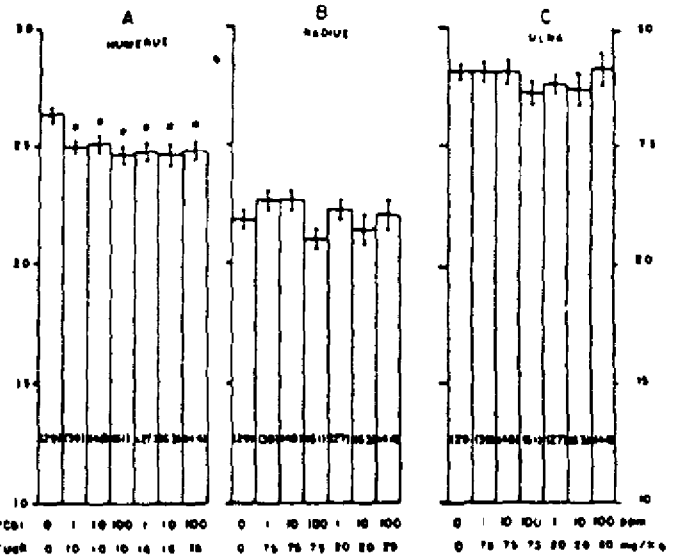

Figure 7. Effects of chronic PCBs in combination with 5-fluorodeoxyuridine on bone length of fetal forelimbs in mice. Other details as in Figures 1 and 2.

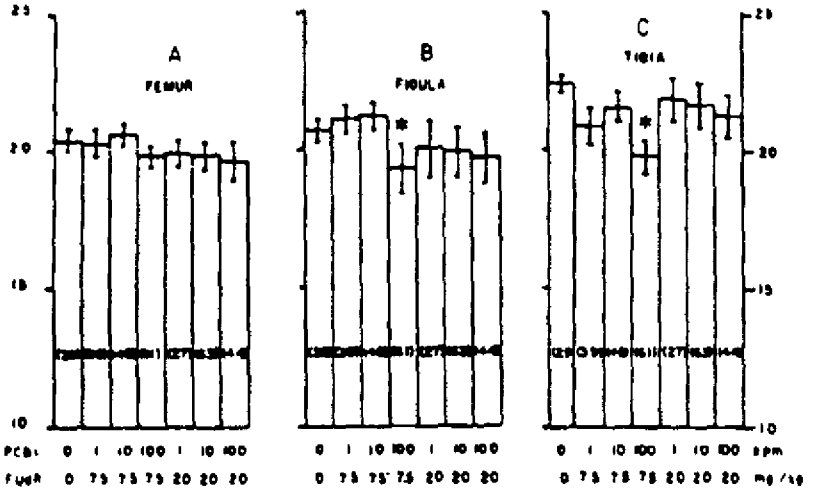

Figure 8. Effects of chronic PCBs in combination with 5-fluorodeoxyuridine on bone length of fetal hindlimbs of mice. Other details as in Figures 1 and 2.

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PART IV

THE EFFECTS OF PCBs ON HUMAN HEALTH

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CHAPTER 20

THE EPIDEMIOLOGY OF PCBs

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INTRODUCTION

This is a review and evaluation of the epidemiologic evidence concerning the health effects of exposure to polychlorinated biphenyls (PCBs), particularly at levels that do not cause acute toxic effects. A study is considered "epidemiologic evidence" if it measures, directly or indirectly, the differences in the risk of ill health among populations with different exposures to PCBs.

In the past several decades there have been many clinical studies of the effects of heavy exposures to PCBs (e.g., Von Wedel et al., 1943; Schwartz, 1936). Such studies are extremely useful in identifying the kinds of effects that should be investigated. However, they do not address the question of the risk of incurring such effects and are, therefore, not included in this review.

The studies reviewed here fall into three categories. First, there are studies of accidental heavy exposures and the resulting acute and chronic effects. In each case the study was prompted by an outbreak of illness or the occurrence of a death in an exposed population, after which the population was studied.

Second, there are studies of the relationship between exposure to PCBs and the resulting body burden of PCBs in serum or adipose tissue. Strictly speaking, these are not epidemiologic studies since they do not deal with health effects. However, if a relationship between level of exposure and body burden cannot be verified, the interpretation of epidemiologic studies becomes difficult if not impossible.

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The third category is studies that were done because the populations in question were known or suspected to be exposed to PCBs, rather than because some untoward health outcome had been observed first.

Many published reports combine some or all of these types of investigations. In the sections that follow, we consider first the studies of accidental over exposure; second, the studies of PCB exposure versus body burden; and third, the epidemiologic studies of exposed populations. In the latter section, the discussion will be organized with respect to the health effects that were investigated. These are:

(1) dermatologic symptoms,
(2) biochemical alterations,
(3) other symptoms and illnesses,
(4) carcinogenicity.

ACCIDENTAL HEAVY EXPOSURE

Two epidemiologic studies of accidental exposure have been reported. The first (Meigs et al., 1954) described an outbreak of chloracne in a plant in which a process change had introduced an unspecified PCB compound into the work environment. Breathing zone levels of PCB were stated to be 0.1 mg/m^3. Seven of 14 exposed workers developed chloracne, but liver function tests were normal in six of these, with some borderline abnormalities in the seventh. The chloracne disappeared after treatment, and the single borderline liver function abnormality improved, but did not disappear after 13 months. Improved process control prevented any recurrence.

Although the estimated PCB level must be accepted with reservation because of the state of the art at that time, it is clear that the chloracne resulted from the PCB exposure. Given the lack of controls and the small rate of abnormal liver function, it is unlikely that the PCB exposure had any connection with the liver function findings.

The second incident is the now famous Yusho incident in 1968 which has been documented in many reports (Kuratsune et al., 1972; Urabe et al., 1979) in which some thousand Japanese became ill after eating cooking oil which had been contaminated with Kanechlor 400, a PCB compound of Japanese manufacture.

The most common acute symptoms observed were hyperpigmentation and acne-like lesions, discharge from the eyes, central nervous system symptoms, and vomiting and diarrhea. There was a dose-response relationship between the amount of oil ingested

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and the proportion of persons reporting symptoms. Three years later about half the patients had improved, but still had symptoms. Six years later many patients still reported such symptoms as headache, stomach pain, numbness of the extremities, joint pain, and respiratory symptoms.

Out of ten live births to women affected by Yusho, nine showed hyperpigmentation and most had increased eye discharges. These symptoms later disappeared. Although there have been reports of premature eruption of teeth (2 children out of a series of 13) and unusally wide fontanelles and sagittal sutures (3 out of 13), it is not at all clear that these findings represent any more than the normal variation to be expected, since no control observations were made (Funatsu et al., 1972).

In general, laboratory tests of the Yusho victims showed elevated serum triglyceride levels, low serum cholesterol in serious cases, and elevated serum glutamic-oxaloacetic transaminase (SGOT) and serum glatamic-pyruvic transaminase (SGPT) levels in serious cases (Higuchi, 1976).

As of the end of 1977, fifty-one deaths among Yusho patients had been identified. The percentage of cancer deaths (35.4) exceeded that of the prefecture in which the deaths occurred (21.1). However, the figures do not appear to be very useful for several reasons. First, after the original incident, the criteria for diagnosis of Yusho had been changed, so that it is impossible to determine the denominator which produced this number. The completeness of ascertainment of the deaths is unknown. In addition, no adjustment for age appeared to have been made in the above comparison. Finally, the average elapsed time from exposure to death was less than ten years, and cannot be calculated precisely because the dates of death are not provided. This may well be too short a period for cancers resulting from the exposure to show up.

Although the Yusho incident represented a massive ingestion of PCBs, recent reanalysis of the cooking oil and of the estimated intake by the patients shows that the exposure to polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs) was about equal to the exposure to PCBs, and current determinations of PCQs in blood and other tissues of Yusho patients have shown levels similar to that of PCBs (Kimbrough, 1980). It is, therefore, doubtful whether any generalization can be made from this incident to lower level environmental or occupational exposures to PCBs.

ENVIRONMENTAL LEVELS AND BODY BURDENS

Two studies of the relationship between ingestion of PCBs and blood levels of PCBs have been reported (MDPH, 1975; Kreiss et al., 1981). In each case the study was concerned with ingestion of fish known to contain relatively high levels of PCBs. In the first, an association was found between blood PCBs and exposure level as estimated by the amount of Lake Michigan sport fish consumed. In the second, the relationship between blood PCBs and a complex of factors was examined in a population in an area with high levels of environmental contamination. Age, sex, and fish consumption, in that order of importance, were associated with blood levels of PCBs. To the extent that fish consumption measures ingestion of PCBs, these studies confirm that blood PCBs are a function of ingestion of PCBs as well as of age and sex. Other associated variables were examined in Kreiss et al. (1981) but will be discussed in the following section.

A number of studies of blood PCBs and exposure to PCBs have been made, most of them in conjunction with studies of health effects. The portions of the studies relevant to this section are reviewed here.

There are three types of studies. The first compares groups which have had different exposure levels as estimated from process considerations or environmental measurements. For convenience, such a study design will be called Type A. The second, which we will designate Type B, measures the change over time in a single group after PCBs have been removed from the environment (or after the group has left the environment). The third, Type C, compares groups that have had different durations of exposure. Often the same report will contain more than one type of study. For example, an exposed group may be compared with an unexposed group (Type A) and within the exposed group long-term exposed workers may be compared with short-term workers (Type C).

The measure of body burden has in most cases been a single number representing, depending on the study, blood PCBs, plasma PCBs, serum PCBs (all of which are called "blood" PCBs in this review), or level of PCBs in adipose tissue. Analytic methods have varied over time and among investigators. More recently, measures of body burden have sought to determine separately the levels of higher chlorinated biphenyls (5 or more chlorine atoms per molecule) and lower chlorinated biphenyls.

Table 1 lists the studies considered in this section, with the type of design and whether or not separate determinations of higher and lower chlorinated biphenyls were made. All of the studies except Baker et al. (1980) are occupational.

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TABLE 1

Studies of Environmental Levels and Body Burden of PCBs by Type of Body Burden Measure

Study	Study Type[a]	High and Low Chlorinated PCBs	Adipose PCBs
Baker et al., 1980	A	No	No
Bumgarner et al., 1973	C	No	No
Chase et al., 1982	A,C	No	Yes
Hara et al., 1974, 1975	B,C	No	No
Hasegawa et al., 1972	A,B,C	No	No
Inoue et al., 1975	A,C	No	No
Karppanen and Kolho, 1973	A	No	Yes
Kitamura et al., 1973	B	No	No
Maroni et al., 1981a	A,C	Yes	No
Ouw et al., 1976	A,B	Yes	No
Smith et al., 1982	A,C	Yes	No

[a] A = Comparisons of groups with different exposure levels
B = Evaluation of results of decreasing or removing exposure
C = Comparisons of groups with different durations of exposure

All of the Type A studies agree in showing a higher body burden of PCBs in populations with higher environmental exposure, except for one anomaly in Baker et al. (1980). There, persons exposed to sludge containing PCBs had slightly lower blood levels than the controls, on the average. However, the sludge-exposed persons and the controls were not matched for age, which Kreiss et al. (1981) showed to be the most important factor associated with blood PCB level. It, therefore, appears unequivocal that higher exposure to PCBs means a higher body burden, all other things being equal.

The Type B studies appear at first glance to be more equivocal (Table 2). Two studies show a decrease when exposure ceased or decreased and two do not. However, the studies showing no decrease remeasured their study groups within a month or two after exposure changed. The ones showing a decrease remeasured after three months and one year.

The fact that Ouw et al. (1976) found no decrease after two months while Kitamura et al. (1973) found over a 50 percent

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TABLE 2

Studies of Blood PCB Levels Before and After Exposure Levels Changed, and Interval From Exposure Change to Remeasurement

Study	Exposure Change	Interval to Remeasurement (months)	Decrease in Blood PCB Level (percent)
Hara et al., 1974, 1975	Ceased	12	ca75
Hasegawa et al., 1972	Ceased	1	None
Kitamura et al., 1973	Ceased	3	>50
Ouw et al., 1976	Decreased	2	None

decrease after three months gives rise to some uneasiness. However, in the former study exposure was decreased but still present, while in the latter study PCB use had ceased. Ouw et al. (1976) also suggest that after exposures in their study plant had decreased, workers did not wear gloves as recommended, so that the blood PCB levels may have resulted from skin contact.

Table 3 shows the findings for the Type C studies other than Maroni et al. (1981a) and Smith et al. (1982) that is, for those that compared duration of exposure with a single measurement of blood PCB level. The results are not consistent. The study of Bumgarner et al. (1973) found very low levels (average 4 ug/kg) in exposed workers, which may have accounted for their failure to find a relationship with duration. On the other hand, the exposed workers in Hasegawa et al. (1977) had an average level of 370 ug/kg and still showed no relationship with duration.

The studies of Maroni et al. (1981a) and Smith et al. (1982) suggest a possible explanation. Maroni et al. (1981a) made separate comparisons of high chlorinated PCBs and low chlorinated PCBs between workers with present and past exposures. They found differences in the low chlorinated PCBs but not in the high chlorinated compounds. Even though their analysis did not adjust for age, it suggests that the relationship between blood PCB levels and duration and recency of exposure may be a function of the level of chlorination of the PCBs. Smith et al. (1982), however, in an elaborate analysis

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TABLE 3

Studies of PCB Levels by Duration of Exposure

Study	Relationship of Blood PCB to		
	Duration of Exposure	Age	Race
Bumgarner et al., 1973	No	No	No
Chase et al., 1982	Yes	Yes	--
Hara et al., 1974, 1975	Yes	--	--
Hasegawa et al., 1972	No	--	--
Inoue et al., 1975	Yes	--	--

of high and low chlorinated blood PCBs versus present and past exposure, found no "evidence either to support or refute different accumulation kinetics in humans for the lower and higher chlorinated biphenyls". Nevertheless, they found a significant correlation between current personal air PCB levels and low chlorinated blood PCBs, but no significant correlation with high chlorinated blood PCBs.

In summary, body burdens of PCBs are clearly related to the level of exposure to environmental PCBs. Observations of a decrease in the burden of PCBs after exposure is eliminated or decreased are not consistent. The lack of consistency may be due to the short periods of observation of some of the studies, or possibly to differences in the average chlorination of the PCBs involved. Studies of the relationship of PCB burden to duration of exposure again are not consistent. There is a suggestion that this may be due to the confounding effects of age and sex, or to differences in the metabolism of high and low chlorinated PCBs, with the higher PCBs being more likely to accumulate in adipose tissue.

EPIDEMIOLOGIC STUDIES OF PCBs AND HEALTH

Excluding mortality studies, there are 18 epidemiologic studies of health effects related to PCB exposure. The accident report of Meigs et al. (1954) is included since it did not

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differ in design from many of the studies that were not motivated by accident reports.

These studies are listed in Table 4 with a summary of the findings by major category. Five of the reports are in Japanese (Hara et al., 1974, 1975; Hasegawa et al., 1972; Inoue et al., 1975; Kitamura et al., 1973). The details of those studies are taken from the NIOSH criteria document for PCBs (NIOSH, 1977).

Two of the studies (Kaappanen and Kolho, 1973; SCDH, 1978) are not specific as to health effects. The first of these is a comparison of groups with different work exposures and different blood PCB levels (74-1900 ug/kg in the 12 persons with the greatest exposure) in which the authors simply state that all persons studied were in good health. The second is a study of 32 workers in a capacitor plant, 10 of whom were exposed regularly to PCBs. The authors state that there is "no evidence of physical harm resulting from working with PCBs".

The remaining 16 studies in Table 4 are reviewed below with respect to their findings in each major category of health effects. The studies are considered in the order of their population.

Dermatologic Effects

There are 12 studies of dermatologic effects associated with PCB exposure. The first is Meigs et al. (1954) described in the above section on accidental heavy exposure, who found that 7 of 14 exposed workers got chloracne where the PCB concentration in their breathing zones averaged 0.1 mg/m^3. Hasegawa et al. (1972) reported an unstated number of cases of hyperpigmentation of the hands, and acne-like lesions of the jaw, back, and thighs in exposed workers. The average blood PCBs in the workers was 370 ug/kg. However, the authors state that skin complaints were unrelated to blood PCB levels and appeared to be due to skin contact. Kitamura et al. (1973) reported a range of skin disorders in 10 of 13 exposed workers with an average blood level of 820 ug/kg. The disorders occurred on parts of the body not normally in direct contact with PCBs. Hara et al. (1974, 1975) reported that about 45 percent of 118 capacitor workers complained of blackheads and other acne-like symptoms while working with PCBs. The complaints were not related to blood levels of PCBs, and virtually disappeared within a year after exposure had ceased.

Inoue et al. (1975) reported one case of chloracne in an exposed worked whose blood PCBs were in the 190 to 210 ug/kg range, but no symptoms in the rest of a small work force whose

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TABLE 4

PCB Epidemiology Studies (Other Than Mortality) and Summary of Findings[a]

Study	Dermatologic Findings	Physiological Parameters	Symptoms and Illness	Other
Alvarez et al., 1977	--	Y	--	--
Baker et al., 1980	N	Y	N	--
Dumgarner et al., 1973	--	N	--	--
Chase et al., 1982	Y	Y	Y	--
Fischbein et al., 1979	Y	N	Y	--
Hara et al., 1974, 1975	Y	Y	--	--
Hasegawa et al., 1972	Y	Y	--	--
Inoue et al., 1975	Y	--	--	--
Kaapanen and Kolho, 1973	--	--	--	N
Kitamura et al., 1973	Y	N	--	--
Kreiss et al., 1981	--	Y	N	N
Maroni et al., 1981b	Y	Y	Y	--
Meiga et al., 1954	Y	Y	Y	--
MDPH, 1975	N	--	N	--
Ouw et al., 1976	Y	N	--	--
Smith et al., 1982	Y	Y	Y	--
SCDHI, 1978	--	--	--	N
Warshaw et al., 1979	--	Y	Y	Y

[a]Y = Findings associated with exposure
N = No findings associated with exposure
No entry = No data presented

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blood PCBs ranged from 130 to 520 ug/kg. The Michigan Department of Public Health (1975) reported no relationship of any Yusho symptoms to consumption of fish with high levels of PCBs. Ouw et al. (1976) reported 14 cases of dermatitis, eye irritation, or burning sensations on the skin out of 34 exposed workers, where air levels of PCBs ranged from 0.32 to 2.22 mg/m^3. The complaints appeared to occur more often in those with higher blood PCB levels. Fischbein et al. (1979) reported that about 50 percent of 326 capacitor manufacturing workers reported a history of dermatological symptoms, the most common symptom being a rash. Those with symptoms had higher blood levels of high chlorinated PCBs. Baker et al. (1980) reported no chloracne in 18 exposed workers (average blood PCBs 75.1 ug/kg) or 19 members of their families (average blood PCBs 33.6 ug/kg). Maroni et al. (1981b) reported 10 cases of dermatitis (5 diagnosed as active or past chloracne) out of 80 exposed workers. The average blood PCB level in the study was 342 ug/kg. Chase et al. (1982) observed chloracne and an increase in other dermatological findings in 86 exposed male railroad workers, but the findings were not significantly associated with blood or fat PCB levels. Smith et al. (1982) found no chloracne in a study population of 324 exposed workers in capacitor manufacturing and transformer repair, whose average blood PCBs ranged from 38 to 546 ug/kg. However, there was a significant association of skin rash or dermatitis with blood levels of high chlorinated PCBs.

Interpretation of this mass of data is complicated by the difficulty of diagnosing chloracne, the uncertainties of blood PCB determinations, and the changing technology for making such determinations. Nevertheless, the data suggest strongly that when PCB blood levels exceed about 150 to 200 ug/kg, chloracne can occur. However, most studies have shown that the occurrence of chloracne is not further associated with blood PCB levels. This suggests that (a) personal idiosyncratic factors may be involved and/or (b) that the high blood levels are an indicator of the existence of environmental contamination which actually produces chloracne by skin contact.

The reports of dermatitis other than chloracne suffer from an additional complication. According to the National Health Survey, about one-third of all Americans of working age have at least one current skin condition serious enough to warrant evaluation by a physician (NCHS, 1979). Clearly, substantially more than one-third must have either a current condition or a history of such a condition in the past. The prevalence figures reported by Maroni et al. (1981b) and Fischbein et al. (1979) are, therefore, not in themselves remarkable, but the agreement of Fischbein et al. (1979) and Smith et al. (1982) on the relationship between dermatitis and

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high chlorinated blood PCBs suggests that this association may be real.

Liver Function -

Ten studies examined liver function. Meigs et al. (1954) found one borderline abnormal liver function in 14 exposed workers. Hasegawa et al. (1972) found mild disturbances in exposed workers (increased SGOT, SGPT, SAP, decreased serum cholninesterase) which they did not consider to be clinically significant. Kitamura et al. (1973), Ouw et al. (1976), Fischbein et al. (1979), and Baker et al. (1980)(a non-occupational study) found no abnormalities associated with exposure, except that Ouw et al. (1976) found a high BSP retention in four out of seven workers with blood levels above 500 ug/kg.

Maroni et al. (1981b) found 16 out of 80 workers with abnormalities in GGT, OCT, and transaminases. Their blood PCB levels were higher than those in the workers with normal liver function. Kreiss et al. (1981)(non-occupational study) found no relation between liver function and blood PCBs when age and alcohol consumption were taken into account. Chase et al. (1982) found among exposed railroad workers a statistically significant correlation between blood PCBs and SGOT after adjusting for age. Smith et al. (1982) found elevated SGOT and GGT levels in persons with higher blood PCB levels.

In summary, six studies of the ten found some mild liver function abnormalities, none of which were associated with any measurable adverse health effects. The two non-occupational studies, Baker et al. (1980) and Kreiss et al. (1981), found no abnormalities associated with blood PCB leve. Fischbein et al. (1979) in their study of capacitor manufacturing workers, noted that "there was a paucity of abnormal results in the biochemical studies."

Finally, Alvares et al. (1977) reported that in five workers occupationally exposed to PCBs, the rate of drug metabolism was significantly higher than in a group of controls matched for age, sex, and smoking and drinking habits.

Fat Metabolism

Six studies considered cholesterol levels. One (Bumgarner et al., 1973) found no relationship between cholesterol level and blood PCB level. One of the remaining five (Hasegawa et al., 1972) found a decrease in cholesterol, glycerides,

phospholipids, and beta-lipoprotein in exposed workers. Three of the other four studies found no relationship of cholesterol to blood PCBs (Baker et al., 1980; Chase et al., 1982; Smith et al., 1982) while one found increased cholesterol at higher blood levels of PCBs (Kreiss et al., 1981). Kreiss et al.)1981) and Smith et al. (1982) also present contradictory findings with respect to HDL cholesterol levels; the former found no relationship to blood PCBs, but the latter found an inverse relationship.

Five studies examined triglyceride levels. Four found an increase with increased blood PCBs (Hara et al., 1974, 1975; Baker et al., 1980; Chase et al., 1982; Smith et al., 1982) while one found no relationship when cholesterol level was taken into account (Kreiss et al., 1981).

In summary, most studies, including one non-occupational study, have associated increased triglycerides with PCB exposure. The data on cholesterol show no relationship in three studies, and an increase and decrease in one study each. HDL cholesterol either decreased or was unchanged (one study each). Even if PCB exposure has some effect on fat metabolism, it appears to be without any apparent clinical significance.

Blood and Blood Pressure

There are five studies of blood chemistry: Bumgarner et al. (1973), Kitamura et al. (1973), Fischbein et al. (1979), Baker et al. (1980), and Maroni et al. (1981b). None of them report any relationship of blood chemistry to PCB levels.

Bumgarner et al. (1973) and Kreiss et al. (1981) measured blood pressure in exposed persons. Bumgarner et al. (1973) found no association with PCBs, but Kreiss et al. (1981) found a statistically significant association between diastolic blood pressure and blood PCBs. Since there was no control group and since Kreiss et al. (1981) are the only investigators to report this finding, its significance is not clear at this time.

Symptoms, Illness, and Other Conditions

Eight studies investigated symptoms, illness, and other conditions in persons exposed to PCBs. None of the three non-occupational studies reported any abnormalities. The first of these (MDPH, 1975) compared the incidence of 18 conditions, most of which were reported in Yusho disease, in consumers of sports fish containing PCBs and in controls. The second (Baker et al., 1980) found none of the following conditions were associated with blood PCB levels in a community study; fever,

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weight loss, anorexia, fatigue, headache, eye irritation, cough, shortness of breath, nausea, vomiting, diarrhea, abdominal pain, arthralgia, and persistent rash. The third study (Kreiss et al., 1981) reported the same thing for prevalence of illness or weight loss in the preceding year, use of medication, use of medical care, history of heart disease, and percentage of pregnancies ending in miscarriage, stillbirth, or infant death.

Of the occupational studies, Chase et al. (1982) reported no evidence of organ toxicity from the medical histories or physical examinations of 86 exposed railroad workers. Three studies reported various symptoms. Fischbein et al. (1979) reported a history of gastrointestinal symptoms in 18 percent of 326 capacitor manufacturing workers, a prevalence of from 3.0 to 15.2 percent of various musculoskeletal symptoms, and a prevalence of from 4.8 to 27.8 of various neurological symptoms. These were, however, unrelated to duration of employment or to level of blood PCBs. Maroni et al. (1981b) reported eight cases of gastrointestinal complaints in 80 exposed workers, with no indication of whether there was a relationship to duration of employment. They also reported two bleeding haemangiomas and one case of chronic myelocytic leukemia. These findings do not appear to have any significance, since they apparently are unrelated to the circumstances of exposure.

Smith et al. (1982) reported an increased prevalence of general malaise and possibly altered peripheral sensation with increased blood PCB levels among occupationally exposed workers, but found no clinical abnormalities on physical examination.

Finally, one study of pulmonary function (Warshaw et al., 1979) reported decreased vital capacity in 245 capacitor workers. However, the pulmonary function values in the study population, most of whom were current or ex-smokers, were compared with a standard population of non-smokers, so that the effect of smoking was not taken into account.

The weight of evidence, as Smith et al. (1982) conclude, is that no studies to date "have shown that occupational exposure to PCBs is associated with any adverse health outcome, to be distinguished from demonstrable subclinical biochemical alterations."

There appear to be no significant clinical effects associated with the occupational or environmental exposures studied in these reports.

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Carcinogenicity

It is generally agreed that epidemiologic evidence for carcinogenicity should fulfill certain requirements in order to be acceptable. These requirements, presented below, deal with the study design, the logic of the observed pattern, and the repeatability of the results (Doll, 1981).

(1) Positive associations in groups of individuals with known exposure (case-control or cohort studies).

(2) That are not explained by bias in recording or detection.

(3) That are not explained by confounding.

(4) That are not explained by chance.

(5) That vary appropriately with dose.

(6) That vary appropriately with period of exposure.

(7) That are observed repeatedly in different circumstances.

There are four studies directed solely or primarily to the question of the carcinogenicity of PCBs. Table 5 lists the studies and their findings. They are reviewed here keeping in mind Doll's requirements.

The most obvious feature in Table 5 is that no study agrees with any other. That is, the requirement of repeatability is not met.

The first study by Bahn et al. (1976, 1977) observed three melanomas in a group of 92 research and development and refinery workers. These workers had an unknown exposure to other possible carcinogens, so that there could have been confounding. In any case, the study was withdrawn for revision in the definition of the exposed population, and has not yet been released (NIOSH, 1977).

Zack and Musch (1982) studied 89 Monsanto workers exposed for at least six months between 1945 and 1965 inclusive. There were no deaths from cancer of the liver or cirrhosis. The excess in respiratory cancer was based on four deaths and was not statistically significant. As with Bahn et al. (1976, 1977), there was confounding because of other chemical exposure at the plant and, in this case, possibly cigarette smoking.

TABLE 5

Inconsistencies in Studies of Cancer in PCB Exposed Populations With Findings

Study	Number Studied	Findings
Bahn et al., 1976; 1977	92	Melanoma[a]
Zack and Musch, 1982	89	Lung
Brown and Jones, 1981	2,567	Liver Rectum
Bertazzi et al., 1981	1,310	Digestive[b], Lymphatic, and hematopoietic

[a]Significant at 1 percent level
[b]Significant at 5 percent level

Brown and Jones (1981) studies 2,567 workers in a capacitor plant. About half the cohort had a latency period of 20 yrs or more. Although there was an excess of liver cancer deaths, it was inversely related to duration and latency of exposure, which does not support an occupational explanation. There was also an excess of rectal cancer. However, the two plants studied are located in an area whose mortality from rectal cancer is greater than the U.S. average (Mason et al., 1975). Since U.S. population rates were used as a basis for comparison, the rectal cancer excess is at least partly an artifact.

Bertazzi et al. (1981) studied 1,310 workers with at least six months employment in capacitor manufacturing between 1946 and 1970. Although excess digestive cancer was observed, there were no liver cancer deaths. The total number of deaths was small (27) and the excess cancer observed was based on two or three deaths for each of the two major sites involved. There is no indication of the duration or latency of exposure for the cancer deaths. The authors state that there were no other major exposures at the plant, and propose to continue the study with a larger cohort. In spite of the statistical significance of the excesses from all cancers, this study must be considered a preliminary report, particularly since it shares with the other studies a failure to agree on any particular pattern of mortality.

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The existing mortality studies of occupational exposure do not show the agreement that would lead one to infer an excess risk of cancer. Much of the conflicting findings can be attributed to the possible effect of confounding exposures, and to the "noise level" of sporadic excesses which would be expected in the absence of any occupational hazard.

SUMMARY AND CONCLUSIONS

The epidemiologic studies of exposure to PCBs show that the body burden in exposed persons, whether the exposure is by ingestion, inhalation, or skin contact, is related to the environmental levels and distribution of PCB. The relation of body burden to duration of exposure is less clear, and appears to differ depending on the degree of chlorination of the PCBs. Nevertheless, the evidence is clear that higher exposures mean higher blood PCB levels, and that persons with occupational exposures have blood PCB levels that may be an order of magnitude greater than that of environmentally (that is, non-occupationally) exposed persons.

Occupational exposure to PCBs at high levels has been associated with the occurrence of chloracne, but the relationship is not straightforward, suggesting that the actual risk of chloracne is also a function of individual susceptibility and personal work habits, as well as possible exposure to other contaminants.

Dermatologic problems other than chloracne are associated with occupational exposure, and may be related to exposure to high chlorinated PCBs.

Alterations of liver function and fat metabolism associated with PCB exposure have been observed in several studies, but are characterized by investigators as mild and of no clinical significance.

The one fact on which all occupational studies of health effects agree is that there has been no clinical illness associated with PCB exposure other than dermatitis. Studies of non-occupationally exposed populations have found neither dermatitis nor other clinical evidence of exposure-related effects, with the exception of a single study which suggests that diastolic blood pressure may be related to blood level of PCBs.

Mortality studies concerned primarily with cancer present problems of interpretation due to the small sample size of some of the studies, and to the confounding effect of other

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exposures. However, they do exhibit a pattern, which is that none of the studies agree on the cancer sites at which an excess mortality was found, and the excesses that were found are in general not statistically significant. One must conclude that the findings of the mortality studies reflect a sporadic pattern of excess mortality at different sites which is not consistent with a carcinogenic effect of PCBs. In addition, where an examination of duration and latency of exposure was possible, no association with these variables was found (Brown et al., 1981).

Taken as a whole, the epidemiologic studies find that high occupational exposures to PCBs may cause dermatitis of various kinds, but that there are no other clinically observable effects, including the occurrence of cancer.

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CHAPTER 21

POPULATION STUDIES OF PCBs IN MICHIGAN RESIDENTS

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INTRODUCTION

Between 1929 and 1977, about 1.4 billion pounds of polychlorinated biphenyls (PCBs) were produced in this country. Although U.S. production of the chemical has ceased, it is estimated that 750 million pounds are still in service (Miller, 1982). The rest has been exported, destroyed, buried, or lost to the environment. Acknowledgment that PCB is a worldwide pollutant serves as proof that past and potential future losses to the environment are not insignificant.

The Great Lakes present a unique situation for long lived contaminants which can bioaccumulate in living organisms. Our lakes act as reservoirs for atmospheric and terrestrial pollutants such as PCB. The relatively slow turnover and removal of contaminants plus biomagnification in the food chain make the aquatic environment of the Great Lakes a potential source for significant human exposure.

PCB has been shown to be toxic in animals, has a long half-life in mammals, and is present in our environment. Most humans are unavoidably exposed to small quantities of this chemical during their lives. It is not certain whether or not contact with additional sources constitutes an increase in exposure which will produce disease or degraded human health. It is of scientific and public interest to define whether such exposure in the Great Lakes basin has the potential for impact on the population using this resource.

At the Michigan Department of Public Health, we are conducting several cohort studies which examine the extent of

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human-exposure to chemical contaminants. We are attempting to define whether or not possible negative health effects have occurred or may appear as a result of such exposure. In this presentation, I will draw on data collected from our long-term polybrominated biphenyl (PBB) study of farmers from Michigan and Iowa (Landrigan et al., 1979), a long-term study of families exposed to farm products contaminated by PCB's from silos, the 1974 evaluation of Great Lakes fishermen (Humphrey, 1976), and our on-going study of persons who consume Great Lakes fish. Human specimens tested in these studies will demonstrate levels of exposure, and evaluation of interview and medical data collected from participants will document the occurrence of health events in these cohorts.

HUMAN EXPOSURE ASSESSMENT

Human breast milk has been reported to be a good predictor of exposure to fat soluble chemicals (Brilliant et al., 1978). The data shown in Table 1 indicate that PCBs are frequently found in women nationally and always found in women residing

TABLE 1

PCB in Mothers Milk

Study	Number of Women	PCB (Fat Basis) Concentration (mg/kg)		
		Detectable (percent)	Median	Range
1975 National	1,038	69	--	--
1977-78 Serv. Testing	1,057	100	1.35	0.3 - 5.1
1976 Random Survey	95	100	0.82	0.1 - 3.3
1980-81 HDET Study	120	100	0.96[a]	0.2 - 3.0
1974 Fish Eater 12.73 kg/yr	1	--	4.0	--
Silo Daughter	1	--	13.0	--

[a]Mean

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in Michigan. Monitoring of the general population indicates that most people receive a background exposure to this ubiquitous chemical contaminant. It is of interest to note that persons exposed to additional known sources of PCB receive significantly greater exposures. The consumption of contaminated fish from the Great Lakes or food from a farm with a PCB coated silo appear to significantly increase contaminant levels in breast milk.

The extent of PCB exposure can also be demonstrated by evaluation of serum specimens from population groups. The lower fat content of blood makes this a less sensitive specimen than breast milk for detecting small exposures to fat soluble chemicals. However, if exposure has been sufficient or long standing as in the case of PCB, circulating levels provide a convenient method for establishing exposure in cohorts. In addition, detection of PCB in blood gives an indication of the level at which the internal organs of the body are exposed to the circulating contaminant. Table 2 shows the range and median levels of PCB found in sera from the four cohorts which we have under evaluation. The data again demonstrate that PCB is commonly found in American citizens at low levels (Michigan and Iowa farmers with median values of between 5 and 6 ug/kg), and at significantly greater levels in persons who consume food which has been shown to be contaminated with PCBs (fish eaters and silo farm families with median values of 56 and 28 ug/kg, respectively). It can be concluded that consumption of Great Lakes fish represents a convenient and substantial way to increase human exposure to PCB.

TABLE 2

PCB Levels Found in Humans

Group	Sample	Number of People	Range (ug/kg)	Median (ug/kg)
Iowa Farmers	Sera	803	5-50	5
Michigan Farmers	Sera	1,631	ND-57	6
Silo Farmers	Sera	149	5-300	28
Fish Eaters	Sera	90	25-366	56

ND = Detection limit of < 5 ug/kg

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Contaminants from environmental sources would be less of a problem if the chemical was quickly excreted from the body and did not accumulate in fat stores. However, for fat soluble chemicals, this is not the case. Because of its long half-life, many small exposures to PCB result in a gradual increase in body burden. The long-term study of over 4,000 Michigan farmers who have had no extraordinary exposure to sources of PCB has shown that serum PCB levels gradually rise with age (Kreiss et al., 1982). This indicates that unavoidable background exposure results in small but significant increases in human body burden over a lifetime. Additional sources of exposure will add to this background body burden, and such additions will also be retained for long periods of time.

EVALUATION OF PERSONS EATING GREAT LAKES FISH

In his talk earlier today, Dr. Swain indicated that cooked Great Lakes fish provide a significantly greater potential dose of PCB than that provided from water and atmospheric sources combined. Table 3 presents these estimates and shows that habitual fish consumption could provide a dose 4,300 times that estimated from background environmental sources.

Our interest in evaluating the significance of this source of human exposure to PCB led to our 1974 study of 178 persons who consume Great Lakes fish (Humphrey, 1976). This investigation showed that persons from four communities who ate greater than 10.91 kg of fish per year had serum PCB levels which were significantly greater than people from the same communities who rarely ate such fish (Table 4). The contrast in serum PCB levels between groups who never eat fish, rarely

TABLE 3

Comparison of Non-Occupational Sources of PCB Exposure

Estimated Human Exposure	Exposure Source
7.8 ug/yr	Ambient air at 1.9 ng/m^3 air level PCB
2.9 ug/yr	Drinking water at 4 ng/l raw water PCB
46.5 mg/yr	Cooked Lake Michigan fish at 0.4 to 5.4 mg/kg PCB

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TABLE 4

Median Serum PCB Values for Persons From Michigan Communities in 1973

City	Median Serum PCB (ug/kg)	
	Comparison (0-2.73 kg/yr)	Exposed (> 10.91 kg/yr)
Traverse City	13	41
Manistee	23	105
Ludington	15	62
South Haven	22	48

TABLE 5

Relationship Between Fish Consumption by Geographical Location and Human Serum PCB Levels

Source of Fish	Consumption (kg)	Number of People	Serum PCB (ug/kg)		
			Range	Mean	Median
--	0	29	ND-41	17.3	15
Lake Michigan	0-2.73	39	ND-41	18.5	20
Lake Michigan	10.91-118	90	25-366	72.7	56
Lake St. Clair	5-66.8	15	ND-38	19.4	17

ND = Detection limit of <5 ug/kg

eat fish, eat more than 10.91 kg/yr of contaminated Lake Michigan fish, and eat uncontaminated fish from Lake St. Clair is shown in Table 5. The study documented a direct relationship between consumption of contaminated fish and elevated serum PCB levels. Individual serum PCB levels varied as a function of the quantity of fish eaten, type of fish eaten, and history of

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fish consumption. Consumption for the "exposed" group ranged from 10.91 kg/yr (an average of about one fish meal per week) to as much as 118 kg/yr. Human blood levels correspondingly ranged from the limit of detection (< 5 ug/kg) to a high of 366 ug/kg. When the exposed group was sorted according to the length of time participants had actively been catching and eating Great Lakes fish, it was found that those who habitually ate fish over the longest period of time had greater serum PCB levels than those who had eaten fish for shorter periods (Table 6).

The 1974 study confirmed that contaminated Great Lakes fish are a source of exposure which contributes to elevated human PCB levels which are significantly greater than background. In addition, the absence of a reduction in PCB levels in the exposed group between fishing seasons when no fish were consumed, and the correlation between the number of years of fish consumption and PCB levels supports the contention that PCB exposure from this source, if sustained, may result in a continuing accumulation of PCB which is retained over time.

The evaluation of human exposure to Great Lakes fish is continuing through a follow-up study currently in progress. In addition to re-evaluation of the participants in the 1974 study, the current work has expanded the cohort to include over 600 persons from 12 communities who eat 10.91 or more kg of Lake Michigan fish per year. An equal number of persons who do not consume fish are being randomly selected and matched for

TABLE 6

Relationship Between Serum PCB Levels and Number of Years of Fish Consumption

Number of Years Fish Eaten	Number of People	Serum PCB (ug/kg)		
		Range	Mean	Median
1-3	9	ND-90	48.9	48
4-6	33	ND-164	56.1	45
7-17	9	15-261	79.8	61
≥ 20	41	12-366	87.1	64

ND = Detection limit of <5 ug/kg

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comparison. This study when finished will provide data on human levels of PCB and 10 other contaminants, 1980-82 fish consumption patterns, regional differences in serum and cooked fish contaminant levels, and comparison to findings from the earlier study. Preliminary data from 1980 on part of the original 1974 cohort show that these people ate less fish in 1980 than they did in 1974 (Table 7). The decline in number of meals and pounds of fish eaten in combination with the general reduction in contaminant levels in Lake Michigan fish reported earlier in this conference appear to have contributed to a decline in serum PCB levels (median of 56 ug/kg in 1974 versus median of 48 ug/kg in 1980). Although these results are encouraging, it should be noted that the range of serum values remains similar to that observed in 1974; many individuals continue to eat large quantities of fish (up to 84 kg/yr in 1980), and the association between consumption of fish and significantly elevated serum PCB levels remains unchanged. Further analysis of the species of fish eaten is also necessary before the data in Table 7 can be confirmed as a real trend or artifact. This evaluation is underway.

EVALUATION OF PCB SILO FARM FAMILIES

Tables 1 and 2 show that persons from farms with silos coated on the interior with a sealant containing PCB are a second group who have received significant non-occupational exposure to PCB. We have had the opportunity to include some of these farm families in our long-term study of PBB exposure. Blood collected from 183 people (60 families) indicated a PCB concentration range nearly equal to that of the fish eater group

TABLE 7

Comparison of Fish Consumption and Serum PCB Levels, 1974 Versus 1980

Persons Consuming >10.91 kg of Fish/Yr	Median Values for Study Year	
	1974	1980
Number of Meals/Yr	60	39
Kilograms of Fish/Yr	14.55	9.55
Serum PCB (ug/kg)	56	48

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and a median serum PCB value (28 ug/kg) which is nearly five times that expected in the general population. Farm family exposure to PCB occurred when the sealant peeled off the silo walls over the years and contaminated the silage eaten by the farm animals. Those families who regularly ate dairy products and beef directly from their own farm unknowingly consumed PCB contaminated food. Because of the relatively small number of farms involved, the domestic food supply for the general public is not believed to have been adversely affected. For the farm families, this situation represents a continuous daily exposure of long duration which contrasts with exposure from fish which is intermittent in nature. Contamination of farm food is presumed to have occurred over many years, possibly greater than twenty since some of the silos which were constructed in the 1940s and 1950s were still in use in the mid-1970s when these families were enrolled. A current survey by the Michigan Department of Agriculture is expected to identify all of the farms in Michigan which have silos contamined by PCBs. Evaluation of persons exposed in this manner is of interest because it provides the opportunity to learn more about the human impact of long-term exposure to PCBs.

HUMAN HEALTH IMPLICATIONS

The cohorts established in Michigan to study persons exposed to halogenated biphenyls constitute the largest such investigation in the country and provide an opportunity to investigate the meaning and significance of such exposure. Specimens from these cohorts have documented the extent of PCB exposure from potential sources of concern. Interview and medical record data which record actual human experiences have been evaluated in an attempt to determine whether or not there is a relationship between symptoms and diseases of toxicological importance and body burden. The difficulty in such an evaluation lies in quantifying subtle or delayed physiological changes in humans which would indicate the presence of a toxic reaction or disease attributable to exposure as predicted from animal experiments. Environmental exposures are seldom extensive enough to produce easily observable toxic effects. Yet, the long half-life of the halogenated biphenyls results in a continuing internal exposure, the outcome of which has not been fully defined in humans.

The medical histories of study participants were obtained by interview and screened for acute, neurological, dermatological, skeletal, and metabolic disorders or diseases characteristic of those presumed to be caused by chlorinated biphenyl exposure. Those exposed to Great Lakes fish did not in 1974 report health problems or medical conditions which could be

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correlated with serum PCB levels or fish consumption. The type and frequency of various medical complaints were similar for exposed and comparison persons. Evaluation of data collected during the current investigation is incomplete at this time. Whether or not the lack of symptomatology is due to insufficient exposure, insufficient time since initiation of exposure, or the lack of sensitivity in detecting slowly emerging toxic effects is undecided at this time. Follow-up studies will help clarify this as time passes and diagnostic techniques improve. It should also be noted that this cohort study was not designed to seek out former fishermen who may no longer be up to the rigors of sport fishing because of medical problems or chronic illness. Instead, it was designed to assess exposure in those currently practicing sport fishing on the Great Lakes.

The silo farm family cohort provides an opportunity to evaluate the outcome of long-term continuous PCB exposure. Medical histories for farmers with PCB contaminated silos were reviewed and compared to those of Iowa farmers and Michigan farmers recently exposed to PBBs.

Comparison of reported symptoms (Table 8) showed that the PCB exposed silo farmers had a greater frequency of joint problems and numbness. To a lesser extent, this was also found among the PBB exposed farmers. These symptoms were found to have weak but positive correlation with serum PCB levels when adjusted for age. Such a correlation was not seen for PBB

TABLE 8

Percent Persons Reporting Health Symptoms

Symptom	Percent of Silo Farmers	Percent of Iowa Farmers	Percent of PBB Farmers
Tiredness	14	3	17
Headaches	10	3	10
Rashes	7	<1	4
Skin Problems	4	1	4
Numbness	19	5	10
Joint Problems	20	6	13
Nausea	5	3	11
Number of People	183	1,636	2,150

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levels. Although the subjectivity of reported symptoms makes a firm conclusion difficult, the correlation with PCB exposure is interesting because central nervous system and connective tissue defects are possible outcomes of prolonged PCB exposure.

The occurrence of diseases which have been confirmed by medical records were also compared for the three cohorts and are shown in Table 9. Among the diseases evaluated, the 3.3 percent frequency of cancer in the silo farm family cohort was significantly greater than the occurrence of this disease in the other two farm groups and was greater than the 0.3 percent rate predicted by the national Surveillance, Epidemiology, and End Results Program (SEER) cancer morbidity rates. The cancers found in the silo group were located in a variety of sites and occurred more frequently in females, 6.1 percent than males 1.8 percent. This observation is interesting because PCB is considered to be a promoter (Nobuyuki, 1973), a carcinogen (Kimbrough, 1974, 1975, 1979), and is regarded as a human carcinogen (IARC, 1978). The silo families have possibly received a chronic repeated exposure from their diet on a regular basis for over twenty years. It has been speculated that prolonged exposure to a potential carcinogen with a long half-life could produce continuous target organ exposure which would result in tumor production. The occurrence of disease events in the silo farm group also serves an indication of health events which could possibly occur in fish eaters in the future. However, this data should be treated cautiously at this time. The PCB silo cohort is too small to provide appropriate statistical

TABLE 9

Percent Persons Reporting Disease Conditions

Symptom	Percent of Silo Farmers	Percent of Iowa Farmers	Percent of PBB Farmers
Heart	6	4	4
Hepatitis	1	1	1
Diabetes	3	1	2
Thyroid	2	1	2
Tumor (benign)	6	3	4
Cancer	3.3	0.8	0.4
Number of People	183	1,636	2,150

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evaluation of events which are occurring and needs to be enlarged to properly evaluate the PCB/cancer hypothesis. The findings to date do demonstrate a lead which should be pursued with continued and expanded surveillance of persons exposed to PCB in this manner.

In conclusion, our cohort studies have provided data which demonstrates a clear relationship between environmental sources of PCB and increased human exposure. Consumption of contaminated fish or farm products results in elevated PCB levels in humans. No acute disease has been identified in exposed individuals, but the long-term outcome of this added body burden remains to be determined. The data generated to date provide viable leads which should be pursued. The cohorts which we have established in Michigan provide an excellent opportunity to continue evaluation of the significance of halogenated biphenyl exposure in humans.

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CHAPTER 22

INTRAUTERINE EXPOSURE OF HUMAN NEWBORNS TO PCBs: MEASURES OF EXPOSURE

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INTRODUCTION

Behavioral assessment is becoming an important tool for evaluating the consequences of intrauterine exposure to chemical agents routinely encountered in the environment (Fein et al., 1983b; Spyker, 1975). However, studies of the effects of these agents on human infants pose several special problems for research design and for the assessment of behavioral outcomes. The purpose of the present paper is two-fold:

(1) to summarize what is known about the pre- and postnatal effects of an especially ubiquitous chemical compound, polychlorinated biphenyls (PCBs); and

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(2) to examine empirically some of the linkages proposed in an analytic model of PCB exposure in human infants. The linkages of interest are those between the source of contamination and the exposure of mother and infant.

Evidence from several sources indicates that PCBs cross the placenta and are teratogenic in human infants exposed at high levels. PCBs are found in umbilical cord serum at birth when exposure results from ordinary dietary sources, and maternal serum levels are moderately related to fetal serum levels (Kodama and Ota, 1980; Masuda et al., 1978; Polishuk et al., 1977). In separate incidents in Japan and Taiwan, infants of pregnant women who consumed rice oil accidentally contaminated with sizable amounts of PCBs showed elevated PCB serum levels and a set of physical characteristics (e.g., chloracne, brown pigmentation of the skin, swollen eyelids) known in the literature as Yusho (rice oil) disease (Harada, 1976; Higuchi, 1976; Wong and Hwang, 1981). Infants exposed in utero were small-for-gestational age and tended to be born prematurely (Funatsu et al., 1972). Follow-up studies of exposed infants reported an average IQ of 70; sluggish, clumsy, and jerky movement; apathy and hypotonia; autonomic disturbances; and growth impairment (Harada, 1976). These disturbances in responsiveness and neuromuscular organization are consistent with reports of slowed sensory and motor nerve conductance in exposed adults (Chia et al., 1981; Harada, 1976). Although PCB blood levels diminish once exposure ceases, infants born several years after the exposure of their mothers showed elevated PCB blood levels, reduced birth weight, and brown pigmentation of the skin (Abe et al., 1975; Harada, 1976).

Placental passage and fetopathy have also been demonstrated in experimental studies with mammals such as rabbits, mice, rats, and rhesus monkeys (Allen et al., 1980; Bowman et al., 1978; Chou et al., 1979; Masuda et al., 1979; Grant et al., 1971; Tilson et al., 1979). PCBs may cross the placenta more freely as gestation progresses. In mice, higher concentrations are found in the fetus, placenta, and amniotic fluid as parturition approaches (Torok and Weber, 1981).

In rhesus monkeys, prenatally exposed infants weighed less at birth than controls and by 2 months of age developed Yusho-like symptomatology. Behavioral tests given between 6 and 24 months of age revealed hyperlocomotor activity and learning retardation (Bowman et al., 1978); but when tested at 44 months of age, these animals were hypoactive relative to controls (Bowman and Heironimus, 1981). In a follow-up study, adult female monkeys were removed from their PCB diet for a 1 yr period prior to conception (Allen et al., 1980). Although the

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physical condition of these animals improved and PCB levels in maternal adipose tissue declined markedly, 4 of the 15 offspring were stillborn. The birth weight of the liveborn infants was reduced relative to nonexposed infants, and four infants died after weaning at 4 months of age. In these studies, animals were fed diets containing only 2.5 or 5.0 mg/kg of PCBs, levels thought at the time to be low. In rhesus monkeys, as in humans (Harada, 1976), teratogenic effects appear in infants whose mothers had consumed PCB prior to, but not during, pregnancy.

When mice were fed relatively low levels of PCBs during pregnancy (32 mg/kg on days 10-16 post-conception), some pups subsequently developed the "spinning syndrome" (Chou et al., 1979; Tilson et al., 1979). More subtle signs of neurobehavioral dysfunctioning appeared in prenatally PCB-exposed mice which did not develop obvious clinical signs of neurotoxicity. Assessments of subtle behavioral functions indicate that exposed but apparently asymptomatic mice have learning deficits and depressed neuromuscular reflexes even though PCBs are no longer detectable in their body tissues (Tilson et al., 1979). A sluggish response to a novel situation and less pronounced habituation have been observed in asymptomatic mice exposed perinatally to PCB doses below those associated with obvious neuromotor disorders (Storm et al., 1981).

Table 1 summarizes the major assessment categories used in teratogenic assessment (Spyker, 1975) and the results of the studies reviewed above. While to date no morphological anomalies have been found to result from fetal exposure to PCBs, such exposure has been associated with clinical symptoms, maturational and growth retardation, and a variety of subtle behavioral deficits.

Consumption of PCB-contaminated fish caught in Lake Michigan constitutes a major source of human exposure to PCBs, with PCB body burden directly related to amount of fish consumed ($r = 0.51$; Humphrey, 1976). Although epidemiological studies of acutely exposed humans and experimental studies of chronically exposed animals indicate that PCBs are injurious, there are problems in extrapolating from studies of humans acutely exposed at high levels to those exposed chronically at low to moderate levels. Even at relatively high levels of consumption of PCB-contaminated fish, chronic exposure is considerably less than that experienced in the rice oil incidents. In contaminated fish eaters, obvious and distinctive Yusho symptoms have not been noted, and infants born to mothers who consume contaminated fish are likely to be clinically asymptomatic. Analyses of the consequences are complicated because the effects of low level chronic exposure are likely to be subtle and may occur in the absence of symptoms typically associated with acute

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TABLE 1

Assessment Categories in the Evaluation of Teratogenic Effects

Assessment Category	Illustration
Morphological characteristics	Anomalies not found in PCB studies
Physical characteristics	Chloracne; brown pigmentation of skin, lips, gums; parchment-like skin; swollen eyelids, face; premature eruption of teeth
Maturational landmarks	Preterm birth (neuromuscular and physical immaturity)
Growth	Small birth size; depressed postnatal growth
Reflexes	"Spinning syndrome" in mice
Activity levels	Hypo- and hyper-activity in an open-field; clinical assessment of apathy
Neuromuscular and sensory motor capacities	Tests of coordination (swimming in mice)
Sensory and attentional functions	Deficits in visual, auditory, olfactory, or attentional functions not found; numbness reported in humans exposed in adulthood
Learning ability	Alteration and reversal learning deficits in monkeys
Autonomic regulation	Inappropriate response to stress; deficits in temperature control; tremulousness
Sexual development	Reproductive failure; menstrual irregularities

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exposure. Although subtle behavioral effects appear in animals exposed to low doses of PCBs, extrapolation from animals to humans is also risky. For example, species differ in their ability to eliminate PCBs, and as a result, the dose required to produce an effect will vary among species. Animal models are an essential aspect of teratogenic testing; however, the findings of this type of research must be corroborated in studies of humans.

The present study involves two groups of humans who are particularly at risk: the pregnant woman and her newborn offspring. The study, which utilizes a prospective longitudinal design, investigates the model shown in Figure 1. In this model, consumption of contaminated lake fish, assumed to be a major source of PCB exposure, results in elevated maternal PCB levels. Elevated maternal body burden has both direct and indirect implications for the developing fetus. Since PCBs cross the placenta, the developing fetus is exposed directly to some part of the mother's body burden. Maternal body burden may also affect maternal health and reproductive capacity, which in turn may influence fetal development. PCBs are also transferred from maternal tissue to breast milk, which provides an additional source of direct exposure for breast-fed infants. In order to evaluate the contribution of these sources of exposure, infant behavioral and medical assessments are administered at birth and again at 5, 7, and 13 months.[1] The longitudinal design is necessary because the effects of low levels of exposure may not appear at birth. Further, subtle behavioral effects may appear in the absence of gross structural anomalies or obvious functional deficits long before classical symptoms of pathology become apparent (Spyker, 1975; Weiss and Spyker, 1974).

Several available measures of PCB contamination are examined. Each of these presents its own set of problems. Since maternal and cord blood are low in lipids, PCBs are difficult to recover. Breast milk, which contains higher lipid levels, can be assessed more reliably but is biologically more removed from the infant, obtained postpartum, and only available for a limited number of women. Maternal reports of fish consumption provide an alternative measure of exposure. They summarize the history of the respondent's exposure in contrast to biological measures, which are limited to a single point in

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[1]Since the fish consumption interviews were not conducted by the same persons who subsequently collected medical and behavioral data, those engaged in assessment activities were blind with respect to the mother's pattern of fish consumption and infant's potential exposure levels.

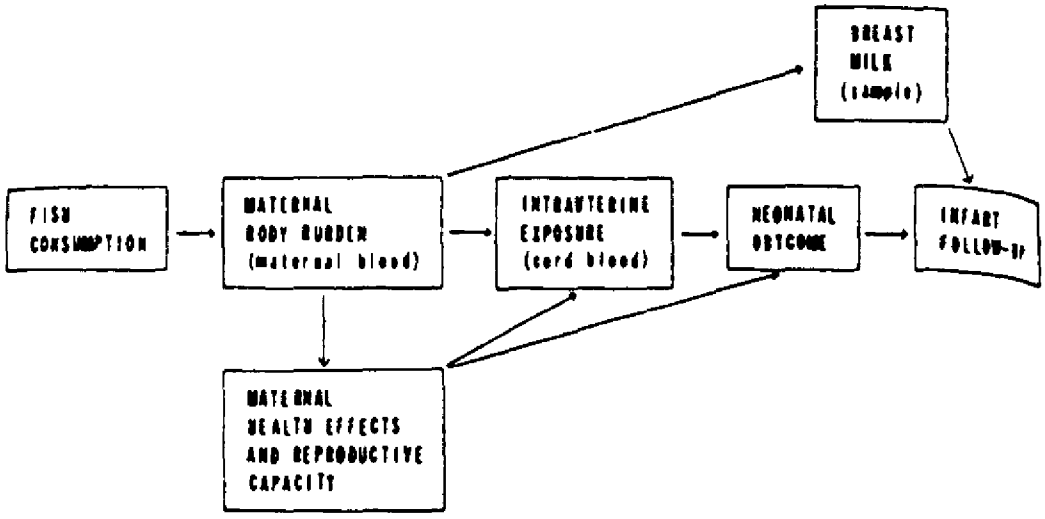

Figure 1. Model of pre- and post-natal exposure to polychlorinated biphenyls via ingestion of contaminated fish.

susceptible to short-term fluctuations. However, maternal recall may be inaccurate, and attempts to adjust for the contaminant levels of the particular species of fish consumed yield at best only rough approximations of exposure. In this report, relations among these various measures of exposure are used to validate critical linkages in the model described above.

METHOD

Subjects

The sample, comprised of 313 infants and their mothers, was drawn from three hospitals in Grand Rapids and one in Muskegon.[2] All mothers delivering at these hospitals were considered eligible to participate with the following exceptions:

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[2]Results of a state-wide survey of breast milk found PCB levels exceeding 2 mg/kg (fat basis) in 27 percent of the counties in the western part of the lower peninsula, in contrast to only 5 percent of the eastern counties (Wickizer et al., 1981). Grand Rapids is the largest metropolitan area located near Lake Michigan. The Grand River connects it to the lake and a fish ladder has made Grand Rapids a popular location for lake trout and spawning salmon. Muskegon is located directly on Lake Michigan.

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mothers had to be at least 18 years of age and have completed 10th grade in high school.

The infant sample consisted of 164 males and 149 females. The proportion of males (52%) did not differ significantly from expected (51%). All infants were white, with the exception of two black infants. Forty-three percent were firstborns. Six were the larger members of twin pairs, none of whom died during infancy. Anthropometric measures are presented in Table 2. Only one infant was below the tenth percentile on weight-for-gestational age (Lubchenco et al., 1963). One severely premature newborn (GA = 26.9 weeks, birth weight = 909 g) died. When the health status of the sample was evaluated on the Postnatal Complications Scale, the mean score was 94.1 percent optimal (Littman and Parmelee, 1978).[3] Only five infants (2.1%) had a 5-minute Apgar score below 7.

Socioeconomic status (SES) of the study sample, based on a weighted sum of father's education and occupational status (Hollingshead, n.d.),[4] was predominantly middle-middle class. Most of the fathers' occupations ranged from semi-skilled laborers to middle-level management, with only 4.5 percent classified as menial or unskilled. Almost all of the women were married and living with the father of their newborn infant.

The sample was also homogeneous in terms of maternal education and age. Only 7.7 percent of the mothers failed to complete high school, while 18.2 percent completed college. Eighty-one percent were between 18 and 30 yr of age and only 3.2 percent over 35. Fifty-seven percent attended prenatal birth classes; 95.8 percent began prenatal medical care by the fourth month of pregnancy, and the remaining 13 women by the sixth month. Their scores on the Obstetrical Complications

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[3]Data from the infant medical records were used to assign infants at-risk scores based on questions from the Postnatal Complications Scale (PCS)(Littman and Parmelee, 1978). The PCS is based on 10 items considered to reflect increased risk of mortality and morbidity to newborns, such as respiratory distress, infection, hyperbilirubinemia, and metabolic and temperature disturbances. The PCS uses an optimal scoring technique, such that high scores indicate few complications.

[4]If the father was a student, his father's education and occupation were used to estimate the family's socioeconomic status. In those cases in which the mother was unmarried, socioeconomic status was based on the occupation and education of the individual from whom the family was receiving most of its financial support.

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Scale (OCS)(Littman and Parmelee, 1978)[5] ranged from a minimum of 63 percent to a maximum of 98 percent optimal, with a median of 85 percent optimal, suggesting little variability in obstetrical history.

The sample was selected to over-represent women who had consumed Lake Michigan fish during some time in their lives. The majority (77%) reported consuming moderate to large quantities of Lake Michigan fish, while the rest (23%) reported consuming none of these fish. This design permits two types of analyses. First, adverse effects can be identified by comparing women who consume Lake Michigan fish with those who do not. Additional analyses can be performed to determine the statistical magnitude of the toxic effects and the particular dose-response relationships.

Procedure

Preliminary Screening

To ensure participation of infants likely to have been exposed *in utero* to a broad range of PCB levels, women were screened for past and present consumption of Lake Michigan fish on the morning following delivery. A questionnaire was used to ascertain the source,[6] amount, and kind of fish consumed in the year prior to the infant's birth, and the number of years of fish consumption at that rate. Women were also asked if there was a time in the past (dating back to 1966) when they ate greater amounts of Lake Michigan fish (e.g., the woman grew up in a family in which the father was a sports fisherman). If so, the amount and kind of fish consumed in the past, as well as the number of years of consumption at that rate, were recorded.

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[5]Data from the maternal interview and medical records are used to assign mothers at-risk scores based on 41 questions in the OCS (Littman and Parmelee, 1978). The OCS score is derived from data relating to pregnancy, such as maternal infection, bleeding, parity, age; the reproductive history, such as previous premature births or stillbirths; and the delivery, such as obstetric medication, duration of labor, type of delivery, and birth weight. Like the PCS, the OCS is based on optimal scoring with high scores reflecting few complications.

[6]Lake Michigan was the primary source of fish. In addition, coho and chinook salmon and lake trout from rivers and lakes connected to Lake Michigan were included since these fish are normal inhabitants of the lake populations.

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TABLE 2

Characteristics of the Sample at Birth (N = 313)

Assessment Parameter	Mean (SD)	Range
Infant characteristics		
Birth weight (g)	3502.7 (560.3)	909.1 - 5028.9
Crown-heel length (cm)	51.1 (2.5)	28.5 - 56.0
Head circumference (cm)	35.1 (1.4)	30.5 - 41.3
Ponderal index[a]	2.7 (0.3)	1.9 - 5.6
Gestational age (weeks)[b]	39.9 (2.3)	26.9 - 45.9
Apgar scores		
1-minute	7.9 (1.3)	1.0 - 9.0
5-minute	8.9 (0.8)	2.0 - 10.0
Postnatal complications score[c]	0.9 (0.1)	0.2 - 1.0
Family characteristics		
Socioeconomic status (SES)[d]	39.3 (13.5)	14.0 - 66.0
Maternal age	26.1 (4.6)	18.0 - 42.0
Maternal education (years)	13.3 (1.9)	10.0 - 19.0
Marital status (married)[e]	283.0 (90.4)	--
Obstetrical complications score[f]	84.0 (0.1)	0.6 - 1.0

[a]Based on equation (Miller and Hassanein, 1971):

$$\frac{\text{birth weight (g)} \times 100}{\text{crown-heel length (cm)}^3}$$

[b]Based on obstetrician's estimated date of confinement
[c]Based on PCS (Littman and Parmelee, 1978)
[d]Based on Hollingshead index (n.d.)
[e]N is presented rather than mean; percent of women married in parentheses
[f]Based on OCS (Littman and Parmelee, 1978)

Sampling for contaminants in Lake Michigan fish has shown that most species tested contain detectable levels of PCBs, with especially high levels in fatty species, such as salmon and lake trout (IJC, 1978; Swain, 1981; Willford et al., 1976). These fish, although high in PCB contamination, may be eaten in small quantities, while other less contaminated fish, such as perch or smelt, may be eaten in large quantities. To obtain a more accurate measure of contaminated fish consumption, a weighted value was assigned to each fish species based on

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average contaminant levels for the species (Table 3). The range of values was normalized to lake trout, salmon, carp, and catfish, species containing the highest concentrations of PCBs (e.g., a fish having half the average PCB level of salmon or lake trout would be weighted 0.5).

The following equation was used to estimate the mother's annual rate of consumption for each type of fish:

Relative PCB Fish Weight	X	Number of Fish Meals/Year	X	0.23 kg (1 Fish Meal)	=	PCB-kg Per Year

This measure is summed across species for each individual to determine a woman's annual fish consumption rate. To estimate

TABLE 3

Relative PCB Values of Lake Michigan Fish[a]

Type of Fish	PCB Weighted Value
Chinook salmon	1.0
Coho salmon	1.0
Lake trout	1.0
Carp	1.0
Catfish	1.0
Bullhead	0.6
Pike or pickerel	0.6
German brown trout	0.4
Perch	0.4
Walleye	0.4
White sucker	0.4
Alewife	0.3
Burbot	0.2
Steelhead or rainbow trout	0.2
Brook trout	0.2
Menominee (round whitefish)	0.1
Smelts	0.1
Whitefish and chubbs (herring)	0.1

[a]Derived from data supplied by the Large Lakes Research Station.

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cumulative exposure, annual PCB fish consumption rate was multiplied by the number of years the mother reported eating contaminated fish at that rate. If she reported eating contaminated fish at a higher rate in the past, the number of years at the current and past rates were determined separately and then multiplied by their respective consumption rates to yield a measure of cumulative exposure as follows:

Present PCB kg/ Year	X	Number of Years at Present Rate	+	Past PCB kg/ Year	X	Number of Years at Past Rate	=	Cumulative Consumption (PCB-kg)

Sampling Criteria: Exposed and Unexposed

Two criteria were used to determine inclusion of women in the study:

(1) If cumulative exposure within a 6 yr period reported by the mother was equal to 11.8 kg (26 pounds) or more of contaminated fish, the mother qualified for inclusion in the study. This criterion was based on evidence that PCBs are retained in body tissues over relatively long periods of time (Humphrey, 1976).

(2) In addition, a control group was selected comprised of newly-delivered mothers who reported consuming no Lake Michigan fish in the past or during pregnancy.

Of the 8,482 women screened (i.e., 96% of all maternity patients in the four participating hospitals), about 4 percent or 343 ate PCB-contaminated fish in sufficient quantities to qualify for inclusion in the exposed group.[7] About 29.3 percent of the women screened reported eating no Lake Michigan fish; 4.6 percent or 114 of these women were invited to serve as controls. As a check on whether women invited to participate in the study, either as fish eaters or as controls, were similar demographically to women who were not asked to participate, a demographic comparison group was selected by matching each potential participant with the next woman whose screening

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[7]The qualification rate of 4 percent of the population screened, coupled with demographic data on the 18 county areas adjacent to Lake Michigan, suggests that almost 100,000 women in this region might qualify as high fish eaters. These figures do not include women in nearby Wisconsin, considered the salmon capital of the world, or those from the Chicago area.

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interview followed her own. This procedure assured a comparison group matched for hospital and approximate date of delivery with the potential sample of exposed and nonexposed mothers. Women invited to participate did not differ significantly from others in their community in socioeconomic status, maternal age, education, marital status, or sex of infant (Table 4). Among those women invited to participate, fish eaters did not differ from control women on these variables (Table 5).

TABLE 4

Characteristics of Qualifier and Demographic Comparison Groups (N=914)

	Qualifiers: Exposed and Control Groups (N=457)		Demographic Comparison Group (N=457)		
Assessment Parameter	Mean	(SD)	Mean	(SD)	t
Socioeconomic status (SES)[a]	38.5	(13.1)	37.6	(12.9)	1.10
Maternal age	25.9	(4.5)	25.9	(4.8)	0.05
Maternal education (yr)	13.2	(1.9)	12.9	(2.0)	1.88
	N	(%)	N	(%)	χ^2
Marital status (married)	419	(91.7)	413	(90.4)	0.18
Sex of infant (male)	224	(49.6)	241	(53.9)	1.71

[a]Based on Hollingshead index (n.d.)

Note: Data on SES, maternal age, and sex of infant were unavailable as follows: SES was unavailable for eight qualifiers and ten comparison women; sex of infant for five qualifiers and ten comparison women; maternal age for one

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TABLE 5

Comparison of Qualifying Exposed and Control Groups (N=457)

Assessment Parameter	Qualifying Exposed Group (N=345) Mean	(SD)	Qualifying Control Group (N=112) Mean	(SD)	t
Socioeconomic status (SES)[a]	38.3	(13.1)	39.4	(13.2)	-0.76
Maternal age	26.0	(4.6)	25.4	(4.3)	1.33
Maternal education (yr)	13.1	(1.9)	13.2	(1.9)	-0.44
	N	(%)	N	(%)	x^2
Marital status (married)	319	(92.5)	100	(89.3)	1.12
Sex of infant (male)	167	(49.4)	54	(49.5)	0.00

[a]Based on Hollingshead index (n.d.)

Note: Data were unavailable on SES for six exposed and two control women; sex for seven exposed and three control infants.

Of the 457 women invited to participate, 144 (32%) refused. Mothers who consented to participate were more educated than refusers, suggesting that greater education may be associated with greater interest in research. Among women who agreed to participate, exposed and non-exposed control groups did not differ in socioeconomic status, maternal age or education, number of offspring (parity), or sex of infant (Table 6). While slightly more of the exposed women were married, this difference was not statistically significant ($p > 0.05$).

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TABLE 6

Study Sample: Exposure and Control Groups (N=313)

Assessment Parameter	Exposure Group (N=242) Mean	(SD)	Control Group (N=71) Mean	(SD)	t
Socioeconomic status (SES)[a]	39.3	(13.6)	39.5	(13.4)	-0.14
Maternal age	26.2	(4.7)	25.7	(4.5)	0.81
Maternal education (yr)	13.3	(1.9)	13.3	(2.0)	0.15
	N	(%)	N	(%)	χ^2
Marital status (married)	223	(92.1)	60	(84.5)	3.70
Sex of infant (male)	124	(51.2)	40	(56.3)	0.39
Parity (first-borns)	100	(42.2)	32	(45.1)	0.18

[a]SES, based on Hollingshead index (n.d.), was unavailable for three exposed women

Measures of Exposure

PCB-Fish Consumption. The principal measures of contaminated-fish consumption were:

(1) highest annual rate of PCB-fish consumption;
(2) cumulative PCB-fish consumption; and
(3) rate of PCB-fish consumption during pregnancy.

These measures were weighted for the contaminant levels of the species reported by the mothers. The first measure (highest annual rate) reflects findings from previous studies that the highest level of contaminated fish consumption predicts

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subsequent PCB serum levels (Humphrey*, 1976), findings consistent with the tendency of PCBs to be poorly metabolized. But PCBs tend to accumulate in body tissues over time, and prediction might be improved when reported values and years at these levels are taken into account. The measure of cumulative PCB-fish consumption, which sums rates over years after normalizing each component of the measure to z scores, was constructed to assess this possibility. The third measure, rate of PCB-fish consumption during pregnancy, was used to assess a somewhat different possibility (i.e., that the impact on the infant is especially pronounced when the mother consumes contaminated fish during pregnancy). PCB-kg refers to a fish consumption score weighted by the contaminant levels of the species reported by the mother. Mean annual rate of PCB-fish consumption at the highest levels reported by the exposed mothers was 6.7 PCB-kg (14.7 PCB-pounds) per yr (SD = 5.8 PCB-kg, range = 1.2 to 41.7 kg/yr). This rate is equivalent to about 0.6 PCB-kg per month or 2 to 3 salmon or lake trout meals (at 0.2 kg/meal). The women reported eating Lake Michigan fish for an average of 16.1 yr (SD = 9.0, range = 1.0 to 40.0 yr). In the year preceding the infant's birth, mean level of fish consumption was 4.4 PCB-kg (9.7 PCB-pounds; SD = 4.4 PCB-kg, range = 0.0 to 26.5 PCB-kg). Therefore, the selection procedure described earlier yielded a range of exposure levels with specific values depending on the particular measure of maternal fish consumption used. The fish consumption variables were positively skewed and were normalized by means of log transformations. One outlier, a women who reported ingesting 54.5 kg of contaminated fish in one year, was eliminated from the analyses.

Laboratory Analyses

Hospital personnel collected samples of umbilical cord blood for every infant born in the participating hospitals at the time of delivery. Cord blood specimens for newborns in the sample were available, therefore, for laboratory analysis, while those of non-participants were discarded shortly thereafter. Samples of maternal blood were collected on the second day following delivery as part of routine blood tests. Sixty-one percent of the infants in the sample were breast fed; and of those, 70.3 percent of the mothers provided breast milk samples between 1 and 16 weeks after delivery. A second sample of breast milk was collected from 45 women who continued breast feeding at 5 months.

Analyses of cord serum, maternal serum, and breast milk samples for PCBs were performed at the Michigan Department of Public Health by means of packed column gas chromatography

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(Burse et al., 1980; Needham et al., 1981). A 4 ml sample of serum was mixed with 2 ml methanol. This mixture was extracted with 5 ml hexane/diethyl ether (1:1, v/v) three times by agitating on a rotary mixer 15 to 20 minutes at 50 to 55 rpm. The extracts were combined in a Kontes concentrator tube, reduced to a small volume (about 0.5 ml), and transferred quantitatively to a miniature Florisil cleanup column from which PBBs, PCBs, and chlorinated hydrocarbon pesticides were eluted with 6 percent diethyl ether/petroleum ether mixture (v/v). The eluate was concentrated to a small volume (1.0 ml), transferred with three x 1.0 ml rinsings of hexane to a column of Silica Gel 60, and eluted with hexane to separate PCBs from the chlorinated hydrocarbon pesticide group (Picer and Ahel, 1978). The fraction containing PCBs, PBBs, and DDE was concentrated to 2 ml and analyzed by electron-capture gas chromatography with a 3 percent SE-30 column. Injector, initial column, final column, and detector temperatures were 240°C, 160°C, 210°C, and 320°C, respectively. Quantification was provided by adapting the Webb-McCall method (Sawyer, 1978; Webb and McCall, 1973) to a computer data system with Aroclors 1016 and 1260 used as calibration standards. Estimation of PCB levels in sample extracts was based on comparison of peaks on the chromatogram with respective peaks of known concentrations in the reference standards. The Aroclor 1016 portion of the chromatogram was used to estimate the quantity of lower chlorinated congeners, while the 1260 portion was applied to measure levels of more highly chlorinated congeners and isomers. Limits of detection were 5 ng/ml for Aroclor 1016 and 3 ng/ml for Aroclor 1260 in the sample extracts. Quality control over time was ensured by addition of a spiked sample of bovine serum with every batch of 10 samples, as well as the use of a glassware blank and a reagent blank. Serum lipids were determined colorimetrically using the Dade Total Standard for plotting the calibration curve of concentration vs. absorbence (Fringe et al., 1972).

A similar procedure was used in analyzing breast milk samples. A 5 g sample of breast milk in a screw-capped (teflon-lined) culture tube was mixed with 0.1 g of potassium oxalate and 5 ml methanol. This mixture was extracted in the same manner as serum samples. Extracts were combined in a micro distilling assembly and concentrated to a small volume. Evaporation of solvent from the concentrated extract was conducted in a small preweighed aluminum dish and the residue dried under vacuum in a desiccator. In contrast to serum analysis, wherein lipid levels were estimated, lipid content of the breast milk sample was determined gravimetrically. The lipid residue was then redissolved in a small amount of petroleum ether and transferred quantitatively to a miniature Florisil cleanup column. Subsequent procedures for serum were

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then applied to the breast milk analyses.[8] (For a review of technical problems associated with these analytical procedures, see IARC Monograph, 1978; Mullin et al., 1983; Humphrey, 1976.)

All serum samples containing lipid levels below 200 mg/dl were omitted from the data analyses, since measurement techniques were judged to be insufficiently sensitive to detect PCB levels at lipid values of this magnitude. The removal of three maternal serum and 43 cord serum samples for this reason did not alter the fundamental nature of the PCB distribution. Twenty-seven additional cord blood samples could not be analyzed because insufficient quantities had been collected, the hospital had mistakenly discarded them, or because of equipment failures in the laboratory. Included in the following analyses were 198 cord serum and 196 maternal serum samples, and 138 neonatal and 45 five-month breast milk samples.

RESULTS

Laboratory results for cord serum, maternal serum, and breast milk samples are presented in Table 7. The column labeled "nondetectable" refers to PCB values of 0.1 ng/ml to five times the noise level on the chromatogram; the right hand column refers to PCB levels that are detectable, but still below the laboratory's quantification limits. The majority of the PCB levels matched to the 1016 standard were below quantification limits. This was particularly true for the cord and maternal sera analyses. Among these samples, only one of 195 and five of 190 cases, respectively, were quantifiable. Since comparisons with the 1260 standard yielded considerably fewer values below the quantification limit, 1260 values may provide a more reliable measure of PCB body burden. Arithmetic means for the more highly chlorinated isomers exceeded the lower chlorinated isomers by a ratio of 2.7 to 1 for the cord samples and as much as 5.5 to 1 for the neonatal breast milk samples. This differential presumably results from the tendency of lower chlorinated isomers to be less stable, more susceptible to degradation in the environment, and metabolized more rapidly in the organism (Matthews, 1983).

PCB levels for a large proportion of the cord serum samples were not quantifiable, even when the 1260 standard was used. A pair-wise comparison of PCB 1260 serum levels on a whole basis indicates that mean PCB levels in maternal serum were

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[8]The summary of the laboratory techniques used to analyze the serum and breast milk samples was written in conjunction with Dr. Harold A. Price of the Michigan Department of Public Health.

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TABLE 7

Polychlorinated Biphenyls in Cord Serum, Maternal Serum, and Maternal Breast Milk (Whole Basis)

Assessment Parameters	N	Mean (SD)	Median	Nondetectable[a] N (%)	Detectable But Nonquantifiable[b] N (%)
Cord serum (ng/ml)					
1016 standard	195	0.9 (0.9)	0.6	23 (11.8)	171 (87.7)
1260 standard	198	2.5 (1.9)	2.0	4 (2.0)	130 (65.7)
Maternal serum (ng/ml)					
1016 standard	190	1.6 (4.5)	0.8	16 (8.4)	169 (88.9)
1260 standard	196	5.5 (3.7)	4.6	0 (0.0)	44 (22.4)
Breast milk - neonatal (ng/g)					
1016 standard	138	4.1 (4.5)	2.9	11 (8.0)	85 (61.6)
1260 standard	138	22.5 (12.3)	20.4	0 (0.0)	2 (1.4)
Breast milk - 5 months (ng/g)					
1016 standard	45	3.7 (3.4)	2.8	3 (6.7)	30 (66.7)
1260 standard	45	17.4 (12.1)	14.1	0 (0.0)	4 (8.9)

[a]Nondetectable refers to values of 0.1 ng/ml to five times the noise level of the chromatogram
[b]Nonquantifiable refers to detectable levels below the quantifiable limits of 5 ng/ml for Aroclor 1016 and ng/ml for Aroclor 1260

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substantially higher than in cord serum (Table 8), confirming previous findings (Akiyama et al., 1975; Kodama and Ota, 1977). Masuda et al. (1978) found a similar differential in a recent Japanese sample and concluded that the placenta may act as a partial barrier to PCBs. However, in the present sample lipid levels in maternal serum are twice those in cord serum. When PCB concentrations are calculated on a fat basis, the mean PCB values are similar for the cord and maternal sera (Table 8), and the differential is no longer significant. Thus, four studies provide evidence that PCBs cross the placenta, thereby exposing the fetus.

PCB values were also obtained for two samples of breast milk, one during the first few weeks after birth and a more limited sample when the infant was 5 months old. Matched pair t-tests indicate that PCB levels on a whole basis were substantially higher in breast milk than cord and maternal sera samples. Again, when samples were compared on a fat basis, differences were no longer significant. Kodama and Ota (1980) suggested that breast feeding may decrease PCB body burden in the mother. Although PCB concentrations in the breast milk of nursing mothers in our sample tended to decline over time, this decline was not significant.

Correlations among PCB levels in the four biological specimens are shown in Table 9. The highly significant correlation of cord with maternal serum levels provides further evidence for the transplacental passage of the PCB molecule and corroborates a similar relation reported by Masuda et al. (1978) and Kodama and Ota (1977), using smaller samples of women. The significant correlation between PCBs in maternal serum and breast milk indicates that PCBs are moderately stable in the mother, an inference further supported by the significant correlations between breast milk samples obtained shortly after the baby's birth and those obtained at 5 months.

Correlations between maternal and cord sera were similar in magnitude, whether calculated on a whole serum or fat basis, $r = 0.41$ and 0.43, respectively (Table 9). While the whole and fat basis findings were also similar for correlations between maternal serum and breast milk, the two approaches yielded different results for the neonatal to 5-month breast milk correlation.

Consistency between analyses derived on a whole and fat basis was also indicated by the pattern of the intercorrelations shown in Table 10. PCB levels in the cord and maternal sera on a whole serum basis were highly correlated with levels calculated on a fat basis ($r = 0.93$). Thus, for serum, it seems to make little difference whether measures are derived on a

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TABLE 8

Pairwise Comparisons of PCBs and Lipids in Cord Serum, Maternal Serum, and Maternal Breast Milk (1260 Standard)

Assessment Parameters	N	Whole Basis (ng/ml or ng/g)[a] Mean (SD)	t	Fat Basis (ng/g) Mean (SD)	t	Lipids Percent	t
Cord serum	148	2.4 (1.9)	-10.18[b]	788.1 (696.5)	-0.82	0.32	-25.69[b]
Maternal serum		5.3 (3.7)		835.3 (557.1)		0.64	
Cord serum	95	2.4 (1.8)	-15.45[b]	824.2 (714.2)	0.13	0.31	-20.45[b]
Breast milk - neonatal		22.8 (13.0)		813.9 (377.9)		2.89	
Maternal serum	91	5.6 (3.2)	-13.36[b]	932.2 (579.1)	1.55	0.63	-17.06[b]
Breast milk - neonatal		22.7 (12.3)		827.8 (380.4)		2.85	
Breast milk - neonatal	42	20.0 (9.3)	1.31	750.5 (408.8)	-0.19	2.96	0.51
Breast milk - 5 month		18.0 (12.2)		772.3 (671.2)		2.82	

[a]Cord and maternal serum values on a whole basis are given in ng/ml and breast milk values in ng/g

[b]$p < 0.0001$

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TABLE 9

Intercorrelations of Log PCBs (1260 Standard) in Cord Serum, Maternal Serum, and Maternal Breast Milk

Assessment Parameter	Cord Serum	Maternal Serum	Breast Milk Neonatal	Breast Milk 5 Month
Cord serum	--	0.41[a] (148)	0.09 (95)	-0.06 (25)
Maternal serum	0.43[a] (145)	--	0.23[b] (91)	0.01 (30)
Breast milk - neonatal	0.16 (93)	0.28[c] (91)	--	0.61[a] (42)
Breast milk - 5 month	-0.01 (24)	-0.10 (30)	.30[b] (42)	--

[a] $p < 0.0001$
[b] $p < 0.05$
[c] $p < 0.01$

Note: Rs above the main diagonal are values calculated on a whole basis, while those below are on a fat basis. N appears in parentheses. Lipid values were missing for three cord serum samples, two neonatal breast milk samples, and one 5-month breast milk sample.

whole or fat basis. Although cord and maternal sera are low in lipids, lipid levels tend to be relatively stable. Because breast milk lipids fluctuate considerably, the same consistency does not appear for breast milk values derived by the two methods. This apparent instability suggests that in the analyses of breast milk, measures that take lipid fluctuation into account are likely to be more reliable.

These findings were further supported by an analysis of the degree to which PCB levels could be predicted from lipid levels in serum or breast milk. While the PCB levels in the cord and maternal sera were unrelated to corresponding cord and maternal lipid levels, there was a significant association between PCB and lipid levels in the neonatal and 5 month breast

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TABLE 10

Intercorrelations of Log PCBs (1260 Standard) in Cord Serum, Maternal Serum, and Maternal Breast Milk

	Whole Basis			
Assessment Parameter	Cord Serum	Maternal Serum	Breast Milk Neonatal	Breast Milk 5 Month
Fat basis				
Cord serum	0.93[a] (194)	0.37[a] (145)	0.07 (93)	0.05 (24)
Maternal serum	0.43[a] (148)	0.93[a] (196)	0.20[b] (91)	0.01 (30)
Breast milk - neonatal	0.16 (95)	0.35[a] (91)	0.62[a] (138)	0.30[c] (42)
Breast milk - 5 month	-0.06 (25)	-0.08 (30)	0.08 (42)	0.39[d] (45)

[a] $p < 0.001$
[b] $p < 0.10$
[c] $p < 0.05$
[d] $p < 0.01$

Note: N appears in parentheses.

milk ($r = 0.58$, $p < 0.0001$; and $r = 0.63$, $p < 0.0001$, respectively).

Women and their offspring were selected for the study on the basis of reported fish consumption patterns. Levels of fish consumption reported by the exposed and control mothers for whom the different biological measures were available are shown in Table 11. When women who breast fed were compared with those who did not, no difference was found for highest annual rate or cumulative consumption measures. While their rate during pregnancy was slightly lower than the rest of the sample ($M = 2.9$ vs. 3.8 PCB-kg/yr), the difference failed to

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TABLE 11

Levels of Reported Contaminated Fish Consumption (PCB-kg) of Women Providing Blood and Breast Milk Samples

Assessment Parameters	N	Mean (SD)	Median	Range
Cord serum analyses				
Consumption at highest rate	198	4.3 (5.5)	3.0	ND - 41.7
Consumption during pregnancy	189	2.8 (3.9)	1.9	ND - 22.4
Cumulative consumption	198	61.3 (97.8)	27.8	ND - 716.6
Maternal serum analyses				
Consumption at highest rate	196	4.4 (5.5)	3.2	ND - 41.7
Consumption during pregnancy	190	2.8 (3.6)	2.2	ND - 22.4
Cumulative consumption	196	62.4 (97.5)	28.6	ND - 716.6
Breast milk - neonatal				
Consumption at highest rate	138	4.7 (5.3)	3.3	ND - 41.7
Consumption during pregnancy	135	2.9 (3.5)	2.2	ND - 20.0
Cumulative consumption	138	62.9 (90.9)	38.4	ND - 716.6
Breast milk - 5 month				
Consumption at highest rate	45	5.5 (8.0)	3.8	ND - 41.7
Consumption during pregnancy	45	2.8 (2.9)	2.2	ND - 9.5

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Table 11 (continued)

Assessment Parameters	N	Mean (SD)	Median	Range
Cumulative consumption	45	82.5 (135.3)	43.4	ND - 716.6

Note: Consumption levels include data on exposed and control women.

reach conventional levels of statistical significance ($t = 1.90$, $p < 0.10$).

Correlations between maternal reports of contaminated fish consumption and the four biological measures of PCB body burden are presented in Table 12. No relationship was found between cord serum PCB levels and maternal fish consumption, possibly because of the detection problems in cord serum analysis described earlier. In contrast, a positive correlation was found between PCB levels in maternal serum and all three reported fish consumption measures. Mean PCB level in maternal serum was 6.1 ng/ml ($SD = 3.7$) among women who ate contaminated fish, as contrasted to 4.1 ng/ml ($SD = 2.7$) among those who abstained ($t = 3.83$, $p < 0.0001$). These data replicate in a sample of women of child-bearing age Humphrey's (1976) finding that Lake Michigan fish consumption predicts PCB body burden in Michigan residents. The data extend this finding by showing a significant correlation between fish consumption and PCB levels in neonatal breast milk. Mean PCB residues were higher in breast milk samples of exposed than in samples of nonexposed women ($M = 865.6$ vs. 622.2 ng/g on a fat basis, $t = 3.21$, $p < 0.005$). The lack of a consistent relationship between maternal report of prenatal fish consumption and breast milk levels at 5 months may be due in part to postpartum ingestion of contaminated fish, which will be examined in future analyses. Figure 2 shows a scatterplot demonstrating the linear relationships between maternal serum 1260 and fish consumption at the highest annual rate. For every pound of contaminated fish ingested by the mother, the PCBs in her serum increase by about 0.15 ng/ml on a whole basis or 23.6 ng/g on a fat basis.

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TABLE 12

Correlations Between Log Contaminated Fish Consumption and Log PCBs in Cord Serum, Maternal Serum, and Breast Milk (1260 Standard)

Assessment Parameters	N	r	Regression Equation
Fish consumption at highest annual rate with			
Cord (whole serum basis)	198	0.09	y = 1.05 + 0.04x
Maternal (whole serum basis)	196	0.38[a]	y = 1.47 + 0.15x
Breast milk - neonatal (fat basis)	138	0.30[a]	y = 6.36 + 0.12x
Breast milk - 5 month (fat basis)	45	0.24	y = 6.24 + 0.11x
Fish consumption during pregnancy with			
Cord (whole serum basis)	189	0.13	y = 1.05 + 0.05x
Maternal (whole serum basis)	190	0.31[a]	y = 1.57 + 0.13x
Breast milk - neonatal (fat basis)	135	0.24[b]	y = 6.47 + 0.10x
Breast milk - 5 month (fat basis)	45	0.36[c]	y = 6.19 + 0.18x
Cumulative fish consumption (normalized) with			
Cord (whole serum basis)	198	0.08	y = 1.05 + 0.02x
Maternal (whole serum basis)	196	0.29[a]	y = 1.52 + 0.07x
Breast milk - neonatal (fat basis)	138	0.21[b]	y = 6.38 + 0.06x

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Table 12 (continued)

Assessment Parameters	N	r	Regression Equation
Breast milk - 5 month (fat basis)	45	0.10	y = 6.31 + 0.04x

[a] $p < 0.001$
[b] $p < 0.01$
[c] $p < 0.05$

DISCUSSION

Despite their widespread distribution in our environment and concern about human accumulation, few studies are currently available on the serum PCB levels of individuals chronically exposed to PCBs via their diet. Moreover, the toxicology of PCBs is little understood in comparison with that of other xenobiotic chemicals, such as DDT and BHC (Hirayama, 1976; Yoshimura and Yoshimura, 1976). The present longitudinal study was designed to investigate effects of PCB exposure from contaminated fish consumption on two potential at-risk groups, pregnant women and their newborn offspring. While several reports have appeared on the transfer of PCBs from mother to child via breast milk (e.g., Kodama and Ota, 1980; Kuwabara et al., 1979), only a few studies examined the transfer of PCBs in utero (Akiyama et al., 1975; Kodama and Ota, 1980; Masuda et al., 1978). These studies used either relatively small unexposed samples or women and infants exposed during the Yusho incident. No study to date has examined the pattern of transfer from mothers to offspring exposed via the food chain.

The data in this report provide empirical support for linkages between source of contamination and body burden shown in the analytic model (Figure 1). They also provide evidence of the preponderance of more heavily chlorinated isomers in the serum and breast milk of women whose exposure to PCBs is due in part to the ingestion of contaminated fish. The small amounts of 1016 present in the biological specimens and the poor reliability of their measurement indicate that values matched to the 1260 standard are more likely to yield meaningful findings.

The present study evaluated the linkages from fish consumption to maternal body burden and subsequently to the

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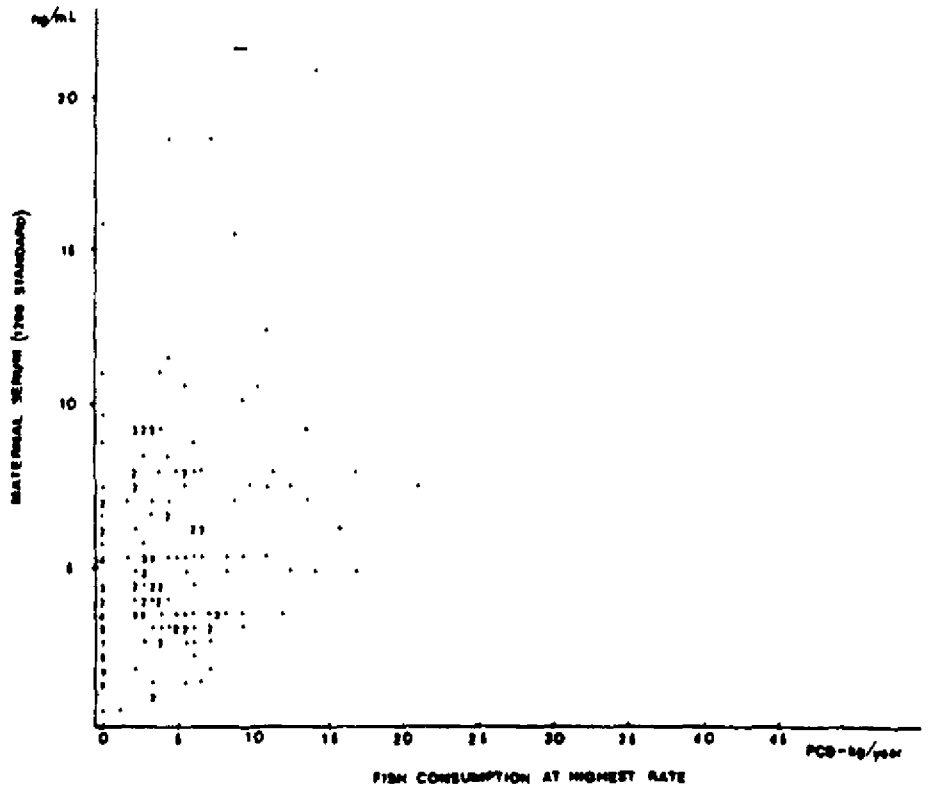

Figure 2. Scatterplot of maternal serum (1260 standard) by fish consumption at the highest annual rate.

developing fetus and breast milk. Even though exposure levels were only moderate in the women studied, reported contaminated fish consumption predicted PCB residues in two measures of body burden, maternal serum and breast milk. These results confirm prior studies which found an association between fish consumption and PCB residues in serum specimens (Kreiss *et al.*, 1981; Kuwabara *et al.*, 1979; Humphrey, 1976), while also demonstrating that the relationship holds for younger women, an age group not previously studied. The particular significance of this finding is that PCBs in the environment may pose a risk to the fetus and newborn, since the women in this age group are in the middle of their childbearing years.

Transplacental passage by the PCB molecule was indicated by the significant positive correlation between maternal and

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cord sera (r = 0.41, $p < 0.0001$), confirming two prior studies which yielded similar findings (r = 0.24, Masuda et al., 1978; r = 0.45, Kodama and Ota, 1977). The transfer of PCBs to breast milk was confirmed by a similar positive correlation (r = 0.27, $p < 0.01$, for maternal serum on a whole basis to neonatal breast milk on a fat basis), confirming the 1978 finding of Masuda et al. (r = 0.29). While cord and maternal sera yield similar results regardless of whether the analysis is performed on a whole serum or fat basis, breast milk residues yield varying results due presumably to fluctuations in lipid levels in breast milk.

The present data are consistent with the notion that PCBs move through the environment and the human body into systems which may potentially threaten the infant both before and after birth (Swain, 1981). At this time it is not clear which of these exposures--prenatal (intrauterine) or postnatal (via breast milk)--has the greater impact on infant development. While the absolute quantity of PCB residues is substantially lower in cord serum than in breast milk, the fetal organism is particularly vulnerable during the prenatal period. One factor that has been overlooked in this debate (e.g., Masuda et al., 1978) is the size of the fetus. When PCB exposure is calculated on the basis of body weight, the infant's prenatal exposure is substantial. In addition, the values for PCBs in cord serum may underestimate actual levels of exposure for reasons discussed earlier. Moreover, different biological systems in the fetus and newborn may be affected depending on the developmental period during which exposure occurs.

The long-term implications for human health of the association between contaminated food ingested at chronic low levels and PCB body burden have only begun to be studied. Unlike findings from studies of persons exposed occupationally to PCBs, preliminary reports suggest possible increases in elevated blood pressure levels (Kreiss et al., 1981) and a greater frequency of reported cancers (Humphrey, 1983) in persons exposed to PCBs through the ingestion of contaminated food. Preliminary analyses of the effect of intrauterine exposure on neonatal behavior indicate a number of subtle behavioral deficits, which may have implications for subsequent development (Fein et al., 1983a). The present study provides empirical support for the use of maternal reports of fish consumption as reliable indicators of PCB exposure, while also predicting transfer of PCBs in utero and in the breast milk.

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PART V

REGULATION OF PCBs

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CHAPTER 23

REGULATION OF PCBs IN MICHIGAN

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Everyone who speaks should make some effort to identify his credentials and, in that regard, I am not sure just what I should say. I come here not having heard what you listened to yesterday, nor will I be able to listen to what may follow. I am sort of hit-and-run and that is not really fair; it is not fair to you and it is not fair to me, but that is the way it is. I guess what I'll tell you is how I view myself. I view myself as a regulator. I think I once qualified as a scientist. I don't think I do anymore; however, some people still tend to be confused as to whether I am a regulator or a scientist. I am responsible to a policy-making citizen board of seven people. I welcome the advice that I hope this conference will provide. I should tell you, however, that I receive a lot of advice. As near as I can count, there are about thirteen commissions that make up a part of state government that, in one way or another, are intended for citizen input into advising the Department or having an even more direct impact on Department of Natural Resources (DNR) programs. In addition to those 13 "core" commissions, give or take one or two, as near as we can tell there are about 200 advisory committees that provide advice to the agency I direct. I spend a lot of time taking advice and I appreciate it; I do the best I can with it. Today I have a semi-prepared set of comments and a few from my cuff. First of all, I hope it is obvious that I am pleased that this conference is taking place. I genuinely expect that your product will be helpful to the DNR and to the State of Michigan regarding fishes of the Great Lakes. It should go without saying we are dealing with a highly controversial area and I hope that you will provide help with regulatory decisions. We've already seen some of the background that may be useful to a number of us to more formally appraise our choices. And I

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hope that regulators will better understood the scientific dilemmas and I hope that scientists will better understand our regulatory dilemmas. I think there is enough for both of us. Now, it is probably not known to most of you, but for the sake of completeness, remember that the DNR deals with a number of issues, a number of responsibilities that relate to the question of polychlorinated biphenyls (PCBs) in fish. First of all, we are charged with controlling air and water pollution in Michigan, the two major sources of PCBs in the Great Lakes. We are charged with regulating sport and commercial fishing in the Great Lakes and we provide and promote sport fishing opportunities. Most trout and salmon in the Great Lakes are paid for by Michigan sportsmen and are released from our hatcheries. They wouldn't be out there, and people wouldn't be eating them, if we--as an agency channeling sportmen's dollars--weren't busily putting them out there. That is a very significant responsibility. I would thus categorize us as both a promoter and regulator in several areas affected by the PCB question, which likens us to the old Atomic Energy Commission--in the position of both promoting and regulating atomic energy. I suggest that this is not a comfortable place for anyone to be, nor is it the kind of structure that I think is ideal. But to some degree, that is how it is. I believe that this presents a dilemma to us that few others face. We are constantly on the defense to justify our position by those who do not believe we should allow fish to be taken that contain any PCBs and, to the other extreme, by those who think that PCBs are not dangerous. Of course, it should be understood that we are not burdened with setting food standards nor are we burdened with inspecting food for compliance. I am glad to share those responsibilities with the appropriate agencies.

But where do we go for realistic advice? I guess the only response to that is to the scientific community. Unfortunately, from our determination prior to this meeting, and I suspect maybe after this meeting, we will find that there is some disagreement on facts and some disagreement on interpretation among the scientific community. I hope that what we would describe as a large gray area will be seen as a somewhat smaller area, and one not quite so gray. I think most scientists and most all of us agree that the less PCBs in food, the better. Most responsible scientists also agree that PCB concentrations in fish in the Great Lakes at least have decreased considerably in recent years. Ripe for discussion, however, are questions regarding acceptable concentration, sampling the fish with the skin on or off, and how to discourage people from eating fish which are over the limit. These are the kinds of questions that produce varying responses.

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One of my staff members was very helpful to me recently when he defined a regulatory decision as something like this: "Regulation by its nature is a pass-fail situation. Either it is or it isn't." In effect, our task is to draw a line across a large gray area, making one side of it black and one side of it white.

Now, perhaps we can realistically expect additional research funding, additional research results. We will improve our scientific base, our data base, regarding the question of PCBs as a human health hazard. Speaking realistically, however, if I read correctly, the opportunities, the funding sources for such scientific investigations, those budgets are shrinking along with everybody else's.

Well, what are we to do and what have we done and what are we doing? Very briefly, I would point out: The record will show that Michigan has led the nation with the PCB Control Act of 1976. Michigan's DNR was an early and strong supporter of this bill. I understand you have been told that we were prodded into it, but I will let you make your own decisions on that. Subsequent national legislation to stop production and usage of PCBs should ultimately pay off in reduced atmospheric inputs of PCBs to the Great Lakes. Within the state of Michigan we have vigorously pursued the removal of PCBs from any use, anywhere. Incidently, we are also oftentimes responsible for disposal, and as of the moment we have no authorized disposal site, incineration, or entombment facility for PCBs within the state of Michigan. The State Department of Agriculture regulates PCB content in food. Of course, you are aware of the debate over whether Michigan should unilaterally reduce the allowable PCB content of fish from 5 to 2 mg/kg. As you examine that question, with or without responsiblity to take action, I ask that you present yourself another question. If PCB content were up to 2 mg/kg in Michigan commercial fish, what would we achieve in reduced exposure and at what cost? I would have to point out that in the quick review of the knowledge that I have of consumption of fish and PCB-tainted fish in Michigan, one species that has consistently shown the higher level of PCB is the lake trout. Under commercial fishing, the only legally caught lake trout in Michigan currently are taken by the Indian fishery. Many of those lake trout go directly to restaurants without Inspection of any kind. Many of those trout also are sent outside the state. It is the DNR's position that commercial fishing in Michigan should be regulated no differently than in other states, and that the best scientific information should be used to decide the national standards. I personally would have no difficulty in going to 2 mg/kg if it were part of a national standard. I see enormous difficulties in attempting to do it unilaterally.

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Obviously, the greatest number of fish, the greatest risk, the greatest exposure, whatever that may be, comes to sport anglers. That is the way that most of the fish are taken, the way most of the fish enter the food chain. We, in conjunction with and guided by the Michigan Department of Public Health, have warned sport anglers of the dangers of eating contaminated fish. We show on the Michigan Fishing Guide, which every person receives upon purchasing a fishing license, just what waters have been found to contain contaminated fish. The fishing guide also tells how to prepare and cook fish to reduce contaminants to maximum extent, and gives a special warning to pregnant women or women who expect to bear children at a later date.

I would say our general philosophy is to respond to the threat of contaminants in what we view should be a balanced manner. We realize that this will not satisfy certain elements of the public who have certain philosophical viewpoints or single-issue interests. However, we feel it is the only way we can fulfill our multiple statutory charges as a regulatory department. I want to preface my next remark very, very carefully, but I would ask you to look at it as an alternative which I definitely would not propose, nor would I support; but if you wanted to go to maximum lengths to limit exposure of people to fish, I think the thing you would do would be to discontinue stocking of trout and salmon. Those fish are not naturally reproduced generally but are there because we as an agency put them there. That ends my prepared remarks. I would just ask you to think about the things I think about, that we think about, as an agency as we view our multitude of roles in this subject. We have to recognize the value of the tourist industry that is supported by the sport fishery. I suspect you are going to get more details about that a little bit later on. It is a very, very large, several hundred million dollar, annual industry. As I said before, obviously most of the fish that are eaten from the Great Lakes are taken by sport fishermen. I am going to use the word "most" a number of times here. Most are taken by sport fishermen. Most trout and salmon would pass the standard of 2 mg/kg most of the time. Most trout and salmon are cooked for eating with the skin off. Fishermen have been advised for years to skin and trim body fat. Most of the PCB exposure is behind us. These are not necessarily in order. Canada, as you are aware, does have a 2 mg/kg standard. It is my understanding that they established that on the basis of "dorsal plug of muscle". This is a very conservative way of sampling; and I would say that based on what we know of our fish, our fish will consistently pass 2 mg/kg if sampled in that manner. It is also my understanding, maybe I should brand it as hearsay, that fish from Canada that will not pass the 2 mg/kg standard are customarily exported. PCB concentrations in

Michigan fish are declining and nearly all salmon will pass the standard of 2 mg/kg any time in 1982 either on the Great Lakes themselves and in the stream harvest in the fall. As we examine the question of going to 2 mg/kg, I think if we looked at the costs in terms of reduced risk that is one of the elements on the board. If the State Department of Agriculture is asked to enforce a 2 mg/kg standard on PCBs in fish, and to do it unilaterally, I think they have every right to ask what other programs, also erected as defenders of risk, do you want them to drop. How much net reduction of risk will be achieved by that?

In closing, I am reminded of something of the PCB situation as I view the question of whether it is appropriate to go to two mg/kg or not, something like a question that was asked of Will Rogers during World War I. Reportedly, Will Rogers was asked, "What should we do about the German submarine mess?" Very quickly he said, "Drain the Atlantic Ocean." The reporter immediately said, "Well, how are you going to do that?" Rogers said, "That wasn't the question you asked me. That is for somebody else to worry about." So don't leave asking the position of Will Rogers. It is harder to drain the Atlantic Ocean than it is to decide how to do it.

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CHAPTER 24

THE SCIENCE-POLICY INTERFACE IN REGULATORY DECISION-MAKING

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INTRODUCTION

Several speakers have noted that decisions to regulate environmental contaminants proceed on uncertain grounds. Scientific data are equivocal. Public demands are in conflict. We are here in hopes of improving our understanding of what should be done to resolve these issues.

If issues are to be resolved, they must be stated clearly. Hopefully, this paper will serve that purpose. My objective is to identify issues that arise because of scientific uncertainty in decisions to regulate environmental contaminants and to examine how social policy is or may be used to resolve these issues.

The following section describes the major types of tasks involved in decisions to regulate environmental contaminants. I use this description to illustrate the science-policy interface that occurs in regulatory decision-making. The next section continues this theme by examining how scientific uncertainty arises and creates a need for resolution of issues by means of policy. How policy is or may be used to resolve issues associated with scientific uncertainty is described in two more sections of the paper. One section examines procedural mechanisms and the second describes sources of policy guidelines for resolving issues in regulatory proceedings. Before concluding, I very briefly examine the implications for scientific uncertainty and how it is resolved that are present in proposals that have been recently made for reforming the regulatory process.

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THE SCIENCE-POLICY INTERFACE

In a very general sense, decisions to regulate environmental contaminants involve balancing risks and benefits. This is not to say that risks to human health are not the primary concern of regulators. Rather, this statement reflects the fact that the act of reducing risks means foregoing some things we value. For example, in order to reduce the risks to health associated with polychlorinated biphenyls (PCBs) we reduce consumption of fish from the Great Lakes and reduce the fire resistance of dielectric fluids used in capacitors and transformers. We give up something and gain something by regulating environmental contaminants. Collective choices would be made irresponsibly if they did not include some consideration of what must be foregone in benefits in order to achieve a reduction of involuntary health risks.

The process of balancing risks and benefits involves many tasks which may be summarized as follows:

(1) identify risks and benefits to be considered;
(2) gather data to be used in assessing risks and benefits;
(3) assess the magnitude of risks and benefits;
(4) weigh and judge the risks and benefits associated with different regulatory options;
(5) choose a performance standard from the list of options.

These tasks do not necessarily proceed in the order I have listed them. Moreover, the extent to which any one of them is carried out depends on a number of factors. Among these are the time available for making a decision, the amount of data that exists, and the policy area (e.g., environmental contamination in food, air, water, or land) that is involved. Despite variation among different decisions, however, there is always an interface where science gives way to policy choice.

The task of determining what risks and benefits are to be included in decision-making (task 1) is a matter of policy. For example, risk consideration may be limited to human health risks or it may encompass a wide range of environmental risks. Benefits might be limited to issues of food supply or they might be expanded to include secondary and tertiary impacts of regulations. The job of making these policy choices belongs in legislatures. Although legislatures are sometimes less than explicit, they do indicate the major categories of risks and benefits to be examined. The extent of consideration is indicated by legislative provisions concerning decisions which must be made rapidly and those that should proceed in a more

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deliberative fashion. Scientific findings inform the specific selection of what risks and benefits are to be included, but choices are guided primarily by policy, not science.

The task of collecting data (task 2) would appear to be a matter of science, but it also involves policy choices. Existing scientific knowledge and ability do determine the extent to which this task can be carried out. But the degree of factual accuracy required of regulators will influence the actual extent to which it is carried out. Requirements about factual accuracy in regulatory decision-making are determined by policy. For some decisions which must be made quickly, accuracy requirements are usually reduced. Regardless of the time frame involved, requirements on factual accuracy may differ greatly from those relied on by the scientific community.

The task of assessing the magnitude of risks and benefits (task 3) is also a matter of science and of policy. Science provides both data and theoretical guidelines for interpretation and inference. Nonetheless, scientists' data may be incomplete, their interpretations of the data may vary, and their inferences may disagree. Despite scientific disputes, regulators must decide. How they choose among different interpretations and inferences amounts to a policy on science.

The fourth and fifth tasks, weighing risks and benefits and choosing a performance level, are policy dominated. In all statutes pertaining to environmental contaminants, the direction of policy is toward reducing risks (McGarity, 1979). However, the amount of reduction of risks that is indicated will depend on the relative weights or values assigned to risks and benefits by policy and policy makers. One may disagree with these relative weights or values, but this disagreement is based on policy preference, not scientific grounds.

To state that weights or values are assigned to risks and benefits is somewhat misleading. I do not mean to imply that the regulatory decision process involves taking a unique set of numbers, assigning them weights, and then performing a kind of linear combination to arrive at an answer. The process is far more subtle. It is subtle because there are few, if any, unique numbers in regulatory decision-making. The task of weighing risks and benefits is not separate from the tasks which precede it. The weights which are assigned to risks and benefits implicitly determine how policy is applied in the tasks of collecting data, interpreting data, and drawing inferences about the magnitude of risks and benefits. Policy weights are not simply applied to numbers, they are used to determine numbers. To understand why this is so, we need to examine the

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nature of scientific uncertainty in more detail, for it is this uncertainty that defines the science-policy interface.

SCIENTIFIC UNCERTAINTY

Some observers contend that risk and benefit assessment is entirely a scientific process, whereas deciding what to do about risk is a question of pure social policy. However, three types of situations diminish our ability to settle questions about the magnitude of risks and benefits on purely scientific grounds (McGarity, 1979). These are:

(1) insufficient data;
(2) disagreements over data interpretations;
(3) disagreements over inferences from data.

The scientific uncertainty created by insufficient data is especially problematic for regulators dealing with environmental contaminants. By definition, these substances are not intentionally added to food, air, water, or land. Therefore, the extent of contamination is initially unknown. Since exposure is unanticipated, little information may exist about the health risks posed by exposure, let alone the economic impacts of regulations designed to reduce risks.

Since existing data is extremely limited in this situation, regulators must decide what data should be collected beyond what currently exists. But additional time spent collecting data means prolonged exposure. Thus, regulators are faced with a choice between resolving issues raised by insufficient data by means of science or by policy conclusions that quick regulatory action is needed. Resolution of issues raised in this situation is based on policy, not science.

Generally speaking, regulators will act on insufficient data when harms due to human exposure are suspected to be irreversible (McGarity, 1979). An added impetus for responding quickly exists if the amount of time and resources required to obtain the needed scientific data would be relatively large. Needed time and resources can be expected to be large when exposure is of the chronic, low-dose variety and where conditions of exposure are not stable. Furthermore, if regulatory action is not expected to result in substantial economic impacts, quick action is more likely to be taken (McGarity, 1979). Where these conditons do not hold, regulators are more likely to await further data. If they did not delay, the likelihood of reversal on appeal in the courts would increase, thus making the possiblity of quick action moot.

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A second situation which creates uncertainty is the problem of scientific disagreement over data interpretation. Even when data is relatively complete, scientists may not agree about the validity of the data or its meaning. This problem occurs frequently in diagnoses of lesions by pathologists, interpretations of epidemiological data, and reviews of test methodologies employed in experiments (McGarity, 1979).

To a certain extent, substantive issues which arise over data interpretation can be resolved by further scientific judgment. Through years of experience in interpreting data and the meaning of the physical world, scientists may develop different outlooks and, thus, judge differently. These differences in scientific judgment are unlikely to be changed by lengthy regulatory proceedings. The crux of the problem for regulation is separating differences in scientific judgments from the public policy preferences of scientists (McGarity, 1979). This matter cannot be settled simply on the basis of a scientist's reputation since highly respected scientsts are not immune to having opinions. Rather, the problem calls for a thorough understanding of and distinction between those issues that require scientific judgment and those that require policy judgment.

A third situation that creates scientific uncertainty is disagreement over inferences about unobserved events to be drawn from observed data. For a variety of practical or moral reasons, some questions posed in scientific terms simply cannot be answered by science. Alvin Weinberg has labeled these types of questions as being "trans-scientific" issues (McGarity, 1979).

One example of a trans-scientific issue is the extrapolation from high dose to low dose. One can give arguments in support of one or another dose response at a very low dose (Weinberg, 1978). The value of a particular set of arguments to regulators depends, of course, on the validity of the assumptions used, a matter which science has yet to settle. Another example of a trans-scientific issue is the problem of using data on other species to arrive at estimates of dose response for humans. Even at the high dose level, uncertainties will persist over this method of inference.

The existence of trans-scientific issues does not mean that regulatory decisions should be postponed until the scientific community resolves them. Indeed, it is precisely because the scientific community is unlikely to provide answers to these questions in the foreseeable future, if ever, that regulatory decisions should not be postponed (McGarity, 1979). Superficially, trans-scientific issues appear to be questions of

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fact. They are not. They are questions that can only be resolved by law and policy.

In order for regulators to resolve uncertainties about appropriate inferences, they must know the type of result intended by policy. For example, if a scientist informs a regulator that a certain assumption will tend to overstate risks or benefits, the regulator must decide whether this result is desirable. If the regulator knows what result is desired by policy, he can resolve the issue on policy grounds. The phrase "erring on the side of safety" reflects this result-oriented approach to resolving issues of scientific uncertainty (McGarity, 1979).

Similarly, regulatory policy may not require the same level of certainty that scientists do in drawing inferences from data (McGarity, 1979). It is routine for scientists to use the 95 percent confidence level for determining statistical signficance. Regulatory decisions may require something less than this. Again, it is a matter of policy, not science, to decide the direction in which one wants to err and how much.

Not all scientific facts involve uncertainty. When this is the case, or when consensus exists among scientists, principles of scientific proof are followed in regulatory decision-making (Ficci and Molton, 1981). But there are many regulatory decisions in which scientific certainty does not exist and disagreement prevails. Policy judgment enters where scientific uncertainty begins. Therefore, assessments of risks and benefits are not uniquely determined by facts, but reflect the weights assigned to them by policy.

The conclusion that regulators must exercise policy judgment in assessing the magnitude of risks and benefits, as well as in balancing risks and benefits, is important. It aids understanding of the respective roles of science and policy in regulatory decision-making. However, while it tells us that policy values may be substituted for facts, it does not tell us to what degree this may be done or what policy guidelines are used. The next two sections explore these questions.

PROCEDURAL MECHANISMS

The degree to which regulators can substitute policy for scientific facts depends on the procedural requirements contained in organic statutes and related laws on administrative procedure. This legislation indicates the degree of factual accuracy required of regulators by the extent to which

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trial-type hearings rather than more informal procedures are required of agencies.

Trial-type hearings are designed to increase the factual accuracy of agency decision-making (McGarity, 1979). These proceedings do not assume pure objectivity of all parties. Rather, through an adversarial process, each party has the opportunity to reveal defects in the reasoning of others (Majone, 1979). Thus, factual accuracy improves as implicit assumptions and biases that color testimony are revealed.

However, trial-type hearings have several drawbacks. They are lengthy. They are costly. And they can only resolve issues of fact (McGarity, 1979). Because a speedy response to health risks is desirable, and because many issues of scientific uncertainty cannot be resolved through trial-type hearings, legislators have made provisions for the use of less formal procedures. As we shall see, however, these procedures may lead to decreased factual accuracy.

One of the less formal alternatives is the "notice and comment" procedures for informal rulemaking (Majone, 1979). In this procedure, regulators publish a rationale for a proposed action and public comments are invited. The agency then publishes its final decision along with a response to written comments. The Food and Drug Administration (FDA) uses a variant of this procedure in regulating environmental contaminants in food (Merrill and Schewel, 1980).

The advantage of the notice and comment procedure is that it permits relatively quick response to situations in which regulators believe postponement may lead to undue harm to exposed populations. It is also useful when conditions, such as scientific evidence or rates of exposure, are changing rapidly. The drawback, however, is that this method provides little incentive to regulators to fully investigate available or soon to be developed scientific information.

Another procedural reform is the use of advisory panels or special commissions comprised of scientists and experts (Majone, 1979). These panels not only provide peer review of scientific findings, but can be helpful in sorting out questions of scientific fact from issues of science policy. They can help improve regulatory proceedings by helping to build consensus and by advising when trial-type hearings would be productive. Too much consensus, however, can result in a retreat from, rather than a confrontation with, important political issues. As a result, scientific advisory groups have been accused of undue enhancement of the extent to which regulatory

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decisions are based on scientific fact rather than policy (Nelkin and Pollak, 1979).

There are other alternatives, such as "paper-hearings" and science courts, but the two alternatives just presented illustrate an important point. While the "notice and comment" procedure minimizes incentives for increased factual accuracy, the scientific advisory panel maximizes incentives to obscure issues while over-emphasizing the objectivity of decision-making. Neither of these alternatives offers sufficient incentives for clarifying where science ends and policy begins. Responsiblity for recognizing the science-policy interface thus depends on the awareness and insight of the individuals involved. In contrast, trial-type hearings focus strictly on factual issues and do not depend solely on the abilities of those who testify.

The extent to which regulators may substitute policy for facts depends on the degree of factual accuracy required of them. This varies from one decision to another, but a trend has developed toward increased use of informal procedures. Some of these (e.g., paper-hearings) seek to remedy the limitations of informal procedures (Majone, 1979). Continued improvement is still needed. Agencies now use a variety of informal procedures, and, for the reasons I have pointed out, each one may be expected to produce different performance outcomes.

POLICY GUIDELINES

Despite the type of procedure followed, all regulatory decisions involve degrees of uncertainty. Policy must be applied to resolve issues that cannot or will not be resolved by scientific fact. In order for regulators to resolve issues, they must know the type of results intended by policy.

Regulators determine desired results by examining their legislative mandate, court decisions, and the political environment (McGarity, 1979). The legislative mandate indicates the direction of desired results, though finding legislative intent is hardly a straightforward affair. Key phases of mandates are important.

For example, the FDA has characterized environmental contaminants as "added" substances that are "unavoidable" in the production of food. This interpretation triggers the "may render injurious" standard of the Food, Drug, and Cosmetic Act. This standard means that the FDA must demonstrate a significant possiblity of harm created by food containing an environmental contaminant. Conclusive proof of injury is not required

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(Merrill and Schewel, 1980). Thus, the FDA's mandate indicates the desired result, providing the agency policy grounds on which to resolve issues caused by uncertainty.

For a variety of reasons, legislatures are sometimes less than clear on the results they desire from legislation. Thus, the courts play an important role in interpreting regulatory mandates. In the area of environmental contaminants, the courts have been especially important in testing agency interpretations of their mandates. Numerous court decisions have been instrumental in distinguishing the regulator's responsibility to resolve trans-scientific issues on policy grounds and the degree of factual accuracy required in regulatory decisions (McGarity, 1979; Ricci and Molton, 1981).

While one should expect that agency interpretations of their mandates and subsequent court decisions are important in determining how they resolve issues by means of policy, it is also true that politics is an important policy referrent as well. Agencies that misinterpret the political climate will quickly find themselves subject to scrutiny by legislators. This is most likely when the intent of legislative mandates are blurred, leaving wide discretion to regulators in construing that intent (Noll, 1971). Inasmuch as an agency must rely on the political environment for policy signals, they should make sure that all affected parties have the opportunity to be heard (McGarity, 1979; Nelkin and Pollack, 1979). But, political winds are fickle. If we desire consistent policy choices of reglators, they should be given more stable policy referrents than the political climate.

A CRITIQUE OF PROPOSALS FOR CHANGE

Critics of regulatory decision-making have charged that current procedures result in irrational decisions and poor social choices. They have proposed a number of analytical frameworks which, they contend, will improve the regulatory decision calculus. Of these frameworks, four apply to environmental contaminants and will be examined here briefly. They are:

(1) risk-benefit analysis;
(2) cost-effectiveness analysis;
(3) regulatory budgeting; and
(4) cost-benefit analysis.

Risk-benefit analysis is a shorthand way of saying that the types of risks and benefits now included in decision-making should be expanded. The steps involved are similar to those I

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described earlier in this paper. The difference is that the consideration of different types of risks and benefits would be encyclopedic rather than delimited by policy. Accordingly, data collection and assessment would be enlarged. Presumably, risks and benefits would be weighed equally. No guidance would be provided as to how issues of scientific uncertainty would be resolved. Greater factual accuracy would be required, thus increasing the response time to contamination problems, but decreasing the substitution of policy for scientific fact.

Cost-effectiveness analysis involves divising an "effectiveness index" based on the goals of regulation. In the case of environmental contaminants, the index might be number of lives saved, years of longevity produced, number of cancers averted, or person-days of illness prevented. Regulatory options would be rated in terms of their output using the effectiveness index as a measure. Each level of effectiveness would be associated with the cost of administering the regulatory option. The ratio of cost to effectiveness for each option would then become an added piece of information to decision-makers, although the most cost-effective option would not necessarily have been chosen.

Many difficulties are presented by this framework. Different results are achieved with different effectiveness indices (Schwing, 1979). Important costs, such as reductions in food supply, are omitted. Scientific uncertainty remains, but with no policy guidance as to its resolution in index measurement.

Regulatory budgeting is similar to cost-effectiveness analysis, except that the notion of costs is expanded to include costs of regulation to society beyond purely administrative costs (Lave, 1981). Agencies would be limited in the total costs they could annually produce. In addition to the problems enumerated for cost-effectiveness, this framework would involve uncertain cost estimations and give greater weight to costs than is now the case. It also adds a new political dimension to regulation through the annual development of the regulatory budget constraint by Congress.

Cost-benefit analysis involves enumerating all the costs and benefits of a regulatory option in terms of dollars, where possible. Under this framework, decision-makers receive the added piece of information of whether or not an option's benefits exceed its costs. In practice, however, techniques for valuing benefits and costs in dollars are unreliable (Baram, 1980). This framework does not resolve problems of inadequate data, disagreement over data interpretation, or disagreement over inferences. In fact, these difficulties are confounded by

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the expansion of the number and types of costs and benefits to be considered. This in turn raises the problem of appropriate procedural means for enhancing factual accuracy while preserving regulators' flexibility for responding quickly to contamination problems. This framework would also give greater weight to economic efficiency goals than is now the case.

Despite their weaknesses, the proposed frameworks do contain a number of valuable suggestions. They would focus increased attention on implicit policy choices and the establishment of consistent grounds for balancing competing objectives. They would also provide a mechanism for comparing different regulatory actions which seek to achieve the same goal--risk reduction--thus enhancing our ability to establish priorities for allocating our limited resources. Finally, they give more attention to what must be given up in order to achieve risk reduction.

Adopting any one of these frameworks would result in a subtle shifting of policy goals. Perhaps we as a society desire such changes. But if that is the case, the appropriate forum for deciding is legislative not regulatory. Before legislators decide, more attention should be given to the consequences of change. In particular, the fact that these frameworks will produce assessments of risk and benefits that are not unique, but are outcomes of both policy and science, needs greater recognition. These frameworks would not simply change the range of numbers used and how they weighed in reaching decisions. They would also change the policies used to resolve the scientific uncertainty encountered in producing estimates of risks and benefits.

CONCLUSIONS

I have attempted to clarify the interface at which science and policy meet and to show how procedural means and policy are used to resolve issues of scientific uncertainty in regulatory decision-making. I have argued that the weights given to risks and benefits by policy not only determine how regulators balance them in choosing a performance level, but determine as well how the magnitude of risks and benefits is assessed.

When scientific uncertainty arises because of questions that transcend science, there is little we can do to improve decision-making except to devise clear policy referrents. Scientists have a role here, I think, in investigating the relative magnitude of risks and benefits that accompany various collective and personal choices. Beyond this, we should expect better decisions by regulators as more and better data are

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collected on questions of fact that do not transcend science. However, we should become more aware of those issues that must be settled on policy grounds. Better procedures can be designed if things that are not issues are resolved in appropriate forums and given policy guidance by legislatures and courts.

We should not be quick to adopt new frameworks for decision-making whose policy consequences have not been thought out. Many of the problems of interpretation of legislative intent are now being resolved in the courts. We should expect that as they are resolved and agency procedures are reformed that the lengthiness, if not the complexity, of regulatory proceedings will be reduced. Scientists can help by carefully examining where their contributions can be made most valuably at the science-policy interface.

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CHAPTER 25

DEALING WITH MULTI-AGENCY AND MULTI-STATE REGULATION OF POLYCHLORINATED BIPHENYLS

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INTRODUCTION

During the early 1960s, interest increased concerning the biological effects of environmental levels of chlorinated pesticide residues such as DDT and chlordane. Measurement of low levels of these compounds in biological samples required the development of sensitive analytical procedures that could both separate the pesticides from each other and from similar compounds and measure the amount of each compound present. The technique that was developed to perform this analysis was gas chromatography. Gas chromatography proved to be a very useful method for determining the concentrations of low levels of pesticides in environmental samples, but the detector often recorded the presence of a number of chemicals that could not be identified by comparison with known pesticide chemicals.

In 1966, Soren Jensen attempted to identify the unknown compounds that were being recorded during routine pesticide analyses. In order to determine when the unknown compounds first appeared in biological samples, he analyzed feathers from eagles that had been taken from museum collections. He found the unknown materials in feathers collected as early as 1944, before the widespread use of chlorinated pesticides, and so concluded that the unknown materials were not pesticides or degradation products of pesticides. By testing chlorinated materials that were in wide use before 1944, he eventually identified commercial polychlorinated biphenyls (PCBs) as the source of the unknown compounds, and published this finding in late 1966 (Jensen, 1966).

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A full discussion of the presence of PCBs in pesticide analyses was published by Widmark (1967), and this set off a number of investigations to determine the extent of environmental contamination by PCBs. The discovery that PCBs were common in the environment in sufficient concentrations to affect the reproduction of wild birds was published by Risebrough et al. (1968). This article was picked up in the press and initiated the widespread concern about possible human health effects from PCBs in the environment.

The Yusho incident that occurred in Japan during the summer of 1968 added to the public concern over the toxicity of PCBs. This was a case of widespread PCB poisoning caused by contamination of cooking oil. The resulting concern over PCBs led to regulatory activity and increased research throughout the world. In July of 1971, a similar incident in the United States contaminated a considerable quantity of chicken feed as the result of leakage of PCB heat transfer fluid. The U.S. Food and Drug Administration (FDA) eventually destroyed thousands of chickens and eggs that were fed this contaminated feed. Starting in 1971, Monsanto voluntarily limited sales of PCBs to closed electrical equipment applications and recommended that existing PCB-filled heat transfer systems be drained and refilled with non-PCB fluid.

PCB USE RESTRICTIONS AND FEDERAL GOVERNMENT REGULATIONS

The Yusho incident created considerable concern in the United States over possible contamination of food by PCBs. The FDA started routine sampling of foods for PCBs in 1969, and soon found that PCBs were present in fish from the Great Lakes, that there was PCB contamination of milk caused by use of PCBs as a solvent in pesticide sprays and as a component of sealants used in farm silos, and that there was contamination of chickens resulting from PCBs introduced into the feed as a component of ground bread cartons and wrappers. It has since become apparent that the presence of PCBs in fish is a problem that has existed since at least 1964, although PCBs were not identified as the cause of the problem until 1971.

From 1969 through 1971, the FDA established temporary tolerance levels for PCBs at 0.2 mg/l in milk, 5 mg/kg in edible flesh of fish, 5 mg/kg in poultry, and 0.5 mg/kg in eggs. In 1970, the FDA prepared a summary of the available information on the chemistry and toxicity of PCBs, and in 1972 published a notice of proposed rulemaking. The U.S. Department of Agriculture (USDA) also prepared a report on ways that it could act to limit PCB contamination of food (USDA, 1972). In 1973,

the FDA formally established limits for PCBs in food and animal feed and proposed a revision of these limits in 1977.

During 1970, the Council on Environmental Quality (CEQ) studied regulatory approaches to the problem of toxic chemicals in the environment. In its report, "Toxic Substances," published in 1971, CEQ identified PCBs as a major problem. The initial response of the responsible agencies was to establish a task force to review the available information on PCBs and recommend regulatory alternatives.

During 1973 and 1974, the U.S. Environmental Protection Agency (EPA) proposed the establishment of water quality criteria for PCBs in industrial discharges as part of a program for establishing such criteria for a larger group of pesticides. However, PCBs were not covered in the effluent standards until 1977.

The Occupational Safety and Health Administration (OSHA) adopted the standards for PCB exposure in industrial air that had previously been established by the American Industrial Hygiene Association. The National Institute of Occupational Safety and Health (NIOSH) conducted a major review of available data and an extensive program of industry assessment in the mid-1970s, and the final report published in 1977 recommended that the allowable concentration of PCBs in the workplace be reduced.

Government actions restricting the use of PCBs were not limited to the United States. Japan banned the manufacture and use of PCBs in the early 1970s because of public pressure following the Yusho incident. Sweden banned the use of PCBs at about the same time. International actions, particularly in the European community, were also taken to reduce the risk of food contamination by PCBs during the early 1970s. United States and Canadian activity to regulate manufacture, use, transport, and disposal followed during 1975 and 1976.

PCB LEGISLATION UNDER THE TOXIC SUBSTANCES CONTROL ACT

Senator Gaylord Nelson introduced a bill to amend the pending proposed Toxic Substances Control Act (TSCA) on March 26, 1976. This bill required the EPA to establish labeling and disposal requirements for PCBs and mandated an eventual ban on the manufacture and processing of PCBs. This provision was incorporated into TSCA as Section 6(e) and became a legislated requirement when TSCA was signed into law on October 11, 1976. The effective date of TSCA was January 1, 1977.

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Section 6(e) of TSCA required the EPA to establish rules to: (1) govern the disposal and marking of PCBs; and (2) prohibit, with certain exceptions, the manufacture, processing, distribution in commerce, and non-totally enclosed use of PCBs.

Final marking and disposal rules appeared in the Federal Register on February 17, 1978 (clarifying amendments to this rule appeared in the August 2, 1978, Federal Register).

On June 7, 1978, the proposed PCB ban rule was published in the Federal Register. The final PCB ban rule appeared in the Federal Register on May 31, 1979; this rule took effect on July 2, 1979.

The May 31, 1979, PCB ban rule specifically:

(1) prohibits the manufacturing, processing, distribution in commerce, and use of PCBs, except in a totally enclosed manner (with certain exemptions), after July 2, 1979;

(2) provides authorizations for certain processing, distribution in commerce, and use of PCBs in a non-totally enclosed manner;

(3) prohibits, unless exempted by EPA, all manufacturing of PCBs after July 2, 1979; and

(4) prohibits, unless exempted by EPA, all processing and distribution in commerce of PCBs after July 1, 1979.

Since the February 17, 1978, PCB disposal and marking rule requirements are integrated into this PCB ban rule, the rule now supersedes all earlier PCB regulations.

STATE LEGISLATION REGULATING PCBs

During the period between 1975 and 1977, significant activity, particularly among the Great Lakes states, occurred with respect to PCB regulation. The following states passed PCB regulations.

Michigan

Michigan Act 60, Public Acts of 1976, was passed by the legislature and signed by the Governor on March 25, 1976. The Act took effect April 1, 1977, and banned the use, manufacture,

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mg/kg PCB, except as a dielectric fluid in electrical transformers and capacitors. Act 60 also provided for labeling, reporting, and proper disposal of PCBs.

Indiana

In February, 1976, the State of Indiana passed PCB legislation similar in scope and intent to Michigan Act 60. The law became effective May 1, 1976, because it was stated that an emergency existed with respect to PCBs in Indiana. The law mandated that the Environmental Management Board promulgate rules required by the law, including rules regarding the disposal of PCBs. In Indiana, however, the law was not applied, nor were rules promulgated because of the pre-emption aspect of the Federal Toxic Substances Control Act.

Wisconsin

The Wisconsin Statute 144.79 (The Manufacture and Purchase of PCBs) was passed on July 1, 1977. This legislation required the Wisconsin Department of Natural Resources to adopt rules prescribing methods and designating sites and facilities for disposal of PCBs and products containing PCBs. The rule required reporting and the use of a manifest for PCB disposal. The rule also granted exemptions for sludge produced by waste water treatment effluents and the manufacture and sale of recycled paper products containing PCBs.

Minnesota

During 1977, the State of Minnesota passed the PCB Prohibited Use Act. This Act required that the Minnesota Pollution Control Agency develop regulations on labeling, use, sale, purchase, handling, and disposal of PCBs. These regulations became effective in October, 1977. Response to PCB spills and PCB disposal has been regulated through more current state waste disposal and regulations.

THE INTEGRATED APPROACH TO LEGISLATION

The primary agencies regulating PCBs at the federal level include the FDA, NIOSH, OSHA, and EPA; and at the state level, include the State Pollution Control Agencies (those in particular having existing regulations) and State Departments of Health. During the past six years, there has been a unified

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effort among these agencies to restrict further PCB contamination caused by this widely used substance.

A recent example of this unified effort may be illustrated by a recent case involving PCB contamination at a scrap yard facility. A state pollution control agency was recently investigating general disposal practices at a scrap yard in the Chicago area. The state inspector noted that PCB-containing transformers were being reclaimed and disposed of indiscriminantly. The inspector called EPA and indicated that violations of the federal PCB regulation were occurring at the facility. EPA performed a follow-up inspection immediately; and while correcting the disposal violations related to the PCB transformers, interviewed a number of workers at the site. A crane operator at this facility complained of skin irritations and recurrent headaches from his particular job of removing copper cores from the PCB transformers. The EPA inspector required the assistance of the State Health Department and the Cook County Hospital Department of Occupational Health in examining and reviewing the case of the crane operator. OSHA and EPA are completing enforcement work on violations of their respective regulations related to the workers' health and work practices and illegal disposal practices at the facility.

Other integrated approaches to PCB regulation often include discovery of PCB-contaminated fish in interstate transport by FDA. Such contamination incidents are generally reported to State Health Departments and State Pollution or Conservation Departments. These departments inform the EPA and a coordinated effort may then be initiated to track environmental and possibly industrial contamination in a particular area.

During the interim period, state warnings are often placed on a watershed advising against the consumption of sport-caught fish or toward limiting consumption. If an industrial facility is isolated as a possible contributor to the PCB contamination incident (from federal and state information), a complete facility inspection is conducted. This inspection may be conducted jointly by state and federal officials provided confidentiality is not requested under TSCA by the facility to be inspected. Enforcement action may then be taken if violations of the PCB regulation are documented.

Other integrated multi-agency approaches to the regulation of PCBs include the establishment of enforcement cooperative agreements with the states of Michigan and Ohio. These recent pilot grant programs (established between EPA and the state pollution control agencies) include the inspection of approximately 300 facilities using or disposing of PCBs. Inspections

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will determine compliance with the TSCA regulations and appropriate follow-up actions such as letters of compliance, notices of violation, or other enforcement proceedings. In cases where the state agency is not to conduct the enforcement activities, the case will be referred to EPA. State personnel are being delegated federal authority to do this work.

CONCLUSION

Multi-agency regulatory approaches to PCB contamination incidents during the past five years have proved to be effective. Both state and federal agencies have observed improved compliance during the period; and proper disposal, labeling, and industrial awareness of the PCB problem seem to be the strongest contributing factors. The joint regulatory approaches to PCB control will continue and will provide a strong base for control of other chemicals of concern to human health and the environment.

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CHAPTER 26

THE ROLE OF THE LEGISLATURE IN THE REGULATION OF TOXIC MATERIALS

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Legislatures must take action on a number of issues that affect the lives of everyone although legislators are often ignorant of the technical aspects of these issues. Only a very small percentage of the people in any legislature are competent in some technical discipline. You may find in the average legislature, similar in size to Michigan's (148 members), at the most 6, 7, or 8 people who have technical competence in some scientific discipline. To deal with this problem, states, with the help of the National Science Foundation (NSF), have established technical advisory mechanisms first for the governors of the several states around the country and then, in recent years, for the special needs of the several legislatures. Michigan is one of about twenty states that now have advisory mechanisms for their legislatures.

The legislature and the legislative process have a definite role in the kinds of issues we are discussing in this conference. In Michigan, the role is clearly stated in the state Constitution and let me take a moment to quote Section 51 of Article 4. It states:

> The public health and general welfare of the people of the state are hereby declared to be matters of primary public concern. The legislature shall pass suitable laws for the protection and promotion of the public health . . . Conservation and development of the natural resources of the state are hereby declared to be of paramount concern in the interest of the health, safety, and general welfare of the people.

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> The legislature shall provide for the protection of the air, water, and other natural resources of the state from pollution, impairment, and destruction.

I am proud to tell you that the Michigan legislature leads the nation in what they have done about these kinds of problems. It has responded by enacting a great number of environmental protection statutes, some of them dating back 20 to 25 yrs, but most dating back to the late 1960s and early 1970s. At that time, there was a rash of legislative action providing for environmental control. I can only give you a sample of the wide variety of those controls. I'm quite well aware of these because I was the sponsor, or one of the sponsors, of many of them. The legislature started out with what is considered to be the most important Michigan act: The Environmental Protection Act of 1970. It allows any citizen of the state to sue any entity or any other citizen of the state (citizen has a broad definition) in behalf of the public trust in the environment. Anybody can sue anybody because of a possible threat to the environment; no proof is needed that something has already happened. The class action opening has been used many, many times since the Act's passage. Twenty-eight other states have tried to pass such a law and 11 have actually passed one. It was even tried several times in the U.S Congress, but unsuccessfully. It was a landmark piece of legislation.

Several important amendments to the Water Resources Commission Act, which dates all the way back to 1929, were made in 1970 and 1973. The Air Pollution Control Act of 1965 was amended several times. The Phosphate Control Act was passed. The Inland Lakes and Streams Act, which dealt with the quality of the water in our inland lakes and streams, was enacted. Other environmental legislation of this period included: The Shoreland Protection Act, The Soil Erosion and Sedimentation Control Act, The Pesticide Control Act, and The Recreational Land Trust Fund Act. I would like to comment on this last one. Senator Kammer, from Pontiac, had the idea that we ought to set aside the oil and gas revenues from the Pigeon River Country State Forest, a second growth area but nevertheless a unique environmental area in which we have great pride. He said we should use this money for the benefit of posterity by buying lands that are sensitive in nature, but which Michigan doesn't now own. The revenues have been set aside for that purpose and, in the last several years, a great many excellent purchases of sensitive, environmentally important land have been made.

In addition, the legislature passed The Sand Dune Protection Act, The PCB Control Act, several acts on PBBs (polybrominated biphenyls), and an act creating The Toxic Substance Control

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Commission. This Commission, which is taking part in this conference, has been bringing to the forefront some important information on the problems that toxic materials and substances are posing for the people of Michigan. The Wetlands Protection Act, which I'll allude to later, was also enacted as was The Land Resource Inventory Act. The Public Health Code was completely revised with many of the revisions dealing with environmental concerns.

A Solid Waste Management Act and a Hazardous Waste Management Act were passed, although with great difficulty. There were many meetings drawing up the language of these acts and interested parties were brought in from all over the country. They were necessary to provide legislators with answers to many of the technical questions. Just yesterday, the House passed three bills which prohibit drilling and exploration for hydrocarbons in the Great Lakes waters. These bills went back to the Senate, will be dealt with this morning, and sent on to the Governor.

We have a long record of trying to deal with the questions you are grappling with here and other questions like them. Many of these Michigan acts preceded federal acts on the same subjects. One of the problems we have in trying to deal with federal acts, and several of the speakers have alluded to it, is the extensive delay often experienced in federal control. The previous speaker talked about all the work that was done in the 1960s on PCBs, the subject of this conference. In 1973, the Food and Drug Administration (FDA) set some limits on how many parts per million could be let into the food chain. In 1975, Congressional action was begun. In 1976, Congress passed The Toxic Substances Control Act and it was 1979 before the final rules were published in the Federal Register. Meanwhile, several of the states found it necessary to take control in hand on their own and they did.

I want to touch briefly on some other things the legislature does besides enacting laws. After a law is enacted, it is fleshed out. The law is pretty generic in nature and doesn't contain many details. A system of rules has to be established. These are also known as administrative procedures or regulations or by other names in different states. In Canada, they are called guidelines. After a bill is passed and becomes an act, the responsible agency works up a series of rules which provide the intimate details. In Michigan, this process requires public hearings, review by the Attorney General for legality, review by the Legislative Service Bureau to see that the words are right, and so on. Then the rules come to a joint legislative committee for review and approval or rejection. The committee

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cannot modify the rules because they are not the legislature's rules, they are the agency's rules. The legislative committee does, however, have a veto power if it doesn't think that the rules agree with the statute. If it thinks that the statute has been circumvented or otherwise distorted, or if it appears that the questions that were raised at public hearings have not been properly dealt with, the agency can be asked to take the rules back and amend them to deal with these concerns. Michigan is the only state of the 50 that has such complete veto power at the legislative level over administrative rules. To get that power, a gubernatorial veto of the bill allowing it had to be overriden several years ago--a very significant gain for the legislative process.

These administrative rules are very, very important and sometimes are extremely difficult to establish (as an example, it took over two years of diligent work to get the rules finally passed for both The Solid Waste Management Act and The Hazardous Waste Management Act, after the acts were passed). The agency had dozens of meetings trying to work out difficulties that people throughout the state had brought up with respect to these rules. They were finally passed, however, and are now under review to see if the rules, or the act itself, need to be changed in any respect.

Once administrative rules have been adopted, another legislative process comes into play--called funding. Funding doesn't seem to be a big word, but it is a very big word when an agency is trying to get it. In the legislative process, funding is set up by the appropriations committees of the two houses. The rules are taken to the appropriations committees and the amount needed to carry them out is requested from the committees through the annual budget review process. More than likely, the committee will say that there isn't any money for that or will ask the agency to see what can be done with less money. A struggle then ensues to get the job done as well as possible with the funding that is available.

Probably no one in this room is unaware of the fiscal trouble besetting Michigan. Such trouble translates into everyone's budget being cut. Michigan State University has been told, for example, that it is going to have to cut back a percentage of its budget and that then results in tuition increases or cutbacks in programs, or perhaps elimination of whole departments. Other agencies of government have been told that they must cut back, or that a particular program must be dropped, or there will be no funding for a particular operation. Funding is an activity that comes into play after all the other activities have been completed and, notwithstanding the

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completion of prior steps, can virtually eliminate a program by its absence or diminution.

I am not going to deal in any significant detail with what has happened at the state level with federal funding except to tell you that the federal funding has been a very real problem for state and local governments throughout the country. One good example is that Michigan had been led to expect a grant of $308,000 to develop a pilot state enforcement program for PCB regulation under TSCA, and it was expected that the money would be available on January 1, 1982. Well, it is now past this date and the funds have not arrived (and probably won't), because this is the way the federal government agencies have been treating people lately. They lead a state to expect a grant and then they change their minds or their policy of payment as a means of control.

Another problem is that the federal administration's budget further proposes to freeze the absolute dollar amounts. For example, if there were $3 million to do a job last year, the same amount is available this year notwithstanding that there are some built-in incremental cost increases in the program. The idea apparently is that the states will find a way to pick up the difference. Well, I don't know how we are going to find a way in Michigan.

The Governor appeared on television the other night saying that, just to keep things at the present level, even allowing some cutbacks in very significant and important areas, we are going to have to consider an income tax increase. I have been in politics for 33 yrs now and I have yet to receive a letter from a constituent saying "please raise my taxes." A letter came in early the next morning after the Governor spoke from a fellow who must have run to the post office to mail it after the Governor's appearance. He said, "Whatever you do, don't vote for Governor Milliken's crazy scheme to raise taxes or you are a dead man at election time." I know that; he didn't have to tell me. I know what gets one elected and what gets one defeated, and voting for taxes is what gets an office holder defeated. For that reason, the programs we are talking about here will probably be cut back more and more severely because it does not seem likely that we will pass the Governor's income tax increase however necessary it appears to many of us, myself included.

Now I want to mention another responsibility of the legislative process, and that is oversight. For example, a special committee was just convened under House Resolution 406 for the purpose of looking at The Hazardous Waste Management Act and

The Solid Waste Management Act to see if these acts are serving the purposes for which they are intended. If they are not, because of certain loopholes or problems, the committee must decide what must be done to change them. So a final legislative responsibility is to see that, once everything is in place, everything is working all right. Oversight is an area of serious legislative concern, but not enough of it is done because of the limitations of time and staff. More ought to be done, and is being done in the legislative process in several states. I hope Michigan can join these ranks.

I want to touch briefly on one aspect of the environmental control situation that some of you may not be aware of. In the early 1970s and late 1960s, there was a worldwide crescendo of environmental movements which originated in America. The aim was to improve the quality of the environment, to remove contaminants from the environment, and to protect the health of the people from pollution and contamination sources of all kinds. As a consequence of this atmosphere, we were able to pass The Environmental Protection Act of 1970, were able to pass PCB controls, PBB controls, and to ban DDT from use in Michigan, as well as other states and other countries in the world. All this resulted from the growth of the feeling that something had to be done to turn around the dangerous condition that had begun to exist in the environment.

Things got tougher, however, around the middle of the decade and it began to be more and more difficult to collect the votes to pass environmental issues. The name of the game in the legislative process is votes. You couldn't pass a bill authorizing motherhood without votes, which have "magic" numbers, varying from state to state. The "magic" numbers of votes in Michigan are 56, 20, and 1: 56 votes in the House, 20 in the Senate, and 1 in the Governor's chair. If you don't have 56 votes in the House, you don't have a bill. If you don't have 20 votes in the Senate, you don't have a bill. If you don't have one in the Governor's chair, you don't have a bill. Regarding environmental issues, those "magic" numbers became harder and harder to reach in the last years of the decade. The Wetlands Protection Act, of which I was one of the sponsors, took 6 yrs of hard, diligent effort to pass. It has gotten tougher and tougher to get any sort of environmental control through the legislative process.

What has happened now in the 1980s? It has become even tougher. What is being experienced is that some of the environmental controls that we passed, some of the prohibitions, some of the regulatory measures from those easier years, are now under attack. Last year, for example, in order to stave off

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an even worse situation, we had to eliminate the air and water pollution surveillance fees which we have been charging industry for the inspections and control processes on their smoke stacks and other outfalls, since about 1969 or 1970. The legislature finally agreed recently to a 5 yr phase out plan in order to avoid an immediate cut off. During this 5 yr phase out, the cost of surveillance will be gradually absorbed by the general fund of the state, and industry, which caused the problem requiring the surveillance operations, won't have to pay special fees for it.

There is now a bill before the state Senate which seeks to amend The Phosphate Control Act which was designed to limit phosphorus compounds reaching surface waters. Actually, the new bill seeks to set the phosphorus level so high that we may as well not have the act. The Sand Dunes Protection Act is under two court suit attacks right now and is also the focus of legislative efforts for repeal. Some other acts are also under this kind of pressure.

We have another problem. The federal government has begun to shift its gears. The present administration has taken a decided posture of trying to eliminate environmental and regulatory control. The Environmental Protection Agency (EPA), for example, is now in the business of eliminating the EPA and it is in the business, moreover, of getting rid of the controls for the benefits of the people that EPA has represented all these years. I consider that to be a dismal occurrence. I am sorry to see it happen but I don't know what to do about it since the President, of course, has more control than I. As long as he is in control, it's going to get worse instead of better, it would seem. The philosophies of the present administration are to minimize the controls and to turn them back to the states, which have demonstrated over time in some areas, that they did not have the capabilities or the interest to deal with them. We are thus scrapping the gains of the past several years.

There is a misshapen notion of how things are done in the legislative process. The notion has to be changed. First, you have to remember that the legislative process takes votes. No matter what you are trying to do, you have to have the votes; again, 56, 20, and 1. You have to have people in the legislative process who have an understanding of and sympathy for the kinds of interests that you have. If you don't, your interests are not going to be reflected in the outcome of the process.

Then, once they get there, it is important that the right people serve on the appropriate committees: appropriations

committees, the conservation committees, or on the administrative rules committee. One of the reasons so many conservation-oriented acts were passed in the past decade or decade and a half in our legislature is that I was given by the speaker good, competent people who agreed with me on many of the things that I thought were important to change. Had those kinds of persons not been on my committee, many good bills would still all be resting in the file.

So it is important who gets elected, important who gets appointed to committees, and important who does the appointing. Thus, each person in our society must go out and express himself or herself at the ballot box so that the candidates he or she thinks will do the kind of thing that is important to him or to her get elected.

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CHAPTER 27

REGULATION OF PCBs IN CANADA

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REGULATION OF USE

Although polychlorinated biphenyls (PCBs) were never manufactured in Canada, they received widespread industrial use for at least 40 yrs. Since 1977 their use has been regulated under the Environmental Contaminants Act. Section 3 of Chlorobiphenyls Regulation No. 1 states:

> For the purpose of subsection 8(2) of the Act, the following commercial, manufacturing and processing uses are hereby prescribed effective September 1, 1977, as uses in respect of which chlorobiphenyls may not be used.
>
> (a) use in the operation, servicing or maintenance of any product, machinery or equipment other than
>
> > i) electrical capacitors, electrical transformers and associated switchgear and machinery or equipment used to manufacture electrical capacitors, electrical transformers and associated switchgear;
> >
> > ii) heat transfer equipment, hydraulic equipment and vapour diffusion pumps that were designed to use chlorobiphenyls and were in use in Canada before March 1, 1977; and

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iii) machinery or equipment, the operation of which is intended to destroy the chemical structure of chlorobiphenyls, and

(b) use as a constituent of any machinery, equipment or product manufactured in or imported into Canada after September 1, 1977, other than electrical capacitors, electrical transformers and associated switchgear. Chlorobiphenyls is defined as "those chlorobiphenyls that have the molecular formula $C_{12}H_{10-n}Cl_n$ in which 'n' is greater than 2." (Canada Gazette Part II, Vol. III, No. 18, 28/9/77)

In 1980, Section 3 of the Chlorobiphenyl Regulations No. 1 was revoked and the following substituted therefore:

3. For the purpose of subsection 8(2) of the Act, the following commercial, manufacturing or processing uses are hereby prescribed as uses in respect of which chlorobiphenyls may not be used:

(a) use in the operation of any product, machinery or equipment other than

i) electrical capacitors, electrical transformers and associated electrical equipment;

ii) heat transfer equipment, hydraulic equipment, electromagnets, and vapour diffusion pumps that were designed to use chlorobiphenyls and were in use in Canada before September 1, 1977; and

iii) machinery or equipment, the operation of which is intended to destroy the chemical structure of chlorobiphenyls:

(b) use in the operation of electromagnets that are used to handle food, animal feed or anything intended to be added to food or animal feed for any purpose whatsoever;

(c) use as a constituent of any product, machinery or equipment manufactured in or imported into Canada after September 1, 1977, other than electrical capacitors, electrical transformers and associated electrical equipment;

(d) use as a constituent of electrical capacitors, electrical transformers and associated electrical

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equipment manufactured in or imported into Canada after July 1, 1980;

(e) use in the servicing or maintenance of any product, machinery or equipment, other than electromagnets, electrical transformers and associated electrical equipment; and

(f) use as new filling or as make-up fluid in the servicing or maintenance of any electromagnet, electrical transformer or associated electrical equipment. (Canada Gazette Part II, Vol. 114, No. 13, 9/7/80)

In addition, regulations will soon be promulgated respecting the release of PCBs into the environment and prohibiting the importation or sale of equipment containing PCBs in a concentration of greater than 50 mg/kg.

The Environmental Protection Service (EPS) of Environment Canada developed a labelling system (Figure 1) to alert people to the presence of PCBs in equipment and to allow preparation of an inventory of PCBs contained in equipment and in storage awaiting disposal. A "Handbook on PCBs in Electrical Equipment" was prepared by EPS to help insure the success of this voluntary labelling program, and to provide guidelines for the management of electrical equipment and wastes containing PCBs.

As an extension of this program, a federal interdepartmental committee was given the task of assessing the hazard potential from equipment containing PCBs in use in the food, feed, and grain industries. Officials from Agriculture Canada, Environment Canada, Health and Welfare Canada, and Fisheries and Oceans developed a joint training program for their inspectors which are located across Canada. To accommodate the various federal inspection agencies, EPS organized and conducted 36 seminars to train the inspectors on the procedures for:

(1) conducting inspections of equipment containing PCBs;
(2) monitoring and evaluating the condition of the equipment; and
(3) assessing the potential hazard of PCB-filled equipment in use in or around food processing areas.

After attending a "PCB inspection training session", the inspectors then integrated this "PCB inspection" into their department's regular inspection program. To obtain uniformity in inspection, a guide "PCBs Inspection Procedures and Guidelines for Completing the Plant Evaluation Form" was prepared by EPS.

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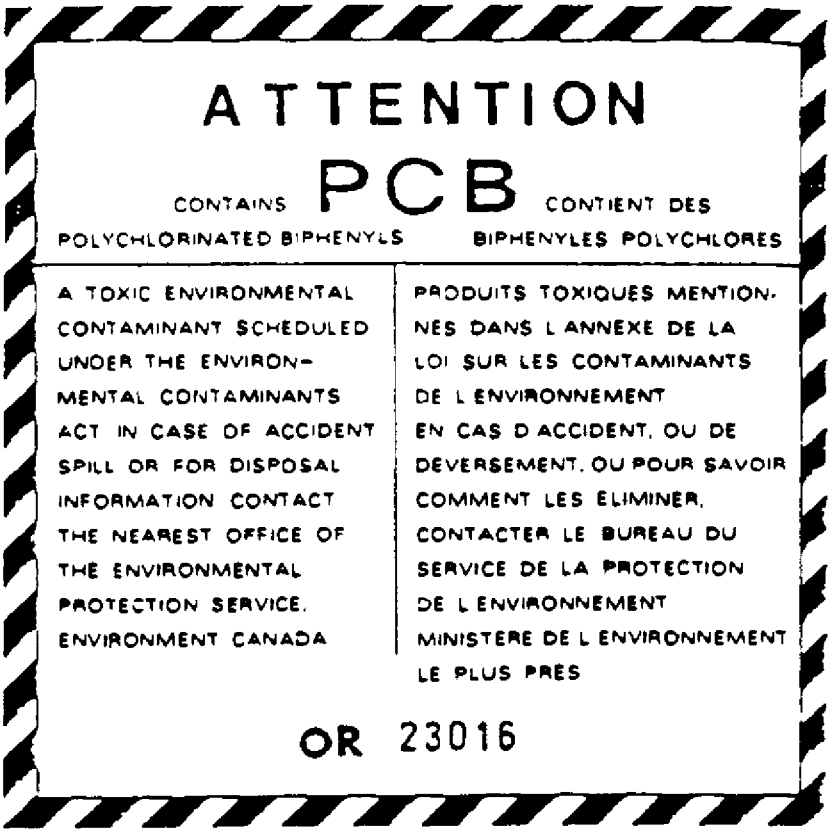

Figure 1. Environmental Protection Services labels for equipment containing PCBs.

A Communique is jointly being prepared by these four federal departments for mailing to the various food, feed, and grain industries. This Communique briefly outlines the reason for our concern and the scope of our inspection program.

The inspection program and the Communique are aimed at making the industrial sector aware of our concern. It is anticipated that industry will volunteer to initiate any remedial action that may be necessary to correct potential problems.

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REGULATING RESIDUES IN FOODS

In 1975, the Health Protection Branch (HPB) announced a guideline of 2 mg/kg for PCB residues in the edible portion of commercial fish. This guideline is administered through the cancellation of commercial fishing licenses for those fish in those waters likely to contain PCB residues greater than 2 mg/kg. This program requires the cooperative participation of the Federal Department of Fisheries and Oceans and the appropriate provincial department which has jurisidiction over commercial fishing.

In Canada, the great majority of the chemical residue analyses of commercial fish are carried out by Fisheries and Oceans. Since the potential for PCB residues is greatest in fish from the Great Lakes, a monitoring program to measure residue trends is conducted in this area. In this program, the samples are collected by the Ontario Ministry of Natural Resources and analyzed by Fisheries and Oceans. The results are used to determine which areas will be closed to commercial fishing. Fisheries and Oceans also sample Great Lakes commercial fish in their compliance program.

Sport fishing comes under the jurisdiction of the provinces. The Province of Ontario publishes, on a yearly basis, 3 booklets entitled "Guide to Eating Ontario Sports Fish -Northern Ontario, -Southern Ontario, -Great Lakes".

Although residues of PCBs are not frequently detected in foods other than freshwater fish, administrative guidelines have also been established for PCB residues in dairy products (0.2 mg/kg, fat basis), poultry (0.5 mg/kg, fat basis), eggs (0.1 mg/kg, whole weight less shell), and beef (0.2 mg/kg, fat basis). These administrative guidelines, as well as the 2 mg/kg guidelines for commercial fish, would be enforced under Part 1, Section 4(a) of the Food and Drug Regulations. This regulation states, "No person shall sell an article of food that has in or upon it any poisonous or harmful substance."

Results of analyses of human tissues for chemical residues are frequently used to provide a basis for measuring exposure to persistent chemicals. Nationwide surveys of adipose tissue in 1972, and of breast milk in 1975, indicated that 100% and 98%, respectively, of the samples contained detectable levels of PCB residues. The mean and range for the adipose tissues were 0.907 and 0.106 to 6.603 mg/kg, respectively. The mean and range for the breast milk were 12 and 0 to 68 ug/kg, respectively.

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In an advisory capacity, the HPB has frequently been asked to comment on the health significance of chemical residues in human milk. To meet these requests, in January, 1978, the Minister of Health and Welfare Canada convened a committee to "consider whether there are any problems related to the presence of PCBs in human milk" (HWC, 1978). In part, the committee concluded:

> The major sources of human exposure to PCBs are occupational exposure and consumption of game fish (such as coho salmon, eels, lake trout, catfish, smelts, and sturgeon) from water contaminated with PCBs. One such area of contamination is the Great Lakes Basin. Women from this area and those women who may have had exposure to PCBs from industrial sources and who intend to breast-feed their babies, should contact their physicians. The physician should carefully consider the woman's lifetime history of exposure to PCBs to determine the advisability of having the breast milk analyzed.
>
> A Health Protection Branch (HPB) national survey indicated that the PCB level of mother's milk ranges between one and sixty-eight micrograms per kilogram (ug/kg) of whole milk. At the present time there are insufficient toxicological data to define precisely the level of PCBs in human milk that could cause health problems in the suckling infant. However, on the basis of available toxicological data in animals, where levels are above 50 ug/kg, the physician should pay particular attention to the mother's history, the child's birth weight, general conditions and subsequent growth and development in advising the mother concerning breast-feeding. In the light of currently available information it was the Committee's opinion that, in view of the benefits of breast feeding in most instances, it would be advisable to continue nursing. In the 1975-76 HPB survey of one hundred samples from across Canada, 98% of the breast milk samples tested were below 50 ug/kg whole milk. Detailed dietary and occupational histories should eliminate the need to have breast milk analyzed in the great majority of cases.

REGULATING RESIDUES IN FEEDS

In 1981, Agriculture Canada published a Trade Memorandum entitled "Polychlorinated Biphenyls (PCBs) in Marine Oils". In part, this memorandum states:

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> Agriculture Canaca is concerned about the use of fish oils containing PCBs in the manufacture of livestock feeds inasmuch as the quality of feeds and feed ingredients are subject to the standards as set out in Section 16(1)(i and j) of the Feeds Regulations. Feed manufacturers are reminded of their legal responsibility under the Feeds Act and Regulations to produce feeds which are safe for all classes of livestock and which do not result in a residue in animal products.
>
> In consultation with toxicologists from Health and Welfare Canada and Agriculture Canada an actionable level of 2.0 mg/kg PCBs in fish oil has been established.

TOXICOLOGICAL EVALUATION

As indicated by the breadth of the papers presented earlier in the symposium, the scope of the scientific literature on the toxicity of PCBs to laboratory animals is very broad.

In our first evaluation of PCB (Aroclors 1242, 1254, and 1260) toxicity, the lowest no-observed effect level (NOEL) in 2 yr rat, 2 yr dog, and 3 generation rat reproduction studies was 10 mg/kg. For the rat and dog, a 10 mg/kg dietary level is considered equivalent to a dose of 0.5 and 0.25 mg/kg/day, respectively. The application of a 100-fold safety factor to the NOEL gave a 2.5 to 5 ug/kg/day "tolerable" exposure. We tended to lean towards the 5 ug level since 2 (Aroclor 1242 and 1254 studies) of the 3 dog studies resulted in a no-observed effect level of 2.5 mg/kg/day.

The "Yusho" incident has provided most of the information on the toxic effects of PCB to humans. Analysis of the rice oil for PCBs and collection of oil consumption data has allowed the estimation of the level of PCB exposure to the Japanese "Yusho" patients. This estimation gave a no-observed effect level of 200 mg/person. One approach to safety evaluation is to use this 200 mg/60 kg person no-observed effect level along with a 1000 day exposure period to estimate a "tolerable" exposure level of 3 ug/kg/day (Kolbye, 1976). This level agrees very well with the 2.5 to 5 ug/kg/day level estimated from laboratory animal data.

However, further analysis of the rice oil (Hayabuchi et al., 1979) indicated the presence of polychlorinated dibenzofurans (PCDFs) at 5 mg/kg, polychlorinated quaterphenyls (PCQs) at 866 mg/kg, and PCBs at 920 mg/kg. This PCB level (920 mg/kg)

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is approximately one-half that which the first analysis indicated. Estimates of exposure from this data gave the patients total mean (geometric) exposure at 1232 mg (633 mg PCBs, 3.4 mg PCDFs, and 596 mg PCQs) compared to the previously estimated mean (arithmetic) of 2000 mg PCBs. Furthermore, the estimated minimum effect level for the sum of PCBs, PCDFs, and PCQs was 56 ug/kg/day. The presence of this cocktail of contaminants in the rice oil makes it impossible to estimate a "tolerable" level of exposure to any one of the contaminants.

Then, in the late 1970s, a number of publications from Dr. Jim Allen's laboratory indicated that the rhesus monkey was more sensitive to the toxic effects of PCBs than was the rat (Allen, 1975; Allen and Barsotti, 1976; Allen et al., 1974; 1980; Barsotti et al., 1976; Bowman et al., 1978). In particular, the reproductive system was very vulnerable. Dietary levels of 2.5 and 5 mg/kg Aroclor 1248 (equivalent to 100 and 200 ug/ kg/day) resulted in reproductive dysfunction in the female rhesus monkey. The findings of hyperpigmentation, chloracne, etc., in the PCB-treated monkeys were also observed in the "Yusho" patients.

These results indicated a need to reconsider our previously estimated 5 ug/kg/day "tolerable" exposure level. After evaluation, it was considered necessary to apply at least a 100-fold safety factor to the lowest level (100 ug/kg/day) in Dr. Allen's monkey reproduction study. The resulting 1 ug/kg/day "tolerable" exposure level should be considered temporary, pending further research. In addition to the regular uncertainties in using animal laboratory data to estimate an "acceptable" exposure level to humans, there is the additional problem that the PCBs which were tested may be somewhat different to those which are present in foods.

ESTIMATION OF EXPOSURE

The estimation of exposure to PCBs derived from the consumption of commercial foods by the average Canadian was made by multiplying the maximum residue limits (MRLs) for the various foods by the quantity of the particular foods consumed by the average Canadian (Table 1). The consumption figures are actually Statistics Canada figures for disappearance of foods and are thus over-estimates of actual consumption. With the exception of the MRL for fish, MRLs were obtained by compiling all available Canadian residue data for the various foods and then choosing a MRL which covers the great majority of the food samples. The choice of the 2 mg/kg MRL for fish took into consideration such factors as: available residue data; "remaining tolerable PCB exposure" (e.g., approximately 40

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TABLE 1

Estimation of Maximum Exposure to PCBs from the Consumption of Commercial Foods

Food		Maximum Residue Limit (MRL)	PCBs
Type	Intake (g/person/day)	(ug/g)	Intake (ug/person/day)
Fish	20	2[a]	40
Dairy Products[b]	32.8	0.2[c]	6.6
Meat, Beef	48	0.2[c]	9.6
Poultry	3.6	0.5[c]	1.8
Eggs	34	0.1[d]	3.4

[a]Edible portion
[b]Milk, cheese, butter
[c]Fat basis
[d]Whole weight less shell

ug/person/day); and economic impact on the fishing industry and potential decrease of food source to the consumer.

FURTHER RESEARCH

Since the lowest level of PCBs administered to rhesus monkeys resulted in reproductive dysfunction, and because of the uncertainty in relating exposure to the infant monkey through suckling to effects observed, a monkey reproductive study is being planned. This study will have a control and four treatment groups. A major effort will be made to relate the level of PCB exposure to the dam:to the blood PCB level:to the PCB level in the milk:to the effects observed in the suckling monkey. This is extremely important since the question most often raised by the public is: "What is the health significance of a certain PCB residue level in human milk."

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CHAPTER 28

FDA REGULATION OF PCB IN FOOD

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INTRODUCTION

Industrial chemicals such as polychlorinated biphenyl (PCB) become contaminants in food from three main sources:

(1) as a result of an industrial chemical accident (e.g., a spill);
(2) from discharges during manufacturing of the chemical; and
(3) from use or disposal of the chemical and eventual reintroduction from the environment into the food chain (FDA, 1979).

FEDERAL AUTHORITIES

The U.S. Environmental Protection Agency (EPA) has authority under the Toxic Substance Control Act to regulate industrial chemicals per se and the effects of chemicals on humans and the environment. However, the authority for controlling food contaminated with these chemicals is assigned exclusively to the Secretary of the Department of Health and Human Services under the provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA) (FFDCA, 1979). The authority vested in the Secretary under the FFDCA for regulation of chemical contaminants in foods has been redelegated to the Commissioner of Food and Drugs (CFR, 1981a, see Part 5.1).

The provisions of the FFDCA prohibit the introduction into interstate commerce, receipt in interstate commerce, and holding for sale after receipt in interstate commerce any foods and drugs which are adulterated or misbranded (FFDCA, 1979).

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Section 402(a)(1) of the Act deems a food to be adulterated:

> if it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance, such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health (FFDCA, 1979).

Section 402(1)(2) deems a food to be adulterated:

> if it bears or contains any added poisonous or added deleterious substance other than one which is a pesticide chemical, a food additive, a color additive, or a new animal drug which is approved for such purposes and controlled by tolerance and regulations (FFDCA, 1979).

Section 406 deems any added poisonous or deleterious substance to be unsafe unless its presence in food is required in the production thereof or cannot be avoided by good manufacturing practice. Section 406 also authorized the agency to promulgate regulations limiting the quantity of such a required or unavoidable substance that can be present legally in foods (FFDCA, 1979).

In the administration of these statutory provisions, the U.S. Food and Drug Administration (FDA) distinguishes between "avoidable" and "unavoidable" sources of contamination for determining the level of contamination at which enforcement action will be as follows.

Avoidable Contamination

Adulteration of food caused by failure to follow good manufacturing practice constitutes "avoidable" contamination of food if the cause of contamination could have been prevented (e.g., by not storing containers of a toxic chemical next to food with subsequent leakage and contamination of food). Contamination due to some known or very apparent episode (e.g., an explosion), with subsequent marketing of an adulterated product in interstate commerce is also considered "avoidable". In such cases, FDA's policy is to set, for uniform enforcement purposes, a limit for the avoidable contaminant that is no higher than the level provided by available residue analytical methoology for detecting, measuring, and confirming the identity of the contaminant (FDA, 1979).

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Unavoidable Contamination

Unavoidable contamination occurs when, in spite of strict adherence to good manufacturing practice, the presence of the added substance in food cannot be completely prevented. Such is the case when an industrial chemical persists in the environment and causes indirect "unavoidable" contamination of food. Because no amount of intervention by man can completely remove the contaminant from food, agency policy is to follow Section 406 of the FFDCA, viz., limit the amount of the contaminant that can be present to the extent necessary to safeguard consumer health while taking into account the extent to which the contaminant is unavoidable. This is accomplished by establishing either an action level or tolerance as the standard for determining whether food containing some specific amount of the substance can legally be marketed (FDA, 1979).

Action Levels

"Action levels" are sometimes used by FDA to determine the legal status of an industrial chemical residue in food or feed. Although any amount of an industrial chemical in the absence of a tolerance may render food adulterated within Section 402, Section 306 of the FFDCA permits FDA to refrain from taking regulatory action for minor violations (e.g., when the residue level poses little or no risk to the public health). This enforcement discretion is often applied when no tolerance for a residue has been established, but the presence of the residue cannot be avoided by good manufacturing practices. Such a situation would be the persistence of an industrial chemical in the environment and the chemical's subsequent "unavoidable" contamination of food. An action level defines this discretionary authority in terms of a specific limit that is used to determine whether FDA will, when the limit is exceeded, take regulatory action. An action level neither condones nor permits the intentional addition of a contaminant to food. In setting an action level, the criteria of Section 406 of the FFDCA are followed; that is, the level must be sufficient to protect the public health, while also taking into account the extent to which the contaminant is unavoidable. FDA is responsible for determining when an action level is to be applied in a particular situation and for enforcing an action level (FDA, 1979).

Tolerances

A "tolerance" may also be established for unavoidable industrial chemical residues under Section 406 and in accordance with the formal rulemaking procedures of the FFDCA. Table 1

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presents the tolerances which have been established for only one such substance, PCBs, on a variety of food and feed commodities. A tolerance for another environmental, but nonindustrial chemical food contaminant, aflatoxin, is pending. When

TABLE 1

Tolerances for Unavoidable Poisonous or Deleterious Substances for PCBs, April 1, 1981[a]

	Type of Food	Tolerance (mg/kg)
1.	Milk (fat basis)	1.5
2.	Manufactured dairy products (fat basis)	1.5
3.	Poultry (fat basis)	3.0
4.	Eggs	0.3
5.	Finished animal feed for food-producing animals, except feed concentrates, feed supplements, and feed pre-mixes	0.2
6.	Animal feed components, including fish meal and other by-products of marine origin and finished feed concentrates, supplements, and pre-mixes	2.0
7.	Fish and shellfish (edible portion) excluding head, scales, viscera, and inedible bones	2.0[b]
8.	Infant and junior foods	0.2
9.	Paper food packaging material intended for use in contact with human food and finished animal feed	10

[a]CFR, 1981b, Part 109.30

[b]The effective date of the 2 mg/kg tolerance for PCB in fish and shellfish was stayed until further notice by a document published in the Federal Register (FR, 1979a). The previous tolerance of 5 mg/kg in the edible portion of fish and shellfish remains in effect until further notice (FR, 1979).

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FDA establishes an action level, the agency publishes a notice in the Federal Register stating that an action level has been established and inserts in the public record documentation describing the scientific and related factors considered by the agency in arriving at the action level. Action levels are particularly useful when available toxicity data are incomplete, or the causes or levels of contamination are not clearly established or are in a state of flux. This explains why tolerances for such contaminants are infrequently used by FDA. The main disadvantage in the informal process for setting action levels for food contaminated by a nonpesticide chemical is that FDA must defend such an action level in court. For a tolerance, FDA only has the legal burden of proving that the tolerance was exceeded (FDA, 1979).

USDA/FSIS and most state regulatory agencies rely on FDA's recommended action levels or established tolerances for unavoidable industrial chemical residues in meat, poultry, and other foods.

ENFORCEMENT AUTHORITY

The FFDCA authorizes FDA to initiate seizure of an interstate shipment of food, seek an injunction against further shipment of adulterated food, and/or criminal penalties against the firm and/or persons responsible for the violation of the law. Food means articles used for food or drink for man or other animals, chewing gum, and components of such articles. Also, FDA may refuse entry into the country of any imported food found adulterated or misbranded (FFDCA, 1979, see Sections 304, 302, 303, 801).

FDA investigators are authorized to sample and analyze food to determine if chemical contaminants are present. FDA investigators also have the authority to conduct investigations and to enter and inspect firms engaged in the manufacture, production, processing, or distribution of food to determine whether such foods are adulterated or misbranded (FFDCA, 1979, see Sections 702, 704).

CURRENT PESTICIDE AND INDUSTRIAL CHEMICAL RESIDUE PROGRAMS

FDA field operations are managed under a complex program planning and management system involving some 36 major project areas which are currently subdivided under 123 compliance programs.

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During Fiscal Year (FY) 82, FDA will spend about 168 operating person years of effort on its chemical contaminants programs which represents about 12 percent of its available field resources. About 50 percent of this person power (85 person years) will enable the agency to analyze 6900 samples of domestic foods and 4900 samples of imported foods for chemical contaminants under 17 different specific programs (FDA, 1982).

The largest program, Pesticides and Industrial Chemicals in Domestic Food, is designed to determine the levels of pesticides and industrial chemicals in selected samples of raw agricultural products, milk, cheese, eggs, grain, and fish (FDA, 1982).

The selection of the products to be sampled and the numbers of samples of each product to be analyzed with the available resources are generally left to the discretion of each FDA district. Districts generally sample and analyze locally produced commodities having dietary significance and where local experience, inspectional information, or other intelligence make it aware of potential food contamination problems (FDA, 1981a).

During FY82, Detroit District is authorized to collect and analyze only 294 samples of foods produced in the states of Michigan and Indiana (FDA, 1982). Detroit District plans to analyze 46 domestic and 20 import samples of fish under this program. In addition, Detroit District plans to analyze a limited number of samples of fish for dioxin residues under a cooperative program with EPA and cooperating officials in seven Great Lakes states (Hoeting, 1981).

The results of the analysis of samples of fish analyzed for PCB in FY79, FY80, and FY81 are shown in Tables 2, 3, and 4, respectively.

When a major problem is identified, FDA field managers are free to use a part or all of the available person power in the home district and other districts as may be needed, for the detection and removal of contaminated products from the market place (FDA, 1981a).

FDA "official samples" must be representative of the shipment and generally consist of 12 fish (or a minimum of 12 one-pound portions) collected at random (IOM, 1978). Samples of fish may be collected from commercial fishermen, fish processing plants, in transit (e.g., from a truck), and from wholesale and retail establishments (FDA, 1981a).

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TABLE 2

Domestic Fish Samples Analyzed for PCB by Detroit District from Known Locations, Fiscal Year 1979

Species	Lake	Number of Samples	Range (mg/kg)	Average (mg/kg)	Samples Over 2 mg/kg PCB
Carp	Huron	5	2.0 - 7.4	3.59	4
Carp	Erie	1	3.16	3.16	1
Perch	Huron	3	0.32 - 0.65	0.45	0
Catfish	Huron	12	0.8 - 7.5	3.2	9
Catfish	Erie	4	3.1 - 5.6	4.3	4
Whitefish	Huron	3	ND - 3	1.5	1
Lake Trout	Huron	6	0.94 - 4.33	2.75	4
Lake Trout	Michigan	4	ND - 4.6	2.85	3
Walleye	Erie	6	Trace - 1.1	0.5	0
Chubs	Michigan	3	0.47 - 1.21	0.9	0
TOTAL		47			26

ND = Not Detected

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TABLE 3

Domestic Fish Samples Analyzed for PCB by Detroit District, Fiscal Year 1980

Species	Number of Samples	Samples With PCB	Range (mg/kg)	Average (mg/kg)	Samples Over 2 mg/kg PCB
Coho Salmon	1	1	--	2.49	1
Chinook Salmon	5	5	0.72 - 5.29	3.27	4
Whitefish	22	9	0.5 - 1.11 (5 with trace)	0.82 (0.4)	0
Lake Trout	12	4	0.31 - 21.7	4.72	3
Chubs	5	1	--	1.41	0
Lake Herring	1	0	--	--	0
King Salmon Eggs	1	1	--	1.48	0
Coho Salmon Eggs	1	1	--	1.35	0
TOTAL	48	22			8

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TABLE 4

Domestic Fish Samples Analyzed for PCB by Detroit District, Fiscal Year 1981

Species	Number of Samples	Samples With PCB	Range (mg/kg)	Average (mg/kg)	Samples Over 2 mg/kg PCB
Coho Salmon	1	1	--	1.67	0
Chinook Salmon	2	2	1.19, 2.62	1.90	1
Whitefish	24	4	--	All Trace	0
Lake Trout	6	1	--	4.87	1
Lake Herring	1	0	--	--	0
Smelt	1	0	--	--	0
Sucker	1	0	--	--	0
Chinook Eggs	2	2	4.32, 5.8	5.06	2
Coho Eggs	1	1	--	1.68	0
TOTAL	39	11			4

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The fish in the sample will be cleaned, scaled, and eviscerated to prepare an edible portion for analysis. Inedible portions such as bones and catfish skin are discarded. Fillets, including all flesh and edible skin, are removed from head to tail and from top of back to belly on both sides of fish. Where extremely large fish are analyzed, three cross-sectional slices from each fish may be taken and combined for analysis (PAM, 1977).

Fish samples are analyzed with the methods specified in the Pesticide Analytical Manual (PAM) I (PAM, 1978) or the method of Luke et al. (PAM, 1980), and the Laboratory Information Bulletin (LIB, 1980; FDA, 1981b).

TOTAL DIET STUDIES

FDA also surveys the total United States diet, in a program designed to obtain information about levels of chemical contaminants to which consumers are exposed. The study is based on 30 "market basket" samples each year, collected from representative areas of the United States, and purchased in retail stores. Since FY75, 20 samples are collected under the adult program and 10 under the infant and toddlers program (FDA, 1981b). Each sample represents the entire 14 day diet. For the adult, the sample represents the diet (approximately 117 individual food items) of a typical 15 to 20 yr old American male in the region of collection. All foods are prepared for table-ready consumption (meats are cooked, vegetables boiled if so eaten, etc.). The prepared foods are then divided into different food class composites (dairy products, meat-fish-poultry, root vegetables, grain and cereal products, etc.) and each composite is analyzed for residue content. The results are used to determine:

(1) the total daily intake of each residue;
(2) which food classes contribute the greatest residues to the diet; and
(3) seasonal and regional trends (Kennedy, 1978).

The FDA initiated the market basket study in 1965 as a supplement to the coverage of individual foods by other compliance programs. It provided the first means for determining the level of residue in the diet as consumed. Originally, only chlorinated hydrocarbon, organophosphorus, and arsenical pesticides were included. Through the years, the program has expanded and now includes analysis for organochlorine and organophosphorus residues, chlorphenoxy acids (herbicides), carbaryl and orthophenylphenol, and six heavy metals (mercury, cadmium, arsenic, lead, selenium, and zinc)(Kennedy, 1978).

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Although most of our activities are directed at ensuring that unsafe residues do not occur in foods, we also have surveillance programs for pesticide residues in animal feeds. Illegal levels of pesticides may result in the adulteration of animal feed, with subsequent deposition of harmful residues in meat, poultry, eggs, fish, and dairy products (Kennedy, 1978).

We have also used special purpose surveys, designed to attack geographically isolated problems. They provide information that compliments the regular data gathering activity described above (Kennedy, 1978; FDA, 1981c, 1981d).

In the past, these Total Diet Studies discovered that PCBs from food packaging materials were contaminating the diet. This source of PCB has been eliminated after the establishment of a tolerance of 10 mg/kg for PCB in food packaging materials (FDA, 1978; CFR, 1981b, see Part 109.3).

After finding no PCB in the Total Diet Samples for FY75 and FY76, the samples for FY77 and FY78 show total relative daily intakes of 0.0164 and 0.0269 mg/kg of body weight per day. During FY78, PCB was found in 6 composite samples of meat, fish, and poultry; 2 composite samples of legume vegetables; and 2 composite samples of oils, fats, and shortening at levels ranging from 0.006 to 0.050 mg/kg (FDA, 1978).

Jelinek and Corneliussen (1975) compiled data on the concentration of PCB obtained in different foods from 1969 through mid 1975. These data show that there has been a significant decrease in PCB levels in all foods with the exception of fish. PCBs were found in 1973 in samples of milk (2.2% of samples contained PCB), eggs (1.1%), cheese (0.9%), feed components (12.7%), animal feeds (2.2%), processed fruits (4.5%), and infant and junior food (1.1%). Most samples of fish containing more than 5 mg/kg PCB originated from the Great Lakes area.

FEDERAL STATE PARTNERSHIP

Thus far, the food chemical contaminant programs at the federal level have been discussed. Collectively, the states analyze about 60,000 samples for a wide variety of pesticides and industrial chemicals each year. FDA has long recognized the significant role of the states in this area and has actively exchanged information and provided assistance as may be needed (Kennedy, 1978). FDA provides state officials:

(1) Copies of analytical results on samples containing pesticides, warning letters, and other information.

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(2) Action levels for chemical contaminants in food when no such levels have been established.

(3) Inspectional information and intelligence about possible sources of food contamination for other states.

(4) Training, methods manuals, and assistance with methodology.

(5) Check samples for verification and uniformity of results.

(6) Analytical assistance when needed.

(7) Analytical reference standards.

By the same token, the Michigan Department of Agriculture and other state agencies have provided FDA with inspectional information, analytical findings on samples, alerts to possible food contamination problems, check samples, analytical methodology, and immediate embargo/seizure of contaminated foods. We share common goals with the Michigan Department of Agriculture and enjoy a close federal-state relationship.

Most states formally adopt or follow the federal action levels and tolerances for contaminants in food. However, FDA has no objection to the adoption by a state of more restrictive standards, such as was done by Michigan with PBB.

TOLERANCES FOR PCB

The original tolerances for PCB, including the 5 mg/kg in fish, were published in 1973. A new tolerance of 2 mg/kg in fish was published in the Federal Register (FR, 1979b). This new tolerance was based upon:

(1) new toxicity data which show the toxic effects of PCB are serious and irreversible;

(2) the declining levels of PCB in the environment permit a reduction of the tolerance (thereby effecting a meaningful risk to consumers) while excluding from commerce only a small amount of food (about $5.7 million landed value in 1974 dollars)(FR, 1979b).

The effective date of this 2 mg/kg tolerance was stayed on October 5, 1979, after written objections concerning the economic impact of the regulations were filed by the National Fisheries Institute and others with the FDA Hearing Clerk (CFR.

1981b, see Part 109.30; FR 1979a). On February 8, 1982, FDA Administrative Law Judge Daniel J. Davidson determined that a 2 mg/kg tolerance for PCB would bar the sale for human food of fish and shellfish with a retail value of $86.7 million in 1980 dollars. The National Fisheries Institute has estimated the total loss at over $500 million when the fish are cleaned, canned, distributed, and sold at retail (Grigg, 1982). Judge Davidson agreed that the retail value is an appropriate measure of the economic impact of the PCB tolerance and that a multiplier of six should be used to convert landed value to retail value (FCN, 1982).

Judge Davidson found the retail losses of fish in 1980 from other tolerances would be $44.9 million at 2.5 mg/kg, $10.6 million at 3 mg/kg, $3.9 million at 3.5 mg/kg, $1.4 million at 4 mg/kg, and $366,000 at 5 mg/kg (Grigg, 1982). In 1979, FDA estimated that a 1 mg/kg tolerance for PCB would result in the loss of food with a 1974 landed value of $16 million (FR, 1979).

FDA Commissioner Arthur Hull Hayes will make the final decision on the tolerance for PCB in fish after exceptions are filed to Judge Davidson's ruling on the economic impact of the proposed tolerance.

FDA has consistently supported the public health warnings and advisories issued by state agencies to sports fishermen and others who consume large quantities of fish from waters contaminated with PCB and other industrial chemicals. These warnings about restriction or non-consumption of PCB contaminated fish are especially significant for young women, and pregnant and nursing mothers because PCBs have been linked in test animals to reproductive problems and toxic effects in young animals exposed to PCB in mothers milk (Kennedy, 1979; FR, 1979b).

PESTICIDE AND INDUSTRIAL CHEMICAL RESEARCH CENTER

A four person Pesticide and Industrial Chemical Research Center (PICRC) was established as a new branch in the Detroit District Laboratory during FY81. This laboratory is responsible for researching new analytical methods in order to improve our ability to detect, quantitate, and confirm the presence of pesticides and industrial chemicals in foods. The laboratory is also responsible for attempting to identify unknown peaks found during analyses of samples for chemical residues.

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CONCLUSION

The FDA works in close cooperation with many federal and state agencies to monitor the food supply to insure that it is free of unsafe chemical residues. Unfortunately, fish from the Great Lakes are more highly contaminated with PCB than are most fish caught in other waters. Since sports fishermen generally consume larger quantities of fish than do average consumers who buy their fish in commercial channels, sportsmen generally consume greater quantities of PCB and other contaminants.

I suggest that the time has come for all interested persons to join together in a cooperative atmosphere in an effort to reduce the exposure of consumers of both commercial and sports fish to toxic PCB residues.

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CHAPTER 29

ECONOMIC IMPACTS OF PCB REGULATION IN FOOD FISH

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On June 29, 1979, the U.S. Food and Drug Administration (FDA) issued its final regulations lowering the allowable polychlorinated biphenyl (PCB) level from 5 to 2 mg/kg in the edible portion of fish and shellfish (Federal Register, June 29, 1979). Twenty objections were filed with the FDA. One objection, filed by the National Fisheries Institute (NFI), requested a formal hearing on the issue of the economic value of the food loss. They contended that the value of the food loss would be $7-10 million per year rather than the FDA's estimated $5.7 million. As a result, the change in PCB tolerance levels was delayed until after a formal evidentiary hearing could be held on the question: What would be the value of the human food loss caused by lowering the PCB standard from 5 to 2 mg/kg?

The hearing was stricly limited to that question--the value of the food lost due to the change in regulations--not whether the regulation was a "good" or "bad" choice. The hearing concluded recently and the hearing examiner has made his recommendations. The FDA Commissioner is now in the process of hearing both the recommendations and any exceptions to the recommendations that may be filed. Then the Commissioner can decide whether or not to execute the rules.

I was only peripherially aware of this proposed rule until last summer when Al Hoeting of the FDA, Detroit, Michigan office, called asking if there were such a thing as a fisheries economist working on Great Lakes fisheries and, if so, could I name some. He wanted some names of independent people who could

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serve as expert witnesses to examine this issue. I agreed, along with Dr. Richard Bishop (University of Wisconsin) and Dr. Gary Johnson (University of Illinois). We testified last fall.

This paper reflects my perspective, after having examined the issues, and drawing whatever conclusions I could from them on "what is the value of the food loss that would be caused by this proposed change in regulations".

This paper will show (1) how a fairly simple issue became complicated quickly, (2) how these values were estimated using greatly-simplifying assumptions, and (3) the findings of the hearing examiner. The paper also briefly contrasts the legal issues and the real social issues. Carlos Fetterolf, in the opening session, summarized the real social issue when he asked, "What is the right tolerance level?" That is a question I can't answer. However, we will examine the issue to see what we can say.

INITIAL ESTIMATE OF LOSSES

Table 1 will summarize the original argument as well as some subsequent data. The species in question were several freshwater species found in the Missiasippi River system (catfish and fuffalo) and the Great Lakes (whitefish, chubs, trout, catfish, and carp). Two saltwater species (striped bass and bluefish) were included. Alewives and lobsters were later added as more information became available. Losses were estimated by first finding the total landings in pounds and the value of those landings. Next the percentage of landed fish that would exceed the 2 mg/kg tolerance level was estimated based upon FDA sampling. For example, the initial loss percentage estimated for whitefish and chubs was 10.5 percent, and for lake trout was 33.3 percent. Finally, the dollar losses were calculated assuming every contaminated fish was excluded.

TABLE 1

It was decided for this hearing that all values would be converted to 1974 dollars to correct for inflation, but not all documents did that, particularly earlier documents. The FDA, in its proposal-regulations, estimated that the value lost would be $5.7 million per year (1974 dollars)(Federal Register, June 29, 1979, p. 38333). The NFI then said that if 1978 landings and value data were used and alewives were added, a loss of about $7.3 million would occur (1978 dollars)(FDA, 1982, Document N-1). Furthermore, NFI argued that adding lost imports and unexploited fisheries, $10.1 million would be lost. Later, PCBs were discovered in lobsters, so lobster losses were also included by FDA and NFI. The value of all lobster landings was about $37 million in 1974 and $64.8 million in 1978. Twenty

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TABLE 1

Comparison of 1974 and 1978 Fish Landing Data and Economic Loss
(Thousands of Dollars and Metric Tons)

Species	Landings 1974	Landings 1978	Landings in Current Dollars 1974	Landings in Current Dollars 1978	Percentage Exceeding 2 mg/kg PCB'S 1978	Percentage Exceeding 2 mg/kg PCB'S 1978-80	Expected Loss in Current Dollars 1974	Expected Loss in Current Dollars 1978
	----Metric Tons----		-----$ x 10^3-----		-----Percent-----		-Current $ x 10^3-	
Whitefish	4,492	2,138	6,266	4,703	10.5	32.5	683	494
Cisco		618		1,700	10.5	34.9		179
Trout	166	159	207	279	33.3	18.2	69	93
Carp	11,158	8,926	1,455	1,963	14.8	16.9	215	291
Catfish	15,935	12,747	11,779	12,339	25.8	33.2	3,039	3,184
Buffalo	11,548	9,238	5,246	6,706	2.8	5.7	147	188
Stripped Bass	5,023	2,044	3,351	4,664	44.9	3.5	1,448	2,094
Blue Fish	4,791	5,256	1,143	1,613	4.3	3.1	49	69
SUBTOTAL	53,114	41,126	29,407	33,967			5,650	6,590
Alewives	31,978	19,218	1,493	702	100.0	(100)	1,493	702
Lobster	12,974	15,645	37,134	64,813	--	22.5	--	14,583
TOTAL	98,066	75,989	37,034	99,482	--	--	7,143	21,875

Source: National Marine Fisheries Service (landings data); FDA (PCB levels data)

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two and half percent were calculated as being over the 2 mg/kg tolerance level in 1979 and 1980 data, resulting in an estimated loss of over $14 million in 1978 dollars (FDA, 1982, Testimony of National Marine Fisheries Service). That is about twice the combined loss from all other species.

ALEWIVES

The FDA regulation included only food for human consumption. Alewives harvested from the Great Lakes are used in pet food, not human food, so the FDA dismissed the industry's argument that alewife values should be used.

LOSS PERCENTAGES

The estimated percentage of a species' catch that would be taken off the market was assumed to be the same as the percentage of samples in which the fish were found to exceed the corresponding PCB level (Table 1). Table 2 illustrates the sketchy nature of this data base in 1978. Later figures expanded the data base by up to several fold, but samples for some species were expanded only slightly. For carp, for example, 54 samples were taken, 8 of which exceeded the 2 mg/kg level. For catfish, 295 samples were taken, 76 of which exceeded 2 mg/kg. The total number of samples was not very great. Lobster loss estimates were based on only 40 samples. Losses were estimated in this manner for tolerance levels of 1, 2, 2.5, 3, 3.5, 4, 4.5, and 5 mg/kg, all based on the same samples.

MORE RECENT DATA

The National Marine Fisheries Service (NMFS) argued in support of the industry, against lowering the tolerance level, but I found their figures to be most reliable. The NMFS calculated the value of losses from 1978, 1979, and 1980 catches, using 1978-1980 FDA fish sampling results, converted back to 1974 dollars for each of these tolerance levels except 1 mg/kg. Table 3 presents the 1980 results at 2 mg/kg. The American lobster is the largest component at $10 million. The total loss was about $14 million. This study did not include alewives. At various levels of PCB regulations (Figure 1), the value of the economic loss goes up quite rapidly after 3 mg/kg.

INDUSTRY'S ANALYSIS

The fishing industry (National Fisheries Institute) presented a different argument. Their updated analysis by Dr.

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TABLE 2

1978 Pesticides and Metals in Fish Program - PCB Levels Data

Species	Number of Samples Violative at 2 mg/kg	Percent	Lost Value $x10?	Number of Samples Violative at 5 mg/kg
Carp	8/54	14.8	215	2/54
Catfish	76/295	25.8	3,039	14/295
Buffalo	1/36	2.8	147	0/36
Lake Trout	29/87	33.3	69	2/87
Whitefish/Chub	2/19	10.5	685	0/19
TOTAL		16.7	4,155	
Sea Trout	0/10	0	--	0/10
Bluefish	1/23	4.3	49	0/23
Scap (Porgy)	0/10	0	--	0/10
Drum	0/12	0	--	0/12
Mackerel	0/21	0	--	0/21
Stripped Bass	4/9	44.4	1,488	0/9

Source: FDA, 1982, Document G-2 (1979)

Ivar Strand confused the issues greatly by (1) using 1980 dollars and 1974 landings even though all parties had previously agreed to use 1974 dollars and 1980 landings, and (2) including Great Lakes alewives which are not used as human food and therefore not even under FDA jurisdiction. Furthermore, East Coast alewives, which are used as food, were apparently not sampled for PCB. In 1980 dollars and including alewives, the value lost, according to the industry, was about $24 million--almost twice as high as the NMFS estimate (Table 4).

The industry also said that there were a number of other values that needed to be considered in calculating this loss (Table 5). First, they reconsidered the assumption that the value of the food taken off the market would be equal to the percent found violative in the FDA samples. That is a questionable assumption because fish shipments are rarely sampled. Many fish could go to market without being sampled; and sampling is slow and expensive, so regulatory agencies may simply remove all fish from the market. An example of this was found in

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TABLE 4

Estimated Annual Economic Impact at Various PCB Tolerance Levels

Species	PCB Tolerance Level (mg/kg) 2.0	2.5	3.5	4.0	4.5	5.0
	(000's $)					
Freshwater						
Alewives	2,813	---	---	---	---	0
Buffalofish	128	128	0	0	0	0
Carp	295	137	118	79	79	73
Catfish	4,740	2,917	1,458	1,094	911	856
Trout	86	47	13	8	6	6
Whitefish and Chubs	1,161	1,161	0	0	0	0
Marine						
Bluefish	68	0	0	0	0	0
Lobster	11,673	11,673	8,735	8,735	5,796	2,898
Striped Bass	2,984	2,210	0	0	0	0
TOTAL	23,948	18,273	10,324	9,916	6,792	3,833

Source: Testimony of Ivar Strand (FDA, 1982, Document N-21); PCB levels based on 1978-1980 FDA sampling; Dollar values are in 1980 dollars; landings data are from 1974

TABLE 5

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TABLE 5

Potential Losses (in $ thousands) Associated With Various PCB Tolerance Levels[1]

Source of Loss	Tolerance Level (mg/kg) 2.0	2.5	3.5	4.0	4.5	5.0
Loss based on % of violative samples	167,636	127,911	72,268	69,412	47,544	26,831
Loss to "recreational" fishermen	257	196	0	0	0	0
Loss based on unviable fisheries	361,200	204,570	0	0	0	0
Loss based on other related species	10,409	---	---	---	---	---
Loss to imported products	31,410	31,056	22,302	14,790	14,774	7,414
Loss due to bad publicity	(32,011)[2]	---	---	---	---	---
TOTAL ECONOMIC LOSS (1980 dollars)	570,912	363,733	94,570	84,202	62,318	34,345
TOTAL ECONOMIC LOSS (1974 dollars)	303,965	217,680	56,596	50,392	37,295	20,554
FDA ESTIMATES (1974 dollars)	56,000	---	---	---	---	---

[1]Includes the seven-fold increase from harvest level to processor
[2]Not included in total because unviable fisheries would already include the loss
SOURCE: Testimony of Ivar Strand (FDA, 1982, Document N-21)

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TABLE 3

Summary of Projected Economic Losses Due to PCBs in 1980 at 2.0 mg/kg (Deflated 1974 Dollars in Thousands)

Species	Losses at 2.0 mg/kg (1980)
Chub	$ 286
Whitefish	707
Lake Trout	54
Buffalofish	229
Carp	199
Bluefish	45
Catfish	2,181
Striped Bass	103
American Lobster	10,130
Total Economic Loss	$13,933
Percent Loss of Total Value of Catch	21.7

Source: National Marine Fisheries Service Testimony (FDA, 1982)

Michigan where chubs were in effect taken off the market when about 50 percent of them were found to be contaminated with dieldrin. The State of Michigan simply eliminated chub harvesting. Thus, 100 percent was lost instead of 50 percent. Furthermore, fishers would find it too risky to harvest fish if shipments were likely to be confiscated. The industry argued that anytime over 25 percent were found violative in FDA's samples, the whole fishery should be assumed to be taken off the market. They attributed a large loss to such "unviable" fisheries (Table 5). However, one could also argue that if less than something like 25 percent are violative, all would go to market because of inefficient sampling. Second, they estimated some loss due to "recreational" fishermen. These are sales of bluefish (saltwater fish) caught by anglers and, therefore, not appearing in commercial fishery statistics and FDA estimates. Third, they contended that, since fisheries for some species might stop, the whole fishing industry in some cases might shut down, so there would be some losses due to other related species as well. Fourth, they estimated that applying the same standards to imported fish would result in

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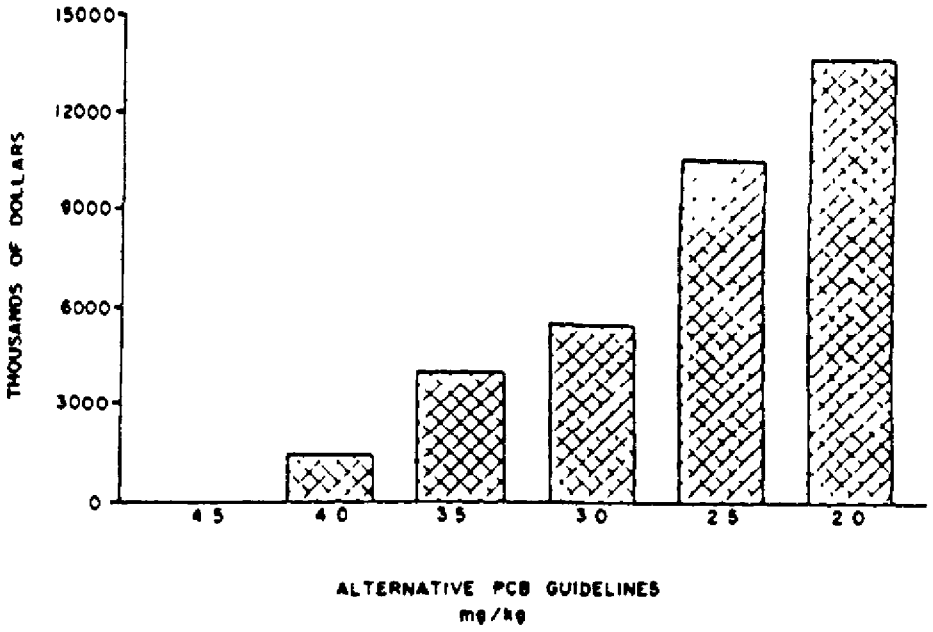

Figure 1. Total economic loss at alternative guidelines - 1980 (deflated 1974 dollars).

an impact of $31 million, apparently assuming that those losses would not be made up by additional imports. Finally, they suggested that the value of fish not taken off the market would also be reduced because of bad publicity.

Ultimately, the hearing examiner found that these four arguments on behalf of industry were irrelevant. They were outside the scope of the problem as it had been narrowly defined.

LOBSTER LOSSES: UNREPRESENTATIVE SAMPLING

In estimating the food loss, the FDA assumed that the percent found violative in the various samples would be the percentage removed from the market. That was accepted as one of the ground rules for the hearing. However, there was one exception: the lobster data. In this case, only those samples from the New Bedford, Massachusetts, area were found to be over the limit. FDA samples fish to spot violations, not to establish national percentages found in violation. When they found

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contaminated lobsters, they naturally intensified their sampling in New Bedford to get a handle on this "hot lobster population". About 22.5 percent of the total samples (1979-80 sampling period) of lobsters from all over the country were shown to be violative at 2 mg/kg, but the only ones shown over the limit were from the New Bedford area. There happens to be a source of PCB contamination in the New Bedford/Hartford area. If we simply removed all the lobsters from New Bedford from the market, and none of the others, the value lost would not be $14.5 million (1978 dollars) but more likely be $.25 million dollars (1974 dollars) because they represent only 1/2 of 1 percent of total U.S. lobster landings (FDA, 1982, Testimony of Dr. John Gates). Or, calculated in a slightly different way based on fishing effort, the loss would be slightly over $1 million ($1.3 million). These later figures are much more representative of the actual prospective impact than the $14.5 million estimate.

PRESENT ESTIMATES

What is the current estimate of losses, considering all of these arguments? Table 3, entered as evidence on behalf of the industry by the U.S. Department of Commerce, National Marine Fisheries Service, is based on the latest PCB data and fish landings. Changing the lobster losses from $10,130 million (Table 3) to $.25 or $1.3 million, the estimate becomes $4.053 million or $5.103 million. At most, the loss as I estimate it has dropped from the original $5.7 million to about $5 million, using 1980 catch and new PCB data, but continuing with 1974 dollars. One additional factor, price elasticity, still remains to be considered.

MULTIPLIER EFFECT

Before we allow for price elasticity, let us consider another issue--the multiplier. If the above is the landed value of the fish lost, what is the total impact on the U.S. economy? Fish are processed, transported, and marketed (wholesale and retail) so the final food value of those fish reflects these costs. The value added in the process of wholesaling, retailing, transporting, and processing fish is only a factor of about three according to recent national studies (Centaur, 1977). In other words, the final sales value of the fish is about three times higher than the initial landed value. After the fish are sold, the income is respent in the community, adding another component of economic impact. This is the multiplier effect. The total of both the multiplier and value added effects is about seven.

In its 1979 regulations statement, the FDA incorrectly multiplied the landed values by a factor of six to convert them to food values. The more correct way of finding the total value of the food lost is to convert the landed values to final sales values by multiplying the landed values by three, the average value added. The hearing examiner, in his findings, recommended a value of six even though all three Great Lakes economists that considered this thought the multiplier should be three instead of six or seven. He used six primarily because that is the multiplier the FDA chemist used to originally estimate the losses officially adopted by FDA.

PRICE ELASTICITY

Another factor that Gary Johnson and I recognized was price elasticity. The price elasticity of fish is low. That means that if fish are taken off the market, the prices of the remaining fish of the same species go up, but in smaller proportion than the amount of fish taken off the market. For example, the price elasticity of whitefish is -0.3 (Ghanbari, 1977), which means that if the quantity of whitefish were reduced by 10 percent, the price of whitefish would increase 3 percent. Fish price elasticities are low because each kind of fish has many substitutes in the market. If new regulations remove fish from the market, the values of the remaining fish will increase. Therefore, the prices of the fish removed from the market will be slightly higher than existing prices. The values of the losses will not be much higher than $4.053 million or $5.103 million because the elasticities are low and the prices will increase only gradually. I testified that the total loss would still be less than $6 million (1974 dollars). Apparently, the hearing examiner misinterpreted what I said; he added another $6 million for the elasticity effect, referring to my testimony.

HEARING EXAMINER'S FINDINGS

The hearing examiner found that the landed value lost would be $13.5 million in 1980 dollars, or $8 million in 1974 dollars. Multiplying $13.5 million by six and adding the $6 million for elasticity, he estimated the total food loss at $86 million. In my opinion, this includes at least five mistakes in addition to the big assumption that the percent violative in FDA samples equals the percent lost. We have discussed the multiplier of six mistake and the elasticity mistake. Two other mistakes were (1) that 10 percent of lobsters would be lost (because he felt a consistent approach to estimatng losses should be taken even if we know better), and (2) that 30 percent of alewives

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would be lost (because those caught outside of the Great Lakes are used as food and comprise 30 percent of the U.S. catch, even though I believe all the violative samples came from Great Lakes fish). He estimated lobster and alewife losses at almost $5 million (combined) in 1980 dollars, or about $3 million in 1974 dollars. His final mistake was that he used different percentage losses than I believe he intended to. He used the percentage found violative in 1980 samples only, rather than the 1978-1980 samples combined, yet he referred to the fact that the parties agreed to a set of losses based on 1978-80 samples. This resulted in significantly higher loss estimates for stripped bass. Other than these errors, the total loss figures are about the same as the original losses estimated by FDA.

CURRENT STATUS

Some groups will soon be filing exceptions to the ruling based on some of those issues. When the period for exceptions expires later this spring, the findings and the exceptions will be presented to the Commissioner of the FDA. He will then decide whether or not to change the PCB tolerance levels.

BROADER ISSUES

This hearing did not consider two broader social issues that have not been addressed by the FDA in the hearing or in any other document I have seen on this issue. I think it is particularly unfortunate that a benefit-cost analysis was not attempted because that would focus on the advantages and disadvantages; whereas the economic impact analysis the hearing focused on would only be one part of that analysis. For example, although the losses in landed and food values were estimated, any associated reduction in the costs of landing and otherwise handling the fish were ignored.

Some of the real issues--the social questions--that should be examined in this case are as follows:

(1) What are the equity considerations? We know that much of the Great Lakes fishing industry would be devasted. Most of the projected losses are species that comprise the bulk of the commercial fishery in Lakes Superior, Huron, and Michigan. If those were taken off the market, the already depressed fishing industry there would be seriously hurt. Is it worth penalizing those particular people when we are not sure there would be any corresponding benefits? On

the other hand, is it fair to expose fish consumers to risks they are not aware of?

(2) What are the benefits and costs? The benefits would be the value of reducing the health risk, increasing life spans, and increasing the security available to fish consumers. The cost would be (1) the final sales value of the fish lost minus the costs that would have been incurred to produce, process, and otherwise handle the fish; plus (2) the cost of regulation. Dr. Van Ravenswaay discussed this issue much more thoroughly than I can here. Much more information would be needed to assess the benefits accurately, and that kind of information is not presently available. However, at least it is the right question, even if we don't have good answers yet.

ANGLING VALUES

Dr. Howard Tanner, Michigan DNR, suggested that I would mention how the sport fishing values would be affected. I have not evaluated that carefully, but I do know the upper limit of sport fishing impacts and values. If sport fishing were discontinued in the Great Lakes, the economic impact would be over $1 billion per year (Talhelm et al., 1979). Anglers spend about $500 million, and the multiplier effect is 2 to 2.5 times that amount. In addition, anglers would lose a fishery they value at about $600 million per year. In other words, not only do anglers spend $500 million for Great Lakes angling, but they would be willing to pay up to $600 million beyond those expenditures in an effort to prevent the loss of the fishery (Talhelm et al., 1979). These values are much greater than the commercial fishery losses.

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CHAPTER 30

PROBLEMS IN LEGISLATING AND REGULATING TOXIC MATERIALS: PANEL DISCUSSION

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COOPER[1]: Over the last few days you have heard the discussion about many aspects of polychlorinated biphenyls (PCBs): the sampling, analyses, health effects, etc. There has probably been more research done on PCBs than on any other single compound in the last five or ten years. Based on all of this, what would you provide Governor Milliken as a consensus recommendation? What I would like you to do is to try to address three questions that need to be answered if you are going to come to such a consensus. First of all, what do action levels mean in terms of the humans that we say we are going to try to protect? The concept of action levels is embedded in federal law and is the primary mode of regulating interstate commerce. The levels are based on nationwide statistics (e.g., on a typical 18 year old from Des Moines, Iowa, who eats 19.2 grams of fish a day). How appropriate is this for people who live on the shores of the Great Lakes and eat much more fish containing higher levels of PCBs?

A second question is whether or not there should be uniformity among the state governments, the federal government, and provincial governments, all of whom have the same regulatory mandates. There is both an economic and an exposure argument in that question. If we are convinced that Michigan consumers are really consuming a

[1]Members of the audience contributing to the Panel Discussion are identified at the end of the chapter. The other speakers are identified in the front matter in the List of Participants.

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much greater percentage of the fish out of the Great Lakes, maybe Michigan should have a lower standard than what is acceptable for the average consumer served by the Food and Drug Administration (FDA).

One other problem is that the population with the greatest exposure is sports fishermen, not the average consumer; and the only way we are dealing with this group is with warnings stamped on the back of fishing licenses and some education programs describing how to clean fish properly. The third question is whether or not these steps are really adequate. Before we focus on these questions, I would like to give panel members an opportunity to make some general comments.

AUST: I would like to make the point that much of the action prior to this meeting relative to a consensus PCB action level in fish has been due to the Toxic Substance Control Commission (TSCC). The TSCC was established to examine state programs and regulations relating to toxic substances in Michigan. The TSCC has been dealing with many subjects; but the one that has been persistent has been the PCBs, probably because they, too, are persistent. The Commission was made aware of a letter to Governor Milliken a number of years ago from the Director of the FDA saying that Michigan was unique in that PCBs in Great Lakes fish were another source of contamination of the people of Michigan and suggesting that the state should consider its own action level. Nothing was really done until the Commission took up the subject with the FDA. Taylor Quinn, from the Bureau of Foods at FDA, wrote back that: "The FDA woulo have to leave it up to the state and local officials to determine whether additional steps are necessary to reduce PCB exposure in situations atypical of the general population and, further, what types of steps should be taken."

That was in January of 1981. Needless to say, no action has been taken; therefore, the Commission decided that we should seriously consider this subject. We argued for many hours as to what the recommendation should be. Should it be an action level? A standard? At what point should it be imposed? I, personally, feel that 2 mg/kg is not low enough. A think many other people at this conference voiced the same opinion. However, the 2 mg/kg action level is at least somewhat similar to what Ontario is proposing. If we do not have a 2 mg/kg standard, I am certain that the Commission could live with some other level as long as it is below the 5 mg/kg federal level. However, the Commission is going to be quite insistent that something

McCRACKEN: I have a few statements that I think partly represent what Dr. Tanner said this morning and partly represent what I think based on what I have heard in the past few days. Together my remarks represent, in effect, a Department of Natural Resources (DNR) position on the issue of PCBs in the Great Lakes.

First of all, because of our combination of regulatory and promotional activities, we feel that the DNR must take a balanced viewpoint on PCBs. In our role as a pollution control agency, we will continue to work diligently to reduce the discharges of PCBs through the National Pollution Discharge Effluent Standards (NPDES) program and otherwise.

We are pleased that PCB control legislation is having a more rapid effect in reducing PCB residues in fish than had been predicted by scientists. By PCB control legislation I mean state and federal laws which ban manufacturing and uses other than in closed systems. We are pleased that most fish now fall below 5 and 2 mg/kg, depending on what portion of the fish is sampled.

We share the concern of the Michigan Department of Public Health (MDPH), and many people here at this conference, that many people eat large amounts of contaminated fish which they or friends catch, especially because this is the primary source of PCB to humans and the FDA risk assessments indicate that even a 2 mg/kg tolerance may not properly protect sport anglers.

We do not believe that unilaterally lowering the PCB tolerance for commercial fish is a particularly useful approach to help sport anglers. We feel that Michigan commercial fish should be regulated just like other states: and we would not object to lowering the tolerance from 5 to 2 if the scientific information led the FDA to make that judgment. We do believe that a better approach is to improve our information and explanations to the people of the state about the concern over PCBs and about how to reduce their intake of PCBs; and I think a good example of that is in the latest DNR magazine. It contains a wonderful article on how to take out the fat which contains most of the PCBs before the fish are cooked. We need to carry out a fish contaminant monitoring program to obtain better data for doing this informational program. As Representative Anderson said, that depends on funds. We can't do it without funds.

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At present, we do not believe there is enough hard evidence on the dangers of PCBs to humans to stop the salmon planting program. The program provides many benefits to the state that have not been discussed in detail at this conference and which must be considered before such a decision is made. I say "at present" because Dr. Greta Fein's study may provide more information on health effects, and it is certainly possible that we might want to change our minds about that.

Last, we think standardization is needed, at least on the type of sample of the edible portion to be taken; and we will propose that to the FDA, the International Joint Commission, and other jurisdictions.

HUMPHREY: The basic issue here is how to reduce exposure to this kind of chemical. I believe the information brought forward at this conference reinforces the literature saying that PCB is not a biologically inert compound. Depending on whose viewpoint you take, you accept or reject certain degrees of how harmful this chemical could be. We do know that it is present in the Great Lakes where the basin and its drainage patterns are unique. More importantly, PCB bioaccumulates and stores in biological tissue. Thus, with our understanding of the nature of the compound and its potential to do harm, we have to consider how we can reduce exposure and the potential for disease.

COOPER: There are two types of exposure: voluntary and involuntary. Involuntary is when you go to the market to buy fish that have no labels to tell you that it is from the Great Lakes. Action levels and tolerances are designed to protect people from this type of exposure. Voluntary exposure is when you put a warning on fishing licenses and people choose whether or not to eat what they catch. The two types of exposure have different societal levels of acceptability. People perceive risks differently if they are chosen or imposed. I've heard that the U.S. federal government recommended lowering action levels to 2 mg/kg because if it did not, every batch of fish landed in Canadian ports by American fishermen would have to be chemically analyzed before it would be allowed in. To what degree is the U.S. government suggesting 2 mg/kg purely in terms of economic stability between the U.S. and Canada and the international fishing agreements with no consideration of toxicology at all?

GRANT: That's news to me at Health and Welfare.

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COOPER: From the FDA's point of view, is there a constraint if Canada and the U.S. have different levels?

HOETING: I am not aware of any problems with marine fish whether they are caught off the coast of the U.S. or of Canada. I do not believe freshwater fish from the Great Lakes are caught by American fishermen and sold in Canada. The reverse is true.

COOPER: Are you saying that the major issues between 2 and 5 mg/kg are biochemistry, risk assessment, exposure rates, and toxicology?

McCRACKEN: The differences between 2 mg/kg in Canada and 5 mg/kg in the U.S. reflect the fact that in Canada they are taking different kinds of samples. The plug of lean muscle used in Ontario is the portion least likely to show high contaminant levels, while the American samples show higher levels. We don't think that there is a lot of difference in which fish pass or fail inspection in the U.S. or Ontario because of the differences in sample type.

GRANT: Dorsal muscle is Ontario's interpretation of the edible portion. Our interpretation of an edible portion is not necessarily the dorsal muscle. The samples which we identify are collected by the Federal Fisheries and Oceans as they would flow into the marketplace.

COOPER: Are you saying that you don't sample at the Federal level in Canada the same way as you do in the Province of Ontario?

GRANT: Not necessarily. If you only eat the dorsal muscle, it is the same.

COOPER: I'd like to ask Dr. Cardwell a question about 2 versus 5 mg/kg. Is the only difference the way you analyze your fish so that if you analyze them all the same way everyone gets the same level? Also, is there any reason that there can't be standardized analytical techniques?

CARDWELL: Because the level of fat in the filet is greater than in the dorsal muscle, I would expect a higher level from our way of making the measurement. I see very little problem in reaching some type of agreement with regard to general standardization.

COOPER: Is that one thing we could pass on to the Governor as a strong recommendation--a standard set of sampling and analytical techniques? Anyone disagree?

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AUST: My stand is that the best available technology be used on the most appropriate samples. We went through these arguments with the polybrominated biphenyls (PBBs), and it was decided that a fat sample was to be used. I don't know if you could use, say, a rendered sample of fish to do a fat analysis. So far I have heard no discussion of the PCBs in the fat or PCBs in fish on a fat basis. We have been talking about a whole fish or a filet where PCBs are present in the ppm range; whereas when the PBBs issue arose, we set a standard of 20 ug/kg in the fat of cattle. Variability was removed by always sampling the fat and reporting the data on a fat basis. Now we are talking about using some other portion and not using the fat basis; and, also, we are discussing a level which is considerably higher than 20 ug/kg on a fat basis. It would appear that there is a large difference here without there being a significant difference in chemicals.

COOPER: One thing I would recommend in considering environmental legislation is to have scientists give not just the means but also the 95 percent confidence intervals around their estimates. If you put in the bimodality of the population you are sampling, the 20 fish the FDA has homogenized from which you take a uniform sample, the analytical variation from lab to lab and sample to sample, and multiply these variations together, I'll bet you couldn't tell 2 from 5 statistically. I think we have to be honest as to where we have precision and where we don't.

What about the concept of uniformity? Is it essential or non-essential from anyone's point of view?

CARDWELL: I would agree to that because at least then we are attempting to compare like situations and like circumstances. At the present time, we are not doing that.

COOPER: Might it be that the one place you would not want to do that is if you had sub-populations in Michigan that had higher exposure rates because of their occupation or sports? With a unique population that has a much higher than average exposure, uniformity might not be the best way to protect health. How are you going to balance the economics of uniformity versus the public health concern to control exposure when you know populations differ?

McCRACKEN: What we have now is uniformity within jurisdictions. We aren't, in every case, using the worst case or series of cases representing all of the various ways fish could be consumed. We have a standard in Ontario, one in Michigan, and so on. These are not based on ethnic food

eating habits. They are based on regulatory policy. What we are saying is why not require the same regulatory policy in all jurisdictions? That's a different question from whether or not we should use the worst case.

Should we protect the person who eats the portion of the fish that has the most fat? Ontario handles this problem by using a lean plug of muscle and saying that if you eat a portion with more fat, beware because these are not serious enough warnings for you. Perhaps that's the way to handle somebody who eats an unusually high fat portion.

COOPER: Dr. Hoeting, you deal mostly with national averages because that is your mandate. How do you handle high-risk or high-exposure sub-populations?

HOETING: We face that problem with many regulatory situations. We have the same problem with saccharin, cyclamates, and sensitivity to anti-perspirants. A certain segment of the population, in fact, is far more sensitive to or consumes much greater quantities of the compound than others. The rational process is to attempt to determine what the no-effect levels are, extrapolate from them, and base a decision on that group which typically represents the greatest majority of the people.

The average consumer of fish eats somewhere in the range of 10 to 15 pounds a year. Humphrey's data show that a sports fisherman in Michigan consumes between 20 and 28 pounds a year. Out of that group of between 400 and 500 subjects, one or two people consume upwards of between 100 and 200 pounds a year. The existing regulation does not provide adequate protection for the person who consumes 200 pounds of fish a year.

COOPER: Dr. Talhelm, from an economist's point of view, is there any great argument for or against uniformity between states or between Canada and the U.S.?

TALHELM: If Michigan adopted its own standard, it would probably put Michigan's industry at some disadvantage; but most of the fish caught would find markets outside the state, assuming that they kept their levels at 5 mg/kg. Good markets for Michigan fish are found in Chicago and New York. The main people who would be put at a disadvantage would be the processors. Consumers would substitute either other kinds of fish or other kinds of food, but the people who processed and handled fish in Michigan would have to find something else to do.

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GRANT: If you want to decrease exposure, do you really help the situation that much by having the same level for the fish that is eaten rarely as opposed to that which is eaten more often? We do not necessarily have the same pesticide tolerance for insecticides on apples and pears, but we have the same level for fish. On the basis of exposure, is there any reason not to have different levels?

COOPER: You could argue that it depends on the distribution of the chemical in the environment and the distribution of access to the resource. Dr. Tanner said he would be willing to support 2 mg/kg as long as it is uniform. Does anyone disagree with that or have any problem with that position?

AUST: The Commission's question is: Does that mean that we simply wait until there is a federal standard?

COOPER: Not at all. All we are saying is the data should be proven to be accurate before we commit ourselves. Let's see that we all agree that if there was a uniform set of standards, 2 mg/kg would be acceptable in terms of the public, the economics, risk assessment, public health concerns, FDA's problems, etc.

ANDERSON: The question of uniformity is very important. I recall that when we were dealing with PBBs, we were passing legislation on the level of containment (i.e., how much would the reading be before you must dispose of the animal). The question came up several times in the midst of arguments from technical people as to how, when, and in what manner to measure PBBs. The question wasn't what level should be set, but what sampling and analysis methods should be used in setting the levels. A standard of uniformity is most important. Another feature of this is that the Governor has to make a determination. He also has to have some sort of a uniform advice mechanism. The broad spectrum of populace deserves, and I think rightly so, some degree of uniformity in its reporting.

COOPER. Let's look at the last issue: Voluntary exposure to sports fishermen. Do you feel that the public notice on the fishing license and the educational program have worked and are sufficient with our current knowledge of PCB risks?

ANDERSON: I can touch on that because I travel the state looking at these kinds of things a lot. I came across a man in Ludington not long ago who told me they canned 30 qts of salmon so far this season and that they were almost out of the salmon that they had canned the previous season. I asked him how he trimmed the fish. He said: "I use the

recommended method of trimming. I take off all the fat, take off the fat along the side, along the backbone, cut off the belly flap." So he had an awareness. I talked to others who had also done the same thing when they trimmed their fish. In our home, we, as a routine practice, cut off the fat. My experience has been that more people than not are aware and are being cautious.

HUMPHREY: Yesterday, I presented some statistics which address this question. We interviewed some people who consumed a considerable amount of fish in 1974 and then we interviewed them again last year. For whatever reason, the quantity they were consuming, numbers of meals per year, as well as pounds, had gone down. I don't know exactly why. One possibility is that they have been hearing the message concerning consumption. It could also simply be that they are not as lucky at catching fish as they were a few years ago.

COOPER: You could say the reflexes slowed up in eight years.

HUMPHREY: No, the fish aren't there.

COOPER: Does anyone in the audience have questions for the panel members?

CHARLES CUBBAGE: I am not sure that you can answer the questions I have been troubled by during the conference. The objective in setting any standard is whether or not man is going to benefit from it, but you can't just limit it to those people who just happen to be in the population right now. Are Homo sapiens going to be impacted by PCBs 20,000 years from now, assuming we will be here for that length of time? We have to consider the health of our life support systems as well as the health of man.

COOPER: There is a legislative mandate to stop the prduction of this PCB except in closed systems. The PCBs are being tied up in the sediments, and the amount in water and fish has been dropping systematically over the past eight years. It looks as if it is working its way through the ecosystem. I think the question is whether or not The Toxic Substances Control Act will keep we from making these same mistakes in the future. Any comments from the panel?

AUST: I want to address another issue. We saw Dr. Ringer's data that 2 mg/kg PCBs in fish that make up 30 percent of a mink's diet led to a reproductive problem. I have been alarmed at the number of individuals who come to the TSCC and say there are human reproductive problems. I don't

know what the relationship might be between PCBs and reproductive problems in humans. It is impossible to compare humans to minks, but what kind of a safety factor are we adding to the mink food level of 2 mg/kg? Another problem is carcinogenesis. I haven't had a chance to really analyze Dr. Humphrey's latest data on "PCB silo farmers", but it may be alarming. We are not going to find the exact risk of PCB to human beings published in some journal because PCBs are unique substances. They are promoters of carcinogenesis and so should always be studied in conjunction with another chemical. This type of data is impossible to obtain for humans. Therefore, we will not have data for risk analysis.

COOPER: We have to put what we know and don't know in balance. There are many chemicals which have been in the environment since World War II, and we are just finding out that they are there. When you look back at the history of environmental episodes, you see that when the ion detector became available for heavy metal analysis we discovered mercury. When the gas chromatograph came into use, you found organic chemicals. To a degree, environmental awareness has come about with the ability to monitor various chemicals. The compounds have been out there for a long time.

AUST: Would you rather discover them with an epidemiological study?

BREMER: I have something I want to add for clarification and maybe ask you a favor. The federal money for PCB enforcement has been available for just about a year now; and the legislature has failed to approve the authority for the DNR to spend those funds. They are in limbo right now; and if the legislature doesn't come along and approve them, they will probably be lost by this time next year.

ANDERSON: I'll check that within the hour.

COOPER: That's one constructive thing to come out of this morning's session.

CARDWELL: The Michigan Department of Agriculture (MDA) is very much interested in anything that will ultimately lower the exposure of the people of Michigan. However, we feel that a uniform process must be utilized. If you are going to lower the allowable level for the commercial fishermen, you must also consider lowering the total exposure for the sports fishermen. The Director of the MDA has indicated that he will go along with the recommendations of the

Hazardous Materials Cabinet, which was formed by the Governor and which met for the first time in December.

GISELA KING: After hearing testimony at this conference, I am very angered and frustrated at the prospect of not being able to nurse a baby, to fulfill this basic need a mother has to nurture and protect her baby. As a consumer, I think what would be important to me to protect myself is a labeling system. As a part-time farmer, for example, I would like to know if any of the equipment I may be purchasing contains PCBs. I would also like to see labels on different food items that are purchased; and on fish, the actual chemical content, and not just the point of origin.

COOPER: One of your questions concerns the degree to which laws that restrict PCBs to closed systems are being enforced. It is true that currently the only PCBs manufactured and sold are in closed transformers and similar equipment.

HUMPHREY: It is my understanding that PCBs are no longer being manufactured and sold in this country. An article that I cited yesterday says that about half of the PCBs ever made are still in use, but in closed systems.

COOPER: But, if she went out and bought a new piece of equipment, would the hydraulic fluids, lubricating fluids, and cutting oils all be PCB-free?

HUMPHREY: I belive they should be.

COOPER: The other question was to what degree you can label a food product as to its PCB concentration. There you have a problem because of the period of time it takes to get food analyzed. With kepone in Chesapeake Bay, it took about two weeks and the fish were either rotten or sold by then. I don't know of any way that you could actually monitor fast enough and label products soon enough so that actual levels would show up in the market place for a fresh item.

KING: Do I understand that there are certain levels of PCBs in milk, eggs, meat, and various other consumer products?

CARDWELL: To the best of my knowledge, based on data from the USDA, that has not been borne out.

HUMPHREY: Mrs. King was disturbed as a mother because she could not breast feed her child. The point we were trying to make is that a woman in Michigan, who is not a consumer

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of large quantities of sports fish or does not live on a farm with a particular type of silo, does not have particularly high levels of PCBs; and there has never been any advice that she should not breast feed her child.

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