TOXICOLOGICAL PROFILE FOR POLYCHLORINATED BIPHENYLS (PCBs)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

A toxicological Profile for PCBs, Draft for Public Comment, was released in December 1998. This edition supercedes any previously released draft or final profile. Toxicological profiles are revised and republished as necessary, but no less than once every three years.

For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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Administrator
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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepared toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by *type of health effect* (death, systemic, immunologic, reproductive), by *route of exposure*, and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

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E-mail: atsdric@cdc.gov ***Internet:*** http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

*The National Institute of Environmental Health Sciences (*NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. The Green Border Review assures the consistency of the profile with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for polychlorinated biphenyls (PCBs). The panel consisted of the following members:

1. Larry Hansen, University of Illinois, College of Veterinary Medicine, Urbana, Illinois;

2. Joseph Jacobson, Wayne State University, Detroit, Michigan;

3. Helen Tryphonas, Bureau of Chemical Safety, Frederick G. Banting Research Center, Ottawa, Ontario, Canada;

4. John Vena, University at Buffalo, Social and Preventive Medicine, Buffalo, New York

These experts collectively have knowledge of PCBs physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about polychlorinated biphenyls (PCBs) and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. PCBs have been found in at least 500 of the 1,598 current or former NPL sites. However, the total number of NPL sites evaluated for PCBs is not known. As more sites are evaluated, the sites at which PCBs are found may increase. This information is important because exposure to PCBs may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to PCBs, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE POLYCHLORINATED BIPHENYLS?

PCBs are a group of synthetic organic chemicals that can cause a number of different harmful effects. There are no known natural sources of PCBs in the environment. PCBs are either oily liquids or solids and are colorless to light yellow. Some PCBs are volatile and may exist as a vapor in air. They have no known smell or taste. PCBs enter the environment as mixtures containing a variety of individual chlorinated biphenyl components, known as congeners, as well as impurities. Because the health effects of environmental mixtures of PCBs are difficult to

evaluate, most of the information in this toxicological profile is about seven types of PCB mixtures that were commercially produced. These seven kinds of PCB mixtures include 35% of all the PCBs commercially produced and 98% of PCBs sold in the United States since 1970. Some commercial PCB mixtures are known in the United States by their industrial trade name, Aroclor. For example, the name Aroclor 1254 means that the mixture contains approximately 54% chlorine by weight, as indicated by the second two digits in the name. Because they don't burn easily and are good insulating materials, PCBs were used widely as coolants and lubricants in transformers, capacitors, and other electrical equipment. The manufacture of PCBs stopped in the United States in August 1977 because there was evidence that PCBs build up in the environment and may cause harmful effects. Consumer products that may contain PCBs include old fluorescent lighting fixtures, electrical devices or appliances containing PCB capacitors made before PCB use was stopped, old microscope oil, and old hydraulic oil. You can find further information on the physical properties and uses of PCBs in Chapters 4 and 5.

1.2 WHAT HAPPENS TO POLYCHLORINATED BIPHENYLS WHEN THEY ENTER THE ENVIRONMENT?

Before 1977, PCBs entered the air, water, and soil during their manufacture and use in the United States. Wastes that contained PCBs were generated at that time, and these wastes were often placed in landfills. PCBs also entered the environment from accidental spills and leaks during the transport of the chemicals, or from leaks or fires in transformers, capacitors, or other products containing PCBs. Today, PCBs can still be released into the environment from poorly maintained hazardous waste sites that contain PCBs; illegal or improper dumping of PCB wastes, such as old transformer fluids; leaks or releases from electrical transformers containing PCBs; and disposal of PCB-containing consumer products into municipal or other landfills not designed to handle hazardous waste. PCBs may be released into the environment by the burning of some wastes in municipal and industrial incinerators.

Once in the environment, PCBs do not readily break down and therefore may remain for very long periods of time. They can easily cycle between air, water, and soil. For example, PCBs can enter the air by evaporation from both soil and water. In air, PCBs can be carried long distances

and have been found in snow and sea water in areas far away from where they were released into the environment, such as in the arctic. As a consequence, PCBs are found all over the world. In general, the lighter the type of PCBs, the further they may be transported from the source of contamination. PCBs are present as solid particles or as a vapor in the atmosphere. They will eventually return to land and water by settling as dust or in rain and snow. In water, PCBs may be transported by currents, attach to bottom sediment or particles in the water, and evaporate into air. Heavy kinds of PCBs are more likely to settle into sediments while lighter PCBs are more likely to evaporate to air. Sediments that contain PCBs can also release the PCBs into the surrounding water. PCBs stick strongly to soil and will not usually be carried deep into the soil with rainwater. They do not readily break down in soil and may stay in the soil for months or years; generally, the more chlorine atoms that the PCBs contain, the more slowly they break down. Evaporation appears to be an important way by which the lighter PCBs leave soil. As a gas, PCBs can accumulate in the leaves and above-ground parts of plants and food crops.

PCBs are taken up into the bodies of small organisms and fish in water. They are also taken up by other animals that eat these aquatic animals as food. PCBs especially accumulate in fish and marine mammals (such as seals and whales) reaching levels that may be many thousands of times higher than in water. PCB levels are highest in animals high up in the food chain. You can find more information about what happens to PCBs in the environment in Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO POLYCHLORINATED BIPHENYLS?

Although PCBs are no longer made in the United States, people can still be exposed to them. Many older transformers and capacitors may still contain PCBs, and this equipment can be used for 30 years or more. Old fluorescent lighting fixtures and old electrical devices and appliances, such as television sets and refrigerators, therefore may contain PCBs if they were made before PCB use was stopped. When these electric devices get hot during operation, small amounts of PCBs may get into the air and raise the level of PCBs in indoor air. Because devices that contain PCBs can leak with age, they could also be a source of skin exposure to PCBs.

Small amounts of PCBs can be found in almost all outdoor and indoor air, soil, sediments, surface water, and animals. However, PCB levels have generally decreased since PCB production stopped in 1977. People are exposed to PCBs primarily from contaminated food and breathing contaminated air. The major dietary sources of PCBs are fish (especially sportfish that were caught in contaminated lakes or rivers), meat, and dairy products. Between 1978 and 1991, the estimated daily intake of PCBs in adults from dietary sources declined from about 1.9 nanograms (a nanogram is a billionth part of a gram) to less than 0.7 nanograms. PCB levels in sportfish are still high enough so that eating PCB-contaminated fish may be an important source of exposure for some people. Recent studies on fish indicate maximum concentrations of PCBs are a few parts of PCBs in a million parts (ppm) of fish, with higher levels found in bottom-feeders such as carp. Meat and dairy products are other important sources of PCBs in food, with PCB levels in meat and dairy products usually ranging from less than 1 part in a billion parts (ppb) of food to a few ppb.

Concentrations of PCBs in subsurface soil at a Superfund site have been as high as 750 ppm. People who live near hazardous waste sites may be exposed to PCBs by consuming PCB-contaminated sportfish and game animals, by breathing PCBs in air, or by drinking PCB-contaminated well water. Adults and children may come into contact with PCBs when swimming in contaminated water and by accidentally swallowing water during swimming. However, both of these exposures are far less serious than exposures from ingesting PCB-contaminated food (particularly sportfish and wildlife) or from breathing PCB-contaminated air.

Workplace exposure to PCBs can occur during repair and maintenance of PCB transformers; accidents, fires, or spills involving PCB transformers and older computers and instruments; and disposal of PCB materials. In addition to older electrical instruments and fluorescent lights that contain PCB-filled capacitors, caulking materials, elastic sealants, and heat insulation have also been known to contain PCBs. Contact with PCBs at hazardous waste sites can happen when workers breathe air and touch soil containing PCBs. Exposure in the contaminated workplace occurs mostly by breathing air containing PCBs and by touching substances that contain PCBs. You can find more information about exposure to PCBs in Chapter 6.

1.4 HOW CAN POLYCHLORINATED BIPHENYLS ENTER AND LEAVE MY BODY?

If you breathe air that contains PCBs, they can enter your body through your lungs and pass into the bloodstream. We do not know how fast or how much of the PCBs that are breathed will pass into the blood. A common way for PCBs to enter your body is by eating meat or fish products or other foods that contain PCBs. Exposure from drinking water is less than from food. It is also possible that PCBs can enter your body by breathing indoor air or by skin contact in buildings that have the kinds of old electrical devices that contain and can leak PCBs. For people living near waste sites or processing or storage facilities, and for people who work with or around PCBs, the most likely ways that PCBs will enter their bodies are from skin contact with contaminated soil and from breathing PCB vapors. Once PCBs are in your body, some may be changed by your body into other related chemicals called metabolites. Some metabolites of PCBs may have the potential to be as harmful as some unchanged PCBs. Some of the metabolites may leave your body in the feces in a few days, but others may remain in your body fat for months. Unchanged PCBs may also remain in your body and be stored for years mainly in the fat and liver, but smaller amounts can be found in other organs as well. PCBs collect in milk fat and can enter the bodies of infants through breast-feeding. For more information on how PCBs can enter and leave your body, see Chapter 3.

1.5 HOW CAN POLYCHLORINATED BIPHENYLS AFFECT MY HEALTH?

Many studies have looked at how PCBs can affect human health. Some of these studies investigated people exposed in the workplace, and others have examined members of the general population. Skin conditions, such as acne and rashes, may occur in people exposed to high levels of PCBs. These effects on the skin are well documented, but are not likely to result from exposures in the general population. Most of the human studies have many shortcomings, which make it difficult for scientists to establish a clear association between PCB exposure levels and health effects. Some studies in workers suggest that exposure to PCBs may also cause irritation of the nose and lungs, gastrointestinal discomfort, changes in the blood and liver, and depression and fatigue. Workplace concentrations of PCBs, such as those in areas where PCB transformers are repaired and maintained, are higher than levels in other places, such as air in buildings that

have electrical devices containing PCBs or in outdoor air, including air at hazardous waste sites. Most of the studies of health effects of PCBs in the general population examined children of mothers who were exposed to PCBs. The possible health effects of PCBs in children are discussed in Section 1.6.

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Rats that ate food containing large amounts of PCBs for short periods of time had mild liver damage, and some died. Rats, mice, or monkeys that ate smaller amounts of PCBs in food over several weeks or months developed various kinds of health effects, including anemia, acne-like skin conditions, and liver, stomach, and thyroid gland injuries. Other effects caused by PCBs in animals include reductions in the immune system function, behavioral alterations, and impaired reproduction. Some PCBs can mimic or block the action of hormones from the thyroid and other endocrine glands. Because hormones influence the normal functioning of many organs, some of the effects of PCBs may result from endocrine changes. PCBs are not known to cause birth defects. Only a small amount of information exists on health effects in animals exposed to PCBs by skin contact or breathing. This information indicates that liver, kidney, and skin damage occurred in rabbits following repeated skin exposures, and that a single exposure to a large amount of PCBs on the skin caused death in rabbits and mice. Breathing PCBs over several months also caused liver and kidney damage in rats and other animals, but the levels necessary to produce these effects were very high. For more information on how PCBs can affect your health, see Chapters 2 and 3.

Studies of workers provide evidence that PCBs were associated with certain types of cancer in humans, such as cancer of the liver and biliary tract. Rats that ate commercial PCB mixtures throughout their lives developed liver cancer. Based on the evidence for cancer in animals, the Department of Health and Human Services (DHHS) has stated that PCBs may reasonably be anticipated to be carcinogens. Both EPA and the International Agency for Research on Cancer (IARC) have determined that PCBs are probably carcinogenic to humans.

1.6 HOW CAN POLYCHLORINATED BIPHENYLS AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

Children are exposed to PCBs in the same way as are adults: by eating contaminated food, breathing indoor air in buildings that have electrical devices containing PCBs, and drinking contaminated water. Because of their smaller weight, children's intake of PCBs per kilogram of body weight may be greater than that of adults. In addition, a child's diet often differs from that of adults. A Food and Drug Administration (FDA) study in 1991 estimated dietary intakes of PCBs for infants (6 months) and toddlers (2 years) of less than 0.001 and 0.002 μg/kg/day. Children who live near hazardous waste sites may accidentally eat some PCBs through hand-to-mouth behavior, such as by putting dirty hands or other soil/dirt covered objects in their mouths, or eating without washing their hands. Some children also eat dirt on purpose; this behavior is called pica. Children could also be exposed by playing with old appliances or electrical devices that contain PCBs.

It is possible that children could be exposed to PCBs following transport of the chemical on clothing from the parent's workplace to the home. House dust in homes of workers exposed to PCBs contained higher than average levels of PCBs. PCBs have also been found on the clothing of firefighters following transformer fires. The most likely way infants will be exposed is from breast milk that contains PCBs. Fetuses in the womb are also exposed from the exposed mother.

In one study of women exposed to relatively high concentrations of PCBs in the workplace during pregnancy, their babies weighed slightly less at birth than babies born to women exposed to lower concentrations of PCBs. Studies of women who consumed high amounts of fish contaminated with PCBs and other chemicals also had babies that weighed less than babies from women who did not eat fish. Similar observations have been made in some studies of women with no known high exposure to PCBs, but not all studies have confirmed these findings. Babies born to women who ate fish contaminated with PCBs before and during pregnancy showed abnormal responses to tests of infant behavior. Some of these behaviors, such as problems with motor skills and a decrease in short-term memory, persisted for several years. However, in these studies, the women may have been exposed to other chemicals. Other studies suggest that the immune system may be affected in children born to and nursed by mothers exposed to increased levels of PCBs. There are no reports of structural birth defects in humans caused by exposure to PCBs or of health effects of PCBs in older children. It is not known whether PCB exposure can cause in skin acne and rashes in children as occurs in some adults, although it is likely that the same effects would occur at very high PCB exposure levels.

Animal studies have shown harmful effects in the behavior of very young animals when their mothers were exposed to PCBs and they were exposed in the womb or by nursing. In addition, some animal studies suggest that exposure to PCBs causes an increased incidence of prenatal death and changes in the immune system, thyroid, and reproductive organs. Studies in monkeys showed that young animals developed skin effects from nursing after their mothers were exposed to PCBs. Some studies indicate that very high doses of PCBs may cause structural birth defects in animals.

Children can be exposed to PCBs both prenatally and from breast milk. PCBs are stored in the mother's body and can be released during pregnancy, cross the placenta, and enter fetal tissues. Because PCBs dissolve readily in fat, they can accumulate in breast milk fat and be transferred to babies and young children. PCBs have been measured in umbilical cord blood and in breast milk. Some studies have estimated that an infant who is breast fed for 6 months may accumulate in this period 6–12% of the total PCBs that will accumulate during its lifetime. However, in most cases, the benefits of breast-feeding outweigh any risks from exposure to PCBs in mother's

milk. You should consult your health care provider if you have any concerns about PCBs and breast feeding. Because the brain, nervous system, immune system, thyroid, and reproductive organs are still developing in the fetus and child, the effects of PCBs on these target systems may be more profound after exposure during the prenatal and neonatal periods, making fetuses and children more susceptible to PCBs than adults.

More information regarding children's health and PCBs can be found in Chapter 3 (Section 3.7).

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO POLYCHLORINATED BIPHENYLS?

If your doctor finds that you have been exposed to significant amounts of polychlorinated biphenyls, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

You and your children may be exposed to PCBs by eating fish or wildlife caught from contaminated locations. Certain states, Native American tribes, and U.S. territories have issued fish and wildlife advisories to warn people about PCB-contaminated fish and fish-eating wildlife. These advisories will tell you what types and sizes of fish and game animals are of concern. An advisory may completely ban eating fish or game or tell you to limit your meals of a certain fish or game type. For example, an advisory may tell you not to eat a certain type of fish or game more than once a month. The advisory may tell you only to eat certain parts of the fish or game and how to prepare or cook the fish or game to decrease your exposure to PCBs. The fish or wildlife advisory may have special restrictions to protect pregnant women, nursing mothers, and young children. To reduce your children's exposure to PCBs, obey these advisories. Additional information on fish and wildlife advisories for PCBs, including states that have advisories, is provided in Chapter 6 (Section 6.7) and Chapter 8. You can consult your local and state health departments or state natural resources department on how to obtain PCB advisories, as well as other important information, such as types of fish and wildlife and the locations that the advisories apply to.

Children should be told that they should not play with old appliances, electrical equipment, or transformers, since they may contain PCBs. Children who live near hazardous waste sites should be discouraged from playing in the dirt near these sites and should not play in areas where there was a transformer fire. In addition, children should be discouraged from eating dirt, and careful handwashing practices should be followed.

As mentioned in Section 1.3, workplace exposure to PCBs can still occur during repair and maintenance of old PCB transformers; accidents, fires, or spills involving these transformers or other PCB-containing items; and disposal of PCB materials. If you are exposed to PCBs in the workplace, it may be possible to carry them home from work. Your occupational health and safety officer at work can tell you whether the chemicals you work with may contain PCBs and are likely to be carried home on your clothes, body, or tools. If this is the case, you should shower and change clothing before leaving work, and your work clothes should be kept separate from other clothes and laundered separately.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO POLYCHLORINATED BIPHENYLS?

Levels of PCBs in the environment were zero before PCBs were manufactured. Now, all people in industrial countries have some PCBs in their bodies. There are tests to determine whether PCBs are in the blood, body fat, and breast milk. These are not regular or routine clinical tests, such as the one for cholesterol, but could be ordered by a doctor to detect PCBs in people exposed to them in the environment and at work. If your PCB levels are higher than the background levels, this will show that you have been exposed to high levels of PCBs. However, these measurements cannot determine the exact amount or type of PCBs that you have been exposed to, or how long you have been exposed. Although these tests can indicate whether you have been exposed to PCBs to a greater extent than the general population, they do not predict whether you will develop harmful health effects. Blood tests are the easiest, safest, and probably the best method for detecting recent exposures to large amounts of PCBs. Results of such tests should be reviewed and carefully interpreted by physicians with a background in environmental and occupational medicine. Nearly everyone has been exposed to PCBs because they are found

throughout the environment, and people are likely to have detectable amounts of PCBs in their blood, fat, and breast milk. Recent studies have shown that PCB levels in tissues from United States population are now declining. Additional information on tests used to determine whether you have been exposed to PCBs can be found in Chapter 3 (Section 3.11) and Chapter 7 (Section 7.1).

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health . Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for PCBs include the following:

The EPA standard for PCBs in drinking water is 0.5 parts of PCBs per billion parts (ppb) of water. For the protection of human health from the possible effects of drinking the water or eating the fish or shellfish from lakes and streams that are contaminated with PCBs, the EPA

regulates that the level of PCBs in these waters be no greater than 0.17 parts of PCBs per trillion parts (ppt) of water. States with fish and wildlife consumption advisories for PCBs are identified in Chapter 6 (Section 6.7) and Chapter 8.

The FDA has set residue limits for PCBs in various foods to protect from harmful health effects. FDA required limits include 0.2 parts of PCBs per million parts (ppm) in infant and junior foods, 0.3 ppm in eggs, 1.5 ppm in milk and other dairy products (fat basis), 2 ppm in fish and shellfish (edible portions), and 3 ppm in poultry and red meat (fat basis).

OSHA regulates that workers not be exposed by inhalation over a period of 8 hours for 5 days per week to more than 1 milligram per cubic meter of air (mg/m^3) for 42% chlorine PCBs, or to 0.5 mg/m^3 for 54% chlorine PCBs.

NIOSH recommends that workers not breathe air containing 42 or 54% chlorine PCB levels higher than 1 microgram per cubic meter of air ($\mu g/m^3$) for a 10-hour workday, 40-hour workweek.

EPA requires that companies that transport, store, or dispose of PCBs follow the rules and regulations of the federal hazardous waste management program. EPA also limits the amount of PCBs put into publicly owned waste water treatment plants. To minimize exposure of people to PCBs, EPA requires that industry tell the National Response Center each time 1 pound or more of PCBs have been released to the environment.

For more information on federal and state regulations and guidelines for PCBs, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: 1-404-639-6359
Internet: http://www.atsdr.cdc.gov

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000

2. RELEVANCE TO PUBLIC HEALTH

2.1 Background and Environmental Exposures to PCBs in the United States

PCBs are a category of chemicals that were manufactured in the United States between about 1930 and 1977, predominantly for use as coolants and lubricants in electrical equipment such as capacitors and transformers due to their general chemical inertness and heat stability. PCBs are complex mixtures of chlorinated biphenyls that vary in the degree of chlorination. For example, the commercial product Aroclor 1254 is a mixture of mono- through heptachlorinated biphenyl congeners with an average chlorine content of approximately 54%. However, significant lot-to-lot differences in congeneric composition occurred among similar mixtures. The manufacture of PCBs in the United States was stopped due to evidence that they accumulate and persist in the environment and can cause toxic effects.

No known consumer product currently manufactured in the United States contains PCBs, but PCBs are still released during some industrial processes. Once released into the environment, the compositions of commercial PCB mixtures are altered through processes such as volatilization and other kinds of partitioning, chemical or biological transformation, and preferential bioaccumulation. These processes are dependent upon the degree of chlorination of the biphenyl molecule. PCBs, particularly the higher chlorinated congeners, adsorb strongly to sediment and soil, where they tend to persist with half-lives of months to years. PCBs bioaccumulate in food chains and are stored in fatty tissues due to their stability and lipophilicity. Bioaccumulated PCBs are of particular relevance to human health because of their persistence in the body.

The general population may be exposed to PCBs by ingesting contaminated food and by inhaling contaminated air (see Chapter 6). Food consumption has been and continues to be the major source of body burden of PCBs in the general population. The estimated dietary intake of PCBs for an average adult was about 0.03 μg/kg/day in 1978, but this had declined to <0.001 μg/kg/day by 1991. There is evidence that diets high in fish from PCB-contaminated waters, such as in the Great Lakes-St. Lawrence River basins, can significantly increase a person's dietary intake of PCBs. Breast-fed infants of mothers who have diets high in contaminated fish may have a particularly increased risk for PCB exposure due to its presence in the milk. Human PCB exposure has also been attributed to inhalation of indoor air, especially at locations that still use electrical equipment containing PCBs.

An important issue related to evaluating health effects of PCBs in humans is exposure assessment. Exposure to PCBs has been assessed by measuring PCBs in blood, breast milk, and adipose tissue. Umbilical cord blood also has been used to estimate exposure *in utero*. In addition, fish consumption has been utilized as surrogate of PCB exposure in some studies, but this measure of exposure has not always been reliable. Mean serum PCB levels range from 0.9–1.5 ppb (µg/L), in recent years, in individuals who do not have diets high in fish from waters contaminated with PCBs. In the absence of human data, environmental sampling (soil, sediment, air, food, water) has also been used to estimate exposure.

2.2 Summary of Health Effects

The preponderance of the biomedical data from human and laboratory mammal studies provide strong evidence of the toxic potential of exposure to PCBs. Information on health effects of PCBs is available from studies of people exposed in the workplace, by consumption of contaminated rice oil in Japan (the *Yusho* incident) and Taiwan (the *Yu-Cheng* incident), by consumption of contaminated fish, and via general environmental exposures, as well as food products of animal origin. As summarized below and detailed in Chapter 3, health effects that have been associated with exposure to PCBs in humans and/or animals include liver, thyroid, dermal and ocular changes, immunological alterations, neurodevelopmental changes, reduced birth weight, reproductive toxicity, and cancer. The human studies of the *Yusho* and *Yu-Cheng* poisoning incidents, contaminated fish consumption, and general populations are complicated by the mixture nature of PCB exposure and possible interactions between the congeneric components and other chemicals (see Chapter 3 for additional information). Therefore, although PCBs may have contributed to adverse health effects in these human populations, it cannot be determined with certainty which congeners may have caused the effects. Animal studies have shown that PCBs induce effects in monkeys at lower doses than in other species, and that immunological, dermal/ocular, and neurobehavioral changes are particularly sensitive indicators of toxicity in monkeys exposed either as adults, or during pre- or postnatal periods.

Hepatic Effects. The hepatotoxic potential of PCB mixtures is well-documented in animals by oral and other routes of exposure. The spectrum of possible hepatic effects in animals is broad and includes microsomal enzyme induction, liver enlargement, increased serum levels of liver enzymes and lipids, and histopathologic alterations that progress to fatty and necrotic lesions and tumors. The findings of human studies, however, are not as obvious. Many of the human studies involving worker and other populations with high body burdens of PCBs report associations between PCBs and hepatic indices such as liver enzymes, lipids, and cholesterol. Studies of people exposed to PCBs by ingestion of contaminated fish or

contaminated rice oil in the *Yusho* or *Yu-Cheng* incidents have reported increases in serum levels of some liver enzymes (e.g., γ-glutamyltranspeptidase [GGT], aspartate aminotransferase [AST], and/or alanine aminotransferase [ALT]) that are suggestive of microsomal enzyme induction or possible liver damage. Tests for some nonroutinely-studied liver indices (e.g., accelerated erythrocyte sedimentation rate, high titer in thymol turbidity, increased M fraction of lactate dehydrogenase, and increased alkaline phosphatase and ribonuclease levels) also indicate possible liver damage in some *Yusho* patients.

Definitive conclusions regarding human hepatotoxiciy are hampered by limitations in study design of available studies, such as exposure misclassification, lack of controls, lack of correction for common confounding variables (e.g., age and alcohol consumption), and natural partitioning of PCBs to serum lipids. The lack of unequivocal evidence in humans that is seen in laboratory animals may result from many factors, including species differences in susceptibility or sensitivity to PCBs, and dissimilarities in exposure levels, durations, and mixture compositions.

Hepatotoxic effects commonly induced in laboratory animals exposed to commercial PCB mixtures include increased serum levels of liver enzymes indicative of hepatocellular damage (e.g., AST and ALT), serum and tissue biochemical changes indicative of liver dysfunction (e.g., altered levels of lipids, cholesterol, porphyrins, and vitamin A), and histopathologic changes (particularly fat deposition), fibrosis, and necrosis. Intermediate- and chronic-duration oral studies have shown hepatotoxic effects in monkeys that include fatty degeneration, hepatocellular necrosis, and hypertrophic and hyperplastic changes in the bile duct at oral doses of PCBs as low as 0.1–0.2 mg/kg/day (Aroclor 1254 or 1248).

Induction of microsomal enzymes appears to be the most sensitive hepatic alteration produced by Aroclors and other PCB mixtures in laboratory animals. While microsomal enzyme induction is not necessarily adverse, it may have indirect implications for human health through protective or toxic effects that are secondary to enhanced metabolic detoxification or bioactivation of exogenous or endogenous substances. Examples of this include possible interference with medical therapy due to increased metabolism of administered drugs, the possibility of disease secondary to the altered metabolism of endogenous substances such as hormones, and increased activation of promutagens and procarcinogens as shown, for example, for the secondary carcinogen dimethylnitrosamine.

Hepatic porphyria is an indicator of liver dysfunction that has been induced in animals following intermediate-duration oral or dermal exposure to Aroclors and other PCB mixtures. Increased urinary excretion of porphyrins has been reported in two studies of PCB workers, and Type B hepatic porphyria

(a uroporphyrin/coproporphyrin ratio >1) was a consistent finding in *Yu-Cheng* patients, including children born to exposed mothers. However, clinically evident porphyrias have not been reported in people with occupational or *Yusho/Yu-Cheng* PCB exposures.

The liver, which is the site of approximately 90% of the vitamin A in the body, has a major role in vitamin A metabolism. Altered vitamin A homeostasis, primarily manifested as decreased hepatic storage of vitamin A, is another demonstrated effect of PCB mixtures and single congeners in orally-exposed rats and rabbits. Vitamin A is essential for normal growth and cell differentiation, particularly differentiation of epithelial cells, and PCB-induced epithelial lesions in monkeys have been observed to resemble those produced by vitamin A deficiency. Whether the PCB-related disturbances in vitamin A homeostasis are due to a direct effect on hepatic regulation or to effects on extrahepatic feedback processes has not been established.

Endocrine Effects. Concern about potential effects of PCBs on thyroid hormones is based on two main considerations: (1) extensively corroborated findings in experimental animals that exposure to PCBs *in utero* and/or during early development (e.g., through breast milk) can deplete levels of circulating thyroid hormones in the fetus or neonate, which may give rise to a hypothyroid state during development; and (2) the recognition of the importance of thyroid hormones in normal development of the brain, as is evident from neurodevelopmental disorders and deficits associated with hypothyroidism. The latter are typified by iodine deficiency (e.g., endemic cretinism), which can produce a wide range of neurodevelopmental deficits, including auditory, motor, and intellectual deficits. These outcomes underscore the importance of thyroid hormones in the normal development of the fetal cochlea, basal ganglia, and cerebral cortex, which begin to develop in humans during the second trimester of gestation. This is also the time period during which the fetal thyroid gland becomes functional.

Direct evidence linking PCB exposures to thyroid morbidity in humans is limited. The risk for goiter was significantly increased among the *Yu-Cheng* cohort, indicating the possibility of excess thyroid disease in an adult population that experienced relatively high exposures to mixtures of PCBs and polychlorinated dibenzofurans (PCDFs). Other more limited observations in adults include reports of increased thyroid gland volume among workers and nearby residents of a PCB production facility. Studies that examined relationships between PCB exposure and thyroid hormone status in children or adults reported a variety of different results, with findings of both positive and negative correlations between PCB exposure and circulating levels of thyroid stimulating hormone (TSH) or thyroxine (T_4) or triiodothyronine (T_3) hormones.

The most compelling evidence for a potential thyroid hormone involvement in PCB toxicity in humans is based on observations made in experimental animals, including rodents and nonhuman primates. Major findings include (1) histological changes in the thyroid gland indicative of both stimulation of the gland (similar to that induced by TSH or a hypothyroid state) and a disruption of the processing of follicular colloid needed for normal production and secretion thyroid hormone; (2) depression of T_4 and T_3 hormone levels, which may effectively create a hypothyroid state; (3) increased rates of elimination of T_4 and T_3 from serum; (4) increased activities of T_4-UDP-glucuronyl transferase (UDP-GT) in liver, which is an important metabolic elimination pathway for T_4 and T_3; (5) decreased activity of iodothyronine sulfotransferases in liver, which are also important in the metabolic elimination of iodothyronines; (6) decreased activity of iodothyronine deiodinases including brain Type-2 deiodinase, which provide the major pathways for the production of the active thyroid hormone, T_3; and (7) decreased binding of T_4 to transthyretin, which is an important transport protein for both T_4 and T_3. These observations indicate that PCBs can disrupt the production of thyroid hormones, both in the thyroid and in peripheral tissues, can interfere with their transport to peripheral tissues, and can accelerate the metabolic clearance of thyroid hormones.

The most convincing evidence that PCBs can exert toxicity by disrupting thyroid hormone system derives from two studies in rats. In one study, neurobehavioral deficits in pups exposed to Aroclor 1254 *in utero* and during nursing, were significantly attenuated by subcutaneous injections of T_4 that increased serum T_4 and T_3 concentrations that were otherwise depressed in the PCB-exposed animals. While this study examined relatively high doses of Aroclor 1254, it nevertheless demonstrated neurodevelopmental effects that are directly relevant to observations made in epidemiological studies and to neurological sequelae of fetal hypothyrodism, including disturbances of motor function and hearing. In the second study, increased testes weight and sperm production in rats that were administered Aroclor 1254 on postnatal days 1–25 were attenuated by injections of T_4 on postnatal days 1–25, which also prevented the depression in serum T_4 concentrations. These observed effects may reflect a disruption of the normal sexual maturation process, which is known to be associated with neonatal hypothyroidism in humans. Other effects of PCBs on endocrine function that have been observed in experimental animals include effects on the adrenal glands and serum adrenal steroid levels.

There is suggestive evidence that PCBs can produce both agonistic and antagonistic estrogenic responses. A wide variability of responses observed across PCB type and assays indicates the involvement of multiple mechanisms. The specific mechanism of action appears to vary, with competitive binding to estrogen receptors being congener/metabolite specific. Anti-estrogenic activities appear to be more

strongly associated with PCBs that are Ah receptor agonists, whereas hydroxylated metabolites of PCBs seem to be at least partly responsible for responses to PCBs that may involve changes in estrogen receptor-dependent physiological processes. In general, results from both *in vitro* and *in vivo* studies indicate that PCBs have much lower estrogenic potency than the endogenous hormone, 17β-estradiol. PCB mixtures have been shown to produce comparatively weak estrogenic responses, and mixtures having multiple *ortho* chlorines (or their hydroxylated metabolites) have been suggested to be to partly responsible for some observed estrogenic responses. For example, immature female offspring of laboratory animals exposed to a PCB congener mixture simulating the congener content of human milk from 50 days prior to mating until birth showed significantly increased uterine weights, a parameter known to be under estrogenic influence. In the case of anti-estrogenic responses to PCBs, effects appear to be concentration dependent. Anti-estrogenic responses have been observed in studies using tissues from both humans and rodents.

Dermal and Ocular Effects. Dermal lesions including skin irritation, chloracne, and pigmentation of nails and skin have been observed in humans following occupational exposure to PCBs, and from the accidental ingestion of rice oil contaminated with high concentrations of PCBs, chlorinated dibenzofurans (CDFs) and other halogenated chemicals during the *Yusho* and *Yu-Cheng* poisoning incidents. Of the dermal effects observed in workers, chloracne (a dermatologic condition that starts with formation of comedones [keratin plugs in the pilosebaceous orifices] and inflammatory folliculitis) is the most likely to have been associated with exposure to PCBs.

Ocular effects including hypersecretion of the Meibomian glands, abnormal pigmentation of the conjunctiva, and swollen eyelids have also been observed in humans occupationally exposed to PCBs. These ocular alterations almost always accompany chloracne. Ocular effects may continue to appear after exposure has ceased, possibly as a result of accumulation of the causative agent in skin adipose. Chronic-duration oral exposure studies in monkeys showed that adverse dermal and ocular effects can occur at dose levels as low as 0.005 mg/kg/day.

Immunological Effects. There are indications of altered immune status in adult and infant human populations that were orally exposed to mixtures of PCBs and other chemicals. The most conclusive findings were in the *Yusho* and *Yu-Cheng* populations that experienced the highest levels of PCB exposure and least complex exposure mixture. Interpretation of the data from the other human studies is complicated by responses that were generally subtle and exposures that included a number of persistent toxic substances in addition to PCBs that are also potentially immunotoxic. As detailed in Chapter 3

(Section 3.2.3.2), there appears to be an overall consistency of effects among the human studies supporting sensitivity of the immune system to PCBs and these other chemicals, particularly in infants exposed *in utero* and/or via breast feeding. For example, susceptibility to respiratory tract infections was increased in *Yusho/Yu-Cheng* adults and their children, and there was an association between infectious illnesses and PCBs in the children of the mothers who consumed Lake Michigan or Sheboygan River fish. Children born to *Yu-Cheng* mothers also had an increased prevalence of middle ear infections, and the incidence of acute otitis media was increased in Inuit infants of mothers whose diets were based on marine mammal fat. Serum IgA and/or IgM antibody levels were decreased in the *Yusho* and *Yu-Cheng* populations as well as in the Inuit children. Monocyte counts were reduced in *Yu-Cheng* patients and in the infants of a Dutch mother-child study, and changes in T lymphocyte subsets were found in the *Yu-Cheng*, Inuit child, and Dutch child populations.

Substantial evidence of the immunotoxicity of PCBs in research animals lends strong support to the human data. Particularly relevant findings in animals include reduced antibody responses and levels of T-lymphocytes and their subsets, which are similar to changes observed in some of the human populations. The antibody response to sheep red blood cell (SRBC) antigens is the immune parameter most commonly and consistently shown to be affected by PCBs in animals; reduced responses have been demonstrated in most tested species, including adult and infant monkeys, which are sensitive to this effect at chronic PCB doses as low as 0.005 mg/kg/day (Aroclor 1254). A no observed adverse effect level for immunological effects was not identified.

Studies of rats, mice, guinea pigs, and rabbits showed that intermediate-duration exposures to relatively high doses of commercial PCB mixtures caused morphological and functional alterations in the immune system. Effects observed in these species included thymic and splenic atrophy, reduced antibody responses to SRBC and other foreign antigens, increased susceptibility to infection by viruses and other microbes, reduced skin reactivity to tuberculin, and increased proliferation of splenic lymphocytes in response to mitogenic stimulation.

Oral studies of Aroclor mixtures in monkeys confirm that the immune system is sensitive to PCBs. Immunological effects of PCBs in monkeys include decreased antibody responses to SRBC, increased susceptibility to bacterial infections, altered lymphocyte T-cell subsets, decreased lymphoproliferative response to mitogens, and histopathologic changes in the thymus, spleen, and lymph nodes. Results of studies in gestationally- and lactationally-exposed infant monkeys are consistent with the data in adult animals showing immunosuppressive effects of PCBs at doses as low as 0.005 mg/kg/day (Aroclor 1254),

with reductions in IgM and IgG antibody levels to SRBC and mitogen-induced lymphocyte transformation that generally paralleled the findings in maternal animals. Immunological alterations were induced in infant monkeys that were orally exposed to a PCB congener mixture simulating the congener content of human milk at a dose level of 0.0075 mg/kg/day for the first 20 weeks of life.

Neurological Effects. The neurological effects of PCBs have been extensively investigated in humans and animals. Substantial data suggest that PCBs play a role in neurobehavioral alterations observed in newborns and young children of women with PCB burdens near background levels. In general, the observed alterations are subtle. In some studies, those alterations were found to disappear as the children grow older (2–4 years old), while other studies have reported neurobehavioral deficits still present in 11-year-old children mostly due to *in utero* exposure to PCBs. Laboratory animal studies provide strong substantiating evidence that PCBs can induce adverse neurological effects in developing animals as well as in adults.

Epidemiological findings in infants and children include abnormal reflexes and deficits in memory, learning, and IQ. Prospective studies of children born to mothers exposed to PCBs by consumption of contaminated fish from the Great Lakes and of children from women in North Carolina, the Netherlands, and Germany strongly suggest that PCBs play a significant role in neurodevelopmental toxicity observed in some of these children at birth and continuing during early life. In the various cohorts studied, some common findings of neurodevelopmental effects have been reported, although affected end points have not been the same in all studies. For example, newborns from women who ate high amounts of contaminated Lake Michigan fish (high PCB exposure) had a greater number of abnormal reflexes and more motor immaturity than newborns of mothers who consumed less fish (low PCB exposure). Similar observations were made in a North Carolina study of children born to women with low PCB levels, and in an Oswego, New York study of children from women with high consumption of PCB-contaminated fish from Lake Ontario. There was a significant association between poorer habituation and autonomic scores for the newborns and highly chlorinated (7–9 chlorines) PCB congeners in umbilical cord blood of Lake Ontario fisheaters, but not with abnormal reflexes. No significant association was found between any neurological scores in newborns of the Lake Ontario fisheaters and lightly (1–3 chlorines) or moderately (4–6 chlorines) chlorinated PCBs, DDE, lead, mercury, or hexachlorobenzene. A study of Dutch children found that neither reflex nor postural cluster scores of a neurological examination were associated with prenatal exposure to four predominant nonplanar PCB congeners (measured in maternal or umbilical cord plasma). However, hypotonia, although not with abnormal reflexes, was related to levels of coplanar (dioxin-like) PCBs in breast milk.

Assessment of infants from the various cohorts with the Bayley Scales of Infant Development has revealed additional consistency across studies. This group of tests yields a mental development index (MDI) and a psychomotor development index (PDI) score, both of which are scaled like a standard IQ test. In the North Carolina cohort, a significant decrease in PDI scores at the ages of 6 and 12 months was associated with prenatal exposure to PCBs (assessed as PCBs in maternal milk at birth), but the association lost statistical significance at the ages of 18 and 24 months. No significant association was observed between PDI scores between 6 and 24 months of age and postnatal exposure to PCBs (in milk during breast feeding). There was no significant association between MDI scores and either prenatal or postnatal exposure to PCBs.

Alterations in memory functions were reported in children from the Michigan cohort at 7 months, 4 years, and 11 years of age. Memory and IQ score deficits were associated with prenatal exposure to PCBs, as measured by PCBs in umbilical cord blood. The most highly exposed children were 3 times as likely to have low average IQ scores and twice as likely to be at least 2 years behind in reading comprehension.

Central nervous system effects of PCBs have been confirmed in laboratory animals. For example, decreased performance on a memory task was reported in 60-day-old rats exposed *in utero* to *ortho*-substituted PCB congeners. In monkeys, effects included neurobehavioral changes in juvenile animals that were treated postnatally for 20 weeks with a low-dose (7.5 μg/kg/day) of a mixture of PCB congeners representing 80% of the congeners found in human milk. At age 20 weeks PCB levels were 1.7–3.5 ppm in fat and 1.84–2.84 ppb in blood, which are very similar to levels found in the general population. These monkeys showed deficits in several tasks, including spatial delayed alternation, acquisition of fixed interval, and differential reinforcement of low rate performance, which were indicative of impaired learning, perseveration, and ability to inhibit inappropriate responding. Numerous studies have investigated neurotransmitter levels in the prefrontal cortex (important in the regulation of short-term memory or representational memory for spatial information) and other brain areas following exposure of laboratory mammals to PCBs. The most consistent finding in such studies has been a decrease in the concentration of dopamine in different areas of the brain; however, more information is necessary to associate specific behavioral alterations with specific neurochemical changes.

It is unknown which specific PCB congeners may be neurodevelopmental toxicants in humans. Data from the Oswego fisheater study showed that behavioral alterations in newborn children were associated with the presence of highly chlorinated (7–9 chlorines) PCB congeners in umbilical cord blood. This is

consistent with findings that the distribution of PCB congeners in Great Lakes contaminated fish is shifted toward more highly chlorinated congeners. Studies with single PCB congeners suggest that both dioxin-like (coplanar) and non-dioxin-like PCB congeners are capable of inducing neurobehavioral alterations in animals, but it appears that ortho-substituted PCB congeners are more active than coplanar PCBs in modifying cognitive processes.

A relatively small amount of information is available on neurological effects of PCBs in adult humans. In a study of aging adults exposed to PCBs through consumption of contaminated sportfish from Lake Michigan, no adverse neurological effects were found attributable to exposure to PCBs. Other studies of adult populations with occupational exposure to PCBs have not been as conclusive for adverse neurological effects attributable solely to PCB exposure.

Reproductive Effects. Limited data indicate that menstrual disturbances in women and effects on sperm morphology and production, which are effects that can result in difficulty in a couple conceiving, may be associated with exposure to PCBs . Overall, the studies of reproductive end points in humans are limited; however, the weight of the existing human and animal data suggests that PCBs present a potential reproductive hazard to humans.

In a small number of occupationally-exposed women, there was no apparent effect of Aroclors 1254, 1242, and/or 1016 on mean number of pregnancies. A study of the general population found that blood PCB levels were higher in women who had repeated miscarriages, but levels of other organochlorine compounds were also elevated. Studies that examined reproductive end points in women whose diets contained Great Lakes fish found suggestive evidence that consumption of the fish may be associated with a slightly shorter length of menstrual cycle and reduced fecundability among couples attempting pregnancy, but not with increased risk of conception delay. The slight decreases in menstrual length seen in this population were considered of unknown clinical relevance. Menstrual cycle changes (altered intervals, duration, and flow) have also been observed in women exposed to higher doses of PCBs during the *Yusho* poisoning incident. However, another general population study did not find an association between endometriosis or increased risk for spontaneous fetal death and concentrations of PCBs in the blood.

These reproductive effects are supported by a number of studies in laboratory animals. Menstrual alterations in monkeys and estrus changes in rats have been observed following oral exposure to Aroclor PCB mixtures. For example, high doses of Aroclor 1254 causes prolonged estrus cycle in adult rats

exposed for several weeks, delayed first estrus in offspring of rats following gestational and lactational or lactational-only exposure, and altered estrus cycle patterns in young and mature offspring of rats following lactational exposure. In monkeys, menstrual cycle durations became erratic or longer following exposure to $0.1 mg/kg/day Aroclor 1248 for 7–9 months, although no clear changes in menstrual cyclicity resulted from chronic exposure to lower dose levels (0.005–0.08 mg/kg/day) of Aroclor 1254. In addition, delayed onset of estrus was also observed in adult mink and their offspring in a 2-generation reproduction study involving exposure to Great Lakes fish.

The reproductive toxicity of commercial PCB mixtures in female animals is well-established. In addition to estrus and menstrual changes, effects that have been observed in various species include reduced implantation rate in adult rats and/or their offspring exposed during gestation and lactation, decreased conception in mice, partial or total reproductive inhibition in minks, and decreased fertility in monkeys. Minks and monkeys are particularly sensitive, with effects occurring in these species at oral doses of Aroclor 1254 and 1248 in the range of 0.1–1 mg/kg/day in intermediate-duration studies, and as low as 0.02 mg/kg/day in monkeys following chronic exposure to Aroclor 1254. Reproductive failure in minks associated with fetal death was attributed to degenerative changes in the placental vasculature. Impaired ability to conceive and decreased fetal survival are well-documented in female monkeys following repeated oral exposure to Aroclors 1254 and 1248. Reduced conception rates, as well as increased incidences of abortions, resorptions, or stillbirths, were observed in monkeys fed Aroclor 1254 at dose levels as low as 0.02 mg/kg/day for 37 months before breeding and subsequently throughout mating and gestation.

The ability of PCBs to cause reproductive effects in males is less clear-cut than in females. Sperm counts, fertility history, and testicular examinations were normal in workers who were exposed to Aroclor PCBs for several years. However, analysis of semen showed that increasing concentrations of some individual congeners, but not total PCBs, were associated with decreasing sperm motility in infertile men.

A limited amount of information is available on reproductive effects of PCBs in male laboratory animals. Four monkeys chronically exposed to 0.1 mg/kg/day Aroclor 1248 developed effects that included clinical signs of toxicity, decreased libido, and marked hypoactivity of the seminiferous tubules, including an absence of mature spermatozoa, after the first year of exposure. Fertility was markedly reduced in male offspring of rats that were lactationally exposed to relatively high doses of Aroclor 1254. The reduction in male fertility appears to be due to impaired ability of sperm to fertilize eggs because sperm production, morphology, and motility were not affected and plasma follicle-stimulating hormone (FSH)

and testosterone concentrations were not reduced. Oral and subcutaneous studies with single congeners have also shown that gestational and neonatal exposures can adversely affect morphology and production of sperm and fertility in male rats and mice.

Developmental Effects. This section summarizes effects of PCBs on anthropometric measures at birth as well as physical growth during infancy. Effects of perinatal exposure to PCBs on other end points in the offspring, such as the thyroid gland and thyroid hormone status, end points known to be very important for structural and functional aspects of normal development of the brain and sexual organs, are discussed in the Endocrine Effects and Reproductive Effects sections, respectively. Neurodevelopmental effects of PCBs are summarized in the Neurological Effects section.

Studies of the children of environmentally-exposed women have produced mixed results. While some studies have shown significant, negative associations between anthropometric measures at birth (and at early ages) and exposure to PCBs, other studies have reported either significant positive associations or no associations at all. The wide range of results may reflect the different degree of controlling for confounders and/or the different exposure measures. For example, of the studies of women who consumed contaminated fish from the Great Lakes, the study of Lake Michigan fisheaters found that reduced birth weight, head circumference, and gestational age in newborns, as well as body weight at 4 years, were associated with prenatal exposure to PCBs (measured in umbilical cord blood). In the Oswego cohort (Lake Ontario fish consumption), there was no significant association between birth weight, head circumference, or gestational age and prenatal exposure to PCBs, as assessed by the same fish consumption measures used in the Michigan study, which had higher levels of PCB exposure. In two additional studies of Lake Michigan women, fish consumption had a positive effect on birth weight. It has been postulated that this may be related to the beneficial effects of certain fatty acids in fish. A study of Swedish wives of Baltic Sea fishermen found an increased risk of low birth weight with increasing maternal blood concentrations of a PCB congener used as surrogate of PCB exposure during the year of childbirth. In a Dutch general population cohort, a reduced birth weight, but not head circumference or body length at 10 days of age, was associated with prenatal exposure to PCBs (measured in umbilical cord blood). Reduced growth between birth and 3 months was associated with prenatal exposure in formula-fed children, but no such association was seen in breast-fed children, suggesting that any detrimental effect observed in newborns due to prenatal exposure to PCBs may have been counteracted by the benefits of breast feeding. In the Dutch children, no significant association was seen between growth between the ages of 3–7 months, 7–18 months, or 18–42 months and any measure of exposure to

PCBs. In addition, a study of the general population in Finland found no significant association between birth weight and the concentration of PCBs in breast milk.

Studies of rodents exposed to relatively high doses of PCBs have commonly found decreased birth weight, and reduced weight gain after birth following exposure *in utero* and through suckling. The latter finding suggests that significant transfer of PCBs may occur through breast feeding. Long-term studies with much lower doses of Aroclors 1016 and 1248 in monkeys also reported decreased birth weight. Studies with low doses of Aroclor 1254 (0.0005–0.08 mg/kg/day) in monkeys found no significant effects on anthropometric measures at birth or on growth thereafter, although dermal and ocular signs of PCB intoxication were noted.

Cancer. Carcinogenicity of PCBs in humans has been investigated in retrospective occupational studies that evaluated cancer mortality in workers exposed during capacitor manufacturing and repairing, and in case-control studies of the general population that examined associations between cancer and serum or adipose tissue levels of PCBs resulting from environmental exposures. Based on indications of PCB-related cancer at several sites, particularly the liver, biliary tract, intestines, and skin (melanoma), the human studies provide suggestive evidence that PCBs are carcinogenic. There is unequivocal evidence that PCBs are hepatocarcinogenic in animals.

The suggestive evidence for the carcinogencity of PCBs in humans is supported by extensive conclusive evidence in animals. PCBs have been classified as probable human carcinogens by both IARC and EPA, based mainly on the sufficient evidence of carcinogenicity in animals. The human evidence of carcinogenicity is regarded as limited by IARC and inadequate but suggestive by EPA, although neither assessment is based on all currently available studies. NTP similarly concluded that PCBs are reasonably anticipated to be carcinogenic in humans based on sufficient evidence of carcinogenicity in animals. (See Chapter 3 [Section 3.2.8] for a detailed discussion of the bases for these determinations.)

2.3 Minimal Risk Levels

As indicated above in the beginning of Section 2.1, people are environmentally exposed to PCB mixtures of different congeneric composition than commercial PCB mixtures. Although the toxicity or potency of environmental PCB mixtures consequently may be greater or less than that of commercial mixtures, there are insufficient mixture toxicity data on which to directly base minimal risk levels (MRLs) for

environmental PCBs. One approach that has been widely considered for estimating the risk from environmental exposure to PCBs is the toxic equivalency factor (TEF) method. As discussed in Chapter 3 (Section 3.5.2), the TEF approach can be used to estimate the potency of PCB mixtures by comparing the relative toxicity of individual PCB congeners to that of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), which is the most toxic and extensively studied of these structurally-related halogenated aromatic hydrocarbons. Although TEFs are used to some extent to guide public health decisions because of the limited toxicological data for complex environmental mixtures and many of their components, the approach has received limited validation and has a number of limitations related to assumptions that the components jointly act in an additive manner through a common Ah-receptor mechanism of toxicity. In particular, the TEF approach does not account for evidence that non-Ah-receptor-binding congeners are major components in PCB-containing environmental mixtures that may contribute to induction of health effects (Hansen 1998; Safe 1998a, 1998b). Although there is certainly a large body of data to support the TEF approach to assessing PCB toxicity, this is by no means without question, primarily because of evidence of non-additive interactions between specific PCB congeners and between some PCB congeners and 2,3,7,8-TCDD (see Chapter 3, Section 3.9), as well as increasing evidence that PCB-induced effects may involve Ah-receptor-dependent mechanisms, Ah-receptor-independent mechanisms, or both. Because of the likelihoods that (1) multiple mechanisms may be involved in PCB-induced health effects, (2) different PCB congeners may produce effects by different mechanisms, and (3) humans are exposed to complex mixtures of interacting PCBs with differing biological activities, commercial PCB mixtures (e.g., Aroclor 1254) and experimental PCB mixtures (e.g., formulations representing the congeners found in human breast milk) are used to develop health guidance values, such as MRLs, for environmental mixtures in assessing health risks from exposure.

Inhalation MRLs

No inhalation MRLs were derived for PCB mixtures due to lack of adequate human and animal data.

Oral MRLs

- An MRL of 0.03 μg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to PCBs.

The intermediate oral MRL is based on a LOAEL of 0.0075 mg/kg/day for neurobehavioral alterations in infant monkeys that were exposed to a PCB congener mixture representing 80% of the congeners

typically found in human breast milk (Rice 1997, 1998, 1999b; Rice and Hayward 1997, 1999a). The MRL was estimated by dividing this LOAEL by an uncertainty factor of 300 (10 for extrapolation from a LOAEL to a NOAEL, 3 for extrapolation from monkeys to humans, and 10 for human variability). Groups of five and eight male monkeys were orally administered doses of 0 or 0.0075 mg/kg/day, respectively, from birth to 20 weeks of age. The dose level represents the approximate daily intake of a nursing human infant whose mother's milk contains 50 ppb PCBs. Beginning at 3 years of age, the monkeys were tested for behavioral effects using a series of nonspatial discrimination reversal problems followed by a spatial delayed alternation task. Additional testing was done at 4.5 and 5 years of age. Treated monkeys showed decreases and variable increases in response latencies across three tasks of nonspatial discrimination reversal, as well as retarded acquisition of a delayed alternation task and increased errors at short delay task responses (Rice 1997). These findings were interpreted as a learning/performance decrement rather than an effect on memory *per se.* Treated monkeys also displayed alterations in fixed-interval and fixed-ratio performance tasks that were interpreted as impaired learning, perseverative behavior, and/or inability to inhibit inappropriate responding as a result of postnatal PCB exposure (Rice 1997). Testing of the monkeys at 4.5–5 years of age showed that treated animals performed in a less efficient manner than controls under a differential reinforcement of low rate (DRL) schedule of reinforcement (Rice 1998). There were no differences between groups on the accuracy of performance on a series of spatial discrimination reversal tasks, although some treated monkeys made more errors than others on certain parts of the experiment. Further tests conducted at about 5 years of age did not find treatment-related effects on a series of concurrent RI-RI (random interval) schedules of reinforcement (Rice and Hayward 1999a). This schedule was designed to study behavior in transition (learning) as well as at steady state. However, there was a difference between treated and control monkeys on performance on a progressive ratio (PR) schedule, which may be indicative of retarded acquisition of the steady-state PR performance.

The 0.0075 mg/kg/day LOAEL is a particularly relevant basis for MRL derivation due to the composition of the PCBs (a congener mixture analogous to that in human breast milk), dose level (approximate daily intake of a nursing human infant whose mother's milk contains 50 ppb PCBs), and resulting PCB adipose tissue and blood levels (near background concentrations found in the general human population). Support for the 0.0075 mg/kg/day LOAEL is provided by occurrence of minimal immunological alterations in the same monkeys (Arnold et al. 1999), as well as clinical signs of toxicity (ocular and dermal changes) and decreased antibody responses in offspring of other monkeys that were exposed to a similarly low dose level of a commercial PCB mixture (0.005 mg/kg/day Aroclor 1254) for approximately 46 weeks during gestation and nursing (Arnold et al. 1995). The next highest intermediate-duration dose level (i.e., above

0.0075 mg/kg/day) tested in any species is 0.02 mg/kg/day, which is a serious LOAEL for fetal toxicity in monkeys (Arnold et al. 1995). Additional information on the critical and supporting studies used to derive the intermediate-duration MRL is provided in Appendix A.

- An MRL of 0.02 μg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to PCBs.

The chronic oral MRL was is based on a LOAEL of 0.005 mg/kg/day for immunological effects in adult monkeys that were evaluated after 23 and 55 months of exposure to Aroclor 1254 (Tryphonas et al. 1989, 1991a). The MRL was estimated by dividing this LOAEL by an uncertainty factor of 300 (10 for extrapolation from a LOAEL to a NOAEL, 3 for extrapolation from monkeys to humans, and 10 for human variability). This study included groups of 16 female Rhesus monkeys that self-ingested capsules containing 0, 0.005, 0.02, 0.04, or 0.08 mg/kg/day doses of the PCBs. Comprehensive immunological evaluations showed that IgM (all doses except 0.02 mg/kg/day) and IgG (all doses) antibody levels to SRBC were significantly reduced compared to controls after 23 months (Tryphonas et al. 1989). Secondary challenge with SRBC after 55 months showed decreasing dose-related trends in the IgM and IgG anamnestic responses, although only IgM was significantly lower than controls at all dose levels (Tryphonas et al. 1991a). Other immunologic changes included changes in numbers of lymphocyte T-cell subsets (significantly decreased ratio of T-inducer/helper cells to T-cytotoxic/suppressor cells) at 0.08 mg/kg/day (only dose level tested) after 23 months, and dose-related trends for several endpoints (e.g., decreasing lymphocyte proliferation in response to mitogenic stimulation, decreasing phagocytic activity of peripheral blood monocytes) after 55 months. Support for the critical LOAEL is provided by mild dermal and ocular manifestations of PCB toxicity, including eyelid swelling and various finger and toe nail changes, in the same monkeys at 0.005 mg/kg/day and higher doses (Arnold et al. 1993a). Additionally, a number of other studies using higher dose levels of PCB have demonstrated immunological and dermal/ocular effects in monkeys following intermediate or chronic exposures. The LOAEL resulted in PCB tissue and blood levels that are near background concentrations found in the general human population (Kimbrough 1995). The next highest dose level, 0.02 mg/kg/day, is a serious LOAEL for reproductive toxicity (reduced conception) and fetal toxicity when monkeys from the same study were bred after 37 months of exposure (Arnold et al. 1995). Additional information on the critical and supporting studies used to derive the chronic-duration MRL is provided in Appendix A.

As affirmed by a panel of international experts (see Appendix E), human data provide support for this chronic oral MRL. Using data from the North Carolina cohort (Gladen et al. 1988; Rogan et al. 1986a,

1986b), Tilson et al. (1990) estimated a NOAEL of 0.093 μg/kg/day for developmental effects in humans. This NOAEL was calculated by first estimating the concentration of PCBs in breast milk that resulted in no significant neurodevelopmental alterations in neonates as assessed with the Brazelton Scale; this concentration was 3.4 ppm (Gladen et al. 1988; Rogan et al. 1986a). The assumption was then made that the concentration of PCBs in women's breast milk is equal to the concentration of PCBs in the fat throughout the rest of the body. It can then be calculated that for 25-year-old women who weigh 60 kg and have 25% body fat, 3.4 ppm would result from a lifetime daily PCB dose of 0.093 μg/kg/day (Tilson et al. 1990). Since the analytical method might have caused the researchers to overestimate the concentration of PCBs in breast milk by a factor of 2 (Tilson et al. 1990), this NOAEL may be appropriately estimated to be 0.05 μg/kg/day, rather than 0.093 μg/kg/day. If an uncertainty factor of 3 were applied to the NOAEL of 0.05 μg/kg/day to account for intraspecies variation, this would result in a rounded dose of 0.02 μg/kg/day, which is exactly equivalent to the chronic-duration oral MRL derived above from data in monkeys. It should be pointed out that because losses of PCBs through excretion, lactation, and metabolism were not factored in the dose calculations, the actual dose that results in 3.4 ppm in breast milk fat would be higher than the reported NOAEL. Also, if dose calculations were based on women older than 25 years, the estimated daily dose would be lower than the reported NOAEL. Finally, it is possible that exposure to other bioaccumulative toxic substances could, in part, have contributed to other effects seen in this study. Nonetheless, it is both meaningful and relevant that the chronic oral MRL for PCBs is lower than the estimated NOAEL for the most sensitive human population in the Tilson et al. (1991) cohort.

3. HEALTH EFFECTS

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3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology and epidemiology of polychlorinated biphenyls (PCBs). It contains descriptions and evaluations of toxicological studies and epidemiological investigations, as well as toxicokinetic and other kinds of data pertinent to assessing the health effects of PCBs. Conclusions on the relevance of this information to public health, where possible, are discussed in Chapter 2 (Relevance to Public Health).

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

The health effects of PCBs have been extensively tested. Most studies investigated commercial PCBs mixtures that were produced in the United States before 1977 under Aroclor trade names. Health effects studies are also available for PCB mixtures produced in foreign countries. Among the most common tested foreign commercial PCB mixtures are Kanechlors, which were produced in Japan, and Clophens, which were produced in Germany. As in the United States, PCBs are no longer produced in Japan or

Germany. Foreign PCB mixtures differed from Aroclors mainly in percentages of individual chlorinated biphenyls, method of production, and level of contaminants. As discussed in Chapter 4, commercial PCB mixtures are comprised of various PCB congeners (there are 209 possible individual chlorinated biphenyls), as well as contaminants from the manufacturing process, particularly chlorinated dibenzofurans (CDFs). Information regarding the numbering system for PCBs and other chemical terms used to define the position of the chlorines on the biphenyl structure are provided in Chapter 4. The acronym PCBs is a general term used to refer to any commercial or other kind of mixture of congeners, such as environmental mixtures or animal tissue residues.

Evaluation of the health effects of PCB mixtures is complicated by numerous factors, particularly their congeneric composition, since ultimately, the toxicity of the mixture is due to the toxicity of the individual congeners, their interactions, and interactions with other structurally related chemicals such as CDFs and dioxins. For example, lot-to-lot differences in the congener distribution of commercial PCBs have been reported, which could contribute to some variations in toxicity observed among studies. The degree of CDF contamination is also a consideration in assessing the toxicity of commercial PCBs, because reported concentrations of CDFs varied among Aroclor formulations as well as with time period of manufacture. Concentrations of CDFs usually were higher in the Japanese and European PCBs than in Aroclors, and PCBs manufactured in the late 1970s had lower levels of contaminates than those produced earlier. In general, this profile is concerned with effects of PCBs in the presence of minimal CDF contamination. However, most health effects studies of PCB mixtures did not determine or report purity, or provide lot numbers that could be used to locate information on CDF contamination or congener distribution. Toxicological data for Kanechlors and Clophens are included in this chapter when these data provide information on effects that are not fully characterized for Aroclors because effects produced by Aroclors, Kanechlors, and Clophens are generally considered to be similar, at least for mixtures with equivalent percentages of chlorine (Kimbrough 1987). In addition, the lowest observed adverse effect levels for commercial PCB mixtures have been determined with Aroclors. Selected toxicity and mechanistic data on individual chlorinated biphenyl congeners also are included in this chapter because this information is potentially useful for assessing health effects and interactions of environmental mixtures of PCBs.

Using current health effects evaluation procedures, toxicity data for individual congeners may over- or underestimate the actual risk of PCB mixtures because the toxicity of congeners may be influenced by other congeners and chemicals in an additive, more than additive (synergistic), or less than additive (antagonistic) way. As discussed in Chapter 2 (Section 2.3), the current approach to assessing risks uses a

commercial mixture (Aroclor 1254) and an experimental mixture (a formulation representing the congeners found in breast milk) to develop health guidance values for environmental exposure to PCBs.

Information on health effects of PCBs in humans is available from studies of people exposed occupationally, by consumption of contaminated rice oil in Japan (the *Yusho* incident) and Taiwan (the *Yu-Cheng* incident), by consumption of contaminated fish and other food products of animal origin, and via general environmental exposures. As discussed in Chapter 6, people are environmentally exposed to PCBs that differ from commercial PCB mixtures due to changes in congener and impurity composition resulting from processes such as volatilization and other kinds of partitioning, chemical or biological transformation, and preferential bioaccumulation. Due to their stability and lipophilicity, PCBs usually accumulate in higher food-chain organisms and are stored in fatty tissues. Food consumption has been and continues to be the major source of body burden of PCBs in the general population. There is evidence that diets high in fish from PCB-contaminated waters, such as those in the Great Lakes and St. Lawrence River basins, can significantly increase a person's dietary intake of PCBs. Breast-fed infants of mothers who have diets high in contaminated fish may have a particularly increased risk for PCB exposure due to its presence in the milk.

PCBs are 1 of 11 persistent toxic substances that have been identified as critical Great Lakes pollutants by the International Joint Commission Water Quality Board (GLWQB 1985). In 1990, Congress amended the Federal Water Pollution Control Act and mandated the Environmental Protection Agency (EPA), in consultation with the Agency for Toxic Substances and Disease Registry (ATSDR) and the Great Lakes states, to submit a research report on the adverse human health effects related to water pollutants in the Great Lakes. Since then, ATSDR has awarded research grants and established cooperative agreements to coordinate basin-wide human health effects research. The primary interests of ATSDR's Great Lakes Human Health Effects Research Program are to document and characterize the exposure, identify populations at higher risk, identify associations between the consumption of contaminated Great Lakes fish and short and long-term harmful health effects, identify the most sensitive end points, establish registries and surveillance cohorts, and identify ways to prevent or mitigate exposure and resulting health effects (Johnson and DeRosa 1999; Johnson et al. 1998, 1999, 2000). PCB-related findings from the Great Lakes Research Program, as well as results from a number of other studies on health effects associated with exposures to PCBs through fish consumption, are included in this chapter.

Health effects have been observed in humans who consumed rice oil contaminated with heat-degraded Kanechlors in the *Yusho* and *Yu-Cheng* poisoning incidents. There is a historical linkage between

Yusho/Yu-Cheng and PCBs, and some health assessment documents ascribe effects from these incidents to PCBs. Unlike usual PCB mixtures, the *Yusho* and *Yu-Cheng* Kanechlors were heated in thermal heat exchangers (before rice oil contamination occurred) and also during cooking, resulting in the production of relatively high concentrations of CDF and polychlorinated quarterphenyl (PCQ) impurities. The concentrations of PCBs and PCQs in the rice oils were 100- to 500-fold greater than the CDFs. CDFs are generally considered the main causal agent, based on the following evidence: comparisons with Japanese workers with higher PCB blood levels who had few or none of the symptoms present in the rice oil poisonings; decreasing serum levels of PCBs in victims with persistent health effects; induction of *Yusho* health effects in animals exposed to reconstituted mixtures of CDF congeners similar to those in *Yusho* oils, but not by exposure to PCBs or PCQs alone; and comparative toxicity evaluations of PCB and CDF congeners in the unheated source mixture, contaminated rice oil, and tissues of victims (Bandiera et al. 1984; Kunita et al. 1985; Ryan et al. 1990; Safe 1990; Tanabe et al. 1989). Although there is a general consensus that CDFs were main contributors to the health effects in the *Yusho* and *Yu-Cheng* victims, certain PCB congeners have the same mechanism of action as CDFs and polychlorinated dibenzo-*p*-dioxins (CDDs). Effects of *Yusho* and *Yu-Cheng* exposure, therefore, are indirectly relevant to assessing health effects of PCBs because they demonstrate the sensitivity of humans to dioxin-like toxicity and suggest that humans might respond to dioxin-like PCB congeners in a similar manner. Additionally, recent evidence indicates that some of the subtle effects can be attributed to non-dioxin-like PCB congeners (Guo et al. 1996; Soong and Ling 1997). Brief summaries of the effects from the *Yusho* and *Yu-Cheng* incidents are presented in this profile; a more complete discussion of the health effects associated with the *Yusho* and *Yu-Cheng* incidents can be found in the ATSDR toxicological profile on CDFs (ATSDR 1994) and CDDs (ATSDR 1998), and reviews by Hsu et al. (1994) and Masuda (1994).

Fires and other sources of high temperatures, such as hazardous waste incinerators and electrical transformer fires, also can greatly increase the toxicity of PCB mixtures by formation of CDFs (Rappe and Buser 1989). For example, in a transformer fire in the Binghamton (New York) State Office Building (BSOB), dielectric fluid composed of 65% Aroclor 1254 and 35% polychlorinated benzenes was pyrolyzed. The pyrolysis led to the formation of a fine, oily soot, which was distributed throughout the building via ventilation shafts. In addition to PCBs, the soot contained high levels of CDFs, CDDs, including 2,3,7,8-tetrachlorodibenzodioxin (TCDD), chlorinated biphenylenes, and other chemicals. Limited information is available on health effects in people who were exposed to this soot dermally, by inhalation, or by ingestion from eating with dirty hands. A discussion of the health effects associated with the BSOB incident can be found in the ATSDR toxicological profile for CDFs and reports by

Schecter (1983, 1986, 1987), Schecter and Tiernan (1985), Schecter et al. (1985a, 1985b), and Fitzgerald et al. (1986, 1989).

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects), and then by human and animal studies subdivided by type of exposure (e.g., occupational, contaminated fish consumption, inhalation, oral, and dermal). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects may start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels at or below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of polychlorinated biphenyls are indicated in Table 3-2 and Figure 3-2. Because cancer effects could occur at lower exposure levels, Figure 3-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for PCBs as discussed in Chapter 2 (Section 2.3) . An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

Table 3-1. Levels of Significant Exposure to PCB Mixtures - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
INTERMEDIATE EXPOSURE							
Systemic							
1	Rat (Sprague-Dawley)	30 d 7 d/wk 23 h/d	Hepatic	0.009 M			Casey et al. 1999 1242
			Endocr		0.009 M (increased thyroid serum T3 and T4 hormones)		
			Bd Wt	0.009			
			Other		0.009 (epithelial hyperplasia in urinary bladder)		
2	Rat (NS)	213 d 5 d/wk 7 hr/d	Hepatic		1.5 (unspecified moderately severe degeneration)		Treon et al. 1956 1254
			Renal		1.5 (slight degeneration of renal tubules)		
			Bd Wt	1.5			
3	Rat (NS)	24 d 5 d/wk 7 hr/d	Hepatic	8.6			Treon et al. 1956 1242
			Bd Wt	8.6			
4	Mouse (NS)	24 d 5 d/wk 7 hr/d	Hepatic	8.6			Treon et al. 1956 1242
			Bd Wt	8.6			
5	Mouse (NS)	213 d 5 d/wk 7 hr/d	Hepatic		1.5 (unspecified slight degeneration)		Treon et al. 1956 1254
			Renal	1.5			
			Bd Wt	1.5			

Table 3-1. Levels of Significant Exposure to PCB Mixtures - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
6	Gn pig (NS)	121 d 5 d/wk 7 hr/d	Hemato	5.4			Treon et al. 1956 1254
			Hepatic	5.4			
			Bd Wt		5.4 (16% decreased body weight gain)		
7	Gn pig (NS)	213 d 5 d/wk 7 hr/d	Hepatic		1.5 (slight vacuolation)		Treon et al. 1956 1254
			Renal	1.5			
			Bd Wt			1.5 (22% reduced body weight gain)	
8	Gn pig (NS)	24 d 5 d/wk 7 hr/d	Hepatic	8.6			Treon et al. 1956 1242
			Bd Wt	8.6			
9	Rabbit (NS)	121 d 5 d/wk 7 hr/d	Hemato	5.4			Treon et al. 1956 1254
			Hepatic	5.4			
			Renal	5.4			
			Bd Wt	5.4			
10	Rabbit (NS)	24 d 5 d/wk 7 hr/d	Hepatic	8.6			Treon et al. 1956 1242
			Bd Wt	8.6			

Table 3-1. Levels of Significant Exposure to PCB Mixtures - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
11	Rabbit (NS)	213 d 5 d/wk 7 hr/d	Hepatic		1.5 (hydropic degeneration, fatty changes)		Treon et al. 1956 1254
			Renal	1.5			
			Bd Wt	1.5			

[a]The number corresponds to entries in Figure 3-1.

Bd Wt = body weight; d = day(s); Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable- adverse-effect level; NS = not specified; wk = week(s); 1242 = Aroclor 1242; 1254 = Aroclor 1254

Figure 3-1. Levels of Significant Exposure to PCB Mixtures - Inhalation

Intermediate (15-364 days)

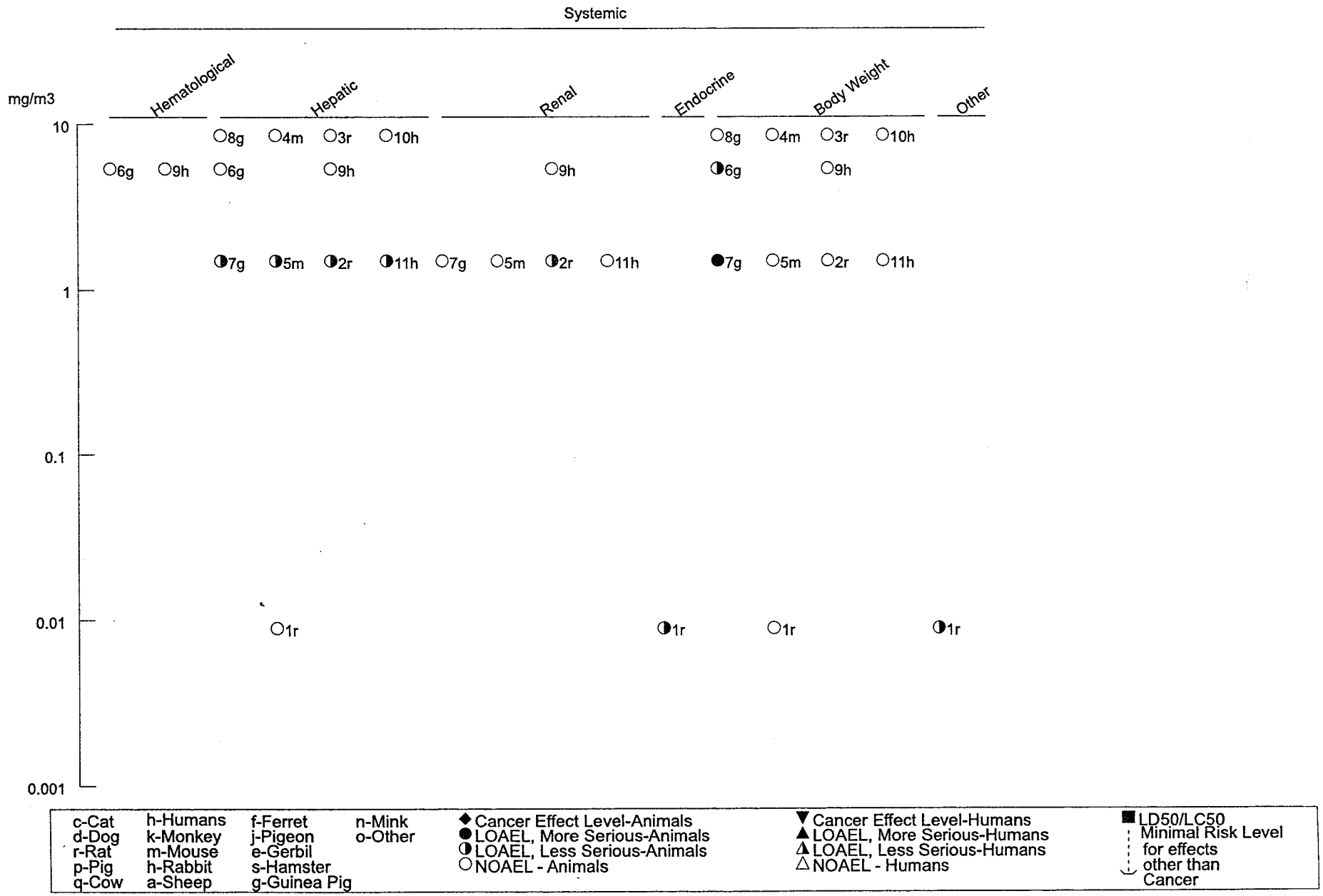


Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	once (GO)				4250 M (LD_{50})	Bruckner et al. 1973 1242
2	Rat (Osborne-Mendel)	once (GO)				1010 M (LD_{50})	Garthoff et al. 1981 1254
3	Rat (Sherman)	once (GO)				1295 M (LD_{50})	Linder et al. 1974 1254
4	Rat (Sherman)	once (GO)				1315 M (LD_{50})	Linder et al. 1974 1260
5	Mouse (ICR)	2 wk (F)				130 M (3/5 died)	Sanders et al. 1974 1254
6	Mink (NS)	once (G)				4000 (LD_{50})	Aulerich and Ringer 1977 1254
7	Mink (NS)	once (G)				750 (LD_{50})	Aulerich and Ringer 1977 1221
	Systemic						
8	Rat (Sprague-Dawley)	4 x (GO)	Bd Wt	25 F			Brown and Lamartiniere 1995 1221

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
9	Rat (Sprague-Dawley)	once (GO)	Resp	4000 M			Bruckner et al. 1973 1242
			Cardio	4000 M			
			Gastro	4000 M			
			Hemato		4000 M (crenated RBCs, increased PMNs)		
			Hepatic		4000 M (fatty vacuoles, necrotic foci)		
			Renal		4000 M (vacuolated, fatty tubular cells; protein casts)		
			Endocr	4000 M			
			Dermal	4000 M			
			Bd Wt	4000 M			
10	Rat (Fischer-344)	4 d (F)	Hepatic	0.5 M	1.0 M (increased serum cholesterol)		Carter 1984 1254
			Bd Wt	3.9 M			
11	Rat (Fischer-344)	4 d (F)	Hepatic	0.5 M	1.0 M (increased relative liver weight; increased serum cholesterol)		Carter 1985 1254
			Bd Wt	1.9 M			
12	Rat (Fischer-344)	2 wk (F)	Hepatic		1.9 M (increased serum cholesterol)		Carter and Koo 1984 1254
			Bd Wt	1.9 M			
13	Rat (Sprague-Dawley)	7 d (F)	Endocr		2.3 M (decreased thyroid serum T_4 hormone)		Hood et al. 1999 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
14	Rat (Wistar)	6 d (F)	Hepatic		50 M (increased serum cholesterol and liver weight)		Kato and Yoshida 1980 1248
15	Rat (Wistar)	14 d (F)	Hepatic		50 F (vacuolar degeneration)		Kling et al. 1978 1254
			Bd Wt			50 F (30% decrease in body weight gain)	
16	Rat (Wistar)	7 d (F)	Hepatic		2.5 M (increased relative liver weight; decrease glucose 6-phosphatase in liver)		Price et al. 1988 1254
			Endocr		2.5 M (increased colloid droplets in thyroid; reduced serum T_4 hormone)		
17	Mouse (ICR)	2 wk (F)	Hepatic	130 M			Sanders et al. 1974 1254
			Endocr		130 M (10-fold increase in serum corticosterone; 2-fold increase in relative adrenal weight)		
18	Pig (NS)	11 d 1 x/d (G)	Gastro			100 (gastric ulceration)	Hansen et al. 1976 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Neurological						
19	Rat (Sprague-Dawley)	once (GO)		1000 M	2500 M (diminished exploratory behavior, decreased response to pain stimuli, unusual gait)	6000 M (ataxia, coma)	Bruckner et al. 1973 1242
20	Rat (Fischer- 344)	10 d Gd 6-15 1 x/d (GO)		2		4 (behavioral alterations; impaired swimming performance and acquisition of one-way avoidance response)	Pantaleoni et al. 1988 1242
21	Rat (Wistar)	once (GO)			500 M (decreased dopamine in caudate nucleus)		Seegal et al. 1986b 1254
	Reproductive						
22	Rat (Holtzman)	5d Ld 1, 3, 5, 7, 9 1x/d (GO)		8 M		32 M (decreased fertility in male offspring; 52% decreased number of fetuses)	Sager 1983 1254
23	Rat (Holtzman)	5d Ld 1, 3, 5, 7, 9 1 x/d (GO)			8 F (reduced uterine weight and mating rate in female offspring)	64 F (reduced implantation rate and increased post-implantation loss in female offspring)	Sager and Girard 1994 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
24	Rat (Holtzman)	5 d Ld 1, 3, 5, 7, 9 1x/d (GO)				8 M (decreased fertility in male offspring; 21% decreased implants, 29% decreased embryos)	Sager et al. 1987 1254
25	Rat (Holtzman)	5 d Ld 1, 3, 5, 7, 9 1x/d (GO)		8 M		16 M (decreased fertility in male offspring)	Sager et al. 1991 1254
	Developmental						
26	Rat (Sherman)	9 d Gd 7-15 1 x/d (GO)		50		100 (60% decreased survival at weaning)	Linder et al. 1974 1254
27	Rat (Wistar)	7 d Gd 10-16 1x/d (GO)			5 (decreased thyroid plasma T_4 hormone in fetuses and 5-day-old pups)		Morse et al. 1996c 1254
28	Rat (Wistar)	10 d Gd 10-20 1x/d (GO)			25 (decreased thyroid serum T_4 hormone in pups)		Schuur et al. 1998a 1254
29	Rat (Sprague-Dawley)	10 d Gd 6-15 (F)		2.5	5 (12% decreased fetal weight)	15 (65% decreased fetal survival)	Spencer 1982 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
30	Rat (Wistar)	10 d Gd 6-15 1 x/d (GO)		100			Villeneuve et al. 1971 1254
31	Mouse (C57BL/ 6N)	once Gd 9 (GO)				244 (hydronephrosis)	Haake et al. 1987 1254
32	Mouse (ICR)	12 d Gd 6-18 (F)		12.5			Welsch 1985 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE							
Death							
33	Monkey (Rhesus)	2-3 mo (F)				4 M (nearly 100% mortality)	Allen 1975; Allen and Norback 1976 1248
34	Rat (Osborne-Mendel)	2.5 wk 2 x/wk (GO)				1530 M (LD_{50})	Garthoff et al. 1981 1254
35	Rat (Sherman)	8 mo (F)				72.4 F (8/10 died)	Kimbrough et al. 1972 1260
36	Mouse (BALB/c)	6 mo (F)				48.8 M (17/25 died)	Koller 1977 1254
37	Mink (NS)	4 mo (F)				2.8 (4/12 died)	Aulerich and Ringer 1977 1254
38	Mink (NS)	247 d (F)				1.9 (death in 2/3 males and 8/10 females)	Bleavins et al. 1980 1242
39	Mink (NS)	28 d (F)				1.2 (1 in 5 died)	Hornshaw et al. 1986 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
40	Monkey (Rhesus)	2-3 mo (F)	Gastro			4 M (hyperplasia, ulceration)	Allen 1975; Allen and Norback 1976 1248
			Hemato		4 M (unquantified anemia, increased macrophages, decreased WBCs)		
			Hepatic		4 M (hypertrophy, decreased serum cholesterol)		
			Dermal		4 M (alopecia, acne)		
			Ocular		4 M (excessive lacrimation, congestion of the conjunctiva)		
			Bd Wt			12 M (25% weight loss)	
41	Monkey (Rhesus)	3 mo (F)	Cardio			12 M (pericardial edema)	Allen and Norback 1973; Allen et al. 1973 1248
			Gastro			12 M (ulceration of gastric mucosa)	
			Hemato		12 M (moderate anemia; 18% decreased Hgb and Hct)		
			Dermal		12 M (alopecia, facial edema)		
			Ocular		12 M (eye discharge)		
			Bd Wt			12 M (26% weight loss)	

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
42	Monkey (Rhesus)	2 mo (F)	Gastro	0.8 F	1.3 F (gastric ulceration)		Allen et al. 1974a 1248
			Hemato	0.8 F	1.3 F (anemia)		
			Hepatic	0.8 F	1.3 F (focal necrosis)		
			Renal	1.3 F			
			Dermal		0.8 F (facial edema, alopecia)		
			Ocular		1.3 F (edema of the eyelids)		
43	Monkey (Rhesus)	2 mo (F)	Dermal		0.1 F (acne, alopecia)		Barsotti et al. 1976 1248
			Ocular		0.1 F (swelling of the eyelids)		
44	Monkey (Rhesus)	8 mo (F)	Hepatic		0.1 (lipid accumulation, focal necrosis, increased serum SGPT, decreased albumin/globulin ratio)		Barsotti et al. 1976 1248
45	Monkey (Rhesus)	2 mo (F)	Gastro		0.12 M (cysts formation in gastric submucosa)		Becker et al. 1979 1242
			Dermal		0.12 M (facial edema)		
			Ocular		0.12 M (reddening of eyelids)		
			Bd Wt		0.12 M (no weight gain)		
46	Rat (Fischer- 344)	10-15 wk 1 x/d (GO)	Musc/skel		0.1 M (increased femur density)		Andrews 1989 1254
			Endocr	25 M			

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
47	Rat (Fischer-344)	5 wk 1 x/d (GO)	Hepatic	1	10 M (increased relative liver weight and serum cholesterol)		Andrews 1989 1254
			Renal	1	10 M (increased relative kidney weight; 3-fold increase in urinary LDH; increase in protein in urine)		
			Bd Wt	10	25 M (12-15% body weight loss)		
48	Rat (Sprague-Dawley)	3 wk 3 d/wk (GO)	Resp	100 M			Bruckner et al. 1973 1242
			Cardio	100 M			
			Gastro	100 M			
			Hepatic		100 M (necrotic foci; increased SGOT)		
			Renal		100 M (lipid vacuoles and protein casts in tubular epithelium)		
			Endocr	100 M			
			Dermal	100 M			

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
49	Rat (Sprague-Dawley)	2-6 mo (F)	Hemato	1.5 M			Bruckner et al. 1974 1242
			Hepatic		0.3 M (increased relative liver weight, lipid content and increased urinary coproporphyrin)		
			Renal	1.5 M			
			Endocr	1.5 M			
			Bd Wt	1.5 M			
50	Rat (Sprague-Dawley)	35 d (F)	Hepatic	0.25 M	1.25 M (increased relative liver weight and liver triglycerides)		Bruckner et al. 1977 1254
			Bd Wt	1.25 M			
51	Rat (Sprague-Dawley)	5 mo (F)	Endocr		0.09 F (decreased thyroid serum T_3 and T_4 hormones)		Byrne et al. 1987 1254
			Bd Wt	4.3 F			
52	Rat (Sprague-Dawley)	5-7 mo (F)	Hepatic	2.5 F			Byrne et al. 1988 1254
			Endocr	0.05 F	0.25 F (decreased adrenal serum corticosterone, DHEA and DHS hormones)		
53	Rat (Osborne-Mendel)	4 wk (F)	Endocr		0.25 M (altered thyroid follicular ultrastructure, increased serum T3 hormone)		Collins and Capen 1980a 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
54	Rat (Osborne-Mendel)	4 wk (F)	Endocr		2.5 M (vacuolated thyroid follicular cells, decreased serum T_4 hormone)		Collins et al. 1977 1254
55	Rat (Sherman)	2 mo (F)	Hepatic		5 F (25% increase in relative liver weight, porphyria)		Goldstein et al. 1974 1254
			Bd Wt	5 F			
56	Rat (Fischer-344)	15 wk 7 d/wk (GO)	Hepatic	0.1 M	1.0 M (increase liver weight; hypertrophy and vacuolar degeneration)		Gray et al. 1993 1254
			Renal	0.1 M	1.0 M (cortical tubular protein casts)		
			Endocr		0.1 M (reduced serum thyroxine levels)		
			Bd Wt	1.0 M	10 M (13% reduced weight gain)	25 M (55% reduced weight gain)	
57	Rat (Holtzman)	5 wk (F)	Endocr	0.025 M	0.25 M (altered thyroid follicular ultrastructure)		Kasza et al. 1978 1254
58	Rat (Wistar)	20 d (F)	Hepatic		15 M (increased liver weight and serum cholesterol)		Kato et al. 1982a 1248
			Endocr	15 M			
59	Rat (Sherman)	8 mo (F)	Hepatic	1.4 M	6.5 M (increased relative and absolute liver weight; cytoplasmic vacuolation)		Kimbrough et al. 1972 1260
			Bd Wt	7.2 F	32.8 M (12% reduced weight gain)	38.2 F (27% reduced weight gain)	

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference Chemical Form
60	Rat (Sherman)	8 mo (F)	Hepatic	1.6 F	6.8 M (increase in relative liver weight; cytoplasmic vacuolation)		Kimbrough et al. 1972 1254
			Bd Wt	7.5 F		36.4 M (35% reduction in weight gain)	
61	Rat (Wistar)	30 d (F)	Hepatic			50 (severe vacuolar degeneration, lipid accumulation and necrosis)	Kling et al. 1978 1254
			Bd Wt			50 (72% decreased body weight gain)	
62	Rat (Osborne-Mendel)	4 wk (F)	Hepatic	2.5 M	25 M (increased liver triglycerides)		Litterst et al. 1972 1242
63	Rat (Wistar)	120 d 7 d/wk (F)	Endocr		7.1 M (degenerative changes in adrenal medulla)	14.3 M (increased severity of the adrenal changes)	Rao and Banerji 1993 1260
64	Rat (Sprague-Dawley)	35 d (gd 0-pnd 15) (F)	Endocr		12.5 F (increased relative thyroid weight; depressed T_4 levels)		Seo and Meserve 1995 1254
			Bd Wt	12.5 F		25 F (27% decreased body weight)	
65	Rat (NS)	10 wk (W)	Endocr	35 M			Wassermann et al. 1973 1221
66	Mouse (Swiss-Webster)	23 wk (F)	Dermal		26 F (hyperkeratosis, erythema, cysts)		Bell 1983 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
67	Mouse (BALB/c)	6 or 11 mo (F)	Hepatic			49.8 M (liver necrosis, adenofibrosis, increased liver weight)	Kimbrough and Linder 1974 1254
			Bd Wt	49.8 M			
68	Mouse (BALB/c)	6 mo (F)	Hepatic	0.5 M	4.9 M (mild degeneration and necrosis of hepatocytes, increased absolute liver weight)	48.8 M (severe liver necrosis)	Koller 1977 1254
69	Mouse (BALB/c)	6 wk (F)	Resp	22 M			Loose et al. 1978a 1242
			Hepatic	22 M			
70	Gn pig (NS)	8 wk (F)	Hemato	4.0 F			Vos and de Roij 1972 1260
			Hepatic	4.0 F			
			Renal	4.0 F			
			Endocr	4.0 F			
			Dermal	4.0 F			
			Bd Wt	4.0 F			
71	Rabbit (New Zealand)	8 wk (F)	Hemato	6.5 M			Street and Sharma 1975 1254
			Hepatic	6.5 M			
			Renal	6.5 M			
			Endocr	6.5 M			
			Bd Wt	6.5 M			

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
72	Pig (NS)	91 d (F)	Gastro		9.2 (gastric erosions)		Hansen et al. 1976 1242
			Endocr		9.2 (increased relative adrenal weight)		
			Bd Wt			9.2 (55-62% decreased weight gain)	
73	Mink (NS)	39 wk (F)	Hemato	0.4			Aulerich and Ringer 1977 1254
			Bd Wt	0.4			
74	Mink (NS)	247 d (F)	Gastro	0.9		1.9 (gastric ulcers)	Bleavins et al. 1980 1242
			Bd Wt	0.9		1.9 (emaciation)	
75	Mink (NS)	28 d (F)	Gastro	1.8	3.9 (hemorrhage)		Hornshaw et al. 1986 1254
			Bd Wt	1.1	1.8 (10% body weight loss in treated, 7% weight gain in controls)		
	Immunological/Lymphoreticular						
76	Monkey (Rhesus)	11 mo (F)		0.1 F	0.2 F (decreased anti-SRBC hemolysin titers)		Thomas and Hinsdill 1978 1248
77	Monkey (Cynomolgus)	238 d (F)			0.1 F (decreased antibody response to SRBC antigen)		Truelove et al. 1982 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
78	Rat (Fischer- 344)	5-15 wk 7 d/wk (GO)		1 M		10 M (decreased natural killer cells at 15 weeks, decreased thymus weight)	Smialowicz et al. 1989 1254
79	Mouse (BALB/c)	6 mo (F)		0.5 M	4.9 M (increased susceptibility to Moloney leukemia virus)		Koller 1977 1254
80	Mouse (BALB/c)	6 mo (F)		0.5 M	4.9 M (increased susceptibility to Moloney leukemia virus)		Koller 1977 1242
81	Mouse (BALB/c)	6 mo (F)		4.9 M			Koller 1977 1221
82	Mouse (BALB/c)	6 wk (F)				22 M (decreased resistance to bacterial endotoxin and protozoans leading to death)	Loose et al. 1978a 1242
83	Mouse (ARSF1)	5 wk (F)			13 F (increased sensitivity to bacterial endotoxin)	130 F (decreased resistance to bacterial infection resulting in death)	Thomas and Hinsdill 1978 1248
84	Gn pig (NS)	8 wk (F)			0.8 F (decreased gamma globulin- containing cells in lymph nodes)		Vos and de Roij 1972 1260
85	Gn Pig (albino)	6 wk (F)		0.8 F	4 F (decreased antibodies to tetanus toxoid and skin reactivity to tuberculin)		Vos and Van Driel-Grootenhuis 1972 Clophen A60

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
86	Rabbit (New Zealand)	8 wk (F)				0.18 M (marked thymic atrophy)	Street and Sharma 1975 1254
	Neurological						
87	Monkey (Cynomolgus)	20 wk Ld 1-140 1 x/d (G)			0.0075[b] M (decreased behavioral performance in nonspatial and spatial discrimination reversal tasks)		Rice 1997, 1998, 1999b; Rice and Hayward 1997, 1999a simulated human milk
88	Monkey (Macaque)	20 wk 7 d/wk (F)			0.8 (decreased dopamine content in caudate, putamen, substantia nigra, and hypothalamus)		Seegal et al. 1990 1016
89	Monkey (Macaque)	20 wk 7 d/wk (F)			0.8 M (decreased dopamine contents in brain areas)		Seegal et al. 1991b 1016
90	Monkey (Macaque)	20 wk 1 x/d (F)			3.2 M (significant reduction in dopamine in several brain areas)		Seegal et al. 1994 1016
91	Rat (Sprague-Dawley)	52 wk (F)		14.1 F			Freeman et al. 2000 1016
92	Rat (Sprague-Dawley)	52 wk (F)		7.5 F			Freeman et al. 2000 1242

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
93	Rat (Sprague-Dawley)	52 wk (F)		6.9 F			Freeman et al. 2000 1254
94	Rat (Sprague-Dawley)	52 wk (F)		6.7 F			Freeman et al. 2000 1260
95	Rat (Long- Evans)	36 d Gd 6-21 Ld 1-21 (GO)			4 (elevated auditory threshold at 1 kHz)		Goldey et al. 1995 1254
96	Rat (Wistar)	80 d (F)				2.4 (impaired avoidance reaction and retention of a learned task)	Lilenthal and Winneke 1991 Clophen A-30
97	Rat (Wistar)	42 d (F)		0.13	1.3 (decreased motor coordination of pups, increased relative liver weight)	13.5 (50% neonatal death)	Overman et al. 1987 1254
98	Rat (Fischer- 344)	21 d ppd 1-21 1 x/d (GO)		1		2 (impaired learning, abnormal swimming behavior, decreased open field activity)	Pantaleoni et al. 1988 1242
	Reproductive						
99	Monkey (Rhesus)	2 mo (F)				0.8 F (reduced conception rate, post-implant resorption and/or abortion)	Allen et al. 1974a 1248

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
100	Monkey (Rhesus)	38 wk 5 d/wk (F)				0.2 F (reduced conception rate, post-implant bleeding and abortion)	Arnold et al. 1990 1254
101	Monkey (Rhesus)	7 mo (F)			0.1 F (increased menstrual length)	0.2 F (reduced conception rate)	Barsotti et al. 1976 1248
102	Rat (Wistar)	1 mo 1 x/d (GO)				10 F (increased estrus, decreased receptivity, vaginal bleeding, delayed parturition)	Brezner et al. 1984 1254
103	Rat (Fischer- 344)	15 wk 7 d/wk (GO)		10 M	25 M (reduced seminal vesicle and epididymal weights and epididymal sperm counts following weanling exposure)		Gray et al. 1993 1254
104	Rat (Sherman)	67 d (F)		6.9		35.4 (decreased litter size)	Linder et al. 1974 1260
105	Mouse (ICR)	108 d (F)		1.25 F		12.5 F (55% decreased conception)	Welsch 1985 1254
106	Rabbit (New Zealand)	12-15 wk 3 x/wk (GO)		4 F			Seiler et al. 1994 1260
107	Mink (NS)	39 wk (F)				0.4 (decreased reproduction rates and litter size)	Aulerich and Ringer 1977 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
108	Mink (NS)	21 wk (F)		0.2		0.9 (decreased reproduction rates and litter size)	Aulerich and Ringer 1977 1254
109	Mink (NS)	247 d (F)				0.9 (no reproduction)	Bleavins et al. 1980 1016
110	Mink (NS)	90 d (F)				1.3 F (48% reduced litter size with no live births)	Kihlstrom et al. 1992 1254
111	Mink (NS)	6 mo (F)		0.1 M			Wren et al. 1987b 1254
	Developmental						
112	Monkey (Rhesus)	2 mo (F)				0.8 (2/3 resorption or abortion)	Allen et al. 1974a 1248
113	Monkey (rhesus, cynomolgus)	20 wk Ld 1 - 140 1x/d (G)			0.0075 (minimal reduction in IgM and IgG antibodies to SRBC, transient decrease in B lymphocytes)		Arnold et al. 1999 simulated human milk
114	Monkey (Cyno-molgus)	238 d (F)				0.1 (100% fetal death)	Truelove et al. 1982 1254
115	Rat (Wistar)	1 mo 1x/d (GO)				10 (35% decreased litter size, decreased pre- and post-weaning survival)	Brezner et al. 1984 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
116	Rat (Osborne-Mendel)	42 d Gd 1-Ppd 21 (F)					2.5	(decreased thyroid function of pups)	Collins and Capen 1980c 1254
117	Rat (Sprague-Dawley)	49 d Gd 1-Ppd 28 (F)			8	(decreased serum T_4 in 60-day pups after exposure through gestation and weaning)			Corey et al. 1996 1254
118	Rat (Long- Evans)	36 d Gd 6-21 Ld 1-21 (GO)			1	(decreased free and total T_4 serum levels in pups on Pnd 7, 14, and 21)	4	(15% pup mortality on postnatal day 21; 3% in controls)	Goldey et al. 1995 1254
119	Rat (Sprague-Dawley)	36 d Gd 1-21 Ld 1-15 (F)			3.1	(significant reduction in serum T_4 and in ChAT activity in brain from pups)			Juarez de Ku et al. 1994 1254
120	Rat (Sherman)	67 d (F)		6.9			35.4	(significantly reduced survival at weaning)	Linder et al. 1974 1260
121	Rat (Sherman)	187 d (F)		0.39	1.5	(enlarged liver cells and vacuolated cytoplasm in F2a)			Linder et al. 1974 1260
122	Rat (Sherman)	186 d (F)		7.2 F			37	(significant increase in preweaning mortality rate, lipid accumulation in hepatocytes from F1b)	Linder et al. 1974 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
123	Rat (Sherman)	129 d (F)		0.32		1.5 (15-24% decreased litter size, lipid accumulation in hepatocytes)	Linder et al. 1974 1254
124	Rat (Wistar)	42 d (F)		0.13		13.5 (50% neonatal death)	Overman et al. 1987 1254
125	Rat (Sprague-Dawley)	51 d Gd 1-Ppd 30 (F)			0.1 (decreased thyroid serum T_3 and T_4 hormones in pups)		Provost et al. 1999 1254
126	Rat (Sprague-Dawley)	36 d Gd 1-Ppd 15 (F)			6.3 (reduced body serum temperature, T_4, oxygen consumption in offspring on day 15; body weight reduced 11%)	12.5 (27% reduction in pup body weight on day 15; reduced T_4; reduced body temperature)	Seo and Meserve 1995 1254
127	Rat (Sprague-Dawley)	35 d (gd 0-pnd 15) (F)			12.5 (reduced body temperature)		Seo and Meserve 1995 1254
128	Rat (Sprague-Dawley)	36 d Gd 6-ppd 21 (F)			1 (decreased thyroid serum T_4 hormone in pups)		Zoeller et al. 2000 1254
129	Mouse (ICR)	108 d (F)		12.5 F			Welsch 1985 1254
130	Gn pig (NS)	42 d Gd 18-60 1 x/d (GO)				2.5 F (34% increased fetal death)	Lundkvist 1990 Clophen A50

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
131	Rabbit (New Zealand)	11 wk (F)				28 F (focal liver necrosis in developing pups, severe vacuolization)	Thomas and Hinsdill 1980 1248
132	Rabbit (NS)	28 d Gd 1-28 1 x/d (GO)		10		12.5 (71% fetal death)	Villeneuve et al. 1971 1254
133	Mink (NS)	6 mo (F)				0.18 (neonatal death)	Wren et al. 1987b 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
CHRONIC EXPOSURE							
Death							
134	Rat (Fischer- 344)	104-105 wk (F)				2.5 M (34% decreased survival)	NCI 1978 1254
Systemic							
135	Monkey (Rhesus)	17 mo (F)	Dermal		0.1 M (alopecia, acne periorbital edema)		Allen and Norback 1976 1248
			Bd Wt		0.1 M (body weight loss not quantitated)		
136	Monkey (Rhesus)	37 mo 1 x/d (C)	Hemato		0.02 F (decreased mean platelet volume)		Arnold et al. 1993a, 1993b 1254
			Hepatic		0.04 F (decreased serum cholesterol)		
			Endocr	0.08 F			
			Dermal		0.005 F (elevated and separated toenails)		
			Ocular		0.08 F (increased incidence of eye exudate; inflammation of Meibomian glands)		
			Bd Wt	0.08 F			

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
137	Monkey (Rhesus)	72 mo (F)	Resp	0.080 F			Arnold et al. 1997 1254
			Cardio	0.080 F			
			Gastro	0.080 F			
			Hemato	0.080 F			
			Hepatic	0.040	0.080 F (increased relative liver weights)		
			Renal	0.080 F			
			Endocr	0.080 F			
			Dermal	0.020	0.040 F (nail and nailbed changes)	0.080 F (severely altered finger and toenails)	
			Ocular	0.080 F			
			Bd Wt	0.080 F			
138	Monkey (Rhesus)	22 mo 1 x/d (C)	Endocr	0.08 F			Loo et al. 1989 1254
139	Monkey (Rhesus)	12 mo 5 d/wk (F)	Gastro		0.2 F (mucinous hypertrophy)		Tryphonas et al. 1986a 1254
			Hemato		0.2 F (hypoproliferative anemia)		
			Hepatic		0.2 F (hepatocyte necrosis, gall bladder and biliary duct hypertrophy)		
			Endocr	0.2 F			
			Dermal		0.2 F (nail loss, facial edema)		
			Ocular		0.2 F (conjunctivitis)		

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
140	Monkey (Rhesus)	28 mo 5 d/wk (F)	Gastro		0.2 F (hypertrophic gastropathy)		Tryphonas et al. 1986b 1254
			Hemato			0.2 F (severe normocytic anemia; 46-47% decreased hemoglobin and hematocrit)	
			Hepatic		0.2 F (liver hypertrophy and necrosis)		
			Endocr		0.2 F (thyroid desquammation)		
			Dermal		0.2 F (nail loss, gingival necrosis)		
			Bd Wt	0.2 F			
141	Rat (Sherman)	21 mo (F)	Bd Wt	5 F			Kimbrough et al. 1975 1260

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
142	Rat (Sprague-Dawley)	24 mo ad lib (F)	Resp	8.0 M 11.2 F			Mayes et al. 1998 1016
			Cardio	8.0 M 11.2 F			
			Gastro	8.0 M 11.2 F			
			Hemato	8.0 M	2.7 F (decreased RBC count and Hb concentration)		
			Musc/skel	8.0 M 11.2 F			
			Hepatic		2.0 M (hepatocellular 2.7 F hypertrophy and vacuolization)		
			Renal	8.0 M 11.2 F			
			Endocr	8.0 M 11.2 F			
			Ocular	8.0 M 11.2 F			
			Bd Wt	8.0 M 11.2 F			

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
143	Rat (Sprague-Dawley)	24 mo ad lib (F)	Resp	4.0 M 5.7 F			Mayes et al. 1998 1242
			Cardio	4.0 M 5.7 F			
			Gastro	4.0 M 5.7 F			
			Hemato	4.0 M 5.7 F			
			Musc/skel	4.0 M 5.7 F			
			Hepatic		2.0 M (hepatocellular 2.8 F hypertrophy and vacuolization, bile duct hyperplasia)		
			Renal	4.0 M 5.7 F			
			Endocr	5.7 F	2.0 M (thyroid follicular cell hyperplasia)		
			Dermal	4.0 M 5.7 F			
			Ocular	4.0 M 5.7 F			
			Bd Wt	4.0 M 2.8 F	5.7 F (10% decreased final body weight)		

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
144	Rat (Sprague-Dawley)	24 mo ad lib (F)	Resp	4.3 M 6.1 F			Mayes et al. 1998 1254
			Cardio	4.3 M 6.1 F			
			Gastro	4.3 M 6.1 F			
			Hemato	4.3 M 6.1 F			
			Musc/skel	4.3 M 6.1 F			
			Hepatic		1.0 M (hepatocellular 1.4 F hypertrophy and vacuolization, bile duct hyperplasia, increased serum cholesterol)		
			Renal	4.3 M 6.1 F			
			Endocr	6.1 F	1.0 M (thyroid follicular cell hyperplasia)		
			Dermal	4.3 M 6.1 F			
			Ocular	4.3 M 6.1 F			
			Bd Wt	1.0 M	2.0 M (12% decreased final body weight)		
					1.4 F (15% decreased final body weight)	6.1 F (28% decreased final body weight)	

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
145	Rat (Sprague-Dawley)	24 mo ad lib (F)	Resp	4.1 M 5.8 F			Mayes et al. 1998 1260
			Cardio	4.1 M 5.8 F			
			Gastro	4.1 M 5.8 F			
			Hemato	4.1 M	1.4 F (decreased RBC count, Hb, and Hct)		
			Musc/skel	4.1 M 5.8 F			
			Hepatic		1.0 M (hepatocellular 1.4 F hypertrophy and vacuolization, bile duct hyperplasia)		
			Renal	4.1 M 5.8 F			
			Endocr	5.8 F	1.0 M (thyroid follicular cell hyperplasia)		
			Dermal	4.1 M 5.8 F			
			Ocular	4.1 M 5.8 F			
			Bd Wt	4.1 M 5.8 F			

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
146	Rat (Fischer- 344)	104-105 wk (F)	Dermal	1.25	2.5 (alopecia, facial edema)		NCI 1978 1254
			Ocular	1.25	2.5 (exophthalmia)		
			Bd Wt		1.25 F (10% decreased body weight gain)		
147	Rat (Wistar)	52 wk (F)	Hepatic	1	10 F (significant increase in absolute liver weight)		Phillips et al. 1972 1254
			Bd Wt	1 F		10 F (36% reduction in final body weight)	
Immunological/Lymphoreticular							
148	Monkey (Rhesus)	23 mo 7 d/wk (C)			0.005[c] F (reduced IgM and IgG antibody responses to sheep red blood cells)		Tryphonas et al. 1989 1254
Neurological							
149	Monkey (Rhesus)	16-21 mo Pmm 6- Ppm 3 (F)				0.1 (impaired learning and hyperactivity in offspring)	Bowman et al. 1978 1248
150	Monkey (Rhesus)	21.8 mo Pmm 7- Ppm 4 (F)		0.03			Levin et al. 1988 1016
151	Monkey (Rhesus)	18.2 mo Pmm 12- Ppm 4 (F)		0.007 F	0.03 F (decreased discrimination performance in offspring)		Schantz et al. 1989 1016

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Reproductive							
152	Monkey (Rhesus)	17 mo (F)				0.1 M (decreased spermatogenesis, and libido)	Allen and Norback 1976 1248
153	Monkey (Rhesus)	37 mo 1 x/d (C)		0.005 F		0.02 F (42% reduced conception rate)	Arnold et al. 1995 1254
154	Rat (Sprague-Dawley)	24 mo ad lib (F)		8.0 M 11.2 F			Mayes et al. 1998 1016
155	Rat (Sprague-Dawley)	24 mo ad lib (F)		4.0 M 5.7 F			Mayes et al. 1998 1242
156	Rat (Sprague-Dawley)	24 mo ad lib (F)		4.3 M 6.1 F			Mayes et al. 1998 1254
157	Rat (Sprague-Dawley)	24 mo ad lib (F)		4.1 M 5.8 F			Mayes et al. 1998 1260
Developmental							
158	Monkey (Rhesus)	18.2 mo Pmm 3-Ppm 3 (F)				0.1 (50% mortality, dermal/ocular effects, and degenerative changes in thymus, spleen and lymph nodes)	Allen and Barsotti 1976 1248

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
159	Monkey (Rhesus)	18 mo (F)				0.1 F (72% infant deaths)	Allen et al. 1980 1248
160	Monkey (Rhesus)	~48 mo pmm 37- Ppw 22 1 x/d (C)			0.005 (inflammation of tarsal glands, nail lesions, gum recession, and reduced IgM antibody levels to SRBC in infant offspring)	0.02 (fetal and post-partum deaths in 4/4 impregnated monkeys)	Arnold et al. 1995 1254
161	Monkey (Rhesus)	72 mo (F)			0.005 F (inflammation of tarsal glands, nails and nail beds in infants)		Arnold et al. 1997 1254
162	Monkey (Rhesus)	12 mo (F)		0.007 F	0.03 (18% reduced birth weight)		Barsotti and Van Miller 1984 1016
163	Monkey (Rhesus)	21.8 mo Pmm 7- Ppm 4 (F)		0.007	0.03 (18% reduced birth weight)		Levin et al. 1988 1016
164	Monkey (Rhesus)	18.2 mo Pmm 12- Ppm 4 (F)		0.007 F	0.03 F (18% lower birth weight)		Schantz et al. 1989 1016
	Cancer						
165	Rat (Sherman)	21 mo (F)				5 F (CEL: liver hepatocellular carcinoma)	Kimbrough et al. 1975 1260

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
166	Rat (Sprague-Dawley)	24 mo ad lib (F)				5.4 F (CEL: liver hepatocellular adenoma)	Mayes et al. 1998 1016
167	Rat (Sprague-Dawley)	24 mo ad lib (F)				2.0 M (CEL: thyroid follicular cell adenoma)	Mayes et al. 1998 1242
						2.8 F (CEL: liver hepatocellular adenoma)	
168	Rat (Sprague-Dawley)	24 mo ad lib (F)				1.0 M (CEL: thyroid follicular cell adenoma)	Mayes et al. 1998 1254
						1.4 F (CEL: liver hepatocellular adenoma)	
169	Rat (Sprague-Dawley)	24 mo ad lib (F)				1.0 M (CEL: thyroid follicular cell adenoma)	Mayes et al. 1998 1260
						1.4 F (CEL: liver hepatocellular adenoma)	
170	Rat (Fischer- 344)	104-105 wk (F)				1.25 (CEL: liver neoplastic nodules, adenoma and hepatocellular carcinoma)	NCI 1978 1254

Table 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
171	Rat (Sprague-Dawley)	24 mo (F)				4.2 (CEL: hepatocellular neoplasms)	Norback and Weltman 1985 1260

[a]The number corresponds to entries in Figure 3-2.
[b]Used to derive an intermediate oral minimal risk level (MRL) of 0.00003 mg/kg/day; dose divided by an uncertainty factor of 300 (10 for extrapolation from a LOAEL to a NOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).
[c]Used to derive a chronic oral minimal risk level (MRL) of 0.00002 mg/kg/day; dose divided by an uncertainty factor of 300 (10 for extrapolation from a LOAEL to a NOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; BUN = blood urea nitrogen; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); DHEA = dehydroepiandrosterone; DHS = dehydroepiandrosterone sulfate; Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; gest = gestation; Gn Pig = guinea pig; (GO) = gavage, oil; Hemato = hematological; Ld = lactation day; LDH = lactate dehydrogenase; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; Pmd = pre-mating day; Pmm = pre-mating month; PMN = polymorphonuclear; Ppd = post-parturition day; Ppw = post-parturition week; Ppm = post-parturition month; RBC = red blood cell; Resp = respiratory; SGOT= serum glutamic oxaloacetic transaminase; SRBC = sheep red blood cell; T3 = triiodothyronine; T4 = thyroxine; (W) drinking water; WBC = white blood cell; wk = week(s); x = time(s); 1016 = Aroclor 1016; 1221 = Aroclor 1221; 1242 = Aroclor 1242; 1248 = Aroclor 1248; 1254 = Aroclor 1254; 1260 = Aroclor 1260

Figure 3-2. Levels of Significant Exposure to PCB Mixtures - Oral

Acute (≤14 days)

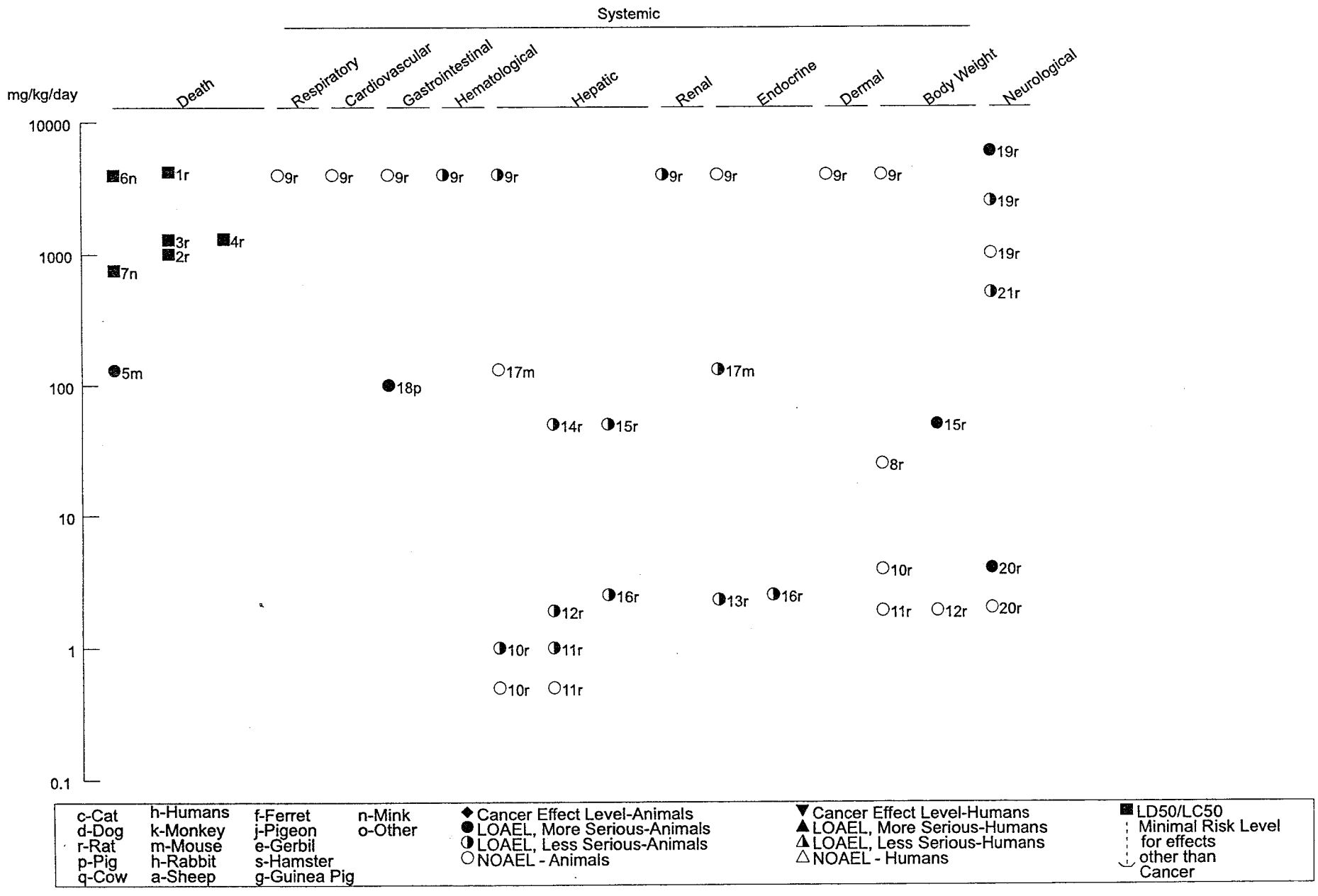


Figure 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (*continued*)

Acute (≤14 days)

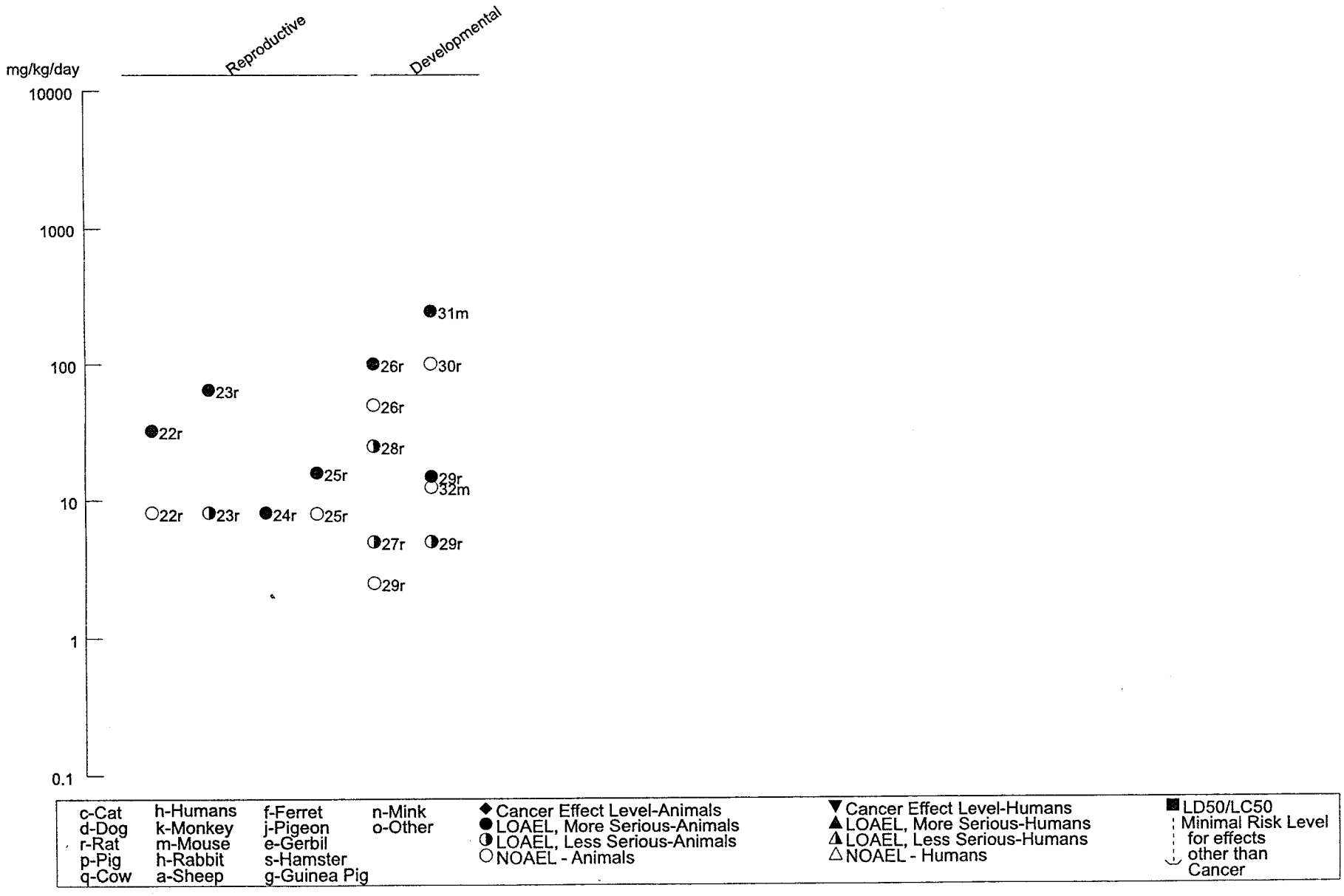


Figure 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (*continued*)

Intermediate (15-364 days)

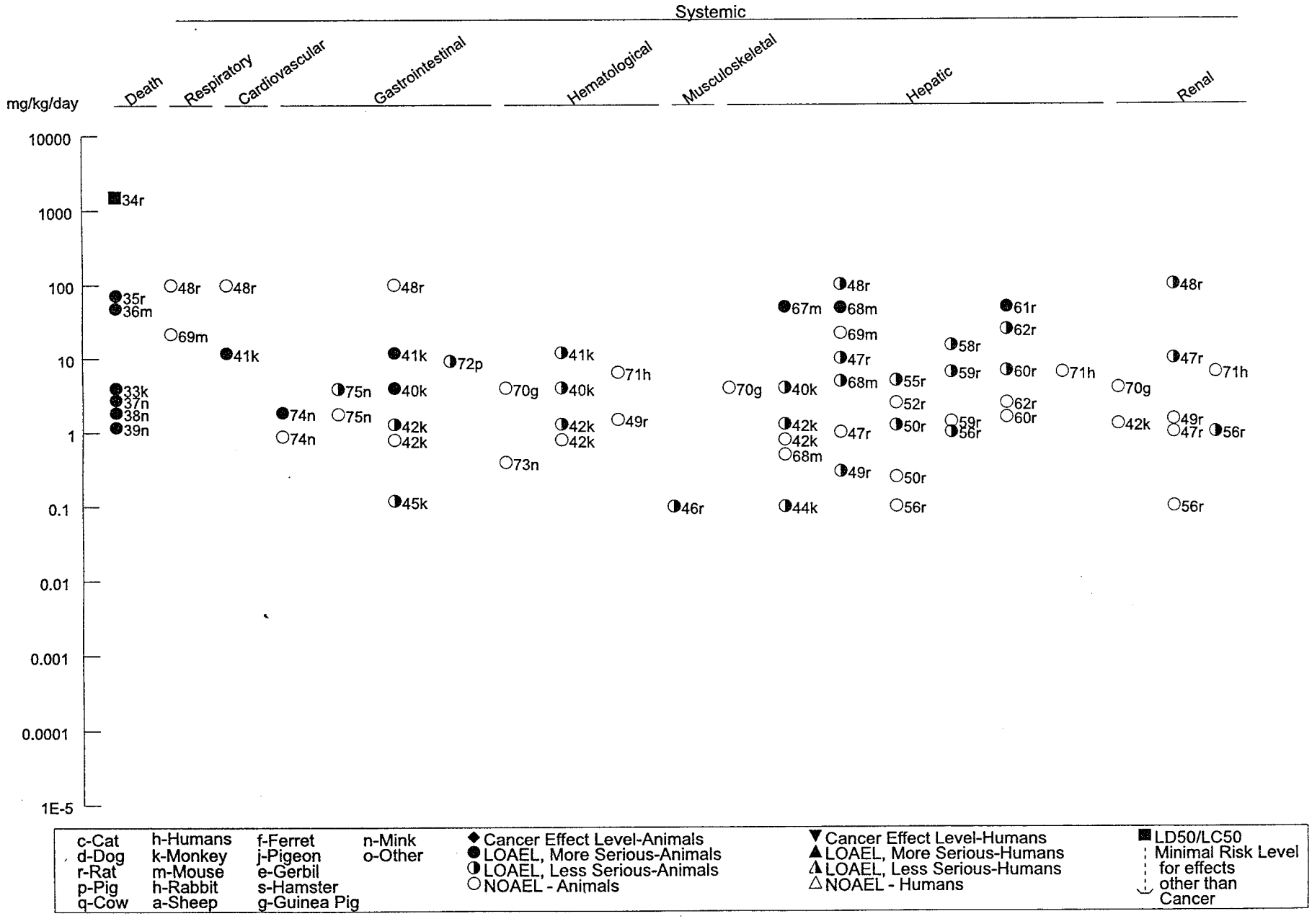


Figure 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (*continued*)

Intermediate (15-364 days)

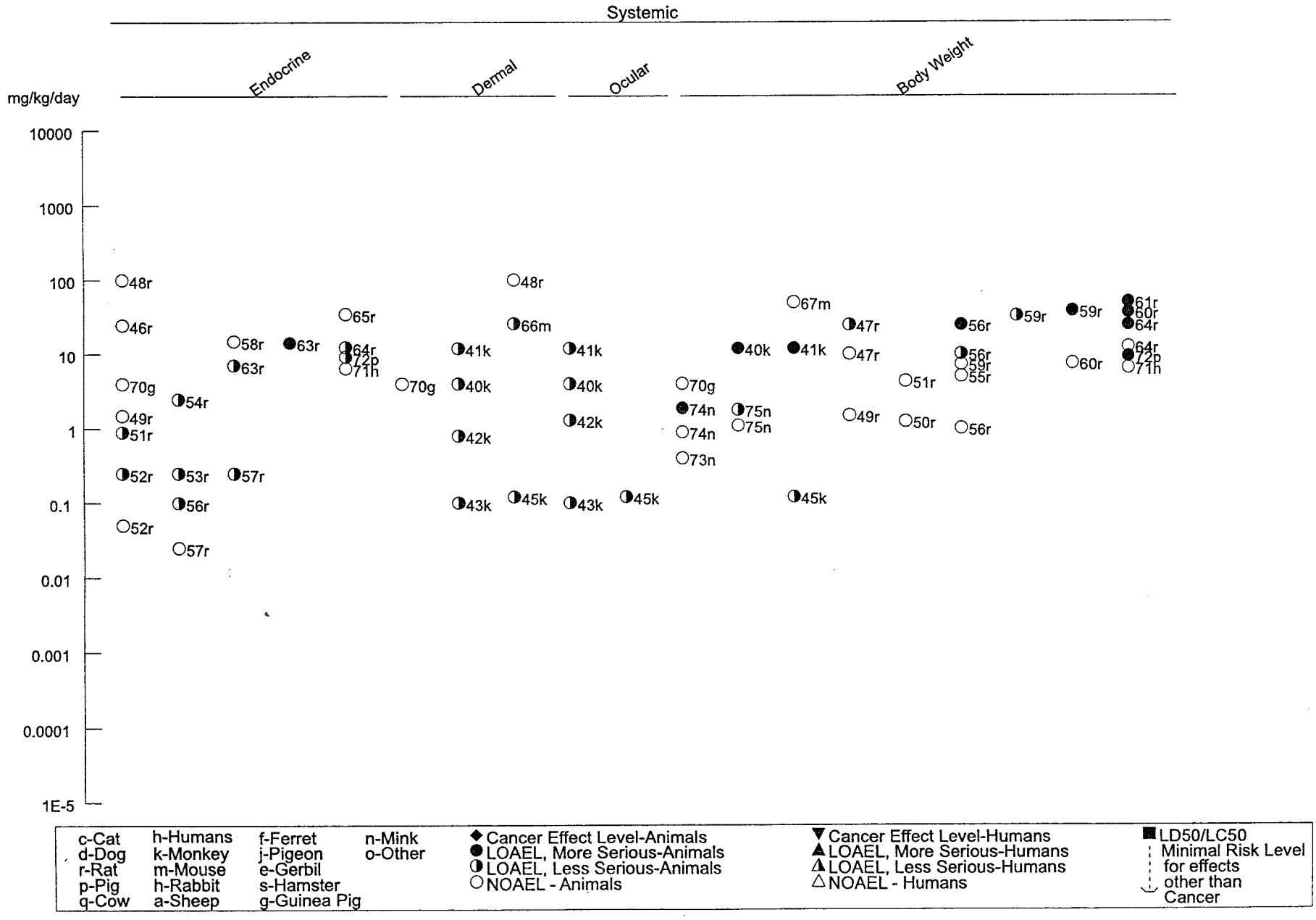
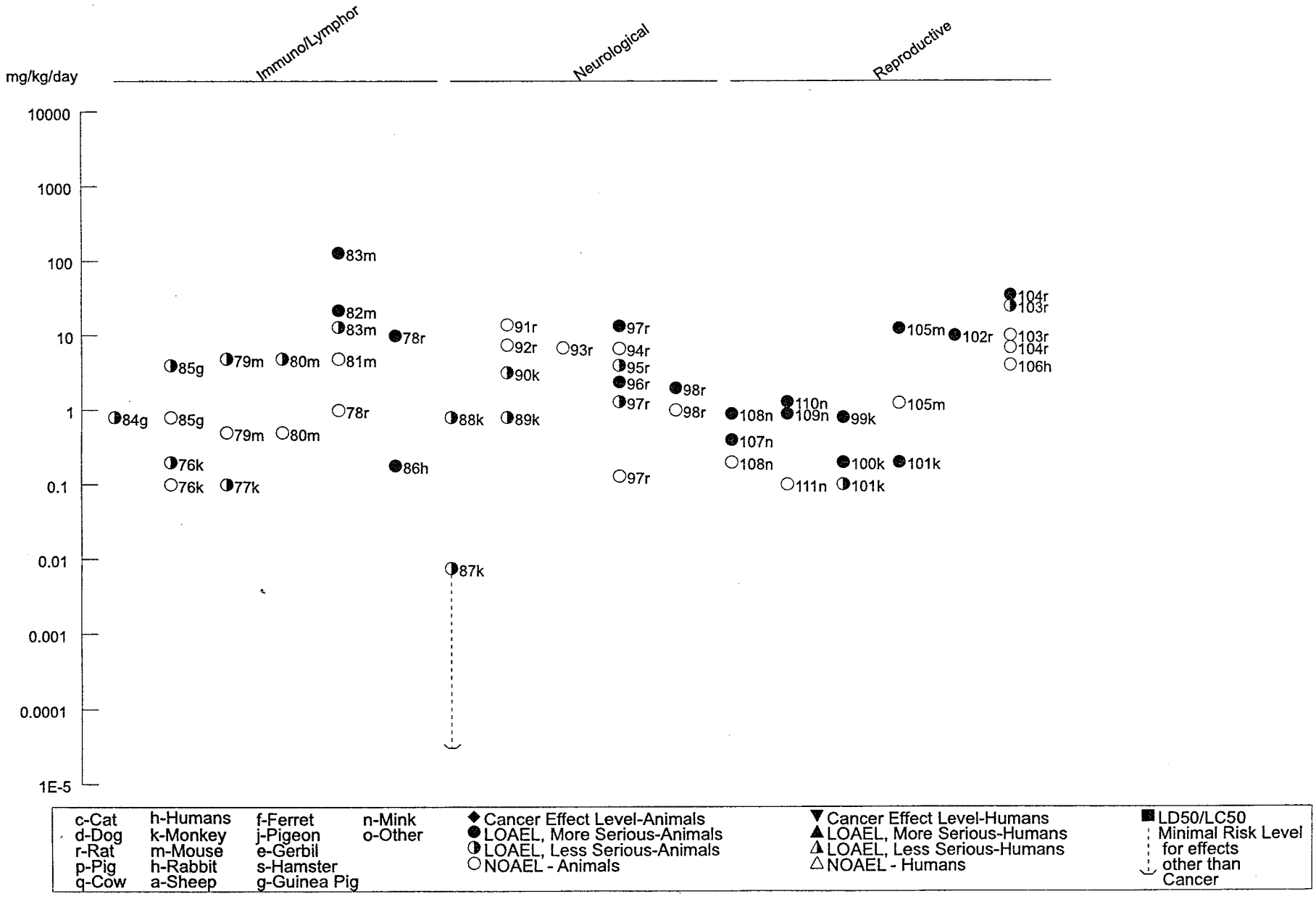


Figure 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (*continued*)

Intermediate (15-364 days)



c-Cat	h-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Figure 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (*continued*)

Intermediate (15-364 days)

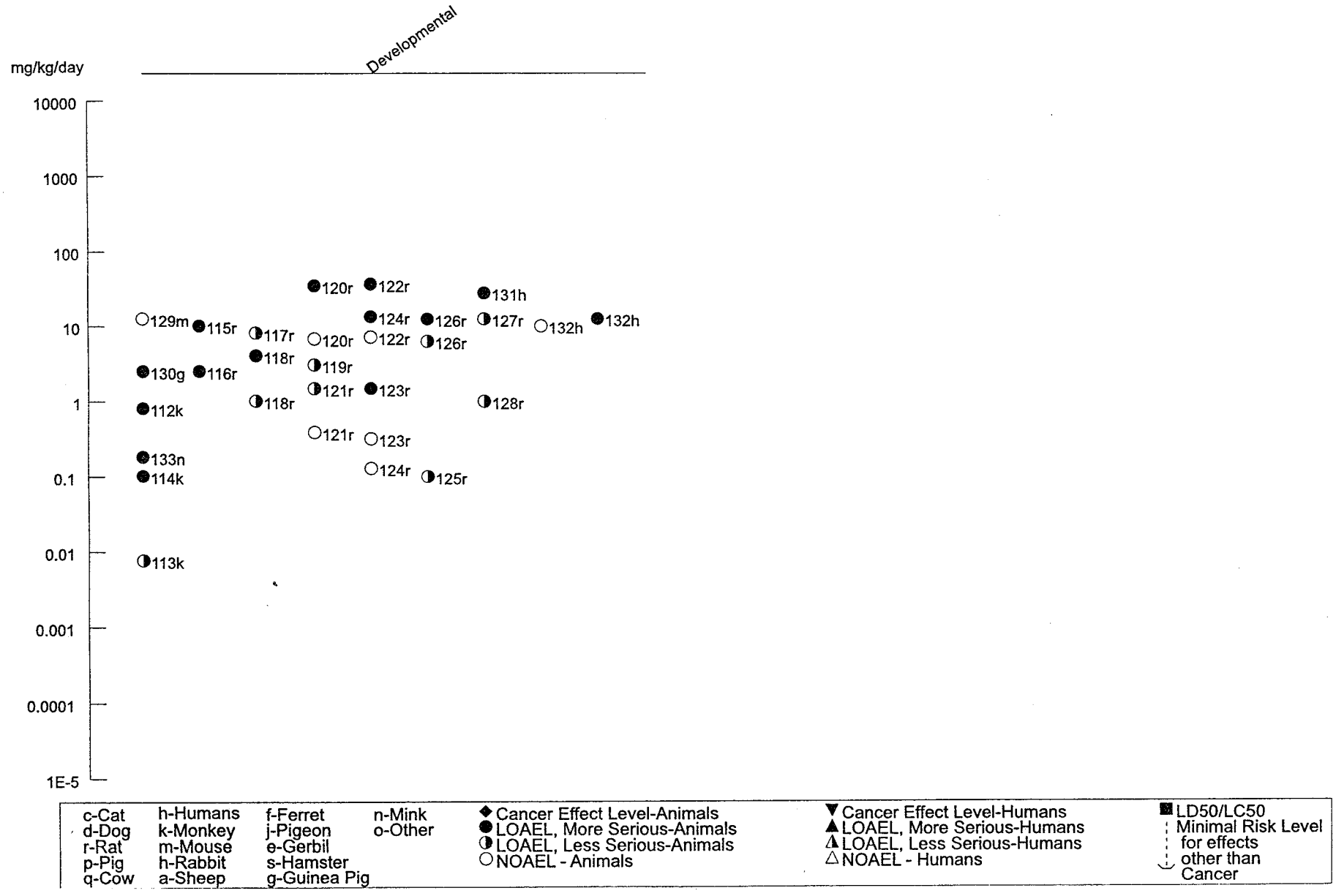


Figure 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (*continued*)

Chronic (≥365 days)

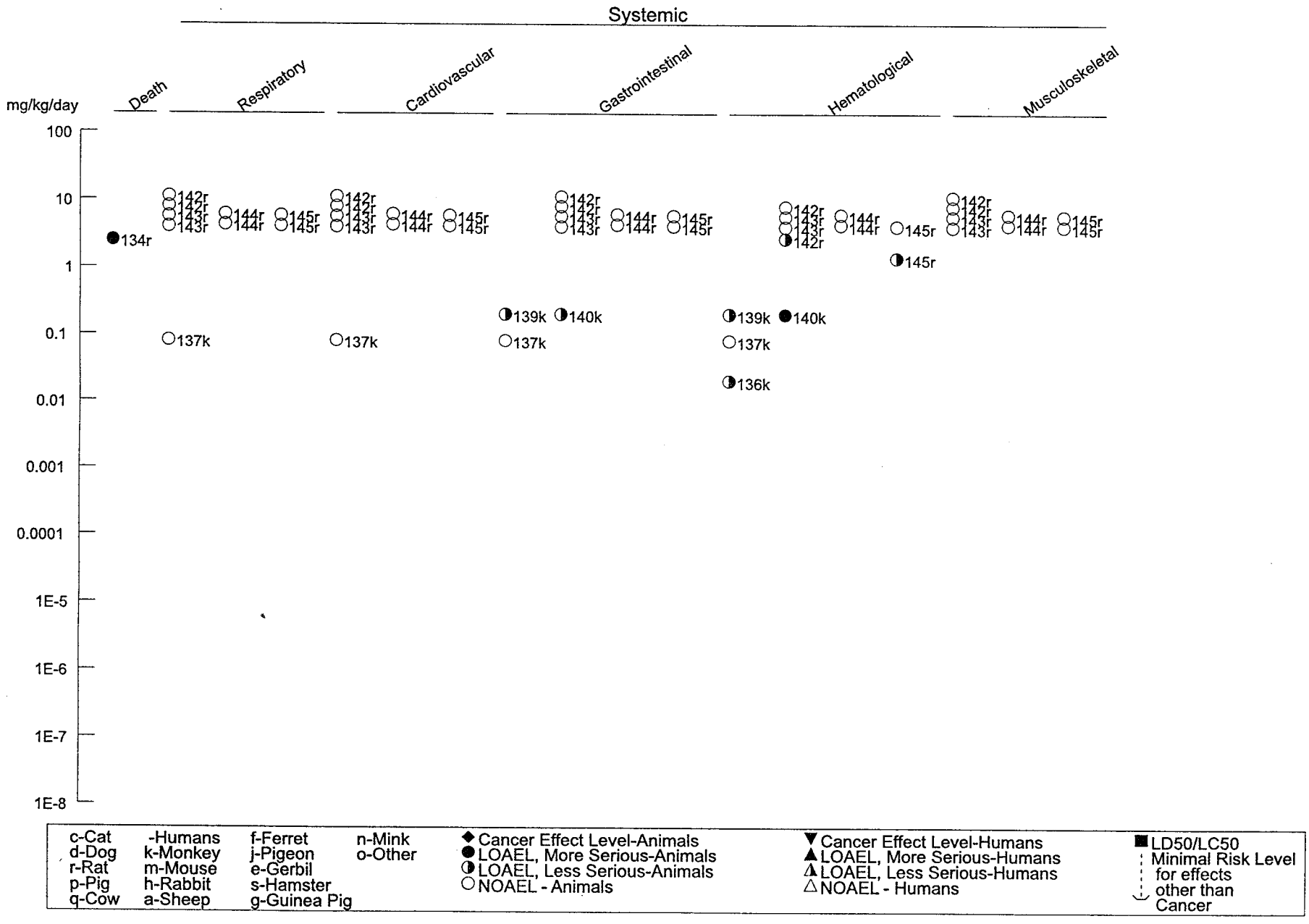


Figure 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (*continued*)

Chronic (≥365 days)

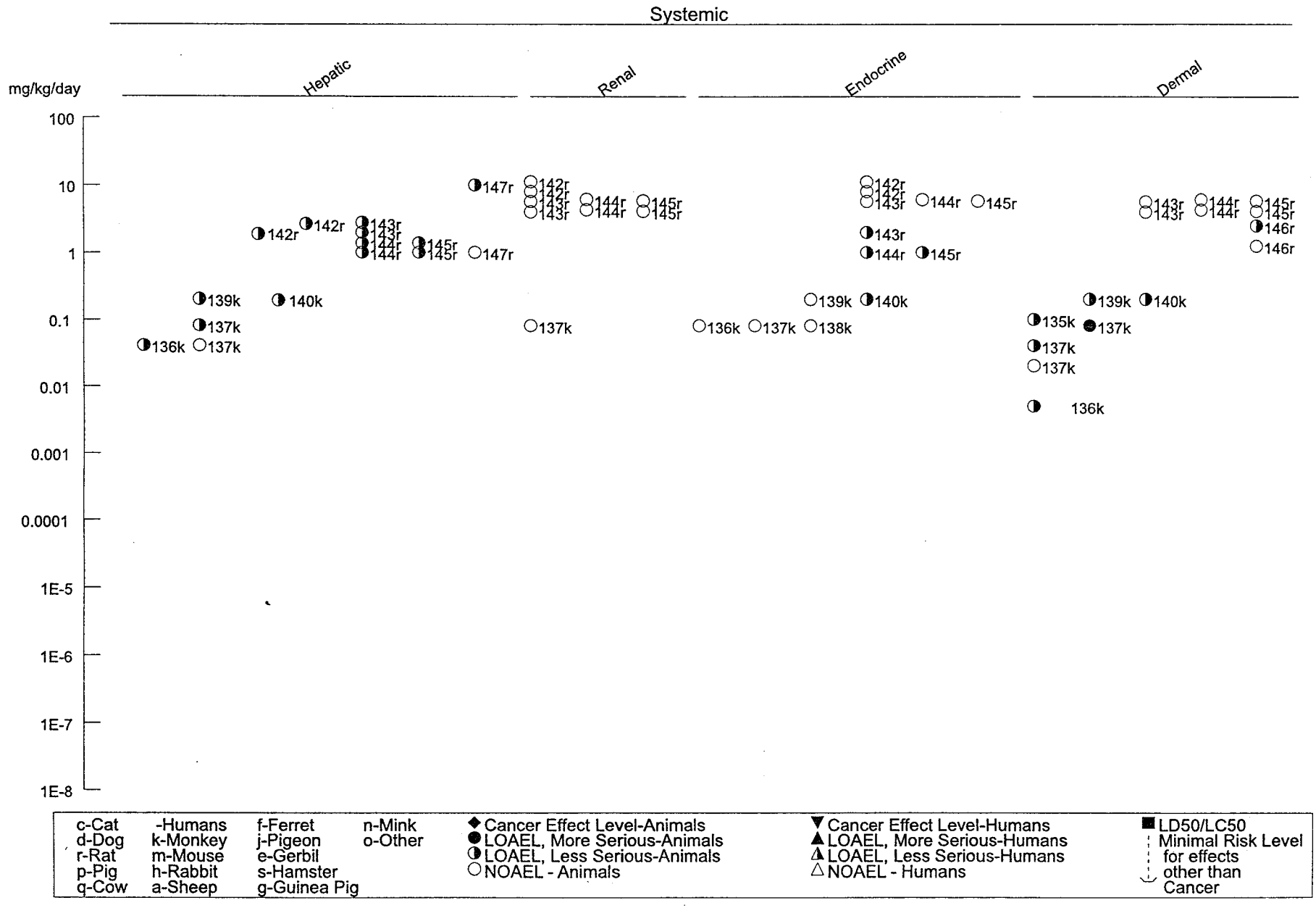


Figure 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (*continued*)

Chronic (≥365 days)

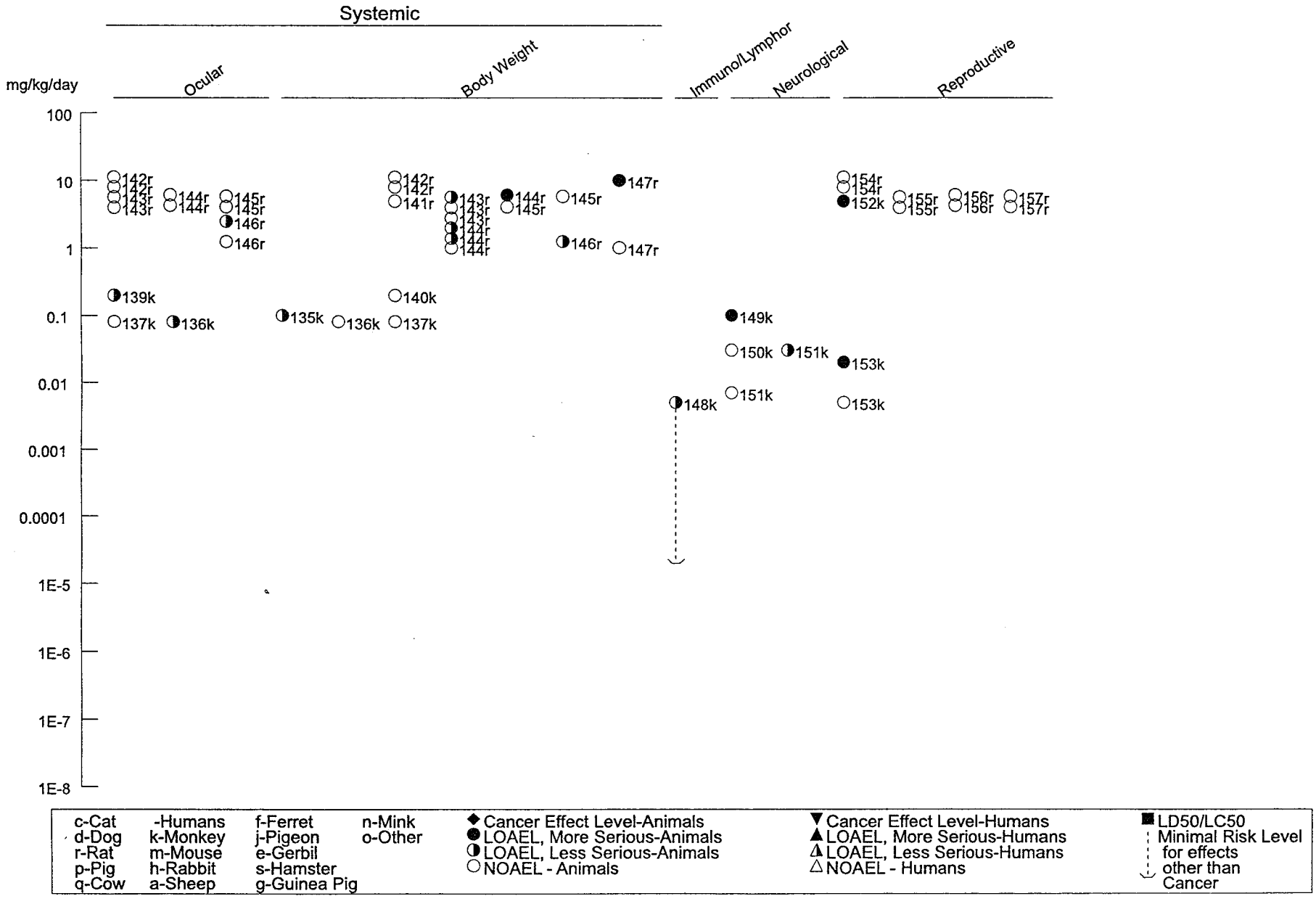
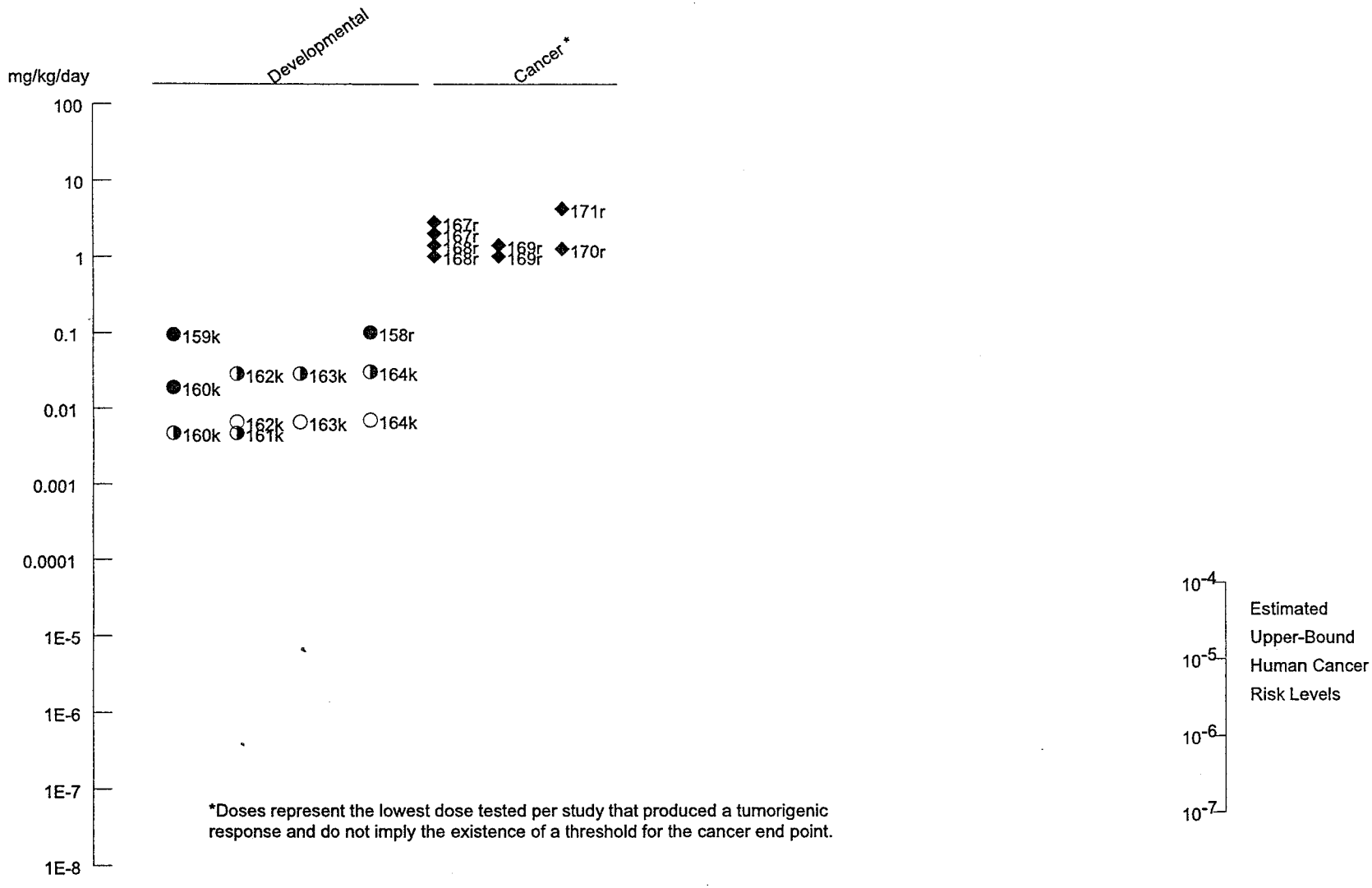


Figure 3-2. Levels of Significant Exposure to PCB Mixtures - Oral (*continued*)

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Table 3-3. Levels of Significant Exposure to PCB Mixtures - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE						
Death						
Mouse (Skh:HR-1)	once				2,273 F (unspecified number of deaths in a group of 3 animals)	Puhvel et al. 1982 1254
INTERMEDIATE EXPOSURE						
Systemic						
Mouse (Skh:HR-1)	6 wk 4 d/wk	Dermal	136 F			Puhvel et al. 1982 1254
Rabbit (New Zealand)	38 d 5 d/wk	Hemato	42.1 F			Vos and Beems 1971 1260
		Hepatic		42.1 F (centrilobular degeneration, focal necrosis, porphyria)		
		Renal		42.1 F (tubular degeneration)		
		Dermal		42.1 F (hyperkeratosis, acne)		
		Bd Wt		42.1 F (decreased body weight)		
Rabbit (New Zealand)	28 d 5 d/wk	Hepatic		44.4 F (hepatomegaly, centrilobular degeneration, focal necrosis, porphyria, increased SGPT and SGOT)		Vos and Notenboom-Ram 1972 1260
		Renal	44.4 F			
		Dermal		44.4 F (hyperkeratosis, acne)		
		Bd Wt		44.4 F (34% decrease in body weight gain)		

Table 3-3. Levels of Significant Exposure to PCB Miixtures - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Immunological/Lymphoreticular						
Rabbit (New Zealand)	38 d 5 d/wk				42.1 F (thymic atrophy)	Vos and Beems 1971 1260
Rabbit (New Zealand)	28 d 5 d/wk				44.4 F (thymic atrophy)	Vos and Notenboom-Ram 1972 1260

Bd Wt = body weight; d = day(s); F = female; Hemato = hematological; LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; wk = week(s); 1242 = Aroclor 1242; 1254 = Aroclor 1254; 1260 = Aroclor 1260

3.2 DISCUSSION OF HEALTH EFFECTS

3.2.1 Death

3.2.1.1 Human Studies

No studies were located regarding deaths in humans from acute exposure by any route. Some studies of longer-term occupational exposures found increased mortality from cardiovascular disease and cancer, as discussed in Sections 3.2.2.2.1 and 3.2.8.2, respectively.

3.2.1.2 Animal Studies

Inhalation Exposure. Intermittent exposure to near-saturation vapor concentrations of heated Aroclor 1242 (8.6 mg/m^3) over 24 days was not lethal in rats, mice, rabbits, or guinea pigs, and no signs of intoxication were reported (Treon et al. 1956). Pneumonia, apparently unrelated to PCB exposure, caused death in some of the test and control animals except those exposed to 8.6 mg/m^3 Aroclor 1242. The vapor concentrations are unknown, as the technique used to estimate them has since been shown to be invalid; possible CDF contamination was not reported because CDFs had not then been discovered. Similar exposures to lower concentrations of heated Aroclors 1242 and 1254 were also found not to produce lethality in these species. No data were located regarding lethality or decreased longevity of animals due to acute or chronic inhalation of PCBs.

Oral Exposure. There are no marked differences in acute LD_{50} values of Aroclor PCB mixtures for observation periods of <30 days. Single-dose LD_{50} values of 4,250 mg/kg for Aroclor 1242 (Bruckner et al. 1973), 1,010 to 1,295 mg/kg for Aroclor 1254 (Garthoff et al. 1981; Linder et al. 1974), and 1,315 mg/kg for Aroclor 1260 (Linder et al. 1974) have been reported in rats. In minks, single-dose LD_{50} values ranged between 750 and 1,000 mg/kg for Aroclor 1221, and were >3,000 mg/kg for Aroclor 1242 and 4,000 mg/kg for Aroclor 1254 (Aulerich and Ringer 1977). In addition to differences in PCB congener composition, the variation in LD_{50} values may be related to factors such as animal strain, age, sex, or formulation purity. There is evidence, for example, that immature rats (3–4 weeks old) are more susceptible than adults (Grant and Phillips 1974; Linder et al. 1974). Causes of death from acute exposure are unclear, but principal signs of toxicity in rats included diarrhea and respiratory depression, and dehydration may be a principal contributing factor (Bruckner et al. 1973). Single-dose oral lethality data for species other than rats and minks were not located.

Three of five mice fed Aroclor 1254 in the diet at an estimated dose of 130 mg/kg/day for 14 days died of unspecified causes by day 15 (Sanders et al. 1974). At the highest Aroclor 1254 dose of 520 mg/kg/day, 5 of 5 mice died within 7 days, but none of the 5 mice treated with 2.5 mg/kg/day died.

Estimated dietary doses of 4 mg/kg/day Aroclor 1248 for 2–3 months (Allen 1975; Allen and Norback 1976) and 0.12–4 mg/kg/day Aroclor 1242 for 92–245 days were lethal for monkeys (Becker et al. 1979). Survival effects were not clearly related to dose in the Becker et al. (1979) study, but this could be due to the small numbers tested (one per dose), which is not unusual in studies of nonhuman primates. Tryphonas et al. (1984) dosed Cynomolgus monkeys (*Macaca fasicicularis*) with Aroclors 1248 and 1254 at 2 and 5 mg/kg/day for 3 days/week for 4 weeks. Aroclor 1248 was more toxic than Aroclor 1254. Minks and monkeys appear to have similar susceptibility to lethal effects of intermediate-duration oral PCB exposure (Aulerich and Ringer 1977; Aulerich et al. 1986; Bleavins et al. 1980; Hornshaw et al. 1986; Ringer et al. 1981). LD_{50} values of 7.1–7.3 and 1 mg/kg/day were determined for minks fed Aroclor 1254 for 28 days (Aulerich et al. 1986; Hornshaw et al. 1986) and 9 months (Ringer et al. 1981), respectively. Death occurred in 33% of the minks fed 2.8 mg/kg/day Aroclor 1254 for 4 months (Aulerich and Ringer 1977). The average time to death in minks fed 1.9 mg/kg/day Aroclor 1242 ranged from 156 to 171 days, with . 67% mortality occurring by 247 days (Bleavins et al. 1980). Death in minks was generally due to visceral hemorrhagic lesions. Female minks are more sensitive than males. Intermediate-duration gavage and feed studies in rats and mice reported that much higher doses of Aroclor 1254 or 1260 caused death (Garthoff et al. 1981; Kimbrough et al. 1972; Koller 1977). Although this may be due to species differences in susceptibility, the shorter and intermittent duration of exposure (2.5 weeks, 2 days/week) and mode of administration (gavage) in rats may account for some of the apparent differences.

Decreased survival occurred in male rats fed diets containing estimated doses $1.25 mg/kg/day Aroclor 1254 for 104–105 weeks (NCI 1978). A dose of 2.5 mg/kg/day induced a 34% decrease in survival. The cause of death was not specified. There was no effect on survival in similarly treated female rats, and a NOAEL for mortality was not identified. There was no attempt to identify or quantitate impurities in the Aroclor 1254 test compound. Decreased survival is not a universal finding in chronic PCB studies, as survival was unchanged or lifespan was extended in rats treated with estimated doses of 3.45–5 mg/kg/day 60% chlorine PCB mixtures (Aroclor 1260 and Clophen A60) via diet (Norback and Weltman 1985; Schaeffer et al. 1984).

Dermal Exposure. A single topical dose of 2,273 mg/kg Aroclor 1254 was fatal to hairless mice within 24 hours (Puhvel et al. 1982). It was not specified whether all three treated mice died or whether the Aroclor was administered in pure acetone or in acetone-mineral oil emulsion. Median lethal doses for single dermal applications of PCBs to rabbits were between 794 and 1,269 mg/kg for Aroclors 1242 and 1248, between 1,260 and 3,169 mg/kg for Aroclors 1221 and 1262, and between 1,260 and 2,000 mg/kg for Aroclors 1232 and 1260 (Fishbein 1974; Nelson et al. 1972). These PCBs were applied undiluted except for Aroclors 1260 and 1262, which were administered in corn oil. Other details regarding the exposure protocol were not provided. Cause of death was not reported, and there was no clear trend of toxicity with degree of chlorination. Lethality data for other species or durations of exposure were not located. The lethal dose from the Puhvel et al. (1982) study is recorded in Table 3-3.

3.2.2 Systemic Effects

3.2.2.1 Respiratory

3.2.2.1.1 Human Studies

There are limited data on potential respiratory effects of PCB exposure in humans. Cross-sectional studies provide suggestive evidence for an association. Upper respiratory tract or eye irritation (48%), cough (14%), and tightness of the chest (10%) were noted among 326 capacitor workers exposed to 0.007–11 mg/m^3 mean air concentrations of various Aroclors for >5 years (Fischbein et al. 1979; Warshaw et al. 1979). The significance of these effects is unknown due to lack of a control group; however, the prevalence of upper respiratory tract or eye irritation (48%) raises concern that they are exposure-related. Other limitations of this study include discrepancies between the reports of Fischbein et al. (1979) and Warshaw et al. (1979), poor definition of the cohort, and failure to distinguish between past and present symptoms. Additionally, capacitor manufacturing plants typically used large amounts of volatile degreasing agents that may have contributed to pulmonary symptom complaints. Chest pain while walking occurred more frequently (16%) in a group of 55 male transformer workers exposed to Aroclor/trichlorobenzene mixtures (Askarels) than in age-matched workers never occupationally exposed to PCBs (Emmett et al. 1988a). The workers were employed for a mean duration of 3.75 years, and the range of PCB personal exposures (primarily Aroclor 1260) measured in the breathing zone was 0.00001–0.012 mg/m^3. CDF contamination ranged from 13 to 116 ppb by weight. The chest pain symptom was not investigated further and was not attributed to a specific cause. A correlation between coughing on the job or soon after work and PCB blood levels in electrical capacitor manufacturing

workers has been reported (Smith et al. 1982). These workers were exposed to various Aroclors and Askarels, in PCB concentrations ranging from 0.003 to 0.08 mg/m^3 (duration of exposure was not reported).

In addition to these reported respiratory tract symptoms, changes in lung function were observed in the PCB workers discussed above. These include a significant decrease in 1-second forced expiratory volume (FEV_1) in the transformer workers (Emmett et al. 1988b); this is the same cohort evaluated by Emmett et al. (1988a). However, when adjusted for smoking habits, FEV was not statistically significant. Fourteen percent of 243 workers examined in the Warshaw et al. (1979) study showed reduced forced vital capacity (FVC) as compared to standard values. Decreased FVC was noted in 8% of the nonsmokers (12.5% males, 4.3% females) and in 17% of the current and former smokers (16% males, 18.7% females). Of all workers with reduced FVC, 80% demonstrated a restrictive pattern of impairment (increased FEV_1/FVC) without radiologic changes. Similar results were initially found in another spirometry study of 179 workers from the same plant population as that studied by Warshaw et al. (1979) (Lawton et al. 1986). The 1976 findings were not confirmed by followup evaluations performed in 1979 and 1983 after no further PCB exposure, and were considered to be artifactual due to deficient pulmonary function testing in 1976 and lack of radiologic changes to account for the restrictive impairment observed (Lawton et al. 1986). The workers had a history of clinically recognized respiratory illness and/or symptomatology, and obstructive impairment (increased FVC, decreased FEV_1/FVC) was found in about 15% of the workers in the initial and followup evaluations (1976 and 1979), but these effects could not be attributed solely to PCB exposure. The occurrence of self-reported respiratory effects was not elevated among residents who lived within 0.5 mile of three PCB-contaminated waste sites (Stehr-Green et al. 1986a).

Potential respiratory effects have also been reported in *Yusho* and *Yu-Cheng* patients. More frequent or severe respiratory infections (Kuratsune 1989; Rogan 1989) and chronic bronchitis accompanied by persistent cough and sputum production (Nakanishi et al. 1985; Shigematsu et al. 1971, 1977) have been reported.

3.2.2.1.2 Animal Studies

No studies were located regarding respiratory effects in animals after inhalation exposure to PCBs. There were no histological alterations in the lungs of rats administered a single 4,000 mg/kg dose of Aroclor 1242 by gavage and evaluated 24 hours posttreatment or in rats treated with 100 mg/kg/day Aroclor 1242 by gavage every other day for 3 weeks (Bruckner et al. 1973). Mice fed a diet that provided .22 mg Aroclor/kg/day for 6 weeks had no changes in lung weight or histology (Loose et al. 1978a, 1978b). Lung inflammation was observed in rats that died following dietary exposure to Phenoclor DP6 at .25 mg/kg/day for 8 days or .50 mg/kg/day for 6 days (Narbonne et al. 1978). Other respiratory end points were not examined in these studies. No histopathologic changes were observed in the trachea or lungs of male or female rats that were fed Aroclor 1016, 1242, 1254, or 1260 for 24 months at intake levels of 8.0–11.2, 4.0–5.7, 4.3–6.1, or 4.1–5.8 mg/kg/day, respectively (Mayes et al. 1998). Rhesus monkeys receiving daily doses of 0.005, 0.020, 0.040, or 0.080 mg/kg/day Aroclor 1254 for 72 months showed no effects on lung tissue (Arnold et al. 1997).

Intermediate-duration dietary exposure to single congeners did not result in histological damage in the lungs of rats fed diets providing #4.1 mg/kg/day of PCB 153 (Chu et al. 1996a), #4.2 mg/kg/day of PCB 128 (Lecavalier et al. 1997), #7.4 mg/kg/day of PCB 126 (Chu et al. 1994), #4.0 mg/kg/day of PCB 105 (Chu et al. 1998b), #3.7 mg/kg/day of PCB 28 (Chu et al. 1996b), #0.77 mg/kg/day of PCB 77 (Chu et al. 1995), or #0.17 mg/kg/day of PCB 118 (Chu et al. 1995).

The highest NOAEL values and all reliable LOAEL values for respiratory effects for each study are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Cardiovascular

3.2.2.2.1 Human Studies

A number of occupational exposure studies have investigated the possible relationship between PCB exposure and increased risk of cardiovascular disease or altered blood pressure; the inconsistency of the results precludes drawing conclusions from these studies. Mortality from circulatory diseases was significantly increased in the high exposure subgroup of a cohort of 242 male capacitor manufacturing workers with >5 years exposure and >20 years latency (Gustavsson and Hogstedt 1997). The standardized mortality ratio (SMR) in the subgroup was 328 (5 observed/1.52 expected deaths, 95%

confidence interval [CI] 33–61, p value not reported). Kimbrough et al. (1999a) found no significant increases in mortality related to ischemic heart disease, hypertension with heart disease, other diseases of the heart, cerebrovascular disease, or circulatory system (arteries, veins, pulmonary circulation) in a study of 7,075 male and female capacitor workers. One of the subgroups (male salaried workers) in this study had a significantly decreased risk of mortality from ischemic heart as indicated by an SMR lower than 100 (44 observed/97.5 expected deaths, SMR=45, 95% CI 107–766, $p<0.01$). Neither of these studies reported adequate quantitative exposure data. The inconsistent results of these studies could be due to differences in exposure levels, durations, and latencies, as well as types of Aroclors and cohort sizes. Additional information on these studies is provided in Section 3.2.8.2.1.

Blood pressure measurements (systolic and diastolic) and electrocardiograms were normal in 194 capacitor plant workers (152 male, 43 female) who were exposed to Aroclors 1254, 1242, and 1016 for an average duration of 17 years (Lawton et al. 1985a). Limited exposure characterization, consisting of monitoring in one area of the plant several months prior to the cardiovascular evaluations, showed a geometric mean PCB concentration of 0.69 mg/m^3. No correlation was found between diastolic blood pressure in capacitor manufacturing workers, when adjusted for age and sex, and serum PCBs (Smith et al. 1982). Abnormal blood pressure measurements or other cardiovascular abnormalities were not reported in other studies of PCB-exposed workers that underwent general physical examinations and medical histories (Baker et al. 1980; Chase et al. 1982; Emmett et al. 1988a; Fischbein et al. 1979).

A 30% increase over the national average incidence of borderline and definite hypertension was observed in Triana, Alabama, residents (Kreiss et al. 1981). Increased systolic and diastolic blood pressure were significantly associated with serum PCB levels. However, the relationship between systolic blood pressure and serum PCB levels disappeared when serum cholesterol and triglyceride levels were factored in, but that between diastolic blood pressure and PCBs remained significant. Consumption of contaminated fish was the only known source of PCB exposure; the actual intake of PCBs was not reported. The population was also exposed to dichlorodiphenyltrichloroethane (DDT) via consumption of fish. Serum DDT and serum PCB levels were highly correlated. Multivariate analysis showed that the PCB-blood pressure association was independent of serum DDT levels, age, sex, and weight. The excess prevalence of hypertension cannot be attributed solely to PCBs (or DDT) with any degree of certainty due to the lack of a matched control group, co-linearity of DDT and PCB serum concentrations, and unknown effects of DDT residues on the metabolism or toxicity of PCBs (Kreiss 1985). Subsequent studies of environmentally exposed populations without exposure to DDT have failed to show an association between hypertension and PCBs. No excess of hypertension was found in 106 people who had lived near

PCB-containing hazardous waste sites for at least 5 years (Stehr-Green et al. 1986a). Mean PCB blood levels were <10 ppb. A significant association between increased diastolic blood pressure and serum PCB levels was observed, but the association failed to achieve statistical significance (p=0.08) when possible confounding effects of both age and smoking were controlled. There was no association between elevated systolic or diastolic blood pressure and serum levels of PCBs in 840 residents of New Bedford, Massachusetts, who were exposed via consumption of contaminated fish (Massachusetts Department of Public Health 1987). However, most subjects in this study had serum PCB levels that were within the typical range of the U.S. population.

3.2.2.2.2 Animal Studies

Data on the cardiovascular toxicity of PCBs in animals are limited to several oral exposure studies conducting histological examinations of the heart and blood vessels. Pericardial edema occurred in four of six monkeys given 12 mg/kg/day Aroclor 1248 in the diet for 3 months (Allen et al. 1973). However, Rhesus monkeys receiving daily doses of 0.005, 0.020, 0.040, or 0.080 mg/kg/day Aroclor 1254 for 25 months showed no effects on cardiac tissue (Arnold et al. 1997). Histological examination of the heart was normal in rats evaluated 24 hours following a single 4,000 mg/kg dose of Aroclor 1242 or 100 mg/kg/day Aroclor 1242 every other day for 3 weeks administered by gavage (Bruckner et al. 1973). No histopathologic changes were observed in the heart of male or female rats that were fed Aroclor 1016, 1242, 1254, or 1260 for 24 months at dose levels of 8.0–11.2, 4.0–5.7, 4.3–6.1, or 4.1–5.8 mg/kg/day, respectively (Mayes et al. 1998). Rhesus monkeys receiving daily doses of 0.005, 0.020, 0.040, or 0.080 mg/kg/day Aroclor 1254 for 25 months showed no effect on cardiac tissue (Arnold et al. 1997).

In a series of 13-week dietary exposure studies using single PCB congeners, no histological alterations in the heart or thoracic aorta were observed in rats fed diets providing #4.1 mg/kg/day of PCB 153 (Chu et al. 1996a), #4.2 mg/kg/day of PCB 128 (Lecavalier et al. 1997), #7.4 mg/kg/day of PCB 126 (thoracic aorta was not examined) (Chu et al. 1994), #4.0 mg/kg/day of PCB 105 (Chu et al. 1998b), #3.7 mg/kg/day of PCB 28 (Chu et al. 1996b), #0.77 mg/kg/day of PCB 77 (Chu et al. 1995), or #0.17 mg/kg/day of PCB 118 (Chu et al. 1995).

Hennig and associates (Hennig et al. 1999; Slim et al. 1999) demonstrated in *in vitro* studies that exposure to PCB 77 disrupts endothelial barrier function in the vascular endothelium; this was not seen for PCB 153.

The highest NOAEL values and all reliable LOAEL values for cardiovascular effects for each study are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.3 Gastrointestinal

3.2.2.3.1 Human Studies

Clinical observations suggestive of gastrointestinal damage have been reported in workers exposed to airborne PCBs and in the *Yusho* cohort. A statistically significant increase in loss of appetite was reported by PCB-exposed transformer workers (20%) as compared to the control group (4%) (Emmett et al. 1988a). PCB levels, primarily Aroclor 1260, ranged from 0.00001 to 0.012 mg/m^3. Gastrointestinal symptoms (anorexia, nausea, vomiting, and abdominal pain) and weight loss were also reported in 18% of capacitor workers exposed to various Aroclors at mean concentrations of 0.007–11 mg/m^3 (Fischbein et al. 1979). The statistical significance of the effects cannot be determined since a control group was not examined. A significant association was found between loss of appetite and increasing PCB blood levels in electrical equipment manufacturing workers who were exposed to various Aroclors and Askarels at PCB concentrations of 0.003–0.08 mg/m^3 (Smith et al. 1982).

Postprandial epigastric distress, epigastric pain with or without a burning sensation, postprandial headache, and intolerance to fatty foods were noted in 50% of workers exhibiting liver effects (Maroni et al. 1981a). The workers (40 males and 40 females) were exposed to concentrations of Pyralene 3010 or Apirolio (Italian PCB formulations) ranging from 0.048 to 0.275 mg/m^3 for an average duration of 12 years. Both of these products were PCB mixtures of unreported purity that had a 42% chlorine content. Some of these workers were also exposed to a PCB mixture containing 54% chlorine. There was no control group in this study, precluding a determination of the significance of the results. Gastrointestinal effects (vomiting and diarrhea) have been observed in *Yusho* patients (Kuratsune 1989). No signs of gastrointestinal effects were reported in community members exposed to PCB-contaminated sludge or in PCB exposed workers (Baker et al. 1980).

3.2.2.3.2 Animal Studies

No histopathologic effects were observed in the stomach or intestines of six rats 24 hours following a single near-lethal dose of 4,000 mg/kg of Aroclor 1242 by gavage (Bruckner et al. 1973). In contrast, hemorrhage into the stomach and foci of ulceration in the stomach and duodenum were observed in rats given a single lethal gavage dose (inadequately quantified) of Aroclor 1254 or 1260 (Kimbrough et al. 1972). Gastric ulcers were observed in two pigs that were treated with 100 mg/kg/day Aroclor 1254 for 11 days (Hansen et al. 1976). The lesions in the pigs were similar in gross and histological appearance to those observed in intermediate-duration studies with monkeys discussed below.

Intermediate-duration dietary administration of Aroclor 1248 (Allen 1975; Allen and Norback 1973, 1976; Allen et al. 1973, 1974a) and Aroclor 1242 (Becker et al. 1979) to monkeys produced gastritis with hypertrophy and hyperplasia of the gastric mucosa. The gastric changes progressed to include mucous-filled cysts in the mucosa penetrating into the submucosa, ulceration of the gastric mucosa resulting from ruptured cysts or erosion, and hemorrhage. Estimated doses of $1.3 mg/kg/day Aroclor 1248 or $0.12 mg/kg/day Aroclor 1242 for 2 months produced these gastric changes in monkeys (Allen 1975; Allen and Norback 1976; Allen et al. 1974a; Becker et al. 1979). Only a minimal number of Aroclor 1242-exposed animals were tested (mostly one monkey per dose group), although the severity of the histopathologic changes was dependent on both exposure length and dose. Gastric ulcers also occurred in minks at similar dietary doses of Aroclor 1016, 1242, or 1254 (Bleavins et al. 1980; Hornshaw et al. 1986), and there is evidence of gastric erosion and necrosis in pigs treated with 9.2 mg/kg/day Aroclor 1242 or 1254 for 91 days (Hansen et al. 1976). In seasoned sows, which are prone to gastric hyperemia, erosions were more severe in two of five sows receiving 9.2 mg/kg/day Aroclor 1242 (Hansen et al. 1975). Gastrointestinal lesions were also observed in Baltic seals, and found to be directly associated with body burdens of PCBs and/or metabolites (Bergman and Olsson 1985; Olsson et al. 1994). There were no histological changes in the stomach or intestines of rats treated with 100 mg/kg/day Aroclor 1242 by gavage 3 times/week for 3 weeks (Bruckner et al. 1973).

Re-examination of the National Cancer Institute (NCI 1978) cancer bioassay showed Aroclor 1254-induced intestinal metaplasia and some adenocarcinoma in the glandular stomach of Fischer 344 rats following chronic dietary treatment (Morgan et al. 1981; Ward 1985) (see Section 3.2.8.3.2). The intestinal metaplasia appeared to be dose-related. Nonproliferative gastric lesions were not observed. No histopathologic changes were observed in the gastrointestinal tract of male or female rats that were fed Aroclor 1016, 1242, 1254, or 1260 for 24 months at dose levels of 8.0–11.2, 4.0–5.7, 4.3–6.1, or

4.1–5.8 mg/kg/day, respectively (Mayes et al. 1998). Moderate mucinous hypertrophic gastropathy was evident in three of four Cynomolgus monkeys treated with 0.2 mg/kg/day Aroclor 1254 in the diet for 12–13 months (Tryphonas et al. 1984, 1986a) and in two of four Rhesus monkeys treated similarly for 28 months (Tryphonas et al. 1986b). No effects on stomach tissue were observed in Rhesus monkeys receiving daily doses of #0.080 mg/kg/day Aroclor 1254 for 72 months (Arnold et al. 1997).

No histological alterations were observed in the organs and tissues of the gastrointestinal tract of rats following a 13-week dietary exposure to #4.1 mg/kg/day of PCB 153 (Chu et al. 1996a), #4.2 mg/kg/day of PCB 128 (Lecavalier et al. 1997), #7.4 mg/kg/day of PCB 126 (Chu et al. 1994), #4.0 mg/kg/day of PCB 105 (Chu et al. 1998b), #3.7 mg/kg/day of PCB 28 (Chu et al. 1996b), #0.77 mg/kg/day of PCB 77 (Chu et al. 1995), or #0.17 mg/kg/day of PCB 118 (Chu et al. 1995).

The highest NOAEL values and all reliable LOAEL values for gastrointestinal effects for each study are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Hematological

3.2.2.4.1 Human Studies

In general, hematological effects have not been observed in humans occupationally exposed to PCBs. Capacitor plant workers (152 males, 43 females) exposed to Aroclors 1254, 1242, and 1016 for an average duration of 17 years showed slightly decreased numbers of polymorphonuclear neutrophil (PMN) white cells and slightly increased lymphocyte, monocyte, and eosinophil counts when compared to normal values (Lawton et al. 1985a). Limited exposure characterization, consisting of monitoring in one area of the plant several months prior to hematological evaluation, showed a geometric mean PCB concentration of 0.69 mg/m^3. Values for other white cells, erythrocytes, hemoglobin, and hematocrit were within normal ranges. Other studies of PCB-exposed workers have reported essentially normal hematology including total and differential white blood cell counts (Chase et al. 1982; Emmett et al. 1988b; Fischbein et al. 1979; Maroni et al. 1981b; Ouw et al. 1976; Smith et al. 1982). Mild normocytic anemia and leukocytosis have been reported in *Yu-Cheng* patients (Rogan 1989).

3.2.2.4.2 Animal Studies

Erythrocyte count, leukocyte count, and hemoglobin level were evaluated in 3–6 rabbits and guinea pigs intermittently exposed to chamber concentrations of 5.4 mg/m^3 Aroclor 1254 or 6.8 mg/m^3 Aroclor 1242 over a period of 120 or 121 days, respectively (Treon et al. 1956). Alterations included increased erythrocytes in the rabbits (Aroclor 1254) and increased hemoglobin in the guinea pigs (both Aroclors); however, although statistically significant, neither change was regarded as physiologically significant.

Packed blood cell volume was increased in male rats given single lethal doses of 4,000 or 6,000 mg/kg Aroclor 1242 by gavage (Bruckner et al. 1973, 1974). Crenated erythrocytes and increased PMNs were observed at 4,000 mg/kg, but not at 6,000 mg/kg. The investigators indicated that the effect on cell volume reflected dehydration rather than a direct hematologic effect.

Anemia has been observed in monkeys treated with Aroclor 1248 or 1254 in intermediate-duration studies (Allen 1975; Allen and Norback 1973, 1976; Allen et al. 1973, 1974a) and chronic-duration studies (Allen 1975; Arnold et al. 1990; Tryphonas et al. 1984, 1986a, 1986b). The anemia was manifested by decreased hemoglobin content, decreased hematocrit, and hypocellularity of erythrocytic and other precursor cells in the bone marrow, occurred at doses of $4 mg/kg/day for 2 months (Allen 1975; Allen and Norback 1976) and $0.2 mg/kg/day for 12–28 months (Arnold et al. 1990; Tryphonas et al. 1986a, 1986b), and may be related to moribund condition of the monkeys. The anemia was not quantified in all studies, but the existing data indicate that it was moderate to severe after intermediate and chronic exposure. Numbers of circulating neutrophils were generally increased and lymphocytes were decreased in these studies. Hematological changes consistent with a picture of anemia have also been observed in monkeys treated with 0.08 mg/kg/day Aroclor 1254 for 37 months; a dose of 0.02 mg/kg/day produced a decrease in mean platelet volume (Arnold et al. 1993b). Rhesus monkeys receiving daily doses of #0.080 mg/kg/day Aroclor 1254 for 72 months, however, showed no effect on hematological parameters (Arnold et al. 1997).

Hematological changes do not appear to be a clear effect of PCB exposure in animals. Small numbers of rats (four per PCB) fed 50 mg/kg/day Aroclor 1248, 1254, or 1262 for 4–6 weeks showed marked neutrophilia and slightly increased hemoglobin and hematocrit (Allen and Abrahamson 1973). No consistent hematologic effects were observed in rats (6 per dose) fed #1.5 mg/kg/day Aroclor 1242 for 2–6 months (Bruckner et al. 1974), in guinea pigs (12 per dose) fed #4 mg/kg/day Aroclor 1260 for 8 weeks (Vos and de Roij 1972), or in rabbits (7 per dose) fed #6.5 mg/kg/day Aroclor 1254 for 8 weeks

(Street and Sharma 1975). There were no treatment-related changes in hemoglobin levels or hematocrit in minks (10 per PCB) fed 0.4 mg/kg/day Aroclor 1016, 1221, 1242, or 1254 for #39 weeks (Aulerich and Ringer 1977). Red blood cell count and hemoglobin concentration were reduced in female rats (50 per group) that were fed Aroclor 1016 or 1260 for 24 months at intake levels $2.7 or $1.4 mg/kg/day, respectively (Mayes et al. 1998). No hematologic effects were observed in female rats that were similarly exposed to #5.7 mg/kg/day Aroclor 1242 or #6.1 mg/kg/day Aroclor 1254, or in male rats exposed to Aroclor 1016, 1242, 1254, or 1260 at intake levels of #8.0, #5.7, #6.1, or #4.1 mg/kg/day, respectively.

Intermediate-duration exposure to single congeners has resulted in hematological effects in rats. Significant decreases in hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, and decreased eosinophils were observed in rats treated with 4.0 mg/kg/day of PCB 105 (Chu et al. 1998b). Decreases in hemoglobin, hematocrit erythrocyte count, mean corpuscular hemoglobin, mean corpuscular volume, and platelets were observed after exposure to 7.4 mg/kg/day of PCB 126 (Chu et al. 1994). In contrast, no hematological effects were observed similarly treated rats exposed to #0.77 mg/kg/day of PCB 77 (Chu et al. 1995), #0.17 mg/kg/day of PCB 118 (Chu et al. 1995), #3.7 mg/kg/day of PCB 28 (Chu et al. 1996b), or #4.2 mg/kg/day of PCB 128 (Lecavalier et al. 1997).

No effects on hemoglobin, hematocrit, or differential leukocyte count were observed in rabbits exposed to 60% chlorine PCBs in isopropanol (Aroclor 1260, Clophen A60, or Phenoclor DP6) applied to the shaved back skin 5 days/week for 38 days at estimated doses of 42 mg/kg/day (Vos and Beems 1971). Total leukocyte count was reduced, but insufficient information was provided to determine whether this effect was adverse, whether it was due to a direct effect on the reticuloendothelial system, or if it was secondary to other toxicity (hepatic and renal damage also occurred). CDFs were found only in the non-Aroclor PCBs (detection limit, 1 ppm).

The highest NOAEL values and all reliable LOAEL values for hematological effects for each study are recorded in Tables 3-1, 3-2, and 3-3, and plotted in Figures 3-1 and 3-2.

3.2.2.5 Musculoskeletal

3.2.2.5.1 Human Studies

There are limited data on the musculoskeletal toxicity of PCBs in humans. Only one report of musculoskeletal effects was located (Fischbein et al. 1979). Joint pain was reported by . 11% of the workers exposed to various Aroclors at mean area concentrations of 0.007–11 mg/m^3. A higher prevalence was noted in female workers (15.2%) than in males (7.7%). Muscle pain was reported by <4% of the males and females. Information on the severity or constancy of the joint and muscle pain was not reported, physiological testing was not performed, and there was failure to distinguish between past and present symptoms. The statistical significance of these symptoms cannot be determined because a control group was not examined. No studies were located regarding musculoskeletal effects in humans after oral exposure to PCBs, although a 10% prevalence of unspecified joint problems was reported among farm families who consumed dairy products and beef that were contaminated with PCBs (Humphrey 1983).

3.2.2.5.2 Animal Studies

Little information exists regarding musculoskeletal effects of PCBs in animals. Changes in femur bone morphology resulting in weaker bones occurred in growing (28-day-old) rats (10 per dose) that were treated with Aroclor 1254 by gavage for 10–15 weeks (Andrews 1989). Effects included increased femur density at $0.1 mg/kg/day; decreased cross-sectional and medullary areas at $10 mg/kg/day; and decreased femur weight, volume, length, and cortical area and strength at 25 mg/kg/day. No definite effects on bone flexibility were observed. Serum and urinary calcium levels were increased, but there were no treatment-related alterations in serum parathyroid hormone concentration

No histopathologic changes were observed in skeletal muscle of male or female rats that were fed Aroclor 1016, 1242, 1254, or 1260 for 24 months at dose levels of 8.0–11.2, 4.0–5.7, 4.3–6.1, or 4.1–5.8 mg/kg/day, respectively (Mayes et al. 1998). Similarly, there were no histological alterations in skeletal muscle of rats exposed to #4.1 mg/kg/day of PCB 153 (Chu et al. 1996a), #4.2 mg/kg/day of PCB 128 (Lecavalier et al. 1997), #4.0 mg/kg/day of PCB 105 (Chu et al. 1998b), #3.7 mg/kg/day of PCB 28 (Chu et al. 1996b), #0.77 mg/kg/day of PCB 77 (Chu et al. 1995), or #0.17 mg/kg/day of PCB 118 (Chu et al. 1995) in the diet for 13 weeks.

The highest NOAEL values and all reliable LOAEL values for musculoskeletal effects for each study are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Hepatic Effects

3.2.2.6.1 Summary

In humans, clinical studies of PCB workers reported associations between increased serum levels of liver-related enzymes, lipids, and cholesterol and serum PCBs. Studies of people exposed to PCBs by ingestion of contaminated fish in Triana, Alabama or contaminated rice oil in the *Yusho* or *Yu-Cheng* incidents have reported increases in serum levels of some liver enzymes characteristic of microsomal enzyme induction or liver damage, but these effects cannot be attributed solely to PCBs due to the mixed chemical nature of the contaminated fish and heated rice oil exposures. Serum cholesterol, but not triglycerides, was increased in consumers of contaminated fish, whereas increased serum triglycerides, but not cholesterol, were associated with *Yusho* and *Yu-Cheng* exposure.

Hepatotoxicity of PCBs is well-documented in animals exposed to commercial mixtures or single congeners for acute, intermediate, or chronic durations by oral and other routes of exposure. PCB-induced liver effects in animals seem to be reversible when mild and include microsomal enzyme induction, liver enlargement, increased serum levels of liver-related enzymes and lipids, altered porphyrin and vitamin A metabolism, and histopathologic alterations that progress to non-neoplastic degenerative lesions (particularly fatty and necrotic changes) and/or tumors with higher doses or longer duration exposures. Intermediate- and chronic-duration oral studies indicate that monkeys are more sensitive than rats to PCB hepatotoxicity.

3.2.2.6.2 Human Studies

3.2.2.6.2.1 Liver Enzymes, Enlargement, and Pathology

Occupational Exposure. Hepatic effects have been investigated in a number of epidemiology studies and clinical surveys of PCB-exposed workers. Increased serum levels of liver-related enzymes, particularly gamma-glutamyl transpeptidase (GTP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), and/or lactate dehydrogenase (LDH), were reported in many of these studies (Chase et al. 1982; Emmett et al. 1988b; Fischbein 1985; Fischbein et al. 1979; Lawton et al.

1985a; Maroni et al. 1981a, 1981b; Ouw et al. 1976). Additionally, increases in levels of these serum enzymes have been correlated with serum PCB levels (Baker et al. 1980; Chase et al. 1982; Emmett et al. 1988b; Fischbein 1985; Fischbein et al. 1979; Lawton et al. 1985a; Smith et al. 1982).

Asymptomatic hepatomegaly and increased serum levels (elevated to slightly above normal range) of GTP, AST, and/or ALT were found in 14 of 80 capacitor manufacturing or repair workers who were exposed to non-Aroclor PCB mixtures with a 42% chlorine content (Italian formulations Pyralene 3010 or Apirolio) for an average of 12 years (Maroni et al. 1981a, 1981b). Two other workers had increased serum enzyme levels without liver enlargement. PCB levels ranged from 48 to 275 $\mu g/m^3$ in the workroom air, 2–28 $\mu g/cm^2$ on the skin surface (palms), and 41–1,319 µg/kg in the blood. The investigators considered the liver enlargement indicative of hepatic microsomal induction. Comparison of the 16 workers with abnormal liver findings and the 64 without abnormal findings showed that those with the abnormalities had statistically significant ($p<0.01$) higher mean concentrations of trichlorobiphenyls, pentachlorobiphenyls, and total PCBs in the blood. Additionally, significant positive correlations were found between the frequency of workers with the abnormal liver findings and increasing levels of blood trichlorobiphenyls ($p<0.001$), pentachlorobiphenyls ($p<0.05$), and total PCBs ($p<0.001$). No matched control group was included in the study, there was no apparent association between severity of hepatomegaly and blood PCB levels, and hepatomegaly was not reported in other studies that included physical examinations conducted even at similar or higher serum PCB levels (e.g., Fischbein et al. 1979; Smith et al. 1982).

Serum enzyme (AST, ALT, LDH, AP) and bilirubin levels were within normal limits in 16 workers exposed to PCBs (type not reported) primarily via dermal contact with used transformer oil containing . 600,000 ppm PCBs or secondary contact with contaminated clothes or shoes (Brandt-Rauf and Niman 1988). No correlation between serum triglyceride levels and serum PCB levels was found. Physical examinations showed no dermal or other abnormalities consistent with PCB exposure, but it is not specifically mentioned if the examinations looked for liver enlargement. Serum PCB concentrations in the study group were low (generally <10 ppb) in comparison to other occupational studies.

Clearance of antipyrine, a known substrate for microsomal hepatic enzymes, was used to test liver function in two studies of PCB-exposed workers (Alvares et al. 1977; Emmett et al. 1988b). A significantly lower mean half-life of antipyrine clearance from blood was found in five workers exposed for an average of 9 years to various Aroclors, including Aroclor 1260, compared to five control subjects matched for age, sex, and smoking/drinking habits (Alvares et al. 1977). The antipyrine clearance half-

lives were 10.8 and 15.6 hours in the exposed and control subjects ($p<0.005$), respectively, suggesting that exposure induced hepatic microsomal enzymes. The exposed workers were a subgroup of the population studied by Fischbein et al. (1979) who were exposed to mean PCB concentrations ranging from 0.007 to 11 mg/m^3. The second study (Emmett et al. 1988b) found no difference in antipyrine plasma half-life in transformer maintenance workers primarily exposed to lower concentrations of Aroclor 1260 (#0.012 mg/m^3) for an average of 3.75 years compared with controls matched for age, race, and marital status, but not for current smoking and drinking habits (Emmett et al. 1988b). The reason for the different antipyrine liver function test findings in these studies is not clear, but is most likely due to levels and durations of exposure since serum PCB levels were higher (up to 125 ppb) in the responding group (Fischbein et al. 1979) and (<15 ppb) in the Emmett et al. (1988b) group. The difference might also be related to smoking and/or drinking habits.

Contaminated Fish Consumption. Limited information is available on hepatic end points in populations who consumed fish contaminated with PCBs and other chemicals in Triana, Alabama (Kreiss et al. 1981) and the Baltic Sea area (Svensson et al. 1994). No data were located on liver effects in fisheaters from the Great Lakes/St. Lawrence River basin.

Serum γ-glutamyl transpeptidase (GGT) and cholesterol (Section 3.2.2.6.2.2), but not serum ALT or bilirubin, were positively correlated with serum PCB levels in 458 residents of Triana, Alabama (Kreiss et al. 1981). These associations were independent of factors such as age and alcohol and fish consumption, although the natural partitioning of PCBs into serum lipids could contribute to the correlation. Consumption of contaminated fish was the only known source of PCB exposure. The mean serum concentration of PCBs (analyzed as Aroclor 1260) was 17.2 ppb. Levels of DDT were also increased in residents and fish, and there was a strong positive correlation between serum concentrations of DDT and PCB. Serum DDT levels did contribute to the variance in serum GGT and other effects, but this does not preclude the possibility of an interaction between PCB and DDT.

A comparison of 23 Swedish males with a high consumption of Baltic Sea fish and 20 men with virtually no fish consumption showed no statistically significant differences in serum levels of AST, ALT, GGT, AP, or bilirubin (Svensson et al. 1994). The fisheaters had elevated blood levels of PCBs and other organochlorines, as well as increased erythrocyte levels of methylmercury.

Yusho and Yu-Cheng Exposures. Clinical alterations that have been observed in people exposed during the *Yusho* and *Yu-Cheng* PCB accidental ingestion incidents include increases in serum liver-related

enzymes and triglycerides and urinary uroporphyrins (Kuratsune 1989; Rogan 1989). Elevations in serum AST and ALT are generally consistent findings in *Yu-Cheng* patients (Rogan 1989), although few abnormalities in AST and ALT and other basic liver function indices have been associated with *Yusho* exposure (Kuratsune 1989; Masuda 1994). Results of non-routine serum tests (e.g., accelerated erythrocyte sedimentation rate, high titer in thymol turbidity, increased M fraction of lactate dehydrogenase, and increased alkaline phosphatase and ribonuclease levels) suggested liver damage in some *Yusho* patients, particularly severe cases (Masuda 1994).

The predominant morphological finding in the liver of *Yusho* patients appears to be ultrastructural changes suggestive of microsomal enzyme induction, particularly alterations in the endoplasmic reticulum and pleomorphic and enlarged mitochondria (Kuratsune 1989; Masuda 1994). Mortality from cirrhosis of the liver and from liver diseases excluding cirrhosis was increased in both sexes in a cohort of 1,940 *Yu-Cheng* victims (>95% of all registered cases) followed for 12 years after exposure (Hsieh et al. 1996). SMRs for cirrhosis and other liver diseases were 2.79 (95% CI 1.39–5.00) and 5.40 (CI 1.47–13.82), respectively, compared to the Taiwan national populations; rates were similarly increased compared to local populations. Mortality from all liver diseases during the first 3 years after exposure (SMR=10.76, 5.37–19.26) was more than 8 times higher than in the subsequent 9 years.

3.2.2.6.2.2 Serum Lipids, Triglycerides, and Cholesterol

Occupational Exposure. Levels of liver-regulated serum lipids, particularly triglycerides and cholesterol, have been studied in PCB-exposed workers. Serum triglycerides, total cholesterol, ALT, and albumin/globulin ratio were increased in capacitor plant workers with a mean length of employment of 17 years (Lawton et al. 1985a). These workers were exposed to various Aroclor mixtures at a mean concentration of 0.69 mg/m^3 (range, 0.2–2.0), based on monitoring performed in only one area of the plant several months prior to clinical evaluation. In other studies, no changes in serum cholesterol, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), and/or serum albumin levels were found in workers exposed primarily to Aroclor 1260 (#0.012 mg/m^3) for a mean of 3.75 years (Emmett et al. 1988b) or to an unspecified Aroclor mixture (PCB air concentration not reported) in transformer fluids for 4–17 years (Chase et al. 1982).

Significant positive correlations between serum triglyceride or cholesterol levels and serum PCBs in PCB-exposed workers have been reported (Baker et al. 1980; Chase et al. 1982; Emmett 1985; Emmett et al. 1988b; Lawton et al. 1985a; Smith et al. 1982), but not all studies were adjusted for all major

confounding variables. For example, when adjusted for all confounders, Emmett et al. (1988b) found no correlation between serum lipids and serum PCBs. Evidence from this and other studies indicates that correlations between serum lipids and PCBs may be due to the partitioning of PCBs between adipose tissue and lipids in the blood (Brown and Lawton 1984; Emmett 1985; Emmett et al. 1988b; Lawton et al. 1985a). Data from the *Yusho* and *Yu-Cheng* incidents (see subsection below) and animal studies (see Section 3.2.2.6.3.2), however, indicate that elevated serum lipids are an effect of oral exposure to high levels of PCBs.

Contaminated Fish Consumption. Serum cholesterol, serum GGT, and blood pressure, but not serum HDL cholesterol or triglycerides, were positively correlated with serum PCB levels in 458 residents of Triana, Alabama (Kreiss et al. 1981). These associations were independent of age, sex, fish consumption, body mass index, and alcohol consumption. Consumption of contaminated fish was the only known source of PCB exposure, but PCB intake was not estimated. DDT was also increased in the serum of the people and in the fish, and serum DDT and serum PCB levels were highly correlated. Serum DDT levels did not contribute to the variance in serum cholesterol, serum GGT, or blood pressure.

General Population Exposures. Serum cholesterol and triglycerides were increased in individuals with elevated serum PCB levels who had resided near waste sites for 5 years (Steer-Green et al. 1986a, 1986b). The increases were not substantially greater than normal, however, and neither levels of cholesterol nor triglycerides correlated with serum PCB concentrations. Other findings included a significant positive correlation of total bilirubin with serum PCB levels, and significant negative correlations of serum albumin with serum PCBs and of AST with serum lipid fraction-adjusted PCB levels. This study used pooled data from combined residential and occupational exposure. Similar results were reported by Steinberg et al. (1986) using uncorrected data. In addition, a positive correlation between the activities of ß-glucuronidase and 5ℕ-nucleotidase and total serum PCBs was observed in individuals who lived or worked near an electrical equipment manufacturing plant. Similar positive correlations were also found with serum dichlorodiphenyl dichloroethene (DDE) (a metabolite of DDT); no correlations were observed when potential confounding factors (e.g., age, cholesterol) were removed.

Yusho and Yu-Cheng Exposures. Markedly elevated serum triglyceride levels with unchanged total serum cholesterol was a laboratory finding characteristic of *Yusho* and *Yu-Cheng* exposures (Oxymora et al. 1979; Masuda et al. 1994; Uzawa et al. 1969). The elevated triglycerides generally persisted for several years following exposure and subsequently declined to normal levels.

3.2.2.6.2.3 Porphyria

Occupational Exposure. Sixty-seven PCB-exposed workers with a mean employment length of 12 years (range, 2–32 years) exhibited increased urinary excretion of total porphyrins and porphyrin homologues (coproporphyrin, pentaporphyrin, hexaporphyrin, heptaporphyrin, and uroporphyrin) compared to a control population of unexposed electrical workers (Colombi et al. 1982). No shift in the relative urinary levels of porphyrin homologues was observed between the exposed and control groups. The exposed workers were exposed to Aroclor 1254 (unquantitated) for up to 17 years and, subsequently, to 0.048–0.275 mg/m^3 Pyralene 3010 (42% chlorine content) for an unspecified duration; dermal exposure to both PCB mixtures could not be ruled out. In another study, urinary coproporphyrin, uroporphyrin, and porphobilinogen did not correlate with serum PCB levels in workers exposed to various Aroclors and Askarels in concentrations ranging from 0.003 to 0.08 mg/m^3 for >13 years (Smith et al. 1982).

Urinary porphyrin excretion and serum GGT activity were significantly increased in 51 workers who were exposed for a mean duration of 10 years, and 28 of 51 subjects had elevated concentrations of PCBs in the blood (Maroni et al. 1984). As discussed by James et al. (1993), average urinary excretion of porphyrins was almost twice as high as unexposed control group values, but no correlation was found between porphyrin excretion and blood PCB levels.

Yusho and Yu-Cheng Exposures. Type B hepatic porphyria (i.e., a uroporphyrin/coproporphyrin ratio greater than 1) is a consistent finding in *Yu-Cheng* patients, including children born to exposed mothers (Chang et al. 1980; Gladen et al. 1988; Hsu et al. 1994; Lu et al. 1980). Abnormal urinary porphyrin levels have rarely been associated with *Yusho* exposure (Masuda et al. 1994).

3.2.2.6.2.4 Evaluation of Human Studies

There is no clear indication that environmental exposure to PCBs has caused adverse liver effects in humans. Evidence for liver effects of PCBs in humans has been sought in numerous studies of exposed workers. Hepatic end points in these studies are essentially limited to serum enzymes (e.g., AST, ALT, and GGT) and other biochemical indices (e.g., bilirubin, serum lipids, and cholesterol) that are routinely-examined in clinical assays. Antipyrine elimination was evaluated in two studies of PCB workers (Alvares et al. 1977; Emmett et al. 1988b). Results suggest a threshold of 100 ppb in serum for phenobarbital-type induction in humans (Brown 1994). A positive correlation between the frequency of workers with hepatomegaly and elevated serum enzyme values and increasing levels of PCBs in the blood

was reported in one study (Maroni et al. 1981a, 1981b), but there was no apparent relationship between severity of the effect and PCB levels, and no matched control group was included in the study. Studies of people exposed to PCBs by ingestion of contaminated fish (Kreiss et al. 1981) or contaminated rice oil in the *Yusho* or *Yu-Cheng* incidents (Kuratsune 1989; Masuda 1994; Rogan 1989) have shown increases in serum levels of some liver enzymes and other hepatic indices that are indicative of microsomal enzyme induction or liver damage. Ultrastructural changes indicative of microsomal enzyme induction are predominant hepatic morphological findings in *Yusho* patients. Due to the mixed chemical nature of the fish and rice oil exposures, the results cannot be attributed solely to PCBs.

Increased levels of serum triglycerides and cholesterol have not been reported consistently in workers with long-term occupational exposure to PCBs. As discussed by James et al. (1993), the variable results can be explained, at least partially, by failure of the studies to control for variables known to affect serum lipid levels, particularly age, alcohol consumption, and medical history. Because tissue concentrations are generally considered to be a better measure of body burdens and dose received than serum lipid levels, this may explain the difficulty in showing a correlation between serum lipid levels and PCB dose. Additionally, both Emmett et al. (1988b) and Lawton et al. (1985a) showed that associations with serum lipid levels and serum PCB levels can be explained by the partitioning behavior of PCBs, suggesting that serum lipid levels may affect serum PCB levels rather than PCB exposure affecting serum lipid levels. However, as described in the following section, animal data indicate that exposure to PCBs can indeed increase serum lipid levels. A limited amount of information is available on serum lipid effects of PCBs in nonoccupational populations. Serum cholesterol, but not triglycerides, was increased in Triana, Alabama, consumers of contaminated fish (Kreiss et al. 1981), and increases in serum triglycerides, but not cholesterol, were associated with Yusho and Yu-Cheng exposure (Masuda et al. 1994; Oxymora et al. 1979; Uzawa et al. 1969).

Increased urinary excretion of porphyrins appears to be associated with occupational exposure to PCBs (Colombi et al. 1982; Maroni et al. 1984; Smith et al. 1982). Hepatic porphyria was commonly observed in people exposed during the *Yu-Cheng* PCB incident, although it was not a usual finding in *Yusho* cases (Chang et al. 1980; Gladen et al. 1988; Hsu et al. 1994; Lu et al. 1980; Masuda et al. 1994).

3.2.2.6.3 Animal Studies

The highest NOAEL values and all reliable LOAEL values for hepatic effects for each study are recorded in Tables 3-1, 3-2, and 3-3, and plotted in Figures 3-1 and 3-2.

3.2.2.6.3.1 Liver Enzymes, Enlargement, and Pathology

Inhalation Exposure

No histological changes occurred in the liver of adolescent male rats that were whole-body exposed to 0 or 900 ng/m^3 Aroclor 1242 vapor 23 hours/day for 30 days (Casey et al. 1999). The generation of the vapor-phase test atmosphere was based entirely on the evaporation of a liquid PCB mixture using a system that did not create aerosol droplets, and the concentration and congener composition of the test atmosphere was well characterized. Limitations of this study include only one exposure level and liver end point and a relatively small number of animals (8/group); however, uptake of PCBs in the liver was confirmed by tissue analysis, and the exposure was sufficient to induce effects in other tissues, including the thyroid, which is known to be particularly sensitive to PCBs.

Histopathologic lesions were found in the livers of rats, mice, rabbits, and guinea pigs that were intermittently exposed to chamber concentrations of 1.5 mg/m^3 Aroclor 1254 for 7 hours/day for 150 days over a total of 213 days (Treon et al. 1956). Alterations varied in severity depending upon species, ranging from cytoplasmic vacuolation in guinea pigs to fatty metamorphosis and other degenerative lesions in rats. Similar exposures of rats, mice, rabbits, or guinea pigs to Aroclor 1242 for 7 hours/day at 1.9 mg/m^3 for 150 of 214 days, or 8.6 mg/m^3 for 17 of 24 days, did not produce histopathology in the liver or other viscera. Relative liver weight, measured in rats, guinea pigs, and rabbits exposed for 7 hours/day to 6.8 mg/m^3 Aroclor 1242 for 82 of 120 days or 5.4 mg/m^3 Aroclor 1254 for 83 of 121 days was increased only in the rats exposed to Aroclor 1254; liver histology was not evaluated in these studies. None of the exposure scenarios produced treatment-related gross liver pathology in any of the species. It was necessary to vaporize the Aroclors by heating to 55–138 EC to attain the concentrations used in the study, although these temperatures are too low to cause formation of CDFs (Morita et al. 1978).

No information was located on hepatotoxicity in animals following acute- or chronic-duration inhalation exposure to PCBs.

Oral Exposure

Commercial PCB Mixtures. Relatively little information is available on hepatic effects of acute-duration oral exposure to PCBs. Liver microsomal enzyme activity (aminopyrine N-demethylation and acetanilide hydroxylation) was increased in rats exposed to 0.5 mg/kg/day (lowest tested level) Aroclor 1254 for durations as short as 1–3 days (Bruckner et al. 1977); no other hepatic end points were evaluated in this study. Relative liver weight and serum total cholesterol were increased in rats that were fed estimated doses of $1 mg/kg/day Aroclor 1254 for 4 days, but not 0.5 mg/kg/day (Carter 1984, 1985); histology was not evaluated. Acute-duration studies evaluating hepatic effects of PCBs other than microsomal enzyme induction at doses lower than those in the Carter (1984, 1985) studies were not located. Effects in rats exposed to higher doses of PCBs in acute-duration studies included increased liver weight, decreased liver glucose 6-phosphatase, and/or decreased serum cholesterol at $1.9 mg/kg/day Aroclor 1254 (Carter and Koo 1984; Price et al. 1988) and 50 mg/kg/day Aroclor 1248 (Kato and Yoshida 1980), as well as degenerative hepatic histopathological changes at PCB doses $50 mg/kg/day as discussed below. Additional information on PCB-induced hypercholesterolemia is included in Section 3.2.2.6.3.2.

The lowest reported hepatic effect levels in intermediate-duration oral studies are NOAELs for microsomal enzyme induction in rats (Bruckner et al. 1974, 1977; Litterst et al. 1972). Liver microsomal nitroreductase and demethylase were induced in rats that were fed $0.03 mg/kg/day (lowest tested dose) Aroclor 1242, 1248, 1254, or 1260 for 4 weeks (Litterst et al. 1972). All of these PCB mixtures also caused increased relative liver weight at $2.5 mg/kg/day and increased liver triglycerides at $25 mg/kg/day; however, histology was not evaluated. The effects were generally dose-related among the mixtures and the maximum increase in liver triglycerides was caused by Aroclor 1248. No histological changes were found in the liver of adolescent rats exposed to dietary doses of 0 or 0.033 mg/kg/day Aroclor 1242 for 30 days (Casey et al. 1999). Limitations of this study include a relatively small number of animals (8/group) and the lack of more than one dose level and hepatic end point, although tissue congener analyses confirmed uptake of PCBs in the liver. Hepatic microsomal enzymes, liver weight, and lipid deposition in the liver were increased in rats fed $0.25 mg/kg/day Aroclor 1242 for $2 months; no other hepatic histopathologic changes were observed, and serum levels of AST and ALT were not increased (Bruckner et al. 1974). Dietary ingestion of $0.25 mg/kg/day Aroclor 1254 for $35 days similarly induced hepatic microsomal enzymes in rats, but other liver effects (increased liver weight and triglyceride content; histology was not evaluated) only occurred at a higher dose of 1.25 mg/kg/day (Bruckner et al. 1977). Another study with Aroclor 1254 found no significant

change in liver weight in rats fed up to 2.5 mg/kg/day for 5 months (Byrne et al. 1988); no other hepatic end points were evaluated.

Increased relative liver weight and hepatocellular hypertrophy, but no additional histological changes in the liver, occurred in mice that were fed 22 mg/kg/day Aroclor 1242 for 6 weeks (Loose et al. 1978a, 1978b). Microsomal enzyme activity (as indicated by decreased pentobarbital-induced sleeping time) and liver weight were increased in mice fed 32.5 or 130 mg/kg/day Aroclor 1254 for 2 weeks (Sanders et al. 1974). No other liver end points (e.g., serum indices, histology) were evaluated, precluding the determination of whether these doses were hepatotoxic in mice. Liver weights were also increased in mice that were fed an estimated dose of 37.5 mg/kg/day Aroclor 1260 for 14 days, but not in mice administered a single 50 mg/kg dose by gavage (Whysner et al. 1998); no other liver toxicity end points were included in either study.

Fatty degeneration and necrotic changes are characteristic hepatic histopathological effects of PCBs that have been induced in rats and mice exposed to relatively high oral doses, including rats given a single 4,000 mg/kg dose of Aroclor 1242 by gavage (Bruckner et al. 1973); rats fed 100 mg/kg/day Aroclor 1242 for 3 weeks (Bruckner et al. 1973), 50 mg/kg/day Aroclor 1248 or 1254 for 2–4 weeks (Allen and Abrahamson 1973; Kling et al. 1978), or $6.5–7.5 mg/kg/day Aroclor 1254 or 1260 for 8 months (Kimbrough et al. 1972), and mice fed 4.88 mg/kg/day Aroclor 1254 for 6 months or 49.8 mg/kg/day for 11 months (Kimbrough and Linder 1974; Koller 1977). Additionally, lipid accumulation occurred in the liver of offspring of rats that were fed 1.5 mg/kg/day Aroclor 1254 or 1260 (Linder et al. 1974), and hepatocellular hypertrophy and vacuolar degeneration developed in weanling rats that ingested $1.0 mg/kg/day Aroclor 1254 for 10 weeks (Gray et al. 1993). Rabbits fed 2.1 or 6.5 mg/kg/day Aroclor 1254 for 8 weeks had increased relative liver weight, but no treatment-related histological alterations (Street and Sharma 1975); other hepatic end points were not evaluated. Similarly, there were no histological changes in the livers of guinea pigs with significantly increased relative liver weight fed #4 mg/kg/day Aroclor 1260 for 8 weeks (Vos and de Roij 1972).

The most comprehensive chronic toxicity study of PCBs in rodents provides comparative clinical and histology data on four Aroclor mixtures (Fish et al. 1997; General Electric Co. 1997a, 1997b; Mayes et al. 1998). Rats were fed Aroclor 1016, 1242, 1254, or 1260 for 24 months at two (Aroclor 1242) or three dose levels per sex at ranges of 2.0–11.2, 2.0–5.7, 1.0–6.1, or 1.0–5.8 mg/kg/day, respectively. Each lot of the basal feed contained <0.15 ppm of PCBs (estimated dose <0.01 mg/kg/day). As discussed in Section 3.2.8.3.2, the Aroclor 1254 test mixture had levels of congener 3,3',4,4',5-pentaCB (PCB 126)

that were about 2 times greater than that of "ordinary" Aroclor 1254. The liver was a target of all four PCB mixtures as indicated by increases in relative liver weight and hepatic mixed-function oxidases, serum enzyme and cholesterol levels, nonneoplastic lesions, and/or tumors. Hepatic enzyme induction varied with time and declined after reaching maxima, demonstrating the dynamic nature of the CYP end points (Fish et al. 1997). These effects were usually much more severe in females than in males and showed the following general pattern of Aroclor toxicity: 1254>1260 . 1242>1016. Carcinogenicity data from this study are summarized in Section 3.2.8.3.2. Nonneoplastic liver effects induced by Aroclor 1016 included increased hepatocellular hypertrophy and vacuolization at $2.0 mg/kg/day, and increased relative liver weight and bile duct hyperplasia at $2.7 mg/kg/day. Effects caused by Aroclor 1242 included increased hepatocellular hypertrophy and vacuolization, altered hepatocellular foci, and bile duct hyperplasia at $2.0 mg/kg/day, with increased liver weight, serum cholesterol, and bilirubin occurring at 5.7 mg/kg/day. Aroclor 1254 induced hepatocellular changes (hypertrophy, vacuolization, altered foci), bile duct hyperplasia, and increased serum cholesterol and liver weight at $1.0 mg/kg/day, with increases in serum AST, ALT, and GGT occurring at $2.9 mg/kg/day. Aroclor 1260 caused hepatocellular changes (hypertrophy, vacuolization, altered foci), bile duct hyperplasia, and increased liver weight at $1.4 mg/kg/day, and increased serum GGT and cholesterol at $2.8 mg/kg/day.

Histopathological changes in the liver also occurred in rats exposed to dietary Aroclor 1254 at 1.25–5 mg/kg/day for 2 years (Morgan et al. 1981; NCI 1978; Ward 1985), Aroclor 1260 at 5 mg/kg/day for 16 months followed by 2.5 mg/kg/day for 8 months and then no treatment for 5 months (Norback and Weltman 1985), or Aroclor 1260 at 5 mg/kg/day for 21 months (Kimbrough et al. 1975). Although preneoplastic and neoplastic liver lesions were induced in these as well as other rat studies (see Section 3.2.8.3.2), no nonproliferative changes, or nonproliferative lesions that did not progress to liver neoplasms after 1 year, were described.

Intermediate- and chronic-duration studies in monkeys indicate that this species is more sensitive than rodents to the hepatotoxic effects of PCBs. For example, lipid accumulation and focal necrosis were found in one female monkey that died after administration of 0.1 mg/kg/day Aroclor 1248 for 173 days and in one female monkey that died after being fed 0.2 mg/kg/day Aroclor 1248 for 310 days (Barsotti et al. 1976). Although only one animal per dose was examined, it is likely that these effects are treatment related due to the characteristic nature of the hepatic response and because similar effects on the liver occurred in monkeys at higher doses in other intermediate-duration studies (Allen 1975; Allen and Norback 1976; Allen et al. 1974a).

Cynomolgus monkeys that were fed relatively high doses of 2 mg/kg/day Aroclor 1248 or 5 mg/kg/day Aroclor 1254 for up to 20–23 weeks had serum biochemistry changes (increased ALT, AST, AP, LDH, cholesterol, triglycerides, and bilirubin) and histopathologic changes in the liver, including hyperplasia, fatty degeneration and degeneration of hepatocytes, and gall duct/gall bladder epithelial cell hypertrophy hyperplasia (Tryphonas et al. 1984). Hepatic effects observed in Rhesus monkeys after 12–28 months of dietary exposure to 0.2 mg/kg/day Aroclor 1254 included liver enlargement, fatty degeneration, hepatocellular necrosis, and hypertrophic and hyperplastic changes in the bile duct (Tryphonas et al. 1986a, 1986b). Rhesus monkeys that ingested capsules containing 0.005, 0.02, 0.04, or 0.08 mg/kg/day Aroclor 1254 for 72 months had increased liver weight attributed to hyperplasia (unspecified) at 0.08 mg/kg/day, as well as decreased serum levels of total bilirubin and cholesterol and increased serum triglycerides as summarized in Section 3.2.2.6.3.2 (Arnold et al. 1993b, 1997; Bell et al. 1994).

Defined Experimental Mixtures. Female Long-Evans rats were pre- and postnatally exposed to pelleted food containing Aroclor 1254 or a laboratory PCB mixture of 14 congeners resembling the congener pattern in human breast milk (Hany et al. 1999b). Exposure began 50 days prior to mating and was terminated at the day of birth (postnatal day [PND] 0), and the offspring were subsequently exposed via maternal milk until PND 21. The reported estimated average daily PCB intake by the dams was the same for both mixtures at 4 mg/kg/day. Relative liver weight was significantly higher than controls on PND 0 in both Aroclor 1254-exposed dams and their offspring, on PND 0 in offspring of the rats exposed to the simulated mixture, and on PND 21 in nonpregnant (unsuccessfully mated) females exposed to Aroclor 1254 or the simulated mixture. Additional information on the experimental design and results of this study, including the congener composition of the simulated mixture and nonhepatic data, are summarized in Section 3.2.6 (Developmental Effects).

Toxicity of a mixture of PCB congeners analogous to that in human breast milk (Canadian women) was studied in monkeys (Arnold et al. 1999). Groups of infant Cynomolgus monkeys (6 control males, 10 treated males) and Rhesus monkeys (2 control and 3 treated males, 1 control and 3 treated females) ingested the congener mixture in a total daily dose of 0 or 7.5 µg PCBs/kg/day from birth until 20 weeks old, and were observed until they were at least 66 weeks old. The dose represented the approximate daily intake of a nursing human infant whose mother's milk contained 50 ppb PCBs (the Health Canada guideline for maximum concentration in breast milk). Reported hepatotoxicity-related end points are limited to serum biochemical indices, including liver enzymes (ALT, AST, GGT, AP), bilirubin, triglycerides, and cholesterol; data for liver weight and histology are not yet published (as of July 2000). Although there were no statistically significant differences between the exposed and control groups for

any of the individual hepatic end points, significant increasing trends with time were found for serum cholesterol in both strains of monkeys and serum GGT in Rhesus monkeys.

Single Congeners. Multiple hepatic end points were evaluated in comparative studies of individual congeners in rats, mice, and monkeys. In the most comprehensive series of studies, rats were exposed to diets containing four dose levels of a congener for 13 weeks (Chu et al. 1994, 1995, 1996a, 1996b, 1998b; Gilroy et al. 1996, 1998; Lecavalier et al. 1997; MacLellan et al. 1994a, 1994b, 1994c; Peng et al. 1997; Singh et al. 1996, 1997). Eight congeners were tested based on frequent occurrence in environmental samples and human tissues or toxic potency. Hepatic effects included increased liver weight, biochemical changes (e.g., increased serum enzymes and cholesterol, increased liver porphyrins, and decreased liver vitamin A), and histopathology (e.g., cytoplasmic vacuolation and fatty alterations). The most toxic congener was PCB 126 with a LOAEL of 0.74 μg/kg/day, which was approximately 1/50 of the LOAEL of 39 μg/kg/day for PCB 105 (the next most toxic congener) and 1/500 of the LOAEL of 425 μg/kg/day for PCB 128 (the least toxic congener). Considering dose-response and severity of liver effects, the order of toxicity was PCB 126 > PCB 105 > PCB 118 . PCB 77 > PCB 153 . PCB 28 > PCB 128. In general, the non-*ortho* and mono-*ortho* substituted congeners were more potent than the di-*ortho* substituted congeners.

The comparative toxicity of four symmetrical hexachlorobiphenyl isomers was studied in mice (Biocca et al. 1981). Male mice were fed several dose levels of PCB 136, PCB 153, PCB 155, and PCB 169 daily for 28 days. The hepatic LOAEL (foamy cells and microabscesses) was 200 μg/kg/day for PCB 169 and much higher for the other congeners at 21.4 mg/kg/day. Liver effects induced at doses higher than the LOAEL included fatty metamorphosis (PCBs 155 and 169) and increased liver porphyrins (PCB 169).

Rhesus monkeys were exposed to PCB 52 or PCB 77 in estimated dietary doses of 0 or 60 μg/kg/day for 133 days (McNulty et al. 1980). Pathologic changes, including dilation of the extrahepatic biliary tree and hyperplastic intrahepatic biliary vessels, were induced by PCB 77 but not PCB 52. Additional liver data were not obtained for PCB 77 due to high systemic toxicity manifested as clinical signs, general emaciation, and marked effects in nonhepatic tissues.

Dermal Exposure. Limited information is available on liver toxicity of PCBs in dermally-exposed animals. Aroclor 1260, Clophen A60, or Phenoclor Dpb (all 60% chlorine PCB mixtures) was applied in isopropanol to the shaved back skin of female New Zealand rabbits (four/group) on 5 days/week for 28 or 38 days at estimated doses of 0 or 42–44 mg/kg/day (Vos and Beems 1971; Vos and Notenboom-Ram

1972). Hepatic effects included increased relative liver weights, histopathologic changes (e.g., centrilobular degeneration and hepatocyte atrophy, focal necrosis, and cytoplasmic hyalin degeneration), and increased fecal porphyrin levels. In general, the effects occurred in all treated animals and were least and most pronounced in the Aroclor 1260 and Clophen A60 groups, respectively. The CDF content of the Aroclor 1260 used in these experiments was below the detection limit (1 ppm); however, the analytical techniques available then were relatively insensitive.

3.2.2.6.3.2 Serum Lipids, Triglycerides, and Cholesterol

Oral Exposure

Commercial PCB Mixtures. Serum total cholesterol, HDL-cholesterol, and relative liver weight were increased in rats that were fed estimated doses of $1 mg/kg/day Aroclor 1254 for 4 days; no effects occurred at 0.5 mg/kg/day (Carter 1984, 1985). Serum LDL- and VLDL-cholesterol fractions were not increased in any dose group (#3.9 mg/kg/day). The lowest level causing increased HDL-cholesterol and liver weight was 1 mg/kg/day in the Carter (1984) study and 1.9 mg/kg/day in the Carter (1985) studies. Effects in rats exposed to PCBs in other acute-duration studies included increased serum cholesterol and liver weight at $1.9 mg/kg/day Aroclor 1254 (Carter and Koo 1984; Price et al. 1988) and 50 mg/kg/day Aroclor 1248 for 4 days (Kato and Yoshida 1980), as well as degenerative hepatic histopathological changes at 50 mg/kg/day Aroclor 1254 and 4,000 mg/kg/day Aroclor 1242 (Bruckner et al. 1973; Kling et al. 1978) as summarized above in Section 3.2.2.6.3.1.

Changes in serum lipid profiles commonly occurred in rats exposed to PCBs in intermediate-duration dietary studies (Andrews 1989; Bruckner et al. 1974, 1977; Gray et al. 1993; Kato et al. 1981a, 1981b, 1982b; Kling and Gamble 1982; Litterst et al. 1972). Effects included increased liver lipids at $0.3 mg/kg/day Aroclor 1242 for 2–6 months (Bruckner et al. 1974), increased liver triglycerides at 1.25 mg/kg/day Aroclor 1254 for 35 days (Bruckner et al. 1977), increased serum cholesterol at $10 mg/kg/day Aroclor 1254 for 5 weeks (Andrews et al. 1989), and increased liver lipids and liver and serum cholesterol at $15 mg/kg/day Aroclor 1248 for 20–24 days (Kato et al. 1981b, 1982b). Serum cholesterol, phospholipids, and triglycerides were similarly increased in rats fed 15 mg/kg/day Aroclor 1248 for 68 days (Oda and Yoshida 1994). Additional analyses performed by Oda and Yoshida (1994) showed that serum total lipoproteins were also elevated, with increases in protein, cholesterol, phospholipid, and triglycerides occurring among the lipoprotein fractions (VLDL, LDL, HDL1, HDL2).

Increased serum cholesterol was one of several manifestations of liver toxicity in rats found in the 24-month comparative study of several Aroclor mixtures (General Electric Co. 1997a, 1997b; Mayes et al. 1998) summarized in Section 3.2.2.6.3.1. Serum cholesterol was increased in females exposed to Aroclors 1242, 1254, and 1260 at 5.7, $1.4, and $2.8 mg/kg/day, respectively; no serum cholesterol changes were induced by Aroclor 1016 at doses as high as 11.2 mg/kg/day. Increased serum cholesterol levels observed in most PCB-exposed males appeared to be treatment-related only for Aroclor 1254. The effect in Aroclor 1254 males was minimal as the increase was slight and not clearly dose-related (statistically significant at 1.0 and 4.3 mg/kg/day, but not at 2.0 mg/kg/day). Increases in serum cholesterol in males exposed to Aroclor 1016, 1242, and 1260 were not consistently dose- or time-related and were considered to be equivocal. Considering the effect levels and sizes of increases in females, the order of toxicity was Aroclor 1254 followed by 1260, 1242, and 1016.

Effects in monkeys that ingested Aroclor 1254 in capsules daily for 37 months included normal plasma lipid profiles at doses #0.02 mg/kg/day, decreased total and VLDL + LDL cholesterol at $0.04 mg/kg/day, and decreased HDL cholesterol and total carnitine (which is involved in fatty acid metabolism) at 0.08 mg/kg/day (Arnold et al. 1993b; Bell et al. 1994). Plasma triglycerides were significantly elevated an apparent maximum of 30–40% at all tested doses (0.005–0.08 mg/kg/day) except 0.04 mg/kg/day. Bell et al. (1994) found statistically significant correlations supporting a causal relationship between PCB intake and the plasma lipid/lipoprotein changes, including an indication that the elevation in plasma triglycerides was not due to the partitioning of PCBs between adipose tissues and blood lipids. No correlation was found between the increases in triglycerides and HDL cholesterol.

Single Congeners. A comprehensive series of toxicity studies was performed in rats that were fed various individual congeners for 13 weeks, as detailed in Section 3.2.2.6.3.1 (Chu et al. 1994, 1995, 1996a, 1996b, 1998b; Gilroy et al. 1996, 1998; Lecavalier et al. 1997; MacLellan et al. 1994a, 1994b, 1994c; Peng et al. 1997; Singh et al. 1996, 1997). Effects included increased serum cholesterol levels that were caused by exposure to PCB 126 at $7.4 µg/kg/day and PCB 105 at $3,960 µg/kg/day. No changes in serum cholesterol were induced by PCB 28 at #3,956 µg/kg/day, PCB 77 at #892 µg/kg/day, PCB 118 at #683 µg/kg/day, PCB 128 at #4,397 µg/kg/day, or PCB 153 at #4,125 µg/kg/day.

3.2.2.6.3.3 Porphyria

Oral Exposure

Commercial PCB Mixtures. Urinary coproporphyrin levels were increased in rats that ingested 0.3 or 1.5 mg/kg/day Aroclor 1242 in the diet for 2–6 months (Bruckner et al. 1974). Rats treated with 5 mg/kg/day Aroclor 1254 in the diet had maximum increases in liver microsomal P-450 concentration and liver weight after 1 week, but onset of porphyria and induction of δ-aminolevulinic acid (ALA) synthetase was delayed until 2–7 months of treatment (Goldstein et al. 1974). A marked accumulation of uroporphyrins occurred in the liver, and urinary excretion of coproporphyrin and other porphyrins was increased; the largest increase was in uroporphyrins. The uroporphyrins in the liver and urine of the treated rats consisted primarily of 8- and 7-carboxyporphyrins.

Single Congeners. Increased hepatic uroporphyin is one of the effects observed in rats that were fed various single PCB congeners for 13 weeks (Chu et al. 1994, 1995, 1996a, 1996b, 1998b; Gilroy et al. 1996, 1998; Lecavalier et al. 1997; MacLellan et al. 1994a, 1994b, 1994c; Peng et al. 1997; Singh et al. 1996, 1997). Liver uroporphyrin was increased by exposure to PCB 126 at $0.74 µg/kg/day, PCB 105 at $3,960 µg/kg/day, or PCB 128 at $4,210 µg/kg/day, but not by PCB 28 at #3,956 µg/kg/day, PCB 77 at #892 µg/kg/day, PCB 118 at #683 µg/kg/day, or PCB 153 at #4,125 µg/kg/day. Additional information on the design and results of these studies is summarized in Section 3.2.2.6.3.1.

Dermal Exposure. Groups of four New Zealand rabbits were dermally treated with 0 or 42–44 mg/kg/day estimated doses of Aroclor 1260, Clophen A60, or Phenoclor Dpb (all 60% chlorine PCB mixtures), on 5 days/week for 28 or 38 days (Vos and Beems 1971; Vos and Notenboom-Ram 1972). The PCBs were dissolved in isopropanol and applied to shaved back skin. All three PCB mixtures caused significantly increased fecal levels of coproporphyrin and protoporphyrin, and ultraviolet fluorescence, indicative of porphyrin accumulation, was increased in the liver and other tissues. Similar dermal exposure to the congener PCB 153 caused higher fecal levels of coproporphyrin and protoporphyrin than those in rabbits exposed to the same dose of Aroclor 1260 (Vos and Notenboom-Ram 1972).

3.2.2.6.3.4 Other Hepatic Effects

Vitamin A homeostasis was altered in rats that were exposed to 100 mg/kg/day (only tested dose) of PCB 169 in the diet for 77 days (Bank et al. 1989). Effects included significantly decreased hepatic vitamin A, increased renal vitamin A, increased serum retinol, decreased plasma clearance and half-time of injected retinol (i.e., intravenously administered [^{3}H]retinol-labeled retinol binding protein-transthyretin complex), decreased hepatic and increased renal uptake uptake of injected retinol, and increased urinary and fecal excretion of injected retinol.

Vitamin A levels in the liver were also reduced in rats following oral exposure to various other congeners for 13 weeks (Chu et al. 1994, 1995, 1996a, 1996b, 1998b; Gilroy et al. 1996, 1998; Lecavalier et al. 1997; MacLellan et al. 1994a, 1994b, 1994c; Peng et al. 1997; Singh et al. 1996, 1997). This effect occurred following ingestion of PCB 126 at $0.74 µg/kg/day, PCB 77 at $768 µg/kg/day, and PCB 153 at $4,125 µg/kg/day), but not by exposure to PCB 28 at #3,956 µg/kg/day, PCB 105 at #4,327 µg/kg/day, PCB 118 at #683 µg/kg/day, or PCB 128 at #4,397 µg/kg/day.

3.2.2.6.3.5 Evaluation of Animal Studies

The hepatotoxicity of commercial PCBs is well-documented in numerous intermediate- and chronic-duration studies in animals, particularly in rats and monkeys, which are the most extensively tested species. These studies also indicate that monkeys are more sensitive to PCBs than rats and other laboratory species. Liver effects are similar in nature among species, appear to be reversible when mild, and characteristically include hepatic microsomal enzyme induction, increased serum levels of liver-related enzymes indicative of possible hepatocellular damage, liver enlargement, fat deposition, fibrosis, and necrosis. Ultrastructural changes include hepatocyte alterations associated with microsomal enzyme induction (e.g., proliferation of endoplasmic reticulum, enlarged and pleomorphic mitochondria), lipid droplets, and enlarged parenchymal cells. There is relatively little information on hepatic effects of commercial PCB mixtures in animals exposed by acute-duration oral exposure or the inhalation or dermal routes, although available data are consistent with the findings of the intermediate- and chronic-duration oral studies. The results of a comprehensive comparative 24-month oral toxicity study in rats indicate that the general pattern of hepatotoxicity was Aroclor 1254 > Aroclor 1260 . Aroclor 1242 > Aroclor 1016 (Mayes et al. 1998).

Other liver-related effects of PCBs include altered lipid and porphyrin metabolism. Increased serum levels of total lipids, triglycerides, and/or cholesterol are characteristic effects of short- and long-term oral exposures to PCBs that are well-documented in rats and monkeys (Carter 1984, 1985; Kato and Yoshida 1980; Kato et al. 1982a, 1982b; Oda and Yoshida 1994; Quazi et al. 1984). The results of comparative studies in rats exposed to various Aroclor mixtures for 24 months (Mayes et al. 1998) or single congeners for 13 weeks (Chu et al. 1994, 1995, 1996a, 1996b, 1998b; Gilroy et al. 1996, 1998; Lecavalier et al. 1997; MacLellan et al. 1994; Peng et al. 1997; Singh et al. 1996, 1997) indicate that Aroclor 1254 and 3,3',4,4',5-pentaCB (PCB 126) are particularly effective in increasing serum cholesterol. Hepatic porphyria is a well-documented effect that has been induced in rats, rabbits, and other species following oral or dermal exposure to PCBs (Bruckner et al. 1974; Chu et al. 1994, 1995, 1996a, 1996b, 1998b; Gilroy et al. 1996, 1998; Goldstein et al. 1974; Lecavalier et al. 1997; MacLellan et al. 1994a, 1994b, 1994c; Peng et al. 1997; Singh et al. 1996, 1997; Vos and Beems 1971; Vos and Notenboom-Ram 1972).

3.2.2.7 Renal Effects

3.2.2.7.1 Human Studies

Urinalysis of PCB-exposed capacitor plant workers showed no abnormalities in blood urea nitrogen (BUN) or other routinely-examined kidney function indices (Fischbein et al. 1979; Lawton et al. 1985a). Most of the workers studied by Fischbein et al. (1979) were exposed to mean concentrations of Aroclors 1254 and 1242 and/or other PCBs ranging from 0.007 to 11 mg/m^3 for $5 years; 40% of the workers were employed for $20 years. The workers in the Lawton et al. (1985a) study were exposed to various Aroclor mixtures for a mean duration of 17 years; the mean PCB concentration was 0.69 mg/m^3 (range, 0.2–2.0), based on monitoring performed in only one area of the plant several months prior to clinical evaluation.

3.2.2.7.2 Animal Studies

Information on the renal toxicity of PCBs comes from an inhalation study, a number of oral exposure studies, and several dermal exposure studies involving PCB mixtures or single congeners. Slight degeneration of the renal tubules was observed in rats exposed to chamber concentrations of 1.5 mg/m^3 Aroclor 1254 over 213 days (Treon et al. 1956). No information was reported on renal histological effects in other species (mice, guinea pigs, and rabbits) exposed to Aroclor 1254 under the same conditions or in rats, mice, guinea pigs, or rabbits similarly exposed to 1.9 mg/m^3 Aroclor 1242.

Interpretation of gross pathology data in this study is complicated by imprecise reporting and/or small numbers of animals, but it appears that there were no gross renal changes. The concentrations of PCBs are uncertain due to an invalid analytical technique and differential enrichment of the more volatile PCB congeners in the vapor phase.

A single near-lethal gavage dose of 4,000 mg/kg of Aroclor 1242 produced renal tubular damage in an unreported percentage of rats evaluated 24 hours following treatment (Bruckner et al. 1973). Effects included vacuolated tubular epithelial cells with fatty deposits and epithelial cells and proteinaceous casts in the tubular lumens and urine. Neither serum sodium or potassium ion concentrations or blood pH values were altered significantly by treatment, but lack of changes in these indices does not necessarily indicate that there was no functional damage in the kidney. No effect on kidney weight was observed in pregnant C57BL/6J mice given #21 mg/kg PCB by gavage on 5 consecutive days beginning on day 1, 6, or 11 of pregnancy (Rodriguez et al. 1997).

Cortical tubular protein casts were observed in the kidneys of rats treated with $1.0 mg/kg/day Aroclor 1254 for 15 weeks (Gray et al. 1993). The same group of investigators had previously observed increased kidney weight and biochemical alterations suggestive of functional renal damage, including increased urinary lactate dehydrogenase and urinary protein in rats treated with $10 mg/kg/day Aroclor 1254 by gavage for 5–15 weeks (Andrews 1989). Histology was not evaluated in the Andrews (1989) study. Renal histopathologic changes (lipid vacuolization and sloughing of the tubular epithelium) occurred in rats with no increase in kidney weight when treated with 100 mg/kg/day Aroclor 1242, 3 days/week for 3 weeks (Bruckner et al. 1973); these degenerative effects are similar to those observed in the acute study described above. No histological effects were observed in the kidneys of rats treated with 1.5 mg/kg/day Aroclor 1242 in the diet for 2–6 months (Bruckner et al. 1974). Similarly, no renal histopathologic changes were observed in male or female rats that were fed Aroclor 1016, 1242, 1254, or 1260 for 24 months at dose levels of 8.0–11.2, 4.0–5.7, 4.3–6.1, or 4.1–5.8 mg/kg/day, respectively (Mayes et al. 1998). There were no treatment-related renal organ weight changes or histological effects in rabbits fed #6.5 mg/kg/day Aroclor 1254 for 8 weeks (Street and Sharma 1975) or guinea pigs fed #4 mg/kg/day Aroclor 1260 for 8 weeks (Vos and de Roij 1972). No renal histological effects were observed in one monkey that died after 128 days of dietary treatment with 1.3 mg/kg/day Aroclor 1248 (Allen et al. 1974a). Rhesus monkeys receiving daily doses of 0.005, 0.020, 0.040, or 0.080 mg/kg/day Aroclor 1254 for 72 months also showed no effects on renal tissue (Arnold et al. 1997).

In a series of 13-week dietary exposure studies using single PCB congeners, no histological alterations in the kidneys were observed in rats fed diets providing #4.1 mg/kg/day of PCB 153 (Chu et al. 1996a), #4.2 mg/kg/day of PCB 128 (Lecavalier et al. 1997), #7.4 mg/kg/day of PCB 126 (Chu et al. 1994), #4.0 mg/kg/day of PCB 105 (Chu et al. 1998b), #3.7 mg/kg/day of PCB 28 (Chu et al. 1996b), or #0.77 mg/kg/day of PCB 77 (Chu et al. 1995). In similarly treated rats exposed to PCB 118, minimal histological damage (cytoplasmic shedding and inclusions in the renal tubules) was observed at 0.17 mg/kg/day (Chu et al. 1995).

Hydropic degeneration of the convoluted tubules, destruction of tubular epithelial cells, tubular dilation, and proteinaceous casts were observed in half of the rabbits treated with Aroclor 1260 in an isopropanol vehicle applied 5 days/week for 38 days at an estimated dose of 42 mg/kg/day (Vos and Beems 1971). No kidney effects were observed in a similar study in which 44 mg/kg/day Aroclor 1260 was applied in the same manner to adult female New Zealand rabbits 5 days/week for 28 days (Vos and Notenboom-Ram 1972). The reason for the discrepancy in the results is unclear since the doses are essentially the same, but it may be related to the small numbers treated (four per study) and to the longer duration of the 1971 study. The Aroclor 1260 used in both studies had undetectable (<1 ppm) levels of CDFs.

The highest NOAEL values and all reliable LOAEL values for renal effects for each study are recorded in Tables 3-1, 3-2, and 3-3, and plotted in Figures 3-1 and 3-2.

3.2.2.8 Endocrine Effects

This section describes effects of exposure to PCBs on the thyroid and other non-reproductive endocrine systems. Estrogenic, anti-estrogenic, and anti-androgenic effects of PCBs are discussed in Sections 3.2.5 (Reproductive Effects), 3.5.2 (Mechanisms of Toxicity), and 3.6 (Endocrine Disruption).

3.2.2.8.1 Summary

A number of studies have examined the relationships between PCB exposure and thyroid hormone status in both children and adults. The results suggest that PCBs can induce thyroid toxicity as well as a variety of changes in thyroid hormone levels. Differing results have been reported for differing Aroclor mixtures and PCB congeners, as well as for differing exposure scenarios and differing ages at the time of exposure. Increased thyroid gland volume has been found among workers at a PCB production facility as well as among nearby residents. An elevated odds ratio for goiter has been found among the *Yu-Cheng* cohort.

In addition, numerous statistically significant positive and/or negative correlations (for a number of different age groups) have been reported between circulating levels of TSH, T_4, and T_3, and varying measures of PCB exposure.

Evidence for a thyroid hormone involvement in PCB toxicity in animals is much stronger and includes findings in rodents and nonhuman primates. Depending on dose and duration, PCBs can disrupt the production and disposition of thyroid hormones at a variety of levels. The major findings include (1) histological changes in the thyroid gland indicative of both stimulation of the gland (e.g., similar to that induced by TSH or a hypothyroid state) and a disruption of the processing of follicular colloid needed for normal production and secretion of thyroid hormone; (2) depression of serum T_4 and T_3 levels, which may effectively create a hypothyroid state (in some studies, low doses resulted in elevated serum T_4 levels while depressed levels occurred at higher PCB doses); (3) increased rates of elimination of T_4 and T_3 from serum; (4) increased activities of T_4-uridine diphosphate-glucuronyl transferase (UDP-GT) in liver, which is an important metabolic elimination pathway for T_4 and T_3; (5) decreased activity of iodothyronine sulfotransferases in liver which are also important in the metabolic elimination of iodothyronines; (6) decreased activity of iodothyronine deiodinases including brain Type-2 deiodinase, which provide the major pathways for the production of the active thyroid hormone, T_3; and (7) decreased binding of T_4 to transthyretin, an important transport protein for both T_4 and T_3. Other effects of PCBs on endocrine function that have been observed in experimental animals include effects on the adrenal glands and serum adrenal steroid levels.

3.2.2.8.2 Human Studies

Occupational Exposures. Total thyroxine (T_4) and free T_4 (T_4 index) were significantly lower (approximately 10%) in a group of 55 transformer maintenance workers compared to a comparison control group of workers (Emmett et al. 1988b), even though thyroid hormone levels were in the normal range for adults in both groups. The transformer workers were primarily exposed to Aroclor 1260 at levels ranging from 0.00001 to 0.012 mg/m^3; the mean length of exposure was approximately 4 years. Although there was a statistically significant increase in thyroxine levels in the PCB-exposed cohort, there was no correlation between PCB levels in serum or adipose tissue and serum T_4 concentrations (adjusted for age, smoking, and alcohol consumption).

Langer et al. (1998) measured thyroid volumes in 238 employees of a factory that produced PCBs, and in 572 adults from “less polluted areas” of Slovakia, which formed a sex- and age-matched control group.

Various serum indices of thyroid status were measured in subsamples of these groups, including total serum T_4, serum TSH, thyroglobulin (TGB); and antibodies for thyroid peroxidase (TPO Ab), thyroglobulin (Tg Ab), and TSH receptor (TSHR Ab). Mean thyroid volume was significantly greater in the workers compared to the control group (18.85±0.69 mL vs. 13.47±0.48 mL, $p<0.001$). Workers also had a significantly elevated prevalence of TPO Ab, Tg Ab, and TSHR Ab. There were no differences between the worker and control groups with regard to serum T_4, TSH, or TGB concentrations. Although larger thyroid volume could reflect a difference in the iodine intakes between the two groups, the investigators indicated that this was not likely because iodine intakes were considered sufficient in Slovakia and urinary iodine concentrations were similar in the worker and control groups (data not reported).

Yusho and Yu-Cheng Exposures. In a case-control study of the Taiwan *Yu-Cheng* cohort, 795 exposed subjects and 693 sex- and age-matched controls were interviewed for information about health and medical history (Guo et al. 1999). The odds ratio (OR) for goiter (men and women combined) was 2.8 (CI, 1.2–7.1) and 4.0 (CI, 1.5–13.9) for goiter that was treated with medication or surgery. The ORs for hypothyroidism or hyperthyroidism were not significant (males, 0.95; females, 1.7).

General Population Exposures. Several studies have examined relationships between indices of PCB exposure and thyroid hormone status, as indicated from measurements of serum thyroid hormones. The results of these studies have been mixed, with negative, positive, or no correlations observed. Osius et al. (1999) examined the relationship between whole blood concentrations of various PCB congeners and serum TSH, free T_4, and free T_3 in children who lived near a hazardous waste incinerator. Although the median and 5th–95th percentile ranges of the hormone concentrations in the study population (671 children, ages 7–10 years) were within expected ranges for children, a significant positive ($\beta=7.129$, $p=0.039$) association was found between concentrations of TSH in serum and PCB 118 in blood. Significant negative associations were found between serum T_3 and PCBs 138, 153, 180, 183, and 187.

Several studies have examined relationships between thyroid hormone levels in infants and maternal or neonatal PCB concentrations, or mixed PCB and CDD concentrations (Koopman-Esseboom et al. 1994a; Longnecker et al. 2000; Nagayama et al. 1998a; Winneke et al. 1998a). Hormone levels were within normal ranges in these studies. In describing hormone levels in the serum or plasma, the designations TT_4 or TT_3 have been used to denote total hormone concentrations, whereas free concentrations are denoted as FT_4 or FT_3. If not specified in the report, the notations T_4 or T_3 have been used. Longnecker et al. (2000) compared PCB concentrations in breast milk of 880 mothers to serum TSH, TT_4, and FT_4 concentrations

in cord blood at delivery. The subjects in this study are from the North Carolina Breast Milk and Formula Project cohort summarized in Section 3.2.4.2.1.2. Concentrations of T_4 and TSH were not shown to be related to breast milk PCB concentrations. However, a significant positive correlation (r=0.15, p=0.029)was found between TSH concentrations in cord blood and total serum PCBs in 170 infants from the German cohort in the European Background PCB Study summarized in Section 3.2.4.2.1.2 (Winneke et al. 1998b). Nagayama et al. (1998) examined the relationship between serum TSH, TT_4, and TT_3 in infants and estimated intake of 2,3,7,8-TCDD toxic equivalent (TEQ) in breast milk during the first year of postnatal life. Significant negative correlations were found for serum TT_4 and TT_3; no relationship was apparent between infant serum TSH or thyroxine binding globulin (TBG) and TEQ intake. The mean total TEQ intake was 34 ng/kg; however, the co-planar PCB contribution to the estimated TEQ intake, and intakes of other PCBs were not reported. As part of the Dutch Mother-Child Study cohort summarized in Section 3.2.4.2.1.2, Koopman-Esseboom et al. (1994a) compared TEQ levels of PCBs and dioxins in maternal milk with TT_3 and TT_4 concentrations in maternal plasma, TSH concentrations in cord plasma at delivery, and TSH concentrations in venous plasma of the infants at ages 2 weeks and 3 months. Higher levels of total PCB-dioxin TEQ, dioxin TEQ, and both planar and non-planar-PCB TEQ in milk were significantly correlated with lower maternal plasma TT_3 concentrations in the last month of pregnancy, lower maternal plasma TT_3 and TT_4 concentrations in the 2nd week after delivery, and higher plasma TSH concentrations in the infants at 2 weeks and 3 months of age.

Langer et al. (1998) measured thyroid volumes in 454 adolescents in Slovakia who lived near a factory that produced PCBs, and in 956 adolescents who lived in “less polluted areas” of Slovakia, which formed a sex- and age-matched control group. Various serum indices of thyroid status were measured in subsamples of these groups, including TSH and TPO Ab. Mean thyroid volume was significantly greater in the group who lived near the factory compared to the control group (9.37±0.17 mL vs. 8.07±0.10 mL, $p<0.001$). There were no differences between the groups with regard to serum TSH or TPO Ab concentrations. As with the worker cohort (discussed with the occupational studies), the investigators indicated that a difference in the iodine intakes between the two groups was not likely because iodine intakes were considered to be sufficient and urinary iodine concentrations were similar in the two groups (data were not reported).

An ongoing epidemiologic study is investigating the potential for health effects in Native Americans from exposure to persistent toxic substances (Dellinger et al. 1997; Tarvis et al. 1997). Fish consumption, species consumed, and medical histories were obtained from 541 Native Americans on eight reservations in Minnesota, Wisconsin, and Michigan. Preliminary results indicated elevated serum PCB levels (mean

was 3.7 ppb and the maximum was 9.6 ppb) were correlated with self-reported diabetes and liver disease in two of the cohorts (Ojibwa and Red Cliff). The average annual fish consumption rate was 23 g/day. No additional information was available regarding the potential link between PCBs and diabetes, although there is growing evidence of an association between dioxin exposure and diabetes (ATSDR 1998).

Evaluation of Human Studies. The epidemiological literature suggests a link between PCBs exposure and thyroid hormone anomalies in humans. Studies that have examined relationships between PCB exposure and thyroid hormone status, in children or adults, have reported a variety of different results, with findings of both negative and positive significant correlations between PCB exposure and circulating levels of TSH, T_4 or T_3 depending on the specific type of analysis for PCB exposure, the age of the cohort, and the specific exposure scenario (Emmett et al. 1988b; Koopman-Esseboom et al. 1994a; Langer et al. 1998; Longnecker et al. 2000; Nagayama et al. 1998; Osius et al. 1999; Winneke et al. 1998a). A comparison of PCB levels in blood and breast milk in some of these studies is included in Appendix A. Although many of the populations examined had thyroid hormone levels within normal ranges, many of these studies also showed statistically significant differences in circulatory thyroid hormone levels in exposed cohorts compared to unexposed controls. In addition, a significantly elevated OR for goiter was found among the *Yu-Cheng* cohort (Guo et al. 1999), suggesting the possibility of excess thyroid disease in a population that experienced relatively high exposures to mixtures of PCBs and CDDs. Other observations include reports of increased thyroid gland volume among workers at a PCB production facility, as well as among nearby residents (Langer et al. 1998). Considering the epidemiologic data as well as the much stronger findings in thyroid studies in animals discussed in the following section, there is mounting evidence of thyroid hormone involvement in PCB toxicity in humans.

3.2.2.8.3 Animal Studies

The highest NOAEL values and all reliable LOAEL values for endocrine effects for each study are recorded in Tables 3-1 and 3-2, and plotted in Figures 3-1 and 3-2.

Effects on Thyroid Gland and Hormones

Commercial PCB Mixtures. Various effects on the thyroid gland and thyroid hormone system have been observed in rats exposed to Aroclor 1254 by the oral route. Descriptions of the histological changes in

the rat are reasonably consistent across studies. Typical findings, depending on the dose, include hyperplasia, hypertrophy, and increased vacuolization of follicular cells, depletion of follicular colloid and reduced follicular size, and thyroid enlargement (Collins and Capen 1980a; Collins et al. 1977). These changes are similar to the histological appearance of the gland during prolonged TSH stimulation (Capen 2000). Additional abnormalities have also been noted when the gland has been examined at the ultrastructural level. Collins and Capen (1980a) observed in PCB-treated rats the accumulation of colloid droplets and large, abnormally shaped lysosomes in the follicular cells that were indicative of a disruption of the normal lysosomal processing of colloid. They also noted distinct abnormalities in follicular microvilli (shortening and abnormal branching) that were uncharacteristic of the TSH-stimulated or iodide-stimulated gland. Thus, the effects of Aroclor 1254 on the thyroid gland are not completely explained solely by a direct or indirect stimulation of the gland through a TSH mechanism. A complex mechanism is further indicated from observations of the forementioned structural changes with or without concurrent changes in circulating thyroid hormone (T_4 or T_3) or TSH levels, or changes in hormone levels without changes in thyroid gland, or changes in hormone levels that vary in magnitude and direction over time (Hood et al. 1999; Saeed and Hansen 1997). Thus, while a general consensus has emerged that Aroclor 1254 produces a stimulation of the thyroid gland and thyroid hormone production (Byrne et al. 1987), it is not clear to what extent this results from a direct effect on the thyroid gland or as an indirect effect resulting from changes in circulating thyroid hormone and induction of TSH. It is likely that both contribute to varying degrees depending on the dosage and duration of exposure (Saeed and Hansen 1997). It is important to emphasize that characteristic structural changes that have been attributed to Aroclor 1254 may not be apparent when the gland is viewed only at the light microscopic level, which has been the approach used in most studies. Furthermore, histopathology of the gland should not be inferred from observed changes in circulating thyroid hormone or TSH levels, alone. Experimental studies that provide evidence for Aroclor-mediated effects on the thyroid gland and/or thyroid hormone status are noted below. In describing hormone levels in the serum or plasma, the designations TT_4 or TT_3 have been used to denote total hormone concentrations, whereas free concentrations are denoted as FT_4 or FT_3. If not specified in the report, the notations T_4 or T_3 have been used.

In an acute-duration study, Hood et al. (1999) observed significant depression of serum TT_4 and FT_4 in rats fed $25 ppm Aroclor 1254 in food (2.3 mg/kg/day) for 7 days and depression of TT_3, but not FT_3 in rats fed $50 ppm (4.6 mg/kg/day). PCBs at exposure levels up to 200 ppm (18 mg/kg/day) had no effect of serum TSH levels or on thyroid structure. TT_4 levels were reduced in rats fed $2.5 mg/kg/day for 7 days, but there were no treatment-related changes in serum TT_3 (Price et al. 1988). This study reports histological changes in the thyroid gland that are typical of Aroclor 1254-related changes that have been

observed in intermediate- and chronic-duration studies; however, it is not clear from the report whether the changes occurred at the 2.5 mg/kg/day dosage or at higher dosages.

Collins et al. (1977) conducted one of the more comprehensive evaluations of the histopathology of intermediate-duration exposures to Aroclor 1254 in rats. Rats were fed 5, 50, or 500 ppm Aroclor 1254 in food for 4 weeks (approximately 0.44, 4.4, or 44 mg/kg/day). Ultrastructural changes in the thyroid were evident at the lowest exposure level and became more pronounced and evident with light microscopy at the 50 ppm exposure level (4.4 mg/kg/day). Serum concentrations of TT_4 were significantly depressed (42%) at the 50 ppm level and both TT_4 and TT_3 were depressed (79 and 13%, respectively) at the 500 ppm level. Thyroid lesions in rats that were exposed to 500 ppm for 6 weeks followed by 250 ppm for 6 weeks were largely absent after a subsequent 12 weeks on a control diet, suggesting substantial recovery, and were not evident at all after a period of 35 weeks on the control diet (Collins and Capen 1980a). A similar time course of recovery of serum TT_4 concentrations was observed. Thus, the observed lesions in this study and at these doses appeared to be reversible.

In other intermediate-duration studies, oral exposures of rats for 1–5 months decreased serum levels of T_4 and T_3 and/or produced histological changes in the thyroid (Byrne et al. 1987; Gray et al. 1993; Kasza et al. 1978). Thyroid effects in rats occurred at oral doses as low as 0.09 mg/kg/day for 35 days (Byrne et al. 1987). In Sprague-Dawley rats, serum levels of T_4 decreased when rats received daily gavage dosages of $0.1 mg/kg/day Aroclor 1254 for 15 weeks; however, no histopathologic alterations were observed in the thyroid after gavage dosages of up to 25 mg/kg/day Aroclor 1254 (Gray et al. 1993). The lack of effect of this dose of Aroclor 1254 on the histological status of the thyroid in the Sprague-Dawley rat, in comparison to histological changes observed in Osborne-Mendel rats at similar dosages and durations (Collins and Capen 1980a; Collins et al. 1977), suggests a possible strain-related difference, or some other unaccounted variable in either study. Byrne et al. (1987) attempted to discern the relative contributions of production and metabolism in the depression of serum T_4 concentrations that occur during Aroclor 1254 exposure. In rats exposed to Aroclor 1254 in diet at concentrations $1 ppm (0.09 mg/kg/day) for $35 days, serum TT_4 and TT_3 levels were depressed; however, the rate of clearance of injected radiolabeled T_4 was not changed by the PCB exposures, relative to a control group, suggesting that the decline in T_4, and possibly T_3 concentrations, was primarily the result of a decline in T_4 production in the thyroid.

In chronic-duration studies, enlarged thyroid glands and follicles with desquamated cells were observed in Rhesus monkeys exposed to 0.2 mg/kg/day Aroclor 1254 for 28 months (Tryphonas et al. 1986b);

serum levels of thyroid hormones were not evaluated. In Cynomolgus monkeys, treatment for 12 months with 0.2 mg/kg/day Aroclor 1254 did not induce histological alterations in the thyroid (Tryphonas et al. 1986a). Rhesus monkeys receiving daily doses of 0.005, 0.020, 0.040, or 0.080 mg/kg/day Aroclor 1254 for 72 months showed no effect on thyroid tissue (Arnold et al. 1997). After 37-months of exposure to 0.08 mg/kg/day Aroclor 1254, serum TT_4 and FT_4 (T_4 index) were not different from controls (Arnold et al. 1993b). The incidence of follicular cell hyperplasia (generally minimal or mild) was increased in a non-dose-related pattern in male rats that were fed Aroclor 1242, 1254, or 1260 for 24 months at dose levels of $2.0, $1.0, and $1.0 mg/kg/day, respectively (Mayes et al. 1998). This thyroid lesion was not observed following exposure to similar doses of Aroclor 1016 in male rats or Aroclor 1016, 1242, 1254, or 1260 in female rats. Thyroid follicular cell adenomas were also increased in the male rats as discussed in the animal cancer section (3.2.8.3.2).

The effects of gestational exposures to Aroclor 1254 on the thyroid gland and thyroid hormone status of neonates have been examined in numerous studies. Lesions in the thyroid were observed in pups born to dams that were exposed to 50 or 500 ppm Aroclor 1254 (2.5 or 25 mg/kg/day) from gestation day 1 through postnatal day 21 (Collins and Capen 1980c). The pups also had depressed serum levels of TT_4 and TT_3. Aroclor 1254 (3.1, 6.2, or 12.5 mg/kg/day, oral) administered to rats during gestation and lactation depressed serum TT_4, but not TT_3, in the neonatal rats (Juarez de Ku et al. 1994). Aroclor 1254 administered to rats on days 10–16 of gestation (5 or 25 mg/kg/day, oral) depressed plasma TT_3 in the dams and both plasma TT_4 and FT_4 in fetuses and 5-day neonates (Morse et al. 1996c). Fetal brain levels of T_4, but not T_3, were also depressed. No changes were detected in fetal or neonatal plasma TSH concentration. Other effects observed that are relevant to the thyroid hormone system included an increase in Type II thyroxine 5'-deiodinase activity in fetal brain and depression of activity in 21-day-old pups, and an increase in T_4-UDP-GT activity in fetal and pup liver. Provost et al. (1999) observed a depression in both serum total T_4 and T_3 concentrations in rats that had been exposed to 1.25 or 12.5 ppm Aroclor 1254 (approximately 0.1 or 1 mg/kg/day) during gestation and through postnatal day 30. Zoeller et al. (2000) fed pregnant rats 0, 1, 4, or 8 mg/kg/day Aroclor 1254 beginning on day 6 of gestation through weaning of pups. Dosages $1 mg/kg/day depressed serum TT_4 levels in the pups. Serum concentrations of TT_4 and FT_4 were depressed in dams and fetuses after gavage doses of 25 mg/kg/day Aroclor 1254 on gestation days 10–20 (Schuur et al. 1998a). Although serum concentrations of the sulfate ester of T_4 were not affected by Aroclor 1254 treatment, the activity of 3,3'-T_2-sulfotransferase in liver cytosol preparations was lower in the treatment group relative to the control group. Activities of iodothyronine deiodinase in liver was also decreased in the dams and fetuses in the treatment group. Type II deiodinase activity was significantly increased in fetal, but not maternal brain in the treatment

group. T_4-UDP-GT activity in maternal liver was significantly increased in the treatment group. These observations suggest that Aroclor 1254 can potentially affect thyroid hormone status by modifying several different metabolic pathways for T_4, including glucuronide and sulfate conjugation, and deiodination of iodothyronines.

Aroclor 1254 (1, 4, or 10 mg/kg/day, oral) administered on gestation day 6 through postnatal day 21 depressed postnatal (day 7–21) serum TT_4 concentration ($1 mg/kg/day) and T_3 concentration ($4 mg/kg/day), without a change in serum TSH concentration (Goldey et al. 1995). Thyroid hormone levels recovered from depressed levels with time and were nearly at control levels by postnatal day 45. Neurobehavioral deficits were observed in the pups, including decreased motor activity and changes in acoustic startle response (see Section 3.2.4.3.3); these changes were significantly attenuated in pups that received subcutaneous injections of T_4 that increased serum T_4 and T_3 concentrations (Goldey and Crofton 1998). Rates of elimination of both hormones from serum were accelerated in the pups that had been exposed to Aroclor 1254, relative to controls. These observations suggest that the observed neurobehavioral deficits may have been attributable to deficits in thyroid hormones. The increased elimination of T_4 and T_3 from serum is consistent with an induction of UDP-GT or other elimination pathways for thyroid hormones (e.g., deiodination of T_4 to T_3).

In a longer feeding study, pregnant rats were exposed to 125 or 250 ppm Aroclor 1254 in food from gestation day 1 through weaning of pups (Corey et al. 1996). The weaned pups either continued the exposure until postnatal day 60 or were fed the control diet. Reported dosages during gestation were 8 or 18 mg/kg/day, and during lactation were 37 or 62 mg/kg/day. Serum TT_4 concentrations, but not TT_3, were depressed (>90% decrease) at postnatal day 60 in all of the exposure groups. In pups that were removed from the PCB exposure after weaning, serum TT_4 concentrations partially recovered, but, unlike the Collins and Capen (1980a) study previously discussed, remained significantly lower than control levels.

Seo and Meserve (1995) reported the effects of maternal ingestion of Aroclor 1254 in pregnant and lactating rats on the development of thermoregulation in neonates. Female pregnant Sprague-Dawley rats (n=6–8) were fed *ad libitum* 125 or 250 ppm (6.3 or 12.5 mg/kg/day) Aroclor 1254 and continued on the diet from conception to completion of the experiment when pups were 15 days old. Serum TT_4 levels were depressed in female rats treated with 6.3 and 12.5 mg/kg/day during pregnancy and lactation. Relative thyroid weight increased (19 mg/100 g ±1.3) significantly in animals given 6.5 mg/kg/day compared to controls, but not at the 12.5 mg/kg/day dose.

In contrast to the depression of circulating levels of thyroid hormone levels that has been observed in rats exposed to Aroclor 1254, rats exposed to Aroclor 1242 (32 µg/kg/day in food or 900 ng/m^3 vapor, whole body exposure) for 30 days had higher serum concentrations of TT_3 and TT_4 than rats in a control group (Casey et al. 1999). Histological changes in the thyroid observed in the rats exposed to the aerosol included increased vacuolization of thyroid follicle cells with reduced follicular colloid, changes that are typical of TSH stimulation of the gland. The elevation in thyroid hormone levels observed in this study supports earlier observations of increased serum T_4 levels following low doses of PCB 153 (Li et al. 1994), PCB 110 (Li et al. 1998), a mixture of PCBs collected in the air over a landfill (Li and Hansen 1996b), and Aroclor 1242, but not Aroclor 1254, in chick embryos (Gould et al. 1997). The rats exposed to the Aroclor 1242 vapor may have received a substantial ingestion dose, because of deposition of PCBs on the fur and because the animals were exposed and housed two animals per cage.

Cooke et al. (1996) demonstrated a possible thyroid hormone-mediated response of the testes to Aroclor 1254. This study found increased testes weight and sperm production in 135-day-old rats that were administered subcutaneous doses of Aroclor 1254 (. 40 mg/kg/day) or Aroclor 1242 (. 80 mg/kg/day) on postnatal days 1–25. Serum TT_4 concentrations were also depressed in these rats, and the effects on the testes were attenuated by injections of T_4 on postnatal days 1–25. In contrast to the results of this study, Gray et al. (1993) found no effect of oral exposure to Aroclor 1254 (up to 25 mg/kg/day) on testes weights or sperm numbers in rats that had substantially depressed levels of serum TT_4 and TT_3; however, the study initiated the dosing of the rats on postnatal day 31, after the development of Sertoli cells is complete in the rat, and, thus, may have missed a vulnerable period in the postnatal development of the testes.

Defined Experimental Mixtures. PCBs were extracted from an NPL site and doses ranging from 3 to 96 mg/kg were administered to 20-day-old female rats for 2 days (Hansen et al. 1995). The animals were sacrificed 24 hours after the last dose. Serum total T_4 declined significantly at doses of $36 mg/kg/day; however, at doses >12 mg/kg/day, thyroid follicular cells increased in size, while the colloid area decreased to <60% of control values, indicative of thyroid gland stimulation. Depression of serum T_4 was also observed in 21-day-old rats that received the same soil mixture and a charcoal filtered mixture, which had considerably lower TCDD equivalents (Li and Hansen 1996a). When compared to extracts of superficial dust and debris and airborne PCBs, the soil extract was somewhat less potent than the air extract (Li and Hansen 1996b).

Single Congeners. Histopathologic lesions of the thyroid gland developed in rats that were exposed to single PCB congeners in food for 13 weeks (Chu et al. 1994, 1995, 1996a, 1996b, 1998b; Lecavalier et al. 1997). The lesions consisted of a reduction in size and collapse of the thyroid follicles, reduced follicle colloid density, and cellular changes, including cytoplasmic vacuolization and nuclear vesiculation of follicle cells. These changes were evident to varying degrees of severity at the following dosages: PCB 28 at $36 mg/kg/day; PCB 77 at $0.070 mg/kg/day; PCB 105 at $0.039 mg/kg/day; PCB 118 at $0.17 mg/kg/day; PCB 126 at $0.00074 mg/kg/day; PCB 128 at $0.43 mg/kg/day; and PCB 153 at $0.35 mg/kg/day.

Depressed concentrations of T_4 have been observed in rats exposed to single PCB congeners in food for 13 weeks (Desaulniers et al. 1997; Van Birgelen et al. 1992, 1994a, 1994b, 1995). Effective dosages were as follows: 75 µg/kg/day PCB 77 decreased serum TT_4, but not serum TSH (Desaulniers et al. 1997); 50 µg/kg/day PCB 126 decreased $FT_4$and TT_4 plasma concentrations; 1.2 mg/kg/day; PCB 156 decreased plasma FT_4 concentration; and 6 mg/kg/day of PCB 156 depressed both free and TT_4 concentrations (Van Birgelen et al. 1995). These same dosages increased activity of UDP-GT in liver homogenate, including activity when either T_4, *p*-nitrophenol, or 1-naphthol were the substrates (Desaulniers et al. 1997; Van Birgelen et al. 1995). This is consistent with the induction of UDP-GT1A1, which utilizes T_4 and simple phenols as a substrate, and with the induction of cytochrome P-450 1A1 at these same dosages of PCB congeners (Chu et al. 1995; Van Birgelen et al. 1995). These observations suggest a possible involvement of the Ah receptor in modifying the metabolism and, thereby circulating levels of T_4.

Rice (1999a) administered oral doses (0.25 or 1.0 µg/kg/day) of 3,3',4,4',5-pentaCB (PCB 126) to female rats, 5 days/week beginning 5 weeks prior to and through pregnancy, gestation, and lactation. Serum T_4 levels were depressed in 21-day-old pups, but not in 60-day-old pups or in the dams. Darnerud et al. (1996a) found no changes in plasma FT_4 or TT_4 concentrations in maternal mice given a single oral dose of up to 10 mg/kg PCB 77 in corn oil on day 13 of gestation; however, FT_4 and TT_4 concentrations in plasma of the 13-day-old fetus were depressed (36 and 45%, respectively). This study also found substantial binding of 4-hydroxylated metabolites of PCB 77 in fetal serum to serum transthyretin and that binding of T_4 to transthyretin was substantially decreased in serum of the exposed pups, relative to the control group. This observation suggests that hydroxylated metabolites of certain PCBs may compete for binding of T_4 to transthyretin, and is consistent with the results of *in vitro* binding studies that have estimated transthryretin binding affinities of 4-OH metabolites of PCB congeners to be similar to that of T_4 (Cheek et al. 1999; Lars et al. 1994).

An intraperitoneal dose of 8 mg/kg/day of 2,3,3',4',6-pentaCB (PCB 110), administered to female rat pups on postnatal days 21 and 22, increased serum TT_4 levels, while higher doses resulted in a dose-dependent decrease in serum TT_4 levels (Li et al. 1998). A PCB 110 preparation contaminated with 0.4% 3,3',4,4',5-pentaCD (PCB 126) produced a dose-dependent decrease in serum T_4 levels (4 mg/kg/day or higher) without an increase in serum T_4 levels.

Effects on the Adrenal Gland and other Endocrine Systems

Commercial PCB Mixtures. PCB-related effects on the adrenal gland have been reported after repeated oral exposure to PCBs; however, a single dose of 4,000 mg Aroclor 1242/kg did not induce histological alterations in the adrenals or pancreas in rats (Bruckner et al. 1973). Significantly increased serum corticosterone levels were reported in mice following $8.1 mg/kg/day Aroclor 1254 for 2 weeks (Sanders et al. 1974); adrenal weight was increased at 130 mg/kg, but histology was not evaluated. Intermediate-duration studies with rats found that serum corticosterone levels were increased by dietary exposure to 15 mg/kg/day Aroclor 1248 for 20 days (Kato et al. 1982a), 35 mg/kg/day Aroclor 1221 for 10 weeks (Wassermann et al. 1973), and 0.1 mg/kg/day Aroclor 1254 for 15 weeks (Miller et al. 1993b). Bergman and Olsson (1984) have attributed much of the pathology in PCB-contaminated Baltic seals to adrenal cortical hyperplasia. Rats fed 0.05–2.5 mg/kg/day Aroclor 1242 or 1221 for 5 months had decreased serum levels of the adrenal cortex hormones, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHS). The decreases in DHEA, DHS, and corticosterone occurred at $0.25 mg/kg/day Aroclor 1254, but not at 0.05 mg/kg/day; no corticosterone data were reported for Aroclor 1242 or 1221 (Byrne et al. 1988). The degree of hormone inhibition was dose related and generally increased with increasing degree of mixture chlorination. These reductions in circulating hormones were accompanied by decreased adrenal weight with Aroclor 1254 (not evaluated with Aroclor 1242 or 1221). There were no changes in plasma corticosteroids in rats fed #1.5 mg/kg/day Aroclor 1242 for 2–6 months or in adrenal weight in rats fed 100 mg/kg/day Aroclor 1242 for 3 weeks (Bruckner et al. 1973, 1974). In another study (Miller et al. 1993b), no histopathological changes were observed in the adrenals from Fischer 344 rats treated with up to 25 mg/kg/day Aroclor 1254 by gavage for 15 weeks. Rao and Banerji (1993), however, reported degenerative changes in the adrenals of Wistar rats treated with $7.1 mg/kg/day Aroclor 1260 in the diet for 120 days. The differing results from these two studies may reflect differences in the congeneric composition of the Aroclors, in strains of animals, and/or in the methods of administration.

Adrenal weight was unchanged in rabbits fed #6.5 mg/kg/day Aroclor 1254 for 8 weeks (Street and Sharma 1975), and adrenal cortex histology was normal in monkeys fed 0.2 mg/kg/day Aroclor 1254 for 12 months (Tryphonas et al. 1986a), but hormone evaluations were not performed. Pigs treated with 9.2 mg/kg/day Aroclor 1242 for 91 days exhibited increased relative weight of the adrenals (Hansen et al. 1976). No histological alterations were observed in adrenals from guinea pigs treated with #4.0 mg/kg/day Aroclor 1260 in the diet for 8 weeks (Vos and de Roij 1972). Monkeys treated with dietary doses of #0.08 mg/kg/day Aroclor 1254 for up to 22 months showed no treatment-related changes in serum hydrocortisone levels (Loo et al. 1989). Histological examinations and higher doses were not tested, and levels of other adrenal cortex hormones were not evaluated. However, Arnold et al. (1997) reported that Rhesus monkeys that received daily doses of 0.005, 0.020, 0.040, or 0.080 mg/kg/day Aroclor 1254 for 72 months showed no effect on adrenal tissue.

No histopathologic changes were observed in the adrenal, pancreas, pituitary, or parathyroid glands of male or female rats that were fed Aroclor 1016, 1242, 1254, or 1260 for 24 months at dose levels of 8.0–11.2, 4.0–5.7, 4.3–6.1, or 4.1–5.8 mg/kg/day, respectively (Mayes et al. 1998). Serum parathyroid hormone levels were not affected in rats treated with up to 25 mg/kg/day Aroclor 1254 for up to 15 weeks (Andrews 1989).

Single Congeners. Histopathologic evaluations of the adrenal glands, ovary, parathyroid, pancreas, and pituitary revealed no treatment-related changes in rats that were exposed to single PCB congeners in food for 13 weeks (Chu et al. 1994, 1995, 1996a, 1996b, 1998b; Lecavalier et al. 1997). The highest dosages in the studies were as follows: PCB 28, 3.8 (males) and 4.0 (females) mg/kg/day; PCB 77, 0.77 (males) and 0.89 (females) mg/kg/day; PCB 105, 4.0 (females) and 4.3 (males) mg/kg/day; PCB 118, 0.17 (females) and 0.68 (males) mg/kg/day; PCB 126, 7.4 (males) and 8.7 (females) µg/kg/day; PCB 128, 4.2 (males) and 4.4 (females) mg/kg/day; and PCB 153, 3.5 (males) and 4.1 (females) mg/kg/day.

Serum concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone concentrations were measured in rats exposed for 13 weeks to PCB 28 or PCB 77 in food (Desaulniers et al. 1997). No changes, relative to the control group, were observed at doses of 500 µg/kg/day PCB 28 or 75 µg/kg/day PCB 77. Acute intraperitoneal administration of PCB 126 in adult rats caused decreased serum concentrations of T_4 at $6.25 µg/kg/day, T_3 at $25 µg/kg/day, LH at $100 µg/kg/day, and FSH at 400 µg/kg/day (Desaulniers et al. 1999). Similar administration of PCB 153 caused an increase in serum T_4 and decrease in serum LH at a dose level of 25 mg/kg/day.

Evaluation of Animal Studies. Studies in animals, including rodents and nonhuman primates, provide strong evidence of thyroid hormone involvement in PCB toxicity. Although the studies differ in design and, the emerging picture is that, depending of dose and duration, PCBs can disrupt the production and levels of thyroid hormones, both in the thyroid and in peripheral tissues, can interfere with their transport to peripheral tissues, and can accelerate the metabolic clearance of thyroid hormones. Exposure to PCBs *in utero* and/or during early development (e.g., through breast milk) can deplete levels of circulating thyroid hormones in the fetus or neonate, which may give rise to effectively a hypothyroid state during development. The most convincing evidence that PCBs can exert toxicity by disrupting thyroid hormone system derives from two studies in rats. In one study, neurobehavioral deficits in pups that experienced exposures to Aroclor 1254 *in utero* and during nursing were significantly attenuated by subcutaneous injections of T_4 that increased serum T_4 and T_3 concentrations that were otherwise depressed in the PCB-exposed animals (Goldey and Crofton 1998). While this study examined relatively high doses of Aroclor 1254 ($1 mg/kg/day), it nevertheless demonstrated neurodevelopmental effects that are directly relevant to observations made in epidemiological studies and to neurological sequelae of fetal hypothyroidism, including disturbances of motor function and hearing. In the second study, increased testes weight and sperm production in rats that were administered Aroclor 1254 on postnatal days 1–25 were attenuated by injections of T_4 on postnatal days 1–25, which also prevented the depression in serum T_4 concentrations (Cooke et al. 1996). Here again, although produced by relatively large doses of Aroclor 1254 (. 40 mg/kg/day, subcutaneous), similar effects can be produced by other hypothyroid-inducing agents, including 6-propyl-2-thiouracil (PTU). Furthermore, the effects observed may reflect a disruption of the normal sexual maturation process, which is known to be associated with neonatal hypothyroidism in humans (Longcope 2000).

Certain PCBs or certain exposures to PCBs may increase serum T_4 levels at low doses and decrease serum T_4 in a dose-dependent manner at higher doses (Gould et al. 1997; Li and Hansen, 1996b; Li et al. 1994, 1998). This effect may reflect stimulation of the thyroid gland as suggested by concurrent morphological changes in the thyroid follicles.

Other effects of PCBs on endocrine function that have been observed in experimental animals include effects on the adrenal glands and serum adrenal steroid levels (Byrne et al. 1988; Kato et al. 1982a; Miller et al. 1993b; Rao ad Banerji 1993; Sanders et al. 1974; Wasserman et al. 1973). Studies that have shown depressed levels of adrenal cortical steroids in PCB-exposed animals are also relevant because depressed levels of adrenal steroids have been associated with hypothyroidism in humans (Dluhy 2000). In

hypothyroidism, this effect is thought to result from decreases in both secretion and metabolism of adrenal steroids.

3.2.2.9 Dermal Effects

3.2.2.9.1 Summary

Chloracne and other dermal alterations are well known markers of exposure to PCBs and structurally-related halogenated aromatic hydrocarbons. Chloracne and other dermal alterations have been reported in subjects occupationally exposed to PCBs and in individuals exposed by accidental ingestion of rice oil contaminated with high concentrations of PCBs, CDFs, and related chemicals (*Yusho* and *Yu-Cheng*). In general, chloracne appears in individuals with serum PCB levels 10–20 times higher than those of the general population, but there is great variability among individuals. Therefore, chloracne is not a sensitive marker of PCB exposure. Long-term oral administration of relatively low doses of PCBs to monkeys resulted in dermal alterations similar to those observed in humans exposed to high concentrations of PCBs. The dermal effects were observed in the monkeys at serum PCB levels not much higher than serum PCB levels in humans with no known point source exposure to PCBs. Offspring from monkeys exposed during gestation and nursed by exposed mothers also developed dermal alterations after a few weeks of suckling. There are reports of rodents also developing skin alterations, but only after high exposures to PCB.

3.2.2.9.2 Human Studies

3.2.2.9.2.1 Occupational Exposure

Chloracne is the most easily recognized effect of exposure to PCBs and structurally-related chlorinated organic chemicals (Rice and Cohen 1996). Chloracne is a high-dose response in animals and humans; and its presence in humans indicates exposure to PCBs and/or other chlorinated organic compounds, but its absence does not preclude such exposure. Furthermore, the variability of the response in more highly exposed individuals suggests that susceptibility varies greatly among individuals. Chloracne can first occur on the face, particularly under the eyes and behind the ears. With increasing exposure, the rest of the face and neck, upper arms, chest, back, abdomen, outer thighs, and genitalia may be affected. When severe, chloracne can cover the entire body. Clinically, changes vary from an eruption of comedones to

the occurrence of papules and pustules. Histologically, the lesions consist of keratinous cysts caused by squamous metaplasia of sebaceous glands. The acute stage is followed by vermiculite skin atrophy.

Mild to moderate chloracne was observed in 7 of 14 workers exposed to 0.1 mg/m^3 Aroclors (formulation not specified) for an average duration of 14.3 months (Meigs et al. 1954). Because PCBs were used as a heat exchange material, it is possible that the workers were exposed to such pyrolysis products as CDFs. In these workers, the chloracne was found primarily on the face, especially the cheeks, forehead, and ears. Three cases of chloracne occurred among an unspecified number of autoclave operators exposed to 5.2–6.8 mg/m^3 Aroclor 1254 for 4–7 months in 1954 (Bertazzi et al. 1987), but pyrolytic formation of CDFs is a confounding factor. In 1977, four more cases of chloracne were diagnosed among 67 workers from the same plant who were engaged in impregnating capacitors with Pyralene 3010 (0.048–0.275 mg/m^3) and had skin contact confirmed as a major exposure route. An increased incidence of nonadolescent acneform eruptions was reported in workers exposed to 0.007–11 mg/m^3 mean concentrations of various Aroclors for >5 years; 40% of the workers were exposed for >20 years (Fischbein et al. 1979, 1982). Maroni et al. (1981a, 1981b) reported 10 cases of acne and/or folliculitis and 5 cases of dermatitis among 80 capacitor manufacturing workers examined in Italy. All of the workers with chloracne were employed in high exposure jobs. Their blood PCB concentrations ranged from 300 to 500 ppb.

Other dermal effects reported in workers include skin rashes, pigmentation disturbances of skin and nails, erythema and thickening of the skin, and burning sensations (Fischbein et al. 1979, 1982; Ouw et al. 1976, 1982; Smith et al. 1982). In these studies, the workers were exposed to various Aroclors at levels as low as 0.003 mg/m^3 for >5 years. Statistically significant associations between dermatologic effects and plasma levels of higher chlorinated PCB congeners have been reported (Fischbein et al. 1979, 1982; Smith et al. 1982). No relationships between the incidence of skin rash or dermatitis and plasma levels of lower chlorinated PCBs were found (Smith et al. 1982).

3.2.2.9.2.2 Accidental Exposure

Effects in the skin were widely reported among victims of the *Yusho* and *Yu-Cheng* poisoning episodes exposure (Guo et al. 1999; Kuratsune 1989; Lu and Wu 1985; Rogan 1989). It is important to mention, however, that the findings from the studies of these groups cannot be attributed solely to exposure to PCBs since the victims also were exposed to CDFs and other chlorinated chemicals (ATSDR 1994). Characteristic skin changes included marked enlargement, elevation and keratotic plugging of follicular

orifices, comedo formation, acneform eruptions, hyperpigmentation, hyperkeratosis, and deformed nails. The acne most commonly developed on the face and other parts of the head, axillae, trunk, and external genitalia, with follicular plugging occurring in the axillae, groin, glenoid regions such as elbow and knee flexures, trunk, thigh, and outer aspect of the forearm. Dark-colored pigmentation frequently occurred in the gingival and buccal mucosa, lips, and nails, and improved only gradually in most patients (Fu 1984; Kuratsune 1989; Lu and Wu 1985; Rogan 1989). Improvement of the dermal changes was gradual. Evaluation of *Yu-Cheng* subjects 14 years after the poisoning incident showed that men and women exposed to PCBs/PCDFs had a higher lifetime prevalence of chloracne, abnormal nails, hyperkeratosis, and gum pigmentation (Guo et al. 1999). Skin lesions were commonly observed in children born to mothers with *Yusho* or *Yu-Cheng* exposure. The dermal changes are consistent with those observed in exposed adults and included hyperpigmentation of the skin, nails and gingivae, deformed nails, and acne (Funatsu et al. 1971; Gladen et al. 1990; Hsu et al. 1985; Rogan et al. 1988; Taki et al. 1969; Yamaguchi et al. 1971; Yoshimura 1974). These effects generally diminished as the babies grew older.

3.2.2.9.2.3 Evaluation of Human Studies

There is conclusive evidence that exposure to high concentrations of PCBs (and other chlorinated hydrocarbons) induce adverse dermal effects in humans. A typical dermal sign of exposure is chloracne and is generally present in individuals with blood PCB levels several times higher than background levels as observed among capacitor workers in the past and in *Yusho* and *Yu-Cheng* victims (Fischbein et al. 1979, 1982; Guo et al. 1999; Hsu et al. 1994; Maroni et al. 1981a, 1981b; Masuda 1994). It is generally accepted that chloracne is induced by exposure to dioxin-like substances (ATSDR 1998); therefore, the contribution of PCBs to this effect in *Yusho* and *Yu-Cheng* was probably minor compared to that of CDFs, which were the main contributors to the total dioxin TEQs of the rice oil. High incidence of chloracne was seen among *Yu-Cheng* victims 14 years after exposure, at a time when the body burden of PCBs and CDFs was still considerably higher than local controls (Guo et al. 1997). No adverse dermal effects have been reported in subjects with high consumption of Great Lakes fish contaminated with PCBs and other environmentally persistent chemicals or in other cohorts from the general population, although it is unknown if this outcome was systematically studied in these cohorts.

3.2.2.9.3 Animal Studies

The highest NOAEL values and all reliable LOAEL values for dermal effects for each study are recorded in Tables 3-2 and 3-3, and plotted in Figure 3-2.

Oral Exposure

Commercial Mixtures. Very limited information is available regarding dermal effects of commercial PCB mixtures following acute-duration oral exposure. Skin histology was normal in rats that were treated with a single gavage dose of 4,000 mg Aroclor 1242/kg and evaluated after 24 hours, no follow-up observations were conducted (Bruckner et al. 1973). Treatment of rats with 100 mg Aroclor 1242/kg/day by gavage every other day for 3 weeks did not result in histological alterations in the skin (Bruckner et al. 1973). Rats exposed in the diet to 2.5 mg/kg/day Aroclor 1254 for 104 weeks or to 5 mg/kg/day for 72 weeks developed alopecia and facial edema (NCI 1978); these effects did not occur after 104 weeks at 1.25 mg/kg/day. No histopathologic changes were observed in the skin of rats that were fed Aroclor 1016, 1242, 1254, or 1260 for 24 months at dose levels of 8.0–11.2, 4.0–5.7, 4.3–6.1, or 4.1–5.8 mg/kg/day, respectively (Mayes et al. 1998). Guinea pigs fed a diet that provided up to approximately 4 mg Aroclor 1260/kg/day for 8 weeks showed no treatment-related gross or microscopical alterations of the skin (Vos and de Roij 1972). Mice treated with 26 mg Aroclor 1254/kg/day in the diet for 23 weeks developed erythema, altered sebaceous gland differentiation, and thickening with occasional hyperkeratosis and cysts in the pinna; other skin areas were not examined (Bell 1983).

Dermal effects were reported in Rhesus monkeys fed diets containing Aroclors for intermediate durations (Allen and Norback 1973, 1976; Allen et al. 1973, 1974a; Barsotti et al. 1976; Becker et al. 1979; Ohnishi and Kohno 1979; Thomas and Hinsdill 1978). These include facial edema (particularly in the periorbital area), acne, folliculitis, and alopecia. The effects appear to be reversible and have been produced by estimated doses as low as 0.1 mg/kg/day Aroclor 1248 for 2 months (Barsotti et al. 1976) and 0.12 mg/kg/day Aroclor 1242 for 2 months (Becker et al. 1979). NOAELs for these effects in monkeys cannot be identified from the available studies. Chronic dietary treatment with 0.1 mg Aroclor 1248/kg/day for 12 months (Allen and Norback 1976) or 0.2 mg/kg/day Aroclor 1254 for 12–28 months (Arnold et al. 1990; Tryphonas et al. 1986a, 1986b) produced progressive dermal effects in monkeys, including alopecia, periorbital edema, acne, fingernail loss, and gingival hyperplasia and necrosis of varying severity (Tryphonas et al. 1986b). The same group of investigators also reported fingernail and toenail changes in monkeys during treatment with as little as 0.005 mg/kg/day

Aroclor 1254 over a 37-month period or 0.04 mg/kg/day over a 72-month period (Arnold et al. 1993a, 1997). Offspring from Rhesus monkeys treated before mating and during gestation with 0.03 mg Aroclor 1016/kg/day showed hyperpigmentation (Barsotti and Van Miller 1984). Doses even smaller of Aroclor 1254 (0.005 mg/kg/day) produced clear signs of PCB intoxication manifested as inflammation and/or enlargement of the tarsal glands, and nail and gum lesions (but not acne or hyperpigmentation) in monkeys exposed during gestation and via breast milk for 22 weeks (Arnold et al. 1995, 1997). Most of these alterations were seen after the infants had been weaned. The concentration of PCBs in breast milk from dams treated with 0.005 mg/kg/day ranged from 5.6 to 15.6 ppm. The geometric mean concentration of PCBs in the blood of these infants after 22 weeks of nursing was 47 ppb (Arnold et al. 1995).

Single Congeners. Treatment of female and male weanling Sprague-Dawley rats for 90 days with several PCB congeners in the diet, both dioxin-like and nondioxin-like (PCBs 28, 77, 105, 118, 126, 128, 153), did not result in any treatment-related histological alterations in the skin (Chu et al. 1994, 1995, 1996a, 1996b, 1998a, 1998b; Lecavalier et al. 1997). Doses ranged from 0.009 mg/kg/day for the dioxin-like PCB 126 to approximately 4 mg/kg/day for some mono- and di-*ortho*-substituted congeners.

Dermal Exposure

Commercial Mixtures. Skin appearance and histology was normal in three hairless mice dermally treated with Aroclor 1254 in estimated doses of up to 136 mg/kg/day on 4 days/week for 6 weeks (Puhvel et al. 1982). Aroclor 1254 was applied in either pure acetone or in acetone-mineral oil emulsion; few experimental details were provided in this study. Dermal effects were produced by application of Aroclor 1260 in an isopropanol vehicle to the shaved back skin of female New Zealand rabbits 5 days/week for 28 or 38 days at estimated doses of 42–44 mg/kg/day (Vos and Beems 1971; Vos and Notenboom-Ram 1972). Effects included thickening of the skin and acneform lesions resulting from hyperplasia and hyperkeratosis of the epidermal and follicular epithelium.

3.2.2.9.4 Evaluation of Animal Studies

PCB-related cutaneous effects are well characterized in monkeys after long-term oral exposure to commercial PCB mixtures and are generally similar to those observed in humans. Infant monkeys exposed *in utero* and via breast milk also developed similar dermal lesions. Chronic-duration oral exposure studies in monkeys showed that adverse dermal effects can occur at dose levels lower than had

been previously observed (Arnold et al. 1993a, 1993b, 1995, 1997). It should be pointed out that dermal effects in monkeys appeared with doses that resulted in tissue (5 ppm) and blood levels (10 ppb) of PCBs near background concentrations found in the general human population. In general, adverse cutaneous effects in rodents followed exposure to relatively high oral doses of PCBs. The series of studies with single congeners by Chu and coworkers found no significant dermal effects at the dose levels tested, and no conclusions regarding a potential ranking for dermatotoxicity of congeners can be drawn based on these studies (Chu et al. 1994, 1995, 1996a, 1996b, 1998a, 1998b; Lecavalier et al. 1997).

3.2.2.10 Ocular Effects

3.2.2.10.1 Summary

Along with dermal alterations, adverse ocular effects are markers of exposure to PCBs and structurally-related halogenated aromatic hydrocarbons. Ocular effects consisting primarily of hypersecretion of the Meibomian glands and abnormal pigmentation of the conjunctiva have been reported in subjects occupationally exposed to PCBs and in individuals exposed by accidental ingestion of rice oil contaminated with high concentrations of PCBs, CDFs, and related chemicals (*Yusho* and *Yu-Cheng*). In general, these effects appear in individuals with serum PCB levels 10–20 times higher than those of the general population, but there is great variability among individuals. Long-term oral administration of relatively low doses of PCBs to monkeys resulted in ocular alterations similar to those observed in humans exposed to high concentrations of PCBs. The ocular effects were observed in the monkeys at serum PCB levels not much higher than serum PCB levels in humans with no known high exposure to PCBs. Offspring from monkeys exposed during gestation and nursed by exposed mothers developed similar ocular alterations after a few weeks of suckling.

3.2.2.10.2 Human Studies

3.2.2.10.2.1 Occupational Exposure

The primary ocular effects reported by workers exposed to airborne PCBs were eye irritation, tearing, and burning (Emmett et al. 1988a; Ouw et al. 1976; Smith et al. 1982). The workers had been exposed to a variety of Aroclors at concentrations between 0 and 2.2 mg/m^3 for >3 years. A significant relationship between the incidence of irritated, burning eyes and plasma levels of higher and lower chlorinated PCB congeners has been found (Smith et al. 1982). Emmett et al. (1988a) suggested that because PCBs have

low volatility and are relatively nonirritating, 1,1,1-trichloroethane used to clean up spills or trichlorobenzene in Askarel may have been responsible for the complaints.

An ocular examination of 181 workers at a capacitor manufacturing plant revealed a 13% prevalence of edema of the upper eyelid, congestion or hyperemia of conjunctiva, eye discharge, and enlargement of Meibomian glands following exposure to 0.007–11 mg/m^3 mean concentrations of various Aroclors for >5 years (Fischbein et al. 1985). The median blood value of lower homologues of PCBs was approximately 60 ppb and of the higher homologues, 18 ppb. There was no significant association between ocular abnormalities and blood concentrations of PCBs (Fischbein et al. 1985).

3.2.2.10.2.2 Accidental Exposure

In addition to dermal effects, ocular effects were the most obvious manifestations of *Yusho* and *Yu-Cheng* exposure (Fu 1984; Kuratsune 1989; Lu and Wu 1985; Rogan 1989). As previously mentioned, victims of these poisoning episodes also were exposed to CDFs and other chlorinated chemicals (ATSDR 1994). Hypersecretion of the Meibomian glands and abnormal pigmentation of the conjunctiva were commonly observed (Masuda 1994). Typical cases showed swollen Meibomian glands filled with yellow infarct-like contents. Abnormal changes in the Meibomian glands as well as eye discharge were still seen 10 years after the poisoning incident (Kono and Yamana 1979). The incidence of ocular signs was closely related to PCB concentrations and patterns in blood. Babies born to *Yusho* mothers also had increased eye discharge. Similar findings were seen in children born to *Yu-Cheng* mothers who also showed high incidence of conjunctivitis, swelling of the eyelid, and eye discharge (Rogan et al. 1988).

3.2.2.10.2.3 Evaluation of Human Studies

There is sufficient evidence that exposure to high concentrations of PCBs (and other chlorinated hydrocarbons) induce adverse ocular effects in humans. Typical responses include hypersecretion of the Meibomian glands and abnormal pigmentation of the conjunctiva. This has been observed among capacitor workers (Fischbein et al. 1985) and in *Yusho* and *Yu-Cheng* victims (Hsu et al. 1994; Kono and Yamana 1979; Kuratsune 1989; Masuda 1994; Rogan et al. 1988). The contribution of PCBs to this effect in *Yusho* and *Yu-Cheng* is unknown since the victims also were exposed to CDFs and other structurally-related chemicals. In the occupationally-exposed subjects described by Fischbein et al. (1985), PCBs seemed to have been responsible for the high incidence of ocular effects since there was no apparent exposure to CDFs or similar chemicals, although such possibility could not be completely ruled

out. No adverse ocular effects have been reported in subjects with high consumption of Great Lakes fish contaminated with PCBs and other environmentally persistent chemicals or in other cohorts from the general population, although it is unknown if this outcome was systematically studied in these cohorts.

3.2.2.10.3 Animal Studies

The highest NOAEL values and all reliable LOAEL values for ocular effects for each study are recorded in Table 3-2 and plotted in Figure 3-2.

Oral Exposure

Commercial Mixtures. Ocular effects were commonly observed in Rhesus monkeys fed diets containing Aroclors for intermediate durations (Allen and Norback 1973, 1976; Allen et al. 1973, 1974a; Barsotti et al. 1976; Becker et al. 1979; Ohnishi and Kohno 1979; Thomas and Hinsdill 1978). The effects consisted of swelling and reddening of the eyelid and eyelid discharge. Females appear to be more sensitive than males. The effects appear to be reversible and have been produced by estimated doses as low as 0.1 mg/kg/day Aroclor 1248 for 2 months (Barsotti et al. 1976) and 0.12 mg/kg/day Aroclor 1242 for 2 months (Becker et al. 1979). NOAELs for these effects in monkeys were not identified in the available studies. Monkeys exposed to 0.005–0.08 mg/kg/day Aroclor 1254 for 37 months showed characteristic dose-related ocular and dermal effects, including eye exudate, inflammation and/or prominence of the tarsal (Meibomian) glands, and various finger and toe nail changes (Arnold et al. 1993a). Eye inflammation is a result of metaplastic changes in the Meibomian glands, which cause the glands to be come keratinaceous. Conjunctivitis was observed in Rhesus monkeys treated in the diet with 0.2 mg/kg/day Aroclor 1254 for 12 months (Tryphonas et al. 1986a). Exophthalmia was observed in rats treated in the diet with 2.5 mg/kg/day Aroclor 1254 for 104–105 weeks (NCI 1978); a dietary level of 1.25 mg/kg/day Aroclor 1254 was a NOAEL. No histopathologic changes were observed in the eye of male or female rats that were fed Aroclor 1016, 1242, 1254, or 1260 for 24 months at dose levels of 8.0–11.2, 4.0–5.7, 4.3–6.1, or 4.1–5.8 mg/kg/day, respectively (Mayes et al. 1998).

Single Congeners. Treatment of female and male weanling Sprague-Dawley rats for 90 days with several PCB congeners in the diet, both dioxin-like and nondioxin-like (PCBs 28, 77, 105, 118, 126, 128, 153), did not result in any treatment-related histological alterations in the eye or optic nerve (Chu et al. 1994, 1995, 1996a, 1996b, 1998b; Lecavalier et al. 1997). Doses ranged from 0.009 mg/kg/day for the dioxin-like PCB 126 to approximately 4 mg/kg/day for some mono- and di-*ortho*-substituted congeners.

3.2.2.10.4 Evaluation of Animal Studies

PCB-induced ocular effects are well characterized in monkeys after long-term oral exposure to commercial PCB mixtures and are generally similar to those observed in humans. Infant monkeys exposed *in utero* and via breast milk also developed similar ocular lesions (Arnold et al. 1995). Chronic-duration oral exposure studies in monkeys showed that adverse ocular and dermal effects occurred at doses of 0.005 mg/kg/day (Arnold et al. 1993a, 1993b, 1995, 1997). Because these effects occurred at the lowest tested dose of any PCB mixture in any species, they are used as part of the basis for the chronic-duration MRL for oral exposure as discussed in Chapter 2 and Appendix A. It is worth mentioning that ocular effects appeared in monkeys given PCB doses that resulted in tissue (5 ppm) and blood levels (10 ppb) of PCBs near background concentrations found in the general human population. The series of studies with single congeners by Chu and coworkers found no significant effects in the eye and optic nerve at the dose levels tested and no conclusions regarding a potential ranking for oculotoxicity of congeners can be drawn based on these studies (Chu et al. 1994, 1995, 1996a, 1996b, 1998; Lecavalier et al. 1997).

3.2.2.11 Body Weight Effects

3.2.2.11.1 Human Studies

No studies were located regarding body weight effects in humans after exposure to PCBs.

3.2.2.11.2 Animal Studies

A number of animal studies have shown that inhalation, oral, or dermal exposure to PCBs results in decreases in body weight gain. Body weight gain was decreased in guinea pigs and mice that were intermittently exposed to 5.4 mg/m^3 Aroclor 1254 over 121 days or in guinea pigs exposed to 1.5 mg/m^3 Aroclor 1254 over 213 days (Treon et al. 1956). Exposure-related changes in body weight were not observed in rats or rabbits that were similarly exposed to 1.5 or 5.4 mg/m^3 Aroclor 1254 or to 8.6 mg/m^3 Aroclor 1242 over 24 days. The concentrations of PCBs are uncertain due to an invalid analytical technique and differential evaporation of the most volatile PCB congeners. A decrease in body weight gain was also observed in rats exposed to 0.009 mg/m^3 Aroclor 1242 for 30 days (Casey et al. 1999); the rate of body weight gain was 33% as compared to 39% in controls.

Reduced body weight (or reduced weight gain) is a characteristic effect of oral exposure to PCBs in animals. Acute-duration studies have shown moderate to severe weight decreases in rats following a single gavage dose of $4,000 mg/kg Aroclor 1242 or dietary administration of 50 mg/kg/day Aroclor 1254 for 14 days (Bruckner et al. 1973; Kling et al. 1978). No significant effect on weight gain was reported in rats administered up to 25 mg/kg/day Aroclor 1254 in several acute-duration studies (Brown and Lamartiniere 1995; Carter 1984, 1985; Carter and Koo 1984) or in rats administered four daily doses of 25 mg/kg of Aroclor 1221 (Brown and Lamartiniere 1995). The weight loss following single high doses appears to be due to dehydration (Bruckner et al. 1973). Effects on animal body weight are often pronounced following intermediate- and chronic-duration dietary administration, constituting a wasting syndrome. Decreases in body weight or body weight gain relative of different toxic doses have been observed with various species and Aroclor mixtures, including rats and minks fed Aroclor 1254 (Andrews 1989; Bleavins et al. 1980; Gray et al. 1993; Hornshaw et al. 1986; Kimbrough et al. 1972; Kling et al. 1978; Mayes et al. 1998; NCI 1978; Phillips et al. 1972), rats fed Aroclor 1260 (Kimbrough et al. 1972), pigs fed Aroclor 1254 or 1242 (Hansen et al. 1976), and monkeys fed Aroclor 1242 or 1248 (Allen 1975; Allen and Norback 1976; Allen et al. 1973; Becker et al. 1979), but not Aroclor 1254 (Arnold et al. 1993a, 1993b, 1997; Tryphonas et al. 1986b). The body weight from guinea pigs treated with 4 mg/kg/day Aroclor 1260 for 187 days was not altered by treatment (Vos and de Roij 1972). In general, Aroclors administered to rats in doses of #5 mg/kg/day for intermediate durations did not significantly affect body weight (Bruckner et al. 1974, 1977; Byrne et al. 1987; Goldstein et al. 1974; Huang et al. 1998a, 1998b). Rats that were fed Aroclor 1254 for 24 months at dose levels of 1.4–6.1 mg/kg/day had final body weights that were 12–28% lower than unexposed animals (Mayes et al. 1998). Decreased body weight was also observed following similar exposure to Aroclor 1242 (10% reduction at 5.7 mg/kg/day), but not to Aroclor 1016 (2.0–11.2 mg/kg/day) or Aroclor 1260 (1.0–5.8 mg/kg/day). The existing data indicate that monkeys and minks may be particularly susceptible species, as effect levels were higher in rats and adverse effects on body weight were not observed in rabbits and mice fed Aroclor 1254 (Kimbrough and Linder 1974; Street and Sharma 1975). Food and water consumption were not measured in most of these studies, but in general decreases in food and water intake were not sufficient to account for the decreases in body weight. In swine and sheep fed Aroclors 1242 and 1254 at 20 ppm in the diet, feed efficiency (unit gain/unit feed) were decreased about the same degree as by diet variations (Hansen et al. 1976).

Body weight gain was not adversely affected in rats fed diets containing #4.1 mg/kg/day of PCB 153 (Chu et al. 1996a), #4.2 mg/kg/day of PCB 128 (Lecavalier et al. 1997), #4.0 mg/kg/day of PCB 105 (Chu et al. 1998b), #3.7 mg/kg/day of PCB 28 (Chu et al. 1996b), #0.77 mg/kg/day of

PCB 77 (Chu et al. 1995), or #0.17 mg/kg/day of PCB 118 (Chu et al. 1995). A significant decrease in body weight gain was observed in rats fed diets containing 7.4 mg/kg/day of PCB 126 (Chu et al. 1994) for 13 weeks.

A significant reduction in body weight gain was observed in rabbits that received estimated doses of 42–44 mg/kg of Aroclor 1260 in isopropanol 5 days/week for 28 or 38 days applied to the shaved back skin (Vos and Beems 1971; Vos and Notenboom-Ram 1972). These studies tested small numbers of rabbits (four) and used Aroclor 1260 that had undetectable levels (<1 ppm) of CDFs.

The highest NOAEL values and all reliable LOAEL values for body weight effects for each study are recorded in Tables 3-1, 3-2, and 3-3, and plotted in Figures 3-1 and 3-2.

3.2.2.12 Other Systemic Effects

Inhalation and oral exposure to Aroclor 1242 resulted in epithelial hyperplasia in the urinary bladders of rats near continuously (23 hours/day) exposed to 0.009 mg/m^3 or 0.033 mg/kg/day in the diet for 30 days (Casey et al. 1999). In contrast, no effects on the urinary bladder were reported in a study by Mayes et al. (1998) involving chronic oral exposure to approximately #6 mg/kg/day Aroclor 1242, 1254, and 1260 or #11 mg/kg/day Aroclor 1016. Additionally, no urinary bladder effects were noted in a series of dietary exposure studies on single PCB congeners in which rats were exposed to #4.1 mg/kg/day of PCB 153 (Chu et al. 1996a), #4.2 mg/kg/day of PCB 128 (Lecavalier et al. 1997), #4.0 mg/kg/day of PCB 105 (Chu et al. 1998b), #3.7 mg/kg/day of PCB 28 (Chu et al. 1996b), #0.77 mg/kg/day of PCB 77 (Chu et al. 1995), #0.17 mg/kg/day of PCB 118 (Chu et al. 1995) or #7.4 mg/kg/day of PCB 126 (Chu et al. 1994) for 13 weeks.

3.2.3 Immunological and Lymphoreticular Effects

3.2.3.1 Summary

Immunologic changes have been observed in human populations exposed to mixtures of PCBs and other persistent toxic substances. Alterations have been associated with consumption of contaminated fish and other marine foods, consumption of contaminated rice oil in the *Yusho* and *Yu-Cheng* poisoning incidents, and general environmental exposures. Findings include increased susceptibility to respiratory tract infections in adults and their children, increased prevalence of ear infections in infants, decreased total

serum IgA and IgM antibody levels, and/or changes in T lymphocyte subsets. Overall, there is a consistency of effects among the human studies suggesting sensitivity of the immune system to PCBs, particularly in infants exposed *in utero* and/or via breast feeding. However, due to the mixed chemical nature of the exposures and generally insufficient information on exposure-response relationships, the human studies provide only limited evidence of PCB immunotoxicity. In contrast to the human data, immunotoxicity of PCBs has been documented in animals that were exposed via commercial mixtures, mixtures of congeners analogous to human breast milk, Great Lakes fish, or single congeners. Effects of commercial PCBs in rats, mice, guinea pigs, and rabbits included morphological and functional changes, such as thymic and splenic atrophy, reduced antibody production against foreign antigens, such as tetanus toxoid and sheep red blood cells (SRBC), and increased susceptibility to microbial infection. Oral studies of commercial mixtures in monkeys confirm the observations in other species and further indicate that the immune system of nonhuman primates is particularly sensitive to PCBs. Suppressed antibody responses to SRBCs is the parameter most consistently affected by PCBs in monkeys and have been observed in adult animals, infants exposed during gestation and lactation, and infants exposed postnatally to a PCB congener mixture simulating the congener content of human milk. Immunological assessments of rodents that were fed Great Lakes fish containing PCBs and other chemicals were generally limited although some alterations were observed that are similar to those in animals exposed to commercial PCB mixtures.

3.2.3.2 Human Studies

Occupational Exposures. A limited amount of information is available on immunological end points in PCB-exposed workers because assessments in most occupational studies were limited to routine clinical measurements of white blood cell (WBC) counts and serum proteins and did not include assessment of immunocompetence. Total and differential WBC counts were determined in 194 capacitor plant workers (152 males, 42 females) who were exposed to Aroclors 1254, 1242, and/or 1016 for an average duration of 17 years (Lawton et al. 1985a). Mean area air concentrations of PCBs were 0.69 mg/m^3 in 1975 and 0.16 mg/m^3 in 1983, and average personal time-weighted average (TWA) levels in 1977 were 0.17 mg/m^3; all PCB use was discontinued in 1977. Clinical examinations in 1976 showed some elevations in total WBCs associated with decreased PMN cells and increased lymphocytes, monocytes, and eosinophils. In 1979, the WBC and lymphocyte counts were near normal and the increases in monocytes and eosinophils were marginal, although there was a strong association between serum PCB levels and monocyte counts.

Other studies of PCB-exposed workers did not report any effects on total and differential WBC counts or changes in serum albumin, globulin, and/or total proteins (Chase et al. 1982; Maroni et al. 1981b; Smith et al. 1982). These included studies of 86 men exposed to unreported levels of unspecified PCBs via transformer fluids for an average of 17 years (Chase et al. 1982), 40 men and 40 women exposed mainly to Pyralene 3010 or Apirolio (Italian PCB formulations containing 42% chlorine) at concentrations ranging from 0.048 to 0.275 mg/m^3 for an average duration of 12 years (Maroni et al. 1981b), 228 electrical equipment manufacturing workers exposed to Aroclor 1242 and 1016 (sex and exposure duration not reported) at a median personal TWA air concentration of 0.081 mg/m^3 (Smith et al. 1982), and 14 and 25 electrical utility workers exposed to Askarel (Aroclor 1254 or 1260 either alone or in combination with tri- or tetrachlorobenzenes) at personal TWA levels of 0.037–0.215 mg/m^3 and 0.0031–0.0823 mg/m^3, respectively (Smith et al. 1982). Exposure durations and worker gender were not reported in the Smith et al. (1982) study.

Delayed-type hypersensitivity was not affected in 55 transformer repairmen compared to 56 unexposed workers who were matched for age, race, and marital status (Emmett et al. 1988a, 1988b). The mean length of employment of the exposed workers was 3.75 years, most (38) of the workers were currently exposed to PCBs, and the predominant exposure was from Aroclor 1260. Measurements of air PCB levels at four work areas showed 8-hour TWA concentrations of 0.0167–0.024, 0.0032–0.007, 0.00001–0.0004, and 0.0007–0.0124 mg/m^3. The percentages of exposed and control workers with positive skin responses to mumps antigen (92 vs. 89%) and trichophyton antigen (17 vs. 8%) were not significantly different, and the mean diameters of the skin reactions were identical in the two groups. Other immunologic end points were not evaluated in the study, and none of the workers had clinical manifestations typical of PCB poisoning.

Contaminated Fish Consumption. Immunological parameters were compared in a group of 23 Swedish men with high consumption of fatty fish species from the Baltic Sea and 20 men with virtually no fish consumption (Svensson et al. 1994). Evaluation of white cell counts, numbers of total lymphocytes and their subsets, and serum immunoglobulin levels showed indications of reduced natural killer (NK) cell activity. The proportions and numbers of NK cells were marginally lower in the fisheaters than in the nonconsumers, although the differences were not statistically significant ($p>0.05$), and the weekly intake of fatty fish was negatively correlated with NK cell activity ($r= -0.32$, $p<0.04$). Concurrent measurements of blood PCBs were not performed. Data from some of the subjects obtained 3 years prior to the study showed weak negative correlations between numbers of NK cells and blood levels of PCB 126 and

PCB 118, but a similar correlation was also found for *p,p'*-DDT. Information on the presence and incidence of infections was not reported.

Lymphocyte subsets were also evaluated in 68 Latvian fisherman who consumed fatty fish from the Baltic Sea (Hagmar et al. 1995). The study group was divided into groups of 19, 24, and 25 subjects with low, intermediate, or high fish consumption (average 0.3, 3.3, and 12 meals/month, respectively). PCBs were not measured in the subjects or fish. High fish consumption was correlated positively with B cell numbers (r=0.41, p=0.0008) and $CD4^+/CD8^+$ ratios (r=0.40, p=0.001), but negatively with levels of cytotoxic ($CD8^+$) T cells (r= -0.38, p=0.002).

Information has been reported on infectious illnesses in breast-fed infants whose mothers consumed contaminated Great Lakes fish (Smith 1984). Seventy-three mother/infant pairs from Sheboygan, Wisconsin were divided into three groups: women who breast-fed and ate Lake Michigan or Sheboygan River fish at least twice a month for $3 years (Group 1, 23 pairs); women who breast-fed and ate Lake Michigan or Sheboygan River fish not more than twice a year for #3 years (Group 2, 39 pairs); and women who bottle-fed and ate Lake Michigan or Sheboygan River fish at least twice a month for $3 years (Group 3, 11 pairs). Mean PCB concentrations in maternal serum (5.48–5.76 ppb) and breast milk fat (1.13–1.14 ppm) were similar among the three exposure groups and at two postnatal sampling times (during the second month and at 4 months of age); PCB levels in maternal serum during pregnancy or in umbilical cord blood were not determined. There were no significant group differences in the mean number of infectious illnesses (colds, earaches, and flu symptoms) during the first 4 months of life. The number of infectious illnesses in the infants (r=0.33, p=0.03) was positively and significantly associated with maternal serum PCB level, although infant illnesses had a weak but significantly negative association with breast milk PCBs. Possible associations between infectious illnesses and other chemicals in the fish were not investigated.

Susceptibility to infections and immune status was studied in 98 breast-fed and 73 bottle-fed Inuit (Eskimo) infants from Arctic Quebec, Canada (Dewailly et al. 2000). The Inuits have high body burdens of various organochlorine compounds (2–10 times higher than those of southern Quebec populations) due to high consumption of marine foods, particularly sea mammal fat. Concentrations of PCBs and other chlorinated pesticides or metabolites were measured in early breast milk fat and used as an index of prenatal exposure to these substances; *p,p'*-DDE showed the highest mean concentration (962 ppb), followed by PCBs (621 ppb; sum of congeners 138, 153, and 180), hexachlorobenzene (107 ppb), dieldrin (30 ppb), and mirex (14 ppb) (Dewailly et al. 1993). Prenatal organochlorine exposure was not

determined in the bottle-fed infants. The number of infectious disease episodes and status of immunologic parameters (WBCs, total lymphocytes and lymphocyte subsets, serum immunoglobulins) were evaluated during the first year of life. Acute otitis media was the most frequent health problem during the first year of life, with 80.0% of ever breast-fed and 81.3% of bottle-fed infants experiencing at least one episode. Relative risk (RR) analysis by follow-up period and number of episodes showed associations between increasing prenatal exposure to organochlorine compounds and otitis media that were more consistent for hexachlorobenzene and *p,p'*-DDE than PCBs. For example, although RRs of experiencing at least one episode of otitis media during the first year of life were similar for hexachlorobenzene (RR, 1.49; 95% CI, 1.10–2.03), *p,p'*-DDE (RR, 1.52; CI, 1.05–2.22), and PCBs (RR 1.28; CI, 0.92–1.77) for the highest tertile of prenatal exposure compared to the lowest tertile, the RR of recurrent otitis media ($3 episodes) was 1.49 (95% CI, 1.10–12.56), 3.48 (CI, 0.86–14.11), and 1.65 (CI, 0.49–5.57), respectively. However, because these and other detected organochlorine compounds originated from the same few food items and have concentrations in breast milk that are correlated with each other due to similar properties such as lipid solubility and persistence, the results precluded identification of which compounds could be responsible for the increased susceptibility to otitis media. Immunologic parameters that were significantly lower in the breast-fed babies compared to the bottle-fed group included numbers of WBCs and lymphocytes (CD4 subtype) at 3 months of age, and serum IgA concentrations at 7 and 12 months of age; CD4/CD8 lymphocyte ratios (helper T-cells/cytotoxic T-cells) were also reduced in the breast-fed infants at 7 and 12 months of age, although the change did not reach statistical significance. None of the immune parameters were associated with prenatal organochlorine exposure.

Yusho and Yu-Cheng Exposures. Clinical observations strongly suggest that *Yusho* and *Yu-Cheng* patients experienced frequent or more severe skin and respiratory infections and lowered resistance to illness (Kuratsune 1989; Nakanishi et al. 1985; Rogan 1989; Shigematsu et al. 1971). Children born to mothers who had *Yu-Cheng* disease had higher prevalence of bronchitis or pneumonia at 6 months of age, respiratory tract infections at 6 years of age, and middle ear infections at 6–14 years of age (Chao et al. 1997; Yu et al. 1998). Total serum levels of IgA and IgM, but not IgG, were reduced in *Yusho* and *Yu-Cheng* patients (Chang et al. 1981; Shigematsu et al. 1971). Other assessments of *Yu-Cheng* patients found various other immunologic changes, including lower percentages of monocytes and PMN leukocytes with immunoglobulin and complement receptors, reduced T lymphocytes apparently due to reduced T-helper/inducer cells, and suppressed dermal delayed-type hypersensitivity responses to streptokinase/streptodornase antigen mixtures tested 1 year after exposure and tuberculin antigen tested 4 years after exposure (Chang et al. 1981, 1982a, 1982b; Lu and Wu 1985). Lymphoproliferative

responses of peripheral lymphocytes to T-cell mitogens (PHA, pokeweed mitogen [PWM], and tuberculin) were significantly enhanced in *Yu-Cheng* patients (Lu and Wu 1985).

General Population Exposures. Immunologic effects of pre- and postnatal environmental exposure to PCBs and dioxins were assessed in a subgroup of 55 infants (Weisglas-Kuperus et al. 1995) from the Dutch Mother-Child study summarized in Section 3.2.4.2.1.2 (Neurological Effects). Prenatal PCB/dioxin exposure was estimated by the sum of PCB congeners 118, 138, 153, and 180 in maternal blood during the last month of pregnancy and the total TEQ level in maternal milk (17 dioxin and 8 dioxin-like PCB congeners), and postnatal exposure was calculated as a product of the total TEQ level in human milk multiplied by the weeks of breast-feeding. No correlation was found between pre- or postnatal exposure and the number of episodes of rhinitis, bronchitis, tonsillitis, and otitis during the first 18 months of life, or with humoral immunity as evaluated by antibody levels to mumps, measles, and rubella at 18 months of age (infants were immunized at 14 months of age). Determination of monocyte, granulocyte, and lymphocyte counts in cord and venous blood at 3 and 18 months of age showed that a higher prenatal as well as postnatal PCB/dioxin exposure was associated with lower monocyte and granulocyte counts at 3 months of age, and that a higher prenatal exposure was associated with increased total numbers of T-lymphocytes and several T-cell subpopulations ($CD8^+$, $TcR\alpha\beta^+$, and $TcR\gamma\delta^+$) at 18 months of age. There were no significant associations between postnatal PCB/dioxin exposure and T cell markers at 18 months of age. Although there were differences in the leukocyte subpopulation between high and low PCB/dioxin-exposed infants, all values were within the normal range (Weisglas-Kuperus et al. 1995). Follow-up evaluations at 42 months of age, reported as a study abstract, found that prenatal PCB exposure was associated with increased T cell numbers and lower antibody levels to mumps, measles, and rubella (Weisglas-Kuperus 2000). Additionally, a higher prevalence of recurrent middle ear infections and chicken pox and a lower prevalence of allergic reactions was reported to be associated with PCB body burden at 42 months of age.

Evaluation of Human Studies. Limited information on immunological effects of PCBs in humans is available from studies of people exposed in the workplace, by consumption of contaminated fish and other marine foods, by consumption of contaminated rice oil in the *Yusho* and *Yu-Cheng* poisoning incidents, and via general environmental exposures. A comparison of PCB levels in blood and breast milk in some of these studies is included in Appendix A.

One study of PCB-exposed workers found no effects on delayed-type hypersensitivity skin reactions to the mumps and trichophyton antigens (Emmett et al. 1988a, 1988b). Other occupational studies reported

no changes in serum albumin, globulin, and/or total proteins, although a transient effect on total and differential WBC counts has been observed (Chase et al. 1982; Lawton et al. 1985a; Maroni et al. 1981b; Smith et al. 1982). Functional and other immunologic end points were not evaluated in any of the worker studies, precluding an assessment of the potential for adverse immune effects following occupational exposure.

The number of infant infectious illnesses (colds, earaches, and/or flu symptoms) during the first 4 months of life were positively correlated with maternal serum PCB levels in a study of women who consumed contaminated Great Lakes fish (Smith 1984), although other immunological end points and possible associations with other chemicals in the fish were not investigated. Susceptibility to infections was also studied in infants of Inuit women who had elevated body burdens of PCBs and other organochlorine chemicals due to high consumption of sea mammal fat (Dewailly et al. 2000). Associations between risk of acute otitis media and increasing organochlorine exposure (levels in breast milk) during the first year of life were found, although the data are insufficient for identifying whether the effect may be due to PCBs, hexachlorobenzene, *p,p'*-DDE, or other chemicals. No statistically significant changes in immunological indices were observed, although there were indications of reduced total serum IgA levels and altered T-lymphocyte subpopulations in breast-fed Inuit infants at 7 and 12 months of age.

Immunotoxic effects have been documented in the *Yusho* and *Yu-Cheng* populations and include changes consistent with those reported in the Inuit and Great Lakes populations, particularly increased middle ear and respiratory tract infections in children of exposed mothers and changes in T lymphocytes and their subsets (Chang et al. 1981, 1982a, 1982b; Chao et al. 1997; Kuratsune 1989; Lu and Wu 1985; Nakanishi et al. 1985; Rogan 1989; Shigematsu et al. 1971; Yu et al. 1998). The Dutch environmental exposure study (Weisglas-Kuperus et al. 1995) also found some changes in lymphocyte T cell subpopulations in infants (although all values were within the normal range), but the clinical significance of these alterations is unclear because there was no significant correlation between the incidence of infection (otitis, rhinitis, bronchitis, or tonsillitis) or antibody levels to common childhood vaccines (mumps, measles, or rubella) during the first 18 months of life and pre- or postnatal exposure to PCBs and dioxins. The human populations that have been studied differ greatly with respect to sources of PCB exposure and consequently are likely to vary with respect to both organochlorine contaminants and nutrient contents which may affect susceptibility to infections. Although the studies are insufficient for determining which specific chemical(s) may be responsible for the observed alterations, the available data support a possible association between PCBs and immune effects in humans that may be manifested as compromised ability to overcome infections, particularly in infants exposed *in utero* and/or by breast-feeding.

3.2.3.3 Animal Studies

The highest NOAEL values and all reliable LOAEL values for immunological and lymphoreticular effects for each study are recorded in Tables 3-2 and 3-3, and plotted in Figure 3-2.

3.2.3.3.1 Inhalation Exposure

No studies were located regarding immunological or lymphoreticular effects in animals following inhalation exposure to PCBs.

3.2.3.3.2 Oral Exposure

Commercial PCB Mixtures. Information on the immunotoxicity of commercial PCBs in orally-exposed animals is available from intermediate- and chronic-duration studies in various species. Findings in nonhuman primates are emphasized in the following summary because monkeys appear to be more sensitive than other species and provide a better animal model due to phylogenetic and biologic similarities to humans (Tryphonas 1994, 1995).

Aroclor 1260 and Similar Mixtures. Immunological effects of 60% chlorinated PCB mixtures were investigated in several guinea pig studies. Dietary exposure to Aroclor 1260 for 8 weeks caused decreases in gamma globulin-containing cells in popliteal lymph nodes following foot pad stimulation with tetanus toxoid at estimated doses of 0.8 and 4 mg/kg/day (lower doses not tested), although the magnitude of response was not dose-related. Increased mesenteric lymph node weights were also observed at $0.8 mg/kg/day, but there were no consistent changes in cervical lymph node weights or serum levels of albumin or globulins. Leukocyte counts and histology of the lymph nodes, thymus, and spleen were unaffected (Vos and de Roij 1972). Effects in guinea pigs that were fed 4 mg/kg/day Clopen A-60 or Aroclor 1260 for 6 weeks included decreases in antibody titers (IgM and IgG) to tetanus toxoid, skin (footpad) reactivity to tuberculin, leukocyte, and lymphocyte counts, and relative thymus weight, with no effects occurring at 0.8 mg/kg/day of Clopen A-60 (low dose of Aroclor 1260 not tested) (Vos and Van Driel-Grootenhuis 1972).

No changes in total or differential WBC counts or histology of the thymus, spleen, or lymph nodes were found in male and female rats that were exposed to Aroclor 1260 at dietary doses as high as 4.1 and 5.8 mg/kg/day, respectively, for 24 months (Mayes et al. 1998).

Aroclor 1254 and Similar Mixtures. Information on immunotoxicity of Aroclor 1254 is available from oral studies in rats, mice, rabbits, and monkeys. A number of significant effects on humoral and cell-mediated parameters were found in rats. Dietary exposure to Aroclor 1254 at estimated doses of 4.3 or 43 mg/kg/day for 10 weeks caused decreased serum total immunoglobulin G (IgG) antibody response to keyhole limpet hemocyanin (KLH) antigen, decreased NK cell activity, and increased interleukin 2 (IL-2) production by concanavalin A (ConA)-stimulated splenocytes in Sprague-Dawley male rats (Exon et al. 1985; Talcott et al. 1985). Male F344 rats treated with Aroclor 1254 by gavage for 5–15 weeks had reduced thymus weight and NK cell activity at 10 and 25 mg/kg/day, and increased PHA mitogen-induced lymphocyte proliferation at 25 mg/kg/day; no significant effects were seen at #1 mg/kg/day. (Smialowicz et al. 1989). Enhanced responses to ConA, PWM, or *Salmonella typhimurium* mitogen (STM) were not observed. Decreased thymus weight and enhanced lymphoproliferative activity in response to stimulation by PHA, but not PWM, were also observed in male Sprague-Dawley rats that were fed Aroclor 1254 at an estimated dose of 21.5 mg/kg/day for 7 days (Bonnyns and Bastomsky 1976). Thymus weight, WBC, and neutrophil counts were reduced in Sprague-Dawley rats fed an estimated dose of 50 mg/kg/day Aroclor 1254 for 6 weeks (Allen and Abrahamson 1973); immune function was not evaluated. No changes in total or differential WBC counts or histology of the lymph nodes, spleen, or thymus were found in male and female rats that were exposed to Aroclor 1254 at dietary doses as high as 4.3 and 6.0 mg/kg/day, respectively, for 24 months (Mayes et al. 1998).

Susceptibility to Moloney leukemia virus (MLV) was increased in male BALB/c mice that ingested $4.9 mg/kg/day estimated dietary doses of Aroclor 1254 for 6 months; no effect was found at 0.5 mg/kg/day (lowest tested dose) (Koller 1977). Similarly, susceptibility to mortality from herpes simplex virus was increased in male ICR mice that ingested Kanechlor 500 in the diet for 21 days at $33 mg/kg/day, but not at the lowest tested dose of 18 mg/kg/day (Imanishi et al. 1980). Swiss-Webster mice were fed Aroclor 1254 at doses of 1.2, 11.7, or 29.2 mg/kg/day for 12 weeks prior to mating with exposure continuing throughout gestation and lactation (Talcott and Koller 1983). Immunologic evaluation of the offspring at 8 weeks of age showed no significant effects on antibody titers to bovine serum albumin (BSA), phagocytosis of SRBC (measured by ingestion by peritoneal macrophages *in vitro*), or delayed-type hypersensitivity to oxazolone, although relative spleen weights were reduced at 29.2 mg/kg/day.

Male New Zealand rabbits that were exposed to 0.18–6.44 mg/kg/day dietary doses of Aroclor 1254 for 8 weeks had no effects on several immunological end points, including hemolysin and hemagglutination

titers against SRBC, gamma-globulin/transferrin ratio, and skin sensitivity to tuberculin, although significant atrophy of the thymus occurred at all doses (Street and Sharma 1975).

Immunological effects of Aroclor 1254 in monkeys were first indicated in pilot studies of general toxicity (Truelove et al. 1982; Tryphonas et al. 1986a). Dietary ingestion of Aroclor 1254 in apple juice-gelatin-corn oil emulsion at doses of 0.1 mg/kg/day (2 Cynomolgus monkeys) or 0.4 mg/kg/day (1 monkey) for 238–267 days, beginning at approximately day 60 of gestation, caused a decreased antibody response to SRBC in all treated animals compared to one control monkey (Truelove et al. 1982). No effect on antibody titers to tetanus toxoid was observed. Both monkeys exposed to 0.1 mg/kg/day delivered stillborn infants, and the 0.4 mg/kg/day monkey delivered a live infant which was nursed, but failed to respond to SRBC and died at 139 days postpartum with acute confluent bronchopneumonia.

Groups of four Cynomolgus and four Rhesus monkeys ingested 0 or 280 µg/kg/day Aroclor 1254 in apple juice-gelatin-corn oil emulsion on 5 days/week for 12–13 months and 27–28 months, respectively (Tryphonas et al. 1986a). Immunologic parameters that were evaluated included serum protein levels, total serum IgG, IgA, and IgM, and antibody titers to SRBC. Total serum IgM levels and anti-SRBC (IgM) titers were reduced in both species.

A subsequent series of tests on Aroclor 1254 was conducted in Rhesus monkeys because they appeared to be more sensitive than Cynomolgus monkeys based on relatively greater severity of clinical signs and higher blood and adipose PCB levels (Tryphonas et al. 1986a). Groups of 16 female Rhesus monkeys were orally administered Aroclor 1254 in capsules at doses of 0, 5, 20, 40, or 80 µg/kg/day, with immunological assessments performed after 23 months (Tryphonas et al. 1989) when blood PCB steady-state was established, and at 55 months (Tryphonas et al. 1991a, 1991b). Average concentrations of PCBs in the 0, 5, 20, 40, and 80 µg/kg/day dose groups around the time of immunologic testing were 0.1, 10.2, 34.0, 74.9, and 112 ppb, respectively, in blood and 0.4, 2.7, 9.0, 15.7, and 31.2 ppm, respectively, in adipose tissue (Tryphonas et al. 1989). Significant dose-related decreases in IgM (all doses except 0.02 mg/kg/day) and IgG (all doses) antibody titers to SRBC were found after 23 months. Secondary challenge with SRBC after 55 months showed decreasing dose-related trends in the IgM and IgG anamnestic responses, although only IgM was significantly lower than controls at all dose levels. Other effects included alterations in lymphocyte T-cell subsets characterized by a significant decrease in the ratio of T-helper/inducer (CD4) cells to T-suppressor/cytotoxic (CD8) cells, due to reduced CD4 and increased CD8 cells, after 23 months at 80 µg/kg/day (not tested at lower doses). No effects on total lymphocytes or B-cells were found, indicating that T-cells were preferentially affected by the PCBs,

although there were no exposure-related changes in T-cell subsets after 55 months suggesting that adaptation had occurred. Statistically significant dose-related trends, but no significant differences between exposed and control groups, were observed after 55 months for decreasing lymphocyte proliferation in response to mitogens (PHA and ConA, but not PWM), increasing NK cell activity, increasing levels of serum thymosin alpha-1, decreasing phagocytic activity of peripheral blood monocytes following activation with phorbol myristate acetate (PMA), and increasing total serum complement activity. End points that were not affected by PCB exposure included IgG antibody response to pneumococcal antigens, total serum immunoglobulins (IgG, IgM, and IgA) levels, and other serum proteins as well as serum hydrocortisone levels.

Offspring from the Rhesus monkeys studied by Tryphonas et al. (1989, 1991a, 1991b) were also evaluated for immunological changes (Arnold et al. 1995). Females were mated after 37 months of exposure to 0, 5, 20, 40, or 80 μg/kg/day of Aroclor 1254. The maternal dosing was continued throughout pregnancy and into lactation until nursing infants were approximately 7 weeks old, and treatment was restarted in the infants at weaning (22 weeks). Immunological testing was initiated at 20 weeks of age although statistical evaluation was limited by small numbers of animals due to fetal and postpartum deaths (see Section 3.2.5.3). IgM and IgG antibody levels were determined 1–3 weeks following immunization with SRBC at 20 and 60 weeks of age. Significant reductions in IgM titers were found at 5 and 40 μg/kg/day at weeks 22 and 23, and 5 μg/kg/day at weeks 61–63; IgM levels were insignificantly reduced in the 40 μg/kg/day group at weeks 61–63. IgG titers were significantly reduced only in the 40 μg/kg/day group at week 22. Other immunological tests were performed at 20, 28, and 60 weeks of age and included assays for lymphocyte proliferation (in response to stimulation by PHA, ConA, or PWM mitogens or leucocyte stimulator cells) and NK cell activity; the only significant finding was a decreased lymphocyte proliferation response at 40 μg/kg/day at weeks 28 and 60.

Aroclor 1248. Immune responses to Aroclor 1248 were investigated in oral studies with mice, rabbits, and monkeys. Female mice (Albino outbred) that were fed Aroclor 1248 for 5 weeks had increased endotoxin sensitivity at estimated doses of 13 and 130 mg/kg/day and decreased resistance to challenge by *S. typhimurium* at 130 mg/kg/day (not tested at lower dose), but no effects on spleen and thymus weight or histology at #130 mg/kg/day (Thomas and Hindill 1978). In a study with New Zealand rabbits, females were exposed to 3.6, 28, or 91 mg/kg/day dietary doses of Aroclor 1248 from 4 weeks before mating until offspring were weaned at 4 weeks of age (Thomas and Hinsdill 1980). Testing at 7 weeks of age showed that skin contact sensitivity response to dinitrofluorobenzene was reduced in the offspring of the 91 mg/kg/day rabbits. This effect was accompanied by reduced body weight, making it unclear

whether the effect was directly due to PCBs or secondary to some other form of toxicity. No exposure-related changes in spleen and thymus weights, plaque forming cell (PFC) response and antibody titers to SRBC, or mitogenic response of peripheral blood lymphocytes to PHA or ConA were observed in the rabbits at any dose level. Thymus weight and WBC and neutrophil counts were reduced in Sprague-Dawley rats fed Aroclor 1248 at an estimated dose of 50 mg/kg/day for 6 weeks (Allen and Abrahamson 1973); these effects were similar in severity to those induced by Aroclor 1254.

Increased susceptibility to bacterial infections was reported in two monkeys after dietary exposure to approximately 0.1–0.2 mg/kg/day Aroclor 1248 (Barsotti et al. 1976). The monkeys, which died after 173 and 310 days of treatment, had clinical signs of PCB toxicity and developed, terminally, a severe enteritis from which *Shigella flexneri* type IV was isolated.

Immunologic changes were investigated in groups of eight Rhesus monkeys that were immunized with SRBC and tetanus toxoid following dietary exposure to 0.1 or 0.2 mg/kg/day Aroclor 1248 for 11 months (Thomas and Hinsdill 1978). Comparison with a control group of five monkeys showed effects at 0.2 mg/kg/day that included reduced anti-SRBC antibody titers at weeks 1 and 12 after primary immunization (i.e., at 2 of 6 postimmunization times), and decreased percent gamma-globulin after 20 weeks. Antibody responses to SRBC were not significantly affected at 0.1 mg/kg/day. The response to tetanus toxoid was not significantly modified at either dose level.

Pathological changes in lymphoid tissues occurred in offspring of Rhesus monkeys that were fed 0.1 or 0.2 mg/kg/day estimated dietary doses of Aroclor 1248 for a 15-month period that included breeding, gestation, and lactation (Allen and Barsotti 1976). The offspring were exposed for approximately 46 weeks from beginning of gestation until they were weaned. The doses were both fetotoxic (early abortions occurred in 5 of 8 low-dose and 4 of 6 high-dose animals) and postnatally lethal (3 of 6 infants died of PCB intoxication between days 44 and 329). Gross and microscopic changes in the deceased infants included reduced cortical and medullary areas in the thymus, reduced lymph nodes and absence of germinal centers in the spleen, and hypocellularity of the bone marrow. The females from the Allen and Barsotti (1976) study were bred again after 1 year on the control diet (Allen et al. 1980). Early infant mortality was observed (2 of 4 in the former 0.1 mg/kg/day group and 2 of 7 in the former 0.2 mg/kg/day group), and histological examinations showed thymus, spleen, and bone marrow effects similar to those described above, as well as findings of hypocellular lymph nodes devoid of germinal centers. Regression of the cortical areas of the thymus and hypoplastic bone marrow were similarly observed in 5 infant

(1-month-old) Rhesus monkeys that were intubated with 35 mg/kg/day Aroclor 1248 for 30 days (Abrahamson and Allen 1973).

Aroclors 1242, 1221, and 1016. Effects of Aroclors 1242, 1221, and 1016 on immune function have been studied in male BALB/c mice. Mice that were exposed to an estimated dietary dose of 22 mg/kg/day Aroclor 1242 for 3 or 6 weeks caused decreased primary and secondary PFC responses to SRBC antigens with concurrent reductions in total serum IgG_1, IgM, and IgA levels (Loose et al. 1977, 1978a, 1978b, 1979). There were no effects on thymus and spleen weights or histological alterations in the thymus, spleen, or mesenteric lymph nodes, and morphometric analysis of the spleens did not show changes in the number, size, or cellular composition of the germinal follicles. Mice that were exposed to 22 mg/kg/day Aroclor 1242 for 3 or 6 weeks also had increased susceptibility to challenge by *Salmonella typhosa* endotoxin or the malarial parasite *Plasmodium berghei* which resulted in increased mortality (Loose et al. 1978a, 1979), although exposure to the same dose for up to 18 weeks did not affect macrophage function (*in vitro* phagocytic capacity and activity or microbiocidal activity) or resistance to challenge by EL-4 lymphoma or kidney ascites tumor cells (Loose et al. 1981). Susceptibility to Moloney leukemia virus was increased in male BALB/c mice that ingested dietary Aroclor 1242 for 6 months at estimated doses of $4.9 mg/kg/day, but not in mice that were similarly exposed to Aroclor 1221 at doses as high as 48.8 mg/kg/day (Koller 1977).

Male C57BL/6 mice that were exposed to Aroclor 1016 in the diet at an estimated dose of 22 mg/kg/day for up to 40 weeks had no consistent effects on thymus and spleen weights, lymphocyte counts, or lymphocyte function as evaluated by the splenic graft-versus-host (GVH) response, mixed lymphocyte response, mitogenic response to stimulation by PHA or LPS, or cytotoxic activity of sensitized lymphocytes to target tumor cells (Silkworth and Loose 1978).

No changes in total or differential WBC counts or histology of the lymph nodes, spleen, or thymus were found in male and female rats following 24 months of dietary exposure to Aroclor 1242 at doses as high as 4.0 and 5.7 mg/kg/day, respectively, or Aroclor 1016 at doses as high as 8.0 and 11.2 mg/kg/day, respectively (Mayes et al. 1998).

Defined Experimental Mixtures. The toxicity of a mixture of PCB congeners analogous to that in human breast milk (Canadian women) was studied in monkeys (Arnold et al. 1999). Groups of infant Cynomolgus monkeys (6 control males, 10 treated males) and Rhesus monkeys (2 control and 3 treated males, 1 control and 3 treated females) were administered the congener mixture in a total daily dose of

0 or 7.5 µg PCBs/kg/day from birth until 20 weeks old (i.e., without *in utero* exposure), and were observed until they were at least 66 weeks old. The dose was divided into thirds and administered prior to the first three daily feedings via syringe to the back of the mouth. The dose represented the approximate daily intake of a nursing human infant whose mother's milk contained 50 ppb PCBs (the Health Canada guideline for maximum concentration in breast milk). Immunological assessment of the infants was started at 22 weeks of age and included IgM and IgG antibody production following immunization with SRBC, lymphoproliferative activity of peripheral leucocytes in response to mitogens (PHA, ConA, and PWM), numbers of peripheral leucocytes and their subsets, and NK cell activity. Few statistically significant changes were observed. Anti-SRBC titers were reduced in the treated Rhesus and Cynomolgus monkeys, but were not significantly different from controls, although antibodies were significantly reduced over postimmunization time (p#0.025 for IgM and IgG in Cynomolgus monkeys, p=0.002 for IgM in Rhesus monkeys). Other changes included reduced absolute mean numbers of B lymphocytes in the treated Cynomolgus monkeys (no change in mean percent); the effect was not observed when re-evaluated in the monkeys at 1 year of age. The investigators concluded that, overall, the effects on the infant immune system were mild and of unclear biological significance due to large inter-animal variability and the small numbers of animals.

Single Congeners. A series of toxicity studies was performed in which groups of 10 male and 10 female Sprague-Dawley rats were exposed to diets containing four dose levels of various single congeners for 13 weeks (Chu et al. 1994, 1995, 1996a, 1996b, 1998; Lecavalier et al. 1997). End points relevant to the immune system included total and differential WBC counts, spleen weight, and histology of the spleen, thymus, mesenteric lymph nodes, and bone marrow. Data on these end points were reported for seven congeners: PCB 28, 77, 105, 118, 126, 128, and 153. Effects were essentially limited to thymic changes, generally reductions in cortical and medullary volume and atrophy, which were observed following exposure to PCB 126 ($0.74 µg/kg/day), PCB 153 ($3,534 µg/kg/day), PCB 28 ($3,783 µg/kg/day), and PCB 105 ($3,960 µg/kg/day). No changes in the immunologic end points were induced by PCB 77 (#892 µg/kg/day), PCB 118 (#170 µg/kg/day), or PCB 128 (#4,125 µg/kg/day).

Contaminated Fish Consumption. Effects on the immune system were investigated as part of a two-generation reproduction study of Sprague-Dawley rats that were fed diets containing 0, 5, or 20% (w/w) of lyophilized protein from chinook salmon from Lake Huron or Lake Ontario (Arnold et al. 1998; Feely and Jordan 1998; Feeley et al. 1998; Tryphonas et al. 1998a, 1998b). Daily intakes of total PCBs in the female F1 rats fed diet containing 0, 5, or 20% lyophilized Lake Ontario salmon flesh were calculated to be 0.22, 23.20, and 82.37 µg/kg/day, respectively (Feely and Jordan 1998). PCB intakes were

qualitatively similar, but generally were somewhat smaller, for males compared with females and for F0 rats compared with F1 rats, although intakes from the Lake Huron diet were about 35–40% lower than from the Lake Ontario diet. The DDT complex (*p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD) accounted for 75 and 60% of organochlorine pesticide residues in the Lake Huron and Lake Ontario fish, respectively, and other major contaminants included CDDs and CDFs, mirex, chlordane, cadmium, lead, mercury, and arsenic. No consistent exposure-related effects were found across generations on various immunological end points, including numbers of splenic leukocytes and T-lymphocyte subsets, PFC response to SRBC antigen, NK cell activity, lymphocyte transformation in response to mitogens (ConA, PHA, and LPS), phagocytic activity of peritoneal exudate cells, and resistance to infection by *Listeria monocytogenes* (Tryphonas et al. 1998b). The most notable finding was an increase in absolute leukocyte and lymphocyte levels in the spleen of the F2 male rats fed the Lake Huron fish compared to controls and to F2 males fed Lake Ontario fish, with higher cell numbers in the 20% group compared to the 5% group in each fish source. Additional data suggested that the increases in splenic leukocyte and lymphocyte levels were due to changes in T-lymphocyte subsets, particularly the T-helper/inducer cells. The changes in spleen cellularity paralleled changes in peripheral WBC and lymphocyte levels (Tryphonas et al. 1998a).

Another study assessed immunological effects in juvenile C57Bl/6 mice that were fed diets containing no fish or 33% coho salmon from Lake Ontario or the Pacific Ocean for 2–4 months (Cleland et al. 1989). Intakes of persistent toxic substances were not reported although the halogenated aromatic hydrocarbons with the highest concentrations in the control chow, Pacific salmon diet, and Lake Ontario salmon diet were total PCBs (0.4, 20, and 2,900 ppb, respectively) and *p,p*-DDE (0.1, 10, and 670 ppb, respectively). Levels of PCDDs and PCDFs, mercury, tin compounds, and other metals were not examined. Evaluations included IgM, IgG, and IgA PFC responses to SRBC and numbers of spleen total lymphocytes, total T-lymphocytes, and T-lymphocyte subsets following 2 months of exposure. Cellular immunity was assessed after 4 months of exposure by the cytotoxic T-lymphocyte response to allogeneic tumor target cells. The only significant finding was a reduced PFC response to SRBC for all three immunoglobulin classes in the mice that consumed the Lake Ontario diet compared to responses in the mice fed the Pacific Ocean salmon or control diets.

3.2.3.3.3 Dermal Exposure

Limited data are available on immunological effects in animals after dermal exposure to PCBs. Dermal application of an estimated 44 mg/kg/day Aroclor 1260, 5 days/week for 4 weeks resulted in moderate atrophy of the thymus in rabbits (Vos and Notenboom-Ram 1972). No treatment-related histological effects were observed in the spleen and lymph nodes. Application of an estimated 42 mg/kg/day of the same Aroclor for 38 days to rabbits produced histological atrophy of the thymus cortex and a reduction in the number of germinal centers in the spleen and lymph nodes (Vos and Beems 1971). No treatment-related effects were observed in control rabbits in either study. These studies tested small numbers of animals and used Aroclor 1260 that had undetectable levels (<1 ppm) of CDFs.

3.2.3.3.4 Other Routes of Exposure

The relative potencies of five Aroclor mixtures and an experimental congener mixture resembling an extract from human milk were evaluated using the splenic plaque-forming cell response to SRBC in C57BL/6 mice treated by single intraperitoneal injection (Davis and Safe 1989). Comparison of ED_{50} values showed that the higher chlorinated Aroclors 1260, 1254, and 1248 (ED_{50} of 104, 118, and 190 mg/kg, respectively) were more potent than the lower chlorinated Aroclors 1242, 1016, and 1232 (ED_{50} of 391, 408, and 464 mg/kg, respectively). The experimental milk mixture contained an average chlorine percentage resembling Aroclor 1254, but did not significantly decrease the number of plaque-forming cells to SRBC, although the tested doses (5–50 mg/kg) were less than the ED_{50} values for Aroclor 1254 and the other mixtures.

A large number of acute intraperitoneal and *in vitro* studies have investigated congeneric structure-activity relationships for the purpose of elucidating mechanisms of immunotoxicity and relative potencies of individual congeners and their potential interactive effects. As summarized in Section 3.4.2 (Mechanisms of Toxicity), there is evidence from various test systems that noncoplanar as well as coplanar and mono-*ortho*-coplanar congeners are immunologically active, indicating that both Ah receptor-dependent and receptor-independent mechanisms are involved in the immunotoxicity of PCB mixtures (e.g., Brown and Ganey 1995; Brown et al. 1998; Davis and Safe 1989, 1990; Ganey et al. 1993; Harper et al. 1993a, 1993b, 1995; Schulze-Stack et al. 1999; Tithof et al. 1995).

3.2.3.3.5 Evaluation of Animal Studies

The immunotoxicity of PCBs has been evaluated in various species of animals that were exposed to commercial mixtures, mixtures of congeners analogous to human breast milk, Great Lakes fish, or single congeners. Studies in rats, mice, guinea pigs, and rabbits have conclusively shown that intermediate-duration oral exposure to $4 mg/kg/day doses of commercial PCB mixtures can induce both morphological and functional alterations in the immune system. Effects in lymphoid tissues were commonly observed, although no generalizations can be made across species. Decreases in thymus weight occurred in rats exposed to Aroclors 1254 or 1248 and rabbits exposed to Aroclor 1254 (Allen and Abrahamson 1973; Smialowicz et al. 1989; Street and Sharma 1975), but not in guinea pigs exposed to Aroclor 1260, mice exposed to Aroclors 1248, 1242, or 1016, or rabbits exposed to Aroclor 1248 (Loose et al. 1978b; Silkworth and Loose 1978; Thomas and Hinsdill 1978; Vos and de Roij 1972). Spleen weight was reduced in mice exposed to Aroclor 1254, but not in mice exposed to Aroclors 1248, 1242, or 1016, rabbits exposed to Aroclor 1248, or guinea pigs exposed to Aroclor 1260 (Allen and Abrahamson 1973; Loose et al. 1978b; Silkworth and Loose 1978; Talcott and Koller 1983; Thomas and Hinsdill 1980; Vos and de Roij 1972). Histological examinations showed no PCB-related changes in the thymus, spleen, and lymph nodes of guinea pigs exposed to Aroclor 1260 or mice exposed to Aroclors 1242, but histopathology data are not available for other orally-exposed species and mixtures (Loose et al. 1978b; Vos and de Roij 1972). Repeated dermal applications of Aroclor 1260 (42–44 mg/kg/day for 4–5 weeks), however, caused histopathologic changes in the thymus (cortical atrophy) and spleen and lymph nodes (reduced germinal centers) in rabbits (Vos and Beems 1971; Vos and Notenboom-Ram 1972).

Effects on immune function, as indicated by altered responses in humoral and cell-mediated immunity assays and host resistance tests, were also induced by intermediate-duration oral exposure to commercial mixtures. Studies in nonprimate species showed reduced antibody responses to tetanus toxoid in guinea pigs exposed to Clopen A-60 (4 mg/kg/day for 3–5 weeks), keyhole limpet hemocyanin in rats exposed to Aroclor 1254 (4.3 mg/kg/day for 10 weeks), and SRBC in mice exposed to Aroclor 1242 (22 mg/kg/day for 3–6 weeks) (Exon et al. 1985; Loose et al. 1977, 1978a, 1978b, 1979; Vos and Van Driel-Grootenhuis 1972). Commercial PCBs also increased susceptibility to infection by foreign antigens, including Moloney leukemia virus in mice exposed to Aroclor 1254 or Aroclor 1242 ($4.9 mg/kg/day for 6 months), herpes simplex virus in mice exposed to Kanechlor 500 ($33 mg/kg/day for 21 days), and *S. typhosa* endotoxin and the malarial parasite *Plasmodium berghei* in mice exposed to Aroclor 1242 (22 mg/kg/day for 3–6 weeks) (Imanishi et al. 1980; Koller 1977; Loose et al. 1979). Proliferative responses of splenic mononuclear leukocytes to PHA, but not to other mitogens (ConA, STM, or PWM),

was enhanced in rats exposed to Aroclor 1254, although no effects on mitogen-induced proliferation of lymphocytes were observed in rabbits exposed to Aroclor 1248 or mice exposed to Aroclor 1016 (Bonnyns and Bastomsky 1976; Silkworth and Loose 1978; Smialowicz et al. 1989; Thomas and Hinsdill 1980). Skin reactivity to tuberculin was reduced in guinea pigs exposed to Clopen A-60, but not in rabbits exposed to Aroclor 1254, and there was no effect on delayed-type hypersensitivity to the skin sensitizer oxazolone in mice exposed to Aroclor 1254 (Street and Sharma 1975; Talcott and Koller 1983; Vos and Van Driel-Grootenhuis 1972). NK cell activity was reduced in rats following intermediate oral exposure to Aroclor 1254 (Smialowicz et al. 1989; Talcott et al. 1985).

Immunological assessments of rodents fed Great Lakes fish that contained PCBs and other chemicals produced some changes that are similar to those observed in the studies of commercial PCB mixtures. Although no consistent exposure-related effects were found on several immunological variables (thymus weights, PFC response to SRBC, mitogen-induced lymphocyte proliferation, NK cell activity, and susceptibility to challenge with *Listeria monocytogenes*) in a multigenerational study of rats fed Lake Huron or Lake Ontario salmon, increases in splenic leukocyte and lymphocyte levels were increased in F2 male rats due to changes in T-lymphocyte subsets (Tryphonas et al. 1998a, 1998b). In addition, juvenile mice that consumed salmon from Lake Ontario for 2–4 months had reduced antibody responses to SRBC compared to mice fed Pacific Ocean salmon or control diets, but no changes in T-lymphocytes or their subsets were observed (Cleland et al. 1989).

Intermediate-duration oral studies of Aroclors in monkeys confirm the observations of PCB immunotoxicity in rats, mice, guinea pigs, and rabbits and further indicate that nonhuman primates are more sensitive than the other species. Early studies found decreased antibody responses to SRBC, increased susceptibility to bacterial infections, and/or histopathological changes in the thymus, spleen, and lymph nodes in adult monkeys and their offspring at 0.1–0.2 mg/kg/day doses of Aroclor 1254 and 1248, although these findings are limited by small numbers of animals and dose levels (Abrahamson and Allen 1973; Allen and Barsotti 1976; Allen et al. 1980; Barsotti et al. 1976; Thomas and Hinsdill 1978; Truelove et al. 1982; Tryphonas et al. 1986a). The most extensive characterization of immunological effects in nonhuman primates involved assessments on groups of 16 monkeys performed after 23 and 55 months of oral exposure to 5 dose levels of Aroclor 1254 ranging from 5 to 80 µg/kg/day (Tryphonas et al. 1989, 1991a, 1991b). The immune parameters that were most consistently affected in the monkeys were IgM and IgG antibody responses to SRBC, which showed significant dose-related decreases at levels as low as 5 µg/kg/day (lowest tested dose). Other effects were either transient (e.g., alterations in T-cell subsets occurring after 23 but not 55 months of exposure) or showed dose-related trends after

55 months without significant differences between exposed and control groups (e.g., decreasing lymphoproliferative responses to mitogens, increasing NK cell activity, increasing levels of serum thymosin alpha-1, decreasing phagocytic activity of peripheral blood monocytes following activation with PMA, and increasing total serum complement activity).

Results of studies in infant Rhesus monkeys are consistent with the data in adults showing immunosuppressive effects of PCBs at doses as low as 5 μg/kg/day. Evaluation of *in utero* and lactationally-exposed offspring from the monkeys in the Tryphonas et al. (1989, 1991a, 1991b) studies indicated exposure-related reductions in antibody levels to SRBC and mitogen-induced lymphocyte transformation that paralleled the findings in the maternal animals (Arnold et al. 1995). Although assessment of the data is limited by small numbers of infants in the exposed groups, statistical significance was achieved for some end points and evaluation times, including reduced IgM titers at 22–23 and 61–63 weeks of age (following gestational/lactational and/or postweaning dietary exposure) in the infants exposed to 5 μg/kg/day. Infant Rhesus and Cynomolgus monkeys that were orally administered a PCB congener mixture simulating the congener content of human milk at a dose level of 7.5 μg/kg/day for the first 20 weeks of life (i.e., from parturition without *in utero* exposure) had minimal immunological changes (Arnold et al. 1999). More specifically, anti-SRBC titers (IgM and IgG) were uniformly reduced in the treated compared to control monkeys, although group differences were not statistically significant due to small numbers of animals. In addition, B lymphocyte numbers in the exposed Cynomolgus monkeys were decreased compared to controls, although the levels were similar when evaluated again at 1 year of age. These results provide further evidence that monkeys are sensitive to low doses of PCBs administered either as commercial mixtures or as a mixture of congeners representative of those commonly found in breast milk.

As summarized above, oral immunotoxicity studies have shown that suppressed antibody response to SRBC is the parameter most consistently affected by PCBs in adult and infant monkeys and that effects on antibody responses have also been demonstrated in other species. Reductions in antibody responses to SRBC were also observed in juvenile mice that ingested diet containing fish from Lake Ontario. The immunologic response to SRBC antigens, as measured using the PFC assay, is a validated sensitive indicator for detecting potentially immunotoxic chemicals (Luster et al. 1992). Because antibody responses to SRBC antigens were suppressed in monkeys at dose levels of Aroclor 1254 as low as 0.005 mg/kg/day, the lowest tested dose of any PCB mixture in any species, this effect is used as the main basis for deriving the chronic MRL for oral exposure as indicated in the footnote to Table 3-2 and discussed in Chapter 2 and Appendix A.

3.2.4 Neurological Effects

3.2.4.1 Summary

The neurological effects of PCBs have been extensively investigated in humans and in animals. The main focus in humans studies has been on the effects in neonates and young children, although studies of adults have also been conducted. A great deal of concern exists that even low levels of PCBs transferred to the fetus across the placenta may induce long-lasting neurological damage. Because PCBs are lipophilic substances, there is also concern that significant amounts might be transferred to nursing infants via breast milk. Studies in humans who consumed high amounts of Great Lakes fish contaminated with environmentally persistent chemicals, including PCBs, have provided evidence that PCBs are important contributors to subtle neurobehavioral alterations observed in newborn children and that some of these alterations persist during childhood. Some consistent observations at birth have been motor immaturity and hyporeflexia and lower psychomotor scores between 6 months and 2 years old. There is preliminary evidence that highly chlorinated PCB congeners, which accumulate in certain fish, are associated with neurobehavioral alterations seen in some newborn children. Subtle neurobehavioral alterations have also been observed in children born to mothers in the general population with the highest PCB body burdens. Due to the limitations of epidemiological studies, these effects cannot be attributed entirely to PCB exposure. In one general population study, there was strong evidence that dioxins as well as PCBs were contributors to the neurobehavioral effects seen in exposed children. Children born to women who accidentally consumed rice oil contaminated with relatively high amounts of PCBs and CDFs during pregnancy also had neurodevelopmental changes. Studies in animals support the human data. Neurobehavioral alterations have been also observed in rats and monkeys following pre- and/or postnatal exposure to commercial Aroclor mixtures, defined experimental congener mixtures, single PCB congeners, and Great Lakes contaminated fish. In addition, monkeys exposed postnatally to PCB mixtures of congeneric composition and concentration similar to that found in human breast milk showed learning deficits long after exposure had ceased. A few other generalizations can be made from the data in animals. It appears that *ortho*-substituted PCB congeners are more active than coplanar PCBs in modifying cognitive processes. In addition, one effect observed in both rats and monkeys—deficits on delayed spatial alternation—has been known to be induced by exposure to *ortho*-substituted PCBs, defined experimental mixtures, and commercial Aroclors. Both dioxin-like and non-dioxin-like PCB congeners have been shown to induce neurobehavioral alterations in animals. Changes in levels of neurotransmitters in various brain areas have also been observed in monkeys, rats, and mice. Of all the observed changes, the most consistent has been a decrease in dopamine content in basal ganglia and

prefrontal cortex, but further research is needed before specific neurobehavioral deficits can be correlated with PCB-induced changes in specific neurotransmitters in specific brain areas.

3.2.4.2 Human Studies

3.2.4.2.1 Neurobehavioral Effects

3.2.4.2.1.1 Contaminated Fish Consumption

The Michigan Cohort. Indices of neurological development were evaluated in 313 newborn infants (Fein et al. 1984a, 1984b). Of these infants, 242 were born to mothers who had consumed moderate to large quantities of Lake Michigan fish sometime during their lives, and 71 were born to mothers who did not consume Lake Michigan fish. In the exposed group, mean fish consumption, estimated by recall and duration of consumption, was 6.7 kg/year and 15.9 years, respectively; this rate is equivalent to 2 or 3 salmon or lake trout/month (Fein et al. 1984a, 1984b). Consumption during pregnancy was 4.1 kg/year. The mean PCB level in maternal serum among those eating Lake Michigan fish was 6.1 ppb (SD=3.7), while the mean among those reporting no fish consumption was 4.1 ppb (SD=2.7). The mean PCB residues also were significantly higher in breast milk samples from the fisheaters as compared to the nonfisheaters, 865.6 ppb (fat basis) versus 622.2 ppb (Fein et al. 1984a). No relationship was found between cord serum PCB levels and maternal fish consumption possibly because of detection problems in cord serum analysis. A list of 68 potential confounders was collected from the maternal interview and medical record. The list contained data pertaining to demographic background, reproductive health history including pregnancy and delivery, anesthesia during delivery, and exposure to other substances such as caffeine, nicotine, and alcohol (Fein et al. 1984a, 1984b). Because many of these mothers had been exposed to polybrominated biphenyls (PBBs), cord serum PBB level also was used as a control variable. Potential confounders were included only if the frequency in each category exceeded 15%. Consequently, data on approximately 37 potential confounders were available for inclusion in the study analyses (Fein et al. 1984a, 1984b).

Gestational age was evaluated by both the Ballard Examination for Fetal Maturity and the mother's report of her last menstrual period. The Ballard Examination was administered at 30 to 42 hours after birth to 209 of 313 (67%) infants with maternal permission granted during the limited time frame available for assessment. The Ballard estimate is based on an assessment of the newborn's neuromuscular and physical maturity. The Neonatal Behavioral Assessment Scale (NBAS) was administered to 284 of 313 (91%)

newborns on day 3 after birth. Three other infants also were tested sometime after their third day of life. In order to enhance the reliability of measures, the 44 NBAS items were reduced to seven summary clusters; response decrement, orientation, tonicity, range of state, regulation of state, autonomic maturity, and reflexes. These reduced clusters were derived by synthesizing the results of factor analyses from studies of six independent samples (Fein et al. 1984a; Jacobson et al. 1984a).

The results of the tests conducted on the newborns showed that decreased neuromuscular maturity, as measured on the Ballard Scale was significantly associated with consumption of contaminated fish (Fein et al. 1984b). However, when the non-fisheater and fisheater populations were divided according to cord serum level (<3 and $3 ppb, respectively), there was no significant difference in neuromuscular maturity outcome. The relationship between seven clusters from the NBAS and contaminated fish consumption was evaluated using linear regression with control for caffeine and alcohol consumption both before and during pregnancy. The potential confounders were chosen based on their statistical significance in prior correlation analyses. Infants of mothers eating contaminated fish were more likely to exhibit hypoactive reflexes, more motor immaturity, poorer lability of states, and a greater amount of startle (Jacobson et al. 1984a).

A follow-up of 39% (92 fisheating mothers, 31 controls) of the children in the Michigan Mother-Child study occurred at 7 months of age (Jacobson et al. 1985). Infants were administered Fagan's test of visual recognition to assess the effect of pre- or postnatal PCB exposure on fixation to familiar and novel stimuli. Cord serum PCB level was a better, but only moderate, predictor of poorer mean visual recognition memory than overall contaminated fish consumption. Recognition memory performance was not related to postnatal exposure from breast-feeding. According to the investigators (Jacobson et al. 1985), there was an inverse relationship between preference for novelty and PCB levels in cord serum (Fein et al. 1984a, 1984b). The investigators further indicated that visual recognition was unrelated to neonatal variables such as birth size, gestational age, and neurobehavioral performance.

Approximately 75% of the children were re-examined at age 4 (Jacobson et al. 1990a, 1990b). Neurobehavioral testing showed that prenatal exposure (maternal exposure before and during pregnancy), assessed by cord serum PCB levels was associated with poorer performance on both the Verbal and the Memory scales of the McCarthy Scales of Children's Abilities. There was no indication of perceptual motor deficits or alterations of long-term memory. Activity level was inversely related to 4-year serum PCB level in a dose-dependent manner and also to maternal milk PCB level. Multivariate analysis of variance indicated that the effect of maternal milk was strongest in children of women with higher-than-

average milk PCB levels ($780 ppb) who breast-fed for at least 12 months. Correlations with fish consumption were not examined. Cognitive performance was unrelated to exposure from breast-feeding, which, according to the investigators (Jacobson et al. 1990a), suggested that the neurobehavioral deficits were due to fetal exposure. Jacobson et al. (1990a) indicated that the deficits found in these studies were not attributable to exposure to PBBs, lead, or seven other organochloride pesticides since these variables were controlled for.

A second evaluation of 226/313 children, 3 months after the McCarthy Scales assessment, was undertaken using adaptions of the Sternberg visual search and recognition memory test, the Kagan's Matching Familiar Figures Test, and the Streissguth vigilance paradigm (Jacobson et al. 1992). Regression analyses were performed with control for statistically selected potential confounders. The exposure variables employed were cord serum and maternal milk PCB levels as well as the duration of breast feeding. Less efficient visual discrimination processing and increased errors in short term memory scanning were associated with prenatal exposure to PCBs, but sustained attention was not. Cognitive performance was unrelated to postnatal exposure via breast milk (Jacobson et al. 1992).

A reanalysis of the assessment at 4 years of age was undertaken using the average of the standardized scores for cord serum, maternal serum, and milk PCB values. All values below the detection level (66.9% of cord and 22.5% maternal serum values) were discarded (Jacobson and Jacobson 1997). Results using this composite score as the exposure and the McCarthy Scales, height, and weight as outcomes were similar to those reported by Jacobson et al. (1990a, 1990b,1992). Potential confounders in these analyses were not delineated. Additional findings were reported using the composite score which indicated that the McCarthy Memory Scale and the General Cognitive Index declines were associated with prenatal PCB exposure only in the most highly exposed children.

An 11-year follow-up was undertaken to assess the relationship between prenatal exposure to PCBs and intellectual impairment. The outcomes studied were the Wechsler Intelligence Scales, the Wide Range Achievement tests, and the Woodcock Reading Mastery tests (Jacobson and Jacobson 1996a). The exposure variable consisted of a standardized average of the cord serum, maternal serum, and breast milk PCB values. These values were available for approximately 178/313 (57%) of the original group of children in the study. Linear regression modeling with confounder control, indicated that prenatal exposure to PCBs was significantly associated with lower full-scale and verbal IQ scores. On the academic achievement tests, prenatal exposure to PCBs was associated with poorer word comprehension and overall reading comprehension. Covariates included in all the models were SES, maternal education

and vocabulary, and the Home Observation for Measurement of the Environment (HOME) inventory. Additional confounders selected on the basis of their statistical relationship to the particular outcome were also included in several models. Mercury was included in two of the Woodcock Reading Mastery test models, while lead was not included in any of the multivariate analyses assessing PCBs and intellectual performance (Jacobson and Jacobson 1996a).

The associations of intellectual performance to lead and mercury were evaluated in separate multivariate linear regression models lacking terms for PCB exposure. Lower verbal IQ scores, lower verbal-comprehension scores, and poorer word, passage, and reading comprehension were significantly associated with higher lead levels at 4 years of age. Poorer spelling was significantly associated with a higher mercury concentration at 11 years of age (Jacobson and Jacobson 1996a).

The Oswego Cohort. A study similar to the one conducted in Michigan was initiated in Oswego County (New York) based on babies born between 1991 and 1994 (Lonky et al. 1996). Pregnant women were recruited from the office of one obstetric practice and, following interviews, were divided into three groups based on their estimated fish consumption. The high fish consumption group was composed of women who reported having eaten $40 PCB-equivalent pounds of Lake Ontario fish in their lifetime (n=152) (the same as Michigan's high fish consumption group). The low consumption group reported eating <40 PCB-equivalent pounds (n=243), while the no fish consumption group had never eaten Lake Ontario fish (n=164). The mean PCB-equivalent pounds consumed in the high fish consumption group was 388.47 (SD=859.0), while the mean among those in the low fish group was 10.14 (SD=17.8). The exposure in the high fish consumption group corresponds to a mean of 2.3 salmon or trout meals per month (belly fat trimmed and skin fat removed). The three groups did not differ with regard to demographic, health and nutritional data, maternal substance use, and infant birth characteristics. The high fish consuming group had a significantly heavier pre-pregnancy weight than the nonfisheating group.

The end points evaluated in the study were based on the NBAS. The NBAS behavioral and reflex items were reduced to seven clusters nearly identical to the clusters used in the Michigan Mother-Child pairs study (Jacobson et al. 1984a). The NBAS was administered twice to each infant, once at 12–24 hours and again at 25–48 hours after birth. A total of 58 potential confounding variables were submitted to principal components analysis. Three sets of analyses were performed; the first set contained demographic, nutrition, and stress variables while the second was composed of substances consumed during pregnancy, chronic medical conditions, and other toxic exposures including the type of plumbing

in the woman's home (lead). The third group of variables included labor and delivery complications as well as birth characteristics. A total of 24 components were derived from these three sets of variables.

Statistical analyses were performed using the change scores from the NBAS evaluation (Time 2–Time 1). Multivariate analysis of covariance (MANCOVA) was performed for each of the NBAS clusters with group membership (high, low, and no fish consumption) as the independent variable and the 24 components representing potential confounders as covariates. Approximately 75% of each fish consumption group was included in the analysis (n=416). The loss of subjects occurred because only subjects with data for all variables were included. Multiple regression was also performed for each of the NBAS clusters with inclusion of component covariates for confounder control.

The results of the MANCOVA analyses indicated that newborns exposed to high concentrations of fish demonstrated a greater number of abnormal reflexes and less mature autonomic responses than newborns in the other two exposure groups. Change scores for the Habituation cluster were analyzed in a separate analysis of covariance due to the large number of subjects with missing data (n=285 in the analysis). For that cluster, infants in the high fish group showed a worsening performance from Time 1 to Time 2. The regression analyses showed that infants in the high fish group had a significantly smaller decrease in the number of abnormal reflex scores from Time 1 to Time 2 than the low and no fish groups. In the Autonomic cluster, the high fish group demonstrated a significant worsening in performance between the first and second testing. Performance for the remaining clusters was not significantly associated with fish consumption in the regression analyses. In this study, birth weight, head circumference, and gestational age were unrelated to fish consumption. The differences in the birth weight and head circumference findings of the Michigan and Oswego studies could be due to the differences in PCB exposure levels.

In a later publication, the Oswego group of investigators examined the validity of using fish consumption as a surrogate for PCB exposure (Stewart et al. 1999). The study included 279 women with complete fish consumption histories, PCB cord blood levels, and demographic and covariate information. The sample included 145 women who reported never having consumed Lake Ontario fish (controls) and 134 who reported consuming at least 40 PCB-equivalent pounds over their lifetime (high fish consumption as defined earlier).

Total PCB levels were divided into three PCB homologue clusters representing the lower, middle, and upper tail of the distribution of all PCB homologues. The lower tail corresponded to lightly chlorinated PCB homologues with one to three chlorines per biphenyl (C1 1–3); the middle, to moderately

chlorinated PCBs with four to six chlorines per biphenyl (C1 4–6); and the upper tail, to heavily chlorinated PCB homologues with seven to nine chlorines per biphenyl (C1 7–9). In a previously conducted study in rats fed Lake Ontario salmon, the highly chlorinated PCB homologues accounted for a greater proportion of the PCBs detected (mole percent) when the fish was fed longer or the absolute concentration of PCBs was higher (Stewart et al. 2000a). The authors predicted the same type of results from the validity study using human cord blood. The average concentration of total PCBs in human cord blood was extremely low, 0.8 ppb among high fisheaters and 1.03 ppb among nonfisheaters (controls) (p=0.36). The relative percent (mole percent) of low- and medium-chlorinated congener PCB clusters from cord blood were similar for fisheaters and controls across each level of total PCB. The mole percent of highly chlorinated congeners was significantly greater in the cord blood of women who ate Lake Ontario fish as compared to the controls who reported no fish consumption (p=0.006). The difference between fisheaters and controls increased significantly (p=0.02) as the total PCB concentration increased.

Eighty-three women in the study also provided breast milk samples within 6 months of the birth of their child. The C17–C19 homologues in breast milk and cord blood were moderately correlated (Pearson's r=0.29; p<0.05), while no correlation was found for the light- and moderately-chlorinated homologues. Actual values of PCBs in milk were not provided.

Based on their findings, the authors concluded that maternal consumption of Great Lakes fish increases the risk of prenatal exposure to the most heavily chlorinated PCB homologues.

A subset of women from the Lonky et al. (1996) study also had cord blood samples collected for total PCB and congener distribution pattern analysis (Stewart et al. 1999). The study group was comprised of mothers who had consumed Lake Ontario fish (n=141) and those who had not (n=152). Each cord blood sample was analyzed for the presence of 69 PCB congeners and several coeluters (e.g., hexachloro-benzene [HCB], mirex, DDE). Exposure was divided into four groups based upon the distribution of heavily chlorinated PCBs (Cl 7–9) in each sample. The exposure variable was an ordinal level measure with the following categories: nondetectable (n=173); bottom 33rd percentile of detectable (n=39); middle 33rd percentile (n=40); and upper 33rd percentile (n=40). The actual lipid-adjusted PCB levels represented by these tertiles among those with detectable PCB levels were: >0–23.2 ng/g fat; 23.3–132.7 ng/g fat; and $132.7 ng/g fat. The heavily chlorinated PCB congeners were used as the measure of PCB exposure since the validity study results support the position that these congeners are the most valid index of fish-borne PCB exposure from Lake Ontario (Stewart et al. 1999, 2000a).

The end points evaluated were based on the seven clusters of the modified NBAS as evaluated by Lonky et al. (1996). The modified NBAS was also used in the Michigan Mother-Child Study (Fein et al. 1984b; Jacobson et al. 1984a). Potential confounders included in the models were selected if preliminary analyses using one-way analysis of variance or linear regression of each covariate in relation to exposure resulted in a p value of <0.20. Those meeting the p<0.20 criterion included: education, SES score, HOME score, maternal prepregnancy weight and weight gain, child gender, birth weight and head circumference, cigarettes/day, and caffeine consumption. Unlike the analyses employing fish consumption as the exposure, the outcomes (i.e., NBAS performance clusters at Time 1 [12–24 hours] and Time 2 [25–48 hours after birth]) were analyzed separately rather than as a change score (Time 2–Time 1) (Stewart et al. 2000b). No associations were noted between PCB cord levels and the NBAS clusters at Time 1. These findings are similar to those described using fish consumption as the exposure variable (Lonky et al. 1996). In looking at Time 2 NBAS cluster indices, significant linear trends were observed between poorer Habituation and poorer Autonomic scores and exposure to heavily chlorinated PCBs. The suggestion of a trend for abnormal reflexes with PCB exposure was observed, but the p value was 0.10 (Stewart et al. 2000b). Linear trend analysis also revealed a significant association between the proportion of poor NBAS clusters and heavily chlorinated PCBs. None of the NBAS performance scores were associated with non-PCB contaminants (i.e., HCB, DDE, lead, mercury, mirex) in linear regression modeling (Stewart et al. 2000b).

Lake Michigan Aging Population Study. This study was designed to assess the neuropsychological functioning of a group of 50–90-year-old fisheaters exposed to PCBs through Great Lakes fish consumption compared to a group of age- and sex-matched nonfisheaters (Schantz et al. 1996a, 1999). Fisheaters were defined as those who regularly consumed one or more meals of Lake Michigan sportsfish/week (>24 pounds/year); nonfisheaters consumed <6 pounds/year. Four classes of control variables were evaluated: a comprehensive list of demographic, life-style, psychological, and health-related variables. Fisheaters and nonfisheaters had very similar demographic characteristics, reported similar patterns of smoking and alcohol consumption, and had comparable scores on measures of intellectual functioning and affect (Schantz et al. 1996a).

The final analysis was conducted on 101 fisheaters and 78 nonfisheaters. Blood samples of the participants were analyzed for PCBs and 10 other contaminants included PBBs, DDE, HCB, oxychlordane, dieldrin, mirex, mercury, and lead. Serum levels of PCBs and DDE were significantly elevated in the fisheaters (PCBs=16.0 ppb) relative to the age- and sex-matched nonfisheaters (PCBs=6.2 ppb), and also relative to the population at large. Lead and mercury were low in both groups,

but were slightly higher in the fisheaters. Because of the high correlation between serum PCBs and DDE, the effects of PCBs and DDE were assessed jointly using a single derived exposure variable categorized as low, intermediate, or high (Schantz et al. 1999). A great majority of the high exposure group were fisheaters and a large majority of the low exposure group were nonfisheaters. However, 15% of nonfisheaters had elevated PCB/DDE exposure and 15% of fisheaters had low PCB/DDE exposure. Based on this, Schantz et al. (1999) stressed the importance of quantitating contaminant levels rather than relying on fisheating status as a surrogate measure for exposure.

Each subject was tested on two fine-motor tasks, the Grooved Pegboard Test (GPT), which assesses visual-motor coordination, and the Static Motor Steadiness Test (SMST), which assesses hand steadiness. Each subject performed the task first with the dominant hand and then with the nondominant hand. The final multivariate model for GPT included age, gender, income, diabetes and use of angiotensin-converting enzyme (ACE) inhibitors, sympatholytic agents, and cardiac glycosides. PCB/DDE exposure was not a significant factor affecting the GPT score; age and gender were the strongest predictors of performance followed by sympatholytics and income. Performance on the SMST was not related to PCB/DDE exposure in initial unadjusted analyses and in the final model, scores on the SMST improved slightly as PCB/DDE exposure increased.

3.2.4.2.1.2 General Population Exposure

The North Carolina Breast Milk and Formula Project. The North Carolina Breast Milk and Formula Project (NCBMFP) is a cohort study designed to assess the relationship between exposure to prenatal and postnatal PCBs and growth and development in infants and children. The NCBMFP was initiated in 1978 and included a cohort of 931 children born between 1978 and 1982. Mothers planning to deliver at one of three participating institutions were recruited from hospital familiarization tours, Lamaze classes, and from both private and public prenatal clinics. No attempt was made to assemble a random sample of women (Rogan et al. 1986a, 1986b, 1987). The participants were administered a questionnaire while in the hospital following delivery. Maternal serum, cord blood, and placenta samples were collected as well as colostrum, breast milk, or formula. The first follow-up visit occurred at 6 weeks with subsequent evaluations at 3 and 6 months postpartum. Breast milk or formula was collected at each of these visits. A second maternal serum specimen also was collected at the 6-week assessment. Subsequent follow-up evaluations occurred at 12, 18, and 24 months, with yearly visits until the age of 5. The children were examined and a health history was taken at each exam. The mothers also were queried about weaning. Breast milk was collected until the mother ceased lactation (Rogan et al. 1987). All biological samples

and a 10% sample of formula specimens were analyzed for PCBs. Because most of the PCB levels from the cord blood and placenta were below the quantitation limits, these two samples were not used as measures of exposure. The median PCB maternal serum level at birth was 9.06 ppb. PCB levels in milk at birth averaged around 1.8 ppm (fat basis). In lactating women, the levels of PCBs in breast milk declined about 20% over six months and about 40% over 18 months (Rogan et al. 1986a).

The participating mothers were not a representative sample of the North Carolina population. Ninety percent of the participants were white, with an age range of 16–41 (median=27). The women were well educated with 53% having a college education. Occupations among the participants were listed as housewife for 16%, while 41% were professionals. Eighteen percent smoked and 40% drank alcohol at least once a week. Twenty-one percent reported eating sportfish at least once during pregnancy. Forty-three percent of the women were primiparous and most (88%) breast-fed their study child to some extent (Rogan et al. 1986a).

The assessment at birth comprised 912 children with at least partial neonatal information. The outcomes evaluated in the neonatal period included birth weight, head circumference, and the presence of jaundice as recorded in the medical record. The NBAS was also administered to the newborns by a trained staff member in the presence of the parents. Fifty-nine percent of the NBAS exams were conducted during the first week of life, 20% in the second, and 16% in the third. The seven cluster scores used in the Michigan Mother-Child Study (Jacobson et al. 1984a) were also employed in this project (Rogan et al. 1986b). The relationships of birth weight, head circumference, and the NBAS clusters to PCB levels were assessed by multiple regression. The covariates (potential confounders) included in the analyses of birth weight and head circumference were infant race, sex, mother's age, education, occupation, smoking, alcohol consumption, prior pregnancies, maternal weight, and center enrolling the participant. The analysis of head circumference also included the birth weight variable (Rogan et al. 1986b). The covariates included in the analyses of the NBAS clusters included mother's age, education, occupation, smoking, alcohol consumption, sportfish consumption, general anesthesia during delivery, infant race and sex, birth weight, presence of jaundice, number of hours since eating, one term for the center, and one for the examiner (Rogan et al. 1986b).

The multiple regression analyses found no associations between birth weight or head circumference and PCB level. For the NBAS assessment, only the cluster scores for tonicity and reflexes were significantly associated with PCB levels. The authors looked at the four scales that make up the tonicity cluster score and found that exposure to PCBs affected the general tone and activity scales; less muscle tone and

activity were associated with higher PCB levels, but only at the highest levels of PCBs. The reflex cluster score was also significantly affected by PCB exposure. When the abnormal reflex scores were separated into high and low, it became apparent that only hypo-reflexia, (not hyper-reflexia), was associated with PCB levels. Since the NBAS were carried out over the first 3 weeks of life rather than during the first 3 days of life (considered to be the best time for this exam according to several investigators), the authors also repeated the same analysis with the population restricted to those whose exams were conducted on day 3 or earlier. The effect of PCB levels on hyporeflexia remained significant while the effect on tonicity was unchanged in size but no longer statistically significant. The authors interpreted the lack of significance to the decrease in sample size rather than confounding due to the age the exam was administered (data were not shown, Rogan et al. 1986b).

The follow-up evaluations at both 6 and 12 months included the administration of the Bayley Scales of Infant Development (Gladen et al. 1988). This exam yields a mental development index (MDI) score and a psychomotor development index (PDI) score, both of which are scaled like a standard IQ test. There were 858 infants (92%) from the original cohort who participated in the study past the neonatal period. Of these, 788 had Bayley scores available at 6 months while 720 had 12-month scores (706 children had scores at each time period). The exposure variable representing prenatal exposure used in the analyses at 6 and 12 months was the estimated PCB levels in milk at birth. The exposure variable representing postnatal exposure used in these follow-up assessments was a combination of the concentration of PCB in breast milk fat and the duration of breast feeding. In addition, milk was assumed to average 2.5% fat over the entire lactation. The authors also assumed that children consumed 700 grams of milk daily, if mostly breast fed, and half of that amount until breast-feeding stopped (Rogan et al. 1987). Children who were not breast fed were counted as having no postnatal exposure (Gladen et al. 1988). Potential confounders included maternal age, race, education, occupation, smoking, alcohol consumption and the infant's sex, gestational age, birth weight, head circumference, jaundice, duration of breast feeding, number of older siblings, number of abnormal reflexes from the NBAS exam, age Bayley administered, and center or examiner.

Linear regression analyses indicated that the psychomotor index scores declined with increasing prenatal PCB exposure at both 6 and 12 months. At 6 months, the PDI was estimated to decrease 0.96 points for every increase of 1 ppm in PCBs. This would mean a drop of 2.6 points if a child moved from the 5th to the 95th percentile of PCB exposure. At 12 months, the drop was estimated at 1.34 points/ppm. Neither the 6-month nor the 12-month mental index scores were related to transplacental PCB exposure (Gladen

et al. 1988). Similar analyses were run to examine postnatal exposure in breast-fed children. Postnatal exposure to PCBs was not associated with the PDI or MDI scores at either time period.

The children also were evaluated by the Bayley Scales of Infant Development at 18 and 24 months. Scores were available for 676 (73%) children at 18 months and for 670 (72%) children at 24 months (Rogan and Gladen 1991). Linear regression modeling was used to assess the relationship between prenatal the Bayley scores and exposure to PCBs. Covariate adjustment included sex, race, age of exam, number of older siblings, maternal age, education, and occupational grouping. Maternal smoking, alcohol consumption, and a term for the examiner were also included. The effects of prenatal PCB exposure on the PDI score at 18 and 24 months were similar to those seen at 6 and 12 months; however, neither were significant. Scores at the age of 18 months, declined 0.38 for every increase of 1 ppm in PCBs. The decline at 24 months of age was 1.16 points for every 1 ppm increase in transplacental PCB exposure. As the score pattern was not linear, the authors also conducted an analysis of variance in which the transplacental exposures were broken into categories. Each category of PCB exposure was then compared to the lowest with adjustment for covariates. At 18 and 24 months, adjusted scores on the psychomotor scales were 4–9 points lower among children in the two highest exposure groups (top 5th percentile of prenatal PCB exposure), significantly so at 24 months ($p < 0.05$). There was no evidence of an effect through postnatal PCB exposure in breast milk. An additional report in this series found that the deficits observed in children through 2 years of age were no longer apparent at ages 3, 4, and 5 years as determined by evaluation with the McCarthy Scales of Children's Abilities (Gladen and Rogan 1991). Finally, evaluation of third and higher grade children showed no significant relationship between the child's work habit or conduct grades and PCB exposure either prenatally or through breast milk, or between hyperactivity reported by parents and exposure (Rogan and Gladen 1992).

The Dutch Mother-Child Study. The Dutch Mother-Child Study was designed as a prospective study to assess the possible adverse health effects of prenatal and postnatal PCB and dioxin exposure. The initial study group consisted of 489 healthy mother-infant pairs recruited between June 1990 and June 1992 during the last month of pregnancy by their obstetrician or midwife (Koopman-Esseboom et al. 1994b). The entry criteria included first or second-born term infants (37–42 weeks gestation) without serious illnesses or complications during pregnancy and delivery. All participants were caucasian (Huisman et al. 1995a). Among the volunteers, 50% of the mothers were planning to breast feed for at least 6 weeks (for postnatal exposure assessment), while the other 50% were planning to use formula from a well characterized batch. This was part of the study design in order to compare breast-fed infants with bottle-fed infants. Seventy-one mother-infant pairs were lost because of the inability to breast feed for 6 weeks

leaving 418 pairs in the study population. Two hundred seven pairs (105 breast-fed and 102 formula-fed) were from Rotterdam, a highly industrialized area, while 211 pairs (104 breast-fed and 107 formula-fed) were from Groningen, a semi-urban area in northern Holland (Koopman-Esseboom et al. 1994b).

The exposure variables used in this study were maternal serum and milk samples as well as cord blood specimens. Maternal serum was collected during the last month (weeks 36–40) of pregnancy while milk samples were collected at 2 and 6 weeks post delivery. Data on the duration of breast feeding in weeks were also collected (Koopman-Esseboom et al. 1996). PCB levels in maternal serum and cord blood were assumed to be a direct measure of prenatal PCB exposure while the breast milk values in the second week after delivery were assumed to reflect the extent of intrauterine and neonatal exposure during the first 2 weeks after birth (Huisman et al. 1995a).

The focus of the authors was to investigate if one of the more easily measurable PCB congener levels could predict the PCB and dioxin exposure of the developing fetus and breast-fed infant. In order to express the potency of the mixture of dioxins and dioxin-like PCBs in breast milk, the authors used the toxic equivalency factor (TEF) approach (Huisman et al. 1995a; Koopman-Esseboom et al. 1994b; Patandin et al. 1999). As discussed in Section 3.5.2, the TEF approach compares the relative potency of individual congeners with that of 2,3,7,8-TCDD, such that the TEF for 2,3,7,8-TCDD is 1. TEQs were calculated by multiplying the concentration of each congener by it's TEF. These values were then multiplied by the number of weeks of breast feeding reported by the mother to obtain a measure of postnatal PCB exposure (Patandin et al. 1998). In breast milk, of the total TEQ value, dioxins contributed 46%, coplanar PCBs 24%, mono *ortho*-substituted PCBs 23%, and di-*ortho*-substituted PCBs 7%.

Because dioxin measurements are time-consuming, expensive, and require large volumes of blood, the authors chose four nonplanar PCB congeners (PCB 118, 138, 153, and 180) as indicators of PCB and dioxin exposure of the developing fetus and breast–fed infant (Koopman-Esseboom et al. 1994b). Although the correlation coefficients between these congeners and congener levels in maternal plasma and PCB levels in cord plasma or PCB and dioxin levels in human milk were highly significant, the 95% predictive interval was too wide to accurately predict the PCB and dioxin levels to which an individual infant is exposed *in utero* or postnatally by breast feeding, from the PCB levels in maternal plasma (Koopman-Esseboom et al. 1994b). The sum of these four congeners in maternal plasma and cord plasma amounted to 2.21 and 0.45 ppb, respectively. A total of 26 PCB congeners, including the four mentioned above, were measured in breast milk and the total PCB concentration in milk was approximately 620 ppb (fat basis). The sum of PCB 118, 138, 153, and 180 in milk totalled 430 ppb.

Data from the obstetrical optimality list were collected in this study as potential confounders and covariates of interest. The list included 72 items that measure SES (demographic, educational, and occupational variables) and pre-, intra-, and immediate postpartum conditions (Huisman et al. 1995a). Other potential confounders were maternal smoking and alcohol consumption (Koopman-Esseboom et al. 1996). The obstetrical optimality score was calculated by counting the number of items that fulfilled preset criteria for optimality. Data on the 5th, 50th, and 95th percentiles of the PCB distributions have been presented in these reports for the biological samples. The PCB levels were logarithmically transformed (natural logarithm). Comparisons of participant levels from Groningen to Rotterdam were made using the chi-square and Wilcoxen rank sum test. Both univariate and logistic regression analyses were conducted to evaluate the relationship between exposure variables and outcomes while controlling for covariates.

Several outcomes were evaluated in the newborn period. The neonatal neurological examination was administered to evaluate age appropriate neurological behavior. Sixty-three percent of the newborns were examined in the second week of life, 31% in the third week, and 6% in the fourth week of life. The examination used in this study included performance on a 10 item reflex cluster and an 11 item postural tone cluster. The scores for each item (0=low, 1=intermediate, and 2=high) were summed for each cluster. A score of #9 was considered to reflect low muscle tone on the postural cluster and a score of #10 was classified as low responsiveness on the reflex score. A neurological optimality score (NOS) was also calculated using a 60 item scale. The NOS score was dichotomized at the median of the pooled population scores (<57=not optimal, $57=optimal) (Huisman et al. 1995a).

Logistic regression analyses with NOS as the dependent variable and maternal serum or cord blood as the measure of prenatal exposure, were conducted with adjustment for maternal age, study center, alcohol, and the interaction of age and alcohol. Models for each of the four nonplanar PCB congeners (118, 138, 153, 180) alone and the sum of the four resulted in odds ratios (ORs) around 1.0 (no association). An OR of greater than 1.0 indicates an increased risk in the exposed group (see Chapter 10, Glossary). The prenatal exposure variables (PCB levels in maternal and cord plasma) were not associated with either the reflex or postural cluster scores. Another logistic regression analysis, with the postural tone cluster as the dependent variable, and adjusting for study center, showed a significantly higher percentage of hypotonia with an increase in planar PCB TEQ in milk. No effect on the reflex cluster was found.

At 18 months of age, the neurological condition of the infants was assessed using an age-specific neurological examination which focuses on the observation of motor functions (grasping, sitting,

crawling, standing, and walking) in a standardized free field situation (Huisman et al. 1995b). Based on this examination, each infant was classified as normal, mildly abnormal, or abnormal. The neurological findings were also evaluated in terms of optimality. Huisman et al. (1995b) also state that special attention was given to the quality of movements in terms of fluency since fluency of motility has been shown to be an indicator for the integrity of brain function in fetuses and prematures. The effect of PCB and dioxin exposure was investigated by a multiple linear regression analysis in which the dependent variables were the neurological optimality score and the fluency cluster score at 18 months. After adjusting for covariates, the results showed that prenatal PCB exposure had a small negative effect on the neurological condition of 18-month-old infants whose fathers did not smoke; no such effect was observed in children of fathers who smoked. Neurological condition was unrelated to exposure to PCBs and dioxins via breast milk.

To assess the mental and psychomotor development of infants exposed to PCBs both pre- and postnatally, the Dutch standardized version of the Bayley Scales of Infant Development were administered at 3, 7, and 18 months of age. Both the MDI and the PDI were included in the assessments. The tests were performed at the infant's home in the presence of the parent(s) (Koopman-Esseboom et al. 1996). The evaluations of the infants using the Bayley Scales of Infant Development were undertaken only for the 207 children from Rotterdam. Rotterdam is an urban area thought to have higher exposures to PCBs than Groningen, a semi-urban area in northern Holland.

Multiple regression analysis assessing the effects of prenatal PCB exposure on the psychomotor scale revealed that prenatal exposure to PCBs was significantly associated with a decrease in the PDI score at 3 months of age. A doubling of the PCB-plasma-sum resulted in a decrease in the psychomotor score of three points. The covariates included in the model were gestational age, parity, the HOME inventory score, education of the mother, and duration of breast feeding. At both 7 and 18 months of age, there was no significant effect of prenatal PCB exposure on the PDI scores (Koopman-Esseboom et al. 1996). Decreased PDI scores at 7 months among infants who were breast fed for longer periods and had higher TEQ scores were associated with postnatal total TEQ (PCB plus dioxin) exposure. The PDI score at 18 months was not associated with postnatal PCB-dioxin exposure. The MDI scores were not significantly associated with either prenatal or postnatal PCB exposure. Higher MDI scores at 7 months of age was positively associated with breast feeding *per se*. Finally, neither the psychomotor nor the mental development scales (at any age) were associated with an exposure variable created with the PCB-milk-sum multiplied by the duration of breast feeding.

At the age of 42 months, follow-up evaluations included both neurological and cognitive outcomes (Lanting et al. 1998c; Patandin et al. 1999). The neurological evaluation was comprised of an age-appropriate clinical exam, which focused on the observation of motor functions (i.e., prehension, sitting, crawling, standing, and walking) as well as the calculation of age appropriate NOS. A movement fluency score also was tabulated (not described).

A preliminary analysis summarizing the plasma PCB levels among children in the Rotterdam group at 42 months (n=173), found that median plasma levels were 3.6 times higher in breast-fed children (0.75 μg/L) than in their formula-fed peers (0.21 μg/L). Breast feeding period and breast milk PCB levels were important predictors of plasma levels in breast-fed children at 42 months, while plasma levels in formula-fed children were significantly related to maternal serum levels during the last month of pregnancy (Patandin et al. 1997). These results were obtained using multivariate linear modeling. The neurological assessment included 394 mother-infant pairs (94% of total participants) from both Rotterdam and Groningen. The clinical exam yielded a diagnosis of "neurologically normal" in 97% of the children.

Linear regression analyses using the NOS as the dependent variable and either maternal PCB-cord sum, maternal PCB-serum sum, or the child's PCB level at 42 months as the exposure found no associations between this outcome and any of these exposure variables. (Each exposure variable was modeled separately). Potential confounders in each model included the study center, the type of feeding during early life, the duration of breast feeding, and several items from the obstetrical optimality score (i.e., SES, obstetrical and perinatal conditions) (Lanting et al. 1998c). A similar model with PCB breast milk levels (TEQ method) as a measure of postnatal PCB exposure with NOS as the outcome, also found no association between the dependent and independent variables. In the last set of four models, fluency score, the dependent variable, was not found to be significantly associated with any of the four exposure variables.

Cognitive abilities also were evaluated at 42 months using the Kaufman Assessment Battery for Children (KABC), an 11 sub-test exam standardized for a large sample of preschool children in the 2.5–4.5 year old range (Patandin et al. 1999). The KABC is constructed to assess two types of mental functioning, sequential problem solving, and simultaneous problem solving. Both the Rotterdam and the Groningen children were administered this test battery. The Rotterdam children also were evaluated for verbal comprehension using the Dutch version of the Reynell Developmental Language Scales (RDLS). Logistical difficulties was stated as the reason for the omission of the Groningen children from this

evaluation. The exposure variables included the two measures of prenatal exposure (maternal serum and cord blood congener sums), postnatal exposure via breast milk (TEQ method), and current PCB body burden based on the serum sample levels in the children at 42 months of age.

The effects of prenatal, postnatal, and current body burden of PCBs on the cognitive outcomes were studied using multivariate linear regression. Potential confounders were chosen based on previous research, clinical expertise relative to the developmental outcomes, and beta coefficient changes observed when adding new variables to the linear regression model. Covariates included in the final regression models were: maternal age at the child's birth; parity; gender; feeding type; duration of breast feeding; HOME score; paternal and maternal educational levels; parental verbal IQ scores; smoking and alcohol use during pregnancy; and study center. Analyses were conducted for the entire group, for breast-fed children, and for formula-fed children.

In the group as a whole, a significant decline ($p<0.05$) in scores on the KABC for the overall scale, the sequential processing scale and the simultaneous processing scale were observed in adjusted regression models with maternal serum PCB levels as the independent variable. When the groups were divided into breast-fed and formula-fed, only formula-fed children showed a significant association between declines in the scores for the same three KABC scales, as well as the RDLS verbal comprehension scale, and maternal serum PCB levels.

Adjusted regression analyses conducted with a categorized version of maternal plasma PCB levels found the mean overall score on the KABC to be four points lower in the group with the highest PCB exposure ($3 ppb) as compared to children in the lowest (#1.5 ppb). Four point deficits in both the simultaneous and sequential scales also were calculated for the highest exposure group as compared to the lowest. Six to eight point deficits were observed for the formula-fed group on the KABC scales while a nonsignificant decline of two points was observed in the breast-fed group. Cognitive performance at 42 months was not related to either lactational exposure or current exposure to PCBs and dioxins.

European Background PCB Study - German Sample. This multicenter European study was designed as a prospective study to assess developmental outcomes associated with prenatal exposure to PCBs in Germany, the Netherlands, and Denmark (Winneke et al. 1998b). This study is very similar in design to the Dutch Mother-Child Study. The German cohort included 171 mother-infant pairs consecutively recruited from the obstetrical wards of three hospitals in Dusseldorf. All infants were term, from German speaking families, with an Apgar score of $7, first or second children, with no serious illnesses or

complications during pregnancy and delivery. Exposure to PCBs was based on the sum of PCB congeners 138, 153, and 180 in cord blood (0.55 ppb). A second measure of PCB exposure in milk was obtained from samples collected at 2 and 4 weeks of age and analyzed for these same three PCB congeners (427 ppb, fat basis). From 171 mother-infant pairs, 169 cord blood and 131 breast milk samples were obtained.

Outcomes measured at 7 months of age included the Bayley Scales of Infant Development (BSID) and the Fagan Test of Infant Intelligence (FTII). The Bayley Scales are comprised of the MDI, the PDI, and the Behavior Rating Scale; only the MDI and the PDI were used in this study. The MDI and PDI were used in the North Carolina Breast Milk and Formula Project (Gladen et al. 1988) and in the Dutch Mother-Child Study (Koopman-Esseboom et al. 1996). A test by Fagan also was used in the Lake Michigan Mother-Child Study (Jacobson et al. 1985). A test of the reliability of the mobile test version of the FTII in the Dusseldorf cohort for 2 observers and 10 children was close to zero (lack of reliability). Confounder selection procedures included a combination of *a priori* selection and statistical significance with the outcome. Linear regression modeling was used to assess the effects of PCB exposure on outcome with adjustment for other covariates.

After adjusting for confounders, there was a significant inverse association between MDI scores and PCBs in milk. There was no association between MDI, PDI, or FTII scores and blood PCBs.

3.2.4.2.1.3 Occupational Exposure

Reports of neurological effects in workers exposed to PCBs are limited. Approximately 49% of workers (64 males, 94 females) exposed to 0.07–11 mg/m^3 mean area concentrations of various Aroclors (early exposure to Aroclors 1242 and 1254; recent exposure to Aroclors 1016 and 1221) at a capacitor manufacturing plant for more than 5 years complained of headache, dizziness, depression, fatigue, memory loss, sleeplessness, somnolence, and nervousness (Fischbein et al. 1979). The prevalence of these symptoms was not compared to a control group. Routine neurological examination did not reveal any remarkable prevalence of abnormalities; extensor weakness was observed in six individuals (1.8%), whereas only one worker presented tremor at physical examination. No further relevant information was provided in this study. In a study by Smith et al. (1982) of three groups of workers occupationally exposed to Aroclors 1242, 1016, 1254, and/or 1260 significant positive correlations of symptoms suggestive of altered peripheral sensation were noted with increasing concentration of serum PCBs. However, there was no overt clinical dysfunction identifiable on physical examinations. Geometric mean

serum levels of up to 500 ppb of low-chlorinated PCBs (#4 chlorines/molecule) and up to 44 ppb of high-chlorinated PCBs were reported for workers in some jobs. Frequent headaches, sleeping difficulties, and memory problems were reported in switchgear workers exposed to Aroclors 1260 and 1242 (0.00001–0.012 mg/m^3) compared to unexposed workers (Emmett et al. 1988a). The geometric mean serum PCBs in the exposed group was 9.7 ppb, and was significantly higher than in the comparison group, 4.6 ppb. Emmett et al. (1988a) stated that the reported symptoms were probably not related to PCBs because they were not consistent with toxic effects ascribed to PCBs in the published literature.

3.2.4.2.1.4 Accidental Exposure

Children from Chinese women accidentally exposed to PCBs and other related chemicals through consumption of contaminated rice (*Yu-Cheng* incident) have been evaluated for cognitive development. Evaluations were conducted when the children were 4–7 years old (Stanford-Binet test and Wechsler Intelligence Scale) and were compared to controls matched for neighborhood, age, sex, mother's age, parent's combined educational level, and parent's occupation. The results showed that at each age, and for each scale other than the WISC-R at the age of 6 years, there was a consistent 5-point difference between the *Yu-Cheng* children and the control children (Chen et al. 1992). Results of the evaluation of the behavior and activity level of these children were published by Chen et al. (1994). Emotional or behavioral disorders were evaluated with the Rutter's Child Behavior Scale A and activity level with a modified Werry-Weiss-Peters Activity Scale. At each year, *Yu-Cheng* children scored 7–43% worse (more disorders) than control children in the Rutter scale. At any fixed age, *Yu-Cheng* children scored 11–63% worse than control children. Furthermore, there was no consistent trend toward decreased differences in scores of *Yu-Cheng* and control children as the interval between the exposure and year of birth increased. Similar results were observed for the activity scores, although the differences between *Yu-Cheng* children and controls were less marked (*Yu-Cheng* children had increased activity levels). The authors also found that children with physical signs had a higher mean score in the Rutter's and activity scores at some age and a lower score at others. There were no consistent relationships between either Rutter or activity scores and cognitive scores of PCB detectability, maternal serum PCB levels, or breast-feeding mode. *Yu-Cheng* children also scored significantly lower than controls in MDI and PDI tests between the ages of 6 months and 2 years (Lai et al. 1994) and in Raven's Colored Progressive Matrices and at ages 6, 7, or 9, and in Standardized Progressive Matrices at age 9 (Guo et al. 1995).

3.2.4.2.2 Neurophysiological Effects

Various neurological symptoms, including numbness, weakness and neuralgia of limbs, hypesthesia, and headaches, are common in *Yusho* and *Yu-Cheng* victims (Chia and Chu 1984, 1985; Kuratsune 1989; Rogan 1989). It is important to mention, however, that the findings from the studies of these groups cannot be attributed solely to exposure to PCBs since the victims also were exposed to CDFs and other chlorinated chemicals (ATSDR 1994). Conduction velocities were reduced in sensory nerves (radial and/or sural) in 9 of 23 *Yusho* patients examined soon after poisoning (Kuroiwa et al. 1969). Sensory fibers may have been preferentially affected as conduction velocities in motor nerves (ulnar and tibial) were reduced in only two cases and motor functions were normal. Follow-up studies were not performed on the *Yusho* patients, but disappearance of related symptoms and signs indicated that the effects on nerve conduction did not persist. Reduced sensory and motor nerve conduction velocities also occurred in *Yu-Cheng* patients (Chen et al. 1985; Chia and Chu 1984, 1985). Evaluation of 110 patients within 1 year of *Yu-Cheng* exposure showed significantly reduced sensory nerve (median and ulnar) and motor nerve (tibial and peroneal) conduction velocities in . 44 and 22% of the patients, respectively (Chen et al. 1985). All of the subjects had developed eye and skin manifestations of toxicity, but there were no significant correlations between nerve conduction values and blood levels of PCBs, CDFs, or PCQs. Electroencephalographic examination of *Yu-Cheng* patients did not show any abnormalities potentially indicative of central nervous system damage (Chia and Chu 1984, 1985). Additional information on the *Yusho* and *Yu-Cheng* poisoning episodes can be found in the toxicological profile for chlorodibenzofurans (ATSDR 1994).

3.2.4.2.3 Evaluation of Human Studies

Several studies are available that evaluated the relationship between prenatal PCB exposure (and postnatal exposure in some instances) and neurobehavioral parameters in infants and children. These studies are the Michigan Mother-Child Study (Fein et al. 1984a, 1984b; Jacobson and Jacobson 1996a, 1997; Jacobson et al. 1984a, 1985, 1990a, 1990b, 1992), the Oswego Newborn and Infant Development Project (Lonky et al. 1996, Stewart et al. 1999, 2000a), the North Carolina Breast Milk and Formula Project (Gladen et al. 1988; Rogan and Gladen 1991, 1992; Rogan et al. 1986a, 1986b, 1987), the Dutch Mother-Child study (Huisman et al. 1995a, 1995b; Koopman-Esseboom et al. 1994b, 1996; Lanting et al. 1998c; Patandin et al. 1999; Weisglas-Kuperus et al. 1995), and the German Study (Winneke et al. 1998b). A comparison of PCB levels in blood and breast milk in some of these studies is included in Appendix A. Related information is also available from the *Yu-Cheng* accidental poisoning incident in

Taiwan (Chen et al. 1992, 1994; Guo et al. 1995; Lai et al. 1994). Data from adults exposed to PCBs are available from studies by Schantz et al. (1996a, 1996b, 1999) and from evaluations of victims from the Taiwan poisoning episode (Chen et al. 1985; Chia and Chu 1984, 1985).

The association between consumption of Great Lakes contaminated sportfish (i.e., PCB exposure) and neurodevelopmental alterations in children has been examined in the Michigan series of studies and in the Oswego series. Despite concerns about the design and analysis of the data from the Michigan Mother-Child Study (Expert Panel 1994; Paneth 1991; Schantz 1996; Seegal 1996a, 1996b), many of the findings of Jacobson and colleagues in the Michigan cohort have been replicated in studies of other cohorts. Jacobson et al. (1984a) found that newborn children exposed to PCBs from mothers who ate PCB-contaminated sportfish were more likely to exhibit hypoactive reflexes, more motor immaturity, poorer lability of states, and greater amount of startle. In the Oswego study, the high PCB exposure group was defined as those who consumed a mean of 2.3 salmon or lake trout meals/month, as done in the Michigan study, and children born to mothers from this group demonstrated a greater number of abnormal reflexes and less mature autonomic responses than those born to low PCB-exposed or non-exposed mothers (low-fisheaters or nonfisheaters) (Lonky et al. 1996). However, Lonky et al. (1996) found no significant association between fish consumption and birth weight, head circumference, and gestational length, as Fein et al. (1984a) had found in the Michigan cohort. Taking advantage of improved analytical techniques available at the time of the study, researchers from the Oswego study observed a significant linear trend between poorer Habituation and Autonomic scores and heavily chlorinated PCBs (Stewart et al. 2000b). The suggestion of a trend for abnormal reflexes with PCB exposure was observed, but the finding was not statistically significant. Linear trend analysis also revealed a significant association between the proportion of poor NBAS clusters and heavily chlorinated PCBs. No significant association was seen for the lightly and moderately chlorinated PCBs, DDE, lead, HCB, and mercury. It is worth noting that in the Oswego cohort, the average concentration of total PCBs in cord blood was 0.8 ppb among high fisheaters and 1.03 among nonfisheaters, such that no association could have been found had total PCBs in cord blood been used as surrogate for exposure.

Neonatal evaluations also were conducted in the North Carolina study (Rogan et al. 1986b). This is a study of women from the general population with no known high exposure to PCBs. PCBs in milk at the time of birth (approximately 1.8 ppm, but may have been overestimated by a factor of 2) was used as indicator of prenatal exposure; the median PCBs in maternal serum at birth was 9.06 ppb. In the Michigan cohort, the mean concentration of PCBs in maternal milk and serum in high fisheaters were approximately 0.9 ppm and 6.1 ppb, respectively. The NCBMFP also found that less muscle tone and

activity were associated with higher PCB levels. The reflex cluster score was also significantly affected by PCB exposure. When the abnormal reflexes were separated into high and low, it became apparent that hypo-reflexia, not hyper-reflexia, was associated with PCB levels.

Evaluations of various cohorts at later ages provide the opportunity to compare results of similar tests conducted at similar ages. For example, the BSID has been administered to infants in the North Carolina cohort, the Dutch children, and the German study. This group of tests yields a MDI and a PDI score, both of which are scales like a standard IQ test. In the North Carolina cohort, a significant decrease in PDI scores at the ages of 6 and 12 months was associated with prenatal exposure to PCBs (assessed by PCBs in maternal milk at birth, 1.8 ppm) (Gladen et al. 1988), although the association lost statistical significance at the ages of 18 and 24 months (Rogan and Gladen 1991). No significant association was observed between PDI scores at 6–24 months of age and postnatal exposure to PCBs (PCBs in milk factored by duration of breast feeding). There was no significant association between MDI scores and either prenatal or postnatal exposure to PCBs. The latter is consistent with a lack of significant association between MDI scores at 7 or 18 months of age and prenatal or postnatal exposure, also observed in the Dutch children (Koopman-Esseboom et al. 1996). *Yu-Cheng* children also had lower PDI and MDI scores when tested between the ages of 6 months and 2 years old (Lai et al. 1994).

Both the Dutch and the German studies assessed prenatal and postnatal exposure by measuring the concentration of a limited number of PCB congeners in cord blood and in breast milk. In the Dutch study, the researchers measured PCBs 118, 138, 153, and 180 in cord blood and the sum of the mean concentration of these congeners was 0.45 ppb (Koopman-Esseboom et al. 1994b). The German study measured PCBs 138, 153, and 180 in cord blood and the sum amounted to 0.55 ppb (Winneke et al. 1998b). The added concentration of these four PCB congeners in breast milk in the Dutch study was 430 ppb, whereas in the German study, the concentration of PCBs 138, 153, and 180 in breast milk was essentially the same at 427 ppb. Both studies evaluated MDI and PDI scores at 7 months of age. In the Dutch study, at this age, neither PDI nor MDI scores were significantly associated with prenatal exposure to PCBs; however, lower PDI scores, but not MDI scores were significantly associated with postnatal exposure. In the German study, also no significant association was found between MDI or PDI scores and prenatal exposure to PCBs, but in contrast with findings from the Dutch children, lower MDI scores, but not PDI scores, was significantly associated with postnatal exposure to PCBs. Thus, it would appear that practically the same exposure assessments in the two studies (including the concentration of marker PCBs) and tests conducted at the same age provided apparently opposite results. This may indicate that more thorough analyses are necessary especially given the importance of ‘minor’ congeners in animal

studies. Also, the results from the German cohort on background PCB exposure in Europeans appear preliminary with few details described.

Evaluations at the age of 4 years have been done on the Michigan (Jacobson and Jacobson 1997; Jacobson et al. 1990a; 1992) and Dutch children (Lanting et al. 1998c; Patandin et al. 1999). Jacobson et al. (1990a) showed that poorer performance on both the Verbal and the Memory scales of the McCarthy Scales of Children's Abilities was associated with prenatal exposure to PCBs. Jacobson et al. (1992) also found that less efficient visual discrimination processing and more errors in short-term memory scanning, but not sustained attention, were associated with prenatal exposure to PCBs. Dutch children evaluated at 42 months of age on neurological optimality scores showed no decrement on performance as a result of exposure to PCBs either prenatally or postnatally (Lanting et al. 1998c). Cognitive abilities evaluated in these children using the KABC showed a significant decreased performance associated with prenatal exposure to PCBs (Patanding et al. 1999). Since the tests from the Patandin et al. (1999) and Jacobson et al. (1990a) are both designed to provide a measure of general intelligence, the data are comparable and the effects observed in the two studies on these end points are consistent.

Evaluation of the children from the Michigan cohort at 11 years of age showed that lower full-scale and verbal IQ scores and poorer reading word comprehension were significantly associated with prenatal exposure to PCBs (Jacobson and Jacobson 1996a). The mean maternal serum PCB concentration among fisheaters in the Michigan study was 6.1 ppb (Fein et al. 1984a). Decreased IQ was also observed among *Yu-Cheng* children (Chen et al. 1992), but exposure levels in this group were significantly higher than in the Michigan cohort and there was also significant exposure to CDFs, dioxins, and other related chemicals.

Evaluation of an adult population (50–90-years old) on a visual-motor coordination test and a hand steadiness test revealed no significant effect from exposure to PCB/DDE through long-term consumption of Lake Michigan fish (>24 pounds/year) (Schantz et al. 1999). Results from cognitive assessment of this cohort have not yet become available. Workers exposed to PCBs have reported adverse neurological symptoms, but routine examination of these workers did not reveal any clinical dysfunction (Emmett et al. 1988a; Fischbein et al. 1979; Smith et al. 1982). There is no indication that cognitive function or fine motor behavior was evaluated in any way in the workers. Neurological examination of *Yusho* and *Yu-Cheng* victims showed reduced both motor and sensory nerve conduction velocities (Chen et al. 1985; Chia and Chu 1984, 1985; Kuroiwa et al. 1969), but due to the mixed chemical nature of the rice oil exposure, the results cannot be attributed specifically to PCBs.

In summary, there is mounting evidence that PCBs can be important contributors to subtle neurodevelopmental alterations in neonates and infants of women who consume high-amounts of sport-caught fish from the Great Lakes and also of women in the general population with the highest PCB body burdens. Most of the studies summarized above have quantitative exposure estimates, associations between the outcome and exposure which are likely free from confounding, and minimal biases, making their findings more convincing. Data from *Yu-Cheng* can only be considered supportive due to the known exposure to other chlorinated aromatic hydrocarbons. Data from the Dutch Mother-Child Study strongly suggest that exposure to dioxins in general, not solely PCBs, may be related to altered developmental effects in neonates and children. The Oswego validity study to assess fish consumption as a measure of PCBs, as well as the reanalysis of the Oswego neurodevelopmental outcomes using cord blood C17–C19 PCB homologue levels as measure of exposure makes this series of studies important in establishing biomarkers of exposure for quantitative risk assessment. Unlike the North Carolina study, the outcomes of the Oswego study are limited to NBAS within the first 2 days of life, although it is expected that these children will be the subject of follow-up evaluations for years to come.

3.2.4.3 Animal Studies

The highest NOAEL values and all reliable LOAEL values for neurological effects for each study are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.4.3.1 Neurobehavioral Effects

Oral Exposure

Neurobehavioral effects of PCBs have been examined in several species exposed for various durations. Experiments have been conducted with commercial mixtures, defined experimental mixtures, contaminated fish, and single congeners.

Commercial PCB Mixtures. Spontaneous motor activity was significantly decreased in male CD_1 mice (unspecified age) 15 minutes to 3 hours following a single gavage dose of 500 mg Aroclor 1254/kg (Rosin and Martin 1981). However, dosing with 30 or 100 mg/kg for 14 days had no significant effect on this end point. Assessment or motor coordination with two tests (screen test and rotor rod) did not reveal any significant effect 15–120 minutes after treatment with a single dose of 500 mg Aroclor 1254/kg. Similar results regarding a decrease in spontaneous motor activity were reported in adult male Long-

Evans rats following single gavage doses of $300 mg Aroclor 1254/kg; no significant effect was seen with 100 mg/kg (Nishida et al. 1997). Incomplete recovery to pretreatment levels of activity occurred over a 9-week period. Repeated administration of Aroclor 1254 resulted in dose-related decreases in activity at doses $30 mg/kg/day, the NOEL was 10 mg/kg/day. In this case, complete recovery of activity occurred 3 weeks after exposure. Kodavanti et al. (1998) also reported decreased motor activity in adult male rats treated with 30 mg Aroclor 1254/kg/day for 4 weeks. Nishida et al. (1997) also conducted flavor aversion conditioning tests and reported that the acute and repeated NOELs for this behavioral test were 15 and 7.5 mg/kg, respectively.

Freeman et al. (2000; General Electric Co. 1995a, 1995b) conducted a 52-week feeding study in rats with various Aroclor mixtures (1016, 1242, 1254, 1260) and found no significant treatment-related effects on a comprehensive number of neurological end points. PCB intakes ranged from 1.3 to 14.1 mg/kg/day depending on the Aroclor mixture. The functional observational battery assessed autonomic function, muscle tone and equilibrium, sensorimotor function, and central nervous system function. Motor activity tests and histopathological examination of the central and peripheral nervous system were also performed.

Open field activity on PND 14 was significantly suppressed in offspring from rats treated by gavage with 2 mg/kg/day Fenclor 42 (a non-Aroclor PCB, similar in composition to Aroclor 1242) on PND days 1–21, but not in offspring from rats treated with 2–4 mg/kg/day on gestation days 6–15 (Pantaleoni et al. 1988). Neurobehavioral alterations including impaired swimming behavior and acquisition of one-way avoidance response were also observed in the pups exposed *in utero* and also following postnatal exposure.

Neurobehavioral alterations were also reported in the offspring of rats treated with 2.4 mg/kg/day Clophen A30 (technical mixture with 42% chlorine) premating and during gestation (Lilienthal et al. 1990). Offspring, which continued on the PCB diet after weaning, were tested for open field activity on PND 22 and 120, active avoidance learning on PND 65–75, and operant conditioning on a fixed interval on PND 380. Spontaneous activity was increased on PND 22, but not on PND 120. Avoidance responses and intertrial responses were increased, as were the responses in the operant conditioning test. No significant behavioral alterations were seen in rats treated with about 0.4 mg Clophen 42/kg/day. In a subsequent cross-fostering experiment, Lilienthal and Winneke (1991) reported that exposure *in utero* resulted in alterations in active avoidance learning and retention of a visual discrimination task similar to those seen in rats exposed *in utero* plus through mother's milk, whereas postnatal-only exposure caused no detectable behavioral changes. Lilienthal and Winneke (1991) also observed that brain levels of

higher chlorinated congeners peaked at weaning in groups with postnatal or postnatal plus prenatal exposure, whereas the concentration of a low-chlorinated congeners was lower at weaning than at birth or at later ages. This suggests that transfer of low-chlorinated congeners may be more pronounced during gestation, while preferential transfer of high-chlorinated PCBs occurs via the milk.

Overmann et al. (1987) reported that pups from rats exposed in the diet to approximately 1.3 mg Aroclor 1254/kg/day during gestation and lactation were significantly slower than controls in the negative geotaxis test when tested on PND 7 and 8, but not on PND 5 or 6. Also, the appearance of auditory startle was slightly delayed on PND 12, but not PND 11, 13, or 14, in pups from dams treated with 0.13 and 1.3 mg/kg/day. The development of air righting ability also was slightly delayed at the 1.3 mg/kg/day dose level on PND 18, but not PND 16, 17, or 19.

Suggested evidence of memory impairment in a radial arm maze in rats resulting from perinatal exposure to Aroclor 1254 was presented by Corey et al. (1996). The pups, tested at age 42–54 days, were exposed *in utero* and via mothers' milk. The dams received 8 or 17.8 mg Aroclor 1254/kg/day during gestation and exposure continued until postpartum day 28. Rats exposed to PCBs made significantly more maze errors than control rats regardless of whether exposure of the pups ceased at weaning or had continued by direct feeding. In a more recent study, the same group of investigators reported that offspring from rats fed approximately 1 mg Aroclor 1254/kg/day during gestation and lactation and tested between 25 and 29 days of age performed significantly worse than controls in a Morris water maze during trials 8, 9, and 10 (Provost et al. 1999). No differences were seen in earlier trials, and interestingly, during the first four trials, control rats performed much worse than treated rats.

Neurobehavioral studies also have been conducted in monkeys born to exposed mothers. In a study by Bowman et al. (1978), the assessment was conducted in three offspring of mothers fed a diet providing approximately 0.1 mg/kg/day Aroclor 1248 for 16–21 months; PCB feeding terminated at the end of 3 months of nursing. All monkeys were tested on a sequence of 11 tasks between the age of 6 and 24 months; four untreated monkeys served as controls. Relative to controls, exposed monkeys showed hyperlocomotor activity at 6 and 12 months of age, which correlated with peak PCB body burdens; they also showed decreased performance in five out of nine discriminating learning tasks. According to the investigators (Bowman et al. 1978), the learning deficits appeared to represent residual toxicity, since they could be observed after almost total clearance of PCBs from the body. The same monkeys tested at 44 months of age appeared to exhibit hypoactive behavior relative to controls (Bowman and Heironimus 1981).

Neurobehavioral deficits reflected as impaired performance on a spatial learning and memory task were seen in the progeny of monkeys fed 0.08 mg/kg/day Aroclor 1248 for 18 months and allowed to breed 32 months postexposure (Levin et al. 1988). The deficit did not appear to be due to memory impairment, but rather to impairment in associational or attentional processes. Aroclor 1016, tested at a dose level of 0.008 mg/kg/day, did not significantly alter performance on that task (Levin et al. 1988), but impaired the monkeys' ability to learn a simple spatial discrimination problem at 0.03 mg/kg/day (Schantz et al. 1989). These long-term studies in monkeys showed that doses of $0.03 mg/kg/day of some PCBs can alter performance in neurobehavioral tests.

Defined Experimental Mixtures. Rice and Hayward (1997) studied the effects on learning in monkeys of postnatal exposure to a PCB mixture representative of the PCBs typically found in human breast milk. Eight male monkeys were dosed from birth to 20 weeks of age with 0.0075 mg/kg/day of PCBs. Five monkeys served as controls. At 20 weeks of age, the levels of PCBs in fat and blood in treated monkeys were 1.7–3.6 ppm and 2–3 ppb, respectively; corresponding values for controls were 0.05–0.2 ppm and 0.30–0.37 ppb. Beginning at 3 years of age, the monkeys were tested on a series of nonspatial discrimination reversal problems followed by a spatial delayed alternation task. Treated monkeys showed decreased median response latencies and variable increases in mean response latencies across three tasks of nonspatial discrimination reversal. There was no difference in overall accuracy of the tests. There was no correlation between performance and tissue levels of PCBs. Treated monkeys also displayed retarded acquisition of a delayed alternation task and increased errors at short delay task responses. These finding were interpreted as a learning/performance decrement rather than an effect on memory *per se.* In a separate portion of this study (Rice 1997), treated monkeys displayed shorter mean interresponse times when compared with controls. The increase in pause time for fixed-interval performance emerged more slowly across the 48 sessions in treated monkeys. For fixed-ratio performance tasks, the control monkeys decreased their mean pause time across 10 sessions, whereas the treated monkeys did not. Rice (1997) interpreted these results as suggesting learning deficit, perseveration, and/or inability to inhibit inappropriate responding as a result of postnatal PCB exposure. Testing of these monkeys at 4.5–5 years of age showed that treated animals performed in a less efficient manner than controls under a differential reinforcement of low rate (DRL) schedule of reinforcement (Rice 1998). There were no differences between groups on the accuracy of performance on a series of spatial discrimination reversal tasks, although some treated monkeys made more errors than others on certain parts of the experiment. Further tests conducted at about 5 years of age did not find treatment-related effects on a series of concurrent RI-RI (random interval) schedules of reinforcement (Rice and Hayward 1999a). This schedule was designed to study behavior in transition (learning) as well as at steady state. However, there was a

difference between treated and control monkeys on performance on a progressive ratio (PR) schedule. Rice and Hayward (1999a) stated that the interpretation of this finding is not straightforward, but may be indicative of retarded acquisition of the steady-state PR performance in treated monkeys.

Contaminated Fish Consumption. The neurobehavioral effects of exposure of rats to feed adulterated with 5 or 20% lyophilized salmon fillets from Lake Huron (LH) or Lake Ontario (LO) were examined by Pappas et al. (1998). The study was conducted in F_1- and F_2-generation 88-day-old male and female rats that had been exposed *in utero*, during lactation, and postnatally until they were tested. Exposure to the contaminated diet caused no observable effects on many behavioral parameters including activity, exploration, sensorimotor function, and stereotypy. Also, there was no diet-induced impairment of spatial learning or long-term memory, and no evidence of an exaggerated response to food reward reduction. The only significant effect found was decreased performance of the F_1 LO-20 and F_2 LH-20 rats in the reference/working memory version of the radial arm maze. Stewart et al. (2000a) examined the effects of feeding adult male rats a 30% diet of salmon from Lake Ontario, Pacific Ocean salmon, or a laboratory chow on performance on a multiple FR-PR reinforcement schedule. Rats were fed for 65 days. Lake Ontario diet contained 739 ppb PCBs, whereas the Pacific Ocean diet and the lab diet contained 45 and 64 ppb PCBs, respectively. Also, the average chlorines per biphenyl for the Lake, Ocean, and lab diets were 5.65, 4.58, and 4.54, respectively. Analysis of PCB homologues in the brain of rats showed that rats fed Lake fish had significantly higher concentrations of homologues with 6, 7, 8, or 9 chlorines per biphenyl than the other groups. These rats' brains also contained DDE and mirex, which were not detected in the Ocean or lab diet groups. Behavioral test results showed that Lake rats responded normally during FR schedules, but quit significantly sooner than control rats on a PR-5 schedule, when response costs were demanding. None of the response rates were significantly related to contaminants.

Single Congeners. Administration of 32 mg 3,3',4,4'-tetraCB/kg (PCB 77) to pregnant CD-1 mice on gestation days 10–16 resulted in motor and behavioral alterations in the offspring tested at 35 and/or 65 days of age (Tilson et al. 1979). Some, but not all, exposed mice exhibited a neurobehavioral syndrome consisting of intermittent stereotypic circling activity (PCB-spinners). Relative to controls and to PCB-nonspinners, PCB-spinners were hyperactive during the dark phase of the diurnal phase, showed decreased muscular strength and impaired ability to traverse a wire rod, altered visual placement responding, and impaired acquisition of one-way avoidance. However, reflex activity and orientation to environmental stimuli were not affected by exposure to PCB 77. No PCB-derived radioactivity could be detected in $28-day-old mice born to dams administered radioactive PCB 77 on gestation days 10–16. Microscopical examination of tissues from PCB-spinners (up to 8 months old) showed cylindrical

peninsulas of central nervous system parenchyma in the cranial and spinal nerve roots as well as alterations in synapses of the nucleus accumbens (Chou et al. 1979). Increased motor activity in PCB-spinners was still evident at 1 year of age (Agrawal et al. 1981). Altered spontaneous motor activity was seen in 4-month-old male NMRI mice given a single gavage dose of 0.41 mg PCB 77/kg at 10 days of age (Eriksson et al. 1991). When tested during three 20-minute blocks, treated mice were hypoactive during the first block, but hyperactive during the third block relative to controls. Similar results were obtained with PCBs 28, 52, and 126, but no such effect was seen with PCBs 118, 156, or 105 (Eriksson and Fredricksson 1996a, 1996b, 1998). There was also a marginal effect of PCB 52 (4.1 mg/kg) on learning and memory assessed by performance on a swim-maze and a radial-arm maze and of PCB 126 (0.46 mg/kg) also on the swim-maze.

Several PCB congeners have been evaluated for neurobehavioral alterations in rats. The most widely studied appears to be PCB 126, a dioxin-like congener, with an estimated dioxin-like toxicity potency 1/10 that of 2,3,7,8-TCDD. Barnhoft (1994) found reduced onset of spontaneous movements and delayed neuromuscular maturation in pups from Lewis rats administered six gavage doses of 10 or 20 μg PCB 126/kg on gestation days 9–19; evaluations were conducted during the first 4 weeks of life. Spontaneous activity level was not affected by treatment. Tests for visual discrimination learning (age 5–18 weeks) did not reveal any significant differences in performance between PCB-treated rats and controls. However, in a later paper, the same group of investigators reported that administration of six doses of 2 μg PCB 126/kg on gestation days 10–20 resulted in both poorer visual discrimination and hyperactivity in treated rats relative to controls; similar, but less marked effects were seen with 2,3',4,4',5-pentaCB (PCB 118) (Holene et al. 1995). In two more recent studies, it was reported that male pups from dams treated with PCB 153 from day 3 to 13 after delivery were hyperactive and had impaired performance in a visual discrimination test (Holene et al. 1998), but female pups showed no significant differences compared with controls (Holene et al. 1999).

Rice and coworkers conducted a series of behavioral studies in offspring from Long-Evans rats dosed with 0, 0.25, or 1 μg PCB 126/kg/day beginning 5 weeks before and continuing through gestation and lactation (Bushnell and Rice 1999; Rice 1999a; Rice and Hayward 1998, 1999b). Exposure to PCB 126 did not significantly alter performance of male or female pups on a multiple fixed interval fixed-ratio schedule of reinforcement or on a DRL schedule at about 200 days of age (Rice and Hayward 1998). Exposure to PCB 126 did produce developmental toxicity as evidenced by reduced birth weight, reduced serum thyroxine, and changes in hematology and serum biochemistry parameters. Assessment of performance on a spatial delayed alternation task also revealed no significant differences between treated

and control rats (Rice 1999a, 1999b); no PCB was detected in pups brain at age 60 days. Further tests conducted in males to assess visuospatial attention and sustained attention showed no significant treatment-related deficits (Bushnell and Rice 1999). Finally, male and female pups were tested under a series of three concurrent RI-RI schedules of reinforcement at about 400 days of age followed by assessment under a PR schedule (Rice and Hayward 1999b). Although there was some indication of less accurate performance in high-dose rats in the RI-RI schedule, there was no difference between treated and control rats in the PR performance.

Schantz and colleagues assessed learning and memory in an 8-arm radial maze and in a T-maze in male and female offspring from Sprague-Dawley rats treated with PCB congeners on gestation days 10–16 (Schantz et al. 1995, 1996b, 1997). Testing started at 60 days of age. The first study tested the *ortho*-substituted congeners PCBs 28, 118, and 153 (Schantz et al. 1995). No treatment-related effects were seen on a memory task on a radial maze test, but female offspring were less accurate than controls on a T-maze spatial delayed alternation task; PCB 118 caused the smallest deficit of the three congeners. Subsequent studies examined 2,3,7,8-TCDD, the dioxin-like congeners PCB 77 and PCB 126, and PCB 95 and found that performance on the radial arm maze task was facilitated by treatment with each of the four compounds, but mostly by 2,3,7,8-TCDD (Schantz et al. 1996b, 1997). No significant group differences were seen on the T-maze test. An additional observation was that exposure to PCB 95 did not alter spontaneous activity in rats tested as juveniles (35 days old), but induced hypoactivity in tests conducted in adulthood (100 days old). In these rats exposed to PCB 95, Schantz et al. (1997) also observed decreased density of ryanodine receptor binding proteins in the hippocampus, increased binding in the cerebral cortex, and a biphasic response in the cerebellum.

Other Routes of Exposure. Altmann et al. (1995) examined the effect of 3,3',4,4'-tetraCB (PCB 77) on long-term potentiation (LTP), a measure of neuronal functional plasticity, in rats. Pregnant Wistar rats were treated with daily subcutaneous injections of 1 mg/kg of PCB 77 on gestation days 7–18. At the age of 180–220 days, offspring were sacrificed and slices were prepared from the visual cortex and hippocampus. Treatment with PCB 77 resulted in inhibition of LTP in visual cortex slices, but not in the hippocampus. A follow-up study reported the same result in slices from 11–19-day-old pups (Altmann et al. 1998). In the latter study, PCB 47 was also tested and was much less effective than PCB 77. Using the same exposure protocol, the effects of these two congeners also were assessed on locomotor activity in the open field, spatial learning in the radial arm maze, catalepsy induced by the dopamine receptor blocker haloperidol, and passive avoidance learning at PND 25, 95, 180, and 220, respectively (Weinand-Harer et al. 1997). Of all of these end points, exposure to PCB 77 altered the haloperidol-induced

catalepsy and impaired performance in passive avoidance behavior; PCB 47 produced changes in the same direction, but the differences relative to controls did not achieve statistical significance.

3.2.4.3.2 Neurochemical Effects

Neurochemical effects of PCBs have been examined in rats, mice, and monkeys exposed to commercial PCB mixtures and to individual PCB congeners. Some studies have assessed both neurochemical and neurobehavioral effects of PCBs in an attempt to link a biochemical alteration to a particular neurobehavioral deficit.

Oral Exposure

Commercial PCB Mixtures. Administration of single, high doses (500 and 1,000 mg/kg) of a mixture of Aroclor 1254 and 1260 to adult male rats reduced serotonin levels in the frontal cortex and hippocampus, increased serotonin in the lateral olfactory tract, and had no effect in the hypothalamus and brainstem (Seegal et al. 1986a). A correlation between the direction of the changes (increase or decrease) and changes in PCB levels in the different areas could not be made. In a similar study, there was a dose-dependent decrease in the levels of dopamine in the caudate nucleus, but not in the lateral olfactory tract, of adult rats treated with 500 or 1,000 mg/kg of a mixture of Aroclor 1254 and 1260 (Seegal et al. 1986b). In a subsequent study, a dose of 1,000 mg/kg of Aroclor 1016 increased dopamine turnover in peripheral neurons of rats, whereas the same dose of an Aroclor 1254/1260 mixture increased dopamine turnover in central neurons (Seegal et al. 1988), suggesting that PCBs with different degrees of chlorination can alter dopaminergic functions in different locations of the nervous system. Treatment of adult male rats with a diet that provided approximately 0, 39, or 79 mg Aroclor 1254/kg/day for 30 days resulted in significant decreases in dopamine concentrations and metabolism in the striatum and the lateral olfactory tract, but not in other brain areas (Seegal et al. 1991a). Analysis of PCB congeners in striatum, lateral olfactory tract, and hippocampus showed that the hippocampus contained the highest PCB concentration and that the major PCB congeners were penta and hexabiphenyls mono- or di-*ortho*-substituted. In contrast to the finding of decreased dopamine concentration by Seegal et al. (1991a), Kodavanti et al. (1998) found no alterations in the concentrations of dopamine, norepinephrine, or serotonin in the striatum or cortex of adult male rats treated with up to 30 mg Aroclor 1254/kg/day for 4 weeks; in addition, tyrosine hydroxylase activity in striatal minces was not significantly altered by PCB treatment. However, treatment with Aroclor 1254 significantly reduced the Ca buffering capacity of microsomes and mitochondria in the cerebellum and of microsomes in the frontal cortex and striatum. Aroclor 1254 also

decreased total protein kinase C (PKC) activity and increased membrane-bound PKC activity in the cerebellum, but not in other brain areas. In this study, treated rats were hypoactive compared to controls.

Doses between 0.8 and 3.2 mg/kg/day Aroclor 1016 in the diet for 20 weeks did not alter the concentrations of noradrenaline, adrenaline, or serotonin in several areas of the brains of monkeys (Seegal et al. 1990). A similar exposure protocol with Aroclor 1016 or 1260 resulted in dose-dependent decreases in dopamine contents in several areas of the brain (Seegal et al. 1991b). Dopamine continued to be depressed 24 weeks after the exposure period ceased (Seegal et al. 1992, 1994); at this time, the concentration of PCBs had greatly decreased. After the 20-week exposure, only PCBs 28, 47, and 52 congeners were detected in the brains of the monkeys treated with Aroclor 1016, and mainly hexa- and hepta-chlorinated di-*ortho*-substituted congeners were detected in the brains of monkeys treated with Aroclor 1260. Seegal et al. (1991b) concluded that the neurochemical changes were caused by a mechanism different than that involved in other toxic responses to PCBs. Because the concentration of total PCBs was higher in the brains of monkeys treated with Aroclor 1260 than in those treated with Aroclor 1016, Seegal et al. (1991b) concluded that lightly-chlorinated congeners were more effective in reducing central dopamine levels than highly-chlorinated ones.

Exposure of rats *in utero* to 0, 5, or 25 mg Aroclor 1254/kg (gestation days [Gd] 10–16) resulted in a significant increase in levels of 5-hydroxyindole acetic acid (5-HIAA), and in the ratio of 5-HIAA/5-hydroxytryptamine in the lateral olfactory tract, prefrontal cortex, and hippocampus from 90-day-old offspring (Morse et al. 1996a). Dopamine, 3,4-dihydroxyphenylacetate, norepinephrine, and homovanillic acid were not affected. In a study of similar design, Morse et al. (1996b) observed significant increases in the glial cell marker GFAP in the lateral olfactory tract and the cerebellum and significant decreases in the brain stem of offspring at 21 and 90 days old. The neuronal marker synaptophysin was significantly decreased in the lateral olfatory tract, prefrontal cortex, and striatum of 90-day-old offspring. These changes were interpreted as reactive gliosis following direct damage to the neurones or glia, or alteration in the regulation of the proliferation or protein expression of specific subpopulations of neural cells.

Choline acetyltransferase (ChAT) activity was significantly decreased in the basal forebrain, but not in the hippocampus, from 15-day-old rats exposed to Aroclor 1254 (125 or 250 ppm in diet) during gestation and via mother's milk (Corey et al. 1996). However, ChAT activity returned toward control levels by 60 days of age. These rats made significantly more maze errors than control rats regardless of whether exposure to PCBs ceased at weaning or had continued by direct feeding. In a follow-up paper,

the authors reported that treatment with much smaller amounts of Aroclor 1254 (1.25 or 12.5 ppm in the diet) resulted in a significant increase in ChAT activity relative to controls in the hippocampus and forebrain from 15-day-old low-dose pups, but not high-dose pups (Provost et al. 1999). In 30-day-old pups, ChAT activity was significantly decreased in both the hippocampus and basal forebrain with the two dietary PCB levels. At this age, high-dose pups performed significantly worse than controls on a Morris water maze.

Contaminated Fish Consumption. The neurochemical effects of exposure of rats to feed adulterated with 5 or 20% lyophilized salmon fillets from Lake Huron (LH) or Lake Ontario (LO) were examined by Seegal et al. (1998). The study was conducted in 88-day-old male and female rats that had been exposed *in utero*, during lactation, and postnatally until they were tested. Dopamine, serotonin, norepinephrine, and their metabolites, as well as ChAT activity were assayed in the frontal cortex, nucleus accumbens, caudate nucleus, hippocampus, and substantia nigra. Significant treatment-related effects included (1) decreased dopamine in the frontal cortex of the high-dose rats, (2) decreased dopamine in the caudate nucleus from all groups, (3) decreased dopamine in the substantia nigra from the high-dose LO rats, (4) reduced epinephrine in all groups except for low-dose LO rats, and (5) no significant effect on ChAT concentration in any experimental group. No specific contaminants were assayed in the fish in this report.

Single Congeners. Mice exposed to 3,3',4,4'-tetraCB (PCB 77) *in utero* (maternal dose 32 mg/kg/day), which exhibited spinning behavior and hyperactivity at 1 year of age, had decreased dopamine levels and dopamine receptor binding sites in the corpus striatum (Agrawal et al. 1981). However, Seegal et al. (1997) reported that *in utero* and lactational exposure of rats to PCB 77 (0.1 or 1 mg/kg/day) resulted in significant and persistent elevations in dopamine concentrations in the frontal cortex and the substantia nigra, but not in the caudate nucleus. In contrast, similar treatment with PCB 47 (1–20 mg/kg/day) significantly decreased dopamine concentrations in the frontal cortex and caudate nucleus (Seegal et al. 1997). Administration of a single dose of 0.41 or 41 mg PCB 77/kg to 10-day-old NMRI mice resulted in a significant decrease (not dose-related) in density of muscarinic cholinergic receptors in the hippocampus 7 days after dosing, but not 24 hours after dosing relative to controls; there was no significant effect on receptor density in the cerebral cortex (Eriksson 1988). In mice similarly exposed but tested at the age of 4 months, muscarinic cholinergic receptor density was slightly but significantly increased (high-dose only) in the hippocampus; no significant changes were detected in the cortex, striatum, or midbrain and thalamus (Eriksson et al. 1991). As previously mentioned, these mice had abnormal spontaneous motor activity at that age. Treatment with PCB 28 and PCB 52 did not alter

muscarinic receptor density in the hippocampus, but PCB 52 increased the density of nicotinic cholinergic receptors in the cortex (Eriksson and Fredriksson 1996a, 1996b). Neither dopamine, serotonin, or metabolites were significantly altered in the striatum by treatment with PCB 28 or PCB 52. At this age (6 months old), the mice showed altered spontaneous activity. Neonatal exposure to 3,3',4,4',5-PentaCB (PCB 126) resulted in increased density of nicotinic cholinergic receptors in the hippocampus at 5 month of age and in impaired learning on a swim maze; no neurochemical or behavioral alterations were seen in mice treated with 2,3,3',4,4'-pentaCB (PCB 105) (Eriksson and Fredriksson 1998).

Treatment of female and male weanling Sprague-Dawley rats for 90 days with PCB 28 in the diet ($0.04 mg/kg/day) resulted in a significant decrease in dopamine concentration in the substantia nigra in females, but not in other brain areas (Chu et al. 1996a); neither norepinephrine, serotonin, or their metabolites were altered in any brain area. Other significant effects in similarly conducted experiments included decreased dopamine in the caudate nucleus and substantia nigra and decreased serotonin in the substantia nigra with PCB 118, $0.2 mg/kg/day in females, decreased dopamine in the caudate nucleus in males and increased serotonin in the substantia nigra in females with PCB 105, $4 mg/kg/day, decreased dopamine and serotonin in the frontal cortex with PCB 153, $0.01 mg/kg/day in males, and decreased dopamine in the frontal cortex with $0.005 mg/kg/day PCB 128 and in the hippocampus with 4.4 mg/kg/day PCB 128 in females; no significant changes were seen with PCB 126 (up to 0.009 mg/kg/day) (Chu et al. 1994, 1995, 1996b, 1998a, 1998b; Lecavalier et al. 1997).

3.2.4.3.3 Other Neurological Effects

Oral Exposure

Commercial PCB Mixtures. The effects of perinatal exposure to PCBs on auditory function has been studied in rats. Goldey et al. (1995) tested the hypothesis that hypothyroidism induced by developmental exposure to PCBs may cause permanent auditory dysfunction. Long-Evans rats were given 0, 1, 4, or 8 mg Aroclor 1254 from gestation day 6 through PND 21 and pups were evaluated at various ages up to 1 year old. Exposure to Aroclor significantly reduced circulating thyroxine concentrations up to PND 45. At PND 24, the high-dose pups showed reduced auditory startle amplitudes, but this was not seen when tested as adults. However, Aroclor induced permanent auditory deficits (20–30 dB threshold shift) at the frequency of 1 kHz in the mid- and high-dose rats. In a subsequent study, by monitoring brain stem auditory evoked responses, the authors concluded that the auditory alterations are consistent with peripheral auditory dysfunction (Herr et al. 1996). In a more recent study, Goldey et al. (1998) reported

that thyroxine replacement therapy significantly attenuated the effect of Aroclor 1254. It is important to note that high mortality occurred among the pups in the mid- and high-dose groups. By PND 12 and 21, 25 and 50% of the pups in the 8 mg/kg/day group had died, respectively. In the control and 4 mg/kg/day groups, 3 and 15% of the pups had died by PND 21, respectively.

Single Congeners. Offspring (76–90 days old) from rats that received 1 µg/kg/day of PCB 126 for 35 days prior to breeding and throughout gestation and lactation had elevated auditory thresholds for 0.5 and 1 kHz tones (Crofton and Rice 1999). There were no treatment-related effects in postnatal mortality or litter size.

Other Routes of Exposure

Single Congeners. Subcutaneous administration of 1.5 mg/kg of PCB 77 to pregnant Long-Evans rats on gestational days 7–18 resulted in altered electroretinogram (ERG) in female offspring recorded at about 200 days of age (Kremer et al. 1999). Specific alterations consisted of decreases in the scotopic b-wave as well as on the a-wave and maximum potential, the first two wavelets of the oscillatory potentials, and the flicker response at the beginning of light adaptation. No significant alterations were observed in male offspring or in male or female offspring from rats injected subcutaneously 1.5 mg/kg of PCB 47.

Numerous *in vitro* studies have been conducted with both commercial PCB mixtures and single congeners in efforts to elucidate the mechanisms of neurotoxicity of these compounds, to possibly discern patterns among structurally similar types of congeners, and to establish toxic potency rankings. These studies are discussed in Section 3.5.2 Mechanisms of Toxicity.

3.2.4.3.4 Evaluation of Animal Studies

Neurobehavioral Effects. For the purpose of this appraisal, the neurobehavioral effects of PCBs in animals are divided into (1) effects on motor activity and (2) effects on higher functions (e.g., learning and memory). Motor activity (spontaneous or open field) has been evaluated in mice, rats, and monkeys exposed to commercial mixtures and single PCB congeners in a variety of experimental designs leading, not unexpectedly, to a wide range of results from which few generalizations can be made. Single or repeated administration of relatively high doses of Aroclor 1254 to adult mice or rats generally decreased spontaneous motor activity (Kodavanti et al. 1998; Nishida et al. 1997; Rosin and Martin 1981). Postnatal (via breast milk) exposure to Fenclor 42 decreased open field activity in pups on PND 14, but

exposure *in utero* did not (Pantaleoni et al. 1988). Exposure to similar doses of Clophen A30 (congener composition similar to Fenclor 42) during gestation and lactation increased open field activity on PND 22 but not on PND 120 (Lilienthal et al. 1990). Exposure of monkeys to Aroclor 1248 during pregnancy and for 3 months after giving birth resulted in hyperlocomotor activity in the offspring at 6 and 12 months of age (Bowman et al. 1978), but these monkeys exhibited hypoactive behavior at the age of 44 months (Bowman and Heironimus 1981). A somewhat similar finding was reported by Schantz et al. (1997) in rats; in this case, offspring from Sprague-Dawley rats treated with the di-*ortho*-substituted PCB 95 on gestation days 10–16 had control levels of spontaneous activity at 35 days of age (juveniles), but were hypoactive as adults (100 days old). A series of studies by Eriksson and coworkers (Eriksson and Fredricksson 1996a, 1996b, 1998; Eriksson et al. 1991) observed altered spontaneous activity (increased followed by decrease in trials separated by 20 minutes) in 4–5-month-old mice administered a single gavage dose of a variety of PCB congeners at the age of 10 days. These effects were observed with both coplanar congeners (dioxin-like) PCB 77, PCB 126, and with the mono *ortho*-substituted congener PCB 28 and the di-*ortho*-substituted PCB 52. No effects were observed with three mono-*ortho*-substituted congeners (PCB 105, 118, or 156). No pattern is apparent from these findings.

The effects of PCBs on higher cognitive functions (i.e., learning, memory, attention) have been examined in rats and monkeys exposed mostly perinatally, but in some cases, testing was done long after exposure occurred. Exposure of rats to Fenclor 42 during gestation or via mother's milk impaired acquisition of one-way active avoidance (Pantaleoni et al. 1988). A different study reported decreased active avoidance learning and retention of a visual discrimination task in rats exposed during gestation to Clophen A30, but not in rats exposed postnatally (Lilienthal and Winnecke 1991). Rats exposed during gestation and lactation made more errors than controls in a radial arm maze (Corey et al. 1996) and performed worse than controls in a Morris water maze (Provost et al. 1999). Studies in monkeys exposed to Aroclors during gestation and lactation, and tested after exposure ceased, showed decreased performance in discriminating learning tasks (Bowman et al. 1978), impaired associational or attentional processes and ability to learn a simple discrimination problem, and failure to learn the irrelevancy of a shape cue (Levin et al. 1988; Schantz et al. 1989). Monkeys that were treated from birth to 20 weeks of age with a defined PCB mixture analogous to the congener composition of human breast milk (comprised mostly of mono- and di-*ortho*-substituted congeners), and tested beginning at age 3 years, had impaired performance in both nonspatial and spatial discrimination reversal tasks and exhibited inability to inhibit inappropriate responding (Rice 1997, 1998, 1999b; Rice and Hayward 1997, 1999a). Because these effects occurred at a level of 0.0075 mg/kg/day, the lowest tested intermediate-duration dose of any PCB mixture in any species, they are used as the basis for deriving the intermediate MRL for oral exposure as indicated in the

footnote to Table 3-2 and discussed in Chapter 2 and Appendix A. Perinatal exposure of rats to the dioxin-like PCB congener PCB 126 during gestation and lactation provided little evidence that it altered behavior (Bushnell and Rice 1999; Rice 1999a, 1999b; Rice and Hayward 1998, 1999a, 1999b). Of five tasks designed to assess a range of cognitive processes, only one provided any suggestive evidence of an effect. Other coplanar PCBs, as well as 2,3,7,8-TCDD, failed to alter the response of rats exposed *in utero* on a T maze test, but facilitated the response on a radial arm maze (Schantz et al. 1995, 1996b). In contrast, *ortho*-substituted congeners had no effect on performance on the radial maze test, but impaired performance of females on the T-maze test. From the data summarized above, few generalizations can be attempted. It appears that *ortho*-substituted PCB congeners are more active than coplanar PCBs in modifying cognitive processes. In addition, an effect observed in both rats and monkeys was a deficit on delayed spatial alternation, and was induced by exposure to *ortho*-substituted PCBs (Schantz et al. 1995), defined experimental mixtures (Rice and Hayward 1997), and commercial Aroclors (Levin et al. 1988).

Neurochemical Effects. The most consistent result from studies that examined the neurochemical effects of PCBs is a decrease in dopamine concentrations in different areas of the brain. This was seen in adult rats and monkeys administered relatively high doses of Aroclor mixtures (Seegal et al. 1986b, 1991a, 1991b) and in 90-day dietary studies that used relatively low doses of single PCB congeners (Chu et al. 1994, 1995, 1996a, 1996b, 1998a, 1998b). Less studies reported alterations in serotonin levels, and for the most part, levels of norepinephrine were unaffected. No single brain region appeared to be a preferred target. Studies with single congeners in rats reported decreases in dopamine levels in the frontal cortex, caudate nucleus, substantia nigra, and striatum. Studies with Aroclors in rats and monkeys observed decreases in dopamine in the caudate, striatum, substantia nigra, putamen, hypothalamus, and olfactory tract. The lowest effective doses in the 90-day single congeners studies were 0.01 and 0.005 mg/kg/day for PCB 153 and PCB 128, respectively, two di-*ortho*-substituted hexachlorobiphenyls. The dioxin-like PCB 126 was ineffective at the highest dose tested, 0.009 mg/kg/day. In contrast with the majority of the findings in adult animals, Seegal et al. (1997) reported an increase in dopamine concentration in the frontal cortex and substantia nigra from rats exposed to the coplanar PCB 77 *in utero* and via mother's milk. In the series of studies by Eriksson and colleagues (Eriksson and Fredricksson 1996a, 1996b, 1998; Eriksson et al. 1991), no significant alterations in biogenic amine levels were seen in brains from adult mice exposed to PCB 28 or PCB 52 at 10 days of age; these mice had altered spontaneous motor activity and those exposed to PCB 52 had impaired learning and memory functions. These investigators also described increases in density of cholinergic muscarinic and nicotinic receptors in certain brain areas in mice exposed to PCB 77, PCB 52, or PCB 126, but no such assays were conducted for PCB 118, PCB 105, or PCB 156. More information is necessary to speculate on patterns of effects among general

classes of PCB congeners or to try to associate specific behavioral alterations with neurochemical changes.

Other Neurological Effects. The findings of Crofton and Rice (1999) of auditory deficits in offspring from rats administered PCB 126 during gestation and lactation without evidence of general toxicity give credence to those of Goldey and coworkers (Goldey and Crofton 1998; Goldey et al. 1995; Herr et al. 1996). In the latter series, high mortality was observed among the exposed pups during the first 3 weeks of life suggesting that survivors may have been in less than optimal health conditions. Whether the effect seen with PCB 126 represents an Ah receptor-mediated effect remains unknown until additional both dioxin- and nondioxin-like PCB congeners are tested.

3.2.5 Reproductive Effects

3.2.5.1 Summary

Information is available on reproductive effects of PCBs in humans. Studies that examined reproductive end points found indications that exposure to PCBs is associated with menstrual disturbances in women and effects on male fertility. Increasing PCB levels have also been observed in women with late miscarriages. In addition, a reduction in the months of lifetime lactation was associated with increasing levels of PCBs in maternal breast milk. The reproductive toxicity of PCBs in animals has been well established. Effects in females have been observed in various species, including rats (prolonged estrus, decreased sexual receptivity, and reduced implantation rate in adults and/or their offpsring exposed via gestation and lactation), mice (decreased conception), minks (partial or total reproductive inhibition), and monkeys (prolonged menstruation, decreased fertility). Female minks and monkeys are particularly sensitive to reproductive effects of PCBs. There is limited evidence for reproductive effects in male adult animals, although it is well documented that gestational and lactational exposure to PCBs can adversely affect morphology and production of sperm and fertility in the male offspring of rats and mice.

3.2.5.2 Human Studies

3.2.5.2.1 Female Reproductive Effects

Occupational Exposure. There were no apparent effects on gravidity (number of pregnancies) in women capacitor manufacturing workers who were exposed to Aroclors 1254, 1242, and/or 1016 for a minimum of 3 months between 1946 and 1975 (Taylor et al. 1989). High-exposure workers were directly exposed to Aroclors during the manufacturing process for at least 1 year prior to birth of an infant, and workers with low exposure were employed in areas where Aroclors were not used directly. Area air samples collected in 1977 showed geometric mean air concentrations of 310 and 27 $\mu g/m^3$ in the high and low exposure groups, respectively. Evaluation of birth data on 172 high-exposure and 184 low-exposure workers showed no significant difference in the mean number of pregnancies (3.2±1.7 and 3.5±2).. As discussed in the Developmental Toxicity section (Section 3.2.6.2), decreased birth weights and gestational ages in the exposed women were associated with increased serum PCB levels. Other reproductive outcomes and well-designed reproductive epidemiologic studies have not been conducted in this highly exposed female occupational cohort.

Contaminated Fish Consumption.

The New York State Angler Cohort. The New York State (NYS) Angler Cohort is a population-based group of New York State anglers who were between 18 and 40 years of age and held fishing licenses for the 1990–1991 season. The cohort was compiled for the study of a variety of reproductive and other health end points (Mendola et al. 1995a, 1995b). Data from the entire cohort were collected from self-administered questionnaires mailed to anglers living in 16 counties in close proximity to Lake Ontario. Responses were received from 10,782 male anglers, 934 female anglers, and 6,579 wives/partners of male anglers for a total response rate, among the anglers, of about 40%. This cross-sectional survey included questions on sportfish consumption patterns (to estimate exposure to PCBs) and reproductive outcomes and associated data focusing on children born between June 1986 and June 1991. A telephone interview with 100 randomly selected nonrespondents revealed that nonresponders did not differ from respondents with respect to fishing habits, knowledge of fishing advisories, and fish consumption patterns, but had sociodemographic differences (were less likely to be married and had lower levels of education and income). Findings for reproductive or developmental end points from this study have been reported in several reports (Buck et al. 1997, 1999, 2000; Kostyniak et al. 1999; Mendola et al. 1995a, 1997).

Shorter menstrual cycles were associated with consumption of sportfish was associated with in women from the NYS Angler Cohort (Mendola et al. 1997). Menstrual cycle data were collected from 2,223 women (mean age 31.2 years) who stated in 1991 that they were considering becoming pregnant in the following 3 years. Lake Ontario fish consumption was measured in terms of exposure duration (total number of years eating fish) and monthly frequency of fish meals in 1991, and an index was developed to estimate cumulative lifetime PCB exposure through fish consumption (subjects were placed in no, low, and combined moderate/high exposure classes). Multiple regression analyses showed that consumption of more than one Lake Ontario fish meal/month was associated with statistically significant reductions in mean menstrual cycle length of >1 day in all 2,223 women (-1.11 days, 95% CI -1.87 to -0.35), and of about half a day for a subgroup of 2,080 women who reported having regular menstrual cycles (-0.51 day, 95% CI -0.92 to -0.10). Similar reductions were found in women in the highest cumulative exposure category (moderate/high); mean cycle length was about 1 day shorter for the main group (-1.03 days, 95% CI -1.88 to -0.19), and about half that reduction in the regular menstrual cycle group (-0.56 day, 95% CI -1.01 to -0.09). No significant differences in mean menstrual cycle length were found when the subjects were classified into groups based on the number of years during which fish were consumed. The strengths of the study include the use of trained nurses to obtain menstrual cycle information. Limitations include the reliance on self-reported exposure data (biological samples were not collected and analyzed for PCBs and other expected contaminants) and outcome data, and the lack of information on potential confounders such as current smoking status, stress, and the use of contraceptives. Mendola et al. (1997) noted that although the small decreases in menstrual cycle length are not likely to be clinically significant or of major public health concern, they may indicate potential endocrine effects on a population level.

No statistically significant association was found between time-to-pregnancy (TTP), a measure of fecundity and conception delay, and consumption of Lake Ontario sportfish in a preliminary analysis of 874 women from the NYS Angler Cohort who were pregnant between 1991 and 1993 (Buck et al. 1997). Exposure was estimated as the total number of years from 1955 to 1991 in which fish caught in Lake Ontario were consumed. The mean duration of fish consumption was 2.2 years (SD 4.5) for all women and 5.2 years (SD 5.6 years) for women who reported any fish consumption. No differences were observed in fish consumption between women who did and did not become pregnant, fish consumption between women with known and unknown TTP, or age distributions for women with and without a pregnancy. Multiple regression analysis was used to assess the linear relation between log-TTP and log-years eating fish (duration of exposure). Analyses were stratified by fish consumption (fish consumers/all women) and parity status (nulliparous/parous), and controlled for maternal age, smoking, gynecologic pathology (e.g., endometriosis), and history of sexually transmitted diseases. R^2 coefficients showed that

duration of fish consumption and maternal age accounted for only a small percentage of the explained variance in TTP (0.5%), even after the analysis was restricted to women who reported eating fish (0.6%). Beta coefficients, calculated to reflect the unit change in log-TTP for every unit change in log-years eating fish, were positive but not statistically significant. A larger beta coefficient was observed for log-years eating fish among nulliparous women (0.1030) in comparison to parous women (0.0095), suggesting that the effect of duration of fish consumption on TTP may have been greater among nulliparous women. Strengths of the study included the use of trained nurse interviews to obtain TTP information. As with other NYS Angler Cohort studies, limitations include the reliance on self-reported exposure data and outcome data, and the lack of information on potential confounding factors such as occupational exposures, alcohol and caffeine consumption, and current smoking status. In addition, women with unplanned pregnancies were necessarily ruled out from the analysis; Buck et al. (1997) noted that this may be a potential bias inherent in the study.

In further analysis of the Buck et al. (1997) study summarized above and the Buck et al. (1999) study summarized in Section 3.2.5.2.2 (Male Reproductive Effects), Buck et al. (2000) combined maternal and paternal fish consumption into one model looking at fecundability ratios as the outcome, rather than TTP (continuous variable used in 1997 paper) or conception delay (>12 months unprotected intercourse used in 1999 paper). The sample included 606 women with known and unknown TTP who discontinued birth control in order to become pregnant during 1991–1993 and for whom the partners' fish consumption data also were available. The exposure measures included the duration, frequency, and lifetime PCB index used in the previous studies. Separate analyses were run for each exposure measure as both paternal and maternal consumption measures were correlated. Statistical analyses included the use of a discrete-time analog of the Cox proportional hazards model to predict the probability of conception (i.e., fecundability-biological capacity for reproduction) at the jth cycle given the absence of conception at an earlier cycle. The natural logarithm of this conditional probability was modeled as a linear function of the covariates and potential confounders (i.e., maternal smoking, gynecologic history [e.g., endometriosis; pelvic inflammatory disease], parental ages, gravidity [number of pregnancies], and history of fertility drugs). The outcome measure used was the conditional fecundability ratio (CFR), the probability of conception during a given menstrual cycle for the exposed fisheaters divided by that for unexposed nonfisheaters. The 95% CI for the CFR was also calculated; exclusion of the value 1.0 from the CI indicates statistical significance at the p=0.05 level. This ratio is conditional upon becoming pregnant; a value <1 indicates reduced fecundability. Fish consumption was generally higher for men than women (68 and 42%, respectively) as was the mean number of years of fish consumption (5.9 and 2.1 for the entire sample whether they consumed fish or not). Men also had higher mean PCB indices than women in the study,

although partners' consumption patterns were related (e.g., both might be in the same category of fish consumption). The adjusted fecundability ratios for parental Lake Ontario fish consumption indicated that maternal consumption of 3–6 years was associated with significantly reduced fecundability (CFR=0.75, 95% CI 0.59–0.91), as was eating more than one monthly fish meal in 1991 (CFR = 0.73, 95% CI 0.54–0.98). Paternal consumption was associated with slightly elevated, but non-significant, CFRs for all three measures of fish consumption, suggesting that maternal but not paternal consumption of contaminated fish may reduce fecundability among couples attempting pregnancy. The investigators considered the findings preliminary, given the retrospective data collection on TTP and fish consumption, limited information on potential confounders, and potential sources of bias. In addition to the limitations indicated for the previous studies, Buck et al. (2000) commented on several biases associated with TTP, particularly pregnancy recognition bias (when or how women became aware of pregnancy). Another possible bias is the fact that the analytic strategy is dependent on a woman achieving a pregnancy; if fish consumption exerts a deleterious effect on fecundability, no pregnancy will be achieved and the women will not be in the sample in the first place. Hence, it is possible that women with the highest exposures were excluded from the study since they did not achieve a pregnancy. Due to the preliminary nature of the findings, the investigators could not speculate as to whether the effect on fecundability could be strong enough to reduce fertility, as measured by a reduction or absence of livebirths, or to impair fecundity, as measured by pregnancy loss.

No statistically significant associations between increased risk for spontaneous fetal death and dietary exposure to Lake Ontario fish were found among 1,820 multigravid, fertile women from the NYS Angler Cohort (Mendola et al. 1995a). Spontaneous fetal death histories (ever having a pregnancy end in miscarriage, spontaneous abortion, or stillbirth) were obtained from New York State live-birth certificates. Fish consumption histories were used to construct four measures of PCB exposure for each subject: (1) lifetime PCB exposure based on species-specific PCB levels (subjects were placed in no, low, moderate, or high exposure classes); (2) number of years of sportfish consumption from 1955 to 1991; (3) kilograms of sportfish consumed in the 1990–1991 season; and (4) lifetime kilograms of sportfish eaten (no, low, moderate, or high exposure classes). Women who never ate Lake Ontario sportfish comprised the referent group. Odds ratios and 95% CI were calculated in bivariate analyses to identify potential confounders including smoking and alcohol consumption, and parental ages, paternal sportfish consumption (none were statistically significant). Unconditional logistic regression models were used to calculate ORs and 95% CI for multivariate analyses. Analyses were stratified by number of prior pregnancies to better describe the relationship between maternal age and spontaneous death at different levels of prior gravidity, and controlled for smoking and maternal age. No consistent relationship was

seen between a history of spontaneous fetal death and any of the four measures of exposure. The ORs in the logistic regression models evaluating lifetime PCB level and lifetime sportfish consumption relative to spontaneous fetal death tended to be slightly above 1.0 (the null value) for the low exposure categories and below 1.0 for the moderate and high exposure categories. Odds ratios of approximately 1.0 also were observed in the models assessing the number of years of consumption and the mass (kg) of sportfish consumed in 1990–1991 (Mendola et al. 1995a). Strengths of the study included sufficient statistical power to detect fairly small increases in ORs and the reliability of reproductive history data on birth certificates. Limitations included the focus on clinically recognized fetal deaths which may not detect early pregnancy loss, the self-reported nature of both exposure and outcome data, and the lack of biomarker monitoring to validate the self-reported exposure data. Because the findings suggested that early fetal loss may be important, a prospective pregnancy study is currently underway (ongoing study by J. Vena, see Section 3.12.3).

Decreasing number of months of lifetime lactation were significantly associated with increasing levels of PCBs or DDE in breast milk (normalized for lipid content) in a group of 98 lactating women from the NYS Angler Cohort (Kostyniak et al. 1999). In this sample, PCB levels in breast milk were significantly associated with self-reported measures of fish consumption, but DDE levels were not. The observed association is likely to be important in estimating dose rates for these chemicals in nursing neonatal populations, but the relevance of the association to reproductive performance is not clear.

The Michigan Anglers Cohort. An association between conception delay and sportfish consumption was found in a survey of 626 married couples conducted between 1993 and 1995 (Courval et al. 1999). At least one person in each couple was a licensed angler residing in 1 of 10 Michigan counties bordering a Great Lake (Lake Erie, Lake Huron, or Lake Michigan). Subjects were categorized into four sex-specific exposure classes (none, low, medium, high) based on an index of lifetime fish consumption (estimated number of sportfish meals consumed in the past 12 months multiplied by the number of years since 1970 in which fish were caught and consumed): 0, 1–114, 115–270, and 271–1,127 for men, and 0, 1–54, 55–138, and 139–1,127 for women. Conception delay, defined as ever having failed to conceive a child after 12 months of trying, was essentially the same in both sexes (reported by 12.9% of the men and 13.3% of the women). Unadjusted logistic regression analysis showed that ORs for conception delay increased in women with increasing exposure class, although results of a trends test were not statistically significant (p=0.35); the OR in the high exposure category for women was 1.4 (95% CI 0.7–2.7). Adjustment for age, race, region of Michigan, household income, smoking, and alcohol consumption did not strengthen the associations in women. The OR in the high exposure category declined in the female

models after the addition of husbands' fish consumption, indicating no risk associated with female consumption after accounting for male partner consumption. In contrast to the findings in women, analysis of the male data provide suggestive evidence that frequent consumption of Great Lakes sportfish may be associated with an increased risk of conception delay for men (see Section 3.2.5.2.2). Although data analysis controlled for several potential confounders, no information was collected regarding the subjects' frequency or timing of sexual intercourse during the period of attempting to conceive, whether the partner providing fish consumption data also was the partner with whom the conception delay had occurred, or levels of PCBs and other persistent toxic chemicals in biological samples from the subjects. The researchers will be addressing many of these limitations in a prospective reproductive health study. Additionally, the participation rate (29%) was extremely low in this study, which could have resulted in nonresponse bias, a bias similar to selection bias.

General Population Exposures. A case-control study was conducted that compared mean plasma concentrations of 14 PCB congeners and 11 chlorinated pesticides in women with endometriosis and women without endometriotic lesions (Lebel et al. 1998). Cases (86) and controls (70) were selected among premenopausal women with no previous diagnosis of endometriosis who underwent laparoscopy for either pelvic pain, infertility, or tubal fulguration, and were matched according to the indication for laparoscopy. Cases and controls did not differ with respect to age, body mass index, history of breast feeding, use of organochlorines, smoking, mean number of fish meals/week, income, and education, although the proportion of women who had never been pregnant was higher in cases than controls. Analysis of covariance was used to adjust means for confounding variables, and ORs were estimated by logistic regression. Crude or adjusted mean concentrations of individual or summed congeners did not differ between the groups. Additionally, there was no significant linear trend in the adjusted ORs for endometriosis as PCB concentrations increased.

In a study of 89 women (87% German) with repeated ($2) miscarriages, Gerhard et al. (1998) found that blood concentrations of PCBs were higher than the reference level in 22% of the cases. The sum of congeners 101–180 was used for evaluation because they were the only congeners detected in significant concentrations. Blood levels of other organochlorine compounds (pentachlorophenol, DDE, β- and γ-hexachlorocyclohexanes, HCB) were higher than reference ranges in 7–15% of the cases. No significant differences in PCB levels were found between women with early or late miscarriages (after #12 or >12 weeks of gestation) and primary or secondary miscarriages (had never delivered or delivered at least one baby). Women with a history of at least four miscarriages (n=25) had significantly elevated blood levels of PCBs, although other organochlorine compounds (γ-hexachlorocyclohexane and HCB)

were also increased. Hormonal disorders were identified as the cause of repeated miscarriages in 31% of the women, including hyperprolactinemia in 9%, hyperandrogenemia in 7%, and luteal insufficiency in 14% of the cases. Correlations were found between increasing PCB concentrations and some hormonal parameters (e.g., increasing FSH and LH, decreasing TSH) and immunological parameters (e.g., increasing IgM, monocytes, and NK cells, decreasing interleukin 2 receptor-positive cells), but none of the associations were specific for PCBs. There were no significant associations between PCB concentrations and further conceptions or the outcome of further pregnancies.

Yusho and Yu-Cheng Exposures. Irregular menstrual cycles (60% of 81 patients) and abnormal basal body temperature patterns (85% of 81 patients) were observed female *Yusho* patients in 1970 (Kusuda 1971). Menstrual irregularities included changes in cycle intervals, duration, and flow that showed no consistent pattern and were unrelated to severity of *Yusho* poisoning as indicated by degree of dermal signs. These alterations were accompanied by decreased urinary excretion of estrogens, pregnanediol, and pregnanetriol. Fertility, fecundity, and rates of spontaneous abortion have not been studied in *Yusho* and *Yu-Cheng* patients (Hsu et al. 1994; Kuratsune 1989; Masuda 1994; Rogan 1989). Sex ratio was not altered in children born to 74 *Yu-Cheng* women during or after the poisoning began (Rogan et al. 1999). Of 137 live births occurring between 1978 and 1985, 69 were girls and 68 were boys.

3.2.5.2.2 Male Reproductive Effects

Occupational Exposure. Sperm counts, fertility history, and testicular abnormalities as determined by physical examination were normal in 55 transformer repairmen compared to 56 unexposed workers who were similar in age, race, and marital status (Emmett et al. 1988a, 1988b). The mean length of employment of the exposed workers was 3.75 years, most (38) of the workers were currently exposed to PCBs, and the predominant exposure was from Aroclor 1260 with lesser exposure to Aroclor 1242. Measurements of air PCB levels at four work areas showed 8-hour TWA concentrations of 0.0167–0.024, 0.0032–0.007, 0.00001–0.0004, and 0.0007–0.0124 mg/m^3. Geometric mean PCB concentrations in the current-exposed, past-exposed, and comparison workers were 2.08, 0.83, and 0.60 ppm, respectively, in adipose tissue and 12.2, 5.9, and 4.6 ppb, respectively, in serum. Interpretation of the negative results of this study is complicated by the similar PCB body burdens in the past-exposed and control groups.

Contaminated Fish Consumption.

The New York State Angler Cohort. Paternal exposure to Lake Ontario fish was not associated with an increased risk of conception delay, as indicated by TTP, in women from the NYS Angler Cohort (Buck et al. 1999). The study sample included 785 spouses of male anglers reporting one or more pregnancies between 1991 and 1993, known TTP, and complete paternal fish consumption histories. Female anglers were excluded from the study, as fish consumption data from their spouses and partners were not collected. Three measures of paternal fish consumption were used: (1) frequency of consumption (number of Lake Ontario fish meals consumed in 1991), (2) duration of consumption (number of years), and (3) an index of lifetime cumulative PCB exposure from fish consumption (categorized as low, moderate, and high). Conception delay was defined as requiring $12 menstrual cycles with unprotected intercourse to achieve pregnancy. Statistical analyses included descriptive methods and unconditional logistic regression modeling to calculate ORs and 95% CIs. Potential and known confounders included maternal age, age at menarche, menstrual regularity, education, income, cigarette smoking; history of prior pregnancy; and history of previous pregnancy loss. Adjusted ORs for paternal fish consumption and risk of conception delay were <1.0 for all categories of meal frequency and duration. For the PCB index measure, the ORs were <1.0 in all categories except moderate consumption. The confidence intervals included one in all analyses. The ORs of <1.0 and inclusion of the value 1.0 in the confidence intervals indicate that paternal fish consumption did not significantly increase the risk of conception delay among the women. When the analyses were restricted to spouses or partners with no Lake Ontario fish consumption (n=445), similar results were obtained for each of the three paternal fish consumption exposure variables. Selection bias is a potential study concern as the study did not include women who may have become pregnant accidentally, although there is no evidence to suggest that fish consumption is systematically related to pregnancy intentions (Buck et al. 1999). Other study limitations include possible underestimation of paternal fish consumption because data did not include the 2 years prior to the TTP assessment, and possible residual confounding as several potential confounders of female fecundity were not collected.

In further analysis of the Buck et al. (1999) study summarized above and the Buck et al. (1997) study summarized in Section 3.2.5.2.1 (Female Reproductive Effects), Buck et al. (2000) combined maternal and paternal fish consumption into one model looking at fecundability ratios as the outcome, rather than TTP (continuous variable used in 1997 paper) or conception delay (>12 months unprotected intercourse used in 1999 paper). The sample included 606 women with known and unknown TTP who discontinued birth control in order to become pregnant during 1991–1993 and for whom the partners' fish consumption

data also were available. The exposure measures included the duration, frequency, and lifetime PCB index used in the previous studies. As described in Section 3.2.5.2.1, Buck et al. (2000) used a discrete time analogue of Cox proportional hazards analysis to estimate conditional fecundability ratios and 95% CI for fish consumption among couples with complete exposure data who discontinued birth control to become pregnant. Fish consumption was generally higher for men than women (68 and 42%, respectively) as was the mean number of years of fish consumption (5.9 and 2.1 for the entire sample whether they consumed fish or not). Men also had higher mean PCB indices than women in the study, although partners' consumption patterns were related. The adjusted fecundability ratios for parental Lake Ontario fish consumption indicated that maternal consumption of 3–6 years was associated with significantly reduced fecundability, as was eating more than one monthly fish meal in 1991 (see Section 3.2.5.2.1). Paternal consumption was associated with slightly elevated, but nonsignificant, CFRs for all three measures of fish consumption (only duration of 1–2 years had a CFR below 1.0). The findings suggest that maternal but not paternal consumption of contaminated fish may reduce fecundability among couples attempting pregnancy.

The Michigan Anglers Cohort. An association between conception delay and sportfish consumption was found in a survey of 626 married couples conducted between 1993 and 1995 (Courval et al. 1999). At least one person in each couple was a licensed angler residing in 1 of 10 Michigan counties bordering a Great Lake (Lake Erie, Lake Huron, or Lake Michigan). Subjects were categorized into four sex-specific exposure classes (none, low, medium, high) based on an index of lifetime fish consumption (estimated number of sportfish meals consumed in the past 12 months multiplied by the number of years since 1970 in which fish were caught and consumed): 0, 1–114, 115–270, and 271–1,127 for men, and 0, 1–54, 55–138, and 139–1,127 for women. Conception delay, defined as ever having failed to conceive a child after 12 months or more of trying, was essentially the same in both sexes (reported by 12.9% of the men and 13.3% of the women). Unadjusted logistic regression analysis showed that ORs for conception delay increased in men with increasing exposure class: 1.2 (95% CI 0.5–2.9), 1.3 (0.6–3.1), and 2.0 (0.9–4.5); results of a trends test were marginally statistically significant (p=0.06). Adjustment for age, race, region of Michigan, household income, smoking, and alcohol consumption minimally increased the odds ratios for men. The addition of the partners' fish consumption in the adjustment further increased the odds ratios associated with fish consumption in the model for men; the high fish consumption category OR was 2.8 (1.0–8.0), indicating that men with the highest fish consumption were at nearly 3 times the risk of conception delay as nonconsumers. The findings provide suggestive evidence that frequent consumption of Great Lakes sportfish may be associated with an increased risk of conception delay for men. As discussed in Section 3.2.5.2.1, there was no evidence of increased risk of conception delay in the exposed

women. Although analysis of the data controlled for several potential confounders, no information was collected regarding the subjects' frequency or timing of sexual intercourse during the period of attempting to conceive, whether the partner providing fish consumption data also was the partner with whom the conception delay had occurred, or levels of PCBs and other persistent toxic chemicals in biological samples from the subjects. Additionally, the participation rate (29%) was extremely low in this study, which could have resulted in nonresponse bias, a bias similar to selection bias.

General Population Exposures. Semen samples from fertile men and those with low sperm counts (idiopathic oligospermia or azoospermia) were analyzed for 74 PCB congeners (Bush et al. 1986). Multiple linear regression analysis of combined sample data showed no association between concentration of any individual congener or total PCBs (summed congeners) and either sperm count, motility, or percentage of normal forms. Analysis of the data by fertility status (fertile, subfertile, infertile) indicated that in the infertile men (sperm count <20 million cells/mL), decreasing sperm motility was associated with increasing concentrations of three congeners (2,3',4,4',5-pentaCB [PCB 118], 2,2',3,4,4',5-hexaCB PCB 137], and 2,2',4,4',5,5'-hexaCB [PCB 153]). The proportion of total variance attributable to the regression (R^2) was 9–16% for these congeners. Another study found that blood concentrations of tetra-CBs and penta-CBs, but not hexa-CBs and total PCBs, were significantly higher in infertile males than in normal individuals (Pines et al. 1987). Levels of *p,p'*-DDT and other organochlorine compounds were also increased in the semen and blood of the men in these studies.

Yusho and Yu-Cheng Exposures. Sexual maturation was not delayed, and testicular and scrotal development was not altered in boys born to *Yu-Cheng* women, although the exposed boys had significantly shorter penises (Guo et al. 1993). Sex ratio was not altered in children born to 74 *Yu-Cheng* women during or after the poisoning began (Rogan et al. 1999). Of 137 live births occurring between 1978 and 1985, 69 were girls and 68 were boys.

3.2.5.2.3 Evaluation of Human Studies.

Information is available on reproductive effects of PCBs in humans from studies of people exposed by the general environment, consumption of contaminated rice oil in the *Yusho* and *Yu-Cheng* poisoning incidents, consumption of contaminated fish, and occupational exposures. A comparison of PCB levels in blood and breast milk in some of these studies is included in Appendix A.

Females. Gerhard et al. (1998) examined a number of university hospital female patients (n=89) with a history of miscarriages. Although other substances were also detected (e.g., hexachlorobenzene), PCB levels were found to be higher in the blood of patients with a history of three or more miscarriages. Another study of the general population found no association between endometriosis and concentrations of PCBs in the blood (Lebel et al. 1998).

Menstrual irregularities (i.e., altered intervals, duration, and flow) were observed in women exposed during the *Yusho* poisoning incident (Kusuda 1971). Heating of the PCB-contaminated rice oil also resulted in the formation of other contaminants of concern (i.e., dibenzofurans and ter-, and quarterphenyls) (Rogan 1989).

In a study of Native Americans, fish consumption has been shown to be a major risk factor for elevated PCB body burdens (Fitzgerald et al. 1996). The studies that examined reproductive end points in women whose diets contained Great Lakes fish found evidence that consumption of the fish may be associated with a slightly shorter length of menstrual cycle (Mendola et al. 1997), but not with increased risk of conception delay in females (Buck et al. 1997; Courval et al. 1999) or increased risk for spontaneous fetal death (Mendola et al. 1995a). Buck et al. (1997) examined time-to-pregnancy (i.e., after stopping birth control, the number of menstrual cycles before pregnancy) as the outcome measure of conception. However, in a more recent study (Buck et al. 2000), their outcome measure was a fecundability ratio (i.e., probability of conception during a given menstrual cycle for the exposed, divided by the same probability for the unexposed). Utilizing this outcome, the researchers found that maternal consumption of fish for 3–6 years was associated with a reduction in fecundability (i.e., biological capacity for reproduction). Significantly higher levels of several PCB congeners (e.g., 153 and 138) were also detected in the breast milk of fisheaters (Kostyniak et al. 1999). The number of months of lifetime lactation declined in these females with a rise in PCB concentration in breast milk.

Mendola et al. (1997) note that the effect on menstrual cycle length in the women fisheaters is a preliminary finding that needs to be interpreted cautiously because of certain limitations (e.g., lack of information on confounders such as stress, use of contraceptives, body mass index, and physical exercise). The decreases in menstrual length were small and were considered not likely to be clinically relevant. However, they may be indicative of potential endocrine effects to the population. At the highest exposure levels, the decrease was approximately 0.5 days for women who reported regular cycles and 1 day for all women who reported cycle length information. The effect did not appear to be mediated through irregular cycles since the fish consumption-based exposure levels were similar for women who

reported regular or irregular cycles. The human populations in which menstrual changes have been observed differ with respect to the sources of PCBs and exposures to other chemicals that may affect susceptibility to menstrual disturbances. Although the studies are insufficient for determining which specific chemical(s) may be responsible for the observed alterations, the available data support a possible association between PCBs and menstrual disturbances.

There was no apparent effect on mean number of pregnancies in women who were occupationally exposed to Aroclors 1254, 1242, and/or 1016 (Taylor et al. 1989). This study had limitations due to small numbers of subjects and the availability of only estimates of exposure based upon job descriptions, manufacturing process, and industrial hygiene data. Additionally, the mean number of pregnancies represented data not adjusted for potential confounders.

The human studies of reproductive effects in females have not always resulted in consistent findings. For example, two studies of fish consumption and conception demonstrated no effect (Buck et al. 1997; Courval et al. 1999). However, a more recent study by Buck et al. (2000) demonstrated that fish consumption of a 3–6 year duration was associated with a reduction in fecundity in females. Despite the variation in results between studies, an association can be observed between the documented reproductive effects (e.g., menstrual irregularities and conception failure), making these findings biologically persuasive.

Males. Analysis of semen for 74 PCB congeners showed that increasing concentrations of three congeners (PCBs 118, 137, and 153), but not total PCBs, were associated with decreasing sperm motility in infertile men (Bush et al. 1986). Another study found that blood concentrations of tetra-CBs and penta-CBs, but not hexa-CBs and total PCBs, were significantly higher in infertile males than in normal individuals (Pines et al. 1987). These results do not necessarily indicate a causative relationship between PCBs and infertility in men for a number of reasons, particularly because levels of *p,p'*-DDT and other persistent toxic chemicals were also increased in semen and blood. Bush et al. (1986) found that the PCB congeners only accounted for a small proportion of the total variance attributable to the linear regression analysis, and hypothesized that the increased levels of PCBs in the low sperm count samples could be due to other factors, such as biological malfunction in the sperm generation system causing lipid leakage. Associations between conception delay and consumption of PCB-contaminated Great Lakes sportfish were reported in exposed men, but not their wives, in the study of the Michigan Anglers Cohort (Courval et al. 1999). Although analysis of the data controlled for several potential confounders, no information was collected regarding the subjects' frequency or timing of sexual intercourse during the period of

attempting to conceive, or levels of PCBs and other persistent toxic chemicals in biological samples from the subjects. Additionally, there was no clear association between paternal exposure to consumption of contaminated fish and conception delay or reduced fecundability in the NYS Angler Cohort, another cohort of Great Lakes Anglers (Buck et al. 1999, 2000). Occupational studies of reproductive effects in men provide no clear indications of PCB-related effects. Sperm counts, fertility history, and testicular examinations were normal in a study of transformer repairmen who were occupationally exposed to Aroclors 1260 and 1242 for a mean duration of 3.75 years (Emmett et al. 1988a, 1988b). Although the overall evidence for associations between PCBs and effects on sperm and conception delay in males has not always been consistent, there are indications of possible reproductive effects in males which are supported by the findings for female study subjects with similar exposure patterns.

3.2.5.3 Animal Studies

The highest NOAEL values and all reliable LOAEL values for reproductive effects for each study are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.5.3.1 Female Reproductive Effects

Commercial Mixtures. Information on reproductive toxicity of commercial PCB mixtures in female animals is available from studies in rats, mice, rabbits, minks, and monkeys. As discussed below, effects on fertility and/or reproductive function have been observed in most of these species with minks and monkeys showing particular sensitivity.

Wistar rats that were administered 10 mg/kg/day Aroclor 1254 by gavage for 4–6 weeks had prolonged estrus cycle, decreased sexual receptivity, and a transient decrease in body weight gain, but no significant effect on the number of ovulations compared to unexposed controls (Brezner et al. 1984). Animals that were subsequently bred (duration of exposure at time of mating not specified) experienced treatment-related vaginal bleeding during gestation, delayed parturition, and decreased litter size. Evaluation of pups following gestational and lactational exposure showed decreased body weight gain, decreased preweaning survival, premature vaginal opening, and delayed first estrus, but there were no effects on sexual differentation, estrous cycle, mating, or pregnancy. There were no significant changes in number of implantation sites, litter size, or offspring sex ratio in Long-Evans rats that were exposed to 4 mg/kg/day Aroclor 1254 in the diet from 50 days prior to mating until birth (Hany et al. 1999b). There were no overt signs of maternal toxicity, and other dose levels were not tested. Body weight (average of

both sexes) was significantly reduced in the pups at birth and PND 7–21, and relative testes weights and serum testosterone levels were reduced in adult male offspring at PND 170.

Two-generation studies were performed in which groups of 20 female Sherman rats were exposed by diet to Aroclor 1254 in doses of 0, 0.06, 0.32, 1.5, or 7.6 mg/kg/day or Aroclor 1260 in doses of 0, 0.39, 1.5, or 7.4 mg/kg/day (Linder et al. 1974). Exposure to Aroclor 1254 caused significantly reduced litter sizes at 7.6 mg/kg/day in the F1a generation (14% smaller than controls) and $1.5 mg/kg/day in the F1b, F2a, and F2b generations (15–72% smaller than controls). No effects on litter size were found in either generation of rats fed 0.06 mg/kg/day of Aroclor 1254 or $0.39 mg/kg/day of Aroclor 1260. Insufficient information is available to determine whether the effect on litter size is due to reproductive or developmental toxicity because fertility and other reproductive end points were not evaluated in the study.

Reproductive effects were evaluated in female offspring of Holtzman rats following maternal exposure to 0, 8, 32, or 64 mg/kg/day of Aroclor 1254 by gavage on lactation days 1, 3, 5, 7, and 9 (Sager and Girard 1994). Young, mature, and older adult offspring were examined at 2–4.5, 5–8, and 8.5–13 months of age, respectively, and mated to untreated males at 112, 200, and 350 days of age, respectively. Effects included a dose-related reduction in preweaning weight gain that was statistically significant at $32 mg/kg/day, delayed puberty as indicated by late vaginal opening and first estrus at $32 mg/kg/day; reduced mating rate (sperm-positive females) in mature offspring at $8 mg/kg/day; reduced implantation rate and mean number of embryos in young and mature offspring at 64 mg/kg/day; reduced uterine weight during proestrus in young, mature, and older offspring at $8 mg/kg/day; and reduced uterine response to exogenous 17-beta estradiol in ovariectomized mature offspring at $8 mg/kg/day. Average estrus cycle length was not significantly different in any of the groups, although cycle patterns were altered in low- and high-dose young offspring and in mid-dose mature rats. Pregnancy and ovulation rates, reproductive aging, and ovarian weights were not affected by exposure Aroclor 1254.

Estrogenic effects of PCBs were also evaluated in *in utero* and lactationally exposed female offspring of Sprague-Dawley rats that were administered 0 or 30 mg/kg/day doses of Aroclor 1221, 1242, or 1260 by gavage on days 12–20 of gestation (Gellert and Wilson 1979). Evaluation of the offspring at approximately 6 months of age showed no exposure-related changes in ovarian weight, ovulatory status, or vaginal estrus cyclicity.

Female ICR Swiss mice that were exposed to Aroclor 1254 in the diet at a dose of 12.5 mg/kg/day for 90 days before mating had a conception rate that was reduced approximately 30% compared to lower

dose groups (#1.25 mg/kg/day) and controls (Welsch 1985). There were no exposure-related effects on fertilization rate or pre- and postimplantation embryonic losses in New Zealand rabbits that were administered 4 mg/kg of Aroclor 1260 (only treatment level) by gavage on 3 days/week for 12–15 weeks before artificial insemination and throughout gestation (Seiler et al. 1994). No other reproductive parameters were examined in these studies.

It is well established that oral exposure to low doses of PCBs causes reproductive failure in minks. For example, in minks that were exposed to Aroclor 1254 at an estimated dietary dose of 0.4 mg/kg/day for a 39-week period that began approximately 6 months before mating and ended when the kits were 4 weeks of age, only two of seven mated females produced offspring with a total of two kits (one alive and one dead) (Aulerich and Ringer 1977). No effects on numbers of females producing offspring or kits born were induced by similar exposure to Aroclor 1242, 1221, or 1016, although 0.4 mg/kg/day was the only dose level tested. Dietary exposure to 0.2 mg/kg/day Aroclor 1254 for a 21-week period that began approximately 4 months before breeding and ceased at the end of gestation had no effect on numbers of females producing offspring or kits born, although marked reductions occurred at 0.9 mg/kg/day, and there were no births at 2.8 mg/kg/day (Aulerich and Ringer 1977). Female minks that were exposed to 1.3 mg/kg/day Aroclor 1254 in the diet from approximately 5 weeks before breeding until 5 days after parturition had an increased frequency of interrupted pregnancies and 48% reduced litter size with no live births (Kihlstrom et al. 1992). Similar effects on reproduction were observed in female minks that were exposed to 0.5–1.7 mg/kg/day Aroclor 1254 or 1.8 mg/kg/day Clophen A50 from before mating until 5 days after parturition for total durations of approximately 3 months (Backlin and Bergman 1995; Backlin et al. 1997, 1998a, 1998b; Jones et al. 1997). No indications of PCB-induced impaired ovulation or implantation have been observed in minks, although histopathological studies of mid- to late-gestation placentae indicate that fetal death is mediated by degenerative changes in maternal (endothelial detachment and thrombosis in maternal vessels) and fetal (trophoblastic disintegration and loss of fetal capillary integrity) tissues (Backlin and Bergman 1995; Backlin et al. 1997, 1998a, 1998b; Jones et al. 1997; Kihlstrom et al. 1992).

Reproductive effects of low doses of commercial PCB mixtures have also been demonstrated in intermediate-duration studies in female monkeys. Exposure to 0.8 mg/kg/day Aroclor 1248 for 2 months caused a reduction in conception rate in monkeys (Allen et al. 1974a). Conception did not occur in two of five monkeys that were bred 3 months posttreatment, resorption and/or abortion occurred in two of the three pregnant monkeys, and the two nonpregnant monkeys were bred twice again during the subsequent 5 months without success. Groups of eight female Rhesus monkeys were exposed to 0.1 or

0.2 mg/kg/day Aroclor 1248 in the diet from 7 months prior to breeding and throughout pregnancy (Barsotti et al. 1976). Increased menstrual duration (5–7 days) and bleeding occurred at $0.1 mg/kg/day, and conception rate was decreased at 0.2 mg/kg/day. Resorptions or abortions occurred in 3/8 and 4/6 of low- and high-dose impregnated monkeys, compared with 0/12 in controls, and the remaining two high-dose animals were bred 5 times without success. Similar effects occurred in four Rhesus monkeys that were mated after 38 weeks of dietary exposure to 0.2 mg/kg/day Aroclor 1248 (Arnold et al. 1990). Following extended post-implant bleeding, all of the treated monkeys aborted within 30–60 days of gestation. Following recovery from the abortions, the monkeys were bred again up to a maximum of 7 times but none appeared to conceive, and the menstrual cycle lengths and durations became erratic and longer during and subsequent to the breeding period.

Information on reproductive effects of chronic exposure to PCBs is available from a study in which groups of 16 female Rhesus monkeys ingested capsules providing 0, 0.005, 0.02, 0.04, or 0.08 mg/kg/day doses of Aroclor 1254 for up to 72 months (Arnold et al. 1993a, 1993b, 1995, 1997). Evaluation during the premating phase of the study (first 37 months) found no exposure-related changes in serum levels of estrogen and progesterone (assessed during one menstrual cycle), menstrual duration (number of days of menstrual flow), or menstrual cycle length (number of days from first day of menses until the day preceding the next menses) (Arnold et al. 1993a, 1993b). The average cycle duration was slightly increased in the 0.04 and 0.08 mg/kg/day groups compared to controls and the average cycle length was slightly shortened in treated groups compared to controls, but none of the differences were statistically significant. There also were no apparent treatment-related effects on incidences of anovulatory cycles or temporal relationships between estrogen peak and menses onset, menses end, or progesterone peak. After 37 months of exposure, the females were mated with untreated males and dosing was continued throughout mating and gestation until the breeding phase of the study (29 months) was completed (Arnold et al. 1995). Incidences for impregnation success were 11/16, 10/16, 4/15, 6/14, and 5/15 in the control to high-dose groups. Statistical analysis of these conception rates, adjusted for either total number of matings or number of matings with positive sires, showed that there was a significant ($p=0.017$) decreasing trend in the rate of impregnation with increasing dose from 0 to 0.08 mg/kg/day. There was no evidence of such a trend when conception rates among only the treated groups were compared. Comparisons between the treated and control groups showed that the conception rates were significantly ($p<0.05$) reduced at doses $0.02 mg/kg/day. Age of the females did not appear to be a confounding factor. A significantly increasing dose-related trend in fetal mortality incidence rates ($p=0.040$) was also found in this study. Comparisons between the treated and control groups showed that fetal mortality was significantly ($p<0.05$) increased at 0.08 mg/kg/day and marginally ($p=0.077$) increased at 0.02 mg/kg/day, indicating that

0.02 mg/kg/day is the LOAEL for both reduced conception and fetal survival. Although the increased fetal mortality in the 0.02 mg/kg/day group was marginally nonsignificant, the number of animals was small; this group had three fetal deaths in four impregnated animals, and the infant that was born died within 2 weeks postpartum. Maternal treatment was discontinued after approximately 7 weeks of lactation to preclude infants from self-ingesting the mother's dosing capsule, and restarted in the adult monkeys when infants were weaned at 22 weeks of age and continued for the following 8 months (Arnold et al. 1997). Necropsies performed at the end of the postweaning exposure period showed no exposure-related histopathological changes in the uterus and other parts of the reproductive system or increased incidences or severity of endometriosis.

Defined Experimental Mixtures. There were no significant effects on number of implantation sites, litter size, or offspring sex ratio in Long-Evans rats that were exposed to 4 mg/kg/day of a PCB congener mixture simulating the congener content of human milk from 50 days prior to mating until birth (Hany et al. 1999b). Overt signs of maternal toxicity were not observed, and other dose levels were not tested. Body weight in the pups (average of both sexes) was significantly reduced at birth and PND 7–21, relative uterine weight was significantly increased in the female offspring on PND 21, and relative testes weights and serum testosterone levels were significantly reduced in adult male offspring at PND 170.

Contaminated Fish. No adverse reproductive effects were found in a 2-generation study in which Sprague-Dawley rats were fed diets containing 0, 5, or 20% (w/w) of lyophilized protein from chinook salmon from Lake Huron or Lake Ontario (Arnold et al. 1998; Feely and Jordan 1998; Feeley et al. 1998). The F0 rats (30 males and 30 females/group) were mated after 70 days on the test diet and the F1 rats (1 male and 1 female from 24 litters) were mated 70 days postweaning. Daily intakes of total PCBs in the female F1 rats fed diet containing 0, 5, or 20% lyophilized Lake Ontario salmon flesh were calculated to be 0.22, 23.20, and 82.37 µg/kg/day, respectively (Feely and Jordan 1998). PCB intakes were qualitatively similar, but generally somewhat lower, for males compared with females and for F0 rats compared with F1 rats, and intakes from the Lake Huron diet were about 35–40% lower than from the Lake Ontario diet. The DDT complex (*p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD) accounted for 75 and 60% of organochlorine pesticide residues in the Lake Huron and Lake Ontario fish, respectively, and other major contaminants included CDDs and CDFs, mirex, chlordane, cadmium, lead, mercury, and arsenic. Comprehensive reproductive assessment, which included evaluation of conception rate and mating, fertility, viability, and lactation indices, showed no significant exposure-related adverse effects in either generation.

A 2-generation reproduction study of Lake Huron fish was conducted in minks (Restum et al. 1998). Although numerous chlorinated pesticides and other persistent toxic substances were present in the fish, the dietary treatments were expressed as targeted concentrations of total PCBs. Diets were formulated to provide 0, 0.25, 0.5, or 1.0 ppm PCBs by substituting carp from Lake Huron for ocean fish in the control diet. To determine whether the effects of exposure were permanent, half of the parental (P1) animals were switched from the treatment diets to the control diet after whelping the first of two F1 generations. Total exposure time for the P1 minks that were switched to the control diet after weaning was about 6 months, and the P1 minks that were continued on the treatment diets until termination of the study were exposed for approximately 16–18 months. Effects of gestational and lactational exposure on reproductive performance of the first F1 generation were examined by switching half of the F1 offspring to the control diet at weaning (offspring were exposed for about 3 months), and continuing the remaining offspring on their parental diet throughout their lifetime (continuous exposure for 12–15 months). The second F1 generation included kits born to the P1 dams that were exposed for 6 months followed by 10–12 months of consumption of control diet prior to whelping, as well as kits born to the P1 dams that were continuously exposed over an 18-month period. F2 generation minks consisted of kits born to the first F1 generation and exposed to PCBs either during gestation and lactation only, or from gestation throughout their lifetime. Effects included delayed onset of estrus, as determined by vulvar swelling and time of mating, in P1 and F1 females that were continuously exposed to the mid and high doses of PCBs. There were no significant differences in breeding performance (numbers of confirmed bred) and reproductive performance (number whelped/number mated) in the P1 and F1 females. Survivability of F1 and F2 offspring was markedly decreased in the mid- and high-dose groups. The reduced survivability of the F1 kits predominately occurred after birth during the lactation period. For example, the first F1 litter produced by the F0 generation showed a 70.5% survivability at birth (compared with 94.6% in controls), but by the end of lactation, 6 weeks after birth, the average survivability was 23% (compared with about 73% in controls). In several exposure groups, there were decreased percentages of mated females that gave birth, but the decreases were not statistically significant. The failure to demonstrate statistical significance may have been due to small sample sizes for several of these groups. For example, in a high-dose F1 group, 2/4 mated females gave birth (50%), compared with 11/14 (79%) in the F1 control group.

Single Congeners. A series of toxicity studies was performed in which groups of 10 male and 10 female Sprague-Dawley rats were exposed to diets containing four dose levels of various single congeners for 13 weeks (Chu et al. 1994, 1995, 1996a, 1996b, 1998b; Lecavalier et al. 1997). Histological examinations of the female reproductive organs and mammary glands showed mild changes in the ovaries in 7/10 rats exposed to PCB 126 at 8.7 µg/kg/day, but not #0.83 µg/kg/day (Chu et al. 1994). The

ovarian changes were characterized by loss of oogonia in the primary follicles with degeneration of the inner layer of the corona. No effects in reproductive tissues were found in females following exposure to PCB 28 at #3,956 µg/kg/day; PCB 77 at 892 µg/kg/day; PCB 105 at #3,960 µg/kg/day; PCB 118 at #170 µg/kg/day; PCB 128 at #4,125 mg/kg/day; or PCB 153 at #4,397 µg/kg/day. Measurements of serum leutinizing hormone and follicle-stimulating hormone concentrations, performed only in the female rats exposed to PCB 28 and PCB 77, showed no exposure-related changes (Desaulniers et al. 1997).

Promotion of surgically-induced endometriosis was studied in B6C3F1 mice that were treated with PCB 126 or PCB 153 by gavage every 3 weeks for a total of 5 doses (Johnson et al. 1997). Dose levels were 0, 100, 300, or 1,000 µg/kg/day for PCB 126 and 0, 3, or 30 mg/kg for PCB 153. No significant changes in the size, weight, or histology of endometriotic lesions were induced by either congener. There also were no significant effects on ovarian or uterine weights, although histological examination of the ovaries (uterus not examined) from a small number of animals (three per group) suggested possible induction of ovarian atrophy by PCB 126.

A reproduction study of PCB 169 was conducted in which offspring of exposed female Wistar rats were mated (Smits-van Prooije et al. 1993). The maternal rats were treated with a single 0, 0.2, 0.6, or 1.8 mg/kg dose of PCB 169 by gavage on day 1 of gestation. Mating of male and female offspring as young adults (age not specified) resulted in significantly reduced mating success (females mated) and pregnancy rate at 1.8 mg/kg. Mating of female offspring with unexposed males as 1-year-old adults caused nearly a completely reduced number of mated females and zero pregnancy rate at 1.8 mg/kg.

Female C57BL/6J mice were fed PCB 77 in estimated dietary doses of 0, 0.6, or 7 mg/kg/day for 2 weeks before mating with unexposed males and subsequently throughout gestation and lactation (Huang et al. 1998b). Female offspring were fed the same diets as the dams from weaning until 7 weeks of age, at which time they were mated with unexposed males. Fecundity (percentage of mated females that gave birth) and pup survival at ages 4 and 21 days were reduced in the F0 females at 7 mg/kg/day. There were no effects on fecundity or litter size in the F1 females, although all of their offspring died before 4 days of age at $0.6 mg/kg/day. Other effects included reduced *in vitro* fertilizing ability of the eggs and increased degenerated eggs in the F1 females at $0.6 mg/kg/day; these end points were not evaluated in F0 females.

Other Relevant Information. Results from *in vitro* studies with oocytes obtained from superovulated $B6D2F_1$ mice showed that and 3,3',4,4'-tetraCB and Aroclors 1221, 1254, and 1268 significantly reduced

fertilization rates and increased the incidence of degenerative ova and abnormal 2-cell embryos (Kholkute et al. 1994a). Of the four PCBs tested, Aroclor 1254 was the most effective.

3.2.5.3.2 Male Reproductive Effects

Commercial Mixtures. High oral doses of commercial PCBs induced testicular effects in weanling rats, but not adult rats or mice. Adult mice that were exposed to 130 mg/kg/day Aroclor 1254 in the diet for 14 days had no treatment-related changes in relative weights of the testes or preputial and vesicular accessory glands (Sanders et al. 1974). Similarly, no effects on testis weight, epididymis weight, or testicular histology or cytogenicity were found in adult rats that were treated with 50 mg/kg/day Aroclor 1254 by gavage for 7 days (Dikshith et al. 1975). Weanling F344 rats that were administered 25 mg/kg/day Aroclor 1254 by gavage for 15 weeks, however, had significant reductions in seminal vesicle and cauda epididymal weights, caudal epididymal sperm counts, and body weight gain (Gray et al. 1993). These effects were not observed at lower doses of 0.1–10 mg/kg/day, and there were no changes in testicular sperm count and motility, testicular weight, serum levels of testosterone, weight of the testicular interstitial fluid, testosterone concentration in the interstitial fluid, or total testosterone in the interstitial fluid compartment of the testis. None of these mouse and rat studies evaluated reproductive capability.

Fertility was markedly reduced in male offspring of Holtzman rats that were lactationally exposed to Aroclor 1254 (Sager 1983; Sager et al. 1987, 1991). The maternal rats were treated with 8, 16, 32, or 64 mg/kg doses by gavage on lactation days 1, 3, 5, 7, and 9, and male offspring were mated with untreated females 130–150 days postweaning (Sager 1983; Sager et al. 1987). Significant decreases in numbers of implants and embryos were observed at 8 mg/kg/day (21 and 29% lower than controls, respectively) and higher doses, and there was either a significant decrease or a decline in number and percent of normal fertilized eggs and eggs at the two- to four-cell blastocyte stages at $16 mg/kg/day. The reduction in male fertility appears to be due to impaired ability of sperm to fertilize eggs because sperm production, morphology, and motility were not affected and plasma FSH and testosterone concentrations were not reduced (Sager et al. 1987, 1991). Seminal vesicle and ventral prostate weights were decreased at $16 mg/kg/day.

In contrast to the effects of Aroclor 1254 summarized above, fertility was not impaired in male offspring of Sprague-Dawley rats that were administered 0 or 30 mg/kg/day doses of Aroclor 1221, 1242, or 1260 by gavage on days 12–20 of gestation (Gellert and Wilson 1979). There were no exposure-related

changes in the percentage of male offspring (F1) siring progeny when they were mated with unexposed females at approximately 6 months of age, or in the sex ratio of the F2 offspring from this mating. Measurements of absolute testes and ventral prostate weights in the F1 males (relative weights not determined) showed no changes except for increased testes weight in the Aroclor 1260 group.

Limited information is available on reproductive effects of commercial PCB mixtures in male minks and monkeys. Mating performance and testicular histology were normal in four male minks that were fed 0.1 mg/kg/day Aroclor 1254 in the diet for approximately 6 months (Wren et al. 1987b). Aulerich and Ringer (1977) noted that long-term dietary exposure to Aroclor 1254 did not exert any apparent adverse effects on spermatogenesis in minks. Matings between unexposed females and PCB-treated males reportedly resulted in acceptable reproduction, but no additional study information was provided.

One of four male Rhesus monkeys that were fed 0.1 mg/kg/day Aroclor 1248 for 17 months developed decreased libido and dermal and ocular signs of PCB toxicity after the first year of exposure (Allen and Norback 1976). A testicular biopsy on the affected animal showed marked hypoactivity of the seminiferous tubules characterized by an absence of mature spermatozoa and a predominance of Sertoli cells. The remaining three males remained healthy and sexually active. Evaluation of sperm morphology and viability and the ability to fertilize unexposed females, performed during the first year of exposure, showed no effects in any of the four males.

Contaminated Fish. There were no effects on breeding performance in male minks in the 2-generation reproduction study of Lake Huron fish summarized in Section 3.2.5.3.1 (Restum et al. 1998). No differences in the number of attempted or confirmed matings, or testicular volumes, were observed among the P1 and F1 generation males.

Single Congeners. Reproductive effects were evaluated in offspring of female Wistar rats that were treated with a single 0, 0.2, 0.6, or 1.8 mg/kg dose of PCB 169 by gavage on day 1 of gestation (Smits-van Prooije et al. 1993). Mating of exposed male and female offspring as young adults (age not specified) resulted in significantly reduced mating success (females mated) and pregnancy rate at 1.8 mg/kg. Mating of exposed male offspring with unexposed females as 1-year-old adults resulted in a zero pregnancy rate at 1.8 mg/kg.

Female C57BL/6J mice were fed PCB 77 in estimated dietary doses of 0, 0.6, or 7 mg/kg/day for 2 weeks before mating with unexposed males and subsequently throughout gestation and lactation (Huang et al.

1998a). Male F1 offspring were fed the same diets as the dams from weaning through 7 and 17 weeks of age, at which time, they were mated with unexposed females. Evaluation of reproductive ability of the F1 males showed no effects es as indicated by changes in fecundity (percentage of mated females that gave birth), litter size, sex ratio, or pup survival. Testes weights were increased in 7 mg/kg/day F1 males at 3 weeks, but not at 9 or 19 weeks of age. Additionally, although there were no effects on breeding, *in vitro* sperm-fertilizing ability was reduced in 7 mg/kg/day F1 males at 19 weeks, but not at 9 weeks of age.

A series of toxicity studies was performed in which groups of 10 male and 10 female Sprague-Dawley rats were exposed to diets containing four dose levels of various single congeners for 13 weeks (Chu et al. 1994, 1995, 1996a, 1996b, 1998; Lecavalier et al. 1997). Histological examinations showed no effects in male reproductive tissues following exposure to PCB 28 at #3,783 µg/kg/day; PCB 77 at #768 µg/kg/day; PCB 105 at #4,327 µg/kg/day; PCB 118 at #683 µg/kg/day; PCB 126 at #7.4 µg/kg/day; PCB 128 at #3,534 µg/kg/day; or PCB 153 at #4,210 µg/kg/day. Measurements of serum testosterone concentrations, performed only in the male rats exposed to PCB 28 and PCB 77, showed no exposure-related changes (Desaulniers et al. 1997).

Other Relevant Data. Daily sperm production was reduced and percentages of abnormal sperm were increased in adult male rats 1–8 weeks following administration of a single subcutaneous dose of 18 or 60 mg/kg of 3,3',4,4'-tetraCB (PCB 77) (Faqi et al. 1998). No effects on testis histology or serum testosterone concentration were observed, and reproductive capability was not evaluated.

Effects on the testis were evaluated in adult male rats that were neonatally exposed to either Aroclor 1242 (. 10, 40, or 80 mg/kg/day) or Aroclor 1254 (. 10 or 40 mg/kg/day) by daily subcutaneous injection from birth to PND 25 (Cooke et al. 1996). Examinations at 135 days of age showed significantly increased testis weight at $40 mg/kg/day Aroclor 1242 and $10 mg/kg/day Aroclor 1254, and increased daily sperm production at 10 mg/kg/day Aroclor 1242 and $10 mg/kg/day Aroclor 1254. Sertoli cell proliferation was also increased in exposed rats (only examined in 15-day-old pups treated with 40 mg/kg/day Aroclor 1242). Both Aroclor 1242 and 1254 also suppressed serum thyroxine (T_4) concentrations and T_4 replacement decreased or eliminated the testicular effects. As discussed in Section 3.2.2.8 (Endocrine Effects), other studies also indicate that hypothyroidism is involved in PCB-induced testicular effects in neonatal rats. Fertility tests showed that all Aroclor 1242-treated rats successfully impregnated unexposed females (Aroclor 1254 was not tested).

3.2.5.3.3 Evaluation of Animal Studies

Reproductive toxicity in female animals has been established in a number of oral studies with commercial PCB mixtures. Effects have been observed in various species, including rats (e.g., prolonged estrus, decreased sexual receptivity, and reduced implantation rate in adults and/or their offpsring exposed via gestation and lactation), mice (decreased conception), minks (partial or total reproductive inhibition), and monkeys (prolonged menstruation, decreased fertility) (Allen et al. 1974a; Arnold et al. 1990, 1993a, 1993b, 1995; Aulerich and Ringer 1977; Backlin and Bergman 1995; Backlin et al. 1997, 1998a, 1998b; Barsotti et al. 1976; Brezner et al. 1984; Jones et al. 1997; Kihlstrom et al. 1992; Sager and Girard 1994; Welsch 1985). Minks and monkeys are particularly sensitive, with effects occurring in these species at doses in the range of 0.1–1 mg/kg/day in intermediate-duration studies, and as low as 0.02 mg/kg/day in monkeys following chronic exposure.

In minks, repeated exposure to 0.4–1.8 mg/kg/day doses of Aroclor 1254 or Clophen A50 caused reproductive failure that has been associated with fetal death following embryo implantation (Aulerich and Ringer 1977; Backlin and Bergman 1995; Backlin et al. 1997, Kihlstrom et al. 1992). No indications of PCB-induced impaired ovulation or implantation have been observed in minks, although histopathological studies indicate that fetal death is mediated by changes in the placental vasculature which cause degenerative changes in the maternal and fetal vessels during gestation (Backlin and Bergman 1995; Backlin et al. 1997, 1998a, 1998b; Jones et al. 1997; Kihlstrom et al. 1992). As discussed in Section 3.5.2, multiple mechanisms are likely to be involved in PCB-induced reproductive impairment in minks. Although these studies provide important information on the mechanism and sensitivity of reproductive toxicity in female minks, it is unclear if this species is an appropriate surrogate for human toxicity. Impaired ability to conceive and decreased fetal survival are well-documented in female monkeys following repeated oral exposures to Aroclors 1254 and 1248 (Allen et al. 1974a; Arnold et al. 1990, 1993a, 1993b, 1995; Barsotti et al. 1976). For example, reduced conception rates, as well as increased incidences of abortions, resorptions, or stillbirths, were observed in groups of 16 female Rhesus monkeys that were fed encapsulated Aroclor 1254 at dose levels of 0.02–0.08 mg/kg/day for 37 months before breeding and subsequently throughout mating and gestation (Arnold et al. 1995). There were no clear effects on reproduction at 0.005 mg/kg/day, the lowest tested dose in this study and in any species. This dose is the LOAEL for immunological effects in the maternal monkeys and developmental toxicity in their offspring (see Sections 3.2.3 and 3.2.6). Mechanisms for the reproductive effects in monkeys have not been elucidated, although Arnold et al. (1995) found no evidence that they were associated with endometriosis.

There is some evidence suggesting that noncommercial mixtures of PCBs may have the potential to induce estrogenic and anti-estrogenic effects in the offspring of exposed animals. There were no significant effects on number of implantation sites or litter size in rats that were exposed to 4 mg/kg/day of a PCB congener mixture simulating the congener content of human milk from 50 days prior to mating until birth (Hany et al. 1999b). Evaluation of the offspring, however, showed significantly increased relative uterine weight in immature females (PND 21) and reduced testes weights and serum testosterone levels in adult males (PND 170). No significant exposure-related adverse effects on reproductive parameters (mating, fertility, viability, lactation indices, litter size) were found in a 2-generation study of rats fed contaminated fish from Lake Huron or Lake Ontario (Feeley et al. 1998). A 2-generation reproduction study of Lake Huron-fed minks similarly found no effects on breeding or reproductive performance, although onset of estrus was delayed in P1 and F1 females and survivability was decreased in F1 and F2 offspring (Restum et al. 1998). From the available information, it is not possible to determine whether the different results from the minks and rat studies are due to physiological or biochemical differences between minks and rats, qualitative or quantitative differences in chemical composition of the fish flesh, or some other cause. Additional information on the estrogenic and antiandrogenic effects of PCBs is discussed in Mechanisms of Toxicity (Section 3.5.2).

A limited amount of information is available on reproductive effects of PCBs in male animals. Short-term exposure to high oral doses of Aroclor 1254 induced no changes in the weight or histology of the testes or accessory glands in adult rats exposed to 50 mg/kg/day for 7 days or mice exposed to 130 mg/kg/day for 14 days (Dikshith et al. 1975; Sanders et al. 1974). Weanling F344 rats that were treated with 25 mg/kg/day Aroclor 1254 by gavage for 15 weeks, however, had significant reductions in seminal vesicle and cauda epididymal weights, caudal epididymal sperm counts, and body weight gain (Gray et al. 1993). These effects were not observed at lower doses of 0.1–10 mg/kg/day, and there were no changes in other testicular end points including sperm count and motility, testicular weight, and serum levels of testosterone. The results of the Gray et al. (1993) study may be related to the age of the rats at the start of dosing (day 31), which is after the development of Sertoli cells is complete, and therefore may have missed the vulnerable period in the postnatal development of the testes (see discussion in Section 3.2.2.8.3). None of these mouse and rat studies evaluated reproductive capability. Observations on small numbers of animals indicated that mating performance and testicular histology were normal in male minks that were fed 0.1–0.9 mg/kg/day doses of Aroclor 1254 for 4–6 months (Aulerich and Ringer 1977; Wren et al. 1987b). One of four monkeys that were fed 0.1 mg/kg/day Aroclor 1248 for 17 months developed clinical signs of toxicity, decreased libido, and marked hypoactivity of the seminiferous tubules, including an absence of mature spermatozoa, after the first year of exposure (Allen and Norback

1976). The remaining three males remained healthy and sexually active, and none of the animals had effects on sperm morphology and viability and the ability to fertilize unexposed females, although the latter end points were only evaluated during the first year of exposure.

In contrast to the limited evidence for reproductive effects in exposed male adult animals, fertility was markedly reduced in male offspring of rats that were lactationally exposed to $8 mg/kg/day Aroclor 1254 (Sager 1983; Sager et al. 1987, 1991). The reduction in male fertility appears to be due to impaired ability of sperm to fertilize eggs because sperm production, morphology, and motility were not affected and plasma FSH and testosterone concentrations were not reduced (Sager et al. 1987, 1991). Fertility was not impaired in the male offspring of rats that were administered 30 mg/kg/day of Aroclor 1221, 1242, or 1260 by gavage during gestation (Gellert and Wilson 1979), but this study did not include postnatal exposure. Results of oral and subcutaneous studies with single congeners have shown that gestational, lactational, or adult exposures can adversely affect morphology and production of sperm and fertility in male rats and mice (Faqi et al. 1998; Huang et al. 1998a; Smits-van Prooije et al. 1993), although congeneric structure-activity relationships are unclear.

3.2.6 Developmental Effects

This section describes effects of exposure to PCBs on anthropometric measures at birth in humans as well as on physical growth during infancy. For consistency, the discussion of animal data is restricted mostly to these same end points. Effects of perinatal exposure to PCBs on other end points in the offspring, including changes in the thyroid gland and thyroid hormones, neurobehavior, and the immune and reproductive systems, are discussed in the respective sections in Chapter 3.

3.2.6.1 Summary

Anthropometric measures have been evaluated in newborn from women (1) exposed to PCBs through consumption of Great Lakes and ocean fish contaminated with PCBs and other environmentally persistent chemicals, (2) from the general population with no known high exposure to PCBs, (3) occupationally exposed to commercial PCB mixtures, and (4) accidentally exposed to PCBs and structurally-related chemicals. Some studies found significant negative associations between anthropometric measures at birth (and at early ages) and exposure to PCBs, whereas others found significant positive associations, and yet a third group reported no significant associations. The wide range of results may reflect the different degree of controlling for confounders and/or the different exposure measures. Of the studies of

women who consumed contaminated fish from the Great Lakes, only the Michigan study reported an association between reduced birth weight, head circumference, and gestational age in newborns and with body weight at 4 years with prenatal exposure to PCBs (PCBs in cord blood). A study of Lake Ontario fisheaters, which used similar measures of exposure as the Michigan study, found no significant association between birth weight, head circumference, or gestational age and prenatal exposure to PCBs. In two additional studies of Lake Michigan women, fish consumption had a positive effect on birth weight. A study of Swedish wives of Baltic Sea fishermen found an increased risk of low birth weight with increasing maternal blood concentrations of the PCB congener PCB 153 used as surrogate of PCB exposure during the year of childbirth. In a study of the general population in the Netherlands, prenatal exposure to PCBs (PCBs in cord blood) was associated with reduced birth weight, but not with head circumference or height at 10 days of age. Prenatal exposure in formula-fed children was associated with reduced growth between birth and 3 months, but no such association was seen in breast-fed children, suggesting that any detrimental effect observed in newborns due to prenatal exposure to PCBs may have been counteracted by the benefits of breast feeding. No significant association was seen between growth during the ages of 3–7, 7–18, or 18–42 months and any measure of exposure to PCBs. A study of the general population in Finland found no significant association between birth weight and the concentration of PCBs in breast milk. No firm conclusions can be made regarding growth and development of children and environmental exposures to PCBs, although perinatal exposure to high concentrations of PCBs and structurally-related chemicals, as occurred in *Yusho* and *Yu-Cheng*, affects birth weight and growth during early life.

Studies have been conducted in animals exposed to commercial PCB mixtures, single PCB congeners, and a reconstituted PCB mixture with a composition of congeners similar to the pattern found in human breast milk. The results of these studies suggest that primates are much more sensitive to the effects of perinatal exposure to PCBs than rodents. It also appears that unless very high doses are used, PCBs are not teratogenic. In general, studies in rodents have used relatively high doses of PCBs. Data in rodents treated with commercial PCB mixtures showed that developmental toxicity can occur in the absence of overt signs of maternal toxicity. Limited data from a study in rats exposed during gestation showed that Aroclor 1254 was more potent than Aroclor 1260 in reducing survival of the pups to weaning. These two Aroclors differ primarily in that Aroclor 1254 lacks congeners with 7–9 chlorines. Reduced birth weight was reported in offspring from Rhesus monkeys treated before mating and during gestation with low doses of commercial PCB mixtures. These monkeys also showed characteristic signs of PCB intoxication such as hyperpigmentation. In all of the monkey studies, signs of PCB intoxication were also evident in the mothers.

3.2.6.2 Human Studies

3.2.6.2.1 Growth and Development

3.2.6.2.1.1 Contaminated Fish Consumption

The Michigan Cohort. Birth weight, length, and gestational age were evaluated in 313 newborn infants in the Michigan study (Fein et al. 1984a, 1984b). A detailed description of the study design is presented in Section 3.2.4 Neurological Effects. Briefly, of the 313 infants, 242 were born to mothers who had consumed moderate to large quantities of Lake Michigan fish sometime during their lives, and 71 were born to mothers who did not consume Lake Michigan fish. In the exposed group, mean fish consumption, estimated by recall and duration of consumption, was 6.7 kg/year and 15.9 years, respectively; this rate is equivalent to two or three salmon or lake trout/month (Fein et al. 1984a, 1984b). Consumption during pregnancy was 4.1 kg/year. The mean PCB level in maternal serum among those eating Lake Michigan fish was 6.1 ppb (SD=3.7), while the mean among those reporting no fish consumption was 4.1 ppb (SD=2.7). The mean PCB residues also were significantly higher in breast milk samples from the fisheaters as compared to the nonfisheaters, 865.6 ppb (fat basis) versus 622.2 ppb (Fein et al. 1984a). Data on approximately 37 potential confounders, including smoking during pregnancy, were considered in the study analyses (Fein et al. 1984a, 1984b).

Overall, lower birth weight, smaller head circumference, and shorter gestational age were positively correlated with consumption of fish and levels of total PCBs in cord serum; however, when the two populations were divided according to the cord serum levels, the great majority in the low-level group were fisheaters, suggesting that fish consumption rates were poor indicators of PCB exposure. Fish consumption only during pregnancy did not predict either birth size or gestational age (Fein et al. 1984b). Approximately 75% of the children were re-examined at age 4 (Jacobson et al. 1990a, 1990b). Levels of total PCBs in maternal milk or cord serum, or total duration of breast-feeding, were not related to height or head circumference at 4 years, but prenatal PCB exposure was associated with lower weight at age 4.

The Oswego Cohort. A study similar to the one conducted in Michigan was initiated in Oswego County (New York) based on babies born between 1991 and 1994 (Lonky et al. 1996) (see also Section 3.2.4.2.1.1, Neurological Effects). Pregnant women were recruited from the office of one obstetric practice and, following interviews, were divided into three groups based on their estimated fish consumption. The high fish consumption group was composed of women who reported having eaten

$40 PCB-equivalent pounds of Lake Ontario fish in their lifetime (n=152) (the same as the Michigan high fish consumption group). The low consumption group reported eating <40 PCB-equivalent pounds (n=243), and the no-fish-consumption group had never eaten Lake Ontario fish (n=164). The mean PCB-equivalent pounds consumed in the high fish group was 388.47 (SD=859.0), while the mean among those in the low-fish-consumption group was 10.14 (SD=17.8). The three groups did not differ with regard to demographic, health, and nutritional data, maternal substance use, infant birth characteristics. The high-fish consuming group had a significantly heavier pre-pregnancy weight than the nonfisheating group. In contrast to findings from the Michigan study, which had higher levels of exposure, birth weight, head circumference, and gestational age were unrelated to fish consumption. In subsequent studies, the investigators analyzed the association between specific groups of PCB congeners (according to degree of chlorination) and neurobehavioral outcomes in the newborn, but they provided no information regarding such analyses being done for birth weight, head circumference, and gestational age.

The Green Bay Wisconsin Study. This study was designed to evaluate the reproductive effects associated with maternal consumption of contaminated Great Lakes fish (Dar et al. 1992). All women between the ages of 18 and 35 with positive pregnancy tests at two Green Bay Wisconsin obstetrical clinics were invited to participate in this study. The recruitment occurred between January 1, 1987 and January 1, 1988. Participants were asked to complete a self-administered questionnaire at the first prenatal visit including questions on fish consumption, socioeconomic status, medical, reproductive, family, and occupational histories as well as a section on maternal behaviors. Of the 1341 eligible women, 1,115 agreed to participate for an overall participation rate of 82.9%. Nonparticipants (n=226) completed a brief questionnaire and were found to have lower education, lower income, and were more likely to be nonwhite. Exposure to PCBs was estimated from fish consumption scores determined from the questionnaire responses and corroborated by serum analyses. Fish consumption scores were calculated for each participant based on the amount and species of fish consumed in the preceding year. Levels of PCBs in the 18 species of fish that participants reported consuming were based on Wisconsin Department of Natural Resources surveys. Estimated PCB mean intake scores were used to establish the exposure variable categories. The low fisheating group (n=522) included women who consumed no locally caught fish, while the medium group (n=401) contained participants whose PCB scores were greater than 0 but less than the 90th percentile. The high exposure group was composed of women whose PCB intake scores were above the 90th percentile (n=104). Neither the actual fish consumption scores nor the means of the PCB scores for each exposure group were reported (Dar et al. 1992).

Due to the high cost of serum PCB analyses, maternal serum specimens were drawn from a random sample of participants (n=100) to assess the validity of the fish consumption variables. Correlation analysis between the fish consumption variables and serum PCB levels yielded a correlation coefficient of 0.666. The sum of the individual congener levels of PCBs in serum ranged from 0.6 to 5.0 ppb. The mean for each exposure group was not provided. The birth size outcomes evaluated in this study included birth weight, birth length, head circumference, ponderal index, and birth weight percentiles for gestational age (method not specified). These data were abstracted from hospital and clinic reports. Only data on birth weight were presented in this publication due to the similarity of results obtained from the other parameters. Multiple regression analyses were performed to assess the relationship between fish consumption and the outcomes of interest. Effect modification was assessed through the inclusion of interaction terms in the models. Factors known to influence birth outcomes were included as potential confounders (sex of child, birth order, smoking, caffeine and alcohol consumption during pregnancy, gestational age, pregnancy weight gain, usual maternal weight, and demographic variables).

Birth weight was found to increase with increasing PCB exposure, based on the fish consumption scores. Maternal weight gain modified the effect of fish consumption (PCB exposure) on birth weight; birth weight increased with fish consumption in women gaining <34 pounds during pregnancy while there was little difference in mean birth weights for the three fish consumption categories in women gaining more than 34 pounds during pregnancy (Dar et al. 1992). Smoking and caffeine consumption were negatively related to birth weight while male infants were found to be slightly heavier than female infants.

The Sheboygan Wisconsin Study. A study of Sheboygan, Wisconsin residents was conducted in 1980 and 1981 to assess the relationship between maternal serum and breast milk PCB levels and infant health, behavior, and development (Smith 1984). Routine testing for PCBs in 1978 along the Sheboygan River in Wisconsin revealed that game fish had PCB levels far in excess of the standard set for fish by the FDA (5 ppm at the time of the study, currently 2 ppm). To ascertain the potential health risks associated with the elevated PCB levels, a study of mother-infant pairs was undertaken in 1980 and 1981. A total of 73 of the mothers were included in the study. The participants were divided into three groups based on their screening survey responses (it is unclear if these groups were meant to be exposure variable categories or simply a description of the study population). Group 1 (n=23 pairs) included women who were breast feeding and ate Lake Michigan or Sheboygan River fish at least twice a month for $3 years. Group 2 (n=39 pairs) included women who were breast feeding and ate Lake Michigan or Sheboygan River fish not more than twice a year (and had not done this for more than 3 years). Group 3 (n=11 pairs)

included women who were not breast feeding and ate Lake Michigan or Sheboygan River fish at least twice a month for 3 or more years.

Maternal serum and a breast milk sample were also taken during each of the mother-infant evaluations. The first evaluation took place during the second month of postnatal life while the second occurred at 4 months of age. Prenatal maternal serum samples were not taken for any of the participants. The maternal survey instrument included questions on demographic variables, work history, medical history including reproductive history and the most recent pregnancy, smoking and alcohol consumption, and general diet. Information on fish consumption also was collected from this questionnaire and included data on species, amount, and frequency of fish meals. The data collected on the infants included a health history, dietary history, and growth and development assessment (Smith 1984). Statistical analyses included preliminary descriptive analyses using t-tests and chi-square tests. Multiple regression and logistic regression were used for the final models.

The mean level of PCBs in the first maternal serum was 5.76 ppb (range=1.29–14.9 ppb) while the mean for the second was 5.48 ppb (range=1.15–14.1 ppb). These levels indicated a low exposure level (Smith 1984). The means were very similar between the three groups of mother-child pairs. The mean breast milk PCB levels (fat basis) in the first sample of Sheboygan women was 1.13 ppm (range=0.29–4.02 ppm) while the mean for the second sample was 1.14 ppm (range=0.34–3.79 ppm).

Several variables were significant predictors of serum PCB levels (first sample) in linear regression modeling. These included the mother's education, a fish diet after birth, occupation, total bilirubin, cholesterol, and phosphorus (negatively associated). Regression analyses indicated that serum PCB level and cholesterol were significant predictors of the first breast milk sample PCB level. Regression analyses examining the relationship between birth weight and serum PCB levels (first sample) found that maternal serum PCB level was positively associated with birth weight after controlling for gestational age, smoking, and mother's weight. Fish consumption was not included as a variable in this analysis. In this investigation, the first breast milk sample was collected 2 months postnatal, and breast feeding would decrease serum concentrations. Therefore, a major confounder not adjusted for was breast feeding duration.

The Wives of Swedish Fishermen Cohort Study. A study of the wives of fishermen from two established cohorts was conducted to investigate whether east coast wives with a presumably higher intake of fatty fish (and PCBs) were more likely to have adverse reproductive outcomes than those living on the west

coast and elsewhere in Sweden (Rylander et al. 1995). Cohorts of fisherman from the east and west coasts of Sweden were established based on membership in fishermen organizations from 1930 forward. Through linkage to the national Swedish population register and to registers at the local parish offices, 1,568 women from the east coast and 4,027 from the west coast who were, or had been, married to these fishermen were identified. From 1973 to 1991, 757 women from the east coast cohort gave birth to 1,501 infants while 1,834 women from the west coast cohort gave birth to 3,553 infants.

Exposure to PCBs was represented by a variable called "east coast affiliation." The east coast of Sweden borders the Baltic Sea, a source of fatty fish (salmon and herring) thought to be contaminated with persistent organochlorine compounds. The west coast of Sweden is thought to have less contamination than the east. The study was designed as a retrospective cohort investigation comparing children born to east coast women (exposed) and west coast women (unexposed) who were, or had been, married to fishermen. The majority of the data in this study was collected from the Swedish Medical Birth Registry, which includes information on maternal demographics, smoking during pregnancy, prenatal care, delivery, and pediatric assessments of the newborns. The principal end points evaluated in this study were birth weight, birth length, and head circumference. Two cutpoints were used as an indicator of low birth weight, 2,500 and 3,000 g.

Smoking was less frequent among west coast women during early pregnancy than among east coast women (22.7 versus 38%). In addition, there was a higher proportion of short women (<165 cm) among the east coast cohort as compared to the west (48.6 versus 39.2%). Weight distributions during early pregnancy were similar for both cohorts.

In order to assess the dietary habits of both the east and west coast fishermen's wives, interviews were conducted with a 5% random sample (n=38) of east coast cohort members and 2% random sample (n=31) of west coast cohort members. Equal numbers of female residents from the general population were also interviewed; these "control" women were matched to the east and west coast wives by age and county of residence. Both the east and west coast women, who were married to fishermen, ate locally caught fish, both lean and fatty species, twice as often as their referents. The fishermen's wives also consumed about 3 times the amount of fatty fish species/month as their referents.

Among the fishermen's wives, west coast cohort members ate significantly more lean fish species than the east coast cohort members. There were no statistically significant differences between the east and west

coast fishermen's wives in the total number of fatty fish meals eaten/month or in the amount of fatty fish consumed on a monthly basis.

Comparison between the cohorts showed that birth weight and head circumference, but not length at birth, were slightly reduced ($p<0.001$) in the east coast group. The effect on head circumference was observed even when multiple births and infants with major malformations were excluded. Odds ratios were calculated to evaluate the effect of cohort affiliation on low birth weight using a stratified analysis to control for confounders. East coast affiliation was significantly associated with low birth weight (<3,000 g) even after adjustment for gender of the child, maternal age, parity, marital status, and smoking. Stratified analyses for head circumference and birth length were not presented in this report.

In a more recent publication from this group, the authors examined the association between the concentration of 2,2',4,4',5,5'-hexaCB (PCB 153) in maternal serum during the year of childbirth and birth weight of 57 east coast low birth weight cases and 135 controls matched on gender, parity, and calendar year of birth (Rylander et al. 1998b). In 1995, blood samples were collected from the wives and ex-wives of fisherman from the east cost who had given birth during the period of 1973–1991. PCB 153 in maternal blood was used as biomarker of exposure to PCBs and the concentration during the year of childbirth was estimated using kinetic models. The median concentration in serum (fresh weight) in 1995 was 1.0 ppb for the case mothers compared to 0.92 ppb for control mothers. Rylander et al. (1998b) found an increase in the risk of a low birth weight at maternal blood PCB 153 concentrations of 300 and 400 ng/g (ppb, lipid basis).

3.2.6.2.1.2 General Population Exposure

The North Carolina Breast Milk and Formula Project. The North Carolina Breast Milk and Formula Project (NCBMFP) is a cohort study designed to assess the relationship between exposure to prenatal and postnatal PCBs and DDE and growth and development in infants and children (Rogan et al. 1986a, 1986b). A detailed description of this cohort study in presented in Section 3.2.4.2.1.2 (Neurological Effects). Briefly, the participants were administered a questionnaire while in the hospital following delivery. Maternal serum, cord blood, and placenta samples were collected at birth as well as colostrum, breast milk, or formula. The first follow-up visit occurred at 6 weeks with subsequent evaluations at 3 and 6 months postpartum. Breast milk or formula was collected at each of these visits. PCB levels in milk at birth averaged around 1.8 ppm (fat basis). A total of 912 children were available with at least

partial neonatal information (Rogan et al. 1986a). The outcomes evaluated in the neonatal period included birth weight and head circumference.

The relationships of birth weight and head circumference to PCB levels were assessed by multiple regression. The covariates (potential confounders) included in the analyses were infant race, sex, mother's age, education, occupation, smoking, alcohol consumption, prior pregnancies, maternal weight, center enrolling the participant, and jaundice. The analysis of head circumference also included the birth weight variable (Rogan et al. 1986a). The multiple regression analyses found no associations between birth weight or head circumference and PCB level. The birth weight decrement was noted for smokers as was the male-female difference. Larger mothers also had significantly larger babies. Head circumference was associated with the infant's birth weight and sex, and the mother's education and occupation (Rogan et al. 1986a).

The Dutch Mother-Child Study. The Dutch Mother-Child Study was designed as a prospective study to assess the possible adverse effects of prenatal and postnatal PCB and dioxin exposure. Details of this study are presented in Section 3.2.4 (Neurological Effects). Briefly, 207 pairs (105 breast-fed and 102 formula-fed) were from Rotterdam, a highly industrialized area, while 211 pairs (104 breast-fed and 107 formula-fed) were from Groningen, a semi-urban area in northern Holland (Koopman-Esseboom et al. 1994b). The exposure variables used in this study were maternal serum and milk samples as well as cord blood specimens.

The effect of prenatal cord blood PCB exposure on birth size at 10 days of age was evaluated using a series of linear regression models (one for each outcome) in 207 mother-infant pairs from Rotterdam. Covariates included in the models were parity, gestational age, smoking, alcohol use during pregnancy, and a factor representing parental height. Gender, an important determinant of size, was not included among the covariables for some reason even though there were significantly more boys in the breast-fed (59%) than in the formula-fed group (46%). This may have resulted in confounded effect measures. A significant decrease in birth weight at 10 days of age was observed with cord blood PCB exposure; birth weight declined by a mean of 86 g at the 50th percentile of exposure relative to the 10th percentile exposure levels while a mean 165 g decrease was observed for those in the 90th percentile of exposure relative to the 10th percentile. Head circumference and height at 10 days of age were not significantly associated with cord blood PCB levels. Similar effects were observed when using maternal plasma PCB levels as the exposure variable with weight, height, and head circumference as outcomes at 10 days of age (Patandin et al. 1998).

The effect of prenatal PCB exposure on growth rate was assessed in the formula-fed group (n=102) using linear regression modeling. Covariates were identical to those described in the previous paragraph, with the addition of the relevant variable value at 10 days of age in each model (e.g., change in birth weight between 0 and 3 months included birth weight at 10 days of age). Gender was not included in these models. Cord blood PCB levels showed a significant inverse association with growth rate at 0–3 months of age for each index (i.e., birth weight, height, and head circumference). Similar findings were observed when maternal plasma PCB levels were used as the exposure. Prenatal PCB levels in formula-fed children were not significantly associated with growth rate for any of the indices from 3–7, 7–18, or 18–42 months (Patandin et al. 1998).

The associations between growth rates and prenatal and postnatal PCB/dioxin levels also were evaluated in 107 children from Rotterdam who were breast-fed. Both cord blood levels and postnatal breast milk levels were included in these models as were the covariates described above. PCB levels (prenatal or postnatal) were not associated with growth rates at 0–3 months of age. Postnatal PCB/dioxin levels were negatively associated with a change in height between 3 and 7 months (p=0.04), but not with weight or head circumference growth rates. Pre- and postnatal PCB levels were not associated with changes in growth rate between 7–18 and 18–42 months of age in the breast-fed children (Patandin et al. 1998).

Finnish General Population Study. This study was part of follow-up studies into levels of dioxins, dibenzofurans, and PCBs in human milk coordinated by WHO/EURO. The objectives of the study were to correlate the birth weight and sex of a child to dioxins/dibenzofurans and PCB concentrations of its mother's milk and to evaluate personal and environmental determinants that correlated with the levels of these chemicals in human milk in two areas in Finland, an urban area and a rural area (Vartiainen et al. 1998). One hundred sixty-seven random human milk samples were collected 4 weeks after delivery for 2 weeks. Information on each mother and child was gathered by a questionnaire that included questions on all relevant covariates.

The concentration of PCBs in breast milk from urban and rural mothers was approximately 500 and 400 ppb (fat basis), respectively. The average weight for all children was 3,630 g and the median was 3,625 g. The mean weight of the urban children was not significantly different from rural children, although dioxin international TEQs were significantly higher in milk from urban mothers. No correlation was found between the weight of children and total PCBs in all of the children, in boys, in girls, among all primiparae, or in primiparae girls or boys. The birth weight, especially of boys, slightly decreased

with increasing concentrations of TEQs, 2,3,4,7,8-penta CDF, 1,2,3,7,8-pentaCDD, and 2,3,7,8-TCDD, but when the analysis was restricted to primiparae, the correlation lost statistical significance.

3.2.6.2.1.3 Occupational Exposure

Upstate New York Capacitor Manufacturers Study. This study comprised women workers of two facilities of the same company located in adjacent communities in upstate New York that manufactured capacitors using PCBs with Aroclors 1254, 1242, and 1016 as their primary dielectric fluid (Taylor et al. 1984). Birth certificates for pregnancies between 1958 and 1975 were used to obtain information on birth weight, maternal age, parity, year of birth, race, sex, and date of the last menses. The high-exposure workers were directly exposed to Aroclors during the manufacturing process for at least 1 year prior to birth of the infant; the workers with low exposure were employed in areas where Aroclors were not used directly.

Fifty-one infants born to 39 women with high exposure to PCBs had lower mean birth weights and shorter mean gestational ages than those of 337 infants born to 280 women with low exposure to PCBs. After adjusting for gestational age, however, the difference in birth weight was markedly reduced, suggesting that the difference in weight may have resulted partially from a shortened gestation period. Furthermore, while the infants born to the high-exposure women were, on the average, lighter than matched community controls, those born to low-exposure women were heavier than matched community controls; thus, a dose-response relationship was not established. While relatively little detail was given regarding the statistical analysis of the results, Taylor et al. (1984) state that they had no information on tobacco use, underlying medical conditions, maternal height, and history of low birthweight, all factors known to influence birthweight. In a follow-up study of the same population in which most of these confounders were accounted for, a significant effect of high-homolog exposure was seen for birth weight and gestational age (Taylor et al. 1989). The difference in birth weight between the two groups was 60 g. However, when gestational age was accounted for in addition to the other variables related to birth weight, estimated serum PCB was no longer a significant predictor of birth weight. Taylor et al. (1989) concluded that the data suggested a significant relation between increased estimated PCB level and decreased birth weight and gestational age, and that the decrease in birth weight is partially related to shortened gestational age.

3.2.6.2.1.4 Accidental Exposure

Yusho and Yu-Cheng. Decreased birth weight was a commonly reported effect of *Yusho* and *Yu-Cheng* exposure (Funatsu et al. 1971; Lan et al. 1987; Rogan 1989; Taki et al. 1969; Yamaguchi et al. 1971). A survey of 128 children known to have been *in utero* during or after *Yu-Cheng* exposure found that mean birth weight was decreased by approximately 15% compared to a group of 115 unexposed controls (Rogan et al 1988). Exposed children also were shorter than controls; these children were a few months to 6 years old. Lan et al. (1987) documented the decreased birthweight of 49 *Yu-Cheng* children exposed transplacentally and born between 1979 and 1986, and showed that the deficit continued through the second child born after the outbreak, but was not detectable in the third. In a review of the *Yusho* poisoning incident, Masuda (1994) stated that most babies were small-for-date and their postnatal growth curves were similar in shape to the national standard curves, but lower for some of the babies. Relative to unexposed controls, height and weight gains of school children with *Yusho* significantly decreased after the poisoning, and the same tendencies were observed in some of the girls (Masuda 1994). These tendencies to reduced growth were later found to be reversed, as subsequent increaments tended to be close to the average value in the control group (Yoshimura and Ikeda 1978). It should be kept in mind that in both the *Yusho* and *Yu-Cheng* poisoning episodes, there was exposure to relatively high concentrations of CDF and PCQ impurities. Further information on *Yusho* and *Yu-Cheng* incidents can be found in ATSDR (1994).

3.2.6.2.2 Evaluation of Human Studies

Anthropometric measures have been evaluated in children from women (1) who consumed Great Lakes fish contaminated with PCBs and other chemicals (Dar et al. 1992; Fein et al. 1984b; Jacobson et al. 1990a, 1990b; Lonky et al. 1996; Smith 1984), (2) who consumed Baltic Sea fish contaminated with organochlorines (Rylander et al. 1995, 1998b), (3) from the general U.S. (Rogan et al. 1986a, 1986b), Dutch (Patandin et al. 1998), and Finnish populations (Vartiainen et al. 1998), (4) who were occupationally exposed to commercial PCB mixtures (Taylor et al. 1984, 1989), and (5) who were accidentally exposed to PCBs and other structurally related chemicals in the *Yusho* and *Yu-Cheng* poisoning incidents (Funatsu et al. 1971; Lan et al. 1987; Rogan 1989; Yamaguchi et al. 1971). A comparison of PCB levels in blood and breast milk in some of these studies is included in Appendix A.

The results have been varied, with some studies finding significant inverse associations between exposure to PCBs and anthropometric measures at birth (and at early ages), some studies reporting significant

positive associations, and yet a third group reporting no significant associations. The wide range of results may reflect the different degree of controlling for confounders and/or the different exposure measures, levels, and substances. Also, in some cases, the difference in serum PCB levels between case studies and controls may have been too small to allow detection of differences between the variables measured. Of the studies of women who consumed contaminated fish from the Great Lakes, the Michigan study (Fein et al. 1984b; Jacobson et al. 1990a, 1990b) reported an association between reduced birth weight, head circumference, and gestational age in newborns and with body weight at 4 years with prenatal exposure to PCBs (PCBs in placental cord blood).

A study of wives of Swedish fishermen found that newborn infants born to mothers from the east coast (Baltic Sea) gave birth to infants with significantly lower birth weight and head circumference compared to infants born to mothers from the west coast (Rylander et al. 1995). East coast mothers were reported to consume more contaminated fatty fish (and PCBs) than women from the west coast where fish contamination was much less. In a subsequent study of east coast/Baltic Sea mothers (Rylander et al. 1998b), their low birth weight infants (1,500–2,750 g weight) were compared with control infants from this same cohort (3,250–4,500 g weight). Blood samples from the mothers were analyzed for PCB congener 153, which was used as a surrogate of total PCB exposure during the year of childbirth. The mothers of the low birth weight infants were reported to have a higher median PCB blood level (1,000 pg/g) compared to the control mothers (920 pg/g). These researchers also found an increased risk of low birth weight with increasing maternal blood concentrations of PCB 153 (at 300 or 400 ng/g, lipid basis).

In the Dutch general population cohort, prenatal exposure to PCBs (PCBs in cord blood) was associated with a reduced birth weight, but not with head circumference or height at 10 days of age (Patandin et al. 1998). Prenatal exposure (as measured by cord and maternal blood PCB levels) in formula-fed children was associated with reduced growth (weight, length, and head circumference) between birth and 3 months. No such association was seen in breast-fed children, suggesting to the investigators that any detrimental effect observed in newborns due to prenatal exposure to PCBs may have been counteracted by the benefits of breast feeding. Additionally, there were no significant associations between growth during the ages of 3–7, 7–18, or 18–42 months and any measure of exposure to PCBs. In an occupational study, Taylor et al. (1989) studied high PCB exposed females employed in capacitor manufacturing facilities and compared them with female workers in low PCB exposure jobs. A significant association was observed between the increased estimated PCB exposure level and decreased birth weight and gestational age. In addition, effects on birth weight and growth during early life have been demonstrated

following perinatal exposure to high concentrations of PCBs and structurally-related chemicals during the *Yusho* and *Yu-Cheng* poisoning incidents.

Consumption of PCB-contaminated fish had a positive effect on birth weight in two studies of Lake Michigan women (Dar et al. 1992; Smith 1984). This finding could be related to the beneficial effects of certain fatty acids in fish (Olsen et al. 1990). In one of these studies (Smith 1984), the concentration of PCBs in breast milk was higher than in breast milk from women from the Michigan cohort (1.13 vs 0.87 ppm) in the Jacobson study discussed above. In the other study (Dar et al. 1992), fish consumption levels were less than in the Jacobson study.

In the Oswego cohort of Lake Ontario fish consumers (Lonky et al. 1996) there was no significant association between prenatal exposure to PCBs, assessed by the same fish consumption measures as in the higher exposure Michigan study, and birth weight, head circumference, or gestational age. In addition, a study of the general population in Finland found no significant association between birth weight and the concentration of PCBs in breast milk (Vartiainen et al. 1998). In this study, the mean concentration of PCBs in milk (0.4–0.5 ppm) was slightly lower than in the Dutch general population study (0.62 ppm) (Koopman-Esseboom et al. 1994b; Patandin et al. 1998).

For those studies with effects, there is consistency in the outcome of lower birth weight for infants exposed *in utero* to maternal body burdens of PCBs. This association remains constant regardless of the method by which PCB exposure is measured (e.g., estimate by fish consumption or actual body burdens in maternal blood). Jacobson et al. (1990b) have demonstrated that, even at the age of 4 years, the children most highly exposed to PCBs weighed less on the average than those with the least exposure. This tendency can also be seen in the Dutch study (Patandin et al. 1998), which reported a significant association between lower infant growth rate in 0–3 month olds and mothers' body burden as demonstrated by cord and maternal PCB levels. The consistency with which this finding has been demonstrated strengthens the position that PCBs (and related substances) are developmental toxicants. In addition, birth weight is a sound indicator of newborn development and health.

3.2.6.3 Animal Studies

Developmental effects discussed in this section are restricted mainly to effects on fetal development, birth weight and weight gain in early life, and teratogenicity. Information regarding effects on the thyroid, immune system, and reproduction in offspring following perinatal exposure to PCBs is presented in Sections 3.2.3, 3.2.4, and 3.2.5, respectively.

The highest NOAEL values and all reliable LOAEL values for developmental effects for each study are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.6.3.1 Birth Weight and Early Development

Oral Exposure

Commercial PCB Mixtures. Doses of #100 mg/kg/day Aroclor 1254 administered on Gd 6–15 by gavage did not affect maternal weight gain nor induce developmental toxicity in Wistar rats, as evidenced by number of litters, litter size and weight, and number of resorption sites (Villeneuve et al. 1971). Morse et al. (1996b) also reported that treatment of Wistar rats on Gd 10–16 with up to 25 mg Aroclor 1254/kg/day by gavage did not affect maternal body weight, fetal body weight, number of live fetuses, late gestational death, number of resorptions, number of live pups born, sex ratio, and postnatal death. However, a study with Aroclor 1254 in Holzman rats reported a significant reduction in fetal weight at 5 mg/kg/day and reduced fetal survival at 15 mg/kg/day after dosing also on Gd 6–15; both effects were dose-related (Spencer 1982). A dose of 2.5 mg/kg/day was without effect. Maternal body weight loss occurred at 30 mg/kg/day. Decreased survival of pups to weaning was found in Sherman rats administered nine doses of 100 mg Aroclor 1254/kg by gavage on Gd 7–15 (Linder et al. 1974), but that treatment did not affect the number of litters or the litter size at birth. Doses of #50 mg/kg/day did not affect survival at weaning. No effect on the number of litters, litter size, survival to weaning, or body weight at weaning were observed in the offspring of rats treated with doses of 100 mg/kg/day Aroclor 1260 on Gd 7–15 (Linder et al. 1974). Offspring from Long-Evans rats exposed to 4 mg Aroclor 1254/kg/day via the diet starting 50 days prior to mating until birth had significantly reduced weight at birth, and on PND 7, 14, and 21 (Hany et al. 1999b). This was observed in the absence of any overt sign of maternal toxicity. There were no significant treatment-related effects on number of pups/litter, number of implantation sites, or sex ratio.

Litter size was significantly reduced in Osborne-Mendel rats fed a diet that provided approximately 25 mg Aroclor 1254/kg/day during gestation and lactation (Collins and Capen 1980c). Body weight of pups at 21 days was significantly reduced with dietary PCB levels of 2.5 and 25 mg/kg/day, but was not affected at birth or at 7 and 14 days. Doses of approximately 13.5 mg Aroclor 1254/kg/day administered during gestation and lactation induced high early mortality in the pups (Overmann et al. 1987). Doses of approximately 1.3 mg/kg/day significantly decreased pups' weight on PND 21 and 14, and doses of 0.13 mg/kg/day decreased pups' weight on PND 14 (Overmann et al. 1987). Doses of 1.3 mg/kg/day had no significant effect on maternal weigh or food consumption. High early mortality was also observed in pups from Long-Evans rats treated with 4 or 8 mg Aroclor 1254/kg/day from Gd 6 through PND 21 (Goldey et al. 1995). Wistar rats that were treated with 10 mg/kg/day Aroclor 1254 by gavage during gestation had delayed parturition and decreased litter size (Brezner et al. 1984). This dose level resulted in no weight gain in the dams. Offspring of these rats that were exposed throughout lactation experienced decreased pre- and postweaning survival, premature vaginal opening, and delayed first estrus, but no effects on sexual differentiation, estrus cycle, mating, or pregnancy.

Offspring of mice exposed to doses up to 12.5 mg Aroclor 1254/kg/day on Gd 6–18 did not show adverse developmental effects, as judged by number of litters, number of dead and reabsorbed fetuses, fetal weight, incidence of gross malformations, and skeletal development (Welsch 1985). A single, but much higher dose (244 mg/kg) of Aroclor 1254 given on Gd 9 to pregnant mice significantly increased the percentage of fetuses with hydronephrosis, did not induce cleft palate, and did not affect the number of resorptions and number of dead and live fetuses (Haake et al. 1987). Maternal weight gain was not influenced by PCB treatment (Haake et al. 1987).

Doses up to 10 mg Aroclor 1254/kg/day administered to rabbits on Gd 1–28 did not induce developmental toxicity, as monitored by total number of fetuses, number of viable fetuses or resorption sites, fetal weight, fetal liver weight, and placental weight (Villeneuve et al. 1971). Doses of 12.5 mg/kg/day or higher, however, significantly increased the number of dead fetuses, resorption sites, and fetuses aborted. Aroclor 1248 did not affect litter size, appearance, or postnatal mortality in New Zealand rabbits administered doses of #91 mg/kg/day in the diet for 11 weeks, but a dose of 28 mg/kg/day induced focal liver necrosis in the offspring (Thomas and Hinsdill 1980).

Administration of 2.2 mg of Clophen A50/kg/day by gavage to pregnant guinea pigs during Gd 16–60 caused high incidence of fetal mortality, but did not cause maternal lethality or any other overt sign of maternal toxicity (Brunstrom et al. 1982). Also, administration of 2.5 mg/kg/day Clophen A50 (50%

chlorine by weight) to guinea pigs on Gd 18–60 significantly increased the frequency of dead fetuses and stillbirth (27.4 versus 9.4% in controls), decreased litter size, and decreased maternal weight gain during gestation and birth weight (Lundkvist 1990). First vaginal opening was abnormal in the surviving offspring, occurring at an older age and with a shorter duration, but there was no significant effect on age at first ovulation.

A dose of 0.1 mg/kg/day Aroclor 1254 administered in a juice-oil emulsion to two Cynomolgus monkeys starting at Gd 60 resulted in delivery of dead, term infants after approximately 105 days of dosing (Truelove et al. 1982). The infant of one monkey that was similarly treated with 0.4 mg/kg/day had reduced birth weight and weight gain, and later died of bronchopneumonia at 139 days of age. The only sign of maternal toxicity was loss of fingernails. Resorption and/or abortion occurred in monkeys that were bred 3 months following dietary treatment with 0.8 mg/kg/day Aroclor 1248 for 2 months (Allen et al. 1974a). Chronic developmental data are limited to studies in monkeys. In these studies, the exposure period ranged from 12 to 37 months. Pregnant Rhesus monkeys that were fed a diet that provided approximately 0.007 or 0.03 mg/kg/day Aroclor 1016 for a total of 12 months (before mating and during gestation) experienced uncomplicated pregnancies, carried their infants to term, and delivered viable offspring (Barsotti and Van Miller 1984). Information regarding maternal body weight and age was not provided. Head circumference and crown-to-rump length were not affected by treatment with Aroclor 1016, but mean birth weight in the high-dose group was significantly lower than in controls. Both groups of neonates showed hyperpigmentation. At weaning, body weight in the high-dose group was still lower than in controls, but the difference was not statistically significant. Dose-related early abortions were reported in female monkeys fed a diet that provided 0.1 or 0.2 mg/kg/day Aroclor 1248 for 15 months (five of eight in the low-dose group and four of six in the high-dose group); this period included breeding, gestation, and lactation (Allen and Barsotti 1976). Mean birth weight in both groups was significantly lower than in controls and remained low for the next 12 weeks. Skeletal development was not affected by PCB treatment. At 2 months of age, the infants had signs of PCB intoxication such as facial acne, swollen eyelids, loss of eyelashes, and hyperpigmentation of the skin, and three of the six infants died of PCB intoxication between days 44 and 329. Gross and microscopic examination of the major organs revealed a rudimentary thymus, extremely small spleen lymph nodes, hypocellularity of the bone marrow, and degenerative changes in the liver. Maternal toxicity, evidenced as facial acne, swollen eyelids, and lack of facial hair, was observed at weaning. One year after receiving a control diet, the same females from the Allen and Barsotti (1976) study were bred again (Allen et al. 1980). Mean birth weights of the infants of the former high-dose mothers were significantly lower than those of controls, and signs of PCB intoxication (hyperpigmentation about the hairline) developed during suckling. Early

infant mortality was also observed (two of four in the former low-dose group and two of seven in the former high-dose group). Histological examination of infant tissues showed hypocellularity of the thymus and of lymph nodes in the spleen and hyperplastic gastritis.

Arnold et al. (1995, 1997) treated female monkeys with Aroclor 1254 for 37 months (0.005, 0.02, 0.04, or 0.08 mg/kg/day) after which time they were mated with untreated males; dosing continued through mating and gestation. Treatment ceased when the infants were 7 weeks old. The young monkeys were sacrificed at the age of 122 weeks. Statistical analysis of the results showed a significant increasing dose-related trend in fetal mortality incidence rates (combined fetal and postpartum deaths). However, when only the treated groups were compared, there was no evidence of such a trend. Results of the Fisher's exact test showed a significant increase rate for only the highest dose group with the 0.02 mg/kg/day dose approaching significance. Mean birth weight was not significantly affected by maternal treatment with Aroclor 1254. The major clinical findings in the offspring from treated females were the presence of inflammation and/or enlargement of the tarsal (Meibomian) gland, nail lesions, and gum recession.

Single Congeners. No effect on maternal body weight or on gestational length, litter size, percent live births, birth weight, or pup weight at weaning was observed following administration of 0.001 mg/kg/day PCB 126 or 8 mg/kg/day PCB 77 to pregnant Sprague-Dawley rats on Gd 10–16 (Seo et al. 1995). Administration of 0.001 mg/kg/day of PCB 126 to Long-Evans rats beginning 5 weeks before and continuing through gestation and lactation did not result in any significant effect on neonatal mortality, birth weight, litter size, or on weight gain monitored up to PND 60 (Rice 1999a)

Pregnant C57BL/6J mice given up to 21 mg PCB 77/kg/day by gavage on 5 consecutive days beginning on days 1, 6, or 11 of pregnancy showed no adverse effect on maternal body weight or on pup weight, crown-rump length, litter size, sex ratio, day of eye opening, or upper incisor eruption (Rodriguez et al. 1997). Administration of a single gavage dose of approximately 0.8 or 1 mg PCB 126/kg to pregnant C57B46 mice on Gd 10 significantly increased the percentage of fetuses with cleft palate (Zhao et al. 1997b). However, no fetuses with cleft palate were seen after administration of up to 271 mg PCB 153. Combined administration of PCB 126 and PCB 153 significantly reduced the incidence of cleft palate compared to that produced by PCB 126 alone.

Defined Experimental Mixtures. Offspring from Long-Evans rats exposed via the diet to 4 mg/kg of a reconstituted PCB mixture composed according to the congener pattern in human breast milk starting 50 days prior to mating until birth had significantly reduced weight at birth, and PND 7, 14, and 21 (Hany

et al. 1999b). This was observed in the absence of any overt signs of maternal toxicity. There were no significant treatment-related effects on number of pups/litter, number of implantation sites, or sex ratio. Arnold et al. (1999) administered a PCB mixture of congeneric composition similar to that found in Canadian breast milk to Rhesus and Cynomolgus monkeys during the first 20 weeks of life; each infant received 0.0075 mg PCBs/kg/day. There was no statistically significant difference between the control and treated groups for body weight gains throughout the study.

3.2.6.3.2 Evaluation of Animal Studies

Studies in animals suggest that primates are much more sensitive to the effects of perinatal exposure to PCBs than rodents. It also appears that unless very high doses are used, PCBs are not teratogenic in animals. Hydronephrosis was reported in mice treated with a single dose of 244 mg Aroclor 1254/kg on Gd 9 (Haake et al. 1987) and increased incidence of fetuses with cleft palate was reported by Zhao et al. (1997b) following treatment of mice with a single dose of 0.8 mg of PCB 126/kg, a dioxin-like congener. Treatment with up to 271 mg/kg of the di-*ortho*-substituted congener PCB 153 did not induce cleft palate (Zhao et al. 1997b). Susceptibility to both hydronephrosis and cleft palate formation by dioxin-like congeners is a trait that segregates with the Ah locus (Hassoun et al. 1984) and Zhao's findings are consistent with this fact.

Data in rats treated with commercial PCB mixtures showed that developmental toxicity can occur in the absence of overt signs of maternal toxicity as evidenced by reduced fetal weight and viability in a study by Spencer (1982) and reduced birth weight and postnatal growth in a study by Hany et al. (1999). It should be noted that Villaneuve et al. (1971) and Morse et al. (1996b) reported adverse developmental effects at Aroclor 1254 doses much higher than those used by Spencer (1982) in similarly designed experiments. It is possible that the Holzman strain of rats, which Spencer (1982) used, is more susceptible than the Wistar rat, which the other two studies used. Hany et al. (1999b), in addition to testing Aroclor 1254, also treated rats with a reconstituted PCB mixture of congeneric composition similar to the pattern found in human breast milk and both mixtures induced similar reductions in birth weight and in weight gain during lactation.

Linder et al. (1974) administered Aroclor 1254 or Aroclor 1260 at the same dose levels on Gd 7–15 to Sherman rats and found that Aroclor 1254 significantly reduced survival to weaning, whereas Aroclor 1260 did not. These two Aroclors differ primarily in that Aroclor 1254 lacks congeners with 7–9 chlorines (Albro et al. 1981), but further information is needed before speculating as to which PCB

congeners might or might not be responsible for neonatal lethality. Studies in rats which included *in utero* and lactational exposure to Aroclors suggest that transfer of PCBs via milk may be considerable, as decreased body weight was seen in the pups after weeks of nursing even though body weight at birth was not significantly different than unexposed rats (Collins and Capen 1980c; Goldey et al. 1995; Overmann et al. 1987). It should be kept in mind that, in general, studies in rats used fairly high doses of Aroclors to the dams such that it is reasonable to assume that breast milk had the potential to accumulate high concentrations of PCBs.

As previously mentioned, monkeys seem to be much more sensitive to developmental effects of PCBs than rodents. Reduced birth weight was reported in offspring from Rhesus monkeys treated before mating and during gestation with 0.03 mg Aroclor 1016/kg/day (Barsotti and Van Miller 1984). These monkeys also showed characteristic signs of PCB intoxication such as hyperpigmentation. Reduced mean birth weight also was reported in monkeys exposed to Aroclor 1248 (Allen and Barsotti 1976; Allen et al. 1980). Doses even smaller of Aroclor 1254 (0.005 mg/kg/day), while not significantly affecting birth weight or growth, produced clear signs of PCB intoxication manifested as skin, nail, and gum lesions (Arnold et al. 1995, 1997). In all of these studies in monkeys, maternal toxicity was also evident.

3.2.7 Genotoxic Effects

3.2.7.1 Summary

The genotoxicity of PCBs has been tested in *in vivo* and *in vitro* studies with generally negative results. End points that have been examined in these studies include gene mutations in bacteria and Chinese hamster V79 cells, chromosomal aberrations in human lymphocytes and rat and mouse bone marrow cells and spermatogonia, micronuclei in mouse bone marrow cells, and dominant lethal mutations in rat sperm cells.

3.2.7.2 *In Vivo* Studies

Available information on *in vivo* genotoxic effects of PCBs in humans is limited by confounding exposures that involved mixtures of chemicals. Chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes were increased in 32 workers involved in the manufacturing of DELOR 103 and DELOR 106 (Czechoslovakia-made PCBs with three and six chlorine atoms in the biphenyl ring, respectively) for 2–25 years (Kalina et al. 1991). These increases over control values

achieved statistical significance in workers exposed for >10 years. Although control and exposed groups were matched regarding smoking and alcohol drinking habits, the exposed workers were also exposed to benzene and formaldehyde. Another occupational study found a moderately increased incidence of chromatid exchanges in peripheral lymphocytes from a group of 12 workers who were exposed to PCBs following a fire in an electric station (Melino et al. 1992). The authors also observed that the number of chromosome breaks per cell was often higher in the exposed subjects than in unexposed controls. Additionally, lymphocytes from the exposed workers appeared to be more fragile than those from unexposed individuals. However, exposure to toxic chlorinated dioxins and/or furans generated during the fire may have occurred.

Six of 16 workers engaged in cleaning oil from old transformers showed abnormal banding pattern for *fes* oncogene-related proteins; all of the 6 were smokers (Brandt-Rauf and Niman 1988). Since none of the nonsmoking workers (six) showed this pattern, the role of PCBs, if any, in the induction of genetic abnormalities described in this study cannot be ascertained. A control unexposed group was not included in this study.

PCBs gave generally negative results in *in vivo* assays in animals (see Table 3-4). Several studies investigated genotoxic effects in rats following acute oral exposure to PCBs. Single doses #5,000 mg/kg of Aroclor 1242 administered by gavage did not induce chromosome abnormalities in bone marrow cells or spermatogonial cells of rats (Green et al. 1975a). In the same study, doses #750 mg/kg/day Aroclor 1254 administered for a 5-day period did not increase the incidence of chromosomal abnormalities in rat bone marrow cells. Dominant lethal mutations were not induced in male Osborne-Mendel rats following gavage treatment with a single dose of 625–2,500 mg/kg Aroclor 1242, or with five daily doses of 125 or 250 mg/kg Aroclor 1242 or 75–300 mg/kg Aroclor 1254 (Green et al. 1975b). Rats treated with a single dose of 1,295 mg/kg Aroclor 1254 showed evidence of DNA damage in hepatocytes 4–12 hours after treatment (Robbiano and Pino 1981). However, this damage was no longer detectable 48 hours after treatment due to DNA repair. Whysner et al. (1998) administered Aroclor 1260 as a single dose of 50 mg/kg or as a concentration of 200 ppm in the diet for 14 days. Neither the single dose nor the exposure in the diet produced detectable DNA adducts in the liver.

Two studies that examined genotoxic effects of intermediate-duration oral exposure to PCBs were identified. Rats administered 0.25–25 mg/kg/day Aroclor 1254 in their diets for #35 days had no evidence of chromosomal damage in bone marrow and spermatogonial cells (Garthoff et al. 1977). Dietary exposure to 1.25 or 5 mg/kg/day Aroclor 1254 for 70 days did not induce dominant lethal

Table 3-4. Genotoxicity of Polychlorinated Biphenyls *In Vivo*

Species (test system)	End point	Results	Reference	Polychlorinated biphenyl mixture
Mammalian cells:				
Rat spermatogonia	Chromosomal abnormalities	–	Dikshith et al. 1975	Aroclor 1254
Rat spermatogonia	Chromosomal abnormalities	–	Dikshith et al. 1975	Aroclor 1254
Rat hepatocytes	DNA fragmentation	+	Robbiano and Pino 1981	Aroclor 1254
Rat spermatogonia	Chromosomal abnormalities	–	Green et al. 1975a	Aroclor 1242
Rat bone marrow cells	Chromosomal abnormalities	–	Green et al. 1975a	Aroclor 1242
Rat bone marrow cells	Chromosomal abnormalities	–	Green et al. 1975a	Aroclor 1242
Rat sperm cells	Dominant lethal mutation	–	Green et al. 1975b	Aroclor 1242
Rat sperm cells	Dominant lethal mutation	–	Green et al. 1975b	Aroclor 1254
Mouse bone marrow cells	Micronuclei	–	Bruce and Heddle 1979	Aroclor 1254
Mouse sperm cells	Chromosomal abnormalities	–	Bruce and Heddle 1979	Aroclor 1254
Nonmammalian cells:				
Chicken embryos	Chromosomal abnormalities	–	Blazak and Marcus 1975	Aroclor 1242
Ring dove	Chromosomal abnormalities	+	Peakall et al. 1972	Aroclor 1254
Drosophila melanogaster	Chromosomal abnormalities	–	Nilsson and Ramel 1974	Clophen 30
D. melanogaster	Chromosomal abnormalities	–	Nilsson and Ramel 1974	Clophen 50

DNA = deoxyribonucleic acid; – = negative result; + = positive result

mutations in male rats (Green et al. 1975b). Lack of dominant lethality was indicated by no consistent changes in numbers of implantations and dead implantations per pregnant untreated female. The 70-day duration of the feeding study covered the spermatogenic cycle of the rat.

PCBs did not induce chromosomal aberrations when tested in *Drosophila melanogaster* (Nilsson and Ramel 1974) and chicken embryos (Blazak and Marcum 1975), although slight effects were reported in ring dove embryos (Peakall et al. 1972).

3.2.7.3 *In Vitro* Studies

PCBs are generally nongenotoxic in *in vitro* assay systems (see Table 3-5). Aroclor 1254 was not mutagenic in the bacteria *S. typhimurium* with or without exogenous metabolic activation (Bruce and Heddle 1979; Heddle and Bruce 1977; Schoeny et al. 1979). Gene mutations also were not induced by Aroclor 1242 or Clophen A60 in Chinese hamster V79 cells (Hattula 1985). Varying results were found in two assays for Aroclor 1254-induced chromosomal damage in cultured human lymphocytes, but the different findings may be the consequence of a higher test concentration in the positive study (Hoopingarner et al. 1972; Sargent et al. 1989). Aroclor 1254 induced DNA damage in rat liver cells *in vitro* as indicated by an increase in unscheduled DNA synthesis (Althaus et al. 1982), but it was not reported whether the genotoxic doses were also cytotoxic.

Chromosome breakage and micronuclei were not induced in human lymphocytes in whole blood or isolated cultures following *in vitro* exposure to the single congener 3,3'4,4'-hexaCB (PCB 77) (Belpaeme et al. 1996). In another study, PCB 77, but not Aroclor 1254, induced DNA adducts in the Hep G2 human cell line and in primary fetal rat and quail hepatocytes (Dubois et al. 1995).

3.2.7.4 Evaluation of Genotoxicity Studies

The generally negative results of *in vitro* and *in vivo* genotoxicity studies indicate that commercial PCB mixtures are not potent genotoxicants. Although PCBs have been found to be generally inactive as mutagens in *S. typhimurium* strains and in several other tests of genotoxicity that may be predictive of tumor initiation activity, *in vitro* studies with rat microsomes have indicated that metabolism of lower chlorinated congeners can lead to covalently modified macromolecules including proteins and DNA (Hayes 1987; Robertson and Gupta 2000; Silberhorn et al. 1990). Therefore, although the available data

Table 3-5. Genotoxicity of Polychlorinated Biphenyls *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Polychlorinated biphenyl mixture
Prokaryotic organisms:					
Salmonella typhimurium (plate incorporation)	Gene mutation	–	–	Schoeny et al. 1979	Aroclor 1254
S. typhimurium (plate incorporation)	Gene mutation	–	–	Heddle and Bruce 1977	Aroclor 1254
S. typhimurium (plate incorporation)	Gene mutation	–	–	Bruce and Heddle 1979	Aroclor 1254
Eukaryotic organisms:					
Chinese hamster V79 cells (tissue culture)	Gene mutation	No data	–	Hattula 1985	Aroclor 1242
Chinese hamster V79 cells (tissue culture)	Gene mutation	No data	–	Hattula 1985	Clophen A60
Human lymphocytes (tissue culture)	Chromosomal abnormalities	No data	–	Hoopingarner et al. 1972	Aroclor 1254
Rat hepatocytes (tissue culture)	DNA repair synthesis	No data	+	Althaus et al. 1982	Aroclor 1254
Human lymphocytes (tissue culture)	Chromosomal damage	No data	+	Sargent et al. 1989	Aroclor 1254

DNA = deoxyribonucleic acid; – = negative result; + = positive result

indicate that PCBs are not potent genotoxicants, there is some experimental support for the possible involvement of genotoxic mechanisms in the development of PCB-induced cancer.

3.2.8 Cancer

3.2.8.1 Summary

The carcinogenicity of PCBs in humans has been investigated in retrospective cohort mortality studies that investigated cancer in exposed workers, and in case-control studies of environmental exposure that examined associations between serum or adipose tissue levels of PCBs and occurrence of cancer. Some of the mortality studies suggest that occupational exposures to PCBs were associated with cancer at several sites, particularly the liver, biliary tract, intestines, and skin (melanoma). A report of liver cancer in *Yusho* victims appears to support the occupational hepatocarcinogenicity data. There is no clear association between occupational exposures to PCBs and cancer in other tissues, including the brain, hematopoietic, and lymphatic systems. Case-control studies of the general population are inconclusive with respect to associations between environmental exposures to PCBs and risk of breast cancer or non-Hodgkin's lymphoma, although there are preliminary indications that particular subgroups of women may be at increased risk for breast cancer. Overall, the human studies provide some evidence that PCBs are carcinogenic. In contrast to the studies in humans, there is conclusive evidence that commercial PCB mixtures are carcinogenic in animals based on induction of tumors in the liver and thyroid.

3.2.8.2 Human Studies

Most of the information on the carcinogenicity of PCBs in humans is available from cohort mortality studies of workers exposed during the manufacture and use of capacitors and case-control studies of breast cancer in women exposed to background levels in the environment.

3.2.8.2.1 Liver, Biliary Tract, and Gall Bladder

Occupational Exposure. A small excess risk of liver-related cancer was found in studies of workers from two capacitor manufacturing plants in New York and Massachusetts (Brown 1987b; Brown and Jones 1981). The workers had completed at least 3 months of employment between 1940 and 1976 in areas of the plants considered to represent the potential for the highest exposure to PCBs. Aroclor 1254 was used at first, but usage was later changed to Aroclor 1242, and finally to Aroclor 1016. Historical exposure

data were not available, but personal time-weighted average concentrations of Aroclor 1016 in 1977 ranged from 0.024 to 0.393 mg/m^3 at Plant 1 and 0.170 to 1.26 mg/m^3 at Plant 2. These data were collected shortly after changes in work practices and engineering controls were effected, and the use of PCBs was reduced to 25% of the 1976 level. The workers were also exposed to additional chemicals, including trichloroethylene, toluene, and methyl isobutyl ketone. The first study (Brown and Jones 1981) included 2,567 total subjects comprised of 968 workers (583 males, 385 females) in Plant 1 and 1,599 workers (675 males and 924 females) in Plant 2. Of these workers, 25.5 and 8.2% in Plant 1 and 19.4 and 8.9% in Plant 2 were exposed for 3–10 years and $10 years, respectively. The second study (Brown 1987b) was conducted after 7 additional years of observation on 2,588 total subjects, comprised of 981 workers (593 males, 388 females) in Plant 1 and 1,607 workers (677 males and 930 females) in Plant 2. Expected numbers of deaths were based on U.S. white male and white female cause-specific mortality rates. A slight increase in mortality due to cancer of the liver, biliary tract, or gall bladder (3 observed/1.07 expected, SMR=280, 95% CI 58–820) that was not statistically significant ($p>0.05$) was found in the first study (Brown and Jones 1981). The follow-up study (Brown 1987b) identified two additional cases of liver/biliary tract/gall bladder cancer, which made the excess statistically significant (5 observed/1.9 expected, SMR=263, CI not reported, $p<0.05$). Four of the five cancer cases occurred in women who worked in Plant 2 (4 observed/0.9 expected, SMR=444, CI not reported, $p<0.05$). Although the four cases in women occurred in the plant with the higher exposure range, there was no clear increase in the risk of liver/biliary tract/gall bladder cancer with increasing latency (time from start of exposure to end of observation) or length of employment; however, the confidence in this analysis is low due to the small numbers of deaths. Reclassification of the data showed that only two of the five deaths were from liver cancer and the remaining three were in the biliary tract (two cases) or gall bladder (one case) (Brown 1987b). Additionally, one of the two liver cancers was not a primary carcinoma as it metastasized from another site (unknown). If the metastatic liver cancer is not included in the analysis, the SMR for liver and biliary tract cancer in the whole cohort loses statistical significance (SMR=210, p$0.05) (Nicholson and Landrigan 1994). Other findings included a slight increase in rectal cancer in the first study, but not in the follow-up (see Section 3.2.8.2.3). Limitations of these studies include small number of deaths, relatively short periods of observation, and possible misclassification of the cause of death because it is not clear in every case if death was due to primary cancer of the liver, biliary tract, or gall bladder.

Liver cancer was not statistically significantly increased in a retrospective cohort mortality study of 7,075 workers from two capacitor manufacturing/repairing plants in New York (Kimbrough et al. 1999a). An unspecified number of the male workers in this study were included in the cohort studied by Brown (1987b) and Brown and Jones (1981) summarized above. The Kimbrough et al. (1999a) cohort was

comprised of hourly workers (2,984 male, 2,544 female) and salaried workers (1,078 male, 469 female) employed for at least 90 days between January 1, 1946 and June 15, 1977, and followed to death or January 31, 1993, whichever came first. Follow-up was essentially complete (98.7%), and the mean age at end of employment ranged from 31 to 35 years in the four subgroups, mean follow-up time was 31 years, mean age of all cohort members alive at the end of follow-up was 57 years, and mean age at death was 62 years. PCB exposures were predominantly to Aroclor 1254 from 1946 to 1954, Aroclor 1242 from 1954 to 1971, and Aroclor 1016 from 1971 to 1977. Exposures were qualitatively classified as high, low, or undefinable based on types and locations of jobs and some area measurements. No personal exposure monitoring was performed, although previously reported data on 290 self-selected workers from one of the plants had serum PCB levels in ranges of 6–2,530 and 1–546 ppb (ng/mL) for lower and higher chlorinated homologs, respectively (Wolff et al. 1982a). Workers with high exposure jobs had direct PCB contact (dermal and/or inhalation), workers with low exposure jobs primarily had inhalation exposure to background levels of PCBs in the plant, and workers with undefinable exposures had exposures that varied depending on where tasks were performed. Exposure-specific analysis was limited to workers with the greatest potential for exposure, (i.e., hourly workers who ever worked in a high-exposure job, worked for at least 6 months in a high-exposure job, or worked for at least 1 year in a high-exposure job). Workers who exclusively worked in high-exposure jobs could not be analyzed as a separate group due to small numbers (112 males, 12 females). SMRs were calculated for hourly and salaried workers by gender, length of employment (6 or 12 months), and latency categories (<20 or $20 years), using age-, sex-, race-, and time-specific U.S. general population rates for comparison. No statistically significant elevations in mortality from cancer of the liver and biliary passages were found in any of the groups, including in the most highly exposed workers, and SMRs for liver/biliary cancer did not statistically significantly increase with length of cumulative employment and latency. SMRs for cancer of the liver and biliary passages were <100 in the male hourly workers (2 observed/2.5 expected, SMR=80, 95% CI 10–289), female hourly workers (2 observed/2.2 expected, SMR=89, CI 11–321), and male salaried workers (1 observed/1.2 expected, SMR=79, CI 2–439), and could not be calculated in the female salaried workers due to no observed cases (0.3 expected). Other findings in this study included a suggestive increase in mortality from intestinal cancer as discussed in Section 3.2.9.2.2. A healthy worker effect was demonstrated by SMRs that were less than expected for mortality from all causes and from all cancers.

Interpretation of the Kimbrough et al. (1999a) findings is complicated by a few study limitations and biases, including some exposure misclassifications related to use of length of employment alone as a surrogate of exposure, potentially insufficient dosage differences between exposed and comparison

groups, a degree of selection bias due to the healthy worker effect that may have resulted in an underestimate of SMRs, concern for low statistical power due to small numbers of deaths from site-specific cancers in some of the groups (e.g., female hourly workers with high exposure and $20 years latency), relatively young age at follow-up, and use of the general population for comparison rather than an internal control group or a group of workers from another company. These issues are discussed by Bove et al. (1999), Frumkin and Orris (1999), and Kimbrough et al. (1999b). Some of the limitations are typical of occupational cohort mortality studies, and strengths of the study include its size (the largest cohort of PCB workers ever studied) and essentially complete follow-up of long duration. Unresolved are the puzzling Kimbrough et al. (1999a) findings of significantly lower than expected mortality from all cancers among males and the lower number of observed cases of liver and biliary tract cancers among females compared to the smaller cohort studied by Brown et al. (1997b), a subset of the same study population. These unresolved findings suggest that ascertainment of cancer mortality was not complete in this study. Overall, the study limitations are sufficient to cast doubt on the negative findings for liver and biliary tract cancer and other site-specific cancers. Increases in mortality from intestinal cancer, rectal cancer, and melanoma are summarized in Sections 3.2.8.2.2, 3.2.8.2.3, and 3.2.8.2.4, respectively.

Mortality from liver and bile duct cancer was increased (2 observed cases/0.78 expected, SIR=256, 95% CI 31–926) in a small group of workers at a Swedish capacitor manufacturing facility (Gustavsson and Hogstedt 1997; Gustavsson et al. 1986). The subjects were exposed to PCBs of 42% chlorine content for an average of 6.5 years between 1965 and 1978. Airborne PCB levels measured on one occasion in 1973 were 0.1 mg/m^3, and dermal exposure was common. The first study of these workers included 142 males and had a median latency time of 13 years (Gustavsson et al. 1986). The second study added 9 years of follow-up and included 242 males (Gustavsson and Hogstedt 1997). Although only two cases were observed in the category for liver and bile duct cancers, both cases were relatively rare bile duct types (a cholangiocarcinoma of the primary bile duct in one high-exposure worker employed for 3 years, and an adenocarcinoma of the Papilla Vaterii in one low-exposure worker employed for 9 years).

Mortality from cancers of the digestive system, which included the liver and biliary tract, was increased in a study of 544 male and 1,556 female workers involved in the manufacture of PCB-impregnated capacitors in a plant in Italy (Bertazzi et al. 1987). The workers were employed for a minimum of 1 week between 1946 and 1978 and were examined during 1946–1982. PCB mixtures containing 54% chlorine (Aroclor 1254 and Pyralene 1476) were used until 1964; these were progressively replaced by mixtures containing 42% chlorine (Pyralene 3010 and 3011) until 1970, when only Pyralene 3010 and 3011 were used. The maximum quantities of PCBs were used in 1967–1968, and the use of PCBs was abandoned

completely since 1980. Area samples taken in 1954 and 1977 showed air PCB concentrations ranging from 5.2 to 6.8 mg/m^3 (Aroclor 1254) and 0.048 to 0.275 mg/m^3 (Pyralene 3010), respectively. Concentrations of total PCBs on workers' hands in 1977 and 1982 ranged from 0.3 to 9.2 and 0.09 to 1.5 µg/cm^2, respectively. Deaths from digestive system cancers were statistically significantly increased in males when compared with national rates (6 observed/1.7 expected, SMR=346, 95% CI 141–721) and local rates (6 observed/2.2 expected, SMR=274, 95% CI 112–572). The digestive system category was not defined, but is not specific for the stomach and intestines as the six cases included cancers of the liver (one case), biliary tract (one case), and pancreas (two cases), as well as stomach (two cases). Follow-up evaluation of the cohort by Tironi et al. (1996) after an additional 9 years of latency found that mortality from digestive system cancers was still increased in comparison to local rates (10 observed/5.1 expected, SMR=195, CI 94–359), although the excess was not as high as found previously. Other findings included increased mortality from hematological neoplasms as discussed in Section 3.2.8.2.6. Limitations of the Bertazzi et al. (1978) and Tironi et al. (1996) studies include questionable grouping of digestive system cancers; small number of cases; short minimum exposure period; lack of pattern or trend when data were analyzed by duration of exposure, latency, and year of first exposure; and some cancer deaths in males with low potential for direct PCB exposure.

Mortality from cancer of the liver, biliary passages, and gall bladder was not increased in the Sinks et al. (1992) study of capacitor manufacturing workers or Loomis et al. (1997) study of electric utility workers summarized in Section 3.2.8.2.4.

Contaminated Fish Consumption. Mortality from liver cancer was not increased in the Svensson et al. (1995a) study of Swedish east coast (Baltic Sea) and west coast fisherman summarized in Section 3.2.8.2.2.

Yusho and Yu-Cheng Exposures. A retrospective study of 887 male and 874 female patients that were observed for an average of 11 years following registration as *Yusho* victims found statistically significantly ($p<0.01$) increased mortality from liver cancer in the males compared to national death rates (9 observed/1.61 expected, SMR=559, 95% CI not reported) (Kuratsune et al. 1987). Elevated mortality from liver cancer was also seen in the females, but the increase was not statistically significant (2 observed/0.66 expected, SMR=304, $p>0.05$). Comparisons based on local death rates also showed a statistically significantly increased mortality from liver cancer in the males (9 observed/2.34 expected, SMR=385, $p<0.01$) but not in females (2 observed/0.79 expected, SMR=253, $p>0.05$), as well as in males when early liver cancer cases (those occurring <9 years after poisoning) were excluded

(4 observed/1.04 expected, SMR=385, $p<0.05$). However, because the geographic distribution of liver cancer deaths was markedly uneven (there was no significant increase in one of two locations), the cancer could not be conclusively associated with *Yusho* exposure.

A retrospective mortality study of 1940 *Yu-Cheng* cases summarized in Section 3.2.8.2.6 found no statistically significantly increased mortality from cancer of the liver and intrahepatic bile ducts (Hsieh et al. 1996).

3.2.8.2.2 Gastrointestinal Tract

Occupational Exposure. Mortality from cancer of the stomach or intestines was not statistically significantly increased in the Kimbrough et al. (1999a) study of capacitor workers summarized in Section 3.2.8.2.1, although the rate for intestinal cancer (large and small intestine) was elevated and approached statistical significance (20 observed/12.7 expected, SMR=157, 95% CI 96–242) in the hourly female subgroup of workers. Most of these cancers occurred in women with $20 years of latency and the increase in this subgroup was statistically significant (SMR=189, 95% CI not reported, $p<0.05$). There was no increasing trend with length of employment and the SMR was 100 for women employed for $10 years with a latency period of $20 years (Kimbrough et al. 1999b). Comparison with the regional population resulted in a SMR which is still elevated (SMR=120, 95% CI 74–186) and similar to the SMR of 157 based on the national rates (Kimbrough et al. 1999b). Due to the small number of cases, healthy worker effect bias, and exposure misclassification bias, it is remarkable that an elevation of intestinal cancer was found among hourly women workers. However, this finding must be viewed as suggestive given the limitations of the study.

Deaths from cancers of the digestive system were statistically significantly increased in the Bertazzi et al. (1987) study of capacitor workers summarized in Section 3.2.8.2.1. This category was not specific for the stomach and intestines as it included other parts of the digestive system, including the liver and biliary tract. Of six observed deaths from digestive system cancers, one was due to hepatocellular carcinoma and another from a cancer of the biliary tract.

Mortality from cancer of the stomach or intestine was not statistically significantly increased in other studies of capacitor manufacturing workers (Brown 1987b; Brown and Jones 1981) summarized in Section 3.2.8.2.1, or in the Loomis et al. (1997) study of electric utility workers summarized in Section 3.2.8.2.4. Mortality from cancer of the digestive organs (not otherwise specified) was not

increased in the Sinks et al. (1992) study of capacitor manufacturing workers summarized in Section 3.2.8.2.4.

Contaminated Fish Consumption. Cancer incidences were studied in cohorts of fisherman from the Swedish east coast (on the Baltic Sea) (2,896 subjects) and Swedish west coast (8,477 subjects) (Svensson et al. 1995a). Both cohorts ate almost twice as much fish as the general regional populations, although intake of fatty fish was higher in the east coast fisherman (Svensson et al. 1995b). Plasma levels of PCB congeners, particularly non-*ortho* PCBs, were also higher in the east coast fisherman compared west coast fisherman and referents from both coasts; the sum of non-*ortho*, mono-*ortho*, di-*ortho*, and other congeners expressed as the TEQ was about 2 times higher in the east coast fisherman than in those from the west coast. The incidence of stomach cancer was increased in the east coast fisherman when compared with both the regional general population (Incidence Rate Ratio [IRR]=1.6, 95% CI 1.0–2.4) and the west coast fisherman (IRR=2.2, CI 1.3–3.5). Stomach cancer was not increased in the west coast fisherman when compared to the regional general population. Although the east and west coast fisherman ate almost twice as much fish as controls, and intake of fatty fish and PCBs was higher in the east coast fisherman compared to the west coast fisherman and referents from both coasts, the east coast fisherman also consumed smoked fish (a risk factor for stomach cancer) twice as often as the west coast fisherman (Svensson et al. 1995a).

Yusho and Yu-Cheng Exposures. The retrospective study *Yusho* victims summarized in Section 3.2.8.2.1 found no statistically significant ($p<0.05$) increased mortality from cancer of the stomach or esophagus (Kuratsune et al. 1987). The retrospective study of *Yu-Cheng* victims summarized in Section 3.2.8.2.6 found no statistically significantly increased mortality from cancer of the stomach or small intestine (Hsieh et al. 1996).

3.2.8.2.3 Rectum

Occupational Exposure. An elevation in rectal cancer was found in the first of two studies of two capacitor manufacturing plants in New York and Massachusetts (Brown 1987b; Brown and Jones 1981). Background information on these studies is provided in Section 3.2.8.2. Brown and Jones (1981) found that rectal cancer mortality was statistically significantly ($p<0.05$) increased in 1,309 females (3 observed/ 0.5 expected, SMR=600, 95% CI not reported) from Plant 2, but not among 675 males from Plant 2 (0 observed/0.20 expected), 924 males from Plant 1 (1 observed/0.31 expected, SMR=323, 95% CI not reported), 385 females from Plant 1 (0 observed/0.18 expected), or 2,567 total males and females from

both plants (4 observed/1.19 expected, SMR=336, 95% CI 92–860). Follow-up evaluation (Brown 1987b) of 2,588 total workers from both plants after a further 7 years of observation found no additional deaths from rectal cancer (4 observed/1.9 expected, SMR=211), and the excess in the females from Plant 2 was no longer statistically significant because of the small numbers of observed and expected cases (3 observed/0.8 expected, SMR=375, p>0.05).

There was a non-statistically significant (p>0.05) increase in rectal cancer mortality (4 observed/ 2.3 expected, SMR=169, 95% CI 46–434) in the female hourly worker subgroup of the capacitor manufacturing workers studied by Kimbrough et al. (1999a) (Section 3.2.8.2.1). Mortality from rectal cancer was not increased in the Sinks et al. (1992) study of capacitor manufacturing workers or Loomis et al. (1997) study of electric utility workers summarized in Section 3.2.8.2.4.

Contaminated Fish Consumption. Mortality from cancer of the rectum or colon was not statistically significantly increased in the Svensson et al. (1995a) study of Swedish east coast (Baltic Sea) and west coast fisherman summarized in Section 3.2.8.2.2.

Yusho and Yu-Cheng Exposures. The retrospective study *Yusho* victims summarized in Section 3.2.8.2.1 found no statistically significantly increased mortality from cancer of the rectum, sigmoid colon, and anus (Kuratsune et al. 1987).

3.2.8.2.4 Skin

Occupational Exposure. Mortality analysis of 3,588 workers (2,742 male, 846 female) employed at an Indiana capacitor manufacturing facility when PCBs were used (1957–1977) provided evidence of exposure-related malignant melanoma (NIOSH 1991; Sinks et al. 1992). The mean latency was 19.2 years (range, 0.04–32.5 years), mean duration of employment was 4.1 years (range, 1 day–20.2 years), and mean age at hire was 27 years (range, 16.8–62.6 years). Aroclor 1242 was used until 1970, and Aroclor 1016 was used subsequently. Area monitoring for PCBs in 1977 showed mean concentrations ranging from 0.016 to 0.076 mg/m^3. The workers were also exposed to various solvents (toluene, xylene, methyl ethyl ketone, trichloroethylene, and 1,1,1-trichloroethane) and unspecified metals from brazing and soldering operations. Mortality from all causes and all cancers was lower than expected, indicating a healthy worker effect. More deaths were observed than expected for malignant melanoma (8 observed/2 expected, SMR=4.1, 95% CI 1.8–8.0, p<0.01). The excess mortality from melanoma affected both men and women. All eight melanoma deaths occurred $5 years after first

employment, and three occurred in individuals who had worked for >10 years. One of the eight cases of malignant melanoma was diagnosed 2 months before starting employment and should not have been included in the analysis; the excess mortality remained when this case was excluded from analysis (SMR=3.5, 95% CI 1.4–7.3). Two other melanoma cases possibly should have been excluded from analysis due to low risk from short-term exposure of <6 months; however, PCBs are bioaccumulative and exposure may have been high. A ninth worker died with malignant melanoma listed as a contributory cause of death; this person had worked at the plant for 1 month and died 20 years after exposure. There was no clear relationship between malignant melanoma and latency or duration of employment. Analysis performed to determine if a dose-response relationship existed between average estimated cumulative PCB exposure (duration of employment multiplied by a primarily qualitative exposure intensity rating) and mortality showed no statistically significant differences in estimated exposures between the workers that died from malignant melanoma and other workers at the same plant. Other findings in this study included a non-statistically significant increase in brain cancer as discussed in Section 3.2.8.2.5. Limitations of this study include possible insensitivity of mortality as an index of risk for malignant melanoma; inability to evaluate risk of cancers with long latency periods (<10% of the person-years at risk were accumulated with $20 years of latency); insufficient monitoring data, which precluded detailed exposure weighting; and exposure intensity ratings, which may have resulted in exposure misclassification and obscured a dose-response relationship. Screening of the affected workers for malignant melanoma was recommended based on the conclusion that the workers were at excess risk (NIOSH 1990).

There were non-statistically significant (p>0.05) increases in mortality from skin melanomas in the hourly male workers (5 observed/3.8 expected, SMR=130, 95% CI 42–303), hourly female workers (3 observed/2.0 expected, SMR=144, 95% CI 30–421), and salaried male workers (4 observed/1.9 expected, SMR=210, 95% CI 57–538 in the Kimbrough et al. (1999a) study of capacitor manufacturing workers summarized in Section 3.2.8.2.1.

Mortality from malignant melanoma was not statistically significantly different than expected in the Gustavsson and Hogstedt (1997) study of capacitor manufacturing workers summarized in Section 3.2.8.2.1.

Preliminary data, reported in letters to the editor of the journal, indicated that the incidence of malignant melanoma was increased in a small group New Jersey petrochemical refinery workers who were involved in processes that used Aroclor 1254 (Bahn et al. 1976, 1977; Lawrence 1977; NIOSH 1977). Two cases

of malignant melanoma were observed in 31 men believed to have been heavily exposed to PCBs; when compared to 0.04 expected cases based on national rates, the increase was statistically significant (p=0.001). An additional malignant melanoma was observed in another group of 41 workers believed to have had less exposure. Aroclor 1254 had been used over a 9-year period ending in the late 1950s, but PCB exposure was not quantified and concurrent exposure to other potential and known carcinogens was not evaluated. Other limitations of this study include the small number of cases and cohort size, and the use of expected cancer rates based on U.S. population data rather than on local New Jersey rates.

Loomis et al. (1997) analyzed cancer mortality among 138,905 men employed as electric utility workers for at least 6 months between 1950 and 1986 at five power plants. No increases in total-cancer mortality were found when data were analyzed by total cohort, duration of employment, job category, or estimated cumulative exposure to PCBs in insulating fluids. Mortality from malignant neoplasms of the skin was not increased in the total cohort (116 observed/111.9 expected, SMR=1.04, 95% CI 0.86–1.24), although relative risk of malignant melanoma by duration of employment appeared to increase in the job category with the greatest potential for dermal exposure to PCBs (i.e., in mechanics, but not in electricians, lineman and cable splicers, or laborers and material handlers). The mortality RR for malignant melanoma in mechanics employed for >0–5 years and >5–10 years were 2.57 (95% CI 1.06–6.20, based on eight deaths) and 3.16 (95% CI 0.92–10.85, based on three deaths), respectively; analysis for >10 years duration was precluded by small number of deaths. Analysis of mortality by cumulative exposure was only performed for the total cohort (all job categories combined). Mortality from malignant melanoma in the total cohort increased with increasing cumulative exposure; the RRs relative to unexposed men were 1.23 (95% CI 0.56–2.52), 1.71 (95% CI 0.68–4.28), and 1.93 (95% CI 0.52–7.14) for men with <2000, >2000–10,000, and >10,000 hours of cumulative exposure, respectively, without consideration of latency. A latency interval of 20 years yielded RRs of 1.29 (95% CI 0.76–2.18), 2.56 (95% CI 1.09–5.97), and 4.81 (95% CI 1.49–15.50) for the same cumulative exposure levels, although the RR for the highest exposure category is based on only one death. Although mortality from melanoma was highest among workers in the job category with the greatest potential for dermal exposures, this study is limited by small numbers of subjects in the higher exposure and longer latency groups, as well as possible incomplete control of confounding due to exposure to sunlight.

Of 55 transformer workers who were exposed to Askarel PCBs (0.00001–0.012 mg/m^3) for a mean duration of 3.75 years, 2 gave a history of removal of a melanoma (type not reported) (Emmett et al. 1988a). No melanomas were reported by 56 age-matched nonexposed subjects, and the difference between the groups was not statistically significant.

Contaminated Fish Consumption. Cancer incidences were studied in the Svensson et al. (1995a) study of Swedish east coast (Baltic Sea) and west coast fisherman summarized in Section 3.2.8.2.2. When compared to the regional general populations, incidences of lip cancer were significantly increased in both the east and west coast fisherman (SIR=2.6, 95% CI 1.1–5.4 and SIR=1.9, CI 1.3–2.8, respectively), and incidences of squamous cell skin cancer were increased in the east and west coast fisherman (SIR=2.3, CI 1.5–3.5 and SIR=1.1, CI=0.9–1.4, respectively). The incidence of skin cancer in the east coast fisherman was also higher than in the west coast fisherman (SIR=1.9, CI 1.2–3.1). Mortality from skin cancer was increased in the fisherman from the west coast (SMR=3.05, CI=0.99–7.13), but not east coast (SMR=0, CI=0.00–15.4). Mortality from melanoma was not increased in either the east coast fisherman (SMR=0, CI=0.00–1.73) or west coast fisherman (SMR=0.67, CI=0.25–1.46). The investigators noted that exposure to ultraviolet (UV) radiation in sunlight is too small to explain the observed difference in skin cancer sunlight and that UV light is not a risk factor for lip cancer.

General Population Exposures. An increased annual occurrence of ocular melanoma was discerned in Ohio residents during 1967–1977 (1.09 cases/100,000 persons/year versus 0.6 in other reports), with no statistically significant difference in the number of cases reported from year to year (Davidorf and Knupp 1979). No relationship between PCB exposure and the occurrence of ocular melanoma was suggested by a crude state-wide geographic comparison, which showed that distribution of the cancer was similar in counties with and without presumed elevated exposures, as indicated by high PCB levels in fish or presence of industries that might use PCBs.

3.2.8.2.5 Brain and Central Nervous System

Occupational Exposure. Suggestive increases in mortality from brain cancer were reported in the Sinks et al. (1992) study of capacitor manufacturing workers and Loomis et al. (1997) study of electric utility workers summarized in Section 3.2.8.2.4. Sinks et al. (1992) found a non-statistically significant increase in brain cancer mortality in 3,588 male and female workers based on five cases in both sexes compared to 2.8 expected (SMR=1.8, 95% CI 0.6–4.2, p>0.05). There was no clear relationship between brain cancer and latency or duration of employment, although there was an indication that brain cancer deaths were more common among those with a longer duration of employment (three deaths occurred after $10 years). Additional analysis was performed to determine if a dose-response relationship existed between average estimated cumulative PCB exposure and mortality from brain cancer. This analysis showed no statistically significant differences in estimated exposures between the workers that died from

brain cancer and other workers at the same plant, although the estimated exposure of the brain cancer fatalities was approximately twice as high as that of the other workers.

Loomis et al. (1997) found that mortality from brain cancer was increased among mechanics who were dermally exposed to PCBs in capacitor fluids for 0–10 years (RR=1.84, 95% CI 0.90–3.78). There were no deaths from brain cancer in mechanics employed for >10 years. Mortality from brain cancer was also increased in the total cohort of electric utility workers with cumulative exposures of <2,000 hours (RR=1.61, 95% CI 0.86–3.01) and 2,000–10,000 hours (RR=1.79, 95% CI 0.81–3.95) and no latency period. The RRs of 1.6–1.8 rose to about 2.0 when a latency period of 5 years was used, but latencies of 10 and 20 years diminished or eliminated the effect. There were no deaths from brain cancer in workers in the highest cumulative exposure category (>10,000 hours). The lack of either strong or consistent associations of brain cancer with exposure, as well as the tendency for brain cancer mortality rates to decline with longer employment and greater exposure, weakens support for a causal relation.

Mortality from cancer of the brain and nervous system was not statistically significantly different than expected in Kimbrough et al. (1999a) and Gustavsson and Hogstedt (1997) retrospective studies of capacitor manufacturing workers summarized in Section 3.2.8.2.1.

3.2.8.2.6 Hematological

Occupational Exposure. Hematological cancers were increased in the Bertazzi et al. (1987) study of 544 male and 1,556 female Italian capacitor manufacturing workers summarized in Section 3.2.8.2.2. Mortality from hematological neoplasms was statistically significantly ($p<0.05$) higher than expected in the females based on local rates (4 observed/1.1 expected, SMR=377, 95% CI 115–877). All four of the hematologic neoplasms in females were associated with lymphatic tissue (three deaths from Hodgkin's disease and one death from lymphosarcoma). Mortality from hematological neoplasms was also increased in females compared to national rates (4 observed/1.5 expected, SMR=266, CI not reported), and males compared to both national rates (3 observed/0.8 expected, SMR=375, CI not reported) and local rates (3 observed/1.1 expected, SMR=263, CI not reported), but these increases were not statistically significant. Follow-up evaluation of the cohort after an additional 9 years of latency found an additional death from a hematologic neoplasm (lymphatic leukemia) in the females (no change in males), although the increase in the women was no longer statistically significant based on local rates (5 observed/3.5 expected, SMR=141, 95% CI 46–330) (Tironi et al. 1996).

Mortality from cancers of the lymphatic and hematopoietic tissues was not increased in other studies of capacitor manufacturing workers summarized in Sections 3.2.8.2.1 and 3.2.8.2.4 (Brown 1987b; Brown and Jones 1981; Gustavsson and Hogstedt 1997; Gustavsson et al. 1986; Kimbrough et al. 1999a; Sinks et al. 1992), or in the Loomis et al. (1997) study of electric utility workers summarized in Section 3.2.8.2.4.

Contaminated fish Consumption. There was no increased mortality from Hodgkin's lymphoma or non-Hodgkin's lymphoma in the Svensson et al. (1995a) study of Swedish east coast (Baltic Sea) and west coast fisherman summarized in Section 3.2.8.2.2. Mortality from multiple myeloma was increased in the fisherman from the east coast (SMR=3.08, 95% CI=1.24–6.35) and west coast (SMR=2.08, CI=0.76–4.53), as was mortality from leukemia was increased in the east coast fisherman (SMR=1.38, CI=0.45–3.22).

General Population Exposures. Two studies reported an association between risk of non-Hodgkin's lymphoma and exposure to PCBs (Hardell et al. 1996; Rothman et al. 1997). Adipose tissue concentrations of total PCBs and 34 non-coplanar congeners were compared in 27 Swedish hospital patients with non-Hodgkin's lymphoma (NHL) (B-cell type) and 17 surgical controls without malignancy (Hardell et al. 1996). Analysis of three coplanar congeners (PCB 77, 126, and 169) was performed in 20 of the cases and all 17 controls. The mean total PCB concentration, calculated as the sum of the non-coplanar congeners, was about 33% higher (p=0.06) in the cases than controls. Mean levels of 11 individual non-coplanar congeners were statistically significantly (p<0.05) increased compared to controls; the difference was most significant (p#0.01) for PCB 156 and PCB 208. Mean concentrations of the three coplanar congeners were not statistically significantly different in the cases and controls. An increased risk of NHL (OR=2.7, 95% CI 0.8–9.4]) was calculated for cases with total PCB concentrations higher than the median concentration (1,300 ng/g lipid) of the total group.

An association between serum PCBs and increased risk of NHL was found in a nested prospective case-control study of Maryland residents (Rothman et al. 1997). Serum levels of total PCBs were compared in 74 cases of NHL and 147 matched controls identified in a cohort established in 1974. The mean time to diagnosis after enrollment into the cohort was 12.1 years. The mean PCB concentration was statistically significantly higher in the cases than controls (10% increase, p=0.0014). Conditional logistic regression analysis showed that the risk of NHL increased significantly with increasing PCB serum concentrations (p for trend=0.0008); the ORs in the two highest concentration quartiles were 2.8 (95% CI 1.1–7.6) and 4.5 (95% CI 1.7–12.0). Additional analysis indicated that the effect of PCBs on risk of NHL was increased among participants who were seropositive for Epstein-Barr virus early antigen.

Yusho and Yu-Cheng Exposures. A retrospective cohort mortality study followed, 1940 *Yu-Cheng* cases (929 males, 1,011 females, >95% of all registered cases) for 12 years following exposure in 1979 (Hsieh et al. 1996). The average age of the subjects was 27 years at the beginning of the study. Mortality from Hodgkin's disease was increased in comparison to Taiwan national or local rates in the males (SMR=61.17, 95% CI 1.55–340.72 or SMR=86.45, 95% CI 2.19–481.52, respectively). There was no statistically significantly increased mortality from leukemia. The retrospective study *Yusho* victims summarized in Section 3.2.8.2.1 found no statistically significantly increased mortality from leukemia (Kuratsune et al. 1987).

3.2.8.2.7 Breast

Occupational Exposure. Mortality from breast cancer was not increased in the Brown and Jones (1981), Brown (1987b), and Kimbrough et al. (1999a) studies of capacitor manufacturing workers summarized in Section 3.2.8.2.1.

General Population Exposures. Eight case-control studies compared breast tissue concentrations of PCBs in women with breast cancer and women with benign breast disease or who died in accidents. Four of these studies found higher average levels of total PCBs or individual congeners in breast fat among the cases than in controls (Dewailly et al. 1994; Falck et al. 1992; Guttes et al. 1998; Wasserman et al. 1976). Wasserman et al. (1976) reported that the mean concentration of total PCBs in malignant breast tissue of nine Brazilian women collected after diagnosis (date not reported) was about 3 times higher ($p<0.01$) than that found in adjacent breast glandular or adipose tissue from the same women, or in normal breast tissue from five controls. Total PCB levels in breast fat were 40% higher ($p<0.02$) in 20 Connecticut patients with breast cancer compared to 20 age-matched controls who had benign breast disease (Falck et al. 1992); adipose samples were obtained near the time of diagnosis in 1987.

Dewailly et al. (1994) measured breast adipose levels of total PCBs and 10 individual congeners in Canadian women with benign breast disease (n=17), breast cancer with estrogen receptor (ER)-positive breast cancer cells (n=9), and breast cancer with ER-negative cells (n=9). Analysis near the time of diagnosis during 1991–1992 showed no statistically significant group differences in total PCBs. Mean congener concentrations in ER-negative cases were generally lower than those in control subjects, although the difference was statistically significant ($p=0.02$) only for PCB 118. ER-positive case patients, however, showed congener levels that were generally higher than controls, with the difference reaching statistical significance ($p=0.05$) for PCB 99. Guttes et al. (1998) measured concentrations of total PCBs

and 12 congeners in breast fat samples from 45 German women with breast cancer and 20 controls with benign breast disease; samples were obtained at the time of diagnosis in 1993–1994. Geometric mean levels of total PCBs were not statistically significantly different in the cases and controls after statistical adjustment for age differences. Mean concentrations of PCB 126 and PCB 153 were 25% (p=0.04) and 24% (p=0.08) higher, respectively, in the cases compared to controls.

In contrast to the findings summarized above, the four other case-control breast tissue studies found no increased levels of total PCBs or individual congeners in patients with breast cancer (Aronson et al. 2000; Liljegren et al. 1998; Mussalo-Rauhamaa et al. 1990; Unger et al. 1984). There was no statistically significant difference in mean PCB levels in breast fat from 14 newly diagnosed Danish breast cancer patients and 21 noncancer patients, or in samples taken at autopsy from groups of 18 deceased women with breast cancer and 35 deceased women without breast cancer (Unger et al. 1984). Mussalo-Rauhamaa et al. (1990) similarly found no statistically significant difference in mean concentrations of PCBs in breast fat of 44 breast cancer cases from Finland and 33 controls without cancer.

Breast adipose tissue concentrations of PCB congeners were assessed in a case-control study of 43 Swedish women with invasive breast cancer and 35 controls with benign breast disease (Liljegren et al. 1998). Total or individual levels of 36 non-coplanar congeners, or individual levels of coplanar congeners 3,3',4,4'-tetraCB (PCB 77), 3,3',4,4',5-pentaCB (PCB 126), and 3,3',4,4',5,5'-hexaCB (PCB 169), did not statistically significantly differ between cases and controls in the entire group or in subgroups of pre- and postmenopausal women. Analysis of coplanar congeners was limited to PCB 77, PCB 126, and PCB 169 in 19 cases and 19 controls. Logistic regression analysis was used to estimate risk associated with exposure to elevated tissue levels of total non-coplanar congeners, and each of the three coplanar congeners in all women, as well as subgroups who were postmenopausal, had ER-positive tumors, or were postmenopausal with ER-positive tumors. Based on age- and parity-adjusted data, increased risks of breast cancer were associated with PCB 77 (tissue concentration >4.5 ng/g lipid) in postmenopausal women (OR=5.8, 95% CI 0.8–42), women with ER-positive tumors (OR=5.0, CI 0.8–28) and postmenopausal women with ER-positive tumors (OR= 33, CI 1.8–588), and PCB 126 (>145 ng/g lipid) in women with ER-positive tumors (OR=5.1, CI 0.8–30). An OR for PCB 126 in postmenopausal ER-positive women was not calculated due to insufficient data.

Aronson et al. (2000) investigated the association between risk of breast cancer and breast adipose tissue concentrations of total PCBs or 14 individual congeners. Analyses were performed on biopsy tissue from 217 Canadian women diagnosed with breast cancer and 213 matched controls with benign breast lesions.

Mean breast fat concentrations of total PCBs and individual congeners were not statistically significantly higher in the cancer cases than in controls. Multiple logistic regression was used to calculate ORs for increasing tissue concentrations of total PCBs and individual congeners. When the whole group was adjusted for age, menopausal status, and other confounders, risk was increased for 2,3,3',4,4'-pentaCB (PCB 105) and 2,3,4,4',5-pentaCB (PCB 118). The ORs for these congeners increased linearly with tissue concentrations (p values for trend #0.01), reaching 3.17 (95% CI 1.51–6.68) for PCB 105 and 2.31 (CI 1.11–4.78) for PCB 118 in the highest concentration categories ($13 and $50 µg/kg, respectively). Risks for breast cancer were even higher among premenopausal women for PCB 105 (OR=3.91, CI 1.73–8.86) and PCB 118 (OR=2.85, CI 1.24–6.52). Risks among postmenopausal women were elevated for PCB 170 and PCB 180, but these were not clearly tissue concentration-related.

Four case-control studies used serum PCB concentrations as the marker of exposure with measurements performed after the diagnosis of breast cancer (Moysich et al. 1998, 1999b; Wolff et al. 1993; Zheng et al. 2000). Studies by Moysich et al. (1998, 1999b) were based on 154 cases of postmenopausal breast cancer and 192 matched postmenopausal controls from western New York. Based on serum congener analysis performed within 3 months of diagnosis in 1986–1991, exposure was characterized as total PCBs, total number of detected peaks, and three congener groups (less chlorinated, moderately chlorinated, and more highly chlorinated PCBs). No statistically significant differences in mean PCB concentrations were found between cases and controls in the total sample, or in subgroups of who breast-fed (85 cases, 106 controls) or never lactated (46 cases, 61 controls), using any of the measures of exposure (Moysich et al. 1998). Additionally, analyses using unconditional logistic regression showed that higher serum levels of total PCBs, moderately chlorinated congeners, more highly chlorinated congeners, or greater number of detected peaks, were not associated with increased risk of breast cancer. There was an indication of a small increase in risk for women with detectable levels of less chlorinated congeners (OR=1.66, 95% CI 1.07–2.88), and in parous women who had never lactated having higher serum levels of total PCBs (OR=2.87, CI 1.01–7.29), moderately chlorinated congeners (OR=3.57, CI 1.10–8.60), and detected congener peaks (OR=3.31, CI 1.04–11.3). Further study of the 154 cases and 192 controls investigated the association between cytochrome P-4501A1 genotype and breast cancer risk in the postmenopausal women (Moysich et al. 1999b). An increased risk of breast cancer was associated with elevated serum PCB concentrations ($3.73 ng/g of serum) among women with *CYP1A1* polymorphism, as indicated by an OR of 2.96 (95% CI 1.18–7.45) in women carrying at least one *CYP1A1* valine for isoleucine substitution allele (*Ile:Val* or *Val:Val)*, compared with women with lower serum PCB levels and who were homozygous for the isoleucine allele (*Ile:Ile*). No effect of *CYP1A1* was found among women with lower serum levels of PCBs or women homozygous for the isoleucine allele.

Zheng et al. (2000) investigated the relationship between serum PCBs and breast cancer risk in a case-control study of 475 Connecticut patients with confirmed cancer and 502 age-matched controls with benign breast diseases. Blood samples were collected at the time of recruitment in 1995–1997 and analyzed for 9 PCB congeners. There were no statistically significant differences in mean serum level of total PCBs between the cases and controls in all subjects or subgroups of cases based on stage of cancer at time of diagnosis, type of cancer treatment, type of cancer or benign breast disease, or ER status. Logistic regression analysis showed no statistically significant association between breast cancer risk (OR) and serum total PCB levels for all subjects or subgroups based on parity, lactation, or menopausal status. Additionally, mean serum levels for each of three structure-activity congener groups (potentially estrogenic, potentially antiestrogenic and immunotoxic (dioxin-like), and phenobarbital-type cytochrome P-450 (*CYP1A* and *CYP2B*) enzyme inducers) were comparable between the cases and controls, and there was no statistically significant increasing trend for risk of breast cancer with increasing serum levels of these congener groups.

Wolff et al. (1993) found that mean concentrations of total PCBs were 19% higher in the sera of 58 New York City women with breast cancer than in 171 matched cancer-free controls, but the difference only approached statistical significance (p=0.058). The blood samples were collected between 1985 and 1991 and analyzed within 6 months of cancer diagnosis. Conditional logistic regression analysis showed that the relative risk of breast cancer increased less than 2-fold for a change in serum PCB levels from 3.9 ng/mL (10th percentile) to 10.6 ng/mL (90th percentile; OR=1.70, 95% CI 0.79–3.68), and that there was no statistically significant positive trend (p=0.16) with increasing concentrations of PCBs.

Wolff et al. (2000) found a more conclusive lack of association between serum total PCBs and breast cancer in a prospective investigation nested within the same cohort from which the women in their 1993 study were selected. Cases (n=148) and individually matched controls (n=295) were identified among women whose blood had been collected at least 6 months before diagnosis in October 1994. In addition, among 84 cases and 196 controls, two or more consecutive annual blood samples were available to estimate elimination half-lives of total PCBs. Cases and controls had similar mean serum levels of PCBs, and this difference remained statistically nonsignificant when ER status of the tumors was considered. Additionally, PCB half-lives did not differ between cases and controls. Conditional logistic regression analysis showed no positive association between serum PCB levels and risk of breast cancer; although ORs were elevated in the three upper concentration quartiles relative to the lowest one, none of the ORs were statistically significant and there was no evidence of a trend (p=0.23). The risk of breast cancer was not influenced by menstrual status, lactation history, or PCB half-life.

Five other prospective studies similarly found no association between serum levels of PCBs and breast cancer incidence using blood samples collected prior to diagnosis (Dorgan et al. 1999; Helzlsouer et al. 1999; Høyer et al. 1998; Hunter et al. 1997; Krieger et al. 1994). Total plasma PCBs were determined in blood samples collected during 1989–1990 in a prospective study of the health of nurses in the United States (Hunter et al. 1997). Mean plasma levels of PCBs did not statistically significantly differ between 230 women who developed breast cancer before June 1992 and pair-matched controls who did not subsequently develop breast cancer. There was no association between plasma levels of PCBs and established or suspected risk factors for breast cancer (e.g., menopausal status, age, age at menarche, age at birth of first child, number of children, and history of lactation), nor any increase in relative risk of breast cancer with increasing concentrations of PCBs. It should be noted that the short follow-up period (not more than 3 years) could have contributed to the negative findings.

A prospective nested case-control study of blood samples collected in 1964–1971 compared serum levels of total PCBs in 150 California women (50 white, 50 black, 50 Asian) who were later diagnosed with breast cancer with levels in matched controls who did not develop breast cancer in the interval at least 6 months after the blood was drawn through the end of 1990 (Krieger et al. 1994). Serum samples were collected an average of 14 years prior to cancer diagnosis. Mean concentrations of PCBs were not statistically significantly different in cases or controls in the total group or racial/ethnic subgroups, regardless of menopausal and estrogen-receptor status. Conditional logistic regression analyses showed no statistically significant trends for increased breast cancer risk with increasing serum PCB levels or by year of diagnosis or length of follow-up.

A case-control study of 240 breast cancer patients and 477 matched controls (two controls for each case) was nested within a prospective study conducted in Denmark (Høyer et al. 1998). Blood samples were collected in 1976 and breast cancer was diagnosed during the following 17 years. Conditional logistic regression analysis indicated no increased risk of breast cancer with increasing serum levels of total PCBs. Exclusion of women who developed breast cancer within 5 years of serum sampling did not alter the results. The average amount of time between the collection of the serum sample and the diagnosis of breast cancer is unclear.

Serum PCBs were measured in blood samples collected in 1974 or 1989 in a breast cancer case-control study nested within a prospective cohort study of Washington County, Maryland residents (Helzlsouer et al. 1999). A group of 346 women who were diagnosed with breast cancer by June, 1994 (i.e., after a follow-up period of up to 20 years) were matched to 346 cancer-free controls by age, race, menopausal

status, and date of blood donation. Mean and median concentrations of total PCBs in 1974 or 1989 were not statistically significantly different in women who subsequently developed breast cancer than in controls. Logistic regression analysis showed that the risk of breast cancer did not statistically significantly increase with increasing serum levels of total PCBs measured in 1974 or 1989. Additionally, there was no statistically significantly increased risk of breast cancer associated with increasing concentrations of 26 individual congeners, or three groupings of congeners based on structure-activity considerations (potentially estrogenic, potentially antiestrogenic and immunotoxic (dioxin-like), and phenobarbital-type cytochrome P-450 (*CYP1A* and *CYP2B*) enzyme inducers). Length of follow-up, menopausal and estrogen-receptor status, lactation and birth history, and putative high-risk genotypes for detoxification enzymes such as glutathione transferase (*GSTM1*, *GSTT1*, *GSTP1*, or *COMT*) did not contribute to an increased risk of breast cancer.

The association between breast cancer and PCB exposure was evaluated in 105 cases and 208 matched controls in a prospective nested case-control study using the Columbia, Missouri breast cancer serum bank (Dorgan et al. 1999). Breast cancer was diagnosed up to 9.5 years after blood samples were obtained between 1977 and 1987. Exposure was estimated using lipid-adjusted serum levels of total PCBs and 27 individual congeners. The percent of participants with total PCBs or individual congeners above the assay detection limit was not statistically significantly higher in cases compared to controls. Conditional logistic regression analysis of the entire group showed no indication of increased relative risk of breast cancer among women with elevated serum levels of total PCBs or individual congeners. A positive association between serum PCB 138 concentration and breast cancer was suggested (p=0.07) when blood was collected close to the time of diagnosis (#2.7 years, 53 cases, 104 controls), based on RRs of 1.7 (95% CI 0.7–4.2) and 1.9 (CI 0.8–4.8) in the middle and highest concentration tertiles, respectively.

3.2.8.2.8 Other Sites

Occupational Exposure. Pancreatic cancer was increased in 1,939 males employed between 1947 and 1975 at a transformer manufacturing plant in Canada (Yassi et al. 1994). Only a very small number of transformers contained PCBs, and there was considerably more exposure to mineral oil refined predominantly from naphthenic base crudes. Therefore, unlike the typical studies of capacitor manufacturing workers who were mainly exposed to PCBs, the transformer plant workers in the Yassi et al. (1994) study were predominantly exposed to mineral oil not containing PCBs. Mortality from pancreatic cancer was statistically significantly increased. Based on 11 observed deaths, SMRs for

pancreatic cancer ranged from 2.92 (95% CI 1.17–6.01) to 12.9 (95% CI 2.59–37.7), depending on cohort definition and acceptability criteria used. The authors also reported that those who entered the cohort prior to 1960 had a higher mortality risk than those who entered later. Additionally, SMRs for pancreatic cancers were higher in the departments in which transformers were assembled than in departments in which the exposures were thought to be lower. The role of PCBs is unclear due to the exposure to other transformer chemicals and study limitations such as the fact that no medical history of the workers was provided. Wong (1995) raises serious concerns about the Yassi et al. (1994) pancreatic cancer findings. For instance, in the group with the highest SMR, three cancers were reported. One of these had worked for <1 year and had died within 1 year of leaving the plant. Another case that was "possibly" linked to employment at the plant had worked at the plant for 1 year. Thus, two of the three cases in the group with the highest SMR had neither sufficient duration of exposure nor latency for their cancers to be considered occupationally related to PCB exposure at the plant.

Kidney adenocarcinoma was found in three male public utility workers (aged 34–56) exposed to unspecified PCBs while servicing and repairing transformers for 5–14 years (Shalat et al. 1989). The workers were employed by the same company during the same period, but the total exposed population was not reported. Although kidney cancer is relatively rare in young men (range, 1.3–29.7 cases/100,000 in the age group of the subjects), an association between PCB exposure and kidney cancer cannot be demonstrated due to limitations of the study, particularly exposure to other chemicals including unspecified organic solvents and herbicides.

Mortality from pancreatic, kidney, or urinary cancer was not statistically significantly increased in other studies of capacitor manufacturing workers summarized in Sections 3.2.8.2.1 and 3.2.8.2.4 (Brown 1987b; Kimbrough et al. 1999a; Sinks et al. 1992), or in the Loomis et al. (1997) mortality study of electric utility workers summarized in Section 3.2.8.2.4.

Contaminated Fish Consumption. Mortality from pancreatic cancer was not increased in the Svensson et al. (1995a) study of Swedish east coast (Baltic Sea) and west coast fishermen summarized in Section 3.2.8.2.2.

Yusho and Yu-Cheng Exposures. The retrospective study of *Yusho* victims summarized in Section 3.2.8.2.1 found no statistically significant ($p<0.05$) increased mortality from cancer of the pancreas (Kuratsune et al. 1987.).

3.2.8.2.9 Evaluation of Human Studies

The carcinogenicity of PCBs in humans has been investigated in retrospective occupational studies that investigated cancer mortality in exposed workers, and in case-control studies of environmental exposure that examined associations between serum or adipose tissue levels of PCBs and occurrence of cancer. As discussed below and summarized in Appendix A, some of these studies provide meaningful evidence that PCBs are carcinogenic in humans.

Occupational mortality data indicate that exposures to PCBs during capacitor manufacturing and repairing were associated with cancer of the liver, biliary tract and/or gall bladder, intestinal cancer, and skin melanoma. A slight but statistically significant increase in cancer of the liver, biliary tract, and gall bladder category was found by Brown (1987b) based on a small number of deaths (five cases) in a cohort of 2,588 workers (SMR=263, $p<0.05$). Of the five deaths, four occurred in women from one plant, and two deaths were from liver, two from biliary tract, and one from gall bladder cancer. One of the two liver cancers was not a primary carcinoma as it metastasized from another site, and the SMR loses statistical significance if the metastatic liver cancer is not included in the analysis. No analysis was performed to assess risk from biliary cancer alone. Mortality from cancer of the liver/biliary tract/gall bladder was not statistically significantly increased in any of the other occupational studies of PCB workers (Bertazzi et al. 1987; Gustavsson and Hogstedt 1997; Gustavsson et al. 1986; Kimbrough et al. 1999a; Loomis et al. 1997; Sinks et al. 1992), although Bertazzi et al. (1987) did observe one death from biliary tract cancer and another from a primary liver cancer in six cases classified as digestive system cancers, and there were two deaths from relatively rare types of bile duct cancers in the small cohort of 242 workers evaluated by Gustavsson and Hogstedt (1997). Because no individual study indicated a statistically significantly increased risk of primary liver/biliary tract/gall bladder cancer, Nicholson and Landrigan (1994) combined the results from the various studies available at the time by summing observed and expected cases. Based on a total of 8 observed and 2.8 expected cases from studies of capacitor manufacturing workers from three cohorts (Bertazzi et al. 1987; Brown 1987b; Brown and Jones 1981; Gustavsson et al. 1986), statistically significant increases were found for liver/biliary tract/gall bladder (SMR=285, $p=0.008$) and for biliary tract/gall bladder separately ($p<0.05$, SMR not reported). Although the Nicholson and Landrigan (1994) analysis is based on combined results from cohorts having different durations and levels of exposure, latencies, and follow-up, and did not include data from the most recent studies (Gustavsson and Hogstedt 1997; Kimbrough et al. 1999a), it provides an indication that PCBs are associated with cancer of the liver, biliary tract, and/or gall bladder in humans. The finding for biliary cancer is particularly meaningful considering its relatively rare nature and the fact that data on liver and

biliary cancers were not reported separately in most studies. Additionally, support for the hepatocarcinogenicity of PCBs in humans is provided by data indicating that mortality from liver cancer was increased following *Yusho* exposure (Kuratsune et al. 1987).

Data suggestive of PCB-related intestinal cancer were reported in the Kimbrough et al. (1999a) mortality study of capacitor workers. Mortality from cancer of the intestines (large and small) was not statistically significantly increased in any of the groups of male or female workers in this study; however, the mortality rate for intestinal cancer in the hourly female subgroup was elevated and approached statistical significance (SMR=157, 95% CI 96–242). Additionally, most of the intestinal cancer cases (18 of 20) in this subgroup occurred in women with $20 years of latency, who had a rate that was significantly elevated (SMR=189, $p<0.05$). There was no trend for increased risk with cumulative exposure; however, there is low precision in this analysis due to a particularly small number of deaths in each exposure duration category. There was no indication of increased mortality from stomach cancer in this study, or from cancer of the intestines or stomach in other studies of PCB workers. Bertazzi et al. (1978) did report a statistically significantly increased mortality from digestive system cancers in male workers (SMR=274, $p<0.05$), but this classification included cancers of the liver, biliary tract, and pancreas as well as stomach, and no deaths from intestinal cancer were reported. Additionally, follow-up evaluation of the same cohort after an additional 9 years of latency showed that mortality from digestive system cancer was no longer statistically significantly increased. The incidence of stomach cancer was significantly elevated in Swedish fisherman that had high intake of PCBs in fish (Svensson et al. 1995a), but the effect cannot be definitely attributed to PCBs because consumption included smoked fish and PCBs were not the only contaminants in the fish.

Mortality from malignant melanoma was statistically significantly increased in one study of capacitor workers (Sinks et al. 1992). The excess mortality affected both men and women (SMR=350, $p<0.01$). Because the number of deaths was relatively small and a dose-response relationship or increase with latency could not be established, the results of this study are not conclusive. Two other studies support the skin cancer finding of Sinks et al. (1992). Bahn et al. (1976, 1977) observed two cases of malignant melanoma in 31 refinery workers believed to have been heavily exposed to PCBs (Bahn et al. 1976, 1977). Although the increase was statistically significant (p#0.001), it cannot definitely be attributed to PCBs because the workers were exposed to other chemicals in the refinery. Mortality from malignant melanoma appeared to increase with cumulative exposure and latency among electric utility power plant mechanics who were dermally exposed to PCBs in capacitor fluids (Loomis et al. 1997). Although SMRs were elevated at 2.57 (95% CI 1.06–6.20) and 3.16 (95% CI 0.92–10.85) in mechanics employed for

>0–5 years and >5–10 years, respectively, the association between malignant melanoma and exposure is unclear due to a small number of deaths, which precluded assessment of employment durations longer than 10 years and analysis by cumulative exposure and latency. Considering the limitations of the Bahn et al. (1976, 1977) and Loomis et al. (1997) studies, the apparent relationships to PCB exposure are more uncertain than in the Sinks et al. (1992) study, although the data from the three studies collectively suggest an association.

Other findings in the Sinks et al. (1992) study of capacitor manufacturing workers and Loomis et al. (1997) study of electric utility workers included slightly increased mortality from brain cancer in some subgroups. Because confidence intervals on risk ratios were broad with lower 95% limits <1.0, and there was no clear relationship between brain cancer and exposure duration, level, or latency, the association between PCBs and brain cancer is uncertain.

There is also no clear association between PCBs and hematopoietic or lymphatic cancers. Investigations of a cohort of Italian capacitor workers found statistically significantly increased mortality from hematological neoplasms in females in the first study (SMR=377, CI 115–877, $p<0.05$) (Bertazzi et al. 1987), but not upon follow-up after an additional 9 years of latency (SMR=141, CI 46–330) (Tironi et al. 1996). All of the cases of hematological neoplasms (five observed) were associated with lymphatic tissues, including three deaths from Hodgkin's disease (Hodgkin's lymphoma). Although mortality from lymphatic or hematopoietic cancers was not increased in any of the other studies of capacitor manufacturing workers, the cases of Hodgkin's disease observed by Bertazzi et al. (1987) may be consistent with the significantly increased mortality from Hodgkin's disease found in *Yu-Cheng* victims (Hsieh et al. 1996). Two background environmental exposure studies found that mean concentrations of PCBs in adipose tissue (Hardell et al. 1996) and serum (Rothman et al. 1997) were statistically significantly higher in patients with NHL than in controls without NHL. Although these studies also showed that the risk of NHL increased significantly with increasing levels of PCBs in adipose and serum, additional information is needed to conclude that the NHL is specifically due to PCBs. The absence of consistent evidence for lymphatic cancers might result from the rarity of these cancers, and not from a lack of an association between PCBs and the cancers.

Associations between exposure to PCBs and breast cancer were investigated in a few of the occupational retrospective cohort mortality studies and in a number of case-control studies of women with background environmental exposures. The occupational studies found no indications of increased mortality from breast cancer in female capacitor manufacturing workers who were mainly exposed to PCBs by the

inhalation and/or dermal routes (Brown 1987b; Brown and Jones 1981; Kimbrough et al. 1999a). The environmental exposure studies assessed relationships between breast cancer and levels of PCBs in breast fat or blood in the general population. These studies were generally conducted to investigate a hypothetical role of organochlorine compounds, including PCBs, in the development of breast cancer. In environmental case-control studies that compared breast tissue PCB concentrations in women with and without breast cancer, some reported higher levels of total PCBs and/or congeners in breast fat among cases than in controls (Dewailly et al. 1994; Falck et al. 1992; Guttes et al. 1998; Wasserman et al. 1976), whereas others found no elevated breast adipose PCB levels in breast cancer cases (Aronson et al. 2000; Liljegren et al. 1998; Mussalo-Rauhamaa et al. 1990; Unger et al. 1984). Risk analyses, performed in two of the tissue studies, suggest increased risks of breast cancer associated with increased tissue levels of some congeners in subgroups of women that were postmenopausal or had estrogen receptor-positive tumors (Aronson et al. 2000; Liljegren et al. 1998). Other case-control studies used serum PCB concentrations as the marker of exposure with blood samples taken after the diagnosis of breast cancer (Moysich et al. 1998, 1999b; Wolff et al. 1993; Zheng et al. 2000), or prospectively collected prior to diagnosis (Dorgan et al. 1999; Helzlsouer et al. 1999; Høyer et al. 1998; Hunter et al. 1997; Krieger et al. 1994; Wolff et al. 2000). None of the serum studies found significantly different mean blood levels of PCBs in breast cancer cases and controls. Additionally, logistic regression analyses showed no statistically significant associations between breast cancer risk and serum PCBs in most of the serum studies. The negative findings in the serum studies were generally not influenced by menopausal or estrogen receptor status, birth or breast-feeding history, types of congeners, and/or other contributing or confounding factors. Increased risks were associated with serum PCBs in postmenopausal women who were parous and had never breast-fed or in postmenopausal women with a putative high-risk *CYP1A1* variant genotype (Moysich et al. 1998, 1999b), but these findings are only suggestive due to small number of subjects and variance with another study (Zheng et al. 2000).

As discussed above, associations between PCBs and breast cancer have been reported in only a few of the many case-control studies. Inconsistencies in the results could be related to methodological differences in the studies. For example, most of the breast tissue studies are limited by small numbers of subjects and/or inadequate control for known breast cancer risk factors, not all of the blood studies adjusted for serum lipids or factors such as menstrual status, parity, and duration of lactation, and only some studies used congener-based exposure assessment or considered timing of exposure assessment relative to the etiology of cancer. Many of the better designed studies have been prospective, using blood samples obtained a number of years prior to the diagnosis of cancer (Dorgan et al. 1999; Helzlsouer et al. 1999; Høyer et al. 1998; Hunter et al. 1997; Krieger et al. 1994; Wolff et al. 2000), but none of the prospective studies found

a relationship between serum PCBs and breast cancer. Interpretations, however, are hampered by differences in target analytes since some studies have found associations with congeners that were not considered in larger studies due to expense of analysis. Although the overall epidemiologic evidence for an association between breast cancer and PCBs is inconclusive, there are meaningful preliminary indications that specific subgroups may be at risk.

The human studies examining the cancer causing effect of PCBs often have methodological limitations. However, the evidence, taken in totality, indicates a potential cancer causing effect for PCBs. EPA determined that the human data are inadequate, but suggestive, of carcinogenicity (IRIS 2000), and IARC (1987) concluded that the evidence for carcinogenicity to humans is limited.

3.2.8.3 Animal Studies

Reliable cancer effect levels (CELs) are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.8.3.1 Inhalation Exposure

No studies were located regarding carcinogenicity of PCBs in animals following inhalation exposure.

3.2.8.3.2 Oral Exposure

Chronic Oral Bioassays. A number of oral cancer studies of commercial PCB mixtures have been performed in animals. As summarized below, these studies demonstrate the hepatocarcinogenicity of PCBs as well indicate that the thyroid is a site of tumorigenesis.

Hepatocellular carcinomas developed in female Sherman rats fed an estimated dose of 5 mg/kg/day Aroclor 1260 (purity not reported) for .21 months (Kimbrough et al. 1975). Almost all treated rats (170 of 184) exhibited a few to multiple tan nodules on the surface of the liver and more upon sectioning. Only one control rat had gross abnormalities of the liver. Hepatocellular carcinomas were diagnosed in 14.1% (26 of 184) of the treated rats and 0.6% (1 of 173) of the controls. Neoplastic nodules were found in 84.7% (144 of 170) of the treated rats with surface nodules and in none of the controls (0 of 173). The total reported incidence of neoplastic liver lesions was 92.4% (170 of 184) in treated rats and 0.6% (1 of 173) in controls. Incidences of neoplastic lesions were not increased in tissues other than liver (all major tissues and organs were examined).

Liver tumors also developed in Sprague-Dawley rats fed an estimated average dose of 4.2 mg/kg/day Aroclor 1260 (purity not reported) for 24 months (Norback and Weltman 1985). In treated rats that survived 18 months or longer, 95.7% (45 of 47) of the females and 15.2% (7 of 46) of the males had hepatocellular carcinomas or neoplastic nodules, indicating a sex-related effect. Of the 47 treated females, 43 had trabecular carcinomas and/or adenocarcinomas, and another 2 had neoplastic nodules only. Of the 46 treated males, 2 had trabecular carcinomas and another 5 had neoplastic nodules. Incidences of hepatocellular neoplasms in control rats were 0% (0 of 32) in males and 2% (1 of 49) in females; the 1 female had a single neoplastic nodule. Hepatocellular lesions progressed as follows: centrilobular cell hypertrophy at 1 month; foci of altered cells at 3 months and areas at 6 months; neoplastic nodules at 12 months; trabecular carcinoma at 15 months; and adenocarcinoma at 24 months. The authors observed that, while the tumors met morphologic criteria for malignancy, they were relatively nonaggressive because they did not metastasize to distant organs or invade blood vessels. Mortality was not affected, probably because of the late appearance and slow growth of the tumors. Preneoplastic lesions in the biliary tract (simple cholangiomas, also referred to as bile duct hyperplasia) occurred at a higher incidence in treated males and females (14 and 21%, respectively) than in control males and females (2 and 2%, respectively).

Liver neoplastic nodules and hepatocellular carcinomas developed in 50% (63 of 126) and 48.4% (61 of 126) of male Wistar rats, respectively, that were fed Clophen A60 (60% chlorine by weight) at an estimated dosage of 5 mg/kg/day for up to 832 days (Schaeffer et al. 1984). The incidences of these lesions were significantly ($p<0.05$) higher than control values of 3.8% (5 of 131) and 0.8% (1 of 131), respectively. Combined incidences of neoplastic nodules and hepatocellular carcinomas were 98.4% (124 of 126) and 4.5% (6 of 131) in the treated and control groups, respectively. Time-dependent progression from altered foci to neoplastic nodules to hepatocellular carcinoma was observed. The Clophen A60 mixture was reported to be free of CDFs, but it is not certain whether these contaminants were absent from the mixture because no information was provided on detection limit or analytical technique, nor is it known whether and how the mixture may have been treated to remove CDFs.

In a study conducted by NCI (1978), male and female Fischer 344 rats were fed Aroclor 1254 (purity not determined) in estimated doses of 1.25, 2.5, or 5.0 mg/kg/day for 104–105 weeks. Low incidences of hepatocellular carcinomas and unspecified adenomas occurred in the middle- and high-dose groups, but in none of the control or low-dose groups, which contained 24 rats each. The incidences of combined tumors were 4.2% (1 of 24) and 12.5% (3 of 24) in the middle- and high-dose males, respectively, and 4.5% (1 of 22) and 8.3% (2 of 24) in the middle- and high-dose females, respectively. Analysis of these

results revealed no statistically significant difference between treated groups and matched controls. Re-examination and reclassification of the NCI (1978) liver data by Ward (1985) found that total tumor incidence (hepatocellular adenomas and carcinomas) was significantly increased ($p<0.05$) in the high-dose males. Tumor incidences for males in the control, low-, middle-, and high-dose groups were 0% (0 of 24), 4.2% (1 of 24), 8.3% (2 of 24), and 29.2% (7 of 24), respectively, and the response showed a significant ($p<0.01$) dose-related trend.

There were no nonhepatic tumors clearly related to Aroclor 1254 treatment in the NCI (1978) study, although adenocarcinomas in the stomach, jejunum, or cecum of two treated males (mid-dose group) and two treated females (low- and mid-dose groups), and a stomach carcinoma in one treated male (high-dose group) were found. Although their incidences were not statistically significant, the low historical incidences of these lesions suggested that they were treatment-related. Morgan et al. (1981) re-examined the NCI (1978) gastrointestinal data and found increased incidences of stomach metaplasia that were dose-related and stomach adenocarcinomas in six treated rats. When compared with incidences of stomach adenocarcinomas in historical controls (1 of 3,548), the total incidence (6 of 144) was statistically significant. This comparison may not be appropriate, however, because the Aroclor 1254-treated animals were specially examined. The investigators commented that the stomach adenocarcinoma and intestinal metaplasia appeared to be related and might have the same initiating mechanism. They concluded that Aroclor 1254 led to induction of intestinal metaplasia and probably to induction of adenocarcinoma in the glandular stomachs of Fischer 344 rats. No correlation between rats having stomach and liver lesions was found. Ward (1985), who also re-examined the NCI (1978) gastrointestinal data, noted that the metaplastic lesions were similar to those seen in monkeys, but differed in being focal and singular, while monkey lesions were diffuse. The appearance of the few metaplastic lesions in the stomachs of controls differed from those in treated rats, which resembled precancerous lesions induced by gastric carcinogens. A significant dose-related trend in combined incidences of lymphomas and leukemias in male rats also was found by NCI (1978), but incidences in each dose group were not statistically significantly different from matched controls.

In another study of Aroclor 1254 (purity not reported), no neoplastic nodules or hepatocellular carcinomas developed in small groups of Sherman rats (10 per sex) treated with estimated dietary doses as high as 72.4 mg/kg/day for 8 months (Kimbrough et al. 1972). Increased incidences of adenofibrosis of the liver were observed, but this lesion was not considered precancerous by the investigators. Sensitivity of this study is limited by the small number of animals, and the short duration may be insufficient to express possible carcinogenicity and to draw any negative conclusions.

The carcinogenicity of a lower chlorinated PCB mixture was evaluated in male Wistar rats that were fed Clophen A30 (42% chlorine by weight) in estimated dosages of 5 mg/kg/day for up to 832 days (Schaeffer et al. 1984). Liver neoplastic nodules and hepatocellular carcinomas were diagnosed in 29.2% (38 of 130) and 3.1% (4 of 130), respectively, in the treated rats compared to 4% (2 of 53) and 2% (1 of 53), respectively, in controls. The increased incidence of neoplastic nodules is statistically significant ($p<0.05$), but this pathology classification could have included nonneoplastic hyperplasia as well as benign adenomas. Combined incidences of neoplastic nodules and hepatocellular carcinomas were 7.7% (10 of 130) and 4.5% (6 of 131) in the treated and control groups, respectively.

A panel of pathologists re-evaluated seven of the PCB cancer studies in rats for the purpose of minimizing differences among studies that may have been due to the diagnostic criteria used or individual variability among pathologists (Moore et al. 1994). Also, under a new diagnostic criteria and nomenclature, lesions that had been previously diagnosed as neoplastic nodules were now classified as either hepatocellular hyperplasia or hepatocellular adenoma. A study was defined as "a protocol that examined the pathological effects associated with the chronic dietary exposure to a PCB mixture in one sex of rat." The studies re-examined were: Kimbrough et al. (1975) (Aroclor 1260), Norback and Weltman (1985) (Aroclor 1260), NCI (1978) (Aroclor 1254), and Schaeffer et al. (1984) (Clophen A30). In general, the results showed consistency in diagnoses between the original reports and the re-evaluation. One key difference was a change in some diagnoses from neoplastic nodule to focus of cellular alteration, which downgraded the finding to a nonneoplastic lesion. The results led the authors to conclude that PCBs with a 60% chlorine content consistently induce a high yield of liver tumors in rats, which supported the original findings. In addition, the reassessed results now showed that the studies in which rats were fed mixtures with 54 or 42% chlorination showed no statistically significant increases in liver tumors, and that there was no clear sensitivity differences in tumor response between males and females.

A more recent carcinogenicity study provides comparative data on the four most widely used commercial Aroclor mixtures (1016, 1242, 1254, and 1260) in rats (General Electric Co. 1997a, 1997b; Mayes et al. 1998). This is a comprehensive investigation designed to clarify carcinogenic differences in the mixtures by allowing direct comparisons of Aroclors using current tumor diagnostic criteria, and thereby address some of the limitations in previous studies and problems associated with inter-study comparisons. Groups of 50 male and 50 female Sprague-Dawley rats were fed Aroclor 1016, 1242, 1254, or 1260 in the diet for 24 months at three dose levels per compound (two for Aroclor 1242) in ranges of 2.0–11.2, 2.0–5.7, 1.0–6.1, or 1.0–5.8 mg/kg/day, respectively. One control group of 100 males and 100 females was used for the entire study (i.e., for all Aroclors). The base feed contained <0.15 ppm of PCBs

(estimated dose <0.01 mg/kg/day). The Aroclor 1016, 1242, 1254, and 1260 test mixtures contained PCDD concentrations of 0.6, 0, 20, and 0 ppb, respectively, and PCDF levels of 0.035, 2.9, 23, and 4.9 ppm, respectively. The Aroclor 1254 was treated for PCDF removal because the level was considered higher than the acceptable range. The cleanup procedure removed >99% of the PCDFs, and additionally reduced the concentration of congener 3,3',4,4',5-pentaCB (PCB 126) by approximately 35%, which was still about 2 times greater than that of "ordinary" Aroclor 1254. It was subsequently found that the tested lot of Aroclor 1254 had been made by a modified procedure that was used only in the final years of manufacture, and accounted for <1% of the total Aroclor 1254 production for the years 1958–1977 (Frame 1999).

Comprehensive histological examinations were performed on all rats in the high-dose and control groups at the end of the study (24 months), as well on animals in all groups that died prior to 24 months (Mayes et al. 1998). Evaluations of all remaining animals included the liver, brain, mammary gland, thyroid (males only), and gross lesions. Statistically significantly increased tumor incidences were found in the liver and thyroid, while significant decreases occurred in the mammary gland. The response in the liver was both Aroclor- and sex-dependent (much greater in females than males), consisted primarily of benign hepatocellular adenomas and, for females, increased with dose and followed the general incidence pattern of Aroclor 1254 > Aroclor 1260 . Aroclor 1242 > Aroclor 1016. For females exposed to Aroclor 1254, percentages with liver tumors were statistically significantly (p#0.05 or p#0.01) increased as follows: hepatocellular adenomas in all dose groups at 1.4, 2.9, and 6.1 mg/kg/day (36, 52, and 54%, respectively, vs. 1% in controls), hepatocellular carcinomas in the middle- and high-dose groups (8 and 12%, respectively, vs. 0%), and hepatocholangiomas in the middle-dose group (12 vs. 4%). For females exposed to Aroclor 1260, hepatocellular adenomas were significantly increased in all dose groups at 1.4, 2.8, and 5.8 mg/kg/day (18, 20, and 42%, respectively, vs. 1% in controls), and hepatocellular carcinomas and hepatocholangiomas were increased at the high dose (10 and 6%, respectively, vs. 0% in controls). For females exposed to Aroclor 1242, hepatocellular adenomas were increased in both dose groups at 2.8 and 5.7 mg/kg/day (20 and 24%, respectively, vs. 1% in controls). For females exposed to Aroclor 1016, hepatocellular adenomas were increased in the middle- and high-dose groups at 5.4 and 11.2 mg/kg/day (10 and 10%, respectively, vs. 0% in controls). In males, liver tumor responses were nonsignificant (p>0.05) in all groups except for increased hepatocellular adenomas at the highest dose (4.1 mg/kg/day) of Aroclor 1260 (14 vs. 4% in controls). The liver neoplasms did not adversely affect survival rates in any of the Aroclor-exposed groups.

Thyroid follicular cell adenomas were significantly (p#0.05 or p#0.01) increased in male rats in a non-dose-related and non-Aroclor-related manner (Mayes et al. 1998). Increased percentages of males with follicular cell adenomas were induced by Aroclor 1242 in both dose groups at 2.0 and 4.0 mg/kg/day (10 and 10%, respectively, vs. 1% in controls), Aroclor 1254 in all dose groups at 1.0, 2.0, and 4.3 mg/kg/day (12, 8, and 10%, respectively, vs. 1%), and Aroclor 1260 in the low and middle-dose groups at 1.0 and 2.0 mg/kg/day (12 and 8%, respectively, vs. 1%). The morphologic appearance of the thyroid tumors were reported to be characteristic of those that developed as a secondary response to chronic overstimulation by thyroid-stimulating hormone. The incidence of spontaneous mammary gland tumors (fibroadenoma, adenoma, and/or adenocarcinoma) in females was statistically significantly decreased by Aroclor 1254 at the high dose of 6.1 mg/kg/day (27 vs. 45% in controls), and Aroclor 1260 in the low and middle-dose groups of 1.4 and 2.8 mg/kg/day (35 and 36%, respectively, vs. 45% in controls). Additionally, statistically significant negative trends (p#0.05) for total mammary tumors occurred for Aroclors 1242, 1254, and 1260.

Oral carcinogenicity evaluations of commercial PCB mixtures in mice are limited to two less-than-lifetime studies that did not examine tissues other than liver (Ito et al. 1973; Kimbrough and Linder 1974). Incidences of benign hepatomas were statistically significantly increased in male Balb/cJ mice fed an estimated dose of 49.8 mg/kg/day Aroclor 1254 (purity not reported) for 11 months, but not in mice similarly treated for 6 months followed by a 5-month recovery period (Kimbrough and Linder 1974). The hepatoma incidences were 0% in two control groups (0 of 34 and 0 of 24), 45.5% (10 of 22) in the 11-month exposure group, and 4.2% (1 of 24) in the 6-month exposure group. No malignant tumors were observed, but the investigators noted that the tested mouse strain only rarely develops hepatomas spontaneously and considered the hepatomas to be potentially malignant. Additionally, adenofibrosis occurred in all of the 22 mice treated for 11 months.

Liver nodular hyperplasia and hepatocellular carcinomas were found in 58.3% (7 of 12) and 41.7% (5 of 12) of dd strain mice, respectively, that were fed an estimated dose of 65 mg/kg/day Kanechlor 500 (52–54% chlorine by weight, purity not reported) for 32 weeks (Ito et al. 1973). Neither of these incidences was significantly increased compared to control values of 0% (0 of 6), but the statistical power of this study is low due to the small number of animals, relatively short treatment duration, and no posttreatment observation period. Proliferative liver lesions were not observed in mice fed lower doses (32.5 or 13 mg/kg/day) of Kanechlor 500, or in mice similarly exposed to the lower chlorinated mixtures Kanechlor 400 (48% chlorine by weight) or Kanechlor 300 (40–42% chlorine by weight) at estimated

dietary doses of #65 mg/kg/day for 32 weeks. Limitations of this study include small numbers of animals, relatively short treatment period, and no observation period following treatment.

The EPA has derived cancer potency estimates for oral exposure to PCBs (Cogliano 1998; EPA 1996c, 2000a). Based on rat liver tumor incidence data for Aroclors 1260, 1254, 1242, and 1016 from the Mayes et al. (1998)/General Electric Co. (1997a, 1997b) study and Aroclor 1260 from the Norback and Weltman (1985) study, a range of upper-bound slope factors were calculated to represent the potency of representative classes of environmental PCB mixtures. A three-category approach is used that considers how environmental processes (partitioning, chemical transformation, and bioaccumulation) affect each exposure pathway or situation by altering the composition and cancer potential of the original PCB mixtures. The highest slope factor (2.0 per [mg/kg]/day) is for the high risk and persistent category, which is used for pathways in which environmental processes are likely to increase risk, such as food chain exposure, sediment or soil ingestion, dust or aerosol inhalation, and exposure to dioxin-like, tumor-promoting, or persistent congeners. Due to the potential for higher sensitivity in early life, the highest slope factor is also used for all early-life exposures. An intermediate slope factor (0.4 per [mg/kg]/day) is used for the low risk and persistence category, which is appropriate for exposure pathways in which environmental processes tend to decrease risk, such as drinking water ingestion of water soluble congeners, inhalation of evaporated congeners, and dermal exposure (because PCBs are incompletely absorbed through the skin). The lowest slope factor (0.07 per [mg/kg]/day) applies to the lowest risk and persistence category, and is used when congener or homologue analyses of an environmental mixture verify that congeners with more than four chlorines comprise <0.5% of total PCBs, as well as the absence of dioxin-like, tumor-promoting, and persistent congeners. For the upper slope factor of 2 per (mg/kg)/day, doses corresponding to risk levels ranging from 10^{-4} to 10^{-7} are $5x10^{-5}$ to $5x10^{-8}$ mg/kg/day, respectively, as indicated in Figure 3-2.

Tumor Promotion Studies. It is well documented that orally administered commercial PCB mixtures can promote tumors in the liver (hepatocellular carcinomas, adenomas, and neoplastic nodules) and lung (alveologenic adenomas) of rats and mice following initiation with carcinogens such as N,N'-dimethylnitrosamine (DMNA), N,N'-diethylnitrosamine, N-ethyl-N'-hydroxyethylnitrosoamine, hexachlorocyclohexanes, 2-acetylaminofluorene, and 3'-methyl-4-dimethylaminoazobenzene (Anderson et al. 1986, 1991, 1994; Beebe et al. 1993; Buchmann et al. 1991; Hirose et al. 1981; Ito et al. 1973; Kimura et al. 1976; Nishizumi 1976; Preston et al. 1981; Silberhorn et al. 1990; Tatematsu et al. 1979). These studies typically administered the tumor initiator with a proliferative stimulus (e.g., hepatotoxic

dose, partial hepatectomy, or neonatal administration) and showed effects using higher chlorinated PCB mixtures (>50% chlorine by weight, particularly Aroclors 1254 and Kanechlor 500) as the promoter.

The promoting activity of PCBs is also indicated by short-term assays in which orally administered commercial mixtures or single congeners promoted development of putative preneoplastic lesions in rat liver following induction by various initiators (Anderson et al. 1991; Buchmann et al. 1991; Deml and Oesterle 1982, 1987; Deml et al. 1983; Hemming et al. 1993; Laib et al. 1991; Oesterle and Deml 1983, 1984; Pereira et al. 1982; Preston et al. 1985; Rose et al. 1985; Sargent et al. 1991; Silberhorn et al. 1990). Enzyme-altered hepatic foci, identified by alterations in adenosine triphosphatase (ATPase), GGT, or placental glutathione S-transferase (PGST) activity, were used as markers of promoting activity. The commercial PCBs showing promotion in these studies were usually the higher-chlorinated mixtures Aroclor 1254 or Clophen A50. The congener studies have shown promoting activity with non-*ortho* PCBs such as PCB 77 and PCB 126; mono-*ortho*-substituted PCBs such as PCB 105 and PCB 114, and di-*ortho* PCBs such as PCBs 47, 49, and 153. Although structurally diverse congeners show promoting activity, the co-planar PCBs appear to be most effective. Additional information on tumor promotion by PCBs is discussed in Section 3.5.2 (Mechanisms of Toxicity).

3.2.8.3.3 Dermal Exposure

Dermal carcinogenicity studies of PCBs consist of skin tumor initiation and promotion assays. A single dose of 0.1 mg of Aroclor 1254 (purity not reported) showed no conclusive initiator activity when applied to the shaved skin of female CD-1 mice followed by promotion with the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) twice weekly for 32 weeks (DiGiovanni et al. 1977). The finding is inconclusive due to low skin papilloma incidence and lack of control mice treated with TPA alone. Aroclor 1254 (purity not reported) was not a skin tumor promoter when applied to the shaved skin of female CD-1 mice (0.1 mg/mouse, twice weekly for 30 weeks) that were initiated with dimethyl-benzanthracene (DMBA) (Berry et al. 1978, 1979), or to female HRS/J hairless mice (1 mg/mouse, twice weekly for 20 weeks) that were initiated with N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) (Poland et al. 1983). These results must be interpreted with caution since only one dose level of Aroclor 1254 was tested, and the doses may have been too low, as indicated by slight, although not statistically significant, promotion in the Poland et al. (1983) study. The initiation and promotion studies tested sufficient numbers of animals and, except as noted above, included positive and negative control groups. Pretreatment with a single topical dose of 0.1 mg of Aroclor 1254 inhibited skin tumor initiation by DMBA in female CD-1 mice by as much as 45% (Berry et al. 1979).

3.2.8.3.4 Evaluation of Animal Studies

The carcinogenicity of several commercial PCB mixtures has been evaluated in a number of chronic oral bioassays in rats. The most comprehensive and adequately performed study compared Aroclors 1016, 1242, 1254, and 1260 and found that all four mixtures induced liver tumors when fed to female Sprague-Dawley rats (General Electric Co. 1997a, 1997b; Mayes et al. 1998). Aroclor 1260 also induced liver tumors in male rats. The liver response was both Aroclor- and sex-dependent (much greater in females than males), consisted primarily of benign hepatocellular adenomas and, in females, increased with dose in the general potency pattern of Aroclor 1254 > Aroclor 1260 . Aroclor 1242 > Aroclor 1016. Previous lifetime dietary exposure studies found that commercial mixtures with 60% chlorine content (Aroclor 1260 and Clophen A60) induced liver tumors in three strains of rats (Kimbrough et al. 1975; Moore et al. 1994; Norback and Weltman 1985; Schaeffer et al. 1984), with indications of a sex-dependent response (stronger in females) in one of these studies (Norback and Weltman 1985). Many of the rat liver tumors were benign, although sequential morphologic analyses demonstrated the eventual progression of the benign liver lesions to malignant carcinomas (Norback and Weltman 1985). Lifetime carcinogenicity tests of commercial PCB mixtures containing <60% chlorine were performed in only a few studies prior to the Mayes et al. (1998) bioassay. Liver tumors were reportedly induced by Aroclor 1254 in Fischer 344 rats (NCI 1978; Ward 1985) and a 42% chlorine mixture (Clophen A30) in Wistar rats (Schaeffer et al. 1984), but re-evaluation of these studies using current diagnostic criteria showed no statistically significant increases in tumor incidences or clear sensitivity differences in tumor responses between males and females. The chronic rat studies provide a limited amount of evidence for neoplastic or preneoplastic changes in tissues other than the liver. Incidences of preneoplastic lesions in the biliary tract were increased in both sexes by exposure to Aroclor 1260 (Norback and Weltman 1985), although the response was greater in females. There was a suggestive indication of Aroclor 1254-induced precancerous intestinal metaplasia and adenocarcinomas in the stomach of rats in one study (Morgan et al. 1981; NCI 1978; Ward 1985). The preneoplastic lesions in the biliary tract and stomach have not been reported in other studies, particularly Mayes et al. (1998). Statistically significant increases in thyroid gland follicular cell adenomas were induced by Aroclors 1242, 1254, and 1260 in males, but not females (Mayes et al. 1998).

The oral carcinogenicity of commercial PCB mixtures has also been tested in mice, but these studies are limited by intermediate-duration exposures, lack of postexposure observation, and histological examinations that were limited to the liver. These studies generally indicate that less-than-lifetime dietary

exposure to commercial mixtures with 42–60% chlorine induced precancerous liver lesions (Ito et al. 1973; Kimbrough and Linder 1974; Kimbrough et al. 1972).

It is well documented that oral exposure to commercial PCBs and single congeners can promote preneoplastic lesions and tumors in the liver and lung of rats and mice following initiation with other carcinogens (Anderson et al. 1986, 1991, 1994; Beebe et al. 1993; Buchmann et al. 1991; Deml and Oesterle 1982, 1987; Deml et al. 1983; Hemming et al. 1993; Hirose et al. 1981; Ito et al. 1973; Kimura et al. 1976; Laib et al. 1991; Nishizumi 1976; Oesterle and Deml 1983, 1984; Pereira et al. 1982; Preston et al. 1981, 1985; Rose et al. 1985; Sargent et al. 1991; Silberhorn et al. 1990; Tatematsu et al. 1979). The commercial PCBs showing promotion in these studies were usually the higher-chlorinated mixtures such as Aroclor 1254. Congeners showing promoting activity are structurally diverse, although the co-planar PCBs appear to be most effective.

Several studies in which relatively low doses (0.1 mg/mouse) of Aroclor 1254 were applied to the skin of mice showed no conclusive initiation or promotion activity (Berry et al. 1978, 1979; DiGiovanni et al. 1977; Poland et al. 1983). Studies corroborating these findings on skin tumor initiation, promotion, and inhibition or evaluating the carcinogenicity of PCBs applied to the skin without initiators or promoters have not been performed.

Before the comprehensive four-Aroclor comparative carcinogenicity study was conducted by Mayes et al. (1998), only commercial PCBs mixtures with 60% chlorine had been adequately tested, and there was controversy about whether mixtures with lower chlorine content were carcinogenic. The liver and thyroid tumor results of the Mayes et al. (1998) rat study, in addition to confirming the carcinogenicity of higher chlorinated PCBs, provide compelling evidence that all commercial PCB mixtures can cause cancer in animals. The sufficiency of the evidence of carcinogenicity of PCBs in animals is recognized by both EPA (Cogliano 1998; IRIS 2000) and IARC (1987).

3.3 HEALTH EFFECTS IN WILDLIFE POTENTIALLY RELEVANT TO HUMAN HEALTH

3.3.1 Overview

The EPA's final rule strictly limiting the manufacture, processing, distribution, and use of PCBs under Section 6(e) of the Toxic Substances Control Act was promulgated in 1979 (EPA 1979a). A technical support document for the EPA rule was comprised primarily of a draft environmental impact statement that outlined the significance of the release of PCBs into the environment from both human and wildlife health perspectives (EPA 1978c). Health effects in wildlife that were cited in the support document included the following: mortality in piscivorous birds; reproductive impairment in monkeys, minks, ring doves, and American kestrels; immunotoxicity in monkeys and birds; and endocrine and neurobehavioral effects in birds. A variety of other health effects have since been evaluated in wildlife, some of which may be relevant to human health. Environmental monitoring studies have shown that PCBs are highly persistent in the environment (see Section 6.3, Environmental Fate), and therefore continue to present a potential health hazard to humans.

Wildlife may be regarded as sentinels for human health. Wildlife sentinel species data may be used for several purposes related to exposure and hazard assessment (NRC 1991; van der Schalie et al. 1999), including the following: (1) provide additional weight of evidence in a human health risk assessment; (2) act as an early warning for potential effects in humans (e.g., by identifying new locations of potential concern for human health, or identifying new end points of potential human concern not previously observed in experimental animal studies); (3) suggest potential cause-and-effect relationships for further study; (4) investigate the bioavailability of contaminants from environmental media; and (5) monitor contamination in the food web, such as during the course of remedial actions. Reviews of public health considerations regarding toxic substances (including PCBs) in the Great Lakes region have incorporated effects in wildlife in a weight-of-evidence analysis of the potential for detrimental effects in humans in the region, particularly in human populations that rely heavily on Great Lakes fish for their dietary protein (Johnson et al. 1998b, 1999).

The purpose of this section is to provide a qualitative synopsis of health effects in wildlife to address the potential concern that effects observed in wildlife that are attributable to PCB exposure may also occur in humans, and to highlight information in the wildlife database that contributes to the weight of evidence supporting the critical effects that form the basis for the chronic- and intermediate-duration oral MRLs.

A hazard identification table (Table 3-6) is provided to quickly scan the wildlife database for taxa or categories of toxicological end points that are of particular interest. Since Table 3-6 is intended for hazard identification, data concerning effects from parenteral exposures were included, as well as oral, inhalation, and dermal routes that are more directly relevant to human environmental exposures. Table 3-6 distinguishes between correlational evidence from field observations and experimental evidence. Correlational evidence from field studies inherently has multiple sources of uncertainty, many of which are controlled in experimental studies. Observations that indicate a positive relation between environmental PCB exposure (sometimes represented by PCB concentration in tissue) and an adverse health effect in free-ranging wildlife are represented in Table 3-6 as correlational field observations. Effects that were observed in experimental studies under controlled or closely monitored exposure conditions were included in the table as experimental observations. However, no entry was made in Table 3-6 for responses that were reported in an experimental study to be equivocal, ambiguous, or not statistically significant.

Several reviews of the PCB ecotoxicological literature (e.g., DOI 1986, 1996; Hansen 1987b; Safe 1994; WHO 1993) provided much of the information included in this section. Information contained in the reviews was supplemented by individual studies that were not otherwise represented, such as more recent studies. The number of sources identified for an individual Table 3-6 entry does not necessarily reflect the number of studies showing that effect for the following reasons: (1) several reviews may have reported the same results from a single study, or (2) a single source document may report effects in multiple studies, but the source is represented only once for a given entry. Information included in Table 3-6 was limited to effects in fish and birds, and in mammals that had not been bred to reduce genetic variability (e.g., Table 3-6 includes data on monkeys and minks, but excludes data on laboratory-bred strains of rats, mice, rabbits, etc.). No data concerning effects in fungi, invertebrates, microbes, or terrestrial or aquatic plants were included. Among the classes of organisms represented in Table 3-6, mustelids (primarily minks and ferrets), galliform birds (primarily domestic fowl and quail), and freshwater fish were the most frequently studied (see Table 3-6). End points that received the most attention in the wildlife toxicology literature on PCBs were mortality, reproductive, developmental, and endocrine effects, and enzyme induction. Additional categories of end points that were relatively frequently addressed were immunological, neurological/behavioral, and hepatic effects. Most of the toxicological information represented in Table 3-6 was derived from experimental studies, but the focus of some experiments was influenced by observations in earlier field studies of correlations between levels of environmental PCBs and the occurrence and/or severity of toxicological effects in wildlife.

Table 3-6. PCB Hazard Identification in Wildlife

Adverse biological effect	Wild mammals				Birds			Reptiles	Amphibians		Fish	
	Primate	Mustelid	Cetacean, pinniped	Other	Piscivore	Galliform	Other	Turtle	Frog	Toad	Freshwater	Marine
Mortality	O_{E1}^{5}	$O_{E1}^{4,5,26,32}$ $O_{E3}^{4,25,28,32}$ O_{E4}^{4}		O_{E3}^{4}	O_{E3}^{4}	O_{E1}^{5} $O_{E3}^{4,7,32}$	$O_{E3}^{4,32}$		O_{E1}^{27} O_{E3}^{32}	O_{E1}^{9} $O_{E3}^{9,32}$	$O_{E1}^{5,28}$ O_{E2}^{5} $O_{E3}^{4,32}$	O_{E3}^{4}
Systemic effects												
Respiratory		O_{E4}^{13}				O_{E3}^{32}						O_{E3}^{32}
Cardiovascular		O_{E3}^{32} O_{E4}^{24}	O_{C4}^{2}			O_{E3}^{32}						
Gastrointestinal	O_{E1}^{5} O_{E3}^{4}	O_{E1}^{5}	O_{C4}^{2}			O_{E3}^{28}						
Hematological		O_{E4}^{13}									$O_{E3}^{4,32}$	
Musculo-skeletal						O_{E3}^{32}					$O_{E3}^{4,32}$	
Hepatic	$O_{E3}^{4,28}$	O_{E1}^{5} $O_{E3}^{19,28}$ $O_{E4}^{13,24}$ $O_{E5}^{4,5}$			O_{E3}^{4}	O_{E1}^{5} O_{E2}^{5} $O_{E3}^{10,28,32}$ O_{E5}^{4}	O_{E1}^{5} O_{E3}^{4}				$O_{E3}^{4,32}$	O_{E3}^{32}
Renal		O_{E4}^{24}	O_{C4}^{2}			O_{E3}^{28}					O_{E3}^{32}	
Endocrine	O_{E3}^{28}	O_{E3}^{32} $O_{E4}^{19,24,30}$ O_{E5}^{5}	O_{E3}^{10} $O_{E4}^{3,32}$ $O_{C4}^{2,23}$		$O_{E3}^{28,32}$ O_{C4}^{3}	O_{E3}^{32}	$O_{E1}^{4,5,7,32}$ $O_{E3}^{28,32}$				$O_{E3}^{4,10}$	$O_{E3}^{3,32}$
Dermal/ ocular	O_{E1}^{5} $O_{E3}^{4,5,28}$	O_{E3}^{32}	O_{C4}^{2}								O_{E3}^{32}	
Body weight	O_{E1}^{5} $O_{E3}^{5,28}$	$O_{E1}^{5,32}$ $O_{E3}^{5,28,32}$				O_{E2}^{5}	O_{E1}^{5}			O_{E3}^{10}	$O_{E3}^{4,32}$	
Metabolic		O_{E5}^{5}					$O_{E1}^{4,32}$		O_{E3}^{9}		$O_{E3}^{4,32}$	

Table 3-6. PCB Hazard Identification in Wildlife *(continued)*

Adverse biological effect	Wild mammals				Birds			Reptiles	Amphibians		Fish	
	Primate	Mustelid	Cetacean, pinniped	Other	Piscivore	Galliform	Other	Turtle	Frog	Toad	Freshwater	Marine
Enzyme induction		O_{E1}[5] O_{E3}[28] O_{E4}[29] O_{E5}[5]				O_{E1}[5,13,28,32] O_{E2}[5,32] O_{E3}[5,10,28,32]	O_{E1}[5] O_{E2}[5] O_{E3}[4]				O_{E1}[5] O_{E3}[5]	O_{C4}[10]
Blood chemistry	O_{E1}[5]	O_{E5}[5]				O_{E3}[28]	O_{E1}[4]				O_{E3}[4,32]	
Immunological/ lymphoreticular	O_{E1}[5] O_{E3}[28]	O_{E4}[13,24]	O_{E4}[16] O_{C4}[3,10,20]		O_{C4}[31]	O_{E1}[5] O_{E3}[32]	O_{E1}[5] O_{E3}[32]				O_{E3}[18,32]	O_{E3}[10]
Neurological/ behavioral	O_{E2}[7] O_{E3}[5,7,10,16,28]	O_{E2}[10] O_{E4}[13,24]		O_{E3}[4]		O_{E3}[7,32]	O_{E3}[4,10,32]				O_{E2}[5] O_{E3}[4]	O_{E3}[32]
Reproductive	O_{E3}[4,5,10,28]	O_{E1}[4] O_{E3}[1,4,5,10,25,27,32] O_{E4}[4,12,17,24,26,32] O_{E5}[32] O_{C4}[7,11]	O_{C4}[2,3,10,32] O_{E4}[3,32]	O_{E3}[10,32]	O_{C4}[3,21]	O_{E3}[4,28,32]	O_{E1}[5] O_{E3}[4,10,28]	O_{C4}[3]			O_{E3}[10,32] O_{C4}[4]	O_{E3}[28,32] O_{C4}[4]
Developmental	O_{E3}[4,5,7,10]	O_{E3}[6,25,32,34] O_{E4}[12,24]		O_{E3}[10]	O_{E1}[5] O_{C1}[7] O_{C4}[10,32]	O_{E1}[4,5,10] O_{E3}[10,32]		O_{E4}[3]	O_{E1}[27] O_{E3}[9]	O_{E1}[9] O_{E3}[9]	O_{E3}[32] O_{C4}[32]	
Egg shell	Not relevant for wild mammals				O_{C4}[4]	O_{E3}[32]	O_{E3}[5] O_{C4}[4]		Not relevant for amphibians or fish			
Genotoxic							O_{E3}[4]					
Cancer	No cancer data											

Entry: Effect Code

O = effect was observed, as reported in the source document.

Blank = effect was either not evaluated, or evaluated but not observed (including equivocal, ambiguous, or not statistically significant responses)

Subscript: Observation Type

E = experimental observation

C = correlational field observation

PCB Exposure

1 = dioxin-like PCB congener (AhR binder; planar; chlorine para-substituted and non- or mono-*ortho*-substituted)

2 = non-dioxin-like PCB congener (poorly binds to AhR; non-planar; chlorine di-, tri-, or quatro-*ortho*-substituted)

3 = commercial PCB mixture (e.g., Aroclor 1016)

4 = "weathered" (i.e., environmentally degraded and/or metabolized) PCB mixture, usually in combination with other chemicals (e.g., PCBs in wild-caught fish)

5 = unspecified PCB

Superscript: Source Documents (including reviews of PCB toxicity in wildlife and experimental studies not otherwise represented)

1 = Backlin et al. 1998b
2 = Bergman and Olsson 1985
3 = Crisp et al. 1998
4 = DOI 1986
5 = DOI 1996
6 = EPA 1980f
7 = Giesy and Kannon 1998
8 = Geisy et al. 1994
9 = Gutleb et al. 1999
10 = Hansen 1987b
11 = Harding et al. 1999
12 = Heaton et al. 1995a
13 = Heaton et al. 1995b
14 = Hornung et al. 1998
15 = Jarman et al. 1996
16 = Johnson et al. 1998
17 = Johnson et al. 1999
18 = Jones et al. 1979
19 = Käkelä et al. 1999
20 = Kannan et al. 1993
21 = Murk et al. 1996
22 = Nisbet et al. 1996
23 = Olsson et al. 1994
24 = Restum et al. 1998
25 = Ringer et al. 1991
26 = Risebrough 1999
27 = Rosenshield et al. 1999
28 = Safe 1994
29 = Shipp et al. 1998a
30 = Shipp et al. 1998b
31 = van der Schalie et al. 1999
32 = WHO 1993
33 = Wren et al. 1987a
34 = Wren et al. 1987b

There is some question as to the relevance of experimental studies in wildlife using single congeners or well-described commercial mixtures to situations involving environmental exposures of free-ranging wildlife to weathered PCBs (i.e., PCB mixtures in environmental media, such as the water column or animal tissues, that have undergone selective environmental degradation, bioaccumulation, and/or metabolism of component PCB congeners). Reviews (Giesy et al. 1994; WHO 1993) identified the following difficulties in extrapolating from toxicity observed in wildlife experimental studies to effects expected in wildlife in the environment: (1) most of the experimental studies in fish and wildlife tested the effects of commercial mixtures of PCBs, so the identity of the particular components (or interactive sets of components) that caused the effects is not generally known; (2) tests were generally conducted in environmentally unrealistic conditions; (3) because of differences between congeners in environmental fate, bioaccumulative potential, and species-specific degree of metabolism, weathered mixtures of PCBs in various environmental compartments (e.g., the water column and animal tissues) frequently bear little resemblance to the original commercial mixture that was released into the environment; (4) PCB exposure in the environment invariably involves co-exposure to other pollutants that may interact to produce effects that were not observed under experimental conditions. For example, among mink studies, weathered total PCBs in fish were found to be more potent than commercial PCB mixtures, possibly because the weathering process selectively removed the less toxic congeners or possibly because of interactions with other contaminants (Giesy and Kannan 1998; Giesy et al. 1994).

3.3.2 Health Effects in Wildlife

Biological responses in wildlife to exposures to individual PCB congeners and commercial PCB mixtures varied widely, possibly reflecting not only variability in susceptibility among species, but also differences in mechanism of action or selective metabolism of individual congeners (DOI 1986, 1996; WHO 1993). More highly chlorinated congeners tend to bioaccumulate most readily, and PCBs tend to biomagnify in the food chain, reaching relatively high, toxic concentrations at higher trophic levels, such as in piscivorous birds (e.g., gulls, terns, and cormorants) and mammals (e.g., minks, otters, seals, and sea lions) (EPA 1978c; WHO 1993). It is generally accepted that dioxin-like PCB congeners (i.e., those that can assume a planar configuration and exhibit high affinity for the Ah receptor) are more potent toxicants than other congeners (i.e., those with multiple chlorine substitution in ring positions 2 and 6) (DOI 1996; Giesy and Kannon 1998; Giesy et al. 1994). Of interest is the observation that the patterns of toxicities in seals may be changing with apparent decreasing global burdens; certain pathological changes are now more closely associated with methyl sulfonyl metabolites of DDE and PCBs than with parent coplanar PCBs (Olsson et al. 1994). Reproductive effects in birds and piscivorous mammals appear to be Ah

receptor-mediated, since planar, dioxin-like PCB congeners are more effective in inducing these effects than non-dioxin-like congeners (Giesy and Kannan 1998). In a comprehensive review of the literature concerning the ecotoxicology of planar PCBs, DOI (1996) concluded that the chinook salmon, domestic chicken, mink, and Rhesus macaque were among the most sensitive species to effects from planar PCB exposure.

In aquatic organisms including fish, PCB toxicity was enhanced by flow-through experimental conditions as compared to static exposure conditions, and commercial Aroclor mixtures with moderate chlorine content were generally more toxic than commercial mixtures with low or high percentage chlorination (WHO 1993). Fish in early life stages were more vulnerable than adults to PCB toxicity (WHO 1993). In birds, acute toxicity in experiments was generally positively related to degree of chlorination of the commercial mixture (WHO 1993). Avian reproduction was impaired primarily due to decreased egg hatchability and increased embryotoxicity (WHO 1993). Available evidence indicates that PCBs do not directly affect egg shell thickness in birds, but may indirectly affect egg shells by decreasing food consumption and thereby reducing body weight (WHO 1993). PCBs are ubiquitous and continuously circulating in the global environment, and appear to be gradually redistributing toward the marine environment (WHO 1993). For this reason, and because marine mammals are near the top of the food chain, piscivorous marine mammals are regarded as potentially the most sensitive wildlife receptors to PCB exposure (DOI 1996; WHO 1993). Field studies suggested, and subsequent experimental studies confirmed, that accumulated PCBs impair pinniped (e.g., seals and sea lions) reproduction by preventing implantation of the embryo; whether this effect is caused by endocrine disruption remains unresolved (WHO 1993). The endocrine disruptive potential of PCBs and other persistent and bioaccumulative pollutants has been critically reviewed in the literature (e.g., Crisp et al. 1998; DeRosa et al. 1998; Risebrough 1999); the wildlife toxicology database summarized in Table 3-6 indicates that PCBs have induced endocrine-related effects in a variety of taxa.

Of particular interest are PCB-induced effects in wildlife that contribute to the weight of evidence supporting the oral MRL derivations, including neurological/behavioral, immunological, and dermal effects. The intermediate-duration MRL is based on neurodevelopmental alterations in infant Rhesus monkeys that were postnatally fed a constituted mixture of PCB congeners analogous to those found in human breast milk. The chronic-duration MRL is based on immunological and dermal/ocular effects in Rhesus monkeys resulting from long-term oral exposure to Aroclor 1254 (see Section 2.3, Relevance to Public Health and Appendix A for further details concerning MRL rationale and derivations). Effects that

occurred in monkeys at doses proximate to the LOAELs used to derive the MRLs included decreased conception and fetal mortality.

Effects in wildlife that are potentially related to neurological impairment included alterations in central nervous system neurotransmitter levels, retarded learning, increased activity, and behavioral changes. Significantly reduced dopamine levels were observed in certain regions of the brain in adult pigtailed macaques provided Aroclor 1016 or Aroclor 1260 orally at 0.8, 1.6, or 3.2 mg/kg/day for 20 weeks; reduced dopamine levels persisted after termination of exposure (Geisy and Kannon 1998; Safe 1994). Offspring of Rhesus monkeys provided Aroclor 1248 in the diet at 0.5–2.5 mg/kg before and during gestation showed hyperactivity and other behavioral deficits (Geisy and Kannon 1998; Hansen 1987). "Long-term neurobehavioral changes" were seen in monkeys provided an unspecified PCB mixture (DOI 1996). Two-and-a-half and 5-year-old monkeys exhibited retarded learning and inefficient response behavior following a 20-week oral exposure to a PCB mixture immediately after birth (Johnson et al. 1998). Similarly, retarded learning, increased locomotor activity, impaired discrimination reversal learning, and increased hyperactivity were observed in monkeys provided Aroclor 1248 for an unspecified duration (Safe 1994). Brain catecholamine levels were altered in minks exposed (by an unreported route and duration) to PCB 136 (Hansen 1987). Minks provided diets of carp containing weathered PCBs for up to 182 days showed listlessness and nervousness, as well as anorexia, hindlimb paralysis, and sporadic seizures prior to death (Heaton et al. 1995b). Brain weight was significantly reduced in F1 adult female minks exposed to weathered PCBs (in carp) *in utero*, during lactation, and through the diet until 1.5–14 months postpartum (Restum et al. 1998). Significantly reduced sleeping times were observed in white-footed mice and raccoons provided diets containing 25–100 ppm Aroclor 1254 for up to 3 weeks (DOI 1986).

Suppressed avoidance response was observed in Japanese quail fed a diet containing 200 µg Aroclor 1254/g diet for 8 days (Geisy and Kannon 1998). Doves provided an unspecified Aroclor mixture showed altered brain catecholamine levels (Hansen 1987). Altered courtship, reproductive, and nesting behavior were seen in mourning doves at 14–44 days after termination of a 6-week dietary exposure to up to 40 ppm Aroclor 1254 (DOI 1986; WHO 1993). Decreased parental attentiveness was seen in ring doves provided Aroclor 1254 at 10 mg/kg diet (WHO 1993). Nest-building activity was reduced in pigeons orally dosed with 15 mg Aroclor 1254/day by gelatin capsule throughout a courtship cycle (WHO 1993). Avoidance response was significantly reduced in Japanese quail following dietary exposure to 200 ppm Aroclor 1254 (unspecified duration), compared to pre-exposure response levels, and persisted for 6 days after exposure (WHO 1993). Increased migratory restlessness was observed in

European robins and redstarts provided diets of mealworms containing Clophen A50 for 11–13 days (WHO 1993).

Guppies appeared sluggish and uncoordinated after consuming diets containing up to 150 mg PCB 133 or PCB 197/kg diet for up to 247 days, or 550–1,400 mg/kg diet for 65 days (DOI 1996). Poor muscle coordination, tetany, and lateral or ventral caudal flexion were observed in salmon and trout after 1 week of dietary exposure to unspecified PCB mixtures (DOI 1986). Whole-brain noradrenalin amd dopamine levels were significantly reduced and swimming activity was increased in Gulf killifish exposed to 4 mg Aroclor 1242/L for 24 hours; increased swimming activity persisted for 2 days after exposure (WHO 1993).

Positive findings in wild mammals, birds, or fish that contribute to the weight of evidence for immunological effects included morphological changes in organs related to the immune system, as well as functional impairment of humoral- and cell-mediated immune responses. Reduced antibody production in response to SRBC erythrocyte challenge was observed in monkeys exposed to Aroclor 1254 and Kanechlor 400 (Safe 1994). Absolute and relative spleen weights were increased in female minks fed diets containing 1 ppm total weathered PCBs (in carp) for approximately 6 months compared to a control group; no such changes were observed in males (Restum et al. 1998). Increased disease susceptibility in California sea lions has been positively associated with tissue PCB residue (Hansen 1987b). Impaired natural killer cell activity and T-lymphocyte function were observed in harbor seals fed diets of Baltic Sea herring containing relatively high levels of organochlorine-compounds, including PCBs, compared to seals fed diets of fish with lower levels of contamination (Johnson et al. 1998). High blubber PCB levels (94 to 670 µg/g) were observed in a population of western Mediterranean striped dolphins affected by a mobillivirus epizootic (Kannan et al. 1993).

In a survey of herring gulls and Caspian terns (piscivorous birds) in the Great Lakes region, suppression of T-cell-mediated immunity was associated with level of prenatal exposure to unspecified PCBs (van der Schalie et al. 1999). Splenic atrophy was observed in groups of cockerels fed diets containing 400 mg/kg Phenochlor DP6, Clophen A60, or Aroclor 1260 for 60 days (WHO 1993). PCB-induced atrophy of lymphoid tissues in chickens and pheasants and increased susceptibility of ducklings to hepatitis virus have been associated with the immunosuppressive effect of PCBs (WHO 1993). Thymic involution and edema were observed in 1-day-old domestic chickens fed diets containing 400 mg/kg PCB 169 for 21 days (DOI 1996). A lymphoid depletion of the spleen was observed in nestling American kestrels administered daily oral doses of 50 µg/kg PCB 126 for 10 days (DOI 1996).

In channel catfish, 100% mortality was observed in an immunized group that was intraperitoneally injected with 70 mg/kg Aroclor 1232 and then challenged with the virulent bacterium *Aeromonas hydrophila*, while an immunized control group had no mortality. The PCB-treated group also showed significantly decreased serum β-globulin levels, slightly elevated serum α-globulin levels, and decreased peritoneal macrophage activity compared to the control group (Jones et al. 1979). Rainbow trout showed a reduction in the lymphatic elements of the spleen after dietary exposure to 10 or 100 mg/kg Aroclor 1254 for 330 days (WHO 1993). Increased disease susceptibility was observed in pinfish and spot fish (marine/estuarine species) exposed to Aroclor 1254 at concentrations as low as 0.005 ppm (Hansen 1987b).

Wildlife findings that contribute to the weight of evidence for dermal/ocular effects include dermal changes in several taxa. Dose- and time-dependent increases in chloracne and histological changes in the sebaceous glands were observed in Rhesus macaques fed diets containing 0.3 to 3.0 ppm PCB 77 for 1 to 6 months (DOI 1996). Scaly skin, hair loss, and abnormal nail growth were observed in cotton top marmoset monkeys orally administered 0.1 to 3.0 mg PCB 77/kg body weight twice/week for 18–28 weeks (DOI 1996). Enlarged, thickened, and deformed toe nails, hyperkeratosis at the junction of the skin and sponchium, and dysplasia of the root and matrix of the nail were observed in ferrets fed a diet containing 20 ppm Aroclor 1242 for 8 months; Aroclor 1016 similarly administered did not cause these effects (WHO 1993). Bilateral epidermal thinning, hyperkeratosis, cystic dilations of hair follicles, and deformations and fractures of the claws were observed in grey seals of the Baltic Sea suspected of having significant exposure to weathered PCBs (Bergman and Olsson 1985). Flagfish (*Jordanella floridae*) exposed to water concentrations of 5.1 and 18 μg Aroclor 1248/L "almost completely lost their fins and tails", while sheepshead minnow fry exposed to 0.1–10 μg/L showed increased fin rot (WHO 1993).

Regarding the weight of evidence for reproductive and developmental toxicity, embryo/fetal loss is one effect among a suite of developmental effects observed repeatedly in Great Lakes wildlife that have been characterized as the Great Lakes embryo mortality, edema, and deformity syndrome (GLEMEDs syndrome) (Giesy et al. 1994; Hansen 1987b). The wildlife database outlined in Table 3-6 includes observations of increased postimplantation embryo/fetal loss in several taxa (e.g., nonhuman primates and mustelids), as well as additional effects that may be indicative of PCB-induced embryo/fetal death (e.g., reduced egg hatchability in bird and fish eggs, and reduced numbers of live births in mammals).

In summary, the wildlife toxicity database for PCBs summarized in Table 3-6 contributes to the weight of evidence supporting the critical health effects used in the MRL derivations (i.e., neurological/behavioral,

immunological, and dermal/ocular effects), as well as other PCB-induced effects that are particularly relevant to human health (e.g., reproductive and developmental toxicity).

3.4 TOXICOKINETICS

Although most toxicological data reviewed in this profile have been obtained from studies in which PCB mixtures were used, Section 3.4.3 (Metabolism) in particular, contains descriptions of studies in which individual PCB congeners were used. This supplemental information is considered necessary since most of the current knowledge regarding biotransformation of chlorinated biphenyls in experimental animals has been derived from such studies. Table 4-2 lists the IUPAC number of the congeners and the corresponding chlorine substitution.

Data regarding toxicokinetics of PCBs in humans are limited to information derived from cases of ingestion of food contaminated with PCBs and cases of occupational exposure by the inhalation and dermal routes. Humans can absorb PCBs by the inhalation, oral, and dermal routes of exposure. PCBs, when administered orally, are well absorbed by experimental animals, but they are absorbed less efficiently when administered by the dermal route. Inhalation absorption data are insufficient for estimating absorption rates. In the gastrointestinal tract, PCBs are absorbed on a congener specific basis by passive diffusion. A high diffusion gradient and nearly complete absorption occurs when the PCB level in the gut contents (lipid basis) is much greater than the concentration in serum lipids. The predominant PCB carriers in human plasma are in the lipoprotein fraction. Due to their lipophilic nature, PCBs, especially the highly chlorinated congeners, tend to accumulate in lipid-rich tissues. Greater relative amounts of PCBs are usually found in the liver, adipose, skin, and breast milk. PCBs are metabolized by the microsomal monooxygenase system catalyzed by cytochrome P-450 to polar metabolites that can undergo conjugation with glutathione and glucuronic acid. State of the art PCB exposure assessment utilizing human serum, milk, and/or tissues should not only include congener specific PCB analysis, but also analyze persistent PCB metabolites. Since certain hydroxylated and methylsulfonyl ($MeSO_2$) PCB metabolites are present in some cases at levels higher than their respective parent compounds, it is necessary to further investigate the potential biological and/or toxicological activities of these persistent metabolites. The major routes of excretion of PCBs are fecal and, especially for metabolites, urinary. Mainly metabolites are found in urine and bile, although small amounts of parent compound may appear in the feces. Some PCB congeners are relatively poorly metabolized and thus can remain in the body for long periods of time (months to years). A flow-limited pharmacokinetic model was constructed to describe disposition of some PCB congeners in adults of various animal

species. In general, the model predicted the experimental data well, although some deviations were apparent. Knowledge of the metabolic rates for PCBs is crucial for meaningful interpretation of data. Enzyme induction over long-term occupational and/or environmental exposure can render some PCBs less persistent in exposed humans than in the general population.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Inhalation exposure is considered to be a major route of occupational exposure to PCBs (Wolff 1985). Indirect evidence of absorption of PCBs by this route in humans is based on the fact that individual congeners have been detected in tissues and body fluids of subjects exposed in occupational settings where air concentrations have also been measured. From data summarized by Wolff (1985), a maximum of 80% of the levels commonly seen in adipose tissue of exposed capacitor workers may have been absorbed by the inhalation route. A maximum of 20% would have been derived from dermal or oral exposure. Exposure to PCBs in air was positively related to mean serum PCB levels in subjects involved in clean-up operations following a PCB transformer fire (Fitzgerald et al. 1986); the relative contribution of the dermal route was not determined. Duarte-Davidson and Jones (1994) estimated that the average total background PCB exposure for the contemporary UK population was 0.53 µg/person/day, with food consumption accounting for 97% of the total PCB exposure, air contributing 3.4%, and water only 0.04%. 2,4,4'-TriCB (PCB 28) was the most abundant congener detected in air samples and accounted for 3.7% of the total exposure to this congener. More highly chlorinated congeners, such as PCB 180 were detected at lower levels in air, with air borne exposure accounting for only 1.7% of the total daily exposure to this congener. Further information regarding tissue levels in occupationally-exposed subjects can be found in Section 3.4.2.

Information regarding absorption of PCBs in animals following inhalation exposure is limited. Male rats were exposed (whole body) to an aerosol of a PCB mixture, Pydraul A200 (42% chlorine), at a concentration of 30 g/m^3 (0.5–3 µm particle diameter) for #2 hours (Benthe et al. 1972). After a 15-minute exposure, the PCB concentration in the liver was . 40 µg/g tissue, and reached a maximum of 70 µg/g after 2 hours of exposure. These results provide qualitative information regarding absorption of this specific PCB mixture, but the data were not sufficient for estimating the amount or rate of absorption. It must be also mentioned that since exposure was not nose-only, the dermal route may have contributed to absorption.

A recent study in ferrets by Apfelbach et al. (1998) reported for the first time that the olfactory system may be a potentially significant portal for the entry of airborne PCBs. Ferrets were exposed for 5 years to low levels of PCBs (total PCBs, 260 ng/m^3 air) in the ambient air of an animal care room which had PCB containing sealants. Tetra-chlorinated PCBs dominated the congener profile of ambient air, with PCB 52 being found at the highest concentration. The PCB congener pattern in the olfactory bulbs resembled that found in the ambient air, with the less chlorinated, more volatile PCBs (52) being retained at the higher levels. In contrast, the congener profile in adipose tissue resembles that of most exposed or unexposed animals, with hexa- and hepta-substituted congeners being the major congeners present. The olfactory bulbs of the exposed animals had the highest total PCB concentration (642 ng/g lipids), while the liver, adipose tissue, and brain had levels of 202, 303, and 170 ng/g lipids, respectively. The data suggest that inhaled PCBs pass into the dentrites of olfactory sensory neurons and are transported via olfactory axons directly to the bulbs where they accumulate. While the olfactory system appears to be a significant site for the disposition of airborne PCBs, further studies are needed to confirm this observation and assess whether greater disposition in the brain is associated with inhalation exposure.

3.4.1.2 Oral Exposure

Oral exposure through consumption of contaminated food is presumed to be the major route of exposure to PCB mixtures for the general population (Duarte-Davidson and Jones 1994; Hansen 1999). Furthermore, oral exposure through ingestion of contaminated water or soil represents a possible additional source of exposure for populations in the vicinity of hazardous waste sites. Duarte-Davidson and Jones (1994) estimated that the average total PCB exposure for the contemporary UK population was 0.53 µg/person/day, with food consumption accounting for 97% of the total PCB exposure, air contributing 3.4%, and water only 0.04%. PCB contaminated fish, milk and dairy products, vegetables, and meat and animal fat were estimated to account for 32, 26, 18, and 16% of the respective exposure. The congener pattern for different food products varied, with vegetables accounting for a major part of the intake of lower chlorinated PCB congeners, while fatty foods, such as fish, dairy products, and meat, played a greater role with exposure to higher chlorinated congeners. For example, vegetables accounted for 78% of the total dietary exposure to PCB 28 and only 0.2% of the exposure to PCB 180. In contrast, freshwater fish account for 1.2 and 27% of the total dietary exposure to PCBs 28 and 180, respectively.

Direct evidence of absorption of PCBs in humans after oral exposure was provided in a study in which a volunteer ingested 329 µg of a ^{13}C-PCB mixture/kg body weight in a single dose dissolved in edible oil (Buhler et al. 1988). The PCB mixture, which was prepared by the investigators, contained 54% chlorine

(mainly penta-, hexa-, and heptachlorobiphenyls). Use of ^{13}C-PCBs allowed the investigators to distinguish between the administered PCBs and ^{12}C-PCBs already present in the body from diet or other exposure. Blood samples obtained during a period of 260 days after dosing revealed the presence of mostly penta- and hexachlorobiphenyls and smaller amounts of heptachlorobiphenyls. From data presented in the report, it appears that the maximum concentration in blood was reached within 2 days of dosing (the first time point examined). Concentrations of PCBs in whole blood declined rapidly, but strong fluctuations were apparent. This was attributed to changes in blood lipids, which depended on factors such as diet, physical activity, and time of day. Also, additional exposure is also possible since diet was unrestricted and ^{12}C-PCB was more than the administered ^{13}C-PCB. The investigators estimated that an intake of 26 µg/kg of PCB 153 would lead to a total concentration in whole blood of 0.5 ppb 1 month later.

A more recent study in a 19-week-old nursing infant provided quantitative data on absorption (McLachlan 1993). Absorption was estimated as the difference between ingestion and the amount of PCBs found in the feces over a period of 12 days. The mother was 32 years old and nursing for the first time. Several PCB congeners were determined in the milk: 2,2N,4,4N,5-pentaCB (PCB 99), 2,2N,4,4N,5,5N-hexaCB (PCB 153), 2,2N,3,4,4N,5N-hexaCB (PCB 138), and 2,2N,3,4,4N,5,5N-heptaCB (PCB 180). The percentage of dose absorbed was estimated at 96–98% after corrections were made for background levels in the diapers. Similar results were observed in a group of four nursing infants where absorption of 56 PCB congeners in milk was measured over two 48-hour periods, 1–3 months apart (Dahl et al. 1995). Absorption of the coplanar congeners 126 and 169 was estimated to be from 93 to 100%, while the absorption of PCB 77 ranged from 71 to 98%. Absorption of non-coplanar tetra- and higher chlorinated congeners was from 90–100%, while absorption of trichlorinated congeners was 60–98%. However, the authors noted that it was difficult to draw conclusions on the absorption of trichlorinated PCBs due to their low levels and the analytical methodology. The primipara mother's milk had the highest levels of generally all PCBs, and the level in milk generally decreased with months of nursing. Absorption of PCBs was unaffected by the age of the infant (1–6 months).

Indirect evidence of absorption results from studies regarding ingestion of contaminated food by the general population. Elevated levels of PCBs were found in the serum and breast milk of women who ate PCB-contaminated fish from Lake Michigan (Schwartz et al. 1983). Blood levels of PCBs were positively correlated with the amount of fish consumed. Two volunteers who consumed a total of 0.181 and 0.128 mg, respectively, of PCBs (mixture of 42, 48, 54, and 60% chlorine content) in contaminated fish showed a maximum 52–60% increase (2.5–4.0 and 2.3–3.5 ppb) in blood levels of total

PCBs . 5 hours after ingesting the meal (Kuwabara et al. 1979). The concentration of PCBs in blood returned to premeal levels 17 hours later. Levels of PCBs in adipose tissues were not determined.

Schlummer et al. (1998), used a mass balance approach to assess the gastrointestinal absorption of PCBs from food in seven individuals, 24–81 years of age, with different contaminant body burdens (Table 3-7). The net absorption is calculated as the difference between contaminant input with food and contaminant output with feces, normalized to the contaminant intake. Positive values in Table 3-7 indicate net absorption and negative values indicate net excretion, with absorption or excretion expressed as a percentage of daily intake. Nearly complete net absorption was observed for PCBs 28, 52, 77, 101, and 126. Incomplete net absorption and/or net excretion (in older subjects) was observed for PCBs 105, 138, 153, 180, and 202. In the case of the coplanar PCBs, 77 and 126, the congener specific levels in blood lipids of the subjects (given in parentheses) were very low and absorption was nearly complete (90% or greater for PCB 126 in all but two subjects). In the 76- and 81-year-old subjects, PCB 126 was found at higher levels in the blood lipids and the estimated net absorption of this congener was 77 and 53%, respectively. Net excretion or limited absorption was observed for PCBs 138, 153, and 180 in the three older subjects which had the highest levels of these congeners in their blood lipids. Thus, the gastrointestinal absorption or excretion of PCBs from food in humans is not only congener dependent, but is directly related to the concentration of a given PCB in blood, or the congener specific body burden. In most cases of background dietary exposures to PCBs, the PCB blood level or body burden increases with the age of the individual.

Table 3-7 illustrates that compounds showing nearly complete net absorption had low levels in the serum lipids, and for other congeners, there was a trend for decreasing net absorption/increasing net excretion with increasing congener concentration in serum lipids. Together, the data support the passive diffusion model for gastrointestinal absorption, where the concentration of the contaminant in the blood is the major factor determining absorption. In addition, the results suggest that the ingestion of highly contaminated food should result in nearly complete absorption due to the high diffusion gradient associated with high levels of PCBs in the gut contents. This may also be the case for the ingestion of PCB contaminated soil and water near hazardous waste sites. It should not be assumed that PCB absorption involves intestinal transfer to the hepatic portal system. As with fats and other fat-soluble chemicals, PCBs are most likely absorbed from the gut via lymphatic circulation and consequently avoid first-pass metabolism in the liver (Hansen 1999).

Table 3-7. Net Gastrointestinal Absorption or Excretion of PCBs in Humans and Dependence on Congener-Specific Blood Lipid Levels[a,b]

Gender (age in years)[c]	F(24)	M (25)	M (28)	M (36)	M (53)	F (76)	F (81)
PCB 28[d]	65	84	85	87	64	89	84
	(5.0)	(2.8)	(1.9)	(1.9)	(4.5)	(7.8)	(6.6)
PCB 52	73	82	90	89	69	93	92
	(1.52)	(1.09)	(0.89)	(<0.46)	(0.75)	(1.84)	(<0.69)
PCB 77	>91[e]	83	>90	>90	>82	>93	92
	(n.d.)[f]	(n.d.)	(n.d.)	(n.d.)	(0.007)	(0.064)	(<0.02)
PCB 101	56	81	91	90	48	92	82
	(1.50)	(1.11)	(1.22)	(0.78)	(1.38)	(2.3)	(1.43)
PCB 105	78	87	99	90	63	3	61
	(2.2)	(1.21)	(1.65)	(0.86)	(2.9)	(3.2)	(5.7)
PCB 126	90	93	95	96	92	77	53
	(0.066)	(0.068)	(0.042)	(0.029)	(0.082)	(0.174)	(0.39)
PCB 138	80	72	70	87	6	33	6
	(55)	(63)	(131)	(50)	(174)	(133)	(270)
PCB 153	74	60	65	85	-54	31	-42
	(89)	(135)	(230)	(84)	(410)	(250)	(600)
PCB 180	83	70	59	82	-41	34	-75
	(51)	(115)	(171)	(67)	(330)	(175)	(380)
PCB 202	51	36	2	19	-324	-63	-123
	(0.69)	(0.97)	(2.3)	(1.59)	(3.4)	(1.53)	(3.3)

[a]From Schlummer et al. 1998
[b]Net absorption is calculated as the difference between contaminant input with food and contaminant output with feces, normalized to the contaminant intake and is expressed as a percentage of the daily intake. Positive values indicate net absorption and negative values indicate net excretion with absorption or excretion expressed as a percentage of daily intake. Congener-specific levels in blood lipids are given in parentheses.
[c]M or F = sex of volunteer with age in parentheses
[d]PCB blood levels: nanograms per gram of blood lipids, shown in parentheses.
[e]< = values did not exceed three times blank values.
[f]n.d. = not determined due to detection problems.

In a related, but much older study, Price et al. (1972) estimated the gastrointestinal absorption efficiency by monitoring the daily PCB intake through food, and the excretion through feces and urine in 7–9 year old girls. They found that 88% of the ingested PCBs were not excreted, and were therefore assumed to be retained in the body. This estimate of PCB absorption in young girls is supported by the more comprehensive, congener specific mass balance study of Schlummer et al. (1998) discussed above.

In experimental animals, the absorption of PCBs by the gastrointestinal tract is well documented; however, few studies provided quantitative estimates. In rats, individual congeners (mono- to hexa-chlorobiphenyls) were readily absorbed when administered by gavage (vehicle not reported) in doses between 5 and 100 mg/kg (Albro and Fishbein 1972). Retention was >90% of the administered dose over a 4-day period, and was apparently dose independent. No relationship between substitution pattern and degree of absorption could be established due to the low levels of excretion, although a later study reported that absorption efficiency decreased in rats as the number of chlorine atoms increased such that dichlorobiphenyls were absorbed with a 95% efficiency, whereas octachlorobiphenyls had an absorption efficiency of only 75% (Tanabe et al. 1981). Results similar to those obtained in rats were reported in monkeys administered a single dose of 1.5 or 3.0 g Aroclor 1248/kg by gavage (Allen et al. 1974b) and in ferrets given 0.05 mg ^{14}C-labeled Aroclor 1254 in the food on days 14 and 35 of gestation (Bleavins et al. 1984). Retention was estimated to be >90% and 85.4% of the administered dose in the monkeys and ferrets, respectively. Over 90% of a single dose of 10 mg PCB 105 was absorbed by minks (Klasson-Wehler et al. 1993). In mice, absorption of a gavage dose of 8 mg/kg of PCB 52 or 100 mg/kg of PCB 77 was rapid, with serum concentrations increasing 4–7-fold in 30–60 minutes; peak serum concentrations were achieved . 2 hours after dosing (Clevenger et al. 1989).

Following a single oral dose of 15 mg/kg Aroclor 1254 to 55-kg growing swine, total PCBs reached maximum blood concentrations (9.8% of dose) in 5 hours (Borchard et al. 1975). The 11 packed-column peaks containing multiple congeners were also calculated individually, reaching maximum levels of 8–20% of the dose in 4–8 hours. In mature ewes receiving 30 mg/kg of the same Aroclor in a single oral dose, absorption was slower and maximum blood levels of 2.2% of the total PCB dose were achieved in 12 hours (Borchard et al. 1975). The absorption half-life for total PCBs was 1.13 hours in swine and 3.83 hours in the ruminants. Maximum blood levels of individual peaks were 3–6 times higher in swine than in sheep; however, sheep readily eliminated the peak containing mainly 2,3,3N,4N,6-pentaCB so that maximum blood levels were 11-fold lower in sheep than in swine for this peak (Borchard et al. 1975).

In weanling swine administered 15 mg/kg Aroclor 1254 in 7 daily oral doses of 2.14 mg/kg, whole blood concentrations peaked near 0.3 ppm between 7 and 28 days (Hansen and Welborn 1977). The concentration in dissectable backfat was about 15 ppm on day 7 and 10 ppm on day 14; however, the body composition was determined by noninvasive means so that the actual amount in body fat was estimated at 70 mg on day 7 and 60 mg on day 14. The slower decline in amount than in concentration was due to disproportionate expansion of the fat compartment in these rapidly growing animals (Hansen and Welborn 1977). The initial decline of total PCBs in fat was due to rapid clearance of lower chlorinated peaks and slower distribution of higher chlorinated peaks from centralized fat to the more peripheral backfat. Simultaneous studies with individual PCBs demonstrated greater amounts of PCB 52 on days 7 and 14 than of PCB 153 if fat PCB content was calculated on the basis of backfat PCB concentration. The total amount of tetrachlorobiphenyl declined linearly through 118 days, but the amount of hexachlorobiphenyl estimated in total fat based on backfat concentration increased gradually so that the 118-day amount was only slightly lower than the 7-day amount (Hansen and Welborn 1977). Further evidence, although indirect, regarding absorption of PCBs after oral exposure in several species can be found in studies on tissue distribution of these chemicals, which are presented in Section 3.4.2.2.

3.4.1.3 Dermal Exposure

The dermal route of exposure has been recognized as a significant contributor to the accumulation of PCBs in adipose tissue of workers in the capacitor manufacturing industry (Maroni et al. 1981a, 1981b; Smith et al. 1982; Wolff 1985). For example, it was reported that the concentration of PCBs in wipe samples from the face and hands of two employees at a private utility company varied from 0.05 to 5 $\mu g/cm^2$ (Smith et al. 1982). Assuming 100% dermal absorption into the main body reservoir (10 kg adipose), Wolff (1985) estimated that the figure of 5 $\mu g/cm^2$ would represent 0.2–20% of a 50-µg/g adipose level, which is commonly seen among capacitor workers.

In addition to contributing to exposure in occupational settings, the dermal route, through skin contact with contaminated water or soil, represents a potential route of exposure to PCB mixtures for populations in the vicinity of hazardous waste sites.

Experimental data on the percutaneous absorption of PCBs in humans is limited to *in vitro* studies thatused human cadaver skin (Wester et al. 1990, 1993). These studies utilized ^{14}C-labeled Aroclor 1242 and 1254 (mixtures containing 42 or 54% chlorine by mass) in soil, mineral oil, and water. Over a 24-hour period, 2.6, 10, and 43% of the dose was retained in human skin when the Aroclor 1242 was

formulated in soil, mineral oil, or water, respectively. Similar results were observed with Aroclor 1254, with 1.6, 6.4, and 44.3% of the dose retained in human skin, following PCB exposure in a soil, mineral oil, or water vehicle, respectively. The *in vitro* data indicate that PCBs readily enter human skin and are available for systemic absorption, and that the dosing vehicle has a major role in regulating the relative retention of PCBs in human skin.

In a related study, Wester et al. (1990, 1993) assessed the *in vivo* percutaneous absorption of PCBs in adult female Rhesus monkeys. ^{14}C-Labeled Aroclor 1242 and 1254 were separately administered iv and topically to Rhesus monkeys and urinary and fecal excretion of radioactivity was measured for the next 30 days. Following iv administration, the 30-day cumulative excretion was 55% of the administered dose (39% urine, 16% feces) for Aroclor 1242 and 27% (7% urine, 20% feces) for Aroclor 1254. The percentage of the dose absorbed following topical administration to abdominal skin (after light clipping of hair) was estimated from the ratio of the total urinary and fecal excretion following topical and iv administration. Topical administration of Aroclor 1242 in soil, mineral oil, trichlorobenzene, or acetone resulted in 14, 20, 18, and 21% absorption of the administered dose, respectively. In contrast to the above *in vitro* results with human skin, the vehicle had little effect on the systemic absorption of the PCBs applied to the skin of monkeys. This may be due to the uncertain viability of the human skin used in the *in vitro* studies and the fact that the *in vitro* study primarily assessed retention of PCBs in human skin and could not estimate systemic absorption.

The effectiveness of methods for decontaminating or removing Aroclor 1242 from Rhesus monkey skin was also investigated by Wester et al. (1990). Use of soap and water was similar in effectiveness to washing with trichlorobenzene, mineral oil, or ethanol. At 15 minutes following dermal exposure, 93% of the applied dose was removed from skin by washing with soap and water. At 24 hours following dermal exposure, only 26% of the dose was removed from skin by washing with soap and water, suggesting that with time, most of the PCB dose undergoes systemic absorption and/or retention in the skin. Thus, washing with soap and water is an effective method for removing PCBs from skin, particularly when washing immediately following a known dermal exposure.

Dermal absorption of PCBs has been measured in monkeys and guinea pigs by comparing excretion following topical administration to excretion following parenteral administration. Single doses of ^{14}C-labeled PCBs (42% chlorine content) in benzene/hexane were applied to the abdominal skin of four Rhesus monkeys and to the lightly clipped skin behind the ear of three guinea pigs (Wester et al. 1983). To an additional group of three guinea pigs, PCB with 54% chlorine content was applied. The

application amount ranged between 4.1 and 19.3 μg/cm^2 skin. The application sites were washed with water and acetone after 24 hours, and radioactivity was monitored in the urine for several weeks postdosing. Absorption efficiency ranged from . 15 to 34% of the applied radioactivity in the monkeys and averaged . 33% (42% chlorine) and 56% (54% chlorine) of the applied radioactivity in the guinea pigs. Washing the skin immediately after PCB application removed 59% of the applied dose. However, only 1% of the applied label from the PCB containing 42% chlorine and 20% of the label from the PCB containing 54% chlorine could be recovered from the application site when the skin was washed 24 hours after dosing. Dermal absorption of PCBs (48% chlorine) has also been demonstrated in rats (Nishizumi 1976); however, quantitative data were not provided.

Dermal penetration rate constants have been measured in male Fischer 344 rats after single 0.4 mg/kg dermal doses of ^{14}C mono-, di-, tetra-, and hexachlorobiphenyls applied for 48 hours to shaved back skin (Garner and Matthews 1998). Congeners used were 4-chlorobiphenyl (PCB 3), 4,4’-dichlorobiphenyl (PCB 15), 2,2’,4,4’-tetraCB (PCB 47), and 2,2’,4,4’,6,6’-hexaCB (PCB 155). Penetration rate and degree of penetration (defined as penetration through the stratum corneum into the viable epidermis) were inversely related to degree of chlorination. Rate constants for penetration were 0.14, 0.074, 0.028, and 0.0058 hour^{-1} for the mono-, di-, tetra-, and hexachlorinated forms, respectively. Rate constants correlated strongly with the logarithm of the octanol-water partition coefficient. Jackson et al. (1993) also reported a strong inverse correlation between octanol-water partition coefficient estimates and the dermal absorption of several halogenated aromatic hydrocarbons, including 3,3',4,4'-tetraCB (PCB 77). Cumulative penetration at 48 hours was near 100% for the mono-, 95% for the di-, 75% for the tetra-, and 30% for the hexachlorinated forms. Absorption of the tetra- and hexachlorinated forms continued after washing the site with acetone at 48 hours, indicating that the viable epidermis served as a reservoir for these higher chlorinated forms. The rate of systemic absorption of radioactivity was kinetically complex and not a first-order process like penetration into the skin. This may be due to metabolism and partitioning within the skin.

The dermal absorption of ^{14}C-3,3',4,4'-tetraCB (PCB 77) and 2,2',4,4',5,5'-tetraCB (PCB 153) in female F344 rats was assessed under conditions where the PCB was applied as either a solid, aqueous paste, aqueous suspension, or dissolved in ethanol (Hughes et al. 1992). The chemicals were applied to the clipped mid-dorsal region of the rat. The treatment area was then occluded, and urine and feces were collected and analyzed for radioactivity. At 24-hours postexposure, the treatment area was washed with soap and water, recovering 61–91% of PCB 77 and 81–92% of PCB 153. The percentage of the dose absorbed ranged from 6 to 8% for PCB 77 and from 5 to 8% for PCB 153, while the treated skin retained

from 3 to 31% of the PCB 77 and from 3 to 12% of the PCB 153. Although significantly greater absorption of PCB 153 was observed when administered as a solid, compared to using the ethanol vehicle, the remainder of the results indicate that the dermal absorption of PCBs 77 and 153 was similar even when the PCBs were applied in four different physical forms.

3.4.2 Distribution

Quantitative data regarding distribution of PCBs to specific organs or tissues of humans after route-specific exposure were not located. However, relevant information regarding the distribution of PCBs in humans following environmental, dietary, and/or occupational exposures are presented below.

Data regarding distribution of PCBs in human tissues and body fluids are derived mainly from the study of populations exposed in occupational settings or from those who have consumed contaminated food. It is generally agreed that the inhalation and dermal routes are the main exposure routes to PCBs in occupational settings (Wolff 1985). For the general population, the oral route is the major route for PCB exposure (Humphrey 1983).

In humans, PCBs are found in highest concentration in adipose tissue. Due to its high fat content, human milk can accumulate a large amount of PCBs, which can then transferred to children through breast-feeding (Ando et al. 1985; Jacobson et al. 1984b; McLachlan 1993). The PCB congener composition in milk differs from that of the commercially produced PCB formulations (Safe et al. 1985b) (see Section 3.8.1). Offspring can be also exposed to PCBs through transplacental transfer. In a sample of 313 women and their newborn infants, placental passage of PCBs was evidenced by a significant maternal to cord serum correlation (Jacobson et al. 1984b). Additional information on the prenatal and postnatal exposure to PCBs are included in Section 3.7.

Average measured concentrations of 0.5–4 ppm total PCBs have been reported for human milk fat, <5 ppb for blood plasma, and 0.5–10 ppm for adipose tissue (Jensen 1987). However, as pointed out by Jensen (1987), due to the heterogeneity of the study populations, the differences in sampling, and the analytical techniques used, the PCB levels reported by different studies may not be comparable. The levels of several di-*ortho*-substituted congeners in human milk (on a lipid basis) ranged from not detected to >300 ppb (Schecter et al. 1994). For comparable exposure levels, PCB levels in plasma and adipose tissue are generally higher in males than in females (Jensen 1987; Wolff et al. 1982a). PCBs have also been detected in ovarian follicular fluid in concentrations ranging from 0.5 to 24.2 μg/kg, in sperm fluid

ranging from 1.8 to 58.6 μg/kg (Schlebusch et al. 1989), and in bone marrow ranging from 2 to 4 mg/kg based on dry lipid weight (Scheele et al. 1994). Analytical techniques for determining PCBs in biological materials are presented in Chapter 7.

The major components in plasma and adipose tissue (subcutaneous) of occupationally exposed individuals were PCB congeners with chlorine atoms in the 4 and 4N positions (Wolff et al. 1982b, 1992), whereas PCBs with unsubstituted 3,4 positions on at least one ring were observed at lower concentrations. On a wet weight basis, the adipose/plasma partition ratio for Aroclor 1248 residues was 185/1; the partition ratio for Aroclor 1254 residues was 190/1. In a study of 173 workers of the same population, adipose/plasma partition ratios of 210/1, 190/1, and 200/1 were determined for residues of Aroclors 1242, 1254, and 1260, respectively (Brown and Lawton 1984). The partition ratios were significantly dependent on the levels of lipids in the serum, but not on albumin content. A 1989 study determined the concentration of individual PCB congeners in both serum and adipose tissue of 35 currently exposed workers, 17 former workers, and 56 control individuals who were never occupationally exposed to PCB mixtures (Fait et al. 1989). Among all exposure categories, the homolog groups present in the highest concentrations were the hexa- and heptachlorobiphenyls, both in sera and adipose tissue, as expected from the highly chlorinated Aroclor 1260. Mono-, di-, tri-, and nonachlorobiphenyls were found at very low levels in adipose tissue, as expected, and no differences were observed among the exposure categories. Currently exposed workers had significantly higher levels of penta-, hepta-, and octachlorobiphenyls than those in both formerly exposed and control groups. The concentration of tetrachlorobiphenyls was significantly higher among currently exposed individuals than among the other groups. No significant differences were seen in serum for tetra- and nonachlorobiphenyls. Mono-, tri-, penta-, hexa-, hepta-, and octachlorobiphenyls were found at significantly higher concentrations ($p<0.0167$) in currently exposed workers than in comparison groups. Hepta- and octa-concentrations were significantly higher ($p<0.0167$) in serum of formerly exposed subjects than in the serum of the other comparison groups. The relative distribution of individual congeners was similar in the three groups, but the amounts varied. The seven major peaks in serum and adipose tissue were mainly penta-, hexa-, hepta-, and octachlorobiphenyls. More standards became available after the study was published and some congener (but not homolog) identifications were corrected (see Hansen 1999).

Mean PCB concentrations of 5.1, 3.2, and 0.76 mg/kg of extractable fat were determined in samples of abdominal fat, liver, and brain, respectively, obtained from autopsies performed in Denmark (Kraul and Karlog 1976). None of the 82 subjects were occupationally exposed to PCBs. The PCB values in liver could be best correlated with those in adipose tissue. A more recent study described 14 different PCB

isomers in tissues and organs obtained at autopsy of three individuals in North America (Schecter et al. 1989). The large differences observed in isomer distribution within a given tissue and between the various tissues of the donors do not allow generalizations to be made on general population isomer distribution. When expressed as the sum of the 14 isomers on a lipid basis, PCB concentrations ranged from 101–573 ng/g (ppb) of fat in adipose, 89–517 ppb in liver, 30–409 ppb in kidney, 83–354 ppb in muscle, 80–42 ppb in adrenal (two patients), 131–193 (ppb) in lung (two patients), 102–341 ppb in spleen (two patients), 103 ppb in bone marrow (one patient), and 102 ppb in testis (one patient).

The existing information regarding distribution of PCBs in humans is limited. Nevertheless, based on experimental data obtained in animals (see Section 3.4.2.2) and the known physicochemical properties of PCBs, it is reasonable to assume that the lipid soluble PCBs, once cleared from the bloodstream, will accumulate in highest concentration in fatty tissues. Initially, however, PCBs could accumulate in the liver due to its high blood perfusion rate. The availability of PCBs for retention in fatty tissues is intimately linked to metabolism (see Section 3.4.3); therefore, it would be expected that the higher chlorinated PCBs would persist for longer periods of time solubilized in fatty tissues.

As with other organisms, PCB residue levels in humans reflects multiple exposure pathways, and congener-specific elimination. PCB profiles in human serum immediately following exposures reflect the profiles in the exposure sources, however, selective metabolism, excretion, and deposition begin to alter the congener profile within 4–24 hours (Hansen 1999). Thus, in most cases, the PCB profile in adults represents a steady state body burden which does not match the profile of commercial PCB formulations (Aroclors, etc.). For example, neither the PCB profile of human adipose nor of a composite human milk sample resemble the pattern of any commercial PCB formulation (Jensen and Sundstrom 1974; Safe et al. 1985). Abbreviated PCB residue analysis indicates that humans, aquatic mammals, birds, fish and other biota retain a similar profiles of the 4–6 more dominant PCBs, but more complete analyses demonstrate unique patterns among the remaining congeners.

Consumption of PCB contaminated freshwater fish is an example of an excess dietary exposure, which can elevate and/or modify serum PCB profiles. Non-coplanar, *ortho*-substituted, PCB congeners were measured in the serum (collected in 1993–1995) from a group of Lake Michigan residents over 50 years of age who eat fish (fisheaters) and an age- and region-matched comparison group that did not eat fish (nonfisheater) (Humphrey et al. 2000). The same general PCB profile was observed in both groups, with the fisheaters having a mean total PCB level in serum of 14.26 ng/g (n=101), and the nonfisheaters having a mean serum level of 4.56 ng/g (n=78). Four congeners, 138/163 (2,2',3,4,4',5/2,3,3',4',5,6),

180 (2,2',3,4,4',5,5') and 153 (2,2',4,4',5,5'), accounted for 55–64% of the total PCB load. Although 90 congener peaks were quantitated, the analysis found that 22 peaks representing 25 PCB congeners comprised 99% of the total PCBs in both the fisheater and nonfisheater groups.

Anderson et al. (1998) assessed serum levels of coplanar and noncoplanar PCBs in 32 anglers that consumed an average of 49 Great Lakes sportfish meals per year for a mean of 33 years. Highly persistent coplanar PCB 126 (3,3',4,4',5) and PCB 169 (3,3'4,4',5,5') were elevated 8- and 5-fold above the respective levels of these congeners in the control unexposed comparison group from Jacksonville, Arkansas. The less persistent coplanar PCB 77 (3,3',4,4') was found at similar levels in the Great Lakes fish consumer and control groups. The highly persistent, most abundant noncoplanar PCB 138 and PCB 153 were 2- and 3-fold higher in the fish consumers, relative to the respective control group. Thus, the long-term consumption of Great Lakes fish results in an increase in the serum levels of persistent PCBs, and particularly the coplanar PCBs 126 and 169. In subsequent studies from these investigators, Falk et al. (1999) found that consumption of lake trout and salmon significantly predicted serum log (total coplanar PCB) levels, and Hanrahan et al. (1999) found that PCB levels were significantly correlated to age, body mass index, and sportfish and Great Lakes sportfish consumption histories. Regression analysis identified years of consuming sport caught fish as the most robust predictor of serum PCB levels.

The above PCB residue data in humans and other animals suggests that tissue or body burdens of PCBs should be based on individual congeners or groups of congeners and not based on profiles of commercial PCB formulations. The simplest approach involves using one congener as a marker of total PCBs in a biological specimen. Levels of PCB 153 (2,2',4,4',5,5'), a very stable and often the most abundant congener, have been shown to correlate with the total amount of PCBs in human breast milk (Johansen et al. 1994) and human plasma, with a correlation coefficient of r=0.99 (Grimvall et al. 1997). PCB 153 was highly correlated (r=0.95) with total PCBs in 460 serum samples from Swedish men and women (Atuma and Aune 1999). PCB 153 was also highly correlated with total PCBs in serum (r=0.99) and follicular fluid (r=0.99) (Pauwels et al. 1999). In addition, PCB 153 levels correlated (r=0.91) with the total PCB-TEQs in human plasma (Grimvall et al. 1997). However, if a more complete profile of congeners is considered, the correlations are lower (Bachour et al. 1998; Hansen 1998, 1999). Total PCBs or PCB 153 as a marker of the total could be a misleading indicator of the differential exposure to other individual or groups of congeners of toxicological significance.

Another important issue related to exposure assessment is whether analysis of PCBs in serum and adipose tissue provide comparable information on body burden. Stellman et al. (1998) measured 14 PCB

congeners in adipose tissue and serum from 293 women with nonoccupational exposure. The relative patterns of the 14 PCB congeners were similar to those reported in other human studies. Significant positive serum to adipose correlation coefficients were obtained for PCBs 74, 99, 118, 138, 146, 153, 156, 167, 170, 180, 183, and 187, while PCBs 172 and 178 did not reach statistical significance. Thus, this study supports the conclusion that either serum or adipose tissue PCB levels may serve as useful biomarkers of body burden and/or exposure.

Recently, Dewailly et al. (1999) measured the concentration of 14 PCB congeners in subcutaneous fat, omental fat, brain, and liver from autopsy tissue samples collected from Greenlanders between 1992 and 1994 (Table 3-8). The PCB body burden of the Inuit population of Greenland is presently among the highest resulting from environmental exposure. The levels of PCB 138, 153, and 180 were 19, 21, and 16-fold higher than the respective congeners measured by the same analytical method in Canadians from Quebec City. The sum of the three most abundant PCB congeners (138, 153, 180) represents 63–68% of the total PCBs in the Greenlander tissue samples. Since PCBs primarily distribute with the tissue lipids, the tissue PCB concentrations were expressed relative to the lipid content (ng/g lipid) of each tissue.

Mean lipid contents were 62% in subcutaneous fat, 59.6% in omental fat, 8.3% in brain, and 4.5% in liver. Table 3-8 summarizes the mean concentration (μg/kg lipid) for the 14 PCBs in the four tissues. PCB concentrations (lipid basis) were similar in omental fat and subcutaneous abdominal fat, while the hepatic concentrations were generally about 20% lower than fat. PCB levels in brain (lipid basis) were about 10–20% of the levels found in subcutaneous fat. The lower concentration in brain cannot be explained by the presence of the blood-brain barrier because PCBs are highly lipophilic and are therefore expected to freely diffuse across this barrier. The difference in accumulation may be due to the nature of more polar brain lipids, which are mainly phospholipids. PCBs may partition to a greater extent into the triglycerides found in adipose tissue.

In support of the above observations, Weistrand and Noren (1998) found that the concentration of PCB congeners (ng/g lipid basis) were similar in paired human intra-abdominal adipose tissue and liver autopsy samples from seven Swedish subjects. The ratio of the sum of PCBs in liver to that in adipose tissue ranged from 0.8 to 1.0 (median 0.8), which was very similar to that reported in more highly exposed human samples from Greenland (Dewailly et al. 1999).

The concentration of PCBs (ng/g lipid) was measured in brain, liver, muscle, and lung tissue from 25 deceased male and female individuals with environmental exposure to PCBs (Bachour et al. 1998).

Table 3-8. Mean PCB Concentrations (Microgram Per Kilogram Lipid Basis) in Autopsy Tissue Samples from Greenlanders

PCB Congeners (IUPAC no.)	Subcutaneous fat (n=26)			Omental fat (n=41)			Brain (n=17)			Liver (n=26)		
	Mean[a]	Range	Per-cent[b]	Mean	Range	Per-cent	Mean	Range	Per-cent	Mean	Range	Per-cent
28	10	(0.2–185)	100	8	(2.3–156)	96	2.4	(0.5–33)	41	4	(0.5–79)	57
52	10	(2–150)	100	13	(1.9–200)	100	1.8	(0.3–19)	29	8[c]	(0.5–92)	65
99	238	(32–857)	100	215	(33–620)	100	31	(15–74)	100	154	(21–486)	100
101	26	(7–100)	100	18	(4–90)	100	8	(2–24)	94	19	(3–92)	92
105	47	(10–152)	100	50	(7–140)	100	3	(0.5–29)	53	18	(0.9–124)	77
118	257	(41–811)	100	267	(46–764)	100	38	(8–127)	100	209	(32–478)	100
128	9	(0.8–70)	85	3	(0.1–27)	100	1.0	(0.5–2.4)	6	2.1	(0.6–15)	15
138	1,103	(273–3,870)	100	1,098	(190–2,450)	100	134	(34–296)	100	855	(161–2,120)	100
153	1,689	(531–5,580)	100	1,582	(280–3,800)	100	198	(53–397)	100	1,177	(242–3,770)	100
156	173	(57–625)	100	195	(27–497)	100	30	(5–88)	100	143	(51–270)	100
170	385	(112–1,550)	100	422	(61–1,100)	100	46	(7–154)	100	327	(105–886)	100
180	1,147	(239–4,420)	100	1,136	(170–3,000)	100	145	(27–378)	100	791	(234–2,310)	100
183	92	(14–413)	100	93	(19–318)	100	10	(0.5–29)	88	69	(11–241)	100
187	499	(113–2,200)	100	507	(99–1,330)	100	82	(14–175)	100	445	(110–1,030)	100

Source: Dewailly et al. 1999

[a]Geometric mean; in calculating mean values, results not detected were attributed a value equal to half of the detection limit.
[b]Percentage of analyzed samples in which the substance was detected.
[c]Mean lipid content of tissues were 62.0% in subcutaneous fat, 59.6% in omental fate, 8.3% in brain, and 4.5% in liver.

Liver and muscle lipids generally contained similar levels of each of the PCB congeners, while the brain contained consistently lower levels. The lung generally had the highest concentration of the lower chlorinated congeners, including PCBs 28, 31, 49, 52, and 101. The levels in the lung were greater than brain and less than muscle or liver for PCBs 138, 153, 156, 170, 180, and 183. The higher levels of the lower chlorinated congeners in the lung may be related to the greater volatility and greater direct pulmonary exposure to these congeners. It is also possible that PCB binding proteins in the lung contribute to the enhanced pulmonary disposition of these congeners (Brandt et al. 1981).

3.4.2.1 Inhalation Exposure

No studies were located regarding distribution in humans following controlled inhalation exposure to PCBs. Occupational data are presented in the preceding section.

Information regarding PCB distribution in animals after inhalation exposure is limited. Rats exposed to 30 g/m^3 of an aerosol of a PCB mixture (Pydraul A 200, 42% chlorine) had 52, 14, and 9 µg PCB/g tissue in the liver, adipose, and brain, respectively, after 30 minutes of exposure (Benthe et al. 1972). The concentration of total PCBs attained in the liver after 2 hours of exposure was 70 µg/g. PCB levels in the liver reached a maximum 2 hours after exposure and slowly declined to less than half of the maximum 12 hours after exposure. Analysis of retroperitoneal adipose tissue revealed only trace amounts of PCBs immediately after exposure; only a slight increase in concentration was detected after 12 hours. Maximum concentration in adipose tissue was attained 36 hours after exposure. In contrast to adipose tissue, PCBs were detected in the brain immediately after exposure, reached a maximum 24 hours after exposure, and slowly declined thereafter.

A recent study in ferrets by Apfelbach et al. (1998) reported for the first time that the olfactory system may be a potentially significant portal for the entry of airborne PCBs. Ferrets were exposed for 5 years to low levels of PCBs (total PCBs, 260 ng/m^3 air) in the ambient air of an animal care room that had PCB-containing sealants. Tetra-chlorinated PCBs dominated the congener profile of ambient air, with PCB 52 being found at the highest concentration. The PCB congener pattern in the olfactory bulbs resembled that found in the ambient air, with the less chlorinated, more volatile PCBs (52) being retained at the higher levels. In contrast, the congener profile in adipose tissue resembles that of most exposed or unexposed animals, with PCBs 153, 138, and 180 being the major congeners present. The olfactory bulbs of the exposed animals had the highest total PCB concentration (642 ng/g lipids), while the liver, adipose tissue, and brain had levels of 202, 303, and 170 ng/g lipids, respectively. The data suggest that inhaled PCBs

pass into the dentrites of olfactory sensory neurons and are transported via olfactory axons directly to the bulbs where they accumulate. While the olfactory system appears to be a significant site for the disposition of airborne PCBs, further studies are needed to confirm this observation and assess whether greater disposition in the brain is associated with inhalation exposure.

3.4.2.2 Oral Exposure

Retention of individual PCB components from commercial mixtures depends upon species and organ, degree of chlorination, and substitution pattern (Hansen 1979, 1987b). The metabolism of specific PCB congeners by different species is influenced by existing residues and can result in considerable variations in metabolite distribution (Hansen 1987b; Safe 1989a) (see Section 3.4.3, Metabolism). Representative examples in various animal species are described below.

In adult mice, repeated administration of 100 mg/kg 2,2N,5,5N-tetraCB or 8 mg/kg 3,3N,4,4N-tetraCB achieved apparent steady-state levels in 8–10 days (Clevenger et al. 1989). Steady-state concentrations in adipose tissue were much higher than in liver and thymus. Liver concentrations increased from steady-state levels for 2 hours after the final dose before beginning to decline. The distribution ratio of the 3,3N,4,4N-isomer for adipose tissue was 2-fold higher than that of the 2,2N,5,5N-isomer, and the ratios for thymus and liver were 3- and 10-fold higher, respectively. The decline in concentration of both isomers in the three tissues followed first-order kinetics. Tissue elimination half-lives for adipose tissue, thymus, and liver ranged from 1.07 to 2.9 days. Similar values were reported in mice for six other tetra-substituted PCBs (Mizutani et al. 1977). No apparent relationship between a substitution pattern and biological half-life could be observed. Preferential accumulation in mice of 3,3N,4,4N-tetraCB in liver and adipose tissue relative to kidney and lung was also observed (Klasson-Wehler et al. 1989a). Results from whole-body autoradiography experiments showed high concentration of radioactivity in adipose tissue of mice administered ^{14}C-2,3,3N,4,4N-pentaCB (Klasson-Wehler et al. 1993); lower, but significant amounts were detected in the liver. No selective tissue retention was observed over a 30-day period that followed dosing. Physical exercise has been shown to increase the PCB levels by a factor of 10 in mice livers due to mobilization of fat deposits from adipose tissue (Kurachi and Mio 1983a).

In monkeys, a single dose of 1.5 or 3.0 g/kg Aroclor 1248 resulted in a dose-dependent liver concentration of Aroclor 1248 (25 or 53 μg/g) 2 times higher than that found in the kidney (12 or 27 μg/g) and brain (17 or 28 μg/g) 4 days after dosing (Allen et al. 1974b). This difference was greatly increased 14 days after treatment due to both a reduction in kidney and brain concentration and an

increase in liver concentration. The blood levels of Aroclor 1254 increased rapidly in monkeys during 10 months of treatment (from approximately 1.2 µg/g at time zero to about 100 µg/g in the high-dose group) with doses between 20 and 80 µg/kg/day (Mes et al. 1989), but this increase leveled off during the remaining 27 months of treatment. A dose of 5 µg/kg/day induced only a slight increase in blood PCB levels during the total treatment period of 37 months. When the data were expressed as relative concentration, it appeared that absorption and bioaccumulation were dose-dependent. However, the concentration/dose levels were, to some extent, affected by background PCB levels of the control group, which would have a greater impact on the relative concentrations of the lowest dose groups rather than on the higher dose groups.

Information regarding distribution of PCB residues in monkeys after long-term feeding of Aroclor 1254 is available. In that study (Mes et al. 1995b), female monkeys were dosed with Aroclor 1254 (0.005, 0.02, 0.04, or 0.08 mg/kg/day) for over 6 years. Throughout the treatment period the monkeys were bred to untreated males and the resulting offspring were nursed by their mother. In dams, PCB residues in blood and tissues (on a lipid basis) increased with dose. On a wet tissue basis and at all dose levels, adipose tissue contained the most PCBs (10 times that found in the liver). At the highest dose, blood had 274 µg/g, followed by the liver (190 µg/g), adipose (171 µg/g), kidney (156 µg/g), and brain (22 µg/g) based on the lipid content in each tissue. Monkeys that were sacrificed before termination of treatment because of poor health had higher PCB levels in their tissues than monkeys killed at termination.

Following a 7-day total dose of 15 mg/kg Aroclor 1254 to growing pigs, lower chlorinated congeners reached peripheral fat (dissectable backfat) more rapidly than did higher chlorinated congeners; however, redistribution (from more central fat) between 35 and 80 days resulted in total estimated amounts of higher chlorinated congeners (Hansen and Welborn 1977). Total PCBs in noninvasively determined total fat were estimated by multiplying body weight times percent body fat times the concentration of PCBs in backfat. Long-term declines in fat concentrations for higher chlorinated PCBs were due mainly to dilution by growth and expansion of the fat compartment.

Administration of a total dose of . 7 mg/kg of PCBs (tetra- and hexachlorobiphenyls) to rats over #50 weeks resulted in the highest PCB concentration being detected in adipose tissue regardless of the treatment duration (Hashimoto et al. 1976). Intermediate concentrations were detected in the skin, adrenal gland, aorta, and sciatic nerve; all other major organs and tissues had lower PCB concentrations. In each tissue, PCBs were preferentially distributed to the lipid fraction. Similar results were observed in rats following administration of a single dose of hexachlorobiphenyl followed by a long-term observation

period (Mühlebach and Bickel 1981). The highest concentration of chlorinated hydrocarbon residues 24 hours following administration by gavage of a single dose of 1,600 mg/kg Aroclor 1254 or 3,200 mg/kg Aroclor 1260 to female Sherman rats was found in fat tissue, followed by kidney, liver, and brain; plasma and muscle contained the least (Curley et al. 1971). Despite the difference in administered doses, the concentration of residues in tissues, derived from both Aroclors, were comparable. When male and female rats were given an oral dose of 73 mg/kg/day Aroclor 1254 for 98 days, fat tissue again had the highest concentration, followed by muscle and liver (Curley et al. 1971). No significant differences were observed between adult male and female rats.

A number of animal studies have demonstrated that PCB mixtures and specific congeners and isomers can cross the placental barrier and enter the fetus. High levels of lipid soluble PCBs accumulate in the fat portion of the milk, also resulting in high exposure of suckling animals. Significantly increased PCB residues were detected in blastocytes (day 6 postcoitum) from female rabbits administered Aroclor 1260 before insemination (Seiler et al. 1994), but no residues could be detected in cleavage stage embryos (day 1 postcoitum). In pregnant mice fed PCBs through the first 18 days of gestation, the highest levels of serum PCBs were found in 1–2-week-old offspring compared with 18-day fetuses or with older offspring (Masuda et al. 1979). In studies that exposed monkeys prior to and during gestation, signs of PCB-induced intoxication were observed in suckling offspring, but not in neonates (Allen and Barsotti 1976; Iatropoulus et al. 1978). PCB blood levels in the offspring continuously increased during lactation, but decreased just before or immediately upon weaning (Mes et al. 1994, 1995c). In rats administered PCBs before gestation, 0.003% of the PCBs accumulated in the dams was transferred to the fetus through the placenta; however, the amount transferred to sucklings increased to 5% of the maternal PCB (Takagi et al. 1986). Similar results have been reported in ferrets administered single doses of PCBs early or late during gestation (Bleavins et al. 1984). Results such as these have led to the conclusion that suckling may account for higher exposure of young offspring than does placental transfer; the fetus, however, may be more sensitive.

Experiments in monkeys have suggested that fetal tissue may be unable to metabolize and excrete certain PCB congeners that are more readily metabolized and eliminated by adults and older infants (Barsotti and Van Miller 1984; Mes et al. 1995b, 1995c).

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans following dermal exposure to PCBs. However, there is no evidence suggesting that distribution is route-dependent. Because of the lipophilic nature of these compounds, it would be reasonable to assume that once they are absorbed, PCBs will distribute to various tissues in proportion to their lipid contents. However, data from humans at autopsy suggest that the disposition of PCBs is congener and tissue specific and not based exclusively on the lipid content of tissues (Bachour et al. 1998; Dewailly et al. 1999; Schecter et al. 1994). Data regarding occupational exposure are discussed in Section 3.4.2.

Total tissue radioactivity has been measured in male Fischer 344 rats after single 0.4 mg/kg dermal doses of ^{14}C mono-, di-, tetra-, and hexachlorobiphenyls applied for 48 hours to shaved back skin (Garner and Matthews 1998). Congeners used were 4-CB, 4,4'-diCB, 2,2',4,4'-tetraCB, and 2,2',4,4',6,6'-hexaCB. Peak total radioactivity in the tissues (excised dose site, samples of blood, adipose tissue, muscle, skin [ears], and the entire liver and kidney) occurred at progressively later times depending on the degree of chlorination. For example, the monochlorinated form reached maximal concentrations (37% of the absorbed dose) in blood and other tissues at 4 hours postadministration and was almost absent (0.2%) at 2 weeks. In contrast, peak tissue concentrations of the tetrachlorinated form (80% of the absorbed dose) occurred at 72 hours and approximately 45% remained in the tissues after 2 weeks. Absorption of the tetra- and hexachlorinated forms continued after washing the site with acetone at 48 hours, indicating that the viable epidermis retained these forms and served as a reservoir. This may be due to partitioning into lipophilic sites in the skin or adsorption to epithelial proteins.

3.4.2.4 Other Routes of Exposure

In general, the results reported by studies in which PCBs were administered to experimental animals by parenteral routes are consistent with those derived from oral administration.

In adult rats with a constant adipose tissue mass, 2,2N,4,4N,5,5N-hexaCB (PCB 153) administered intravenously distributed preferentially to adipose tissue (about 5 µg/g), followed by the skin, lung, and liver (all about 0.3 µg/g) (Wyss et al. 1986). Four days after dosing, only adipose tissue, skin, and muscle contained significant amounts of the PCBs (. 75% of the dose). Between 2 and 4 weeks later, PCB levels in adipose tissue and skin reached a maximum, corresponding to 68 and 15% of the administered dose, respectively, which indicates a slow redistribution process of the chemical. In rats given 3,3N,5,5N-tetra-

CB intravenously, 20–40% of the administered dose was found in adipose tissue over 42 days; the blood, liver, muscle, and skin had <20% (Tuey and Matthews 1977).

In pregnant mice injected intravenously with ^{14}C-labeled 3,3′,4,4′-tetraCB (PCB 77), most of the radioactivity was localized in the fetus and consisted mainly of a hydroxylated metabolite (Klasson-Wehler et al. 1989b). However, after a dose of 3,3′,4,4′,5-pentaCB (PCB 126), no radioactivity was found in the fetus, except for traces in the liver. This differential distribution is probably due to differences in maternal metabolism for the tetra- and pentachlorobiphenyls (see Section 3.4.3, Metabolism).

3.4.3 Metabolism

The metabolism of PCBs has been extensively reviewed (Hansen 1999; Hu and Bunce 1999; Safe 1989a, 1993). Differential accumulation and retention of PCBs is related to exposure and the relative biological stability (rate of biotransformation) of each congener. Limited excretion of parent PCBs does occur (see Table 3-7), but biotransformation is necessary for the majority of PCB excretion.

The initial step in the biotransformation of PCBs involves CYP enzyme (cytochrome P-450) (CYP1A1, 1A2, and CYP2B1/2B2) mediated oxidation of arene oxides, which readily undergo further metabolism (Matthews 1982; Preston et al. 1984). CYPs of the 3A family are also very likely to participate and, perhaps, are more important than CYPs of the 2B family (see Hansen 1998, 1999). Coplanar (non*ortho*) PCBs are dioxin-like inducers of CYP1A and PCB 77 is preferentially oxidized by these isozymes. Many *ortho*-substituted, nonplanar, PCBs are inducers of CYP 2B isozymes and are also metabolized by these enzymes (Brown 1994). Mono-*ortho* PCBs are often mixed inducers of CYP1A and CYP2B isozymes (Safe et al. 1985a). Some congeners induce P-450s from the 3A and 4A families, but the structure-activity relationships are incomplete (Huang and Gibson 1992; Schuetz et al. 1986). Arene oxides are mainly transformed to hydroxylated aromatic compounds but also to sulfur-containing metabolites via the mercapturic acid pathway (Haraguchi et al. 1999b; Matthews 1982). Depending on the number and position of the chlorine-substitutions, one or more arene oxide intermediate may be formed from a given PCB. Unsubstituted *meta* and *para* carbon atoms are the preferred site for oxidation (Borlakoglu and Wilkins 1993b). Hydroxylation of coplanar PCBs usually predominates at the para position in the least chlorinated phenyl ring, and the rate of metabolism generally decreases with increasing chlorine substitution (Hu and Bunce 1999). Nonplanar PCBs are generally hydroxylated at an open *meta* position. The presence of vicinyl hydrogens (adjacent unchlorinated carbons) favors the metabolism of higher

chlorinated PCBs. Comparison of the molecular structures of the biologically persistent congeners reveals different molecular weights, substitution patterns, feasibility to rotate on the phenyl-phenyl bond, and intramolecular distances determined by nonelectrostatic forces (Borlakoglu and Walker 1989). Despite these physicochemical differences, it appears that higher chlorinated PCBs and congeners that lack unsubstituted *meta-para*-vicinal positions are better candidates for bioaccumulation.

Information regarding the metabolism of PCBs in humans is limited. Chromatographic analysis of adipose tissue samples of volunteers revealed almost 60 individual PCB components (Jensen and Sundström 1974). Examination of these results showed that <12 congeners accounted for . 80% of the total PCBs. For example, 2,2N,4,4N,5,5N-hexaCB (PCB 153) was the congener found in the highest concentration, whereas 2,2N,4,4N,6,6N-hexaCB (PCB 155) was not detected. PCB 155 is neither in commercial PCB mixtures nor in the environment at appreciable levels (Table 4-5). As PCB 153 is found in commercial PCB mixtures and in the environment, the presence of this congener in adipose tissue appears to be related to biologic persistence and/or to metabolism. The results of *in vitro* metabolism with human liver microsomes entirely support the conclusions drawn above. Human liver microsomes did not metabolize PCB 153 under various conditions, but did metabolize PCB 136 (Schnellmann et al. 1983). The major metabolites identified, 2,2N,3,3N,6,6N-hexachloro-4-biphenylol, and 2,2N,3,3N,6,6N-hexachloro-5-biphenylol, suggest that this congener is metabolized through an arene oxide. PCB 153 is often the most prevalent PCB detected in humans, due to exposure and the slow rate of biotransformation of this congener. More recently, 3-hydroxy-2,4,5,2',4',5'-hexaCB was identified as the major metabolite of PCB 153 formed by human CYP2B6 (Ariyoshi et al. 1995). CYP2B6 is constitutively expressed in humans, but only accounts for a maximum of 1–2% of the total CYPs in human liver. Approximately 75% of the subjects examined had no detectable level of CYP2B6 protein by immunoblotting (Mimura et al. 1993). This may be the reason why no metabolite of PCB 153 was detected in an earlier *in vitro* study using human liver microsomes (Schnellmann et al. 1983). The *in vitro* metabolism of 4,4N-diCB by human liver microsomes produced six metabolites, with 4,4N-dichloro-2-biphenylol being the most abundant (Schnellmann et al. 1984). These data also suggested that 4,4N-diCB is metabolized through an arene oxide and that migration of substituents from the site of hydroxylation to the adjacent carbon atom (NIH shift) occurs (Gardner et al. 1973; Safe et al. 1975). The major hydroxylated PCB metabolite in human plasma from unexposed people is 4-hydroxy-2,2N,3,4N,5,5N,6-heptaCB, originating from either 2,2N,3,4N,5,5N,6-hepta- and/or 2,2N,3,4,4N,5N,6-heptaCB (Bergman et al. 1994). All major 1-*ortho*-PCBs are transformed to 4-hydroxy-chlorobiphenyl metabolites, retained in plasma or blood. Changes in residue patterns, including actual increases over

time, indicating possible dechlorination products were observed by Wolff et al. (1992). Brown (1994) further suggested that humans were capable of very slow PCB dechlorination.

Most hydroxylated PCB metabolites are excreted in feces and/or in urine, or are conjugated to glucuronic acid or sulfate. However, several hydroxylated PCB metabolites are retained in the body, either due to their high lipophilicity or reversible binding to proteins. Although several of the OH-PCBs are present in rat plasma and seal blood, the spectrum of OH-PCBs is different in human plasma, compared to that in rats or seals (Bergman et al. 1994). For example, 4-OH-2,3,5,6,2',4',5'-hepta PCB, the major OH-PCB in human plasma (Bergman et al. 1994; Sandau et al. 1998), was found in seal blood but was not detected in rat plasma. This major metabolite may originate from 2,3,5,6,2',4',5'-heptaCB (PCB 187) and/or 2,3,4,6,2',4',5'-heptaCB (PCB 183), which are present in human milk. The 4-OH-2,3,5,3',4'-pentachloro-biphenylol, the major hydroxy PCB metabolite detected in rat plasma, is also a major contributor to hydroxy-PCBs in seal blood and in human plasma (Bergman et al. 1994). This metabolite is formed after a 1,2-shift of a chlorine in the para position in the 2,3,4-trichlorinated phenyl ring of PCB 105. In addition to PCB 105 and 118, this metabolite could arise from the PCB 156 3,4- or 4,5-arene oxide with the loss of a chlorine. A similar rearrangement is also observed to occur in the 3,4-dichloro-substituted phenyl rings of PCBs 77, 105, 118, and 156 (Klasson-Wehler et al. 1993). Thus, all of the major 1-*ortho*-PCBs can be biotransformed to 4-OH PCB metabolites that are retained in plasma or blood. Hydroxylated PCBs are retained in lung, liver and kidney tissue, which may be explained by the blood residues in these tissues. It is important to note that the concentration of the 4-OH metabolite of PCB 105 in rat liver or lung is similar to that of PCB 153, one of the most persistent and abundant PCB congeners. Persistent 3-OH PCB metabolites have also been identified at lower levels. In general, the persistent OH-PCBs have chlorine atoms on the adjacent carbons to the OH-group and contain five or more chlorine atoms.

Methylsulfonyl ($MeSO_2$) metabolites of PCBs have been widely detected in the tissues of marine mammals (Bergman et al. 1994; Letcher et al. 1995) and of humans (Haraguchi et al. 1986; Noren et al. 1996; Weistrand and Noren 1997). The $MeSO_2$-PCBs are formed via P-450 dependent epoxidation (Safe 1989a, 1989b) and subsequently via the mercapturic acid pathway (Preston et al. 1984). The most abundant $MeSO_2$ metabolites in wildlife and humans are originated from 2,2',4,5,5'-pentaCB (PCB 101) or 2,2',3,4',5',6-hexa (PCB 149) (Bergman et al. 1994; Haraguchi et al. 1992; Noren et al. 1996). Human milk in Sweden was analyzed for methylsulfonyl metabolites of PCBs, which decreased from approximately 9 to 2 ng/g milk lipid from 1972 to 1992 (Noren et al. 1996). The levels of these metabolites also correlated with the levels of total PCBs. The major $MeSO_2$-PCBs in the milk were

4-$MeSO_2$-2,5,2',3',4'-PCB (87) and 4-$MeSO_2$-2,3,6,2',4',5'-PCB (149). Methylsulfonyl metabolites of PCBs were also analyzed in autopsy tissues from seven Swedish individuals (Weistrand and Noren 1997). Twenty $MeSO_2$-PCBs were detected in liver and adipose tissues, with 4-$MeSO_2$-2,5,2',3',4'-PCB (87) and 4-$MeSO_2$-2,3,6,2',4',5'- PCB (149) also being found at the highest levels in these tissues. 3-$MeSO_2$ metabolites were detected in adipose tissue, but at lower levels. However, in the liver, the 3-$MeSO_2$ metabolites were most abundant, with 3-$MeSO_2$-2,2',3',4',5,6-PCB (132) contributing 61–82% of the sum of all $MeSO_2$-PCBs in the liver. The methylsulfonyl metabolite profile in one lung sample was similar to that observed in adipose tissue, with 4-$MeSO_2$ metabolites dominating the profile. The ratios of the sum of all methylsulfonyl metabolites to total PCB levels were 1/250 and 1/28 in adipose tissue and liver, respectively, calculated for the median values. Thus, methylsulfonyl metabolites of PCBs are selectively retained in different human tissues and therefore require further study regarding their biological and/or toxicological activity.

The metabolism of PCBs in experimental animals has been extensively reviewed (Safe 1980, 1989a; Sipes and Schnellmann 1987; Sundstrum et al. 1976a, 1976b). Many substrates have been tested, and the PCBs were usually administered by the oral or parenteral routes. In general, these studies showed that the metabolism rate of PCBs depends on the number and position of chlorine atoms on the phenyl ring and on the animal species. In rats, the elimination half-lives of four PCBs with one, two, five, or six chlorines increased as the number of chlorines increased (Matthews and Anderson 1975). The decreased excretion rate with increasing chlorination was directly related to the decreased rate of metabolism of the more highly chlorinated congeners. Sheep liver microsomes converted 2,2N,5-triCB to at least 5 more polar metabolites within 1 minute and at least 10 metabolites by 15 minutes; however, within the homologous series, 2,2N,5,5N-tetraCB and 2,2N,4,5,5N-pentaCB were oxidized to only 3 metabolites at rates 7- and 14-fold slower, respectively (Hansen 1987b; Hansen et al. 1977). Not only does the number of chlorines affect the rate of biotransformation, but the position of the chlorines on the phenyl rings is also critical. This was demonstrated in rats, which excreted four symmetrical hexachlorobiphenyls at different rates depending on the chlorine positions (Kato et al. 1980). As the number of unsubstituted *meta* positions or adjacent unsubstituted carbon atoms increases, the percentage of the dose excreted increases. The major hydroxylated PCB metabolite in rat plasma after administration of 25 mg/kg Aroclor 1254 in peanut oil by gavage is 4-hydroxy-2,3,3N,4N,5-pentaCB. From days 1 to 14 after exposure, this metabolite is found at concentrations 7–10 times the concentration of the major PCB 153 (Bergman et al. 1994).

The following generalizations based mostly on data obtained from experimental animals can be made (Safe 1980):

1. Hydroxylation is favored at the para position in the least chlorinated phenyl ring unless this site is sterically hindered (i.e., 3,5-dichloro substitution).

2. In the lower chlorinated biphenyls, the para position of both biphenyl rings and carbon atoms that are para to the chloro substituent are all readily hydroxylated.

3. The availability of two vicinal (adjacent) unsubstituted carbons atoms (particularly C5 and C4) also facilitates oxidative metabolism of the PCB substrate, but it is not a necessary requirement for metabolism.

4. As the degree of chlorination increases on both phenyl rings, the rate of metabolism decreases.

5. The metabolism of specific PCB isomers by different species can result in considerable variations in metabolite distribution.

The major PCB metabolites are phenolic products; however, sulphur-containing metabolites (Klasson-Wehler et al. 1987), trans-dihydrodiols (Norback et al. 1976), polyhydroxylated congeners, and methyl ether derivatives (Koga et al. 1989) have also been identified. The occurrence of trans-dihydrodiol metabolites suggests that the metabolism of PCB congeners proceeds through formation of arene oxide intermediates (Gardner et al. 1973). Due to their high reactivity, arene oxide intermediates are difficult to detect. They hydrate to give trans-dihydrodiols and spontaneously rearrange to phenols with the concomitant 1,2-migration of substituents from the site of hydroxylation to the adjacent carbon atom (NIH shift) (Daly et al. 1972). Arene oxides are potential electrophiles, and have been implicated in cellular necrosis, mutagenicity, and carcinogenicity (Safe 1989b). Experimental evidence using P^{32}-postlabeling supports the hypothesis that lower chlorinated biphenyls are metabolically activated to electrophilic species which bind to DNA (McLean et al. 1996; Oakley et al. 1996). The incubation of 2-chloro-, 4-chloro-, 3-chloro-, 3,4-dichloro-, and 3,4,5-trichlorobiphenyl with calf thymus DNA and rat liver microsomes followed by oxidation with a peroxidase, produced 1–3 major DNA adducts. The reactive metabolites may result for arene oxides and/or catechol and p-hydroquinone species, which are oxidized to semiquinones and/or quinones. The results raise the possibility that lower chlorinated biphenyls may be genotoxic and may explain the fact that commercial PCB mixtures are complete rodent carcinogens.

The formation of 3-hydroxy-2,2N5,5N-tetraCB as a metabolic product of 2,2N,5,5N-tetraCB suggested that a nonarene oxide direct hydroxylation mechanism is an alternative metabolic route for some chlorinated biphenyl congeners (Billings and McMahon 1978; Preston et al. 1983). Sipes and Schnellmann (1987) review and confirm additional routes for PCB oxidative metabolism.

Methylsulphonyl metabolites of PCBs have received considerable attention since these compounds are possibly etiologically connected to the respiratory toxicity described in *Yusho* victims (Brandt and Bergman 1987; Haraguchi et al. 1986). PCB methyl sulfones are formed as follows: products of the reaction between arene oxides and glutathione are degraded and excreted in the bile into the large intestine where they undergo cleavage by a microbial C-S lyase. The thiols formed are methylated, reabsorbed, and further oxidized on the sulfur to the corresponding methyl sulfones, which are distributed by the blood (Brandt et al. 1985). The methylsulphonyl-PCBs are initially bound to a uteroglobin-like protein found in high concentrations in rat and mouse lung cytosol (Lund et al. 1985) of the Clara and goblet cells. This protein-sulfone complex is subsequently secreted into the airway lumen and spread over the surface lining. It has also been suggested that this complex is transported by the mucociliary system to the pharynx and swallowed (Brandt and Bergman 1987). In the gastrointestinal tract, the complex may be released, reabsorbed, and recirculated to the lung, which could contribute to the long retention times for methylsulphonyl-PCBs in rodents (Brandt and Bergman 1987). Methylsulphonyl-PCBs have also been localized in rodent kidney cortex (Brandt et al. 1985), but the mechanism of accumulation in the proximal tubules appears to be different than that operating in respiratory airways since only trace amounts of the lung binding protein are present in rodent kidney (Lund et al. 1985). Methylsulphonyl metabolites of PCBs are also retained in the fat of seals (Jensen et al. 1979) and in liver and muscle of minks (Bergman et al. 1992).

It has also been shown that the 3-$MeSO_2$ metabolites from PCBs with 2,5-chlorine substitution were selectively retained in the liver of marine mammals (Bergman et al. 1994), whereas the isomeric 4-$MeSO_2$ metabolites were localized in the lung of mice (Bergman et al. 1979; Klasson-Wehler et al. 1996). Although the binding mechanism for 3-$MeSO_2$ metabolites is not clear, the binding protein for 4-$MeSO_2$ metabolites has been identified as a uteroglobulin-like protein present in the nonciliated bronchiolar (Clara) cells of the lung, also referred to as Clara cell secretary protein (CCSP) (Hard et al. 1995; Stripp et al. 1996). Exposure to 4-$MeSO_2$-2,2',4',5,5'-PCB demonstrated that CCSP-deficient mice no longer accumulate this metabolite within lung or kidney tissue (Stripp et al. 1996). These data demonstrate that CCSP is the 4-$MeSO_2$-PCB binding protein in mice and suggests that 4-$MeSO_2$-PCBs will accumulate at sites of CCSP localization, such as the respiratory and reproductive tracts of humans.

Haraguchi et al. (1999a) recently investigated the tissue distribution of methylsulfonyl metabolites derived from PCB 101 and 149 in male Wistar rats. Both congeners are metabolized primarily by hydroxylation at the 3-position and methylthiolation at the 4-position. The 3-/4-$MeSO_2$ metabolite ratios in liver and adipose tissue for both congeners were 0.41–0.61 at day 4, increasing to 0.85–1.00 for up to

42 days. In contrast, the ratios in lung were 0.03–0.04, and then decreased to 0.01 at 42 days. The ratio of metabolite to parent compound in tissues provides an estimate of the relative persistence or abundance of the methylsulfonyl metabolites. In the liver, the ratio of 3-$MeSO_2$ to PCB 101 was 0.46 and the ratio of 3-$MeSO_2$ to PCB 149 was 0.21. 4-$MeSO_2$ metabolites were highly retained in the lung, with metabolite to parent compound ratios of 9.5 and 4.0 for PCBs 101 and 149, respectively.

Persistent $MeSO_2$-PCBs also have been reported to induce hepatic P-450s in rats. 3-$MeSO_2$-PCBs identified in mammals were strong phenobarbital type inducers of CYP2B protiens, while the 4-$MeSO_2$ metabolites were inactive (Kato et al. 1995, 1997). Specifically, the inducing ability of 3-$MeSO_2$-PCB 101 was more than 500 times greater than the parent PCB101.

A summary of the structures of PCB metabolites that have been identified using various substrates and biosystems is presented in Figure 3-3.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

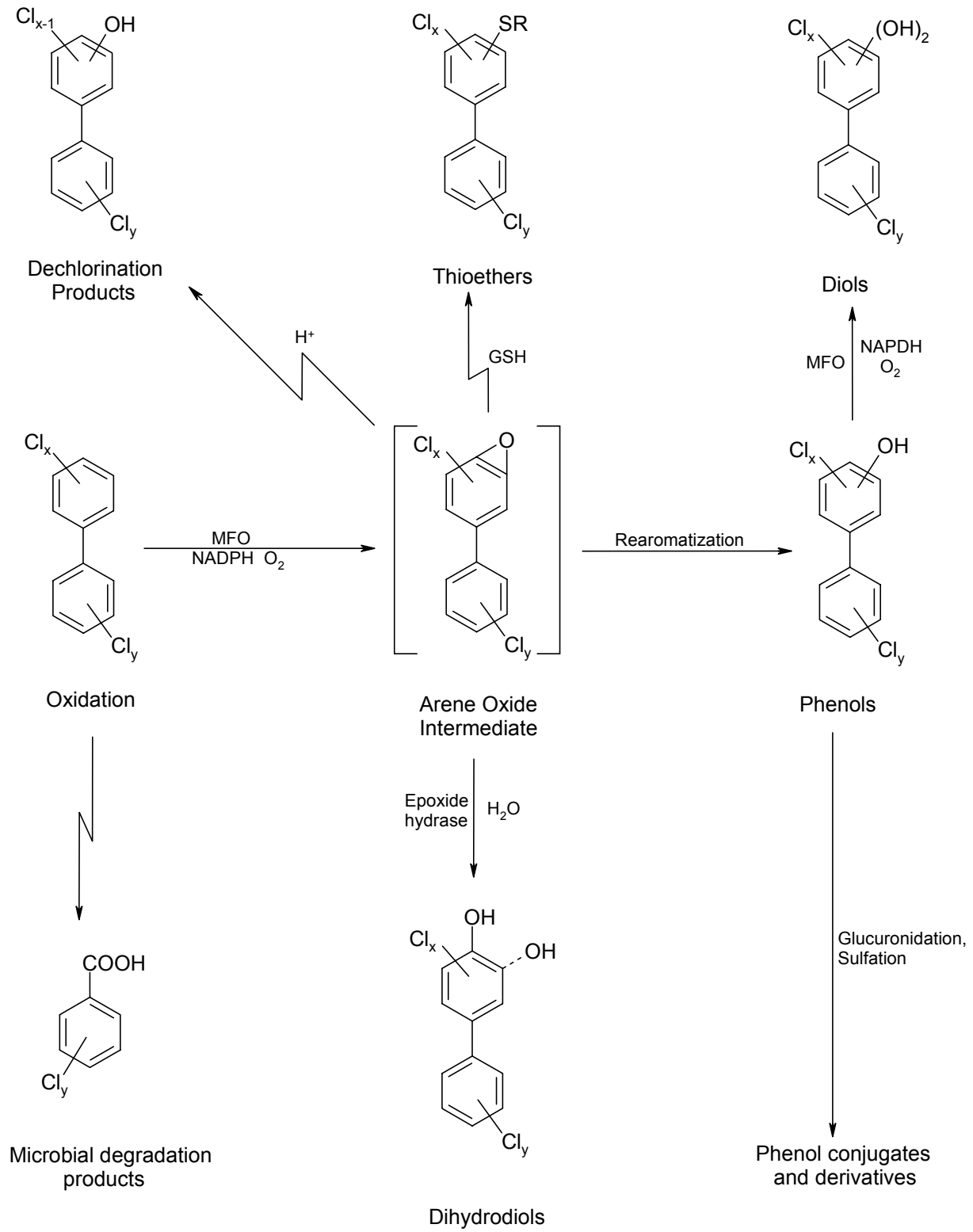
No studies were located regarding excretion in humans or animals following controlled inhalation exposure to PCBs. However, there is no reason to believe that once absorbed by inhalation, the excretion pattern of PCBs will differ from that observed after oral absorption. Much greater amounts of PCBs are excreted in the feces than in the urine following oral absorption.

3.4.4.2 Oral Exposure

Human Studies. Estimates for the half-lives for elimination of PCBs from humans have been based on body burden measurements at two or more time points form the same individual. A simple mass balance approach is commonly employed to characterize the elimination of PCBs from humans. In general, a simplified single compartment model is used where only intake and first order elimination are assumed to occur. In most cases, the intake is assumed to be negligible and the following equation is used to estimate k, the first order loss or rate constant (day $^{-1}$), where C_o and C_t are the initial and final tissue concentrations, respectively, and t is the time between sampling.

$$C_t = C_0 e^{-kt} \qquad (1)$$

Figure 3-3. Metabolic Pathways for Polychlorinated Biphenyls



Source: Safe 1984

This relationship assumes that the mass of the adipose tissue compartment and daily intake remaining constant over the observed time period and that daily intake is negligible. If these conditions are not met or are unknown, the k in the above equation represents an apparent rate constant (k'). The apparent half-life from the above equation can then be expressed as follows:

$$t_{1/2} = \frac{-\ln 2 \cdot t}{\ln \frac{C_t}{C_0}} \qquad (2)$$

Equation (2) was used to calculate apparent half-lives when human body burden data, such as blood, serum, plasma, or adipose tissue concentrations of PCBs are available at two or more time points.

It is often useful for the purposes of risk assessment to estimate the daily intake of PCBs needed to maintain a steady state body burden or tissue level of PCBs. The daily intake, I, required to produce a steady state body burden of $C \cdot M_{fat}$ is as follows:

$$I = k \cdot (C \cdot M)_{fat} \qquad (3a)$$

$$I = \frac{\ln 2}{t_{1/2}} \cdot (C \cdot M)_{fat} \qquad (3b)$$

Tables 3-9 and 3-10 summarize data from multiple studies on the apparent half-lives (years) of PCB congeners and PCB mixtures in humans. Although analysis of human blood, serum, plasma, adipose tissue, or other tissues does not match the specific profile of commercially produced PCB mixtures (Aroclors, etc.), the studies in Table 3-10 did not use congener specific analysis and estimated apparent half lives for PCB profiles with varying degrees of chlorination. Most of the studies cited in Table 3-9 utilized congener specific analysis; however, this was not the case for several studies. The studies report apparent half-life estimates as low as 0.02 years and as long as infinity, with no apparent loss in body burden despite removal of a known source of exposure. Thus, it is important to evaluate the variability between studies and use caution in interpreting results from a given study. Absolute values for PCB congeners and mixtures must also be interpreted with caution, since methods for analysis have improved in recent years. However, even with high resolution gas chromatography and electron capture detection (congener specific analysis), a given peak may represent more than one chemical (see Table 3-9).

Extensive sample preparation followed by gas chromatography/mass spectrometry (GC/MS) analysis is necessary to validate that a given peak is a PCB. This is the method of choice for the quantitation of very low levels of coplanar PCBs. However, for comparison of half-life estimates, it is not necessary to compare absolute PCB concentrations in different studies. Half-life estimates for a given study do depend on a consistent analytical method used to quantify PCB levels in biological samples obtained at two or more time points. The studies cited in Tables 3-9 and 3-10 are often limited by small sample size, short sampling intervals, and low initial body burdens.

Half-life estimates of less than one year have been reported by several studies in Tables 3-9 and 3-10. Buhler (1989) reported elimination in a single volunteer that ingested a single dose of a uniformly ^{13}C-labeled PCB mixture similar to Aroclor 1254 (329 μg/kg). Blood samples were taken during a 260 day period and analyzed for the concentration of ^{13}C- and ^{12}C-PCB using GC/electron capture detection (ECD) and GC/MS. Elimination of congeners followed first order kinetics and resulted in half lives of <1 year in this individual. These short apparent half-life estimates may be measuring a redistribution of the PCBs among body compartments during this relatively short sampling time rather than actual elimination from the body. Luotamo et al. (1991) estimated very short apparent PCB half-lives of 0.02–0.13 years in 12 individuals involved in a capacitor accident at a pulp mill. Apparent half-life estimates were based on blood and adipose tissue taken 1 and 30 days following the accident. Since the first sample was taken only 1 day following the accident, it is likely that equilibrium had not yet been reached and that absorption and/or distribution of the PCB exposure/dose was still occurring at that early time point. The sampling interval (29 days) was also very short in this study, particularly for highly persistent PCB congeners. These limitations must be considered in interpreting the half-life data from this study, which is much shorter than other studies.

Wolff and Schecter (1991) investigated an accident where four children (2–6 years of age) were exposed to PCBs while playing with parts of a capacitor. The excess exposure resulted in a serum PCB concentration of lower chlorinated congeners, similar to Aroclor 1242, that was about 4-fold above the reference group. Half-life estimates in Table 3-9 were based on serum samples obtained on 1–4 children at 5 and/or 11 months following the accident. Packed column GC of the serum samples resulted in detected peaks that often contained more than one PCB congener. Infinite half-lives were reported for seven congeners in Table 3-9, based on the fact that the levels of these congeners did not decline over time. One explanation for this observation was that the accidental exposure did not markedly increase the levels of these congeners, which appear to be at steady state. Furthermore, there was no correction for the growth of the children, which would dilute the PCB concentration over time. The remaining four

Table 3-9. Apparent Half-lives (Years) of PCB Congeners from Multiple Studies

Congener	Brown et al. 1989	Buhler et al. 1988	Chen et al. 1982[a,b]	Chen et al. 1982[a,c]	Luotamo et al. 1991[d]	Luotamo et al. 1991[e]	Ryan et al. 1993[f]	Wolff and Schecter 1991[g]	Wolff et al. 1992[h]	Yakushiji et al. 1984
18					0.02	0.03				
31								0.5[i]		
28	1.4				0.05	0.12		0.5[i]	4.8	3.0
33					0.02	0.02				
52								0.3[j]	5.5[k]	
47					0.2			0.3[j]	5.5[k]	
44								4	1.6	
72								4	1.2	
74	3.2				4	4		4[l]	4[m]	8.4
70								4[l]		
66						0.03	2.5	4[l]	4[m]	
95								0.4[n]	3[n]	
60									3[n]	
56								4	3[n]	
101					0.02	0.04		4[o]	5.7[o]	
99	3.3							4[o]	5.7[o]	
108		0.3–0.8[p]								
118	5.8	0.3–0.8[p]	0.83	0.77			1.2		9.6	

Table 3-9. Apparent Half-lives (Years) of PCB Congeners from Multiple Studies *(continued)*

Congener	Brown et al. 1989	Buhler et al. 1988	Chen et al. 1982[a,b]	Chen et al. 1982[a,c]	Luotamo et al. 1991[d]	Luotamo et al. 1991[e]	Ryan et al. 1993[f]	Wolff and Schecter 1991[g]	Wolff et al. 1992[h]	Yakushiji et al. 1984
153	12.4	0.93	47	26		4	3.8		4[q]	27.5
105	3.9		0.58	0.51					4[q]	
138	6–7	0.88	32	20			3.4		16.7	16.3
163	>20									
183						0.13			7.9[r]	
128			5.2	5.4					7.9[r]	
171						0.08			24	
156			4	4			4.0			
180		0.34	4	4			4.3			9.9
169							10.4			
170			47	71			3.9			
n	39	1	17[s]	7[s]	12	12	1, 3	1–4	18–165	8
Data[t]	Geomean	nr	Median	Median	Mean	Mean	Median	Mean	Geomean	Mean

Source: Modified from Shirai and Kissel (1996)

[a]Recalculated using median concentration ratios
[b]First and second samples
[c]First and third samples
[d]Serum
[e]Adipose
[f]Half-life of congener 169 was not recalculated due to inadequate data.
[g]Does not include adjustment for growth
[h]Based on a 46-month interval
[i]Co-eluting 28/31
[j]Co-eluting 47/48/52
[k]Co-eluting 47/49/52
[l]Co-eluting 74/66/70
[m]Co-eluting 74/66
[n]Co-eluting 95/56/60
[o]Co-eluting 99/101
[p]Co-eluting 108/118
[q]Co-eluting 153/105
[r]Co-eluting 183–128
[s]For congener 105, the n's were 14 and 6
[t]Mean = arithmetic mean; geomean = geometric mean; nr - not reported

Table 3-10. Apparent Half-lives (Years) of PCB Mixtures from Multiple Studies

Mixture	Elo et al. 1985	Hara 1985	Phillips et al. 1989	Steele et al. 1986[a]	Taylor and Lawrence 1992	Wolff and Schecter 1991[b]	Wolff et al. 1992[c]	Yakushiji et al. 1984	Yakushiji et al. 1984
Clophen A30	0.02								
Kanechlors									
300		5.1							
300/500		>15						0.67	7.1, 2.8[d]
Aroclors									
1242			2.6	2.0	1.8	0.9, 4[e]			
1248							8.6		
1254			4.8		3.3		65		
1260				27.6	4.1	1.2, 0.5[e]			
n	12	20, 14	58	5	148, 148, 121	4–5	18–165	1	8, 18
Data[f]	nr	Mean	Median	Median	Geomean	Mean	Geomean	Mean	Mean

Source: Modified from Shirai and Kissel (1996)

[a]Recalculated using median concentration ratio
[b]Not adjusted for growth rate
[c]Based on a 46- month interval
[d]Mothers and children, respectively
[e]Direct and indirect exposure groups, respectively
[f]Mean = arithmetic mean; geomean = geometric mean; nr = not reported

reported congeners had apparent half-lives of 0.3–0.5 years, and due to lack of chromatographic resolution, represent at least eight PCB congeners. Thus, there are serious limitations of the apparent half-life estimates from the congener data of Wolff and Schecter (1991) (Table 3-9). Apparent half-life estimates for PCB mixtures (Aroclor 1242 and 1260) are presented in Table 3-10 for these four children and five adults and teenagers that had an opportunity for indirect exposure, since they lived in the same households as the children (Wolff and Schecter 1991). Half-lives of 0.9 and 1.2 years were reported in the children for lower and higher chlorinated congeners, respectively. The PCB levels in the five teenagers and adults were not different from unexposed individuals, and were likely to be at steady state. Thus, although apparent half-lives were reported for the five teenagers and adults, the lack of excess exposure in this group makes half-life estimates of limited value.

Chen et al. (1982) measured blood PCB levels in 17 subjects from Taiwan that consumed PCB contaminated rice-bran oil in March and April of 1979 (*Yu-Cheng* episode). Blood was sampled for PCB analysis in 1980 and 1981. The authors estimated apparent half-lives of 0.83 and 0.58 years for PCB 118 and 105, respectively. The authors stated that half-lives of other congeners in blood were not calculated because they were either too long or too short to calculate or because the concentrations of these PCBs in blood were too small to accurately measure. Shirai and Kissel (1996) estimated the apparent half-lives for the other congeners reported by Chen et al. (1982), which ranged from 5.2 years to infinity. PCB exposures in this study were relatively low (0.7–4.7 ppb initially) and thus, the long half-lives may reflect near steady state conditions over this relatively short sampling period and, should be interpreted cautiously.

Wolff et al. (1992) estimated the apparent half-lives of PCBs in up to 165 capacitor manufacturing workers with initial serum total PCB levels of 1.2–24 ppb. Blood samples were taken in March of 1976 and in December of 1979 and the serum PCB levels were measured by packed column GC, which often results in two or more PCBs co-eluting in the same peak. Apparent half-lives in Table 3-9 range from 1.2 years to infinity. One explanation for the longer half-lives of certain congeners is that excess exposure to PCBs occurred in some individuals during the interval between 1976 and 1979. Excess occupational exposure could have occurred from 1976 to 1977, when all PCB use stopped. Although PCBs may not have been in use in the manufacturing facilities from 1977 to 1979, residual contamination at and around the work site could have contributed to additional occupational exposure. Secondary exposures from nonoccupational sources such as high fish consumption rates, and/or exposure in homes may also impact on loss rates. The apparent half-life estimates in Table 3-9 do not consider excess exposure to PCBs during the sampling interval and thus may be an over estimate of the relative

persistence of particularly the congeners with half-lives in excess of 10 years. The above factors also contribute to the long apparent half-lives reported by Wolff et al. (1992) for the low and particularly the highly chlorinated PCBs (Table 3-10).

Brown et al. (1989) investigated a subgroup of 39 individuals, originally from the study of Lawton et al. (1985a, 1985b), who had occupational exposure to PCBs from two capacitor plants. Inhalation and dermal contact were considered the main routes of occupational exposure. PCBs were measured in serum from blood samples obtained in 1976 and 1983. Apparent half-lives ranged from 1.4 years for PCB 28 to >20 years for PCB 163. Once again, excess occupational exposure to PCBs was possible over the sampling period, particularly from 1976 to 1977, which would increase the apparent half-life estimates. However, strengths of the study include the 7-year sampling period and the 39 subjects. Brown et al. (1989) made an interesting comparison between this population and that reported for a Taiwan population (*Yu-Cheng*) which was accidentally exposed via ingestion of contaminated rice oil (Chen et al. 1982). It was found that the mono-*ortho* congeners (PCBs 74, 118, 105) were cleared 3–7 times faster in the *Yu-Cheng* population than the capacitor workers, while the di-*ortho* congeners (PCBs 99, 153, 138) were eliminated 3–7 times more slowly in the *Yu-Cheng* population. Brown et al. (1989) speculated that these differences may have been related to alterations in the cytochrome P-450 mediated metabolism of PCBs in the *Yu-Cheng* population that was exposed to PCBs and PCDFs. Specifically, they speculated that PCDF exposure in the *Yu-Cheng* population may have produced an increase in CYP1A and depression of CYP2 forms.

Ryan et al. (1993) estimated the apparent half-lives of the seven most abundant PCBs in three individuals who ingested PCB contaminated rice oil in Taiwan (*Yu-Cheng*) in 1979. Blood samples were obtained 171, 425, 1,049, 2,025, and 3,502 days following the first sampling in May of 1980. Total PCBs levels in 1980 ranged from 150 to 400 ppb and 9 years later, decreased to about 30–35 ppb. PCB 180 was the most persistent, with apparent half-lives ranging from 3.7 to 5.7 years (median of 4.3 years). PCB 118 was the least persistent of the measured congeners, with apparent half-lives ranging from 1.1 to 1.3 years (median of 1.2 years). The apparent half-life for total PCBs ranged from 3.2 to 4.6 years (median of 3.5 years). This study was not limited by short sampling intervals, low initial body burdens, or the method for PCB analysis. Although the results were obtained from only three subjects, this study provides a good estimate of the apparent half-lives of the most abundant PCB congeners in humans (Table 3-9). Half-lives may still have been extended from ambient exposures, though.

Yakushiji et al. (1984) studied PCB elimination over a 3-year period in eight Japanese women occupationally exposed to Kanechlor 300 (similar to Aroclor 1242). Apparent half-lives for this mixture of 7.1 and 2.8 years were reported for these eight women and their children (1–13 years of age), respectively (Table 3-10). Initial whole blood mean PCB concentrations were 42 and 30 ppb for the women and children, respectively. The shorter half-life in children may be related to growth over the 3-year sampling period and subsequent dilution of PCB blood levels with increasing mass. Apparent half-lives for four PCB congeners in the eight occupationally-exposed women were also reported in Table 3-9.

In 1977 and 1985, serum PCB concentrations were determined for 58 workers in a factory that used PCBs in capacitor manufacturing until 1977 (Phillips et al. 1989a). This study expanded upon the earlier investigation in five members of this cohort (Steele et al. 1986). Less chlorinated PCBs were quantitated as Aroclor 1242, and more highly chlorinated congeners were quantitated as Aroclor 1254. The workers had excess occupational exposure, as documented by serum PCB levels of 2–3,300 and 5–250 ppb in 1977 for Aroclors 1242 and 1254, respectively. Median apparent half-lives of 2.6 and 4.8 years for Aroclors 1242 and 1254, respectively (Table 3-10). The half-lives of the respective mixtures in each individual varied inversely with the initial (1977) serum concentrations, with more rapid elimination occurring at higher PCB levels. This relationship may be a result of continued low level PCB exposure, variations in the time of exposure, and/or cytochrome P-450 induction, with the resulting increase in PCB metabolism and elimination at high initial PCB body burdens. Strengths of the study by Phillips et al. (1989a) are the population size (n=58) and the 8-year sampling interval. The study was limited by not providing congener specific analysis.

Taylor and Lawrence (1992) reported apparent half-lives in another occupational cohort, where serum PCB levels were available from 1979 and 1983 on 148 workers for Aroclors 1242 and 1254, and 121 workers for Aroclor 1260. The range of concentrations in serum in 1979 were 0–3,133, 4–639, and 4–377 ppb for Aroclors 1242, 1254, and 1260, respectively. The apparent half-lives in this study (Table 3-10) were similar to those reported by Phillips et al. (1989a) for another occupationally exposed group. As in the earlier report by Phillips et al. (1989), this study observed more rapid elimination of PCBs in individuals with higher initial (Phillips et al. 1979) serum PCB levels. Again, this relationship may be a result of continued low level PCB exposure, variations in the time of exposure, and/or cytochrome P-450 induction, with the resulting increase in PCB metabolism and elimination at high initial PCB body burdens.

In summary, the studies by Phillips et al. (1989a) and Taylor and Lawrence (1992) on apparent half-lives of PCB mixtures (Table 3-10) are in general agreement. These are well designed studies in two different occupational cohorts that are not limited by small sample size, short sampling intervals, or low initial body burdens. The main limitation of these studies was that congener specific PCB analysis was not conducted. Nevertheless, these studies provide the best estimates of the apparent half-lives of PCB mixtures following occupational exposure.

Animal Studies. In experimental animals, the major PCB excretion pathways were the fecal and urinary routes (Lutz and Dedrick 1987; Sipes and Schnellmann 1987), although trace amounts were reported in expired air of rats 24 hours after gavage administration of hexa- and tetrachlorobiphenyl (Hashimoto et al. 1976). Biliary excretion represents a major source of the PCB compounds found in the feces (Allen et al. 1974b; Norback et al. 1976). Significant amounts of PCBs can also be eliminated through lactation (see Section 3.7, Children's Susceptibility). At equilibrium, chlorobiphenyl congeners are eliminated from tissues according to individual kinetic parameters. For example, rats that received six weekly doses of PCBs showed three general patterns of elimination (Tanabe et al. 1981). One group of compounds, primarily di- and trichlorobiphenyls, had elimination half-lives of 1–2 days; a second group, primarily tetrachlorobiphenyls, had two elimination constants: one between 2 and 10 days and a second one of #90 days. A third group, composed mostly of penta- and hexachlorobiphenyls, had single elimination half-lives of >90 days. Thus, highly chlorinated PCBs are preferentially retained, probably because of a lower metabolism rate.

A 2-phase elimination process was also described in monkeys fed 2,4N,5-triCB for 84 days. When dosing was discontinued, the initial rapid phase had a whole body elimination half-life of 30–32 hours and was followed by a slower process, with a combined urinary and fecal excretion half-life of 4.5–4.8 days (Felt et al. 1977).

Elimination half-lives from blood between 0.3 and 7.6 years were estimated for a group of mono-*ortho*-chlorine-substituted PCB congeners in monkeys dosed with Aroclor 1254 for over 6 years (Mes et al. 1995a). In these monkeys, steady-state in adipose tissue had apparently been achieved after 37 months of dosing. Half-lives were estimated from blood measurements every 2 weeks after treatment ceased and monthly during the subsequent 2 years. The half-lives did not seem to be dose-dependent over the dose range tested (0.005, 0.02, 0.04, or 0.08 mg/kg/day). The wide range estimates were probably due to the small sample size (n=3) and the great degree of variation among the individual monkeys.

The very long half-lives of some PCBs introduces a dilution-by-growth variable that must be considered in making comparisons. Weanling pigs were given seven daily oral doses of one of three single-congener PCBs, or Aroclor 1254 for a total of 15 mg/kg (Hansen and Welborn 1977). Blood and biopsied backfat were monitored for up to 118 days, and the increase in total body fat was determined. If elimination was based on concentration in the backfat, half-lives of 24, 24, 63, and 42 days were determined for the three single congeners and Aroclor 1254, respectively. Half-lives based on estimated total body PCBs increased to 108, 268, >300, and 284 days, respectively. Body weights increased 370–560% in these rapidly growing animals and percent fat increased disproportionally from about 21% body weight to near 28% body weight during the duration of the study. The long total body half-lives in swine compared to rats (Anderson et al. 1993; Mühlebach and Bickel 1981) reflect sequestering in a larger and expanding compartment, making less PCB available for metabolism as well as elimination. This may be more relevant to some humans with fluctuating body weight and composition, contributing to the long half-lives reported by Wolff et al. (1992a, 1992b).

An important factor in the elimination process of PCBs is the location of the chlorine atoms in the phenyl rings. This was studied in mice administered a series of PCBs with different molecular configurations (Gage and Holm 1976). For the series of PCB congeners tested, the results show that differential biotransformation results in compounds having at least one pair of unsubstituted *ortho-meta* vicinal carbon atoms (positions two and three) being excreted much faster than those with other configurations, but this was greatly diminished by chlorines in the 2,2'- or 2',2'-positions.

The chemical identity of the PCB metabolites excreted by different species greatly depends on the structure of the parent compound. This has been studied by numerous investigators. In rats, 85% of the fecal excretion of metabolites derived from a hexachlorobiphenyl was hexane-extractable, indicating the presence of nonpolar compounds as opposed to urinary metabolites, which are usually polar derivatives (Mühlebach and Bickel 1981). Analysis of the feces of rats dosed with 3,3N,4,4N-tetraCB revealed parent compound (indicative of incomplete absorption), 5-hydroxy-tetraCB, 6-hydroxy-tetraCB, and 4-hydroxy-3,3N,4N,5-tetraCB, whereas the urine contained mainly conjugated hydroxylated metabolites (Klasson-Wehler et al. 1989a, 1989b). Rats treated with 2,3-diCB and 2,4,6,-triCB excreted compounds hydroxylated in the 4-position in the feces; a dihydroxy metabolite in position 3- and 4- was also identified (Goto et al. 1974). The major metabolites found in the urine of monkeys treated with 2,5,4N-triCB were free and conjugated monohydroxy derivatives; the feces were not examined (Felt et al. 1977). The urine of rabbits administered 2,2N,5,5N-tetraCB revealed 3-hydroxy-2,2N,5,5N-tetraCB, 4-hydroxy-2,2N,5,5N-tetraCB, and a trans 3,4-dihydro-3,4-dihydroxy-2,2N,5,5N-tetraCB (Gardner et al.

1973). Excretion of radioactive material in the urine of ferrets treated with ^{14}C-labeled Aroclor 1254 accounted for <10% of the amount excreted in the feces (Bleavins et al. 1984). During the first week after dosing, 22.1 and 1.8% of the dose was excreted in the feces and urine, respectively. Total excretion diminished considerably during subsequent weeks.

3.4.4.3 Dermal Exposure

Limited data were found regarding the excretion of PCBs in experimental animals following dermal exposure. The urinary excretion half-life of an undefined PCB containing 42% chlorine applied to the abdominal skin was 6.9 days in monkeys (Wester et al. 1983). In guinea pigs in which the same mixture was applied to the back of the ear, a 2-phase urinary excretion process was observed. The first phase was rapid, with an elimination half-life of 1.9 days, and was followed by a slower phase, with an elimination half-life of 12.6 days. However, the elimination half-life of a PCB containing 54% chlorine was 2.9 days and was linear for the duration (16 days) of the urine collection (Wester et al. 1983). Wester et al. (1990) reported that following percutaneous application of 4 μg ^{14}C-labeled Aroclor 1242/cm^2 to the abdominal skin of monkeys (four per group), a maximum of 11% of the dose (as ^{14}C-derived radioactivity) was excreted over a 30-day period when the solvent was mineral oil, while 10% was excreted when the solvent was trichlorobenzene (unspecified isomer). Excretion was virtually complete after the first 10 days. Urinary excretion of ^{14}C-derived radioactivity was approximately 2 times fecal excretion. Following application of 4.8 μg ^{14}C-labeled Aroclor 1254/cm^2 in mineral oil or trichlorobenzene, 5.5 and 3.9% of the dose, respectively, was excreted over a 30-day period. The probability that the authors measured only excretion for the most readily metabolized components is increased because in the most recent study, which specified Aroclor mixtures, urinary excretion was 2 times fecal excretion and urinary excretion was virtually complete after 10 days.

3.4.4.4 Other Routes of Exposure

Excretion of PCBs and metabolites after parenteral administration follows the same general pattern as after oral administration: much greater amounts are excreted in the feces than in the urine. Furthermore, nonpolar derivatives are found in the feces, whereas polar metabolites are preferentially found in the urine.

In rats, 80% of an intravenous dose of ^{14}C-labeled 3,3′,5,5′-tetraCB was excreted in the feces over a 42-day period, whereas only 6.1% was excreted in the urine (Tuey and Matthews 1977). Less than 10%

of the radioactivity in bile, feces, and urine was parent compound. The terminal half-life for whole-body elimination was 9.8 days. In contrast to the tetrachlorobiphenyl, excretion of ^{14}C-labeled 2,2N,4,4N,5,5N-hexaCB was minimal after intravenous injection in rats. Only 16% of the dose was excreted in the feces over 40 weeks, while urinary excretion accounted for 0.8% of the dose (Mühlebach and Bickel 1981). It has been suggested that the hexachlorobiphenyl, which is minimally metabolized, was stored after redistribution (Hansen and Welborn 1977; Mühlebach and Bickel 1981). The higher lipid solubility of the hexachlorobiphenyl may have also contributed to the greater retention of this congener. The significance of the chlorine substitution in the phenyl rings was examined by Kato et al. (1980), who injected four symmetrical hexachlorobiphenyls intravenously in rats. Most of the administered doses underwent predominantly fecal elimination. The 2,2N,3,3N,6,6N-hexaCB congener, which has unsubstituted vicinal carbon atoms, was rapidly and extensively (90%) excreted over a 7-day period. For the other isomers, <15% was excreted over the 7-day period.

Following intravenous injection of 32.7 µg Aroclor 1242 to Rhesus monkeys, 39.4% of the administered dose was excreted in the urine, and 16.1% was excreted in the feces over a 34-day period (Wester et al. 1990); the bulk of the dose (>90%) was excreted within the first 10 days. For Aroclor 1254, 7% of the administered dose (47.4 µg) was excreted in the urine and 19.7% in the feces over a 30-day period. The duration of the study probably accounted for only the most rapidly metabolized components of the mixtures (Kato et al. 1980; Lutz and Dedrick 1987).

In rats with ligated bile ducts, unchanged 2,3N,4,4N-tetraCB appeared in the small intestine 1 hour after intravenous injection suggesting that the wall of the small intestine is an important site of PCB excretion (Yoshimura and Yamamoto 1975). Lactation was also shown to be a major route of excretion of PCBs from postpartum mice administered the compounds before pregnancy (Gallenberg and Vodicnik 1987).

The time-course of elimination of several PCB congeners (mono and di-*ortho*-substituted penta-, hexa-, and heptachlorobiphenyls) was examined in the liver, lungs, and carcass of mice over a period of several weeks after a single intraperitoneal dose of 500 mg Aroclor 1254/kg at 8 days of age (Anderson et al. 1993). The concentration of total PCBs decreased in the three compartments as a function of time. Analyses of elimination half-times for total PCBs from carcass and liver, and of changes in body weight indicated excretion as well as dilution. All congeners were efficiently retained in the lung and decreased only as a function of dilution due to growth. In general, congeners with pairs of unsubstituted carbons were eliminated faster than those without unsubstituted carbon pairs. The changes in liver over time were complex: there was retention of all congeners during the prepubertal growth phase, with specific

enrichment of 2,3,3N,4,4N-pentaCB. This was followed by more rapid elimination of certain congeners at a later time. The investigators suggested that changes in the liver may have reflected differences or changes in amounts or types of lipids, in binding proteins, and/or in metabolizing enzymes.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

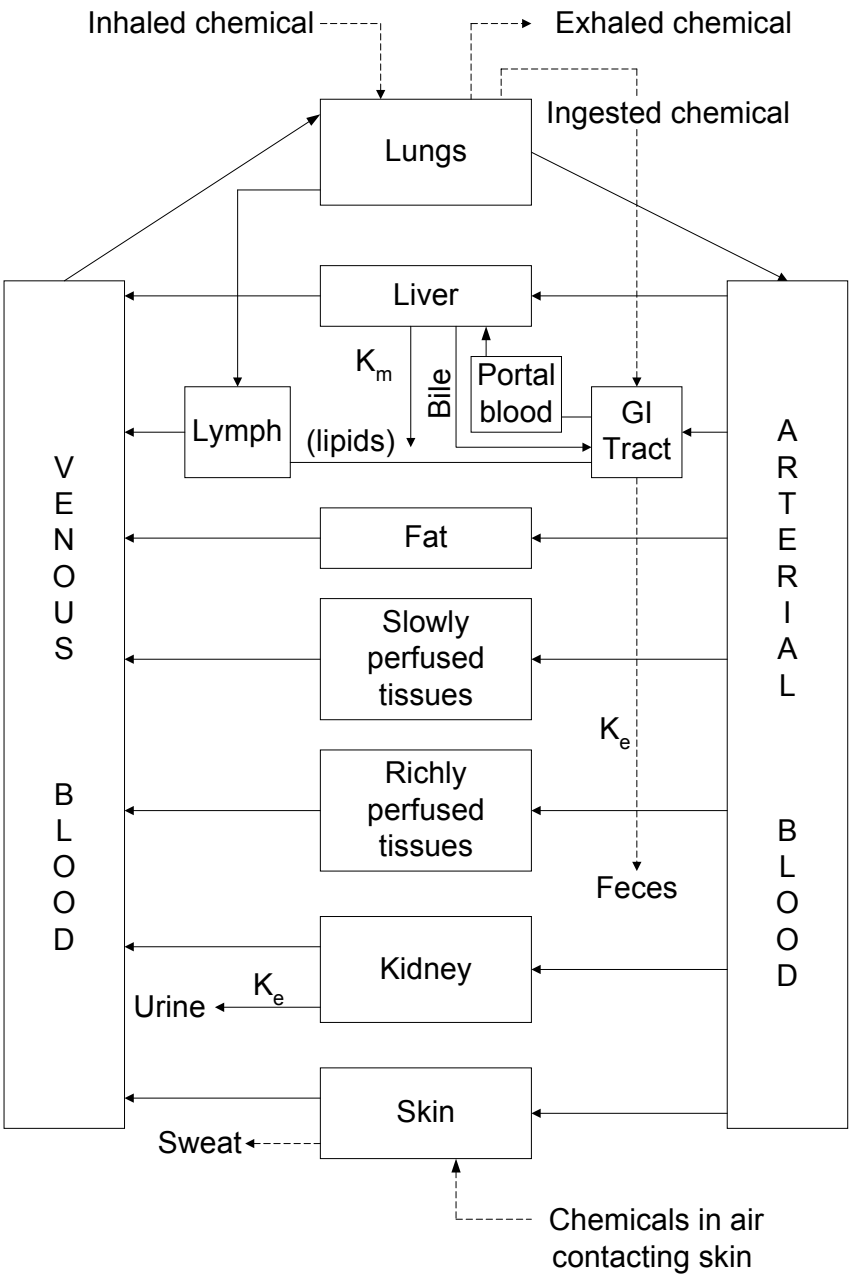
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

3.4.5.1 Summary of the PBPK Model

A flow-limited physiologic pharmacokinetic model was formulated to describe the individual kinetics of the tissue distribution, metabolism, and excretion of several PCB congeners in the rat, mouse, dog, and monkey. In general, the model predicted well the experimental data, but some deviations were apparent. Rates of metabolism were species specific, and there was no apparent scaling factor, such as body weight or surface area, for predicting metabolic rates from species to species. Meaningful extrapolation of data among species is dependent on accurate estimates of the rates of PCB congener metabolism.

The information presented below has been extracted from studies by Lutz et al. (1977), Tuey and Matthews (1980), and Lutz et al. (1984), and from reviews of those studies by Matthews and Dedrick (1984) and Lutz and Dedrick (1987). Models for the prediction of congener-specific PBPK parameters (tissue:blood partition coefficients, rates of metabolism) from structural information are discussed at the end of this section.

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. (1994) and Hansen (1999)

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed by inhalation, by ingestion, or via the skin; metabolized in the liver; and excreted in the urine, bile, feces, sweat, or by exhalation. Lymphatic absorption from the gastrointestinal tract avoids the first-pass effect of liver metabolism and is very important for lipophilic chemicals (e.g., PCBs). Important first-order rate constants are K_e (elimination) and K_m (metabolism).

3.4.5.2 Description of the Model

The PBPK model for PCBs includes several compartments (Figure 3-4) thought to represent regions of substantial chemical uptake, regions involved in the clearance process, or regions of interest due to their toxic response to PCBs. Transport of the PCBs occurs by the inflow and outflow of blood through the compartment, by transcapillary transport, and by transport across cell membranes. The concept of blood flow-limited uptake was used because experimental data appeared to indicate that PCBs leave the blood and enter tissues very rapidly. Therefore, the assumption was made that the uptake is flowlimited. In Figure 3-4, dashed lines within compartments represent rapid equilibrium partitioning between blood and tissue space. In order to simplify the model, metabolism of PCBs was assumed to occur in the liver compartment as a single step leading to the formation of one metabolite that is excreted in the urine and bile as the glucuronide conjugate. The mathematical model consists of a set of differential equations describing mass balances on each PCB congener in each compartment. For example, for a tissue in which metabolism may occur, such as the liver, the mass balance takes the form

$$d(V_L C_L)/dt = Q_L(C_B - C_L/R_L) - (k_m \times C_L/R_L)$$

where t = time, V = tissue volume or mass, C = concentration, Q = blood flow rate, k_m = metabolic rate constant, and R = tissue/blood distribution coefficient. The subscripts L and B refer to liver and blood, respectively.

The PCB model was initially constructed to describe the distribution of 4-monoCB, 4,4N-diCB, 2,2N,4,5,5N-pentaCB and 2,2N,4,4N,5,5N-hexaCB in Sprague-Dawley rats following a single intravenous dose (0.6 mg/kg) of the PCB congeners (Lutz et al. 1977). The same model was subsequently applied to these congeners in CD-1 mice administered a single 0.6 mg/kg intravenous dose of the same PCB congeners (Tuey and Matthews 1980). In the dog (beagle) and monkey (Cynomolgus), 4,4N-diCB, 2,2N,4,4N,5,5N-hexaCB, and 2,2N,3,3N,6,6N-hexaCB were modeled, also after a single intravenous dose of 0.6 mg/kg (Lutz et al. 1984). The latter two congeners were chosen since they have the same number of chlorines, but 2,2N,3,3N,6,6N-hexaCB has two adjacent unsubstituted carbons, which has been shown to enhance metabolism.

Many of the parameters used in the model, in particular anatomical parameters and blood flow rates, were available from the literature. The skin flow rate used in the model had to be reduced by 10-fold in order to simulate the behavior of PCBs in the skin. Use of measured values or literature values resulted in

overprediction of the skin PCB concentration at early times by a considerable amount. This may have reflected a deviation from a flow-limited transport mechanism in the skin. Distribution coefficients (R) for both parent and metabolite were estimated for each compartment by taking the respective ratios of the specific tissue concentration to the blood concentrations at times when the compartments (tissues) were assumed to be in equilibrium with effluent venous blood. This implies that elimination is sufficiently slow so that the venous blood is a fair representation of the effluent venous blood from each tissue. Metabolic rate constants (k_m) for rapidly metabolized PCB congeners were estimated by dividing the amount of PCB appearing in the urine, feces, and tissue, by area under the blood concentration-time curve for a given time interval. For slowly metabolized PCB congeners, k_m was estimated by dividing the average rate of excretion of metabolite by the average blood concentration of metabolite. The rate of urinary excretion was assumed to be proportional to the blood metabolite concentration. Urinary clearance (k_K) was estimated by dividing the amount of PCB metabolite collected in the urine by the area under the metabolite blood curve. Biliary excretion (k_B) was estimated from direct cannulation of the bile duct or calculated from fecal excretion rates. Liver equations for the dog and monkeys carried an additional term that allowed for preferential and rapid removal of a specified fraction (F) of the PCB from the liver blood pool; this fraction was rapidly and irreversibly transferred to the bile fluid. Some metabolism parameters (metabolism rate, kidney clearance rate, biliary clearance rate) for the mouse were scaled from values reported for the rat.

3.4.5.3 Discussion of the Model

Anatomical parameters used in the model are listed in Table 3-11. Metabolism and clearance parameters are listed in Tables 3-12, 3-13, and 3-14. Table 3-12 shows that in the animal species examined k_m decrease as chlorination increases, but the chlorine position also determines the rate of metabolism. This is suggested by the difference in k_m values between 2,2N,3,3N,6,6N-hexaCB and 2,2N,4,4N,5,5N-hexaCB in the rat, dog, and monkey. It appears that the *meta* and *para* positions are preferred sites for arene oxide formation, which would explain why the k_m for 2,2N,3,3N,6,6N-hexaCB is even larger than for 4,4N-diCB. Table 3-12 also shows no apparent interspecies correlation of k_m with body weight or surface area. As body size increased, k_m increased, but when the parameters are normalized by either body weight or body surface area, no consistent pattern of k_m is evident. On any basis, k_m values for the dog are greater than those for the mouse, rat, or monkey. Based on these data alone, it cannot be ascertained which species, if any, would predict PCB metabolism in humans; however, the collective data integrated with human residue data have been developed into what appears to be a reliable model (Brown 1994).

Table 3-11. Volumes and Flow Rates in Several Tissues of Four Species[a]

	Volumes (mL)				Blood flow rates (mL/minute)			
	Mouse 30 g	Rat 250 g	Monkey 5 kg	Dog 12 kg	Mouse 30 g	Rat 250 g	Monkey 5 kg	Dog 12 kg
Blood	2.89	22.5	300	1000	–	–	–	–
Muscle	17.1	125	2068	5530	1.42	7.5	103	275
Liver	2.24	10	118	480	3.1	16	125	342
Skin	5.51	40	470	1680	0.12	0.5	2.7	11.7
Fat	3.72	17.5	389	777	0.1	0.4	10.7	17.9

[a]Values were used in physiologic pharmacokinetic model.

Source: Lutz and Dedrick 1987

Table 3-12. Metabolism Rate Constant (k) from the Physiologic Model[a,b]

	4-MCB	4,4'-DCB	2,2',4,5,5'-PCB	2,4,5-HCB	2,3,6-HCB
k_m mL/min					
Mouse (30 g)	2.4	0.37	0.095	0.01	–
Rat (250 g)	10	2	0.39	0.045	5
Monkey (5 kg)	–	7	–	0.67	15
Dog (12 kg)	–	470	–	16	183
k_m mL/min/kg					
Mouse	68.5	9.7	2.5	0.25	–
Rat	40	8	1.56	0.18	20
Monkey	–	1.4	–	0.13	3
Dog	–	39	–	1.33	15.2
k_m mL/min/kg$^{0.7}$					
Mouse	25	3.7	0.94	0.1	–
Rat	26.4	5.2	1.02	0.12	13
Monkey	–	2.3	–	0.22	5
Dog	–	82	–	2.8	32

[a]Source: Lutz and Dedrick 1987

[b]Middle set of numbers is per-unit animal body weight, mL/min/kg. Bottom set is mL/min/kg$^{0.7}$, since body surface area is approximately proportional to body weight to the 0.7 power.

DCB = dichlorobiphenyl; HCB = hexachlorobiphenyl; MCB = monochlorobiphenyl; PCB = pentachlorobiphenyl

Table 3-13. Tissue-to-blood Distribution Coefficients for Parent Polychlorinated Biphenyls (R) and Metabolites (R')

	4-Monochlorobiphenyl				4,4′-Dichlorobiphenyl				2,2′4,5,5′-Pentachlorobiphenyl			
	Mouse	Rat	Monkey	Dog	Mouse	Rat	Monkey	Dog	Mouse	Rat	Monkey	Dog
Parent, R												
Muscle	1	1	–	–	2	2	5	4	5	1	–	–
Skin	10	10	–	–	10	10	50	12	20	7	–	–
Fat	30	30	–	–	70	70	300	40	200	70	–	–
Liver	1	1	–	–	5	3	20	6	14	12	–	–
Metabolite, R′												
Muscle	0.14	0.14	–	–	0.4	0.4			0.1	0.1	–	–
Skin	0.25	0.25	–	–	0.8	0.3			0.1	0.1	–	–
Fat	0.4	0.4	–	–	1	0.6			0.4	0.4	–	–
Liver	2	2	–	–	4	5			2	2	–	–

	2,4,5-Hexachlorobiphenyl				2,3,6-Hexachlorobiphenyl			
	Mouse	Rat	Monkey	Dog	Mouse	Rat	Monkey	Dog
Parent, R								
Muscle	5	4	7	6	–	–	4	4
Skin	35	30	70	30	–	–	40	8
Fat	300	400	500	300	–	–	250	30
Liver	10	12	30	10	–	–	20	2
Metabolite, R′								
Muscle	3	0.3	1	0.2	–	–	0.1	0.1
Skin	5	2	3	0.7	–	–	0.5	0.2
Fat	1	2	9	2	–	–	1	0.25
Liver	10	4	5	10	–	–	5	10

Source: Lutz and Dedrick 1987

Table 3-14. Kidney Clearance (k_k) and Biliary Clearance (k_g) for Selected Polychlorinated Biphenyls in Several Species[a,b]

	4-MCB		4,4N-DCB		2,2N,4,5,5N-PCB		2,4,5-HCB		2,3,6-HCB	
	k_g	k_k	k_g	k_k	k_g	k_k	k_g	k_k	k_g	k_k
Mouse (30 g)	0.05	0.05	0.15	0.069	0.10	0.009	0.074	0.018	–	–
Rat (250 g)	0.2	0.2	0.35	0.133	0.3	0.033	0.30	0.03	1.0	0.03
Monkey (5 kg)	–	–	0.083	1.5	–	–	0.70	0.041	0.5	0.4
Dog (12 kg)	–	–	10.2	2.7	–	–	1.8	0.15	7.0	2.0

[a]Source: Lutz and Dedrick 1987
[b]Clearance values are in mL/minute.

DCB = dichlorobiphenyl; HCB = hexachlorobiphenyl; MCB = monochlorobiphenyl; PCB = pentachlorobiphenyl

Table 3-13 lists tissue/blood distribution coefficients (R) for parent compounds and metabolites. In the four species tested, and for all the PCB congeners modeled, the rank order for R is fat >skin >liver >muscle >blood. The large R for parent PCBs in adipose tissue is not unexpected considering the lipophilic nature of the compounds. Also, as expected, Rs for metabolites were considerably lower than those for the parent compounds. This is likely because glucuronide conjugates of the parent compound are less lipophilic and more water soluble. The largest R for metabolites were found in the liver, reflecting the fact that metabolism of PCBs occurs primarily in the liver. Clearance parameters for biliary and urinary elimination listed in Table 3-14 do not show any apparent interspecies scaling correlations.

3.4.5.4 Validation of the Model

The model used to simulate the data described well the kinetics of distribution, metabolism, and excretion of the PCB congeners studied in adult animals. However, some deviations were apparent. For example, in the rat the model predicted a faster rate of clearance from blood and tissues for lower chlorinated biphenyls beyond 48 hours. This was tentatively attributed to the formation of minor metabolites, which have different pharmacokinetic behavior than the major metabolites. Formation of metabolites covalently bound to tissue macromolecules also was a possibility. The model overpredicted the concentration of PCBs in the skin at early times, suggesting that the use of measured or literature values of skin-flow rate in the flow-limited skin compartment may not have been appropriate. Among the possibilities offered to explain this phenomenon were: the existence of an additional barrier in the skin that reduced uptake, inaccurate measurement of skin blood-flow rates because of shunt flow, and presence of subcutaneous skin fat serving as reservoir for the diffusion of PCBs from the skin tissue. Also, in order to obtain a good simulation of the behavior of the poorly metabolized 2,2N,4,4N,5,5N-hexaCB in rats, a term describing changes in fat volume of the growing rats had to be incorporated into the model. Without this term, the simulations overpredicted the long-term data. Apparent elimination of the PCB congener from blood or adipose tissue was in reality a dilution effect due to the increased fat volume. When the physiological compartment model for the rat was scaled to the mouse, the disposition of PCBs in the latter was in reasonable agreement with the experimental data. An exception was the finding that greater biliary clearance rates than the corresponding rate scaled from the rat for the di-, penta-, and hexachlorobiphenyl were observed. Model simulations of tissue disposition of parent compounds in the monkey were in reasonably good agreement with the experimental data. This was not the case for the dog, a species in which, except for 2,2N,4,4N,5,5N-hexaCB, the simulations underpredicted the experimental data at longer time points. The data showed that the dog metabolized the three PCB congeners tested considerably faster than the monkey. As with the rat, simulations of blood-flow rate to

the skin in the dog and monkey had to be reduced to one-tenth its physiologic value in order to fit the experimental data.

The results of these studies show that pharmacokinetic modeling is a valuable tool for predicting PCB disposition in one animal species by extrapolation of data from other animal species. However, while many similarities exist from species to species, some important differences were also apparent. The most important parameter in the model appeared to be the k_m. Knowledge of this parameter in a species of interest is crucial if reliable predictions of PCB disposition are to be made. Lutz et al. (1984) recognized that "without additional information about metabolism, extrapolation of the present model to simulation of human disposition would be suspect." The model constructed by Lutz and co-workers provides kinetic and metabolic information regarding a very small number of PCB congeners, but not toxicity information that could eventually be used for developing risk assessment approaches for PCBs. The most extensively studied PCB congeners from the point of view of their toxic properties are the dioxin-like congeners. These congeners lack chlorine substitution in the *ortho* position and are isostereomers of 2,3,7,8-TCDD (dioxin). The mechanism of toxicity for these congeners is related to the enhancement of gene expression triggered by initial binding to a cytosol receptor (Ah receptor) (see Section 2.5.2 for further details). Although no PBPK model has been constructed for the dioxin-like congeners, information exists for 2,3,7,8-TCDD. PBPK models for 2,3,7,8-TCDD account not only for determinants of disposition, such as tissue partitioning, biotransformation rates, and protein-binding constants, but also describe pharmacodynamic events related to the induction of specific dioxin-binding proteins in the liver (Leung et al. 1988). Recent refinements of the model incorporate information on the interactions of the dioxin-Ah receptor complex with regulatory regions of specific genes (Andersen et al. 1993). This level of information is expected to provide a basis for investigating the scaling across species of the PBPK model for dioxin and chemicals with common-mediated mechanisms of toxicity.

3.4.5.5 Prediction of Congener Specific PBPK Model Parameters.

Since the toxicity of a given PCB mixture is related to its congener composition, congener-specific information on kinetic parameters is necessary if PBPK models are to be used as part of risk assessment. Methods to predict the tissue:blood partition coefficient (Parham et al. 1997) and metabolic rate constants (Parham and Portier 1998) for all 209 congeners based on structural information are discussed below.

Data from a study of occupationally exposed humans allowed the authors to calculate the adipose:plasma partition coefficient for 24 PCB congeners (Wolff et al. 1982b). In an effort to predict these results by

modeling (Parham et al. 1997), a total of 27 structural descriptors were identified for PCBs (e.g., total number of chlorines, number of *ortho*-chlorines, number of chlorines on most-substituted ring, etc.). A stepwise regression method was used to identify a small set of descriptors that would adequately predict the observed adipose:plasma partition coefficients for each congener. It was found that the three most important structural descriptors for the prediction of the adipose:plasma coefficient were (1) whether the congener had a ring with unsubstituted adjacent *meta* and *para* carbons, (2) the congeners nonplanarity, and (3) the polarity of the congener. The adipose:blood partition coefficient can be derived from the adipose:plasma partition coefficient if the ratio between plasma and whole blood is known for the congener. Stepwise regression was similarly used to predict a data set for the distribution between plasma and the cellular component of blood of eight PCB congeners and biphenyl in the rat (Matthews et al. 1984). In this case, a good fit with the experimental data was obtained with the use of only one structural descriptor, the number of adjacent unsubstituted *meta* and *para* carbons. Conversion from rat blood to human blood was accomplished by adjusting for the higher proportionate volume of the cellular component in rat blood and assuming that all PCBs in plasma are bound to protein in both species. A factor was derived for conversion of the predicted adipose:plasma partition coefficient to the adipose:blood partition in humans; this factor depends on the number of unsubstituted *meta-para* carbon pairs (0-4) in the specific congener. Adjustment factors for partition coefficients for other tissues (liver, muscle, and skin) were developed based on lipid fraction in the tissue, percent nonneutral lipid, and percent neutral lipid.

A similar stepwise regression process has been applied to the prediction of metabolic rate constants for specific PCB congeners from structural descriptors (Parham and Portier 1998). The metabolic rates used as the input for the stepwise regression were derived from *in vitro* rates of formation of metabolites for 25 congeners in rat liver microsomes (Borlakoglu and Wilkins 1993a, 1993b) and from a modification of the Lutz et al. (1977) PBPK model using data from four intravenous injection studies in rats employing nine congeners (Abdel-Hamid et al. 1977; Matthews and Anderson 1975; Tuey and Matthews 1977, 1980). The *in vitro* data included 14 congeners tested with microsomes from Aroclor 1254-induced rats and 11 congeners from noninduced rats. The stepwise regression resulted in seven descriptors included in the model. Five were structural descriptors (degree of chlorination, noncoplanarity, and three that described the presence of adjacent unsubstituted carbon atoms) and two were nonstructural (whether the data was from [1] induced or noninduced rats and [2] *in vitro* or *in vivo* experiments). The final model was used to predict the blood radioactivity data from intravenous injection studies and appeared to fit the experimental data well. Some individual misfits could be attributed to the fact that Borlakoglu and Wilkins (1993a, 1993b) measured only primary metabolites but used prolonged incubation times.

3.5 MECHANISMS OF ACTION

PCBs are lipophilic compounds that are readily absorbed from the gastrointestinal tract. While PCBs in many cases entered the environment as commercial formulations containing a relatively defined mixture of specific PCB congeners, the accumulation and retention of specific PCB congeners in various environmental matrices, wildlife, and humans does not directly reflect the PCB profile of the commercial mixtures. Therefore, it is important to consider the biological fate and activity of individual PCB congeners when assessing the risk that PCBs pose to human health. Although PCBs are found in all tissues analyzed to date, they are stored in high concentration in adipose tissue since they are lipophilic. PCB congeners are metabolized in the liver by microsomal cytochromes P-450 to less lipophilic metabolites that can undergo conjugation with glutathione or glucuronic acid. The rate of congener metabolism is highly dependent on the chlorine substitution pattern in the biphenyl ring. Strong evidence suggests that the mechanism of toxicity for dioxin-like congeners is related to the enhancement of gene expression triggered by initial binding to the same cytosol receptor (Ah) involved in 2,3,7,8-TCDD toxicity. The mechanism(s) of toxicities for other groups of PCB congeners, such as those showing estrogenic or neurotoxic activity, and the mechanism of PCB carcinogenicity, has not been elucidated. Similarly, disruption of neutrophil function and calcium homeostasis appear to be mediated by mechanisms other than the Ah receptor. Disruption in thyroid hormone homeostasis occurs through mechanisms that transcend all congener groups of PCBs.

3.5.1 Pharmacokinetic Mechanisms

The mechanism of absorption of PCBs by the inhalation and dermal routes of exposure is not known. PCBs are well absorbed from the gastrointestinal tract. Diet is the main source of background human exposures to persistent lipophilic organic pollutants, such as PCBs (Duarte-Davidson and Jones 1994; Hansen 1999). Because PCBs are lipid soluble, transfer from the aqueous environment of the intestine across cell membranes is a passive process (Albro and Fischbein 1972; Gage and Holm 1976; Matthews and Anderson 1975). The concentration gradient favors partitioning across the cells into blood serum or lymph. As with other fat-soluble chemicals, PCBs are most likely absorbed from the gut via lymphatic circulation rather than by transfer to the hepatic portal system (Hansen 1999). Absorption efficiency appears to increase with the degree of ring chlorination up to a certain point. Schlummer et al. (1998) calculated the net gastrointestinal absorption of PCBs in humans as the difference between contaminant input with food and contaminant output with feces, normalized to the contaminant intake. PCB congeners showing nearly complete net absorption had very low or nondetectable levels in the serum lipids, while

for other congeners, there was a trend for decreasing net absorption and /or increasing net excretion with increasing congener concentration in serum lipids. Together, the data support the passive diffusion model for gastrointestinal absorption, where the concentration of the contaminant in the blood is the major factor determining absorption. This suggests that the ingestion of more highly contaminated food should result in nearly complete absorption due to the high diffusion gradient associated with high levels of PCBs in the gut contents. In blood, PCBs are associated with red blood cells, albumin, and lipoproteins (Matthews et al. 1984). Distribution in plasma is determined primarily by partition among the various proteins according to lipid solubility and concentration (Matthews and Dedrick 1984). As the degree of halogenation increased, the binding to lipoproteins also increased (Matthews et al. 1984). Partition of PCBs between blood and tissues also seems determined primarily by lipid content and concentration gradient. The fraction associated with red blood cells is more rapidly removed from the blood by the tissues than fractions associated with plasma proteins (Matthews et al. 1984).

Borlakoglu et al. (1990) proposed a model for the transport and cellular uptake of PCBs following oral exposure. Following the ingestion of PCBs, the absorbed congeners are secreted into the bloodstream in association with chylomicrons and then are associated with the VLDLs synthesized in the liver. As the congeners come in contact with the lipoprotein lipase located on the surface of the capillary endothelial cells of adipose tissue, the PCB congeners are transferred into the adipocytes. Mobilization of PCBs from adipose tissue will release PCBs into the bloodstream, where they will associate with HDL and plasma proteins, such as albumin, by non-covalent binding. Noren et al. (1999) found PCBs mainly associated with the lipoprotein depleted (LPDP) fractions (containing primarily albumin). On average, 44% of the PCBs and 61% of the methylsulfonyl metabolites of PCBs ($MeSO_2$-CBs) were distributed in the LPDP fraction. This may be expected due to the more polar character of the $MeSO_2$-CBs. Among the lipoprotein fractions, LDL was the main carrier of PCBs, while $MeSO_2$-CBs were distributed equally between the LDL and HDL fractions. When the concentrations of PCBs were calculated in relation to apolipoprotein B, the levels were about 10 times higher in VLDL than LDL.

As with other organisms, PCB residue levels in humans reflects multiple exposure pathways, and congener-specific elimination. PCB profiles in human serum immediately following exposures reflect the profiles in the exposure sources; however, selective metabolism and excretion begin to alter the congener profile within 4–24 hours (Hansen 1999). Thus, in most cases, the PCB profile in adults represents a steady state body burden which does not match the profile of commercial PCB formulations (Aroclors, etc.). For example, neither the PCB profile of human adipose nor of a composite human milk sample resemble the pattern of any commercial PCB formulation (Jensen and Sundstrom 1974; Safe et al. 1985).

Humans, aquatic mammals, birds, fish, and other biota retain unique profiles of PCB congeners consistent with exposures and toxicokinetic principles. Borlakoglu and Walker (1989) reported that fish-eating sea birds, human fat, American breast milk, and German breast milk have similar PCB congener profiles, reflecting fish residues, which differ from Aroclor 1260 or Clophen A60. Hansen (1999) cites several studies reporting diet-dependent PCB profiles in various birds, and a larger breast milk study shows regional differences in congener profiles in Canadian breast milk (Newsome et al. 1995).

PCBs are rapidly (minutes to hours) cleared from the blood of adult animals and accumulated in the liver and muscle (Matthews and Dedrick 1984; Safe 1980, 1989a). This appears to be due to the high perfusion in the liver and the relatively large muscle volume. Due to their high affinity for lipophilic tissues, PCBs are subsequently translocated to adipose tissue and skin for storage. Subcutaneous fat accumulates PCBs more slowly than central fat stores (Hansen and Welborn 1977). Stored residues are less available for elimination or metabolism by the liver. A dynamic equilibrium of PCB concentrations is established among all tissues for each PCB homolog (Matthews and Dedrick 1984). As previously discussed, mathematical models that incorporate anatomical as well as pharmacokinetic parameters have been developed to describe distribution and body burden of PCBs in adults of species such as mice, rats, dogs, and monkeys (Lutz and Dedrick 1987). Pharmacokinetic modeling of PCB disposition predicts that, at equilibrium, changes in the PCB concentration or changes in tissue volume of any tissue will lead to a corresponding change in all tissues (Matthews and Dedrick 1984). For instance, if the concentration of a PCB congener in the liver is reduced by metabolism or excretion, then the concentration of that PCB congener in all tissues will be reduced proportionally. Congeners that cannot be metabolized or excreted will concentrate in adipose tissue, but will still circulate to other tissues. Exposure to other tissues will be proportional to the respective tissue/blood ratios and the concentration in the main storage tissues. This dynamic distribution results in accumulation of persistent congeners in all tissues and depletion from all tissues of those congeners that can be cleared (Matthews and Dedrick 1984). Metabolites, however, may accumulate in specific tissues due to solubility differences as well as tissue binding (Section 3.4.3). Relatively little is known regarding the biological and toxicological activity of these persistent PCB metabolites.

A possible explanation for the highly selective retention of the OH-PCBs in blood may be their structural resemblance with thyroxin. Both rats and mice metabolize PCB 77 by CYP1A to the 1,2-shift metabolite, 4-OH-3,5,3',4'-PCB, 5-OH 3,3',4,4'-PCB, and 6-OH-3,3',4,4'-PCB (McKinley et al. 1993; Morse et al. 1995). Only the 4-OH metabolite was selectively retained, with blood containing 4-OH-3,5,3',4'-PCB at a concentration 15 times higher than the parent compound, 5 days after oral exposure to PCB 77 in mice

(Bergman et al. 1994). This metabolite was found to be bound to a thyroxin-transporting protein (transthyretin) in the blood (Brouwer et al. 1986). Competitive binding studies of OH-PCBs relative to T_4 and computer modeling showed that OH-PCBs with the substituents in *meta* or *para* positions were much more effective competitors for T_4 than if the substituents were bound in an *ortho* position (Rickenbacher et al. 1986).

Methylsulfonyl ($MeSO_2$) metabolites of PCBs have been widely detected in the tissues of marine mammals (Bergman et al. 1994; Letcher et al. 1995) and of humans (Haraguchi et al. 1986; Noren et al. 1996; Weistrand and Noren 1997). Although the binding mechanism for 3-$MeSO_2$ metabolites is not clear, the binding protein for 4-$MeSO_2$ metabolites has been identified as a uteroglobulin-like protein present in the nonciliated bronchiolar (Clara) cells of the lung, also referred to as Clara cell secretary protein (CCSP) (Hard et al. 1995; Stripp et al. 1996). Exposure to 4-$MeSO_2$-2,2',4',5,5'-PCB demonstrated that CCSP-deficient mice no longer accumulate this metabolite within lung or kidney tissue (Stripp et al. 1996). These data demonstrate that CCSP is the 4-$MeSO_2$-PCB binding protein in mice and suggests that 4-$MeSO_2$-PCBs will accumulate at sites of CCSP localization, such as the respiratory and reproductive tracts of humans.

Experimental evidence using P^{32}-postlabeling supports the hypothesis that lower chlorinated biphenyls are metabolically activated to electrophilic species which bind to DNA (McLean et al. 1996; Oakley et al. 1996). The incubation of 2-chloro-, 4-chloro-, 3-chloro-, 3,4-dichloro-, and 3,4,5-trichlorobiphenyl with calf thymus DNA and rat liver microsomes followed by oxidation with a peroxidase, produced 1–3 major DNA adducts. The reactive metabolites may result for arene oxides and/or catechol and p-hydroquinone species, which are oxidized to semiquinones and/or quinones. The results raise the possibility that lower chlorinated biphenyls may be genotoxic and may explain the fact that commercial PCB mixtures are complete rodent carcinogens.

The major routes of excretion of PCBs are fecal and urinary. For higher chlorinated congeners such as penta- and hexachlorobiphenyls, the predominant route of excretion is via the feces (up to 60% of total excretion); for lower chlorinated congeners, the situation seems to reverse (Lutz and Dedrick 1987). Mainly metabolites are found in urine and bile, although small amounts of parent compound may appear in the feces, in particular congeners that are poorly metabolized such as 2,2N,4,4N,5,5N-hexaCB. Elimination kinetics tend to follow first-order processes with elimination rates directly related to their metabolic rates (Gage and Holm 1976). An important route of PCB elimination is milk. This varies considerably with the species due to volume and lipid content of the milk, but the basic mechanisms are

the same for all species. Because PCBs are in dynamic equilibrium with all tissues, they move passively from blood to milk at the beginning of lactation to maintain their respective tissue/blood ratios.

PCBs are metabolized by microsomal cytochrome P-450 to polar metabolites that can undergo conjugation with glutathione and/or glucuronic acid. The rate of metabolism of some PCB congeners depends on (1) the degree of ring chlorination, (2) the chlorine ring substitution pattern, and (3) the pattern and levels of P-450 isozymes and other enzymes in the target tissue. PCB congeners of low chlorine content are transformed into hydroxylated derivatives that are predominately eliminated in the urine. Highly chlorinated congeners with nonsusceptible substitution patterns are either retained or excreted unchanged in the feces. Extensive information regarding the mechanism of metabolism of PCBs is provided in Section 3.4.3.

Because of the many factors that may determine the toxic response associated with exposure to PCBs, caution should be exercised when extrapolating high-dose response to low-dose responses, and/or single-dose exposures to chronic exposures. Caution is warranted for two main reasons. First, the dynamic mechanism involved in the distribution of PCB congeners, in which lipophilicity plays a crucial role, will influence the amount of circulating PCBs. For example, one can predict that because lean individuals have a smaller fat compartment, all of their body tissues will have higher concentrations of PCBs than those in fatter individuals of the same exposure. Also, the dosing schedule (single compared to repeated) will determine whether steady-state is achieved. Secondly, because PCBs can induce their own metabolism, data obtained with exposure levels associated with a significant induction of CYP1A1 and CYP1A2 may not necessarily reflect toxicokinetic behavior at low exposure levels. This has been illustrated in the model proposed by Brown (1994) in comparing high-exposed humans to low-exposed humans. In addition, serum residues of 2,2N,4,4N,5,5N-hexaCB are lower in prepubertal rats when the total of two doses is high enough to induce P-450 2B (Li et al. 1994). Toxicokinetic data for PCBs do not suggest route-dependent toxicity.

3.5.2 Mechanisms of Toxicity

Mechanisms by which the broad array of toxic effects observed in animals orally exposed to PCB mixtures develop are incompletely understood, but there is evidence to suggest that PCB congeners differ qualitatively and quantitatively in biological activities and that multiple and diverse mechanisms are involved in responses to PCB mixtures. Research in the 1970s and 1980s focused on mechanistic similarities between PCBs and CDDs involving initial mediation of effects by the Ah receptor (Poland

and Knutson 1982; Safe 1990, 1994), but research through the 1990s has found increasing evidence for the involvement of alternative mechanisms for several PCB-induced effects (Chauhan et al. 2000; Cheek et al. 1999; Fischer et al. 1998; Hansen 1998; Harper et al. 1993a, 1993b; Safe 1994; Tilson and Kodavanti 1998). An in-depth and all-inclusive review of the many recent and ongoing research efforts regarding PCB mechanisms of action is outside of the scope of this profile; rather, an overview of this large body of research is presented with the intent of providing information relevant to public health issues.

PCB Effects Involving Ah-receptor Dependent Mechanisms

Induction of Hepatic CYP1A Oxygenases and Phase II Enzymes. PCBs induce hepatic Phase I enzymes (CYP oxygenases) and Phase II enzymes (e.g., UDP glucuronyltransferases, epoxide hydrolase, or glutathione transferase) to varying degrees and specificities (Connor et al. 1995; Hansen 1998; Safe 1994). The demonstration of relationships between PCB molecular structure and induction of CYP isozymes has provided a framework within which much mechanistic research has been conducted. In general, commercial mixtures of PCBs induce both 3-methylcholanthrene-type (CYP1A1 and 1A2) and phenobarbital-type (CYP2B1, 2B2, and 3A) CYPs. Strong structure-activity relationships have been demonstrated between CYP1A1/1A2 induction in rodents and non-*ortho* and mono-*ortho* PCBs, which can assume a coplanar molecular configuration and bind to the Ah receptor (Connor et al. 1995; Hansen 1998; Safe 1994). In structure-activity studies of CYP1A induction in hepatocytes from Cynomolgus monkeys by 20 PCBs varying in degree and pattern of chlorine substitution (4–7 chlorines), the most potent inducers were without *ortho* chlorines (van der Burght et al. 1999). Many PCBs with *ortho* chlorines (mono-, di-, tri-, and tetra-*ortho* congeners) displayed no CYP1A induction activity, but a few mono-*ortho* and multiple-*ortho* congeners displayed activities that were about 1,000- and 10,000-fold less than the most potent non-*ortho* congeners, respectively (van der Burght et al. 1999). A working mechanistic hypothesis involves initial binding of coplanar PCBs to the Ah receptor in the cytosol of target cells, transport of the ligand-receptor complex to the nucleus, and subsequent changes in gene expression (e.g., induction of CYP1A1/1A2) leading to toxic responses via subsequent and/or parallel molecular mechanisms that are largely unexplored. Support for this hypothesis comes from the similarity in the array of PCB effects compared with the array produced by 2,3,7,8-TCDD and related halogenated aromatic hydrocarbons via initial Ah-receptor mediation, results from *in vitro* binding studies, and results from congener-specific *in vivo* studies of specific end points (e.g., enzyme induction and down regulation, body weight, and immunological responses to SRBC) in mouse strains and rat genders differing in responsiveness to Ah-receptor mediation (Hori et al. 1997; Safe 1990, 1994).

The complexity of Ah-receptor mediated effects on hepatic enzyme levels is illustrated by results from a study with mouse strains differing in Ah-receptor responsiveness and three PCB congeners (Hori et al. 1997). Ah responsive (C57BL/6) and Ah nonresponsive (DBA/2) mice were given single intraperitoneal doses of 3,3',4,4',5-pentaCB (a congener with high Ah receptor affinity), 3,3',4,4'-tetraCB (a congener with lesser affinity), and 2,2',5,5'-tetraCB (a low-affinity ligand). Only the high-affinity 3,3',4,4',5-congener produced body weight wasting in the dose range tested (up to 50 mg/kg) in Ah-responsive C57BL/6 mice, and this effect was accompanied by a decrease in selenium-dependent glutathione peroxidase and an increase in θ glutathione *S*-transferase. The effect on levels of these Phase II enzymes was not produced by the other congeners in C57BL/6 mice, and did not occur in DBA/2 mice exposed to any of the congeners, indicating the involvement of Ah-receptor mediation. These Phase II enzymes both play protective roles in scavenging intracellularly generated peroxides and the balance of their activities is likely to influence a cell's ability to withstand damage from peroxides.

Body Weight Wasting, Thymic Atrophy, and Porphyria. In addition to induction of hepatic levels of CYP1A1/1A2/1B1 and induction or repression of some Phase II enzymes, PCB-induced effects that appear to predominately involve Ah-receptor initiated mechanisms include body weight wasting and thymic atrophy from acute exposure (Hori et al. 1997; Safe 1994) and porphyria and porphyria cutanea tardea (Franklin et al. 1997; Smith et al. 1990a, 1990b). For example, single intraperitioneal doses of 5 mg/kg 3,3',4,4',5-pentaCB, a potent inducer of CYP1A1 and a high-affinity Ah-receptor agonist (relative to other PCBs), produced marked body weight wasting in Ah-responsive C57BL/6 mice, but not in DBA/2 mice that have a low-affinity Ah-receptor (Hori et al. 1997). Showing a link between Ah-receptor responsiveness and development of uroporphyria, female F344 rats had significantly higher hepatic levels of porphyrins and ethoxyresorufin deethylase activity (an indicator of CYP1A1) in response to exposure to 0.005% Aroclor 1254 in the diet for 15 weeks than did male rats (Smith et al. 1990b). A similar gender-specific correlation between porphyrinogenic response and CYP1A induction was observed in iron-loaded F344 rats exposed to single intraperitoneal doses of 63 mg Aroclor 1254/kg (Franklin et al. 1997). In mice of the Ah-responsive C57BL/6 strain, a single dose of iron-dextran (600 mg Fe/kg), followed by feeding of a diet containing 0.01% Aroclor 1254 for up to 12 months, produced markedly increased hepatic levels of porphyrins and liver enlargement, but this response to iron and Aroclor 1254 was not observed in similarly treated DBA/2 mice (Smith et al. 1990a). Exposure to iron-dextran alone caused a moderate porphyria in C57BL/6 mice, but not in DBA/2 mice, lending support to a postulate that there are constitutive genetic differences between these strains that influence porphyria development and do not involve Ah-receptor mediation (Smith et al. 1990a). One mechanistic hypothesis proposes that induction of CYP1A2 by the Ah-receptor-PCB complex leads to generation of a

competitive inhibitor of uroporphyrinogen decarboxylase in the liver and subsequent accumulation of porphyrins (see Franklin et al. 1997).

Ah Receptor TEF Approach to Health Hazard Assessment. A TEF approach to evaluating health hazards from exposure to complex environmental mixtures containing PCBs, CDDs, and CDFs has been developed and used to some extent to guide public health decisions because humans are exposed to complex and varying mixtures of these halogenated aromatic hydrocarbons and there are limited toxicological data for these complex mixtures and many of their components (ATSDR 1998; Safe 1990, 1994; van den Berg et al. 1998). PCBs were included in this component-based approach because (1) the spectrum of effects in animals exposed to some PCB mixtures and congeners is similar to the spectrum produced by 2,3,7,8-TCDD (via Ah receptor initial mediation) and (2) coplanar PCBs display Ah receptor binding affinities that were related to their potency in producing health effects in rodents such as body weight wasting and inhibition of immunological responses to SRBC (Safe 1990, 1994). The TEF approach compares the relative potency of individual congeners, based on *in vitro* or acute *in vivo* data, with that of 2,3,7,8-TCDD, the best-studied member of this chemical class, so that the TEF for 2,3,7,8-TCDD is 1. The concentration or dose of each active component in a mixture of concern is multiplied by its TEF to arrive at a TEQ, and the TEQs are added to give the total toxic equivalency of the mixture which is compared with reference exposure levels for 2,3,7,8-TCDD expected to be without significant risk for producing health hazards. TEFs have recently been recommended by the World Health Organization for 7 CDD, 10 CDF, and 12 PCB congeners (Van den Berg et al. 1998).

Limitations in using the TEF approach for assessing health hazards from PCB-containing environmental media revolve around the inherent assumptions that the components jointly act in an additive manner through a common Ah-receptor initial mechanism and the evidence that Ah-receptor-binding congeners in PCB-containing environmental mixtures are minor components (Hansen 1998; Safe 1998a, 1998b) Several studies have provided evidence of nonadditive interactions between specific PCB congeners and between some PCB congeners and 2,3,7,8-TCDD (Safe 1998a, 1998b), and there is evidence, discussed below, that several Ah-receptor-independent mechanisms may make contributions to toxic effects from PCB mixtures.

PCB Effects Involving Ah-receptor Independent Mechanisms

Induction of Hepatic CYP2B Oxygenases. In contrast to the distinct relationships between CYP1A1/1A2 induction, PCB molecular structures, and Ah-receptor initiation of toxic effects,

relationships between potency in inducing CYPs 2B1/2B2/3A, PCB structural properties, and toxic effects are less clear (Connor et al. 1995). For example, some PCBs with two *ortho* chlorines and lateral chlorines induce both types of CYPs and display a very small affinity for the Ah receptor, whereas other di-*ortho* PCBs with one or two para chlorines predominately induce CYP2B1/2B2/3A and have no measurable affinity for the Ah receptor (Connor et al. 1995; Hansen 1998). Some noncoplanar congeners, such as 2,2',4,4'-tetraCB, also induce CYP3A through the glucocorticoid-sensitive pregnane X receptor (PXR) (Schuetz et al. 1986, 1998). It is clear that PCB induction of phenobarbital-type CYPs is independent of the Ah receptor and that the most potent inducers of CYP have at least two *ortho* chlorines and one or two para chlorines.

Other PCB-induced effects involving Ah-receptor independent mechanisms include neurological and neurodevelopmental effects involving changes in brain dopamine levels (Seegal 1996b, 1998; Seegal et al. 1989, 1990; Shain et al. 1991); inhibition of dopamine vesicular uptake (Mariussen et al. 1999) and/or changes in brain cell intracellular calcium homeostasis and related signal transduction processes (Kodavanti and Tilson 1997; Tilson and Kodavanti 1997, 1998; Tilson et al. 1998; Wong and Pessah 1996, 1997; Wong et al. 1997); tissue injury related to activation of neutrophils (Brown and Ganey 1995; Ganey et al. 1993; Tithof et al. 1995); thyroid disruptions not involving UDP-GT induction (Chauhan et al. 2000; Cheek et al. 1999; Darnerud et al.1996a; Li and Hansen 1996; Ness et al. 1993; Van Birgelen 1992); and PXR and ryanodine receptor (RyR) mediated mechanisms (Schuetz et al. 1986, 1998).

Brain Dopamine Levels and Neurological Effects. Aroclor 1254 decreased cellular levels of dopamine in cultured pheochromocytoma cells, which synthesize, store, release, and metabolize dopamine in a manner similar to the intact mammalian central nervous system (Seegal et al. 1989). Daily oral exposure of adult nonhuman primates (*Macaca nemestrina*) to Aroclor 1016, a commercial mixture of lightly chlorinated PCB congeners, for 20 weeks, likewise, produced decreased dopamine concentrations in brain regions including the caudate, putamen, substantia nigra, and hypothalamus (Seegal et al. 1990). In these brain regions, only three PCB congeners were detected (2,4,4'-triCB and 2,2',4,4'- and 2,2',5,5'-tetraCB), suggesting that nonplanar PCBs, which are poor Ah receptor agonists, may have been responsible for the effect. Structure-activity studies of 50 PCB congeners in the pheochromocytoma *in vitro* system found that the most active congeners had at least two *ortho* chlorines (e.g., 2,2',4,6-, 2,2',5,5'-, and 2,2',4,5-tetraCB) and that congeners that were relatively strong Ah receptor agonists (e.g., 3,3',4,4'-tetraCB and 3,3',4,4',5-pentaCB) were inactive or had minimal effects on dopamine levels (Shain et al. 1991). However, *ortho* substitution was not the sole determinant of activity in this system; for example, a congener with four *ortho* chlorines (2,2',6,6'-tetraCB) had no effect on dopamine levels in

pheochromocytoma cells (Shain et al. 1991). The effect on dopamine levels has been postulated to involve decreased dopamine synthesis via direct or indirect PCB inhibition of tyrosine hydroxylase (Choksi et al. 1997; Seegal et al. 1996b) or L-aromatic amino acid decarboxylase (Angus et al. 1997) and/or decreased uptake of dopamine into vesicles (Mariussen et al. 1999). For example, several congeners that were inactive in causing dopamine level changes in pheochromocytoma cells (e.g., 2,2',6,6'- and 3,3',4,4'-tetraCB) were much less active in inhibiting vesicular uptake of dopamine than other more active congeners (e.g., 2,2',4,6- and 2,2',4,5'-tetraCB) (Mariussen et al. 1999).

Disruption of Ca^{+2} Homeostasis and Neurological Effects. Neurological and/or neurodevelopmental effects from exposure to PCBs also have been hypothesized to involve interference with calcium homeostatic mechanisms and intracellular second messenger systems by PCB congeners that are not effective Ah receptor agonists (see reviews by Kodavanti and Tilson 1997; Tilson and Kodavanti 1998; Tilson et al. 1998). In agreement with structure-activity relationships observed for PCB effects on dopamine levels in pheochromocytoma cells (Shain et al. 1991), 2,2'-diCB altered intracellular calcium homeostasis in cultured rat cerebellar granule cells (increased free calcium levels and inhibited calcium buffering systems) at noncytotoxic exposure concentrations (higher concentrations were cytotoxic) (Kodavanti et al. 1993). In contrast, 3,3',4,4',5'-pentaCB, one of the most effective Ah receptor agonists among tested PCBs (Safe 1994), was not cytotoxic in the tested concentration range and did not alter calcium homeostasis to as great an extent as 2,2'-diCB (Kodavanti et al. 1993). Using phorbol ester binding in rat cerebellar granule cells as a measure of protein kinase C translocation (which is thought to play key roles in cellular signal transduction in neurons and be regulated by several intracellular factors including intracellular levels of free calcium), commercial mixtures of PCBs (Aroclors 1016, 1254, and 1260) were shown to increase protein kinase C translocation in a concentration-dependent manner with varying potencies (Kodavanti et al. 1995). Aroclors 1016 and 1254 were more potent than Aroclor 1260. Examination of 24 PCB congeners showed that the most potent congeners (e.g., 2,2'-diCB, 2,2',5,5'-tetraCB, and 2,2',4,6,6'-pentaCB) had multiple *ortho* chlorines, whereas congeners without *ortho* chlorines tended to have either no or lower activities (Kodavanti et al. 1995). Similar results were found in structure-activity studies of 24 PCB congeners and their effects on *in vitro* Ca^{+2} sequestration by microsomes and mitochondria from freshly isolated rat cerebellar cells (Kodavanti et al. 1996a). Structure activity relationships for PCB congeners and protein kinase C translocation in rat cerebellar granule cells and Ca^{+2} sequestration were similar to relationships for PCB congener-induced changes in dopamine levels in pheochromocytoma cells. For example, 2,2',5,5'- and 2,2',4,6-tetraCB were among the most potent congeners and 2,2',6,6'- and 3,3',4,4'-tetraCB were inactive in all three systems (Kodavanti et al. 1995, 1996a; Shain et al. 1991).

One proposed molecular target for PCB disruption of calcium homeostasis that may be involved in neurological and neurodevelopmental effects is ryanodine-sensitive Ca^{+2} channels. Commercial PCB mixtures with intermediate to high degrees of chlorination (Aroclors 1248, 1254, and 1260) enhanced ryanodine binding to calcium release channels in sarcoplasmic reticulum membranes from skeletal or cardiac rabbit muscles, and mixtures with lower (Aroclors 1221, 1232) or higher (Aroclor 1268) chlorination showed little enhancement (Wong and Pessah 1996). Examination of selected pentachlorobiphenyls indicated that *ortho* substitution favored activity; 2,2',3,5',6-pentaCB induced the greatest enhancement of ryanodine binding, whereas the 3,3',4,4',5-isomer did not enhance binding (Wong and Pessah 1996). The 2,2',4,6,6'-isomer with full substitution at the *ortho* positions produced less enhancement than the 2,2',3,5',6-isomer, indicating that some degree of rotation about the biphenyl bond may be important for full activity. Results from studies with hippocampal slices from freshly dissected rat brains indicated that perfusion with a tri-*ortho* congener (2,2',3,5',6-pentaCB) enhanced ryanodine binding and inhibited electrophysiological responses to electrical pulse stimulations, but a mono-*ortho* congener (2,3',4,4'-tetraCB) showed no enhancement of ryanodine binding and no inhibition of electrophysiological responses to stimulation (Wong et al. 1997). Offspring of rats exposed to gavage doses of 8 or 32 mg/kg/day 2,2',3,5',6-pentaCB on gestation days 10–16 displayed neurobehavioral changes as adults (depressed open field locomotor activity, faster acquisition on a working memory task, and no changes in a delayed spatial alternation task) and changes in ryanodine binding to calcium channels in specific regions of the brain (e.g., decreased in hippocampus and increased in cerebral cortex) (Schantz et al. 1997). Although it is not understood how these changes in ryanodine binding are specifically related to the observed neurobehavioral changes, the results from this series of studies emphasize the potential importance of Ah receptor independent mechanisms in PCB-induced neurological and neurodevelopmental effects.

Neutrophil Function and Immunological Effects and Tissue Damage. PCB-induced functional changes in neutrophils may be involved in impaired immune defenses against pathogens or enhanced inflammatory responses (e.g., production of reactive oxygen species and cytolytic enzymes) leading to tissue injury. Incubation of quiescent cultured rat peritoneal neutrophils with Aroclor 1242 stimulated neutrophil production of superoxide anion and induced degranulation in a concentration-dependent manner without producing cytotoxicity (Ganey et al. 1993). In neutrophils that were activated for these functions, Aroclor 1242 produced further increases in superoxide anion production, but inhibited the activated degranulation process. Similar effects were observed when neutrophils were incubated with 2,2',4,4'-tetraCB, a congener that has little affinity for the Ah receptor and induces phenobarbital-type CYPs, but 3,3',4,4'-tetraCB, an Ah receptor agonist and inducer of 3-methylcholanthrene-type CYPs, did

not affect neutrophil function (Ganey et al. 1993). The effects of 2,2',4,4'-tetrachlorbiphenyl on *in vitro* production of superoxide anion by neutrophils were inhibited when neutrophils were incubated in the absence of extracellular calcium or in the presence of TMB-8, an antagonist of the intracellular mobilization of calcium (Brown and Ganey 1995). In addition, neutrophil degranulation induced by 2,2',4,4'-tetraCB was enhanced by coexposure with the calcium ionophore A23187 (Brown and Ganey 1995). A mono-*ortho* congener, 2,3,4,5-tetraCB, displayed somewhat different effects on neutrophil functions than those from the 2,2',4,4'-congener: it stimulated degranulation in quiescent and activated neutrophils, but only increased superoxide anion production in activated neutrophils, not in quiescent cells. The results from the neutrophil studies suggest the involvement of an Ah-receptor independent mechanism that involves PCB-induced increases in intracellular calcium or PCB effects on a signal transduction pathway that is dependent on calcium availability (Brown and Ganey 1995). Recent work suggests activation of phospholipase A2, release of arachidonic acid from triglycerides, and production of prostaglandins as a probable mechanism (Tithof et al. 1996; Olivero and Ganey 2000). This mechanism could also contribute to other pathologies.

PCB Effects Involving Ah-receptor Dependent and Independent Mechanisms

PCB-induced effects that may involve both Ah-receptor dependent and independent mechanisms include liver hypertrophy (Hori et al. 1997); neurodevelopmental effects or reproduction effects involving changes in steroid hormone homeostasis (Arcaro et al. 1999; Connor et al. 1997; Gierthy et al. 1997; Fischer et al. 1998; Li and Hansen 1997; Nesaretnam and Dabre 1997; Nesaretnam et al. 1996; Seegal et al. 1997) and/or thyroid hormone disruption (Brouwer et al. 1998b; Hansen 1998; Li and Hansen 1996a, 1996b, 1997); immunological effects (Harper et al. 1993a, 1993b; Silkworth and Grabstein 1982; Stack et al. 1999); and cancer through nongenotoxic mechanisms involving promotion of oncogenic cells (Cogliano 1998; Safe 1994) and/or genotoxic mechanisms (Robertson and Gupta 2000).

Liver Hypertrophy. Liver hypertrophy in animals is produced by oral exposure to commercial PCB mixtures and appears to involve both Ah-receptor dependent and independent mechanisms. An illustration of this phenomenon is the observation that single intraperitoneal doses of any one of three PCB congeners varying in affinity for the Ah receptor produced liver hypertrophy in Ah responsive (C57BL/6) and Ah nonresponsive (DBA/2 mice (Hori et al. 1997). The studied congeners were 3,3',4,4',5-pentaCB, a congener with high Ah receptor affinity, 3,3',4,4'-tetraCB, a congener with lesser affinity, and 2,2',5,5'-tetraCB, a low-affinity Ah-receptor ligand.

Reproductive Effects. There are several studies examining female reproductive function variables in rats (Brezner et al. 1984; Hany et al. 1999b; Linder et al. 1974; Sager and Girard 1994), mice (Welsch 1985), rabbits (Seiler et al. 1994), minks (Aulerich and Ringer 1977; Backlin and Bergman 1995; Kihlstrom et al. 1992), and monkeys (Arnold et al.1995, 1996; Barsotti et al. 1976) repeatedly exposed orally to commercial PCB mixtures, predominately Aroclor 1254. In general, results from these studies identify minks and monkeys as sensitive species.

In minks, repeated exposure to low doses of Aroclor 1254 or Clophen A50 (0.4–1.8 mg/kg/day) caused reproductive failure that has been associated with fetal death following embryo implantation (Aulerich and Ringer 1977; Backlin and Bergman 1995; Backlin et al. 1997; Kihlstrom et al. 1992). This effect may predominately involve Ah-receptor mediation, as evidenced by observations that only 1/10 minks exposed to 2.5 ppm Aroclor 1254 in the diet from 1 month prior to breeding through parturition produced offspring, whereas exposure by a similar protocol to 2,2',4,4',5,5'-hexaCB or 2,2',3,3',6,6'-hexaCB at concentrations up to 5 ppm did not influence reproductive performance (Aulerich et al. 1985). In contrast, exposure to dietary concentrations as low as 0.1 ppm 3,3',4,4',5,5'-hexaCB in this study (Auerlich et al. 1985), and 0.05 ppm in another study (Aulerich et al. 1987), caused mortality and prevented the minks for reproducing. Dietary exposure of minks to a fraction of Aroclor 1254, containing only congeners with no *ortho*-chlorines or a single *ortho*-chlorine and representing <20% of the total weight of Aroclor 1254, reduced litter size and fetal survival, and increased incidence of interrupted pregnancies to a similar degree as doses of the complete Aroclor 1254 mixture (1.3 mg/kg/day) containing the same amount of these congeners (Kihlstrom et al. 1992). These results suggest the importance of Ah-receptor mediation of PCB-induced reproductive impairment in minks.

Another mink study comparing reproductive effects from intraperitoneal doses of 2,2',4,4',5,5'- and 3,3',4,4',5,5'-hexaCB reinforces the idea that congeners with high Ah-receptor affinity are more potent than congeners with low Ah-receptor affinity, but also provides evidence that Ah-receptor independent mechanisms may be involved (Patnode and Curtis 1994). Administration of single 20-mg/kg doses of the 2,2',4,4',5,5'-isomer (a poor Ah-receptor agonist that has been detected in wild mink tissues at concentrations 50-fold greater than the 3,3',4,4',5,5'-isomer) to pregnant minks on the approximate date of implantation did not affect the number of implantation sites (assayed 14 days after dose administration), but significantly decreased the number of embryos and embryonic weight, crown-to-rump length, and head length. The 3,3',4,4',5,5'-isomer (at lower dose levels of 0.4 or 0.8 mg/kg) also did not affect the number of implantation sites, but produced more severe effects on embryo survival and the weight, crown-to-rump length, and head length of surviving embryos (Patnode and Curtis 1994).

The mechanisms involved in PCB-induced reproductive impairment in minks are unknown, but examination of mid- to late-gestation placentae from minks exposed to Clophen A50 by light and electron microscopy revealed degenerative lesions in maternal (endothelial detachment and thrombosis in maternal vessels) and fetal (trophoblastic disintegration and loss of fetal capillary integrity) tissues (Backlin et al. 1998b). Jones et al. (1997) postulated that the mechanisms are likely to be multifactorial given the possibility of direct and/or indirect tissue damaging actions of PCBs and the wide range of reported effects of PCBs on steroid hormone synthesis and functions including PCB regulation of CYP oxygenases that activate or deactivate different endogenous steroid hormones, estrogenic and antiestrogenic effects of PCBs, and PCB regulation of estrogen and progesterone receptor levels (see Battershill 1994; Li and Hansen 1997; Patnode and Curtis 1994).

Impaired ability to conceive and decreased fetal survival have been observed following repeated exposure of female Rhesus monkeys to commercial PCB mixtures. Exposure to dietary levels of 2.5 or 5 ppm Aroclor 1248 (approximately 0.1 or 0.2 mg/kg/day) for 16–19 months (including a 7-month period before breeding with nonexposed males) produced resorptions or abortions in 3/8 and 4/6 impregnated female Rhesus monkeys, compared with 0/12 in a control group (Barsotti et al. 1976). In this study, 12/12, 8/8, and 6/8 females became impregnated in the 0-, 2.5-, and 5-ppm groups, respectively. Another study fed encapsulated Aroclor 1254 at dose levels of 0, 0.005, 0.02, 0.04, or 0.08 mg/kg/day to female Rhesus monkeys for 37 months before breeding with nonexposed males and continued dosing through mating and gestation (Arnold et al. 1995). Incidences of abortions, resorptions, or stillbirths were 2/11, 5/10, 3/4, 2/6, and 4/5 in impregnated monkeys in the control through high-dose groups, respectively; respective incidences for impregnation success were 11/16, 10/16, 4/15, 6/14, and 5/15 (Arnold et al. 1995). Mechanisms for these effects in monkeys are unknown, but microscopic examination of tissues from control and exposed monkeys in the second monkey study found no evidence for an association with endometriosis (Arnold et al. 1996).

The plausibility that PCB effects on reproductive function (and other functions such as neurobehavior and immunological competence) may involve PCB effects on endocrine functions has led to investigations of the estrogenic and anti-estrogenic activities of PCB mixtures and individual congeners, and the effects of PCBs or related halogenated aromatic compounds on steroid hormone metabolism via induction of Phase I or Phase II enzymes. How these PCB effects are specifically related to PCB effects on reproductive function is unknown, but the results of these investigations provide further evidence that reproductive effects from PCB mixtures may not be restricted to Ah-receptor mediation alone and are

likely to involve multiple mechanisms that have yet to be elucidated. Related information on endocrine disruption is discussed in Section 3.6.

The estrogenic and anti-estrogenic activities of some commercial PCB mixtures, PCB congeners, and hydroxylated derivatives of PCB congeners have been assayed by examining uterine variables in immature or ovariectomized female rodents, cell proliferation or gene expression variables in cultured cells including human breast cancer or HeLa cells, and *in vitro* binding to estrogen receptor preparations (see Andersson et al. 1999; Arcaro et al. 1999; Battershill 1994; Connor et al. 1997; Gierthy et al. 1997; Hansen 1998; Kramer et al. 1997; Krishnan and Safe 1993; Li and Hansen 1997; Moore et al. 1997; Safe 1999; Safe et al. 1998b for reviews). In general, (1) PCB-induced estrogenic activities have been characterized as weak compared to the endogenous hormone, 17β-estradiol, (2) a wide variability of responses has been observed across types of PCBs and assays indicating the involvement of multiple mechanisms (e.g., direct binding to the estrogen receptor is not the only way that estrogenic or anti-estrogenic physiological effects may be mediated), (3) anti-estrogenic activities have been most strongly associated with PCBs that are Ah-receptor agonists, and (4) hydroxylated metabolites of PCBs are postulated to be at least partly responsible for physiological responses to PCBs that may involve changes in estrogen receptor-dependent physiological processes. Recent demonstrations that hydroxy PCBs inhibit hydroxy steroid sulfotransferase suggest that PCB metabolites indirectly exert estrogenic activity via inhibition of estradiol metabolism (Kester et al. 2000).

Early studies showed that subcutaneous administration of 8 mg of Aroclors 1221, 1232, 1242, or 1248 increased uterine weight and glycogen content in rats, but similar exposure to Aroclors 1254, 1260, 1262, or 1268 did not produce this estrogenic effect (Bitman and Cecil 1970). More recent studies have provided further evidence that PCB mixtures can produce estrogenic responses (albeit weak) and that PCB congeners with multiple *ortho* chlorines (or their hydroxylated metabolites) may be at least partly responsible for these responses. Intraperitoneal doses of Aroclor 1242 (8 mg/rat on day 20 or 0.08 or 0.32 mg/rat on days 20 and 21) significantly increased uterine wet weight in immature female rats to about 40% of the increase produced by 0.001 mg 17β-estradiol (Jansen et al. 1993). Similar increases in uterine wet weight were produced by exposure to di-*ortho* congeners or hydroxylated derivatives (0.640 mg 2,2',5,5'-tetraCB or 0.250 mg 2,4,6-trichloro-4'-hydroxy-biphenyl on days 20 and 21), but not by exposure to a coplanar congener without *ortho* chlorines (0.160 mg 3,3',4,4'-tetrachlorobiphenyl). In another study, the tetra-*ortho* congener, 2,2',6,6'-tetraCB, displayed similarly weak estrogenic responses in an *in vitro* human breast cancer cell assay and an *in vivo* immature female rat assay (Arcaro et al. 1999). This congener did not competitively bind *in vitro* to recombinant human estrogen receptors α and

β, but a hydroxylated metabolite, 2,2',6,6'-tetrachloro-4'-hydroxy-biphenyl, competitively bound to estrogen receptor α and produced proliferative responses in the breast cancer assay at concentrations about 10-fold lower than effective concentrations of the parent molecule (Arcaro et al. 1999).

Combined exposure of immature rats to 0.32 mg Aroclor 1242 and 0.001 mg 17β-estradiol produced a response similar to estradiol alone, indicating no obvious anti-estrogenic activity, but combined exposure to 0.001 mg estradiol and 0.160 mg 3,3',4,4'-tetraCB markedly diminished the estradiol-induced increase in uterine wet weight (Jansen et al. 1993). Anti-estrogenic effects similar to those from 3,3',4,4'-tetraCB were also observed in rodent uterine tissue (Astroff and Safe 1990) and human breast cancer cells (Krishnan and Safe 1993) by other congeners with no or single *ortho* chlorines (e.g., 3,3',4,4',5-pentaCB, 2',3,3',4,4',5-hexaCB), but commercial PCB mixtures were not anti-estrogenic in the breast cancer cell assay. Whereas the data collected by Krishnan and Safe (1993) suggest that anti-estrogenic activities of PCBs may be related to Ah receptor binding affinity of nonmetabolized PCBs, anti-estrogenic activities of hydroxylated metabolites of PCBs with no *ortho* chlorines, with single *ortho* chlorines, or with multiple *ortho* chlorines have been observed in in several assay systems (Connor et al. 1997; Moore et al. 1997; Nesaretnam et al. 1996; Safe et al. 1998b). Thus, whether or not a specific PCB mixture will be anti-estrogenic appears to be at least partly dependent on the chlorine substitution pattern of the parent PCBs and on the degree of formation of hydroxylated metabolites.

Structure-activity relationships for estrogenic activities of PCB congeners or their metabolites are less clear. Some hydroxylated PCBs (2,4,6-trichloro-4'-hydroxy-biphenyl and 2,3,4,5-tetrachloro-4'-hydroxy-biphenyl) have been demonstrated to competitively bind to mouse estrogen receptor preparations and to increase uterine weight and glycogen in immature mice (Korach et al. 1988). In other estrogenic assays, 2,2',4,4',6-tetraCB, 2,4,4',6-tetrachloro-4-hydroxy-biphenyl, and 2,4,6-trichloro-4'-hydroxy-biphenyl were equally effective in stimulating proliferation of human breast cancer cells, but only 2,4,6-trichloro-4'-hydroxy-biphenyl caused significant induction of vitellogenin in cultured brown trout hepatocytes (Andersson et al. 1999). A structure-activity study of eight hydroxylated PCBs in a series of *in vivo* and *in vitro* estrogenic assays found that structure activity relationships were complex and differed from one assay to the next (Connor et al. 1997; Safe et al. 1998b). For example, all but one of the compounds displayed competitive binding to rat and mouse cytosolic estrogen receptors (affinities ranged from about 10^{-3} to 10^{-5} of 17β-estradiol's affinity), but no estrogenic activities (wet weight, peroxidase activity, progesterone receptor level) were produced in the uteri of immature rats and mice exposed to three consecutive daily doses of the individual hydroxylated PCB congeners at levels of 25, 50, or 100 mg/kg.

In contrast, four of the hydroxylated congeners produced estrogenic effects in cultured human breast cells and HeLa cells (Connor et al. 1997; Safe et al. 1998).

Complex effects on male reproductive organs and functions have been observed in animals exposed to commercial PCB mixtures including reduced testes weight in adult male offspring of guinea pigs exposed during gestation to Clophen A50 (Lundkvist 1990), reduced testes weight in adult male offspring of female rats exposed from 50 days prior to mating through birth of offspring to 4 mg/kg/day Aroclor 1254 or a mixture of PCBs reflective of the composition of human milk samples (Hany et al. 1999b), reduced fertility (without changes in reproductive organ weights, sperm production, or sperm morphology) in adult male offspring of female rats exposed to doses of 8 mg/kg Aroclor 1254 and higher on lactation days 1, 3, 5, 7, and 9 (Sager et al. 1987, 1991), and elevated testes weight and increased sperm production in adult rats exposed to subcutaneous doses of Aroclor 1242 or 1254 (10–80 mg/kg/day) on postnatal days 0–25 (Cooke et al. 1996). Mechanisms involved in these effects on male reproductive organ development are unknown, but have been postulated to involve developmentally specific periods of responsiveness such as long-lasting elevation of testosterone-metabolizing enzymes from *in utero* exposure leading to reduced testes weight (Hany et al. 1999b) and continued depression of thyroid hormone levels during the neonatal period leading to Sertoli cell proliferation and increased testes weight (Cooke et al. 1996).

Disruption of Thyroid Hormone Homeostasis. Concern that the thyroid hormone system may be important in PCBs mechanisms of toxicity stems from mainly two important types of observations (Brouwer et al. 1998b; Porterfield and Hendry 1998): (1) extensively corroborated findings in experimental animals that exposure to PCBs *in utero* and/or during early development (e.g., through breast milk) can deplete levels of circulating thyroid hormone in the fetus or neonate, which may give rise to effectively a hyopothyroid state during development (Collins and Capen 1980c; Cooke et al. 1996; Corey et al. 1996; Darnerud et al. 1996a; Goldey et al. 1995; Juarez de Ku et al. 1994; Li et al. 1998; Morse et al. 1996c; Rice 1999a; Provost et al. 1999; Schuur et al. 1998a; Seo and Meserve 1995; Zoeller et al. 2000); and (2) the recognition of the importance of thyroid hormones in normal development of the brain, as evident from neurodevelopmental disorders and deficits associated with hypothyroidism (Boyages 2000). The latter are typified by iodine deficiency (e.g., endemic cretinism), which can produce a wide range of neurodevelopmental deficits, including auditory, motor, and intellectual deficits. These outcomes suggest an importance of thyroid hormones in the normal development of the fetal cochlea, basal ganglia, and cerebral cortex, which begin to develop in humans during the second trimester of gestation. This is also the time in which the fetal thyroid gland becomes functional.

Evidence for a potential thyroid hormone involvement in PCB toxicity rests largely on observations made in experimental animals, including rodents and nonhuman primates (see Section 3.2.2.8.3). Although the studies differ in design and, in particular, the emerging picture from these studies is that, depending on dose and duration, PCBs can disrupt the production and disposition of thyroid hormones at a variety of levels. The major findings include (1) histological changes in the thyroid gland indicative of both stimulation of the gland (e.g., similar to that induced by TSH or a hypothyroid state) and a disruption of the processing of follicular colloid needed for normal production and secretion thyroid hormone (Chu et al. 1994, 1995, 1996a, 1996b, 1998b; Collins and Capen 1980a; Collins et al. 1977; Hansen et al. 1995; Tryphonas et al. 1986b); (2) depression of serum T_4 and T_3 levels, which may effectively create a hypothyroid state (Byrne et al. 1987; Collins and Capen 1980c; Cooke et al. 1996; Corey et al. 1996; Darnerud et al. 1996a; Desauliniers et al. 1997; Goldey et al. 1995; Gray et al. 1993; Hansen et al. 1995; Hood et al. 1999; Juarez de Ku et al. 1994; Kasza et al. 1978; Li et al. 1998; Morse et al. 1996c; Price et al. 1988; Provost et al. 1999; Rice 1999a; Schuur et al. 1998a; Seo and Meserve 1995; Van Birgelen et al. 1995; Zoeller et al. 2000); (3) increased rates of elimination of T_4 and T_3 from serum (Goldey and Crofton 1998); (4) increased activities of T_4-UDP-GT in liver (Chu et al. 1995; Desauliniers et al. 1997; Morse et al. 1996c; Schuur et al. 1998a; Van Birgelen et al. 1995), which is an important metabolic elimination pathway for T_4 and T_3; (5) decreased activity of iodothyronine sulfotransferases in liver which are also important in the metabolic elimination of iodothyronines (Schuur et al. 1998a, 1998b, 1999); (6) decreased activity of iodothyronine deiodinases including brain Type-2 deiodinase, which provide the major pathways for the production of the active thyroid hormone, T_3 (Morse et al. 1996c; Schuur et al. 1998a); and (7) decreased binding of T_4 to transthyretin an important transport protein for both T_4 and T_3 (Cheek et al. 1999; Darnerud et al.1996a).

The above observations suggest that PCBs can disrupt the production of thyroid hormones, both in the thyroid and in peripheral tissues, can interfere with their transport to peripheral tissues, and can accelerate the metabolic clearance of thyroid hormones. The most convincing evidence that PCBs can exert toxicity by disrupting thyroid hormone system derives from two studies in rats. In one study, neurobehavioral deficits in pups that experienced exposures to Aroclor 1254 *in utero* and during nursing, were significantly attenuated by subcutaneous injections of T_4 that increased serum T_4 and T_3 concentrations that were otherwise depressed in the PCB-exposed animals (Goldey and Crofton 1998). While this study examined relatively high doses of Aroclor 1254 ($1 mg/kg/day), it nevertheless demonstrated neurodevelopmental effects that are directly relevant to observations made in epidemiological studies and to neurological sequelae of fetal hypothyroidism, including motor disturbances and hearing.

In the second study, increased testes weight and sperm production in rats that were administered Aroclor 1254 on postnatal days 1–25 were attenuated by injections of T_4 on postnatal days 1–25, which also prevented the depression in serum T_4 concentrations (Cooke et al. 1996). Here again, although produced by relatively large doses of Aroclor 1254 ($40 mg/kg/day, subcutaneous), similar effects can be produced by other hypothyroid-inducing agents, including PTU. Furthermore, the effects observed may reflect a disruption of the normal sexual maturation process, which is known to be associated with neonatal hypothyroidism in humans (Longcope 2000).

The effects PCBs on thyroid hormone status appear to involve Ah-receptor mediated or modulated actions as well as actions that appear to be independent of the Ah receptor. Depressed levels of serum T_4 have been observed in rats given oral doses of coplanar PCB congeners (Desauliniers et al. 1997; Price et al. 1999; Van Birgelen et al. 1994b) or di-*ortho*-substituted congeners that have relatively low affinity for the Ah receptor (Ness et al. 1993; Van Birgelen 1992). At least one potential Ah-receptor mediated mechanism for this effect is the induction of UDP-GT, which catalyzes the metabolic elimination of T_4 to the T_4-glucuronide conjugate (Desauliniers et al. 1997; Van Birgelen et al. 1995). However, the UDP-GT mechanism does not appear to be important in the depression of T_4 levels produced by non-coplanar PCBs. Li and Hansen (1996) observed depressed serum T_4 levels in rats administered a PCB mixture extracted from soil. Treatment of the mixture with activated charcoal greatly reduced the content of co-planar PCBs in the mixture, substantially decreased the potency of the mixture for inducing UDG-GT and EROD, but had little effect on the potency for depressing T_4 levels. This suggests that an Ah-independent mechanism may exist that is not related to UDP-GT induction.

PCBs, including poly-*ortho*-substituted PCBs, which have a very low affinity for the Ah receptor, inhibit the binding of T_4 to transthyretin, an important transport protein for both T_4 and T_3 (Chauhan et al. 2000; Cheek et al. 1999; Darnerud et al. 1996a). Inhibition of binding of thyroid hormones to transthryetin could alter hormone delivery to target tissues, including the brain, and could also result in depressed levels of serum total TT_4 or TT_3 (Brouwer et al. 1998).

Immunological Effects. Studies with inbred mice strains differing in Ah-receptor responsiveness indicate that immunosuppression from PCB mixtures involves Ah-receptor mediation (e.g., Silkworth and Grabstein 1982; Harper et al. 1993a), but there is evidence that other mechanisms also may contribute to PCB-induced immunological effects (Harper et al. 1993a, 1993b; Stack et al. 1999). Illustrating the importance of Ah-receptor mediation for some PCB congeners, Ah-responsive C57BL/6 mice given single intraperitoneal doses of 100 mg/kg 3,3',4,4'-tetraCB showed marked decreases in the number of

splenic PFCs formed in response to immunization with SRBCs (which are T-cell dependent antigens) compared with similarly treated Ah-nonresponsive DBA/2 mice (Silkworth and Grabstein 1982). In addition, ED_{50} values for 2,3,7,8-TCDD, three CDFs, and two PCBs without *ortho* substitution (3,3',4,4',5-pentaCB and 3,3',4,4',5,5'-hexaCB) in this immunotoxicity assay were lower in C57BL/6 mice than in DBA/2 mice, and the order of immunotoxic potency of these six compounds was the same as that for potency in inducing CYP1A1 (Harper et al. 1993a). In another study, a series of four hexachlorinated biphenyls with differing chlorine substitution patterns displayed varying ED_{50} values in the same immunotoxicity assay as follows: 2, >1,000, 120, and >1,000 μmol/kg for a mono-*ortho*- (2,3,3',4,4',5'-), di-*ortho*- (2,2',4,4',5,5'-), tri-*ortho*- (2,2',4,4',5',6-), and tetra-*ortho* (2,2',4,4',6,6'-)-isomer, respectively (Harper et al. 1993b). Harper et al. (1993b) concluded that immunotoxic potency decreases (i.e., ED_{50}s increase) with increasing *ortho*-chlorine substitution of PCBs, but, as shown above, the decrease was not monotonic with increasing degree of *ortho* chlorination. Furthermore, this relationship did not apply to more highly chlorinated PCBs with three or four *ortho* chlorines that are inactive as Ah-receptor agonists and only minimally induce CYP1A1 (Harper et al. 1993b). Three nonachlorobiphenyls (2,2',3,3',4,4',5,5',6-, 2,2',3,3',4,4',5,6,6'-, and 2,2',3,3',4,5,5',6,6'-nonaCB) and decachlorobiphenyl displayed ED50s for inhibition of the splenic PFC response to SRBC in C57BL/6 mice that were less than those for hexachlorobiphenyl isomers with multiple *ortho* chlorines reported above: 15, 7, 17, and 35 μmol/kg, respectively. These results are consistent with the hypothesis that some PCBs induce immunotoxicity via Ah-receptor *independent* mechanisms. In an *in vitro* assay of cell proliferation in response to lipopolysaccharide (a T-cell independent antigen), Aroclors 1221, 1242, 1254, or 1260 inhibited the proliferative response similarly in splenocytes from either C57BL/6 or DBA/2 mice (Stack et al. 1999). Two non-*ortho* and two mono-*ortho* PCBs that have been demonstrated to be effective Ah-receptor agonists and CYP1A1 inducers did not inhibit the *in vitro* proliferative response to lipopolysaccharide, but two di-*ortho* congeners (2,2',3,4,4',5- and 2,2',4,4',5,5'-hexaCB) significantly inhibited the response. These *in vitro* results provide supporting evidence for the existence of mechanisms of PCB immunotoxic actions that are independent of the Ah receptor.

Cancer. Lifetime oral exposure to any one of four commercial PCB mixtures (Aroclors 1016, 1242, 1254, and 1260) has been demonstrated to produce liver tumors in female rats; Aroclor 1260 also induced liver tumors in male rats (Mayes et al. 1998). Mixtures with high chlorination content (e.g., Aroclor 1254) were generally more potent than mixtures with low chlorine content (e.g., Aroclor 1016) (Mayes et al. 1998). Tumor promotion by commercial PCB mixtures following initiation by a variety of chemical agents also has been investigated in a number of animal systems including rat liver, rat kidney, mouse skin, and newborn mouse liver and lung (see Silberhorn et al. 1990 for review). The tumor

promoting effect of extended exposure to PCB mixtures was demonstrated principally in the liver of rats; there is some evidence that PCB mixtures also can promote tumors in mouse lung and mouse skin, but not in rat kidneys. The mechanism of PCB-induced cancer is poorly understood, but there is evidence to suggest that both Ah-receptor dependent and independent mechanisms may be involved.

PCB promotion of tumors does not appear to be solely an Ah-receptor mediated process, since individual congeners that are not Ah receptor agonists have tumor promotion capabilities in animal systems. For example, 2,2',5,5'-tetraCB, 2,2',4,4'-tetraCB, and 2,2',4,4',5,5'-hexaCB were shown to promote liver tumors in female Sprague-Dawley rats (Hemming et al. 1993; Preston et al. 1985). In addition, 2,2',5,5'-tetraCB, 2,2',3,3',4,4'-hexaCB, and 2,2',4,4',5,5'-hexaCB were potent inhibitors of *in vitro* gap junctional cellular communication, an assay that is indicative of tumor promotion capacity (Bager et al. 1997; De Haan et al. 1996). A general working mechanistic hypothesis for PCB promotion of liver tumors involves indirect stimulation of cell proliferation following cell or tissue injury by reactive metabolites of PCBs (Silberhorn et al. 1990). Alternatively, the cell injury could be caused by increased intracellular concentrations of other reactive species (e.g., superoxide anion or other reactive oxygen species) caused by an overall imbalance from PCB-induced perturbations of cellular biochemical processes, including induction of CYP oxygenases and glutathione S-transferases, repression of selenium-dependent glutathione peroxidases, and/or disruption of calcium homeostatic processes and signal transduction pathways (Silberhorn et al. 1990).

PCB mixtures have not shown consistent tumor initiating activity in animal initiation-promotion protocols (Silberhorn et al. 1990), but demonstration that chronic oral exposure to commercial PCB mixtures induced liver tumors in female rats (Mayes et al. 1998) suggests that PCBs may have both tumor initiating and promoting activities. Although PCB mixtures generally have been found to be inactive as mutagens in *S. typhimurium* strains and in several other tests of genotoxicity that may be predictive of tumor initiation capability (see Silberhorn et al. 1990 for review), *in vitro* studies with rat microsomes have indicated that metabolism of lower chlorinated PCBs (e.g., 4-CB, 3,4-diCB, and 3,4,5-triCB) can lead to covalently modified macromolecules including proteins and DNA (see Robertson and Gupta 2000 for review). Studies demonstrating the Ah-receptor dependence or independence of this potential genotoxic effect from PCBs were not located. The available data indicate that PCBs are not potent genotoxicants, but the possible involvement of genotoxic mechanisms (involving covalent modification of proteins and/or DNA) in the development of PCB-induced cancer is not without some experimental support.

The relative contribution that Ah-receptor dependent and independent mechanisms may make to carcinogenic responses to PCB mixtures is unknown. Safe (1994) compared carcinogenic responses of female rats to 2,3,7,8-TCDD in the diet with responses of female rats of the same strain to Aroclor 1260 in the diet using the TEF approach. TCDD at a TEQ feed concentration of 2,100 ppt induced hepatic adenocarcinomas in 11/50 (22%) rats, whereas a TEQ of only 1,040 ppt from Aroclor 1260 induced adenocarcinomas in 24/47 (51%) rats. For this situation, the TEF approach markedly underestimated the carcinogenic response to Aroclor 1260. A possible explanation is that PCB congeners that are not Ah receptor agonists and are abundant in Aroclor 1260 make significant contributions to the mixture's carcinogenicity. Although this comparison suggests that the TEF approach may underestimate cancer responses to complex PCB mixtures, another study of the tumor promotion activity of a simpler mixture of two CDDs, one CDF, and three PCBs in female rats found that the TEF approach overestimated the observed response by a factor of about 2 (van der Plas et al. 1999). The mixture contained 2,3,7,8-TCDD, 1,2,3,7,8-pentachlorodibenzo-p-dioxin, 2,3,4,7,8-pentachloro-dibenzofuran, 3,3',4,4',5- and 2,3',4,4',4-pentaCB, and 2,3,3',4,4',5-hexaCB at relative levels found in Baltic Sea herring. The rats were initiated with an injection of diethylnitrosoamine, 24 hours after a partial hepatectomy and were administered weekly subcutaneous injections of the mixture for 20 weeks starting 6 weeks after initiation. The volume and volume fraction of glutathione *S*-transferase-positive altered hepatic foci were taken as indicators of tumor promotion activity in this study (van der Plas et al. 1999). Although the composition of this mixture reflected relative concentrations and accounted for >90% of total TEQs in Baltic Sea herring, it did not contain PCBs with multiple *ortho* chlorines, which comprise the predominant bulk of PCB weight in most commercial and environmental mixtures. For example, non-, mono-, and di-*ortho* congeners accounted for <1, 18, and 82% of PCB weight per gram of fat in human milk samples from Italy (Larsen et al. 1994). Another group of rats was similarly treated with the same synthetic mixture plus a di-*ortho* PCB congener (2,2',4,4',5,5'-hexaCB), which is one of the predominant PCB congeners in environmental mixtures and has minimal Ah receptor agonist activity (van der Plas et al. 1999). Mean foci volume and foci volume fraction were increased in rats treated with the supplemented mixture compared with the mixture without the di-*ortho* congener, but the observed responses were still less than that predicted by the TEF approach. Better understanding of the relative contributions of Ah receptor dependent and independent mechanisms to the carcinogenicity of PCB mixtures awaits further research.

3.5.3 Animal-to-Human Extrapolations

As with other organisms, PCB residue levels in humans reflects multiple exposure pathways, and congener-specific elimination. PCB profiles in human serum immediately following exposures reflect the profiles in the exposure sources, however, selective metabolism and excretion begin to alter the congener profile within 4–24 hours (Hansen 1999). Thus, in most cases, the PCB profile in adults represents a steady state body burden which does not match the profile of commercial PCB formulations (Aroclors, etc.). For example, the PCB profile of a composite human milk sample does not resemble the pattern of any commercial PCB formulation (Safe et al. 1985). Furthermore, PCB residue analysis indicates that humans, aquatic mammals, birds, fish, and other biota retain a similar profile of PCB congeners. Borlakoglu and Walker (1989) reported that fisheating sea birds, human fat, American breast milk, and German breast milk have similar PCB congener profiles, which are different from that of Aroclor 1260 or Clophen A60. The hexachlorinated PCBs, 138 (2,2',3,4,4',5') and 153 (2,2',4,4',5,5'), were major congeners present in all samples from this study, while PCB 149 (2,2',3',4',5',6) was only found as a major component of Aroclor 1260 and Clophen A60. PCB 118 (2,3',4,4',5) was a major congener in biological samples and only a minor component of the commercial PCB formulations. McFarland and Clarke (1989) reported that PCBs 118, 138, 153, 156, 170, 180, and 187 were PCBs retained at a high relative abundance in porpoise, carp, duck, oligochaete, seston, shrimp, and human fat and milk. PCB 153 was the most abundant congener present in porpoise, carp, duck, oligochaete, and human fat and milk. In contrast to PCB residues present in the above populations with normal background exposures, humans retained PCB 74 as the most abundant PCB in human fat and serum following a case of occupational exposure (Stellman et al. 1998; Wolff et al. 1982a, 1982b). Thus, selective high level exposures, such as an occupational exposure, may result in an altered profile of retained PCB congeners, relative to that observed in cases of normal background exposure. However, the above studies generally find similar PCB congener profiles in different tissues and species, indicating that the biological fate of PCB congeners is qualitatively similar in various animal species.

Significant interspecies differences in the quantitative metabolism of PCBs contributes directly to the species differences in the relative persistence (biological half-life) of PCB congeners. For example, PCB 153 is often the most prevalent PCB detected in humans, due to exposure and the slow rate of biotransformation of this congener. 3-Hydroxy-2,4,5,2',4',5'-hexaCB was identified as the major metabolite of PCB 153 formed by human CYP2B6 (Ariyoshi et al. 1995). CYP2B6 is constitutively expressed in humans, but only accounts for a maximum of 1–2% of the total CYPs in human liver. Approximately 75% of the subjects examined had no detectable level of CYP2B6 protein by

immunoblotting (Mimura et al. 1993). This may be the reason why no metabolite of PCB 153 was detected in an earlier *in vitro* study using human liver microsomes (Schnellmann et al. 1983). 3-Hydroxy-PCB 153 is also the major metabolite in the feces and bile of monkeys treated with PCB 153 (Norback et al. 1981). The CYP2B isoform represents about 5% of the total P-450 in monkey liver, and this may account for the approximately 5-fold more rapid elimination of PCB 153 from monkeys and the resulting shorter half-life in monkeys, relative to humans (Mes et al. 1995a, 1995b, 1995c; Ohmori et al. 1992). The dog has a unique ability to more rapidly metabolize and eliminate PCB 153 through the CYP2B11- mediated 3-hydroxylation of PCB 153 via a 2,3-arene oxide intermediate (Ariyoshi et al. 1992; Duignan et al. 1987; Sipes et al. 1982). Thus, the high potential for accumulation and persistence of PCB 153 in humans is due to the very low levels of CYP2B6 and low catalytic activity for 3-hydroxylation of this congener.

PCB congeners that are structurally similar to 2,3,7,8-TCDD exhibit Ah receptor-mediated responses. These congeners appear to be the most potent for some PCB-induced effects. Therefore, it would seem reasonable to assume that, at least for these specific toxic effects, differences in susceptibility among animal species could be explained by differences in receptor levels in target tissues or by differences in the affinity of binding of the specific congeners. Information on this subject is mainly derived from studies with 2,3,7,8-TCDD. Data summarized by Okey et al. (1994) indicate that differences in receptor level or receptor affinity cannot explain marked differences in susceptibility to halogenated aromatic hydrocarbon toxicity across species. It is possible that differences in sensitivity among species may be determined by some event or events occurring after the initial binding of the ligand to the receptor.

The Ah receptor has been identified in many human tissues and human cell lines (Okey et al. 1994). Several differences between human and animal Ah receptor protein have been described. Perhaps the most important difference is that the human Ah receptor has a lower affinity for 2,3,7,8-TCDD than the Ah receptor from rats or from responsive strains of mice. This information, although limited, leads to the conclusion that the biochemical and toxicological responses (those that exhibit a threshold) to dioxin-like aromatic hydrocarbons in humans would require higher doses or exposures than in animal species possessing a receptor of higher affinity (Okey et al. 1994).

3.6 ENDOCRINE DISRUPTION

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some concern over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

In recent years, concern has been raised that many industrial chemicals, PCBs among them, are endocrine-active compounds capable of having widespread effects on humans and wildlife (Crisp et al. 1998; Daston et al. 1997; Safe et al. 1997). (Effects on wildlife are summarized in Section 3.3.2). Particular attention has been paid to the possibility of these compounds mimicking or antagonizing the action of estrogen. Estrogen influences the growth, differentiation, and functioning of many target tissues, including female and male reproductive systems, such as mammary gland, uterus, vagina, ovary, testes, epididymis, and prostate. In addition, there is evidence that some of these environmentally-persistent chemicals alter the thyroid hormone system, which is very a important system in normal structural and functional development of sexual organs and the brain.

Several studies in humans have examined possible associations between body burdens of PCBs and other organochlorines and the incidence of alterations in tissues and systems. Evaluations of blood samples from women who aborted, miscarried, or delivered prematurely showed positive associations between these effects and concentrations of PCBs (Bercovici et al. 1983; Leoni et al. 1989; Wassermann et al. 1980, 1982). However, other chlorinated chemicals were also increased, and the specific contribution of

PCBs, if any, could not be determined. Similar findings were reported in a more recent study of the general population (Gerhard et al. 1998). Another general population study found no association between endometriosis and concentrations of PCBs in the blood (Lebel et al. 1998).

Breast Cancer. The issue of breast cancer has received special attention following reports of high levels of organochlorine compounds in breast cancer patients. However, the hypothesis that environmental exposure to PCBs can cause breast cancer in humans is controversial (Safe and Zacharewski 1997; Wolff and Toniolo 1995). Breast adipose levels of total PCBs or individual congeners were increased in women with breast cancer in some (Dewailly et al. 1994; Falck et al. 1992; Guttes et al. 1998; Wasserman et al. 1976) but not all studies (Aronson et al. 2000; Liljegren et al. 1998; Mussalo-Rauhamaa et al. 1990; Unger et al. 1984), but methodological limitations such as small numbers of subjects and/or inadequate control for known breast cancer risk factors could have contributed to the inconsistent findings. Two of these studies included analyses that suggested increased risks of breast cancer associated with increased tissue levels of some congeners in subgroups of women that were postmenopausal or had estrogen receptor-positive tumors (Aronson et al. 2000; Liljegren et al. 1998). Other environmental exposure studies used serum PCB concentrations as the marker of exposure with blood samples taken after the diagnosis of breast cancer (Moysich et al. 1998, 1999; Wolff et al. 1993; Zheng et al. 2000), or prospectively collected prior to diagnosis (Dorgan et al. 1999; Helzlsouer et al. 1999; Høyer et al. 1998; Hunter et al. 1997; Krieger et al. 1994; Wolff et al. 2000). None of the serum studies found significantly different mean blood levels of PCBs in breast cancer cases and controls. Additionally, there were no significant associations between risk of breast cancer and serum PCBs in most of these studies, although some data suggest that risk may be increased in some subgroups of postmenopausal women (Moysich et al. 1998, 1999). Many of the better designed studies were prospective, and none found that PCBs were associated with the occurrence of breast cancer (Dorgan et al. 1999; Helzlsouer et al. 1999; Høyer et al. 1998; Hunter et al. 1997; Krieger et al. 1994; Wolff et al. 2000). However, the prospective studies are limited by one biomarker of exposure in the distant past, which would not reflect differences over time in exposure, absorption, enzyme induction, or other factors influencing body burden such as breast-feeding. It is still possible that the PCB measurements were too abridged to detect abnormally high proportions of the more labile congeners, which appear to have greater estrogenic activities (Hansen 1998, 1999). Mortality from breast cancer was not increased in studies of workers who were occupationally exposed to relatively high levels of PCBs (Brown 1987b; Brown and Jones 1981; Kimbrough et al. 1999a), providing an additional indication that lower level environmental exposures to PCBs are unlikely to contribute significantly to the disease. Overall, the evidence for an association between breast cancer and PCBs remains inconclusive and needs further study.

Estrogenic and Anti-Estrogenic Activity. In early studies of experimental animals, research was focused on the effects of chemicals administered orally or by parenteral routes. In recent years, most of the research has focused on elucidating the mechanisms of action involved using test systems *in vitro* which, although not without limitations, are easier to manipulate and can be developed into biomarker assays for (anti)estrogenic activity. In general, results from *in vivo* and *in vitro* studies indicate that PCBs have much lower estrogenic potency than the endogenous hormone, 17β-estradiol. Subcutaneous administration of 8 mg of Aroclors 1221, 1232, 1242, or 1248 increased uterine weight and glycogen content in rats, but similar exposure to Aroclors 1254, 1260, 1262, or 1268 did not produce this estrogenic effect (Bitman and Cecil 1970). More recent studies have provided further evidence that PCB mixtures can produce estrogenic responses (albeit weak) and that PCB congeners with multiple *ortho* chlorines (or their hydroxylated metabolites) may be at least partly responsible for these responses. Intraperitoneal doses of Aroclor 1242 (8 mg/rat on day 20 or 0.08 or 0.32 mg/rat on days 20 and 21) significantly increased uterine wet weight in immature female rats to about 40% of the increase produced by 0.001 mg of 17β-estradiol (Jansen et al. 1993). Similar increases in uterine wet weight were produced by exposure to di-*ortho* congeners or hydroxylated derivatives (0.640 mg PCB 52 or 0.250 mg of 2,4,6–trichloro-4'-hydroxy-biphenyl on days 20 and 21), but not by exposure to 0.160 mg of the coplanar congener PCB 77. In another study, the tetra-*ortho* congener, PCB 47, displayed similarly weak estrogenic responses in an *in vitro* human breast cancer cell assay and an *in vivo* immature female rat assay (Arcaro et al. 1999). This congener did not competitively bind *in vitro* to recombinant human estrogen receptors α and β, but a hydroxylated metabolite, 2,2',6,6'-tetrachloro-4'-hydroxy-biphenyl, competitively bound to estrogen receptor α and produced proliferative responses in the breast cancer assay at concentrations about 10-fold lower than effective concentrations of the parent molecule (Arcaro et al. 1999). Evaluation of the offspring from rats given a PCB congener mixture simulating the congener content of human milk from 50 days prior to mating until birth showed significantly increased relative uterine weight in immature females on PND 21 (Hany et al. 1999b).

Anti-estrogenic properties of PCBs also have been examined in numerous studies. Combined exposure of immature rats to 0.32 mg Aroclor 1242 and 0.001 mg 17β-estradiol produced a response similar to estradiol alone, indicating no obvious anti-estrogenic activity, but combined exposure to 0.001 mg estradiol and 0.160 mg of PCB 77 markedly diminished the estradiol-induced increase in uterine wet weight (Jansen et al. 1993). Anti-estrogenic effects similar to those from PCB 77 were observed in rodent uterine tissue (Astroff and Safe 1990) and human breast cancer cells (Krishnan and Safe 1993) by other congeners with no or single *ortho* chlorines (e.g., 3,3',4,4',5-pentaCB, 2',3,3',4,4',5-hexaCB), but commercial PCB mixtures were not anti-estrogenic in the breast cancer cell assay. Whereas the data

collected by Krishnan and Safe (1993) suggest that anti-estrogenic activities of PCBs may be related to Ah receptor binding affinity, anti-estrogenic activities of hydroxylated PCB congeners with multiple *ortho* chlorines have been observed in several assay systems (Connor et al. 1997; Moore et al. 1997; Safe et al. 1998b).

Structure-activity relationships for estrogenic activities of PCB congeners or their metabolites are less clear. Some hydroxylated PCBs (2,4,6-trichloro-4'-hydroxy-biphenyl and 2,3,4,5-tetrachloro-4'-hydroxy-biphenyl) have been demonstrated to competitively bind to mouse estrogen receptor preparations and to increase uterine weight and glycogen in immature mice (Korach et al. 1988). In other estrogenic assays, PCB 104, 2,4,4',6-tetrachloro-4-hydroxy-biphenyl, and 2,4,6-trichloro-4'-hydroxy-biphenyl were equally effective in stimulating proliferation of human breast cancer cells, but only 2,4,6-trichloro-4'-hydroxy-biphenyl caused significant induction of vitellogenin in cultured brown trout hepatocytes (Andersson et al. 1999). A structure-activity study of eight hydroxylated PCBs in a series of *in vivo* and *in vitro* estrogenic assays found that structure-activity relationships were complex and differed from one assay to the next (Connor et al. 1997; Safe et al. 1998b). For example, all but one of the compounds displayed competitive binding to rat and mouse cytosolic estrogen receptors (affinities ranged from about 10^{-3} to 10^{-5} of 17β-estradiol's affinity), but there was no evidence of estrogenic activities (wet weight, peroxidase activity, progesterone receptor level) in the uteri of immature rats and mice exposed to three consecutive daily doses of the individual hydroxylated PCB congeners at levels of 25, 50, or 100 mg/kg. In contrast, four of the hydroxylated congeners produced estrogenic effects in cultured human breast cells and HeLa cells (Connor et al. 1997; Safe et al. 1998). These results suggest that PCB-induced estrogenic activities are weak compared to the endogenous hormone, 17β-estradiol. Further, the wide variability of responses observed across types of PCBs and assays indicates: (1) the involvement of multiple mechanisms, (2) anti-estrogenic activities appear strongly associated with PCBs that are Ah receptor agonists, and (3) hydroxylated metabolites of PCBs seem to be at least partly responsible for physiological responses to PCBs that may involve changes in estrogen receptor-dependent physiological processes.

The results of some studies summarized above suggest that PCBs can produce estrogenic and anti-estrogenic responses by interfering with the binding of natural ligands to their receptors. The type of response varied between assays and was dependent of the concentration of the test material. Reviews of published data suggest that the amount of naturally occurring estrogens ingested daily through a normal diet is far greater than the daily intake of estrogenic organochlorine chemicals (Safe 1995). Moreover, results from many assays indicate that estrogenic organochlorines have a potency of 0.000001 times that of 17β-estradiol, compared to 0.001–0.0001 times for naturally-occurring estrogenic substances. In

addition, many naturally-occurring estrogenic substances, such as bioflavonoids, are also antiestrogenic at some concentrations. Dietary levels of anti-estrogen equivalents (industrial or natural) are significantly higher than the estrogen equivalents of organochlorine chemicals (Safe 1995).

Reproductive Effects. Sager and Girard (1994) have provided evidence of reproductive effects of PCBs that may be related to PCB-induced endocrine disruption. After giving birth, adult female rats were exposed to 0, 8, 32, or 64 mg Aroclor 1254/kg/day by gavage on lactation days 1, 3, 5, 7, and 9. Young, mature, and older adult female offspring were examined at 2–4.5, 5–8, and 8.5–13 months of age, respectively, and mated to untreated males at 112, 200, and 350 days of age, respectively. Effects included a dose-related reduction in preweaning weight gain that was statistically significant at $32 mg/kg/day, delayed puberty as indicated by late vaginal opening and first estrus at $32 mg/kg/day; reduced mating rate (sperm-positive females) in mature offspring at $8 mg/kg/day; reduced implantation rate and mean number of embryos in young and mature offspring at 64 mg/kg/day; reduced uterine weight during proestrus in young, mature, and older offspring at $8 mg/kg/day; and reduced uterine response to exogenous 17β-estradiol in ovariectomized mature offspring at $8 mg/kg/day. Average estrus cycle length was not significantly different in any of the groups, although cycle patterns were altered in low- and high-dose young offspring and in mid-dose mature rats. Pregnancy and ovulation rates, reproductive aging, and ovarian weights were not affected by exposure Aroclor 1254.

Fertility was markedly reduced in male offspring of Holtzman rats that were exposed via lactation to Aroclor 1254 (Sager 1983; Sager et al. 1987, 1991). The maternal rats were treated with 8, 16, 32, or 64 mg/kg doses by gavage on lactation days 1, 3, 5, 7, and 9, and male offspring were mated with untreated females 130–150 days postweaning (Sager 1983; Sager et al. 1987). Significant decreases in numbers of implants and embryos were observed at $8 mg/kg/day (21 and 29% lower than controls, respectively), and there was either a significant decrease or a decline in number and percent of normal fertilized eggs and eggs at the two- to four-cell blastocyte stages at $16 mg/kg/day. The reduction in male fertility appears to be due to impaired ability of sperm to fertilize eggs because sperm production, morphology, and motility were not affected and plasma FSH and testosterone concentrations were not reduced (Sager et al. 1987, 1991). Seminal vesicle and ventral prostate weights were decreased at $16 mg/kg/day.

Fertility was not impaired in male offspring of Sprague-Dawley rats that were administered 0 or 30 mg/kg/day doses of Aroclor 1221, 1242, or 1260 by gavage on days 12–20 of gestation (Gellert and Wilson 1979). There were no exposure-related changes in the percentage of male offspring (F1) siring

progeny when they were mated with unexposed females at approximately 6 months of age, or in the sex ratio of the F2 offspring from this mating. Measurements of absolute testes and ventral prostate weights in the F1 males (relative weights were not determined) showed no changes except for increased testes weight in the Aroclor 1260 group. Conflicting results regarding fertility in the aforementioned studies may be related to the difference in exposure periods. In the experiments by Sager and others, exposure was postnatal via breast milk, whereas in the Gellert and Wilson (1979) study, the male rats were exposed *in utero*.

Studies that examined reproductive end points in women found indications that exposure to PCBs may be associated with menstrual disturbances. Mendola et al. (1997) reported that consumption of Lake Ontario sportfish was associated with shorter menstrual cycles in women from the New York State Angler cohort. This is a preliminary finding that needs to be interpreted cautiously because of limitations in the data analysis, particularly the lack of information on confounders such as stress, use of contraceptives, body mass index, and physical exercise. The decreases in menstrual length were small and were considered not likely to be clinically relevant. At the highest exposure levels, the decrease was approximately 0.5 days for women who reported regular cycles and 1 day for all women who reported cycle length information. The effect did not appear to be mediated through irregular cycles since the fish consumption-based exposure levels were similar for women who reported regular or irregular cycles. Menstrual cycle changes (altered intervals, duration, and flow) have also been observed in women exposed to higher doses of PCBs during the *Yusho* poisoning incident (Kusuda 1971). The human populations in which menstrual changes have been observed differ with respect to the sources of PCBs and exposures to other chemicals that may affect susceptibility to menstrual disturbances. Although the studies are insufficient for determining which specific chemical(s) may be responsible for the observed alterations, the available data support a possible association between PCBs and menstrual disturbances.

In a study of 89 women (87% German) with repeated ($2) miscarriages, Gerhard et al. (1998) found that blood concentrations of PCBs were higher than the reference level in 22% of the cases. The effect cannot be specifically attributed to PCBs because blood levels of other organochlorine compounds (pentachlorophenol, DDE, β- and γ-hexachlorocyclohexanes, HCB) were higher than reference ranges in 7–15% of the cases. No significant differences in PCB levels were found between women with early or late miscarriages (after #12 or >12 weeks of gestation) and primary or secondary miscarriages (had never delivered or had delivered at least one baby). Women with a history of at least four miscarriages (n=25) had significantly elevated blood levels of PCBs, although other organochlorine compounds (γ-hexachlorocyclohexane and HCB) were also increased. Hormonal disorders were identified as the

cause of repeated miscarriages in 31% of the women, including hyperprolactinemia in 9%, hyperandrogenemia in 7%, and luteal insufficiency in 14% of the cases. Correlations were found between increasing PCB concentrations and some hormonal parameters (e.g., increasing FSH and LH, decreasing TSH) and immunological parameters (e.g., increasing IgM, monocytes, and NK cells, decreasing interleukin 2 receptor-positive cells), but none of the associations were specific for PCBs. There were no significant associations between PCB concentrations and further conceptions or the outcome of further pregnancies.

Thyroid Effects. Concern that the thyroid hormone system may be important in the mechanism of toxicity of PCBs stems from mainly two important types of observations (Brouwer et al. 1998b; Porterfield and Hendry 1998): (1) extensively corroborated findings in experimental animals that exposure to PCBs *in utero* and/or during early development (e.g., through breast milk) can deplete levels of circulating thyroid hormone in the fetus or neonate, which may give rise to effectively a hypothyroid state during development (Collins and Capen 1980c; Cooke et al. 1996; Corey et al. 1996; Darnerud et al. 1996a; Goldey et al. 1995; Juarez de Ku et al. 1994; Li et al. 1998; Morse et al. 1996c; Rice 1999a; Provost et al. 1999; Schuur et al. 1998a; Seo and Meserve 1995; Zoeller et al. 2000); and (2) the recognition of the importance of thyroid hormones in normal development of the brain and sexual organs.

Studies in animals have shown that, depending of dose and duration of exposure, PCBs can disrupt the production and disposition of thyroid hormones at a variety of levels. The major findings include (1) histological changes in the thyroid gland indicative of both stimulation of the gland (e.g., similar to that induced by TSH or a hypothyroid state) and a disruption of the processing of follicular colloid needed for normal production and secretion thyroid hormone (Chu et al. 1994, 1995, 1996a, 1996b, 1998b; Collins and Capen 1980a; Collins et al. 1977; Hansen et al. 1995; Tryphonas et al. 1986b); (2) depression of serum T_4 and T_3 levels, which may effectively create a hypothyroid state (Byrne et al. 1987; Collins and Capen 1980c; Cooke et al. 1996; Corey et al. 1996; Darnerud et al. 1996a; Desaulniers et al. 1997; Goldey et al. 1995; Gray et al. 1993; Hansen et al. 1995; Hood et al. 1999; Juarez de Ku et al. 1994; Kasza et al. 1978; Li et al. 1998; Morse et al. 1996c; Rice et al. 1988, 1999a; Provost et al. 1999; Schuur et al. 1998a; Seo and Meserve 1995; Van Birgelen et al. 1995; Zoeller et al. 2000); (3) increased rates of elimination of T_4 and T_3 from serum (Goldey and Crofton 1998); (4) increased activities of T_4-UDP-GT in liver (Chu et al. 1995; Desaulniers et al. 1997; Morse et al. 1996c; Schuur et al. 1998a; Van Birgelen et al. 1995), which is an important metabolic elimination pathway for T_4 and T_3; (5) decreased activity of iodothyronine sulfotransferases in liver which are also important in the metabolic elimination of iodothyronines (Schuur et al. 1998a, 1998b, 1999); (6) decreased activity of iodothyronine

deiodinases including brain Type-2 deiodinase, which provide the major pathways for the production of the active thyroid hormone, T_3 (Morse et al. 1996; Schuur et al. 1998a); and (7) decreased binding of T_4 to transthyretin, an important transport protein for both T_4 and T_3 (Cheek et al. 1999; Darnerud et al. 1996a).

The above observations suggest that PCBs can disrupt the production of thyroid hormones (in the thyroid and in peripheral tissues), can interfere with their transport to peripheral tissues, and can accelerate the metabolic clearance of thyroid hormones. The most convincing evidence that PCBs can exert toxicity by disrupting thyroid hormone system derives from two studies in rats. In one study, neurobehavioral deficits in pups that experienced exposures to Aroclor 1254 *in utero* and during nursing were significantly attenuated by subcutaneous injections of T_4 that increased serum T_4 and T_3 concentrations which were otherwise depressed in the PCB-exposed animals (Goldey and Crofton 1998). While this study examined relatively high doses of Aroclor 1254 ($1 mg/kg/day), it nevertheless demonstrated neurodevelopmental effects that are directly relevant to observations made in epidemiological studies and to neurological sequelae of fetal hypothyroidism, including motor disturbances and hearing.

In the second study, increased testis weight and sperm production in rats that were administered Aroclor 1254 on postnatal days 1–25 were attenuated by injections of T_4 on postnatal days 1–25, which also prevented the depression in serum T_4 concentrations (Cooke et al. 1996). Here again, although produced by relatively large doses of Aroclor 1254 ($1.6 mg/kg/day, subcutaneous), similar effects can be produced by other hypothyroid-inducing agents, including PTU. Cooke and coworkers have proposed that the increased testis weight and sperm production is the result of PCBs extending the proliferative period of Sertoli cells, thus increasing their number. A prolonged period of cell division in turn results in a greater total number of germ cells per testis, creating an enlarged testis that produces more sperm than normal (see Chapin et al. 1996 for review). Neonatal hypothyroidism in humans also is known to be associated with disruption of the normal sexual maturation process (Longcope 2000).

In summary, PCBs can affect a wide variety of endocrine systems by directly affecting the components of the endocrine system such as hormones, metabolic enzymes, carrier proteins, receptors, endocrine glands, and feedback regulation systems. Effects on these components can lead to alterations in neurodevelopment, reproduction, and in induction of endocrine-sensitive tumors.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient

tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Children are exposed to PCBs in the same manner as the general population, primarily via consumption of contaminated foods, particularly meat, fish, and poultry (Gunderson 1988). Exposure also may occur by transfer of PCBs that have accumulated in women's bodies to the fetus across the placenta. Because PCBs are lipophilic substances, they can accumulate in breast milk and be transferred to nursing infants. Transfer across the placenta, although it may be limited in absolute amounts, is of great concern because of the effects of PCBs on sensitive immature tissues, organs, and systems, with potentially serious long-lasting consequences. Transfer of PCBs via breast milk can be considerable and, like prenatal exposure, has the potential to contribute to altered development.

Although embryos, fetuses, and nursing infants may be exposed to relatively high amounts of PCBs during sensitive periods of development, it is not known if the susceptibility of children to the health effects of PCBs differs from that of adults. Younger children may be particularly vulnerable to PCBs because, compared to adults, they are growing more rapidly and generally have lower and distinct profiles of biotransforamtion enzymes, as well as much smaller fat depots for sequestering the lipophilic PCBs.

The best documented effect of exposure to high concentrations of PCBs in adults is the induction of skin alterations, in particular, chloracne. This has been observed in individuals occupationally exposed to PCBs (Bertazzi et al. 1987; Fischbein et al. 1979, 1982; Maroni et al. 1981a, 1981b; Meigs et al. 1954) and in *Yusho* and *Yu-Cheng* victims, who consumed rice oil contaminated with high concentrations of PCBs and other dioxin-like chemicals (Hsu et al. 1994; Masuda 1994). Children born to *Yusho* and *Yu-Cheng* victims also exhibited acneform eruptions. It is reasonable to assume that children exposed to high amounts of PCBs, particularly dioxin-like congeners, also will develop dermal alterations as occurs in adults.

Numerous studies have investigated the effects of exposure to PCBs in newborn and young children. The main studies can be divided into those of women who consumed high amounts of contaminated fish, primarily from the Great Lakes (Fein et al. 1984a, 1984b; Jacobson and Jacobson 1996a, 1996b, 1997; Jacobson et al. 1984a, 1984b, 1985, 1990a, 1990b, 1992; Lonky et al. 1996, Stewart et al. 1999, 2000a), women from the general population with no known high exposure to PCBs (Gladen et al. 1988; Huisman et al. 1995a, 1995b; Koopman-Esseboom et al. 1994b, 1996; Lanting et al. 1998c; Patandin et al. 1999; Rogan and Gladen 1991, 1992; Rogan et al. 1986a, 1986b, 1987), and women who ingested rice oil accidentally contaminated with high amounts of PCBs and structurally-related compounds (Chen et al. 1992, 1994; Guo et al. 1995; Hsu et al. 1994; Lai et al. 1994; Masuda 1994). The main focus of these studies has been the evaluation of neurobehavioral end points, but information on other end points such as anthropometric measures at birth and growth rate (Dar et al. 1992; Fein et al. 1984b, Jacobson et al. 1990a, 1990b; Lan et al. 1987; Lonky et al. 1996; Patandin et al. 1998; Rogan 1989; Rylander et al. 1995, 1998b; Smith 1984; Taylor et al. 1984, 1989; Vartiainen et al. 1998), immune status (Chao et al. 1997; Dewailly et al. 2000; Weisglas-Kuperus et al. 1995; Yu et al. 1998), and thyroid status (Koopman-Esseboom et al. 1994a) is also available.

Surrogate measures of exposure that have been used in human studies include PCB measurements of maternal blood, breast milk, and cord blood. Cord blood is the most direct marker of fetal exposure, but because of its relatively low fat content, it requires sensitive analytical methods for accurate PCB analysis; analysis of breast milk does not present this difficulty. Analytical techniques have improved enormously in recent years, such that cord blood analysis of PCBs is now more accurate and reliable, but still of concern due to the low concentration of fat in cord blood.

There is evidence that PCBs play a role in neurobehavioral alterations observed in newborn and young children from women with PCB burdens near background levels, but the possibility cannot be ruled out that other lipophilic compounds may contribute to the observed effects, particularly in the studies of consumption of Great Lakes fish contaminated with other chemicals such as CDDs, DDE, and mercury. Newborns from women who ate high amounts of contaminated Lake Michigan fish had a greater number of abnormal reflexes and more motor immaturity than low-fisheaters (Jacobson et al. 1984a). Similar observations were made by Rogan et al. (1986b) in the North Carolina study of children born to women with no known high PCB exposure and in the Oswego study of children from women with high Lake Ontario fish consumption (Lonky et al. 1996). By measuring individual PCB congeners in cord blood of Lake Ontario fisheaters, Stewart et al. (2000b) observed a significant association between highly chlorinated PCBs and poorer Habituation and Autonomic scores of the NBAS for the newborns, but there

was no significant association with abnormal reflexes. No significant association was seen for the lightly and moderately chlorinated PCBs, DDE, lead, mercury, and hexachlorobenzene with any of the neurological scores for newborns of the Lake Ontario fisheaters. In the study of Dutch children, prenatal exposure to four predominant PCBs (PCB levels in maternal or cord plasma) was not associated with either reflex or postural cluster scores of a neurological examination (Huisman et al. 1995a), but there was a significant association between increasing levels of planar PCB TEQ in breast milk and increases in percentage with hypotonia but not percentage with abnormal reflexes. There is limited support from animal studies for the findings of hypotonia and hyporeflexia in newborn humans exposed to PCBs. Overmann et al. (1987) reported that newborn rats from dams exposed to 1.3 mg Aroclor 1254/kg/day showed slower development of air righting ability (an index of neuromuscular maturation) on 1 of 4 testing days and also were slower than controls in a negative geotaxis test on 2 out 4 days of testing.

Assessment of infants from the various cohorts with the Bayley Scales of Infant Development has revealed some additional consistency among the studies. This group of tests yields a mental development index (MDI) and a PDI score, both of which are scaled like a standard IQ test. In the North Carolina cohort, prenatal exposure to PCBs (assessed by PCBs in maternal milk at birth, 1.8 ppm) was associated with a significant decrease in PDI scores at the ages of 6 and 12 months (Gladen et al. 1988), but the association lost statistical significance at the ages of 18 and 24 months (Rogan and Gladen 1991). No significant association was observed between postnatal exposure to PCBs (PCBs in milk factored by duration of breast feeding) and PDI scores between 6 and 24 months of age. Neither prenatal nor postnatal exposure to PCBs showed a significant association with MDI scores. The latter is consistent with a lack of significant association between prenatal or postnatal exposure and MDI scores at 7 or 18 months of age also observed in the Dutch children (Koopman-Esseboom et al. 1996). *Yu-Cheng* children also had lower PDI and MDI scores when tested between the ages of 6 months and 2 years old (Lai et al. 1994). Alterations in memory functions were reported in children from the Michigan cohort at 7 months of age (Jacobson et al. 1985) and at 4 years of age (Jacobson et al. 1990a, 1990b, 1992), but not in other cohorts studied. In both instances, memory deficits were associated with prenatal exposure to PCBs, as measured by PCBs in cord blood. Decreased performance in memory tests has been reported following perinatal exposure to commercial PCB mixtures in rats (Corey et al. 1996; Lilienthal and Winneke 1991) and in monkeys (Levin et al. 1988; Schantz et al. 1989). In addition, decreased performance on a memory task was reported in 60-day-old rats exposed *in utero* to *ortho*-substituted PCB congeners (Schantz et al. 1995).

A brain area of critical importance in the regulation of short-term or representational memory for spatial information is the prefrontal cortex (Brozoski et al. 1979; Goldman et al. 1971). Some studies in animals have found changes in the concentration of neurotransmitters in the frontal cortex following exposure to PCBs. For example, Morse et al. (1996a) reported that rats exposed during gestation days 10–16 to 5 or 25 mg Aroclor 1254/kg/day had a significant increase in the levels of 5-HIAA and in the ratio 5-HIAA/5-hydroxytryptamine in the prefrontal cortex at 90 days of age. These rats also showed a significant decrease in the neuronal marker synaptophysin in the prefrontal cortex, which was interpreted as reactive gliosis (Morse et al. 1996b). A decrease in dopamine in the frontal cortex was also observed in rats exposed to contaminated Great Lakes fish *in utero*, during lactation, and until 88 days of age (Seegal et al. 1998). Exposure of weanling rats to PCB 153 (0.01 mg/kg/day) or PCB 128 (0.005 mg/kg/day) for 90 days also resulted in decreased dopamine levels in the frontal cortex (Chu et al. 1996a; Lecavalier et al. 1997). Changes in neurotransmitter levels have also been observed in other brain areas, but further research is needed before specific neurobehavioral deficits can be correlated with changes in specific neurotransmitters in specific brain areas.

As previously mentioned, neurobehavioral alterations have been observed in rats and monkeys following pre- and/or postnatal exposure to commercial Aroclor mixtures, defined experimental congener mixtures, single PCB congeners, and Great Lakes contaminated fish. Monkeys exposed from birth to age 20 weeks to PCB mixtures of congeneric composition and concentration similar to that found in human breast milk showed learning deficits long after exposure had ceased (Rice 1997, 1998, 1999b; Rice and Hayward 1997, 1999a). This type of study appears to be the most relevant to evaluating risk of PCB exposure by infants since they mimic the exposure scenario for a nursing human infant.

Results from evaluation of anthropometric measurements in newborn and young children have been mixed. Of the studies of women who consumed contaminated fish from the Great Lakes, only one out of four, the Michigan study (Fein et al. 1984b; Jacobson et al. 1990a, 1990b), reported an association between reduced birth weight, head circumference, and gestational age in newborns and with body weight at 4 years with prenatal exposure to PCBs (PCBs in cord blood). In the Oswego cohort (Lake Ontario fish consumption), there was no significant association between prenatal exposure to PCBs, assessed by the same fish consumption measures as in the Michigan study, and birth weight, head circumference, or gestational age (Lonky et al. 1996). In two additional studies of Lake Michigan women (Dar et al. 1992; Smith 1984), fish consumption had a positive effect on birth weight. This finding could be related to the beneficial effects of certain fatty acids in fish (Olsen et al. 1990). In one of these studies (Smith 1984), the concentration of PCBs in breast milk was higher than in breast milk from women from the Michigan

cohort (1.13 vs 0.87 ppm). A study of Swedish wives of Baltic Sea fishermen found an increased risk of low birth weight with increasing maternal blood concentrations of the PCB congener PCB 153 used as a surrogate of PCB exposure during the year of childbirth (Rylander et al. 1998b). In the Dutch cohort, prenatal exposure to PCBs (PCBs in cord blood) was associated with a reduced birth weight, but not with head circumference or height at 10 days of age (Patandin et al. 1998). Prenatal exposure in formula-fed children was associated with reduced growth between birth and 3 months, but no such association was seen in breast fed children, suggesting to the investigators that any detrimental effect observed in newborns due to prenatal exposure to PCBs may have been counteracted by the benefits of breast feeding. No significant association was seen between any measure of exposure to PCBs and growth at the ages of 3–7 months, 7–18 months, or 18–42 months. A study of the general population in Finland found no significant association between birth weight and the concentration of PCBs in breast milk (Vartiainen et al. 1998). In this study, the mean concentration of PCBs in milk (0.4–0.5 ppm) was slightly lower than in the Dutch study (0.62 ppm) (Koopman-Esseboom et al. 1994b). Overall, it seems that if there is an adverse effect of prenatal exposure to PCBs on growth, it is transient, as documented in children from the *Yusho* poisoning episode (Yoshimura and Ikeda 1978).

Studies in rodents, generally with relatively high doses of PCB mixtures or congeners, have shown decreased birth weight and reduced weight gain after birth. This occurred in animals exposed *in utero* and through breast milk, even though their weight at birth was not significantly different than in unexposed controls (Collins and Capen 1980c; Overmann et al. 1987). This suggests that a significant transfer of PCBs occurred via breast feeding. Long-term studies with much lower doses of Aroclors 1016 and 1248 in monkeys also reported decreased birth weight (Allen and Barsotti 1976; Barsotti and Van Miller 1984). Studies with low doses of Aroclor 1254 (0.005–0.08 mg/kg/day) found no significant effects on anthropometric measures at birth or on growth thereafter (Arnold et al. 1995, 1997).

As indicated above, there is information regarding the effects of perinatal exposure to PCBs on immunocompetence in children. In a study of fisheating women from Sheboygan, Wisconsin (Lake Michigan), maternal serum PCB level (mean 5.48–5.76 ppb) was positively and significantly associated with the number of infectious illnesses in the infants ($r=0.33$, $p=0.03$), although breast milk PCB levels (mean 1.13 ppm) had a weak but significantly negative association with infant illnesses (Smith 1984). Possible associations between infectious illnesses and other chemicals in the fish were not investigated.

Susceptibility to infections and immune status were studied in 98 breast-fed and 73 bottle-fed Inuit (Eskimo) infants from Arctic Quebec, Canada (Dewailly et al. 2000). The Inuits have high body burdens

of various organochlorine compounds due to high consumption of marine foods, particularly sea mammal fat. Concentrations of PCBs and other chlorinated pesticides or metabolites were measured in early breast milk fat and used as an index of prenatal exposure to these substances; *p,p'*-DDE showed the highest mean concentration (962 ppb), followed by PCBs (621 ppb; sum of congeners 138, 153, and 180), hexachlorobenzene (107 ppb), dieldrin (30 ppb), and mirex (14 ppb) (Dewailly et al. 1993). The number of infectious disease episodes and status of immunologic parameters (WBCs, total lymphocytes and lymphocyte subsets, serum immunoglobulins) were evaluated during the first year of life. Acute otitis media was the most frequent health problem during the first year of life, with 80.0% of ever breast-fed and 81.3% of bottle-fed infants experiencing at least one episode. Relative risk (RR) analysis by follow-up period and number of episodes showed associations between increasing prenatal exposure to organochlorine compounds and otitis media that were more consistent for hexachlorobenzene and *p,p'*-DDE than PCBs. Because these and other detected organochlorine compounds originated from the same few food items and have concentrations in breast milk that are correlated with each other due to similar properties such as lipid solubility and persistence, the results precluded identification of which compounds could be responsible for the increased susceptibility to otitis media. Immunologic parameters that were significantly lower in the breast-fed babies compared to the bottle-fed group included numbers of WBCs and lymphocytes (CD4 subtype) at 3 months of age, and serum IgA concentrations at 7 and 12 months of age; CD4/CD8 lymphocyte ratios (helper T-cells/cytotoxic T-cells) were also reduced in the breast-fed infants at 7 and 12 months of age, although the change did not reach statistical significance. None of the immune parameters were associated with prenatal organochlorine exposure.

Immunologic effects of pre- and postnatal environmental exposure to PCBs and dioxins were assessed in a subgroup of 55 infants from the Dutch Mother-Child study (Weisglas-Kuperus et al. 1995). No correlation was found between pre- or postnatal exposure to PCBs/dioxin and the number of episodes of rhinitis, bronchitis, tonsillitis, and otitis during the first 18 months of life, or with humoral immunity as evaluated by antibody levels to mumps, measles, and rubella at 18 months of age (infants were immunized at 14 months of age). Determination of monocyte, granulocyte, and lymphocyte counts in cord and venous blood at 3 and 18 months of age showed that a higher prenatal as well as postnatal PCB/dioxin exposure was associated with lower monocyte and granulocyte counts at 3 months of age, and that a higher prenatal exposure was associated with increased total numbers of T-lymphocytes and several T-cell subpopulations ($CD8^+$, $TcR\alpha\beta^+$, and $TcR\gamma\delta^+$) at 18 months of age. There were no significant associations between postnatal PCB/dioxin exposure and T cell markers at 18 months of age. Although there were differences in the leukocyte subpopulation between high and low PCB/dioxin-exposed infants, all values were within the normal range (Weisglas-Kuperus et al. 1995). Follow-up

evaluations at 42 months of age, reported as a study abstract, found that prenatal PCB exposure was associated with increased T cell numbers and lower antibody levels to mumps, measles and rubella (Weisglas-Kuperus 2000). Additionally, PCB body burden at 42 months of age was reported to be associated with a higher prevalence of recurrent middle ear infections and chicken pox and a lower prevalence of allergic reactions.

Children born to mothers from the *Yu-Cheng* poisoning episode had higher prevalence of bronchitis or pneumonia at 6 months of age, respiratory tract infections at 6 years of age, and middle ear infections at 6–14 years of age (Chao et al. 1997; Yu et al. 1998). This group ingested rice oil accidentally contaminated with high concentrations of PCBs and other dioxin-like chemicals.

Results of studies in infant Rhesus monkeys from dams exposed during gestation and lactation to as low as 5 μg Aroclor 1254/kg/day indicated exposure-related reductions in antibody levels to SRBC and mitogen-induced lymphocyte transformation that paralleled the findings in the maternal animals (Arnold et al. 1995). Although assessment of the data is limited by small numbers of infants in the exposed groups, statistical significance was achieved for some end points and evaluation times, including reduced IgM titers at 22–23 and 61–63 weeks of age (following gestational/lactational and/or postweaning dietary exposure) in the infants from dams exposed to 5 μg/kg/day. Infant Rhesus and Cynomolgus monkeys that were orally administered a PCB congener mixture simulating the congener content of human milk at a dose level of 7.5 μg/kg/day for the first 20 weeks of life (i.e., from parturition without *in utero* exposure) had minimal immunological changes. These included uniformly reduced anti-SRBC titers in the treated monkeys compared to controls, although group differences were not statistically significant due to small numbers of animals; and decreased B lymphocyte numbers in the exposed Cynomolgus monkeys compared to controls, but this change was transient since levels returned to normal when monkeys were retested at 1 year of age (Arnold et al. 1999). Anti-SRBC titers were also uniformly reduced in the treated compared to control monkeys, although group differences were not statistically significant due to small numbers of animals. The only other notable immunologic effect was a decrease in B lymphocyte numbers in the exposed Cynomolgus monkeys compared to controls, but this change was transient since levels were similar at 1 year of age. The apparently weaker immunologic response in the infant monkeys exposed to the breast milk congener mixture compared to those exposed *in utero* and lactationally to Aroclor 1254 could be related to the lack of gestational exposure and different congener composition of human and monkey breast milk. These findings provide an indication that monkeys are sensitive to low doses of PCBs whether they are administered as commercial mixtures or as a mixture of congeners representative of those commonly found in breast milk.

The recognition of the importance of thyroid hormones in normal development of the brain, as evident from neurodevelopmental disorders and deficits associated with hypothyroidism, has triggered considerable interest in the thyroid hormone system (Boyages 2000). Hypothyroidism, typified by iodine deficiency (e.g., endemic cretinism), can produce a wide range of neurodevelopmental deficits, including auditory, motor, and intellectual deficits. These outcomes suggest an importance of thyroid hormones in the normal development of the fetal cochlea, basal ganglia, and cerebral cortex, which begin to develop in humans during the second trimester of gestation. This is also the time in which the fetal thyroid gland becomes functional. Key cell migration for brain development occurs prior to the time fetal thyroid produces T_3, and is therefore dependent on maternally produced thyroid hormone.

The results of several studies that examined relationships between indices of PCB exposure and thyroid hormone status in children have been mixed, with negative, positive, or no correlations observed. Evaluation of thyroid status of 105 mother/infant pairs from the Dutch cohort during the first months of life revealed that higher CDD, CDF, and PCB levels in breast milk, expressed as TEQs, correlated significantly with lower plasma levels of maternal total T_3 and total thyroxine, and with higher plasma levels of TSH in the infants in the 2nd week and 3rd month after birth (Koopman-Esseboom et al. 1994a). Infants exposed to higher dioxin TEQ levels also had lower plasma free and total thyroxine in the 2nd week after birth. It should be noted, however, that plasma total T_3, T_4, free T_4, and TSH levels of all mother-infant pairs were in the normal range. Longnecker et al. (2000) assayed umbilical cord sera from 160 children from the North Carolina cohort for total thyroxine, free thyroxine, and TSH. The cord blood had been stored frozen since its collection in 1978–1982. The investigators found that background-level exposure to PCBs had no effects on levels of thyroid-related hormones at birth. Since the exposure levels between the Dutch and the North Carolina cohorts appeared comparable, the difference in the results for TSH across studies is unclear.

A small (correlation coefficient, 0.15), but statistically significant positive correlation was found between total serum PCB and TSH concentrations in cord blood of 170 infants from the general population in Düsseldorf, Germany (Winneke et al. 1998a). Nagayama et al. (1998a) examined the relationship between serum TSH, total T_4, and total T_3 in 1-year-old infants and estimated intake of 2,3,7,8-TCDD TEQ in breast milk during the first year of postnatal life. The mothers had no known high exposure to PCBs. Small, but significant negative correlations were found for serum T_4 and T_3; no relationship was apparent between TEQ intake and infant serum TSH or TBG. The mean total dioxin TEQ intake was 34 ng/kg; however, the co-planar PCB contribution to the estimated TEQ intake, and intakes of other PCBs were not reported. Osius et al. (1999) examined the relationship between whole blood

concentrations of various PCB congeners and serum TSH, free T_4, and free T_3 in children who lived near a hazardous waste incinerator. All values were within expected ranges for children. A significant positive association was found between blood PCB 118 concentration and serum TSH concentration. Significant negative associations were found between serum T_3 and PCBs 138, 153, 180, 183, and 187.

Most studies that examined effects of PCBs on thyroid function in young animals have been conducted in rats that were administered commercial PCB mixtures or single PCB congeners during gestation and/or lactation. A common finding has been a decrease in circulating T_4 in both the dams and the fetus/offspring, whereas T_3 levels may or may not change (Corey et al. 1996; Goldey and Crofton 1998; Goldey et al. 1995; Juarez de Ku et al. 1994; Morse et al. 1996c; Provost et al. 1999; Schuur et al. 1998a; Zoeller et al. 2000). Goldey et al. (1995) reported neurobehavioral deficits in the pups, which were attenuated by subcutaneous injections of T_4 that increased serum T_4 and T_3 concentrations (Goldey and Crofton 1998). Rates of elimination of both hormones from serum were accelerated in the pups that had been exposed to Aroclor 1254, relative to controls. These observations suggest that the observed neurobehavioral deficits may have been attributable to deficits in thyroid hormone. The increased elimination of T_4 and T_3 from serum is consistent with an induction of UDP-GT or other elimination pathways for thyroid hormones (e.g., deiodination of T_4 to T_3). Reduction in T_4 levels in pups also have been induced by maternal administration of the dioxin-like congeners 3,3',4.4',5-pentaPCB (PCB 126) (Rice 1999a) and 3,3',4,4'-tetraPCB (PCB 77) (Darnerud et al. 1996a).

There is no evidence that PCBs are teratogenic in humans, and studies in rodents suggest that teratogenicity may occur, but only at very high doses (Haake et al. 1987; Zhao et al. 1997b). Adverse reproductive effects have been observed in male animals following perinatal exposure to PCBs. Fertility was markedly reduced in male offspring of rats that were lactationally exposed to $8 mg/kg/day Aroclor 1254 (Sager 1983; Sager et al. 1987, 1991). The reduction in male fertility appears to be due to impaired ability of sperm to fertilize eggs because sperm production, morphology, and motility were not affected and plasma FSH and testosterone concentrations were not reduced (Sager et al. 1987, 1991). Fertility was not impaired in the male offspring of rats that were administered 30 mg/kg/day of Aroclor 1221, 1242, or 1260 by gavage during gestation (Gellert and Wilson 1979), but this study did not include postnatal exposure. Results of oral and subcutaneous studies with single congeners have shown that gestational, lactational, or adult exposures can adversely affect morphology and production of sperm and fertility in male rats and mice (Faqi et al. 1998; Huang et al. 1998a; Smits-van Prooije et al. 1993), although congeneric structure-activity relationships are unclear. There were no significant effects on number of implantation sites or litter size in rats that were exposed to 4 mg/kg/day of a PCB congener

mixture simulating the congener content of human milk from 50 days prior to mating until birth (Hany et al. 1999b). Evaluation of the offspring, however, showed significantly increased relative uterine weight in immature females (PND 21) and reduced testes weights and serum testosterone levels in adult males (PND 170). There is increasing evidence that thyroid hormone serum concentrations play a crucial role in testicular development by binding to thyroid hormone receptors expressed in Sertoli cells during a critical window of time neonatally (Cooke et al. 1996).

PCBs have been shown to have both estrogenic and anti-estrogenic properties. These properties of some commercial PCB mixtures, PCB congeners, and hydroxylated derivatives of PCB congeners have been assayed by examining uterine variables in immature or ovariectomized female rodents, cell proliferation or gene expression variables in cultured cells including human breast cancer or HeLa cells, and *in vitro* binding to estrogen receptor preparations (see Andersson et al. 1999; Arcaro et al. 1999; Battershill 1994; Connor et al. 1997; Gierthy et al. 1997; Hansen 1998; Kramer et al. 1997; Krishnan and Safe 1993; Li and Hansen 1997; Moore et al. 1997; Safe 1999; Safe et al. 1998 for reviews). In general, PCB-induced estrogenic activities have been characterized as weak compared to the endogenous hormone, 17β-estradiol, a wide variability of responses has been observed across types of PCBs and assays indicating the involvement of multiple mechanisms, anti-estrogenic activities have been most strongly associated with PCBs that are Ah receptor agonists, and hydroxylated metabolites of PCBs are postulated to be at least partly responsible for physiological responses to PCBs that may involve changes in estrogen receptor-dependent physiological processes. Further details of some of these studies are presented in Section 3.6, Endocrine Disruption.

There is no information regarding possible transgenerational effects of PCBs in humans and limited information is available in animals. Dominant lethal mutations were not induced in male Osborne-Mendel rats following treatment by gavage with a single doses of 625–2500 mg/kg Aroclor 1242, by gavage with five daily doses of 125 or 250 mg/kg Aroclor 1242 or 75–300 mg/kg Aroclor 1254, or in the diet with estimated doses of 1.25 or 5 mg/kg/day Aroclor 1254 for 70 days (Green et al. 1975b). Lack of dominant lethality was indicated by no consistent changes in numbers of implantations and dead implantations per pregnant untreated female. The 70-day duration of the feeding study covered the spermatogenic cycle of the rat.

There is no information regarding the pharmacokinetics of PCBs in children or the nutritional factors that may influence the absorption of PCBs. Both phase I and phase II metabolic enzymes participate in the biotransformation and elimination of PCBs and metabolites. Because the metabolism of PCB congeners

depends not only on the degree of chlorination, but also on the chlorine substitution pattern, many different cytochromes P-450 (CYP enzymes) are involved. Thus, metabolism of PCBs in fetuses, neonates, and children may differ from adults depending on whether a particular cytochrome P-450 (CYP) subfamily is developmentally regulated or not. Phase II enzymes such as glucuronosyltransferases (UGT) and sulfotransferases also are involved in PCB metabolism and both are known to be developmentally regulated (Leeder and Kearns 1997). Because PCBs are lipophilic substances, they are stored in the mother's body and can be transferred to offspring through the placenta, as well as accumulate in breast milk and be transferred to nursing infants. This has been well documented by measurements of PCBs in both umbilical cord blood and breast milk (Fein et al. 1984a; Greizerstein et al. 1999; Jacobson et al. 1984b; Koopman-Esseboom et al. 1994b; Kostyniak et al. 1999; Mes et al. 1993; Rogan et al. 1987; Stewart et al. 1999). Placenta passage of PCBs is further evidenced by findings of significant correlations between maternal and cord serum PCB levels in groups of women and newborn infants (e.g., Jacobson et al. 1984b). Additionally, increased PCB residues were detected in blastocytes (day 6 postcoitum) from female rabbits administered Aroclor 1260 before insemination, but not in cleavage stage embryos (day 1 postcoitum) (Seiler et al. 1994). In pregnant mice fed PCBs through the first 18 days of gestation, the highest levels of serum PCBs were found in 1–2-week-old offspring compared with 18-day fetuses or with older offspring (Masuda et al. 1979). Results such as these have led to the conclusion that suckling may account for higher exposure of young offspring than does placental transfer, although the fetus may be more sensitive. Both prenatal and breast milk exposures have been associated with neurodevelopmental deficits in newborn and young children as discussed above. No PBPK models have been developed specifically for PCBs that could be used to quantitatively predict transfer of PCBs across the placenta or via breast milk.

Since adverse health effects are of concern, particularly for prenatal exposure to PCBs, Lackmann et al. (1999) investigated the influence of maternal age and duration of pregnancy on serum concentrations of PCBs in full-term neonates. Blood samples were taken from 80 full-term German neonates within the first 12 hours of life, before the first oral feeding. The median serum concentration of total PCBs was 0.96 μg/L (<0.30–3.14, range), with PCBs 138, 153, and 180 detected at median levels of 0.34 (<0.10–1.01), 0.42 (<0.10–1.42), and 0.17 (<0.10–0.78) μg/L, respectively. All detectable PCB congeners and total PCBs correlated significantly with the gestational age of the newborns, with 50–140% higher serum levels in children born at 42 weeks of gestation as compared with neonates born in the 38th week. Although the correlation between the PCB congeners and maternal age was not quite statistically significant, higher PCB concentrations were observed with rising age. PCB levels were not correlated with birth weight. As expected, the distribution pattern of the PCB congeners in newborns also

corresponds to that previously observed in adults. Thus, the neonatal body burden of PCBs depends on maternal age and duration of pregnancy, reflecting the increase in body burden with time as well as the continuous transplacental transfer of PCBs from mother to fetus during pregnancy.

Hagmar et al. (1998) measured PCB levels in whole blood, and cord blood from 30 Finnish women. The concentrations of PCBs 118, 138, 153, and 180 in cord blood were generally 2- to 3-fold lower than in the whole blood from the mothers. Positive correlations were observed between PCB concentrations in whole blood and cord blood (r=0.67–0.80). The correlation from this study was better than that reported earlier between PCB levels in maternal and cord serum in the Lake Michigan study (r=0.42; Jacobson et al. 1984b); however, the correlation was consistent with the findings in the Dutch study on delivering mothers (Koopman-Esseboom et al. 1994a, 1994b). Although the concentration of PCB congeners in cord blood is 2- to 4-fold lower than in maternal blood, cord blood represents a significant route for prenatal exposure to PCBs as confirmed by the direct measurements made on the serum of new full-term neonates (Lackmann et al. 1999).

Several human studies have investigated the levels of PCBs in human breast milk, not only because it offers a means to assess body burden, but also because it represents a significant route for maternal excretion and neonatal exposure.

In women not known to have been exposed to high concentrations of PCBs, Masuda et al. (1978) reported a significantly higher PCB level in infants' blood than in maternal blood; PCB levels in cord blood were lower than in maternal blood. These results suggested that larger amounts of PCBs are transferred through milk compared with placental transfer. Based on PCB levels in Canadian women's milk, it was estimated that after the first 14 days of breast-feeding, infants would have ingested 144 μg of PCBs, and their PCB body burden would be 0.32 ppm (Mes et al. 1984). The average PCB concentration in maternal whole blood was 2 ng/g (whole blood), whereas the average concentration in breast milk in 1982 was 26 ng/g (whole milk) (Mes et al. 1984). In 1986, the average PCB concentration in breast milk had declined to 6 ng/g (whole milk) (Mes 1994). Data summarized by Kimbrough (1995) indicate that in some industrialized countries an infant may accumulate 6.8% of its lifetime PCB body burden during a nursing period of 6 months.

Lanting et al. (1998a) measured the levels of PCB congeners 118, 138, 153, and 180 in cord plasma, breast milk, and plasma from 42-month-old children (n=126) living in the Groningen area, The Netherlands. In 42-month-old children who were fully breast-fed for at least 6 weeks, the median total

plasma PCB level was 0.81 μg/L (range: 0.23–2.2), compared to the formula-fed children that had levels of 0.18 μg/L (range: 0.07–1.49). The median total PCB concentration in breast milk was 11.9 μg/L (range: 3.3–28.2), while the levels of PCBs 118, 138, 153, and 180 were below the limit of detection in the formula milk samples. While the plasma level of each of these congeners increased in the breast-fed children between birth (cord blood) and 42-months of age, the formula-fed children exhibited a decrease in the plasma level of each of these congeners over this same time period. The relative abundance of PCB congeners was similar within samples of cord plasma, breast milk, and plasma at 42-months of age, with PCB 153>138>180>118. Based on regression analysis of the above data, Lanting et al. (1998a) proposed a model to estimate total PCBs in the plasma of 42-month-old children. Using this model, each week of additional breast-feeding is estimated to increase the ΣPCB_{42mo} by 0.28% (SE=0.05%) of the ΣPCB_{milk}. For a mother with a median ΣPCB_{milk} of 11.9 μg/L, as in this study, this results in an increase the ΣPCB_{42mo} level of 0.033 μg/L per week of full breast-feeding.

Similar results were observed in 93 formula-fed and 100 breast-fed children at 3.5 years of age in the Rotterdam Area, The Netherlands (Patandin et al. 1997, 1999). ΣPCBs 118, 138, 153, and 180 in plasma of formula-fed children had a median level of 0.21 μg/L (range: 0.08–0.46), compared to the breast-fed group which had a median level of 0.75 μg/L (range: 0.23–5.9). PCB levels in maternal plasma (2.04 μg/L, range: 0.59–7.35) and cord plasma (0.40 μg/L, range: 0.08–2.08) were significantly correlated with the PCB levels at 3.5 years in the breast-fed and formula-fed groups. In the breast-fed group, PCB levels were significantly correlated with the period of breast feeding and milk PCB levels. A higher body weight of the child was significantly associated with lower plasma PCB levels at 3.5 years in both groups, suggesting that growth in body mass is diluting the plasma PCB level. With the assumptions that the half-life for plasma PCBs is 2.8 years in children (Yakushiji et al. 1984), and that dietary intake of PCBs after weaning is negligible, compared to prenatal and lactational exposure, it seems likely that plasma levels of PCBs in infants during breast-feeding are similar to that of their mother's.

Dietary exposure to dioxin-like coplanar PCBs (77, 126, 169) and PCDDs and PCDFs from infancy until adulthood was also estimated in this group of breast-fed and formula-fed children (Patandin et al. 1999). The ΣPCB 77, 126, and 169 in breast milk had a median level of 14.8 pg TEQ/g milk fat (range: 4.4–45.7), while the TEQ due to PCDDs and PCDFs in breast milk was 30.6 pg TEQ/g milk fat (range: 11.1–76.4). Thus, the coplanar PCBs contribute about one third of the total dioxin TEQs in human breast milk. The daily TEQ intake per kg body weight is about 50 times higher in breast-fed infants and 3 times higher in toddlers than in adults. Based on a model that included intake measures, food questionnaires, and national food consumption and contamination data, breast-feeding for 6 months contributed about

12% (boys) or 14% (girls) of the cumulative PCB/dioxin TEQ intake until 25 years of age. In toddlers, dairy products contribute 43% of the PCB-TEQ, meat and meat products contributed 14%, and processed foods 23%. Further information on exposures of children can be found in Section 6.6.

There are no biomarkers of exposure or effect for PCBs that have been validated in children or in adults exposed as children. There are no biomarkers in adults that identify previous childhood exposure. No studies were located regarding interactions of PCBs with other chemicals in children or adults. No information was located regarding pediatric-specific methods for reducing peak absorption following exposure to PCBs, reducing body burden, or interfering with the mechanism of action for toxic effects. In addition, no data were located regarding whether methods for reducing toxic effects in adults might be contraindicated in children.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to [substance x] are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by polychlorinated biphenyls are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Polychlorinated Biphenyls

PCBs are pervasive environmental contaminants that are found in body tissues and fluids of the general population. Because they are lipophilic and generally have half-lives longer than 1 week, PCBs are preferentially stored in adipose tissue and are present in serum, blood plasma, and human milk. Serum, including umbilical cord serum, and adipose tissues are indicators of exposure, but serum or plasma PCB concentrations can be significantly influenced by serum lipid content due to partitioning of PCBs between adipose tissue and serum lipids (Brown and Lawton 1984). Therefore, serum or plasma lipid PCB concentrations are better indicators of body burden than PCB levels uncorrected by lipid content (Brown and Lawton 1984). This was clearly illustrated in a study by Phillips et al. (1989b). These authors showed that the concentration of PCBs in nonfasting serum samples from 20 healthy adult males was 29% higher than in fasting serum samples. Total serum lipids (total cholesterol, free cholesterol, triglycerides, and phospholipids) were 20% higher in the nonfasting group. When the concentration of PCBs was corrected by total serum lipids, the difference between fasting and nonfasting samples was no longer statistically significant. Differences in metabolic profiles among different congeners will also influence the serum concentration at any given time. Variations in procedures and methods of reporting data can make interlaboratory comparison difficult (Jensen 1987). It should also be mentioned that, except for large exposures, blood should be collected quickly (days to weeks after exposure) if elevation

is to be found to document a given exposure. The lack of obvious elevation months to years after exposure does not, of itself, indicate lack of exposure.

Quantitative exposure to PCB mixtures can be estimated if the steady-state body burden and the elimination half-life for the mixture are known. In the simplest model, it is assumes that elimination of PCBs from the body can be described as a first-order process. Elimination half-lives of 6–7 months and 33–34 months were estimated for Aroclor 1242 and 1260, respectively, in two groups of capacitor workers (Steele et al. 1986). In a subsequent study, the same group of investigators (Phillips et al. 1989a) indicate that recalculation of the half-life for Aroclor 1242 yielded a median value of 1.9 years. This was comparable to a half-life of 2.6 years estimated in a different group of workers over a period of 8 years (Phillips et al. 1989a). In individuals exposed to river water contaminated with PCBs, it was estimated that the half-life elimination from blood for the PCB mixtures was . 8–9 months, whereas skin lipid PCBs had half-lives of 5 months (Jan and Tratnik 1988).

Short-term exposure to PCB mixtures that are rapidly eliminated may not result in the achievement of a steady-state blood level, in which case, the elimination half-life determined will be misleading. If a true half-life is substantially longer than the calculated half-life, the steady-state burdens may actually be higher than reported. On the other hand, an underestimate of half-life, given adequate steady-state body burden data, will result in an over-estimation of intake.

PCB congeners with a high degree of chlorination and congeners that lack unsubstituted *meta-para* positions are better candidates for bioaccumulation (see Section 3.4.3, Metabolism). This conclusion is consistent with the finding that congeners with unsubstituted 3,4 positions on at least one of the phenyl rings were found at a lower concentration in the blood and adipose tissue of capacitor manufacturing workers than those with substitutions in the 2,4 or 3,4 positions on both rings (Wolff et al. 1982a). This means that fatty tissues will preferentially accumulate the retained congeners leading to a different congeneric pattern compared with the original PCB source.

Eighty-nine PCB peaks were identified and confirmed in serum and adipose tissue of exposed workers (past and/or present exposure) and nonexposed subjects (Fait et al. 1989). Elimination of PCBs over time was inferred from the fact that the total PCB levels in adipose tissue of previously exposed workers were not significantly different than in nonexposed subjects. Congeneric composition of adipose tissue did not differ between previously exposed and nonexposed individuals indicating that single PCB congeners are not good indicators of previous exposure. However, the concentration of hepta- and octachlorobiphenyls

in the serum of previously exposed workers was significantly higher than in the comparison group and equivalent to the currently exposed group. Differences in serum levels of specific PCB congeners have been observed in individuals exposed to PCB mixtures occupationally, accidentally, or environmentally (Luotamo 1988). Differences in the concentrations of trichlorinated and tetrachlorinated isomers were found in the serum samples of the three groups. Only one pentachlorinated isomer was found in individuals environmentally exposed to PCBs, whereas five other pentachlorinated isomers were found in accidentally exposed individuals. The congeners that best indicated occupational exposure were 2,4,4N-triCB, 2,4,4N,5-tetraCB, 2,3,4,4N-tetraCB, and 2,3N,4,4N-tetraCB (Luotamo et al. 1993). Those that indicated accidental exposure were 2,4,4N-triCB, 2N,3,4-triCB, and 2,3N,4,4N-tetraCB (Luotamo et al. 1993). Thus, it would appear that in some cases isomer-specific monitoring of serum levels of PCB congeners in humans can determine likely exposure sources (Luotamo 1988).

PCB residue data in humans and other animals (see Section 3.4.2, Distribution) suggest that tissue or body burdens of PCBs should be based on individual congeners or groups of congeners and not on profiles of commercial PCB formulations. The simplest approach involves using one congener as a marker of total PCBs in a biological specimen. Levels of 2,2',4,4',5,5'-hexaCB (PCB 153), a very stable and often the most abundant congener, have been shown to correlate with the total amount of PCBs in human breast milk (Johansen et al. 1994) and human plasma, with a correlation coefficient of r=0.99 (Grimvall et al. 1997). PCB 153 was highly correlated (r=0.95) with total PCBs in 460 serum samples from Swedish men and women (Atuma and Aune 1999). PCB 153 was also highly correlated with total PCBs in serum (r=0.99) and follicular fluid (r=0.99) (Pauwels et al. 1999). In addition, PCB 153 levels correlated (r=0.91) with the total PCB-TEQs in human plasma (Grimvall et al. 1997). However, if a more complete profile of congeners is considered, the correlations are lower (Bachour et al. 1998; Hansen 1998, 1999). Total PCBs or PCB 153 as a marker of the total therefore could be a misleading indicator of the differential exposure to other individual or groups of congeners of toxicological significance.

Another important issue related to exposure biomarkers is whether analysis of PCBs in serum and adipose tissue provide comparable information on body burden. Stellman et al. (1998) measured 14 PCB congeners in adipose tissue and serum from 293 women with nonoccupational exposure. The relative patterns of the 14 PCB congeners were similar to those reported in other human studies. Significant positive serum to adipose correlation coefficients were obtained for PCBs 74, 99, 118, 138, 146, 153, 156, 167, 170, 180, 183, and 187, while PCBs 172 and 178 did not reach statistical significance. Thus,

this study supports the conclusion that either serum or adipose tissue PCB levels may serve as useful biomarkers of body burden and/or exposure.

Due to its high fat content, human milk concentrates PCBs, which are then transferred to children through lactation (EPA 1984d; Jacobson et al. 1984b). For example, among 122 mothers' milk samples in Massachusetts screened for PCBs, 4 had total PCB levels ranging from 1,100 to 2,400 ng/g milk fat, which were significantly higher than the group mean of 320 ng/g milk fat (Korrick and Altshul 1998). PCB levels in milk have been positively correlated with consumption of PCB-contaminated fish (EPA 1984d). With the use of high resolution analytical techniques, it has been possible to compare the congeneric composition of PCBs in milk with that of commercial PCB mixtures (Safe et al. 1985b). Gas chromatograms of human milk samples from Michigan did not resemble the pattern of any commercial mixture; however, several PCB congeners possessing common structural features, which rendered them metabolism resistant, were major components of both milk and Aroclor 1260 (Safe et al. 1985b). Conversely, other PCB congeners that are minor components of Aroclor 1260 were major components of the human milk. Yet, a different group of congeners, comprised only 28% of the PCBs present in Aroclor 1260, only composed 0.81% of the human milk PCBs; this latter group was formed by congeners having two adjacent unsubstituted carbons, which facilitates metabolic degradation (Safe 1989a). Burse et al. (1994) showed that PCB chromatograms of human serum matched the pattern of goats fed Aroclors better than Aroclor standards. This led the authors to suggest that some animal species could be useful in delineating the source of the PCB exposure in humans. In breast milk, most of the dioxin-like activity in the milk was due to the high concentrations of (coplaner) PCB congeners (Dewailly et al. 1991). Similar findings were reported for milk from Norwegian mothers (Johansen et al. 1994). In summary, highly chlorinated PCB congeners and congeners that lack unsubstituted *meta-para* positions constitute the most reliable biomarker of long-term exposure because they are metabolism resistant and, therefore, tend to accumulate in tissues. However, the specific PCB congeners or group of congeners to be used as exposure biomarkers will be dependent on the outcomes under study (e.g., immunological effects, reproductive end points, cancer).

Chloracne and other dermal alterations are well known markers of exposure to PCBs and structurally-related halogenated aromatic hydrocarbons (Rice and Cohen 1996). Chloracne and other dermal alterations have been reported in subjects occupationally exposed to PCBs (Bertazzi et al. 1987; Fischbein et al. 1979, 1982; Maroni et al. 1981a, 1981b; Meigs et al. 1954; Ouw et al. 1976, 1982; Smith et al. 1982) and in individuals exposed by accidental ingestion of rice oil contaminated with high concentrations of PCBs, CDFs, and related chemicals during the *Yusho* or *Yu-Cheng* poisoning incidents

(Guo et al. 1999; Kuratsune 1989; Lu and Wu 1985; Rogan 1989). Skin lesions consistent with those observed in exposed adults were also commonly observed in children born to mothers with *Yusho* or *Yu-Cheng* exposure (Funatsu et al. 1971; Gladen et al. 1990; Hsu et al. 1985; Rogan et al. 1988; Taki et al. 1969; Yamaguchi et al. 1971; Yoshimura 1974). No adverse dermal effects have been observed in subjects with high consumption of Great Lakes fish contaminated with PCBs and other environmentally persistent chemicals or in other cohorts from the general population. In general, chloracne appears in individuals with serum PCB levels 10–20 times higher than those of the general population, but there is great variability among individuals. Therefore, chloracne is not a sensitive (or specific) biomarker of PCB exposure.

3.8.2 Biomarkers Used to Characterize Effects Caused by Polychlorinated Biphenyls

Several studies of PCB-exposed workers and general population subjects attempted to correlate serum PCB levels with health indices. Statistically significant correlations of serum PCB levels with serum levels of liver-related enzymes (e.g., AST, ALT) and levels of serum lipids (cholesterol, triglycerides) have been reported in workers occupationally exposed to PCBs (Baker et al. 1980; Emmett et al. 1988a, 1988b; Fischbein 1985; Fischbein et al. 1979; Lawton et al. 1985a, 1985b; Smith et al. 1982). However, associations between serum PCBs and these hepatic effects are inconclusive due to small and inconsistent increases, lack of correction for confounding variables such as alcohol consumption, and other study limitations. Additionally, correlations between serum PCBs and lipids are influenced by partitioning of PCBs between lipids in adipose tissue and serum. This indicates that measurements of serum triglycerides and cholesterol are more useful for correcting serum PCB levels to more accurately reflect body burden than for detecting effects of PCBs. It must also be pointed out that PCB mixtures display different induction profiles, so that individual PCB congeners can be phenobarbital-type, 3-methylcholanthrene-type, or mixed-type mixed-function oxidase (MFO) inducers, or they may be inactive as enzyme inducers. Furthermore, the clinical significance of the alterations in liver-associated enzymes is uncertain, as the increases may be nonspecific and are often in the normal range, and indices of obstructive liver disorders have not been demonstrated even in occupationally exposed groups. The existing evidence in animals suggests that liver enzyme induction is perhaps the most sensitive biomarker of PCB effects, but it is nonspecific (Nims et al. 1992). MFO induction has been demonstrated indirectly in PCB-exposed workers by increased metabolic clearance of antipyrine (Alvares et al. 1977). The caffeine breast test (CBT) appears to be a sensitive method for characterizing exposure/and or effects of certain PCBs and related chemicals (Lambert et al. 1992). In this test, ^{13}C-methyl caffeine is ingested by subjects, and hepatic cytochrome P-4501A2-dependent caffeine 3-N-demethylase activity is monitored by

determining the amount of caffeine exhaled as radiolabeled CO_2. The CBT is not specific for PCBs since PCDFs, PCDDs, and other polyaromatic hydrocarbons also induce cytochrome P-4501A.

Results from a study with a feral mouse species showed that induction of hepatic EROD (CYP1A1-mediated activity) was a sensitive biomarker of effect (and/or exposure) for Aroclor 1254 (Lubet et al. 1992). Based on hepatic levels of the enzyme, the investigators could clearly distinguish between a population of mice living in a PCB-contaminated area and a population of the same species from a nonPCB reference site. Furthermore, the relative levels of the enzyme correlated well with hepatic PCB burdens. When the results based on feral mice were compared to results obtained in female Fischer 344/NCr rats exposed for acute or intermediate durations to Aroclor 1254 or in male $B6C3F_1$ mice exposed acutely to Aroclor 1254 in the laboratory, the order of responsiveness was Fischer 344/NCr > $B6C3F_1$ > feral mice. Results from a study by Nims et al. (1992) showed that increased CYP1A1 activity could be detected directly or indirectly in rats treated with relatively low doses of Aroclor 1254 (0.1 mg/kg/day for 7 days) in the diet. CYP2B1 activity was a much less sensitive indicator of effect (and/or exposure). It should be noted that induction of CYP1A1-mediated activity may also result from exposure to a variety of other environmental contaminants. Recently, a human hepatoma cell line, HepG2, was used to determine the dose response of various Aroclor mixtures as well as several dioxin-like PCB congeners (Anderson et al. 1995). In this assay, the human CYP1A1 gene was engineered such that, when activated by an inducer, produces luciferase instead of P-450. The reaction is then monitored by measuring luminescence and protein content. Of the seven Aroclor mixtures assayed, Aroclor 1260 produced the greatest induction. Aroclor 1016 and 1221 induced the lowest levels; for the remaining Aroclor mixtures, 1232, 1242, 1248, and 1254, induction did not correlate with the percentage of chlorination. The order of inducing potential for the congeners was 3,3',4,4',5-pentaCB >3,3',4,4',5,5'-hexaCB >2,3,4,4',5-pentaCB > 3,3',4,4'-tetraCB >2,3,3',4,4',5-hexaCB. Based on the results of the assays, the authors estimated that except for Aroclors 1016 and 1221, the approximate detection limit in environmental samples for the other Aroclors would be in the 2–4 μg/g range; for the congeners the detection limit was in the range 0.01–1 μg/g. For the purpose of comparison, for 2,3,7,8-TCDD the detection limit would have been 0.00005 μg/g.

Correlations between serum PCB levels and hypertension or various hepatic indices (e.g., serum enzymes and lipids) in people who were environmentally exposed to PCBs are also generally unclear due to confounding variables (Kreiss et al. 1981; Stehr-Green et al. 1986a, 1986b; Steinberg et al. 1986). These exposures involved consuming contaminated fish or living or working near an electrical manufacturing plant.

3.9 INTERACTIONS WITH OTHER CHEMICALS

As discussed in Section 3.5.2 (Mechanisms of Toxicity), PCBs represent a group of 209 structurally related chemicals with several subgroups displaying biological actions involving different potential mechanisms. Some biological activities of PCBs involve initial Ah-receptor mediated mechanisms (e.g., induction of hepatic CYP1A oxygenases and Phase II enzymes such as UDP glucuronyl transferases, epoxide hydrolases, or glutathione transferase, body wasting, thymic atrophy, and porphyria), other activities involve Ah-receptor independent mechanisms (e.g., induction of CYP2B and CYP3A oxygenases, induction of changes in brain dopamine levels, and disruption of Ca+2 homeostasis), and other biological activities of PCBs may involve both Ah-receptor dependent and independent mechanisms (e.g., liver hypertrophy, disruption of steroid hormone homeostasis or thyroid hormone homeostasis, disruption of immune functions, and induction and promotion of liver cancer). Because of this diversity in biological activities, there is a large potential for opportunities for PCB mixtures to alter the toxicity of other chemicals or other chemicals to alter the toxicity of PCBs.

Interactions Due to PCB Induction of Hepatic Enzymes

One type of interaction that received considerable early research attention involves PCB-induced changes in hepatic profiles of Phase I and II enzymes, leading to altered metabolism of other xenobiotic agents, and subsequent alteration of their toxicity. For example, observed effects of PCB pretreatment on toxicity of other chemicals in animals include increased metabolism and excretion of pentobarbital and decreased pentobarbital sleeping times (Villeneuve et al. 1972), increased genotoxicity of numerous carcinogens (e.g., benzo[a]pyrene) *in vitro* (Hayes 1987; Hutton et al. 1979), increased duodenal ulcerogenicity of acrylonitrile (Szabo et al. 1983), and increased renal toxicity of trichloroethylene (Kluwe et al. 1979). The capacity of PCB mixtures to induce cytochrome P-450 has resulted in increased toxicity of other chemicals whose toxicity depends on metabolic activation. For example, pretreating animals with PCB mixtures resulted in increased hepatotoxicity due to halothane, vinylidene fluoride, diethylnitrosamine, trichloroethylene, carbon tetrachloride, 1,1,2-trichloroethane, tetrachloroethylene, and 2,2,2-trifluoroethylvinyl ether (Conolly et al. 1979; Gans and Pintauro 1986; Kluwe et al. 1979; Moslen et al. 1977; Murphy et al. 1979; Sipes et al. 1987).

Interactions Between PCB Congeners, PCBs and CDDs, and PCBs, CDDs, and CDFs

Research in the 1970s and 1980s focusing on mechanistic similarities between PCBs, CDDs, and CDFs led to the development and use of a TEF approach to evaluating health hazards from complex environmental mixtures of these halogenated aromatic hydrocarbons. The approach relies on an assumption that components in these complex mixtures jointly act in an additive manner through a common Ah-receptor initial mechanism. Concern about this assumption has led to several investigations of possible interactions between specific PCB congeners, between some PCB congeners or PCB mixtures and 2,3,7,8-TCDD, and among PCBs, CDDs, and CDFs. Evidence for additivity and nonadditive interactions (e.g., potentiation or antagonism) has been found depending on the PCB congeners involved, end point examined, and dose levels of examined agents.

Interactions Between PCB Congeners. Observations of nonadditive interactions between specific PCB congeners include: 2,2',4,4',5,5'-hexaCB (10–50 mg/kg) antagonism of embryo malformations, edema, and liver lesions in chickens exposed to 2 μg/kg 3,3',4,4',5-pentaCB (Zhao et al. 1997a); 2,2',4,4',5,5'-hexaCB (271 mg/kg) antagonism of cleft palate formation in mice exposed to 0.78–1.04 mg/kg 3,3',4,4',5-pentaCB (Zhao et al. 1997b); 2,2',4,4',5,5'-hexaCB (18–72 mg/kg) antagonism of impairment of immune response in mice exposed to 6–12 μg/kg 3,3',4,4',5-pentaCB (Harper et al. 1995; Zhao et al. 1997b); synergism between 20 weekly subcutaneous doses of 5 mg/kg 2,2',4,4',5,5'-hexaCB and 1–10 μg/kg 3,3',4,4',5-pentaCB in promoting formation of γ-glutamyl transpeptidase-positive hepatic foci in partially hepatectomized rats initiated with 30 mg/kg nitrosodiethylamine (Bager et al. 1995); strong antagonism by 2,2',5,5'-tetraCB (10 or 25 μM) or 2,2',3,3',4,4'-hexaCB (12.5 or 25 μM) of luciferase expression induced by 3,3',4,4'-tetraCB (10 nM) in cultured recombinant Hepa1c1cc7 mouse hepatoma cell lines, but not in guinea pig GPC16 colon adenocarcinoma cells or human HepG2 hepatoma cells (Aarts et al. 1995); weak antagonism between 20 weekly subcutaneous doses of 0.13–6.6 μg/kg 3,3',4,4',5-pentaCB and 66–3,302 μg/kg 2,3,3',4,4'-pentaCB in promoting formation of γ-glutamyl transpeptidase-positive hepatic foci in partially hepatectomized rats initiated with 30 mg/kg nitrosodiethylamine (Haag-Grönlund et al. 1998; Johansson et al. 1999); and weak antagonism between 0.13–6.6-μg/kg doses of 3,3',4,4',5-pentaCB and 220–11,003-μg/kg doses of 2,2',4,4',5,5'-hexaCB in promoting formation of γ-glutamyl transpeptidase-positive hepatic foci, in changing concentrations of plasma retinol and liver retinoids, in increasing relative liver weight, and in inducing liver CYP2B1/2 activities (Haag-Grönlund et al. 1998; Johansson et al. 1999).

Interactions Between PCBs and CDDs. Acute parenteral administration of several commercial PCB mixtures (Aroclors 1242, 1248, 1254, and 1260) and a synthetic mixture of PCB congeners reflective of PCBs detected in human milk antagonized 2,3,7,8-TCDD-induced impairment of the immune response to SRBC in mice at PCB:TCDD dose ratios >1000:1 (Bannister et al. 1987; Davis and Safe 1989). Aroclor 1232 had no effect on TCDD-induced immunotoxicity in these studies (Davis and Safe 1989). Aroclor doses that antagonized the acute immunotoxicity of single doses of 0.0012 or 0.0036 mg/kg 2,3,7,8-TCDD ranged from about 1 to 50 mg/kg/day (Bannister et al. 1987; Davis and Safe 1989). Among seven individual PCB congeners examined for their ability to influence this immunotoxic action of single intraperitoneal doses of 0.0012 μg/kg 2,3,7,8-TCDD in mice (six hexachlorobiphenyls and one pentachlorobiphenyl with different chlorine substitution patterns), three were antagonistic (the 2,3,3',4,5,5'-, 2,3,3',4,5'- and 2,2',4,4',5,5'-congeners), and 4 showed no influence (the 2,3,3',4,4',5' -, 2,3',4,4',5',6-, 2,2',4,4',5,6'-, and 2,2',4,4',6,6'-congeners) (Biegel et al. 1989b; Davis and Safe 1990; Smialowicz et al. 1997). In these studies, doses of individual PCB congeners ranged from about 1 to 100–300 mg/kg.

Oral co-exposure of pregnant mice to 244 mg/kg Aroclor 1254 and 0.020 mg/kg 2,3,7,8-TCDD, at an Aroclor:TCDD dose ratio of 12,200:1, completely antagonized TCDD-induced cleft palate formation in offspring (Haake et al. 1987). The complexity of interactions between PCBs and TCDD-induced developmental toxicity is illustrated by observations that, among one tetrachlorobiphenyl and two hexachlorobiphenyl congeners examined, one (the 2,3,3',4,4',5-congener) potentiated TCDD-induced cleft palate formation (Birnbaum et al. 1985) and the other two (the 2,2',4,4'- and 2,2',4,4',5,5'-congeners) antagonized TCDD's actions (Biegel et al. 1989a, 1989b; Birnbaum et al. 1985; Morrissey et al. 1992). Antagonism of TCDD-induced cleft palate formation in mouse offspring by 2,2',4,4'-tetraCB and 2,2',4,4',5,5'-hexaCB showed complex (i.e., inverted U-shape) relationships with dose (Morrissey et al. 1992). For example, no antagonistic effect (against a TCDD dose of 0.0015 μg/kg) was produced by 10–20 mg/kg doses of 2,2',4,4',5,5'-hexaCB, but antagonism increased with increasing 2,2',4,4',5,5'-hexaCB dose to a maximum (500 mg/kg), and then declined to no antagonism at 1,000 mg/kg 2,2',4,4',5,5'-hexaCB (Morrissey et al. 1992). 2,2',4,4',5,5'- HexaCB also antagonized TCDD-induced hydronephrosis in mouse offspring showing a similar inverted U-shape relationship with dose (Biegel et al. 1989b; Morrissey et al. 1992). In contrast, combined exposure of pregnant mice to 2,3,3',4,4',5-hexaCB and 2,3,4,7,8-pentachlorodibenzofuran appeared to additively produce hydronephrosis and cleft palate in the offspring (Birnbaum et al. 1987).

Several 13-week oral exposure studies have examined possible binary interactions between three PCB congeners (at several dietary concentrations delivering daily doses ranging from about 0.1 to 10 mg/kg/day) and 2,3,7,8-TCDD (at several dietary concentrations delivering daily doses ranging from about 0.00003 to 0.3 mg/kg/day) in influencing several end points in rats (van Birgelen et al. 1992, 1994a, 1994b, 1996a; van der Kolk et al. 1992). The PCB:TCDD concentration ratios administered in these studies were selected to reflect relative concentrations in samples of human milk and fat. 2,2',4,4',5,5'-HexaCB and 2,3,7,8-TCDD showed joint additive action in decreasing thyroid hormone levels at 4 weeks, but synergistic action at 13 weeks (van Birgelen et al. 1992), whereas 2,3,3',4,4',5-hexaCB (van Birgelen et al. 1994a) and 3,3',4,4',5-pentaCB (van Birgelen et al. 1994b) showed less-than-additive joint action with 2,3,7,8-TCDD in decreasing thyroid hormone levels. 2,2',4,4',5-Hexachlorobiphenyl did not influence TCDD-induced effects on body weight and thymus weight, and additively increased relative liver weight with TCDD (van der Kolk et al. 1992), whereas 2,3,3',4,4',5-hexaCB and 3,3',4,4',5-pentaCB showed less-than-additive joint action with TCDD on these end points. 2,2',4,4',5,5'-hexaCB and 2,3,7,8-TCDD showed a distinct synergism in increasing hepatic porphyrin levels, but 2,3,3',4,4',5-hexaCB and 3,3',4,4',5-pentaCB showed no such synergism with 2,3,7,8-TCDD (van Birgelen et al. 1996a). All three of these congeners individually decreased hepatic levels of retinol and retinylpalmitate. In combination with TCDD, less-than-additive joint actions were noted, but TCDD doses used in these studies produced a near maximal response in decreasing retinoid levels (van Birgelen et al. 1992, 1994a, 1994b).

Interactions Among PCBs, CDDs, and CDFs. Liver tumor promotion activity was examined in partially hepatectomized rats exposed to a mixture containing 68 ppm 2,3,7,8-TCDD, 223 ppm 1,2,3,7,8-pentachloro-*p*-dioxin, 1,151 ppm 2,3,4,7,8-pentachlorodibenzofuran, 4,130 ppm 3,3',4,4',5-pentaCB, 866,604 ppm 2,3',4,4',5-pentaCB, and 127,824 ppm 2,3,3',4,4',5-hexaCB and compared with predicted tumor promotion activity using TEFs based on tumor promotion activity of the individual components compared to TCDD activity (Van der Plas et al. 1999). The mixture composition was reflective of relative concentrations, and accounted for about 90% of total TCDD TEQs, found in samples of Baltic Sea fish. Observed tumor promotion activity of the mixture was about one-half of predicted activity. Another mixture, containing, in addition to the above components, 20,000 g 2,2',4,4',5,5'-hexaCB per g of 2,3,7,8-TCDD, showed a tumor promotion activity that was also less than that predicted by the TEF approach. A possible explanation of the differences between the observed and TEF predicted values is that the components may have interacted in a less-than-additive manner (e.g., less potent PCBs may antagonize tumor promotion by the more potent 2,3,7,8-TCDD), but equally as plausible is the possibility that the TEFs are inaccurate and overestimate tumor promotion potencies (van

der Plas et al. 1999). In related studies, 2,2',4,4',5,5'-hexaCB antagonized TCDD promotion of malignant transformations of carcinogen-initiated mouse fibroblasts (Wolfe 1998), whereas 3,3',4,4',5-pentaCB added to promotion of fibroblast transformation in the presence of 2,3,7,8-TCDD (Wolfe 1998) and to promotion of liver tumors in rats with co-exposure to 2,3,7,8-TCDD (Hemming et al. 1985).

The possibility that interactions among PCBs, CDDs, and CDFs may influence reproductive end points (blockage of ovulation, reduction of ovarian weight gain, and changes in preovulatory hormone levels) was examined in gonadotropin-primed immature female rats given single oral doses of 0.057–0.457 mg/kg 3,3',4,4',5-pentaCB (a PCB with known Ah receptor agonist activity) or 0.010–0.160 mg/kg 2,3,4,7,8-pentachlorodibenzofuran alone or together in combination with 2,3,7,8-TCDD, 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin, and 1,2,3,4,7,8-hexachlorodibenzo-*p*-dioxin, all of which were shown to be effective blockers of ovulation in this assay (Gao et al. 1999, 2000). The mixture was administered at TCDD-TEQ doses ranging from 0.0038 to 0.0303 mg/kg. Parallel dose-response relationships for inhibition of ovulation were found for the individual agents and for the equipotent mixture. This finding is consistent with the hypothesis that the agents in the tested mixture are likely to block ovulation by additive joint action in a similar mechanism and supports the use of the TEF approach for this type of endocrine disruption. Another PCB congener, 2,2',4,4'-tetraCB (which has no detectable Ah receptor agonist activity), was inactive at the dose examined in this assay (41.9 mg/kg). The effect of its presence in a mixture with effective components, however, was not studied (Gao et al. 2000).

Interactions Between PCBs and Methylmercury

PCBs and methylmercury represent a combination of agents of public health concern that are potential neurotoxicants found in the complex mixture of biopersistent toxicants in contaminated fish from the U.S. Great Lakes and the Baltic Sea. Changes in neurological function or development from PCBs and methylmercury have been proposed to at least partly involve disruption of calcium homeostatic mechanisms in neural cells leading to changes in neurotransmitter release (e.g., dopamine) or cell damage. Exposure of rat striatal tissue for 4 hours with methylmercury alone at concentrations ranging from 1 to 40 μM or a 1:1 mixture of Aroclors 1254 and 1260 at concentrations ranging from 10 to 200 ppm resulted in a significant, dose-dependent depletion of tissue dopamine levels (Bemis and Seegal 1999). Bemis and Seegal (1999) noted that these concentrations were, in general, higher than those measured in samples of Great Lakes fish (0.84–1.9 ppm PCBs and 0.34 ppm mercury). Combined *in vitro* exposure of rat striatal tissue to methylmercury and this 1:1 mixture of Aroclors 1254 and 1260

(10–200 ppm) synergistically depleted tissue levels of dopamine (Bemis and Seegal 1999). For example, combined exposure to 4 μM methylmercury and 200 ppm PCBs, or 10 μM methylmercury and 20, 40, 100, or 200 ppm PCBs, showed a significant statistical interaction (in an analysis of variance) indicative of synergistic effects on depleting tissue dopamine levels. These results suggest a possible synergism in affecting neurological dysfunction and development, but no *in vivo* demonstration of such a synergism is available.

A study of combined oral exposure of pregnant female mice to methylmercury (0.4 or 4 mg/kg/day) and Kanechlor 500 (about 940 mg/kg/day) from gestation day 15 to day 21 after delivery found no evidence for obvious synergistic effects on righting and swimming ability, hindlimb support, general open field activity, and learning ability in offspring evaluated at several postnatal periods or on reproductive performance in the F0 and F1 generations (Tanimura et al. 1980). Methylmercury, at 4 (but not 0.4) mg Hg/kg/day, potentiated PCB-induced decreased postnatal survival in mice (Tanimura et al. 1980). Survival of male offspring in all Kanechlor groups showed a marked decline, compared with controls, at about 5 weeks after birth; at 10 weeks after birth, male offspring survival percentages were about 60, 60, and 40% for the groups with Kanechlor plus 0, 0.4, and 4 mg Hg/kg, compared with >90% in the control and methylmercury alone groups. Autopsies revealed no obvious or specific cause of death. Survival data for female offspring were reported to have been similar.

In a study of minks, reproductive end points, serum thyroid hormone levels (T3 and T4), and histology of brain, kidney, adrenals, pituitary, and thyroid were evaluated in groups of adult ranch-bred minks fed a commercial mink food supplemented with 0 or 1 ppm Aroclor 1254, 1 ppm Hg as methylmercury, 1 ppm Aroclor 1254 + 1 ppm methylmercury, or 0.5 ppm Aroclor 1254 + 0.5 ppm methylmercury for 8 months that spanned one breeding period (December 1984 through June 1985) (Wren et al. 1987a, 1987b). Exposed groups contained 12 females and 4 males; control groups had 15 females and 5 males. Food intake and body weight data were not reported, but estimates of 0.2 mg/kg/day Aroclor 1254 and 0.2 mg Hg/kg/day are derived for the 1-ppm treatment based on a food intake of 150 g/day and body weight of 0.9 kg for minks (Aulerich et al. 1987). During the third month of exposure, eight females and one male in the 1 ppm methylmercury group, and three females in the 1 ppm Aroclor + 1 ppm methylmercury group, died, displaying convulsions, tremors, and lethargy. The mortality was attributed to a combination of cold stress and methylmercury poisoning, and surviving minks were fed diets containing 1 ppm methylmercury every other day for the remainder of the study. No exposure-related effects were found on the thyroid, pituitary, adrenal glands, or serum T_4 or T_3 levels in adult minks that survived the 8-month exposure period. Fertility of adult male minks, percentage of females whelped, or number of offspring

born per female were not significantly affected by any of the treatments. The average number of offspring per female at weaning (5 weeks after birth) was significantly ($p < 0.05$) lower in the 1 ppm Aroclor + 1 ppm methylmercury group (2.1 offspring/female) than in the control (4.5), 1 ppm Aroclor (5.0), 1 ppm methylmercury (4.0), or 0.5 ppm Aroclor + 0.5 ppm methylmercury groups (3.6), indicating that postnatal offspring mortalities were increased by combined exposure to the high levels of methylmercury and Aroclor 1254.

Wren et al. (1987b) concluded that these observations showed a synergistic effect of Aroclor 1254 and methylmercury on decreased postnatal survival of mink offspring. An alternative interpretation of the results is that combined exposure induced postnatal mortality at concentrations of the individual agents (1 ppm) that did not induce postnatal mortality, but it is not possible to discern if they acted together in a less-than-additive, additive, or greater-than-additive manner without including treatments involving 2 ppm concentrations of the individual agents alone. A clear demonstration of synergistic action would have involved increased postnatal mortality produced by the 0.5 ppm Aroclor + 0.5 ppm methylmercury treatment; however, postnatal mortality was not changed, compared with control, by this treatment.

Intermediate-duration exposures of quail to methylmercury or Aroclor 1260 in the diet led to accumulation of porphyrins in liver; hepatic porphyrin levels in quail exposed to both agents simultaneously were similar to levels predicted based on additivity of response (Leonzio 1996b). Combined exposure of rats or quail to commercial PCB mixtures and methylmercury appears to counteract PCB induction of hepatic CYP enzymes (Leonzio et al. 1996a; Takabatake et al. 1980), but the toxicological significance of this interaction is unclear.

Interactions Between PCBs and *p,p'*-DDE

Results from animal (and some human) studies identify several sensitive shared targets of PCBs and *p,p'*-DDE oral toxicity including the liver (hepatomegaly, degenerative histological effects, and liver cancer), immune system (suppression of cell-mediated immunological responses), neurological development (altered neurobehavior in offspring exposed *in utero* or during nursing periods), and altered reproductive function or development. A limited amount of *in vitro* and *in vivo* data regarding possible interactions between PCBs and *p,p'*-DDE are available as reviewed below.

Incubation of an estrogen receptor preparation from alligator oviducts with a mixture containing 18 μM *p,p'*-DDE, 2.6 μM *p,p'*-DDD, 0.63 μM dieldrin, 0.53 μM Aroclor 1242, 0.25 μM *trans* nonachlor,

0.16 μM *cis* nonachlor, 0.22 μM chlordane, and 0.2 μM toxaphene inhibited the binding of tritium-labeled 17β-estradiol to estrogen receptors by 57% (Vonier et al. 1996). The individual agents, at the concentrations used in this mixture, did not inhibit the *in vitro* binding of 17β-estradiol to the estrogen receptors, with the exception that 2.6 μM *p,p'*-DDD inhibited binding by 20%. Vonier et al. (1996) concluded that combinations of these chemicals decreased estradiol binding "in a greater-than-additive manner." Design limitations of this study, however, preclude drawing definitive conclusions whether the mode of joint toxic action among these chemicals in this screening assay was less-than-additive, additive, or greater-than-additive.

Combined dietary exposure of mallards to 40 ppm *p,p'*-DDE and Aroclor 1254 did not alter DDE-induced egg shell thinning, but appeared to decrease the number of intact eggs that were produced compared with values for control groups or groups exposed to either agent alone (Risebrough and Anderson 1975). Dietary exposure of groups of mallards (4 drakes and 10 hens) to 40 ppm *p,p'*-DDE or 40 ppm *p,p'*-DDE + 40 ppm Aroclor 1254 for 5 months caused 17 and 19%, respectively, reduction in mean egg shell thickness compared with control groups (Risebrough and Anderson 1975). Exposure to 40 ppm Aroclor 1254 alone did not affect egg shell thickness. Combined exposure reduced total egg production over the study period by about 35% compared with controls. Egg production in the first 7 weeks was similar in all groups, but markedly dropped thereafter in the DDE+Aroclor 1254 group. About 25% of the decline in egg production in the combined exposure group was attributed to egg eating. Further information or studies regarding this apparent synergism between *p,p'*-DDE and Aroclor 1254 were not located. Additional research may help to determine if a similar synergism may occur between *p,p'*-DDE and PCBs in affecting reproductive function in mammals.

Interactions Between PCBs and Other Chemicals

An initial report (Arnold et al. 1996) that binary mixtures of hydroxylated PCBs and weakly estrogenic pesticides (dieldrin, endosulfan, toxaphene, and chlordane) resulted in synergistic increases in estrogen receptor binding and reporter gene-expression in transfection-facilitated yeast and endometrial carcinoma-derived cell cultures was subsequently withdrawn by the investigators due to the inability to reproduce the results (McLachlan 1997). A subsequent examination of possible synergy among binary mixtures of two hydroxylated PCBs (2,4,6-trichloro-4'-biphenylol and 2,3,4,5-tetrachloro-4'-biphenylol) and two pesticides (endosulfan and dieldrin) in two *in vitro* estrogenic activity assays (competitive estrogen receptor binding and induction of multicellular nodules in human cancer-derived MCF-7 cells) found no evidence for synergy between these hydroxylated PCBs, between these pesticides, or between

2,4,6-trichloro-4'-biphenylol and physiologically relevant concentrations of 17β-estradiol (Arcaro et al. 1998). Likewise, no evidence for obvious synergy was found between tributyltin (50 nM) and 3,3',4,4',5-pentaCB (100 nM) or Aroclor 1016 (50 ppm) in inhibiting human natural killer cell *in vitro* lytic actions against leukemia cells (Whalen et al. 1998) or among methylmercury (0.1–2 μg/mL), a CDD/CDF mixture of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin, 1,2,3,4,7,8-hexachlorodibenzo-*p*-dioxin, 2,3,7,8-tetrachlorodibenzofuran, and 1,2,3,7,8-pentachlorodibenzofuran (1–15 pg/mL), and three commercial PCB mixtures, Aroclor 1242, 1254, and 1260 (0.01–0.5 μg/mL) in altering several *in vitro* activities (mixed leukocyte reaction, natural killer cell activity, and phagocytic activities) of rat leukocytes (Omara et al. 1998).

Simultaneous exposure of rats to Aroclor 1254 or 1260 and chemicals of environmental concern such as the pesticides mirex, photomirex, and/or kepone in the diet resulted in increased severity of the liver lesions attributed to exposure to chlorinated biphenyls alone (Chu et al. 1980). Induction of hepatic AHH activity by Aroclor 1254 in the diet of lactating rats was increased in an additive manner by simultaneous dietary exposure to polybrominated biphenyls such as Firemaster BP-6 (McCormack et al. 1979).

The induction of liver carcinogenesis by Aroclor 1254 in C57BL/10ScSn mice is markedly increased by iron (Madra et al. 1995). A single dose of iron dextran in mice fed Aroclor resulted in a significant increase in octoploid nuclei within 2 weeks; it persisted for 6 months and resulted in massive hepatic porphyria. In another study (Madra et al. 1996), the iron-enhanced toxicity appears to be due to the induction of P-450 1A1 isoforms in the nuclear membrane as well as in the microsomes.

Pretreatment of rats with Aroclor 1254 protected against hepatotoxicity due to inhalation of 1,1-dichloro-ethylene, suggested that MFO induction by PCBs may be responsible for detoxification of 1,1-dichloro-ethylene (Reynolds et al. 1975). This detoxification might occur if the epoxide of 1,1-dichloroethylene isomerizes rapidly to an aldehyde before reacting with tissues.

Increased dietary ascorbic acid may protect against some of the toxic effects of PCBs, such as altered enzyme activity and liver histopathology, perhaps by inhibiting lipid peroxidation (Chakraborty et al. 1978; Kato et al. 1981a). The exact mechanism is not known.

Co-administration of cadmium and Aroclor 1248 resulted in a significant increase in growth retardation and plasma cholesterol, compared to controls or rats fed a diet containing cadmium or Aroclor 1248 alone. The effects were found to be additive (Suzuki 1980).

Pretreatment of rats with Aroclor 1254 markedly accelerated the biotransformation and bioactivation of the industrial chemical 2,6-dinitrotoluene (Chadwick et al. 1993). This resulted in an increased formation and excretion of mutagenic metabolites in the urine. Also, Aroclor 1254 potentiated the formation of 2,6-dinitrotoluene-derived DNA adducts in the liver.

PCBs can interact with structurally diverse carcinogens in various ways. Oral studies have shown that Aroclor 1254 and other PCBs with similar percentages of chlorine by weight (e.g., Kanechlor 500, Clophen A50) promote the development of liver preneoplastic foci, liver tumors, and lung tumors in rats or mice that have been treated with other carcinogens as initiators, including nitrosamines and 2-acetylaminofluorene (Anderson et al. 1986; Deml and Oesterle 1987; Kimura et al. 1976; Oesterle and Deml 1983, 1984; Pereira et al. 1982; Preston et al. 1981; Tatematsu et al. 1979). PCBs also can enhance or inhibit the activity of other hepatocarcinogens when simultaneously administered orally (Ito et al. 1973; Kimura et al. 1976; Makiura et al. 1974). There is no conclusive evidence that Aroclor is a skin tumor promoter when repeatedly applied to the skin of mice that were initiated with DMBA or MNNG (Berry et al. 1978, 1979; Poland et al. 1983), but a single dermal application of Aroclor 1254 to mice showed weak initiator activity when promoted with TPA (DiGiovanni et al. 1977). Pretreatment with a single dermal dose of Aroclor 1254 inhibited skin tumor initiation by DMBA in mice (Berry et al. 1979). Intraperitoneal injection of Aroclor 1254 to mice on Gd 19 protected the offspring from lung tumors, but increased the incidence of liver tumors, following injection of N-nitrosodimethylamine on postnatal day 4 or 14 (Anderson et al. 1983). The genotoxicity of numerous carcinogens is potentiated *in vitro* by PCBs, but this does not indicate that PCBs should be regarded universally as tumor promoters because of the protective role of PCBs against carcinogenicity of many genotoxic carcinogens *in vivo* (Hayes 1987).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to PCBs than will most persons exposed to the same level of PCBs in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of PCBs, or compromised function of organs affected by PCBs. Populations who are at greater risk due to their unusually high exposure to PCBs are discussed in Section 5.7, Populations With Potentially High Exposures.

The potential susceptibility of embryos, neonates, and children are discussed in detail in Section 3.7, Children's Susceptibility.

Other subpopulations that are potentially more susceptible to PCBs include those with incompletely developed glucuronide conjugation mechanisms (Calabrese and Sorenson 1977; Lester and Schmid 1964), such as those with Gilbert's Syndrome. Gilbert's Syndrome is a relatively common and benign congenital liver disorder that is characterized by mild, fluctuating increase in serum bilirubin, and is estimated to occur in 3–7% of the adult population (American Liver Foundation 2000). Persons with hepatic infections may have decreased glucuronide synthesis, making them more sensitive because of their decreased capacity to detoxify and excrete PCBs (Calabrese and Sorenson 1977). Those with compromised liver function, such as in the case of liver cirrhosis or hepatitis B, could also be considered more susceptible to PCB toxicity. PCBs, via induction of ALA synthetase, might be capable of precipitating an attack of porphyria in patients with acute intermittent porphyria.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to PCBs. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to PCBs. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. No texts were found that provided specific information about treatment following exposures to PCBs.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to PCBs can occur by inhalation, ingestion, or by dermal contact. PCBs are readily absorbed through the gastrointestinal tract, respiratory system, and skin. Data from animal studies suggest that the rate of absorption following oral exposure is greater than that following inhalation or dermal exposures. Specific information regarding the prevention or reduction of toxicological effects following acute exposure to PCBs was not located in the literature. General recommendations for reducing absorption of PCBs following acute exposure include removal of contaminated food, water, air, and/or clothing from the exposed individual. Multiple washes of contaminated skin with soap and water immediately following dermal exposure to PCBs have also been recommended (HSDB 1995). Washing is most effective immediately following exposure, since PCBs are readily absorbed through the skin.

Trichlorobenzene and mineral oil have been found useful in decontaminating exposed areas of skin in rats (Wester et al. 1990). However, using hydrocarbon-based solvents to cleanse PCB-contaminated skin could carry the risk of increasing the dermal absorption of those fat-soluble compounds in humans.

Many of the clinical symptoms that result from PCB exposure, such as chloracne, are delayed in onset. Therefore, ingestion of PCBs is normally not recognized until long after the time when inducing emesis might be beneficial. In addition, emesis may result in aspiration of the lipid materials into the lungs, possibly causing lipoid pneumonitis. The value of administering activated charcoal to decrease the absorption of PCBs is unknown, but is frequently recommended as a slurry, either aqueous or mixed with a saline cathartic or sorbitol (HSDB 1995). Repetitive administration of activated charcoal might be useful in preventing reabsorption of metabolites. In rats, rice bran fiber decreased absorption of PCBs in the intestinal tract and had a stimulatory effect on fecal excretion of PCBs (Takenaka and Tarahashi 1991). It is unclear that rice bran would be of benefit in PCB-poisoned humans.

3.11.2 Reducing Body Burden

There are no known treatment methods for reducing body burden of PCBs. It should be noted that significant amounts of PCBs can be eliminated through lactation (see Section 3.7, Children's Susceptibility), indicating that breast feeding can reduce maternal body burden of PCBs. However, in most cases, the benefits of breast feeding outweigh any possible PCB risks to the mother from the body burden or to the child from exposure via the milk.

Limiting or preventing further exposures appears to be the most practical method for reducing body burden of PCBs. For the general population, especially subgroups that consume diets high in contaminated fish (e.g., sport fisherman), this can be achieved through public health advisories on fish consumption. A listing of fish advisories for PCBs is provided in Chapter 8 (Table 8-1).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No specific information was located regarding clinical methods of interfering with PCB mechanisms of toxic action. Some of the toxic effects, such as immunological effects, body weight loss, enzyme induction and porphyria, appear to be mediated by a common initial mechanism involving the Ah cytosolic receptor (Poland et al. 1976; Safe 1984, 1990), as discussed in Section 3.5.2 (Mechanisms of Toxicity). The responsiveness of a particular organ to PCB congeners may depend on the presence of

functional Ah receptors. PCB binding to the Ah receptor is followed by a series of events that lead to the accumulation of occupied nuclear receptor complexes and enhanced CYP1A gene expression. Although speculative, it is possible that interference with this mechanism may lead to a more specific treatment for reducing some of the toxic effects of PCB congeners that exert this mechanism of toxic action. Future research on Ah receptor antagonists may provide new insight for clinical treatment of PCB Ah receptor-mediated toxicity, but at present, only symptomatic and supporting therapy is available for PCB-exposed humans.

Toxic effects of PCBs may also involve Ah-receptor independent mechanisms, or both Ah-receptor dependent and independent mechanisms (see Section 3.5.2). For example, PCBs can be metabolized to reactive arene oxide intermediates that may alkylate critical cellular macromolecules and result in injury (Gardner et al. 1973; Safe 1990). Clinical intervention to interfere with Ah-receptor independent mechanisms have not been developed.

In summary, presently no specific treatments are available for patients with acute or long-term exposure to PCBs. Additional research is necessary to develop specific methods to mitigate PCB toxicity.

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of polychlorinated biphenyls is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of polychlorinated biphenyls.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Polychlorinated Biphenyls

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to polychlorinated biphenyls are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of polychlorinated biphenyls. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

This section identifies information needs regarding PCB mixtures which, if met, would contribute to a more precise association between levels of exposure at hazardous waste sites and adverse health effects. Most of the information evaluated in this report has been obtained from studies in which commercial PCB

mixtures were used, and this is the most practical basis for hazard evaluation. People are environmentally exposed to PCB mixtures of different congeneric composition than commercial PCB mixtures. Although the toxicity of environmental PCB mixtures consequently may be increased or decreased compared to commercial mixtures, there are insufficient mixture toxicity data on which to assess hazards and directly base minimal risk levels for environmental PCBs. One approach that has been widely considered for estimating the risk from environmental exposure to PCBs is the TEF method. As discussed in Section 3.5.2, the TEF approach can be used to estimate the potency of PCB mixtures by comparing the relative toxicity of individual PCB congeners to that of 2,3,7,8-TCDD, which is the most toxic and extensively studied of these structurally-related halogenated aromatic hydrocarbons. Although TEFs are used to some extent to guide public health decisions because of the limited toxicological data for complex environmental mixtures and many of their components, the approach has received limited validation and has a number of limitations related to assumptions that the components jointly act in an additive manner through a common Ah-receptor mechanism of toxicity. In particular, the TEF approach does not account for evidence that non-Ah-receptor-binding congeners are major components in PCB-containing environmental mixtures that may contribute to induction of health effects. Due to evidence of non-additive interactions between specific PCB congeners and between some PCB congeners and 2,3,7,8-TCDD (see Section 3.9), as well as increasing evidence that PCB-induced effects may involve

Figure 3-5. Existing Information on Health Effects of Polychlorinated Biphenyls

	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
	Systemic									
Inhalation				●	●	●	●	●	●	●
Oral				●		●	●	●		
Dermal				●				●		

Human

	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
	Systemic									
Inhalation	●		●							
Oral	●	●	●	●	●	●	●	●	●	●
Dermal	●		●		●					●

Animal

● *Existing Studies*

Ah-receptor-dependent mechanisms, Ah-receptor-independent mechanisms, or both Ah-receptor-dependent and Ah-receptor-independent mechanisms (see Section 3.5.2), the accuracy of the TEF approach is questionable. Due to the current lack of any alternative validated congener-based risk assessment methodology, and considering the likelihoods that (1) multiple mechanisms are involved in PCB-induced health effects, (2) different PCB congeners may produce effects by different mechanisms, and (3) humans are exposed to complex mixtures of interacting PCBs with differing biological activities, it appears reasonable to use commercial mixtures as a surrogate for environmental mixtures in assessing health risks from exposure to environmental mixtures of PCBs. Because toxicity data on commercial PCB mixtures are likely to provide a better approximation of the toxicity of environmental mixtures than existing methods based on unmixed congeners, since a congener based approach would poorly reflect the net contribution of components to the toxicity of a mixture, toxicity data on commercial mixtures are the most appropriate basis for deriving minimal risk levels for environmental mixtures of PCBs. Consequently, although additional congener studies are necessary to further elucidate the significance and mechanisms of neurological, immunological and other effects of concern, studies of commercial PCBs and other relevant mixtures of congeners (e.g., the mixture simulating the congener composition of breast milk used in the intermediate MRL study) are most relevant to human health risk assessment.

Information on the human health effects of PCBs containing low levels of CDF contaminants is primarily available from occupational exposure studies of industries in which PCBs are no longer used. Information on effects in children exposed to PCBs during gestation and/or lactation also is available, particularly regarding neurodevelopmental effects. These studies examined the effects in children born to women with no known high exposure to PCBs as well as children from women who consumed, for a long time, fish contaminated with PCBs and other persistent chemicals, especially from areas surrounding the Great Lakes. The relative contribution of the inhalation and dermal routes in the occupational exposures is unknown, but existing information on health effects in exposed workers is included with inhalation exposure in Figure 3-5. Health effects information is available on humans who were exposed to heated PCBs during the *Yusho* and *Yu-Cheng* incidents, but, as discussed in Section 3.1, CDFs are considered to be the main causal agent due to relatively high levels of these contaminants. The other human data are generally limited by insufficient exposure information and other factors, but seem to be consistent with effects observed in animals. Information on health effects in animals is extensive and available for all effect categories, but is almost completely limited to oral exposure studies. This appears to reflect experimental practicality and concern for what is thought to be the most prevalent and likely route of environmental exposure.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The hepatotoxicity of PCBs in rats is reasonably well characterized for acute-duration oral exposure (Carter 1984, 1985; Carter and Koo 1984; Kato and Yoshida 1980; Kling et al. 1978; Price et al. 1988), but it is unclear if the liver is the most sensitive target organ for acute exposure. Other targets appear to include the kidneys, stomach, and thyroid (Bruckner et al. 1973; Hansen et al. 1976; Kimbrough et al. 1972; Price et al. 1988), but insufficient information exists to determine if effects in these or other tissues occur at lower doses or are more critical than effects in the liver. Acute oral studies in other species are needed to determine the most sensitive target and species for acute exposure basis and the possible basis for an acute oral MRL. Studies with monkeys would be informative because intermediate- and chronic-duration studies indicate that this species is more sensitive than the rat and that developmental, endocrinological, and immunological effects are particularly sensitive end points.

Information on toxic effects of acute-duration exposure to PCBs by routes other than oral are limited to LD_{50} values for dermal exposure (Fishbein 1974; Puhvel et al. 1982), but these data may not be reliable due to possible delayed lethality. PCBs are well absorbed after exposure by all routes, and distribution to and retention by adipose tissue has been observed in humans after inhalation, oral, and/or dermal exposure (Brown and Lawton 1984; Fait et al. 1989; Jensen 1987). Mobilization of PCBs from adipose tissue to target organs is likely to be similar regardless of the route of exposure. Additional acute dermal studies are relevant because the skin is a route of concern for exposure at or near hazardous waste sites, particularly due to possibilities for brief contact. Acute inhalation toxicity studies may be relevant due to the potential for inhalation exposure from electrical appliances in buildings and downwind from PCB disposal facilities and incinerators.

Intermediate-Duration Exposure. The preponderance of toxicity data for PCBs is available from animals exposed to PCBs in the diet in intermediate-duration studies. Studies have been performed with various species, but the rat, monkey, and mink have been tested most extensively, and the monkey and mink consistently appear to be the most sensitive. The liver, skin, and stomach are unequivocal targets, but existing studies do not identify NOAELs for effects in these organs in monkeys and minks (Allen 1975; Allen and Norback 1973, 1976; Allen et al. 1973, 1974a; Andrews 1989; Barsotti et al. 1976; Becker et al. 1979; Bell 1983; Bleavins et al. 1980; Bruckner et al. 1973, 1974, 1977; Goldstein et al. 1974; Hansen et al. 1976; Hornshaw et al. 1986; Kimbrough and Linder 1974; Kimbrough et al. 1972; Kling et al. 1978; Koller 1977). Anemia consistently occurs in monkeys at doses similar to those

producing other effects, but a NOAEL and the relative importance of this effect is not known (Allen 1975; Allen and Norback 1976; Allen et al. 1973, 1974a). There is evidence suggesting that effects occur in the thyroid and adrenal glands of rats at doses lower than those producing effects in other tissues in monkeys and minks (Bruckner et al. 1973, 1974; Byrne et al. 1987, 1988; Collins and Capen 1980b, 1980c; Collins et al. 1977; Kasza et al. 1978; Kato et al. 1982a; Tryphonas et al. 1986a; Wassermann et al. 1973), but these doses are in proximity to those producing developmental toxicity in monkeys. A series of intermediate-duration studies in infant monkeys found neurodevelopmental effects of a low dose (7.5 μg/kg/day) of a congener mixture that simulated the congener composition of human breast milk (Rice 1997, 1998, 1999b; Rice and Hayward 1997, 1999a). The single dose level tested was a LOAEL that was used as the basis for the intermediate MRL. Additional intermediate-duration oral studies are needed to better characterize the neurodevelopmental effects of similarly low doses of PCB mixtures as well as the LOAEL region for immunological, endocrinological, and other sensitive end points. Additional studies could also corroborate evidence indicating PCB-related changes in bone structure in growing rats (Andrew 1989) and on PCB-related endocrine disruption.

Some information is available on effects of PCBs in animals by inhalation (one study with rats, mice, rabbits, and guinea pigs, and a second study with rats) (Casey et al. 1999; Treon et al. 1956) or dermal exposure (two studies with rabbits, one study with mice) (Puhvel et al. 1982; Vos and Beems 1971; Vos and Notenboom-Ram 1972) for intermediate durations. Although limited by various study inadequacies including insufficient numbers of animals, dose levels, end points and NOAEL data, this information is essentially consistent with the oral data in indicating that the liver, kidneys, thyroid and skin are main targets of toxicity. The limitations of these studies and lack of intermediate-duration inhalation studies in other species known from oral studies to be more sensitive than rats precludes the derivation of an MRL for this route and duration. Well-designed intermediate-duration studies in the more sensitive species, particularly monkeys, are needed to determine thresholds for other targets. Additional investigation could help determine whether the respiratory system effects observed in workers exposed by inhalation (Emmett et al. 1988a, 1988b; Fischbein et al. 1979; Lawton et al. 1986; Smith et al. 1982; Warshaw et al. 1979) were truly PCB effects or were caused by other contaminants. Toxicity studies by the inhalation route would be relevant due to the potential for environmental exposure by this route, particularly in the vicinity of waste sites, but may not be practical due to low volatility. Additional intermediate-duration dermal studies, especially in sensitive species, are relevant because the skin is a route of concern for exposure at or near hazardous waste sites.

Chronic-Duration Exposure and Cancer. Some epidemiological studies of PCB-exposed workers, which involve inhalation and dermal exposure, have provided evidences that PCBs were associated with adverse health effects, including hepatic and dermal changes (Alvares et al. 1977; Baker et al. 1980; Bertazzi et al. 1987; Chase et al. 1982; Colombi et al. 1982; Emmett 1985; Emmett et al. 1988a, 1988b; Fischbein 1985; Fischbein et al. 1979, 1982, 1985; Kimbrough et al. 1999a, 1999b; Lawton et al. 1985a, 1985b, 1986; Maroni et al. 1981a, 1981b; Meigs et al. 1954; Ouw et al. 1976, 1982; Smith et al. 1982; Warshaw et al. 1979). Reported effects on the respiratory system and gastrointestinal tract in these workers are suggestive. Hypertension in a population that consumed fish containing PCBs and DDT or other environmentally-exposed populations cannot be attributed conclusively to PCBs (Kreiss 1985; Kreiss et al. 1981; Massachusetts Department of Public Health 1987; Stehr-Green et al. 1986a). As discussed in following subsections, there is growing evidence that immunologic, reproductive, and thyroid effects are effects of concern in PCB-exposed populations. Relatively few toxicity studies of animals with chronic oral exposure to PCBs have been performed (Allen and Norback 1976; Arnold et al. 1993a, 1993b, 1995; General Electric Co. 1997a, 1997b; Kimbrough et al. 1975; Loo et al. 1989; Mayes et al. 1998; NCI 1978; Phillips et al. 1972; Tryphonas et al. 1986a, 1986b, 1989, 1991b), and chronic inhalation and dermal toxicity studies with animals, which could support or refute the findings of occupational studies, are lacking. Although limited in quantity, the available chronic animal oral toxicity data essentially corroborate the results of intermediate-duration studies with respect to effects in the liver, skin, stomach, blood, and thyroid, but provide no information on renal effects. Additional studies could help explain a lack of adrenal effects in monkeys exposed chronically (Loo et al. 1989) and changes in this organ in rats exposed in intermediate-duration studies. Additional studies would be necessary to determine the most sensitive animal target organ and species for chronic exposure and verify that immunologic effects are the most appropriate basis for the MRL. Additional human studies could help verify and elucidate suggestive effects, including whether gastrointestinal symptoms in workers are secondary to liver toxicity and the possible association between PCBs and hypertension. Additional evaluations of the thyroid would be particularly informative because intermediate-duration animal studies indicating that the thyroid may be a particularly sensitive target of toxicity in monkeys has limitations (Tryphonas et al. 1986b). Other chronic-duration exposure studies targeting the potential of specific PCB congeners to act as endocrine disruptors would be useful.

There is sufficient evidence that commercial PCB mixtures containing 60% chlorine by weight are carcinogenic in rats (General Electric Co. 1997a, 1997b; Kimbrough et al. 1975; Mayes et al. 1998; Norback and Weltman 1985; Schaeffer et al. 1984). Aroclor 1254 and other lower chlorinated commercial PCB mixtures have a lower carcinogenic potential than the 60% chlorine mixtures (General

Electric Co. 1997a, 1997b; Ito et al. 1973; Kimbrough and Linder 1974; Kimbrough et al. 1972; Mayes et al. 1998; Morgan et al. 1981; NCI 1978; Schaeffer et al. 1984; Ward 1985). Although the evidence that PCBs are carcinogenic in rats is conclusive, additional studies could provide information on interspecies differences. Further studies with PCB congeners aimed at elucidating the mechanism of promotion and the possible role of intercellular communication in tumor promoting activity (Hemming et al. 1992) would be valuable.

Human studies provide suggestive evidence that PCBs are carcinogenic. The carcinogenicity of PCBs in humans has been investigated in retrospective cohort mortality studies, which investigated cancer in exposed workers, and in case-control studies of environmental exposure that examined associations between serum or adipose tissue levels of PCBs and occurrence of cancer. Some of the mortality studies suggest that occupational exposures to PCBs were associated with cancer at several sites, particularly the liver, biliary tract, intestines, and skin (melanoma) (Bahn et al. 1976, 1977; Bertazzi et al. 1987; Brown and Jones 1981; Brown 1987b; Gustavsson and Hogstedt 1997; Gustavsson et al. 1986; Hardell et al. 1996; Hsieh et al. 1996; Kimbrough et al. 1999a, 1999b; Kuratsune et al. 1987; Loomis et al. 1997; Nicholson and Landrigan 1994; Rothman et al. 1997; Shalat et al. 1989; Sinks et al. 1992; Tironi et al. 1996). There is no clear association between occupational exposures to PCBs and cancer in other tissues, including the brain, hematopoietic, and lymphatic (e.g., non-Hodgkin's lymphoma). The hypothesis that environmental exposure to PCBs can cause breast cancer in humans is controversial and needs to be further studied. A number of case-control studies have investigated possible associations between breast cancer and concentrations of PCBs in breast tissue or blood in the general population. Breast adipose levels of total PCBs or individual congeners were increased in women with breast cancer in some but not all studies (Aronson et al. 2000; Dewailly et al. 1994; Falck et al. 1992; Guttes et al. 1998; Liljegren et al. 1998; Mussalo-Rauhamaa et al. 1990; Unger et al. 1984; Wasserman et al. 1976). Other environmental exposure studies used serum PCB concentrations as the marker of exposure with blood samples taken after the diagnosis of breast cancer (Moysich et al. 1998, 1999; Wolff et al. 1993; Zheng et al. 2000), or prospectively collected prior to diagnosis (Dorgan et al. 1999; Helzlsouer et al. 1999; Høyer et al. 1998; Hunter et al. 1997; Krieger et al. 1994; Wolff et al. 2000). None of the serum studies found significantly different mean blood levels of PCBs in breast cancer cases and controls. There also were no significant associations between risk of breast cancer and serum PCBs in most of these studies, although some data suggest that risk may be increased in some subgroups of postmenopausal women (Moysich et al. 1998, 1999). Many of the better designed studies were prospective, and none of the prospective studies found that PCBs were associated with the occurrence of breast cancer (Dorgan et al. 1999; Helzlsouer et al. 1999; Høyer et al. 1998; Hunter et al. 1997; Krieger et al. 1994; Wolff et al. 2000). Additional studies,

including follow-up of existing cohorts, are needed to better characterize the relationship between PCBs and cancer in humans.

Genotoxicity. An increased percentage of chromosomal aberrations was reported in a study in which workers were exposed to PCBs for >10 years (Kalina et al. 1991). However, there was simultaneous exposure to benzene, which is known to cause genotoxic effects in humans. A different study reported a slight increase in the incidence of sister chromatid exchanges in 12 men exposed to PCBs following a fire in an electric station (Melino et al. 1992). It is quite possible, however, that toxic chlorinated dioxins and/or furans were generated during the fire. Studies with Aroclor 1254 in human lymphocytes *in vitro* gave conflicting results; Hoopingarner et al. (1972) found no evidence of chromosomal damage at a concentration of 100 μg/mL, whereas Sargent et al. (1989) observed chromosomal damage at a concentration of 1.1 μg/mL. Aroclors 1242 and 1254 were not genotoxic in rats and mice when administered orally in acute- and intermediate-duration studies (Garthoff et al. 1977; Green et al. 1975a, 1975b; Robbiano and Pino 1981); however, longer term studies were not located. Furthermore, other PCB mixtures have not been tested. Studies by the inhalation and dermal routes would help develop dose-response relationships for these routes. Available pharmacokinetic data do not suggest route-specific target organs. Aroclor 1254 was not mutagenic in *Salmonella* (Bruce and Heddle 1979; Heddle and Bruce 1977; Schoeny et al. 1979). Studies with other mixtures, and using other prokaryotes, would provide information regarding differences in potencies of different mixtures and in the sensitivities of different organisms. Cytogenetic analysis of human populations exposed to PCBs in occupational settings or exposed by consumption of food contaminated with PCBs would provide an opportunity to assess the genotoxic potential of these compounds in humans. However, the generally negative results of *in vitro* and *in vivo* animal studies indicate that commercial PCB mixtures are not likely to pose a genotoxic threat to humans.

Reproductive Toxicity. Limited information is available on reproductive effects of PCBs in humans. In women, there was no apparent effect of occupational exposure to various Aroclor mixtures on mean number of pregnancies (Taylor et al. 1989). Due to study limitations and lack of information on gravidity in other studies, the effect of PCBs on human conception is unclear. Studies that examined reproductive end points in women whose diets contained Great Lakes fish found suggestive evidence that consumption of the fish may be associated with a slightly shorter menstrual cycle length (Mendola et al. 1997), but not with increased risk for spontaneous fetal death (Mendola et al. 1995a). Studies of one cohort of Great Lakes fisheaters indicated that women were more likely to have positive associations with conception delay than their exposed husbands (Buck et al. 1997, 1999, 2000), although contrary results were found in

another cohort which found an association between conception delay and Great Lakes fish consumption in exposed men, but not in their wives (Courval et al. 1999). The strength of the human evidence that consumption of Great Lakes fish may or may not be associated with adverse effects on conception and other reproductive abilities is weak given the small magnitude of effects when they have been detected and study limitations as discussed in Section 3.2.5.2. Additional long-term prospective or longitudinal epidemiology studies are needed are needed to follow these PCB-exposed populations for reproductive end points as well as to assess the clinical relevance of the effects.

Oral studies with animals provide conclusive evidence for reproductive toxicity of PCBs in females of various species and some evidence for effects in male rats. Effects that have been induced in female animals include estrus changes and reduced implantation rate in adult rats and/or their offspring, decreased conception in mice, partial or total reproductive inhibition in minks, and menstrual alterations and decreased fertility in monkeys (Allen et al. 1974a; Arnold et al. 1990, 1993a, 1993b, 1995; Aulerich and Ringer 1977; Backlin and Bergman 1995; Backlin et al. 1997, 1998a, 1998b; Barsotti et al. 1976; Brezner et al. 1984; Jones et al. 1997; Kihlstrom et al. 1992; Sager and Girard 1994; Welsch 1985). Monkeys (Rhesus) and minks are the most sensitive species tested, although reproductive effects were not induced at doses quite as low as those inducing the critical neurobehavioral, immunological, and dermal/ocular effects used to derive the intermediate and chronic MRLs. In male animals, short-term exposure to high oral doses of Aroclor 1254 induced no changes in the weight or histology of the testes or accessory glands in adult rats (Dikshith et al. 1975; Sanders et al. 1974), although seminal vesicle weights and caudal epididymal weights and sperm counts were reduced in rats that were exposed for several months as weanlings (Gray et al. 1993). No studies in male mice or rats evaluated reproductive capability. There is limited evidence of hypoactivity of the seminiferous tubules in monkeys that were chronically exposed to a dose of Aroclor 1248 that also caused clinical signs of toxicity (Allen and Norback 1976). In contrast to the limited evidence for reproductive effects in male adult animals, fertility was markedly reduced in male offspring of rats that were lactationally exposed to relatively high doses of Aroclor 1254 (Sager 1983; Sager et al. 1987, 1991), and results of oral and subcutaneous studies with single congeners have also shown that gestational and neonatal exposures can adversely affect morphology and production of sperm and fertility in male rats and mice (Faqi et al. 1998; Huang et al. 1998a; Smits-van Prooije et al. 1993). As discussed in Section 3.5.2, effects on male reproductive organs appear to involve postnatal developmentally-specific vulnerable periods of responsiveness. Additional animal studies could help characterize effects on fertility in exposed adults, interspecies and sex differences in sensitivity, and define the NOAEL region for reproductive effects.

Developmental Toxicity. There is mounting evidence that perinatal exposure to PCBs induces adverse developmental effects in humans, specifically, but not limited to, neurobehavioral alterations in newborn and children exposed during gestation and/or via breast milk. This has been seen in children born to mothers exposed to PCBs by consumption of contaminated fish from the Great Lakes (Fein et al. 1984a, 1984b; Jacobson et al. 1984a, 1990a, 1990b, 1992; Lonky et al.1996; Stewart et al. 1999, 2000b) and in children from women with no known high-exposure to PCBs in North Carolina (Gladen et al. 1988; Rogan and Gladen 1991; Rogan et al. 1986a, 1986b, 1987), The Netherlands (Huisman et al. 1995a, 1996b; Koopman-Esseboom et al. 1996; Lanting et al. 1998a; Patandin et al. 1999), and Germany (Winneke et al. 1998b). In the various cohorts studied, some common findings of neurodevelopmental effects have been reported, other affected end points have not been the same in all studies. This is not unexpected given the different degrees of control for confounders and the different measures of exposure used. Moreover, apparent inconsistencies between studies may reflect not only limitations in study design, but also problems inherent in detecting neurobehavioral deficits at exposure levels near the threshold for effects. Effects associated with PCB exposure included abnormal reflexes and more motor immaturity in newborns (Jacobson et al. 1984a; Lonky et al. 1996; Rogan et al. 1986b), altered PDI scores at 1–2 years of age (Gladen et al. 1988; Koopman-Esseboom et al. 1996), and alterations in memory functions at 7 months of age (Jacobson et al. 1985) and at 4 years of age (Jacobson et al. 1990a, 1990b, 1992) and in cognitive abilities at 42 months using the Kaufman Assessment Battery for Children (Patandin et al. 1999). It must be kept in mind, however, that in all of these studies, there is a possibility that other lipophilic compounds may have contributed to the observed effects, particularly in the studies on consumption of Great Lakes fish contaminated with other chemicals such as CDDs, DDE, and mercury. It is expected that children from these prospective studies continue to be monitored in order to assess the impact of these subtle neurobehavioral alterations as they grow older and their potential implications at a population level. It is also important to address the issue of continuity of effect over time. This means establishing whether the children who showed impaired performance in some tests at 18 and 24 months are the same who performed poorly in tests given as neonates. This would help interpretation of the biological significance of the exposure.

Improvements in analytical methods for measuring PCBs should greatly facilitate analysis of PCB congeners in cord blood, the most accurate surrogate of exposure during gestation. This should allow researchers to establish more precise potential associations between specific PCB congeners and health outcomes, as done for example by Stewart et al. (2000b) in their study of Lake Ontario fisheaters. It is also important that researchers provide as much information as possible regarding not only the analytical

methods used for measuring PCBs, but also the methods for measuring lipids so that comparisons between studies can be made.

Studies in animals support the findings in humans. Studies in rodents have provided valuable information, but monkeys, whether exposed during gestation and/or during infancy, have proved to be much more very sensitive to PCBs and some structurally-related chemicals. Investigators should continue efforts to develop an operant test battery that measures a variety of functions that can be validated for use in rodents, monkeys, and humans and that can be applied in epidemiological studies. Studies with single congeners are valuable in that they provide information on possible mechanisms of action, but people, specifically nursing infants, are exposed to a mixture of PCB congeners in the milk. Therefore, further studies that administer PCB mixtures of congeneric composition similar to that of human breast milk represent the most relevant approach to mimicking real life exposure to infants. Varying the congener composition of the reconstituted milk sample may help associate specific PCB congeners with specific neurodevelopmental outcomes.

Some studies in humans have suggested that gestational exposure to PCBs and other chemicals can affect the thyroid hormone system in infants (Koopman-Esseboom et al. 1994a; Nagayama et al. 1998a; Winneke et al. 1998a). These observations have been extensively corroborated in experimental animals (Collins and Capen 1980c; Corey et al. 1996; Goldey et al. 1995; Juarez de Ku et al. 1994; Li et al. 1998; Morse et al. 1996b; Seo and Meserve 1995). Yet, further information is needed comparing thyroid hormone levels in the brain and histological changes of exposed animals during crucial periods of nerve tract development and neuronal differentiation. Normal thyroid status is also crucial for the normal development and functioning of reproductive organs, and further research in this area is also needed.

Perinatal exposure to PCBs also has been associated with alterations in immunocompetence in children (Dewailly et al. 2000; Smith 1984; Weisglas-Kuperus 2000; Weisglas-Kuperus et al. 1995). These children should continue to be observed for any indication of reduced immunocompetence which may potentially lead to increased incidence of illnesses. The findings of immune alterations following PCB exposure are consistent with observations in animals. Immunological alterations have been reported in adult monkeys and their offspring after long-term exposure to commercial PCB mixtures at doses as low as 0.005 mg/kg/day (Arnold et al. 1995; Tryphonas et al. 1989, 1991a, 1991b).

Immunotoxicity. There are indications of altered immune status in adult and infant human populations who were orally exposed to mixtures of PCBs and other chemicals. Information on immunological effects of PCBs in humans is mainly available from studies of people exposed occupationally (Chase et al. 1982; Emmett et al. 1988a, 1988b; Lawton et al. 1985a; Maroni et al. 1981b; Smith et al. 1982), by consumption of contaminated fish and other marine foods (Dewailly et al. 2000; Smith et al. 1984), by consumption of contaminated rice oil in the *Yusho* and *Yu-Cheng* poisoning incidents (Chang et al. 1981, 1982a, 1982b; Chao et al. 1997; Kuratsune 1989; Lu and Wu 1985; Nakanishi et al. 1985; Rogan 1989; Shigematsu et al. 1971; Yu et al. 1998), and via general environmental exposures in a Dutch population (Weisglas-Kuperus et al. 1995). The occupational studies provide little information for assessing immunotoxicity because evaluations were essentially limited to inconclusive routine clinical measurements of WBC counts and serum proteins with no investigations of functional immune parameters. The most conclusive findings were in the *Yusho* and *Yu-Cheng* populations who experienced the highest levels of PCB exposure and least complex exposure mixture. Interpretation of the data from the other human studies is complicated by responses that were generally subtle and exposures that included a number of persistent toxic substances in addition to PCBs that are also potentially immunotoxic. Overall, there appears to be a consistency of effects among the human studies suggesting sensitivity of the immune system to PCBs and these other chemicals, particularly in infants exposed *in utero* and/or via breast feeding. For example, susceptibility to respiratory tract infections was increased in *Yusho/Yu-Cheng* adults and their children, and there was an association between infectious illnesses and PCBs in the children of mothers who consumed Lake Michigan or Sheboygan River fish. Children born to *Yu-Cheng* mothers also had an increased prevalence of middle ear infections, and the incidence of acute otitis media was increased in Inuit infants of mothers whose diets were based on marine mammal fat. Serum IgA and/or IgM antibody levels were decreased in the *Yusho* and *Yu-Cheng* populations as well as in the Inuit children. Monocyte counts were reduced in *Yu-Cheng* patients and the infants of the Dutch mother-child study, and changes in T lymphocyte subsets were found in the *Yu-Cheng*, Inuit child, and Dutch child populations. However, due to the mixed chemical nature of the exposures and generally insufficient information on possible exposure-response relationships, the human studies provide only limited evidence that exposed adults and infants exposed *in utero* or via breast feeding may have compromised their immune system rendering them unable to overcome infection. Additional studies are needed to better characterize the immunologic potential of PCBs in exposed humans, particularly by incorporating an immunological component in the early design of epidemiologic studies, as well as establishing a broad database of normal values for clinical immunology end points to which experimental results can be compared. The hypothesis that a possible

relationship between PCBs and non-Hodgkin's lymphoma could be related to the immunosuppressive effects of PCBs is another area requiring further research.

The immunotoxicity of PCBs in animals has been documented in various species that were orally exposed via commercial mixtures, mixtures of congeners analogous to human breast milk, Great Lakes fish, or single congeners. Studies in rats, mice, guinea pigs, and rabbits showed that intermediate-duration exposures to relatively high doses of commercial PCB mixtures caused morphological and functional alterations in the immune system. Effects observed in these species included thymic and splenic atrophy, reduced antibody responses to SRBC and other foreign antigens, increased susceptibility to infection by viruses and other microbes, reduced skin reactivity to tuberculin, and increased proliferation of splenic lymphocytes in response to mitogenic stimulation (Allen and Abrahamson 1973; Bonnyns and Bastomsky 1976; Exon et al. 1985; Imanishi et al. 1980; Koller 1977; Loose et al. 1977, 1978a, 1978b, 1979; Smialowicz et al. 1989; Street and Sharma 1975; Talcott and Koller 1983; Talcott et al. 1985; Vos and Van Driel-Grootenhuis 1972). Immunological assessments of rats and mice that were fed diets containing low doses of PCBs and other chemicals in Great Lakes fish were generally mixed, although some alterations were found that are similar to those observed in the studies of commercial PCB mixtures (Cleland et al. 1989; Tryphonas et al. 1998a, 1998b).

Oral studies of Aroclor mixtures in monkeys confirm the findings of immunotoxicity in the other species and further indicate that the immune system of monkeys is particularly sensitive to PCBs. Immunological effects of PCBs in monkeys include decreased antibody responses to SRBC, increased susceptibility to bacterial infections, altered lymphocyte T-cell subsets, decreased lymphoproliferative responsed to mitogens, and histopathological changes in the thymus, spleen, and lymph nodes (Abrahamson and Allen 1973; Allen and Barsotti 1976; Allen et al. 1980; Barsotti et al. 1976; Thomas and Hinsdill 1978; Truelove et al. 1982; Tryphonas et al. 1986a, 1989, 1991a, 1991b). The parameters most consistently affected in monkeys are reduced IgM and IgG antibody responses to SRBC, which were induced at chronic oral doses as low as 0.005 mg/kg/day (Tryphonas et al. 1989, 1991a, 1991b). Results of studies in gestationally- and lactationally-exposed infant monkeys are consistent with the data in adult animals showing immunosuppressive effects of PCBs (Aroclor 1254) at doses as low as 0.005 mg/kg/day, with reductions in IgM and IgG antibody levels to SRBC and mitogen-induced lymphocyte transformation that generally paralleled the findings in maternal animals (Arnold et al. 1995). The 0.005 mg/kg/day LOAEL for immunological effects in monkeys was used as the basis of the chronic oral MRL for PCBs. Also, minimal immunological alterations were induced in infant monkeys that were orally exposed to a similar dose (0.0075 mg/kg/day) of a PCB congener mixture simulating the congener content of human milk for

the first 20 weeks of life (Arnold et al. 1999). Additional immunological studies in animals are needed to verify that the immune system is the most sensitive target of PCBs and the most appropriate basis for chronic MRL derivation, as well as better characterize dose-response relationships in sensitive species following intermediate-duration exposure.

Neurotoxicity. As previously mentioned under Developmental Toxicity, one of the main focus of research on PCBs has been the evaluation of a possible association between exposure to PCBs during gestation and/or lactation and neurobehavioral alterations in newborn and young children. Thus far, there is no evidence that PCBs at the levels found in the environment are neurotoxic to adults. There is no conclusive evidence that workers who were exposed to commercial PCB mixtures for long periods and had high PCB body burdens developed neurological deficits (Emmett et al. 1988a; Fischbein et al. 1979; Smith al. 1982). However, sensory and motor nerve alterations were observed in *Yusho* and *Yu-Cheng* patients who ingested rice oil contaminated with high amounts of PCBs, CDFs, and other structurally-related chemicals (Chia and Chu 1984, 1985; Kuratsune 1989; Rogan 1989). Evaluation of an adult population on a visual-motor coordination test and a hand steadiness test revealed no significant effect from exposure to PCB/DDE through long-term consumption of Lake Michigan fish (Schantz et al. 1999). The results from cognitive assessment of this cohort are expected to be available in the near future.

The mechanism(s) of neurotoxicity of PCBs is not entirely clear, but evidence accumulated in recent years suggests that multiple mechanisms may be involved including alterations in levels of neurotransmitters in various brain areas, of calcium homeostasis (Kodavanti et al. 1993), inositol phosphates (Shafer et al. 1996), protein kinase C (Kodavanti et al. 1995), ryanodine receptor binding (Wong and Pessah 1996), and neutrophil activation (Ganey et al. 1993). Continued research in these areas is necessary to establish correlations between biochemical, morphological, and functional alterations in the brain of PCB-exposed animals, as well as to determine possible preferential accumulation of PCB congeners in specific brain areas that could be associated with specific neurobehavioral effects. Establishing relationships between *in vitro* and *in vivo* effects is important for the development of appropriate *in vitro* preparations in which putative neurotoxicant PCBs can be easily tested.

Epidemiological and Human Dosimetry Studies. Consumption of contaminated food (particularly diets high in fish from contaminated waters) and inhalation of indoor air in buildings that have electrical parts that contain PCBs are the main sources of exposure for the general population. PCBs can pass across the placenta and also can accumulate in breast milk such that breast-fed infants and

unborn children are at risk of being exposed to PCBs (DeKoning and Karmaus 2000; Fein et al. 1984a, 1984b; Huisman et al. 1995a, 1996b; Jacobson et al. 1984a, 1990a, 1990b; Rogan et al. 1986a, 1986b, 1987). Although PCBs are no longer manufactured in the United States, PCB-containing transformers and capacitors remain in use. Thus, occupational exposure may occur in workers during accidents or repair of electrical equipment containing PCBs. Present and future occupational exposure to PCBs may also occur from residual PCBs in workplaces, from disposal of PCBs and/or contaminated equipment, or during cleanup of hazardous waste sites. A number of studies have examined possible associations between health effects and exposure to PCBs, particularly in adults occupationally exposed to PCBs (Alvares et al. 1977; Baker et al. 1980; Bertazzi et al. 1987; Chase et al. 1982; Colombi et al. 1982; Emmett 1985; Emmett et al. 1988a, 1988b; Fischbein 1985; Fischbein et al. 1979, 1982, 1985; Kimbrough et al. 1999a; Lawton et al. 1985a, 1985b, 1986; Maroni et al. 1981a, 1981b; Meigs et al. 1954; Ouw et al. 1976, 1982; Smith et al. 1982; Taylor et al. 1989; Warshaw et al. 1979), adults and/or their children following maternal consumption of contaminated fish from the Great Lakes and other waters (Buck et al. 1997, 1999, 2000; Courval et al. 1999; Dewailly et al. 2000; Fein et al. 1984a, 1984b; Jacobson et al. 1984a, 1990a, 1990b, 1992; Kreiss 1985; Kreiss et al. 1981; Lonky et al. 1996; Mendola et al. 1995a, 1997; Smith 1984; Stewart et al. 1999, 2000b), and in children from women in North Carolina (Gladen et al. 1988; Rogan and Gladen 1991; Rogan et al. 1986a, 1986b, 1987), the Netherlands (Huisman et al. 1995a, 1995b; Koopman-Esseboom et al. 1994a, 1996; Lanting et al. 1998; Patandin et al. 1999; Weisglas-Kuperus 2000; Weisglas-Kuperus et al. 1995), and Germany (Winneke et al. 1998b) with no known high-exposure to PCBs. Chloracne and other skin changes, and various hepatic alterations including increased serum levels of liver enzymes and lipids have been associated with occupational exposures. There are also reports of respiratory, gastrointestinal, hematological, skeletal, developmental, and neurological effects in exposed workers, but the evidence is not strong enough to conclusively establish cause-effect relationships. The epidemiologic studies of the contaminated fisheating populations and people exposed via the general environment raise concern for reproductive effects in adults and neurodevelopmental and immunological alterations in children of exposed parents, as discussed above in the Reproductive Toxicity, Developmental Toxicity, Neurotoxicity, and Immunotoxicity data need subsections. Additional well conducted epidemiological investigations, particularly follow-up studies and transgenerational studies of high risk populations, are needed to better characterize the potential for PCBs to induce these effects. These studies should also address limitations that constrain some of the existing human studies, such as unmeasured PCB exposure concentrations, lack of controls for confounding co-exposures, and lack of comparative population data.

Concern that even low levels of PCBs transferred to the fetus across the placenta and that greater amounts might be transferred to nursing infants via breast milk has triggered many of the epidemiological studies. The results from some of these studies suggest that perinatal exposure to PCBs may induce subtle long-lasting neurological damage in children (Fein et al. 1984a, 1984b; Gladen et al. 1988; Huisman et al. 1995a, 1996b; Jacobson et al. 1984a, 1990a, 1990b, 1992; Koopman-Esseboom et al. 1996; Lanting et al. 1998a; Lonky et al. 1996; Patandin et al. 1999; Rogan and Gladen 1991; Rogan et al. 1986a, 1986b, 1987; Stewart et al. 1999, 2000b). Suggestive evidence for immunological (Dewailly et al. 2000; Smith 1984; Weisglas-Kuperus et al. 1995; Weisglas-Kuperus 2000) and thyroid effects (Koopman-Esseboom et al. 1994a; Nagayama et al. 1998a; Winneke et al. 1998a) in children also has been presented. Many of these are prospective studies that have followed-up the children for many years and are expected to continue to do so in order to ascertain the duration and real life significance of these subtle alterations.

Biomarkers of Exposure and Effect.

Exposure. PCBs are stored at highest concentrations in adipose tissue and are present in serum and human milk. Several studies have shown that serum and adipose PCB levels are biomarkers of exposure (Brown and Lawton 1984; EPA 1984d; Fait et al. 1989; Jacobson et al. 1984b; Jan and Tratnik 1988; Luotamo 1988; Safe et al. 1985b; Schecter et al. 1994; Steele et al. 1986; Wolff et al. 1982a). It has been proposed that measurement of PCB levels in both serum and adipose tissue may be more predictive of body burden than each value separately, although either serum or adipose tissue PCB levels may serve as useful biomarkers of body burden and/or exposure (Stellman et al. 1998). Further studies on the predictive value of levels of PCBs (particularly congeners) in serum and adipose tissue in individuals exposed to PCBs for short, intermediate, and chronic durations would provide valuable information that could lead to early detection of PCB exposure.

PCB residue data in humans and other animals (see Section 3.4.2, Distribution) suggest that tissue or body burdens of PCBs should be based on individual congeners or groups of congeners and not based on profiles of commercial PCB formulations. The simplest approach involves using one congener as a marker of total PCBs in a biological specimen. For example, levels of 2,2',4,4',5,5'-hexaCB (PCB 153), a very stable and often the most abundant congener, have been shown to correlate well with the total amount of PCBs in human breast milk, plasma, or follicular fluid (Atuma and Aune 1999; Grimvall et al. 1997; Johansen et al. 1994; Pauwels et al. 1999). However, if a more complete profile of congeners is considered, the correlations are lower (Bachour et al. 1998; Hansen 1998, 1999). Use of PCB 153 or congener groups as a marker of the total therefore could be a misleading indicator of the differential

exposure to other individual or groups of congeners of toxicological significance. Further studies are needed to assess the feasibility of using individual congeners or groups of congeners as a marker for total exposure to PCBs.

Effect. There are no specific biomarkers of effects for PCBs. Numerous studies have attempted to correlate serum PCB levels with liver-associated enzymes in PCB-exposed workers and general population subjects; however, no conclusive association has been found (Baker et al. 1980; Emmett et al. 1988a, 1988b; Fischbein 1985; Fischbein et al. 1979; Kreiss et al. 1981; Lawton et al. 1985a, 1985b; Smith et al. 1982; Stehr-Green et al. 1986a, 1986b; Steinberg et al. 1986). Further studies to identify specific biomarkers of effects of PCBs would facilitate medical surveillance leading to early detection of potentially adverse health and possible treatment. Congener-specific analysis combined with TEF calculations may be useful for characterizing dioxin-like health effects. However, as discussed in the introduction to Section 3.11.1, use of congener-specific analyses is not yet practical for most laboratories, and the TEF approach for PCBs is still under development and limited to dioxin-like congeners' effects only.

Absorption, Distribution, Metabolism, and Excretion. There are no quantitative data regarding absorption in humans by the inhalation or dermal route, but data from occupationally exposed individuals suggest that PCBs are well absorbed by these routes (Wolff 1985). Only one study was located that provided quantitative oral absorption data in a volunteer (Buhler et al. 1988). Schlummer et al. (1998) used a mass balance approach to assess the gastrointestinal absorption of specific PCB congeners from food in seven individuals, 24–81 years of age, with different contaminant body burdens. Together, the data support the passive diffusion model for gastrointestinal absorption, where the concentration of the contaminant in the blood is the major factor determining absorption. PCB congeners showing nearly complete net absorption had very low or nondetectable levels in the serum lipids. For other congeners, there was a trend for decreasing net absorption and/or increasing net excretion with increasing congener concentration in serum lipids. Similar congener specific, mass balance human studies are needed to confirm and extend these findings. The animal data indicate that PCBs are efficiently absorbed by the oral route (Albro and Fishbein 1972; Hansen 1999), but most of the information is derived from excretion data. Inhalation and dermal absorption data are limited. No studies were located in which a range of doses of PCB mixtures of different chlorine contents were administered by the inhalation, oral, and dermal routes, and for various exposure periods.

As with absorption, distribution data in humans are limited to serum, milk, and/or tissue PCB residue data from occupationally and environmentally exposed subjects, and suggest that PCBs distribute preferentially to tissues with high fat content regardless of the route of exposure (Brown and Lawton 1984; Fait et al. 1989; Jensen 1987). As with other organisms, PCB residue levels in humans reflects multiple exposure pathways, and congener-specific elimination. PCB profiles in human serum immediately following exposures reflect the profiles in the exposure sources; however, selective metabolism and excretion begin to alter the congener profile within 4–24 hours (Hansen 1999). In large population based studies, it is often necessary to summarize large quantities of congener-specific data from many individuals in order to highlight mean and range data for each PCB congener. While this approach is necessary to summarize data for publication, congener profiles for individuals are often never reported. Thus, it may not be possible to identify a few individuals that may have had an unusual profile or elevated congener level due to a recent PCB exposure. Human studies reporting congener specific PCB residue data should consider citing electronic databases, which could contain the complete data set for each subject in the study.

Moysich et al. (1999) recently evaluated proposed frameworks for grouping PCBs, including a more simple approach based on relative abundance and degree of chlorination. McFarland and Clarke (1989) proposed an approach to grouping PCB congeners based on their potential risk to the environment and human health. Another framework for grouping PCB was proposed by Wolff et al. (1997), based on the biological activities of the congeners and their presence in house dust and humans. Numerous factors, such as the analytical methods used by various labs for sample preparation and analysis, the type of human sample (milk, serum, plasma, adipose), sample size, year sample was collected, subject age, and exposure history are all critical to the detection and quantification of a specific congener in a given sample. These factors need to be considered when adopting an optimal framework for grouping PCB congeners to assess exposure and relative risk .

Recently, Dewailly et al. (1999) measured the concentration of 14 PCB congeners in subcutaneous fat, omental fat, brain, and liver from autopsy tissue samples collected from Greenlanders between 1992 and 1994. PCB concentrations (lipid basis) were similar in omental fat and subcutaneous abdominal fat, while the hepatic concentrations were generally about 20% lower than fat. PCB levels in brain (lipid basis) were about 10–20% of the levels found in subcutaneous fat. The lower concentration in brain cannot be explained by the presence of the blood-brain barrier because PCBs are highly lipophilic and are therefore expected to freely diffuse across this barrier. The difference in accumulation may be due to the nature of more polar brain lipids, which are mainly phospholipids. PCBs may partition to a greater extent

into the triglycerides found in adipose tissue. Further investigation is needed to understand factors regulating the tissue specific distribution of PCB congeners, particularly to critical target organs such as the brain.

Studies in animals that could provide a basis for assessing the comparative distribution of PCBs when administered by the inhalation, oral, and dermal routes of exposure were not located. A recent study in ferrets by Apfelbach et al. (1998) reported for the first time that the olfactory system may be a potentially significant portal for the entry of airborne PCBs. The olfactory bulbs of the exposed ferrets had the highest total PCB concentration (642 ng/g lipids), while the liver, adipose tissue, and brain had levels of 202, 303, and 170 ng/g lipids, respectively. The data suggest that inhaled PCBs pass into the dentrites of olfactory sensory neurons and are transported via olfactory axons directly to the bulbs where they accumulate. While the olfactory system appears to be a significant site for the disposition of airborne PCBs, further studies are needed to confirm this observation and assess whether greater disposition in the brain is associated with inhalation exposure.

Data derived from oral administration of PCBs to animals indicate that PCBs distribute first to liver and muscle, and are subsequently translocated to adipose tissue and skin for storage (Allen et al. 1974b; Curley et al. 1971; Hashimoto et al. 1976; Klasson-Wehler et al. 1989a). Studies regarding distribution through the placenta after inhalation and dermal exposures were not available.

Other than isolated studies with human microsomes (Schnellmann et al. 1983), data regarding biotransformation of PCBs in humans are limited to information about occupationally exposed individuals, whose PCB intake is assumed to derive mainly from inhalation and dermal exposure (Fait et al. 1989; Jensen and Sundström 1974; Wolff et al. 1982b). The use of human cell systems in culture might be considered a useful alternative to studying the metabolic fate of PCBs, but limited expression of a complete profile of enzymes reduces their value. The metabolism of PCBs after oral administration in experimental animals has been extensively studied (Safe 1989a). Although information regarding metabolism following inhalation or dermal exposure is lacking, there is no reason to believe that other pathways would operate after exposure by these routes.

State of the art PCB exposure assessment utilizing human serum, milk, and/or tissues should not only include congener specific PCB analysis, but analyze persistent PCB metabolites. Since certain hydroxylated and methylsulfonyl ($MeSO_2$) PCB metabolites are present in some cases at levels higher

than their respective parent compounds, it is necessary to further investigate the potential biological and/or toxicological activities of these persistent metabolites.

Studies regarding urinary or fecal excretion of PCBs in humans were not located; however, elimination of PCBs through maternal milk is well documented (Masuda et al. 1978; Mes et al. 1984). Fecal excretion is the main route of elimination of PCBs in animals after oral exposure (Lutz and Dedrick 1987). Although data regarding excretion in animals after inhalation exposure were not located, there is no reason to suspect different patterns of excretion. Dermal data suggest that excretion of certain PCBs may follow a two-phase elimination process, as described for oral exposure, but this information is derived from a single study (Wester et al. 1990).

Comparative Toxicokinetics. The existing evidence suggests that qualitative differences in the toxicokinetic disposition of PCBs exist among humans and the numerous animals species studied and also among animal species (Lutz and Dedrick 1987; Safe 1989a; Sipes and Schnellmann 1987). However, these differences appear to be highly dependent on the specific congener or mixture studied. Further pharmacokinetic modeling studies with additional groups of PCB congeners would be valuable to determine the validity of extrapolating data. In addition, studies with human cell systems *in vitro* could help estimate metabolic rate constants for use in pharmacokinetic models. In general, all species absorb PCBs efficiently and accumulate PCBs in tissues rich in fat. Once absorbed, PCBs distribute in a biphasic manner in all species examined (Lutz and Dedrick 1987). Identification of metabolites in humans and animals suggests that all species examined share some common biochemical reactions. Experimental data in animals indicate that fecal elimination is the main route of excretion (Bleavins et al. 1984; Klasson-Wehler et al. 1989a, 1989b; Mühlebach and Bickel 1981), but no human information was located in the existing literature. Analysis of the excreta of humans exposed in the workplace and near hazardous waste sites would provide information regarding biotransformation and elimination kinetics in humans. In addition, similar target organs have been identified across animal species. Monkeys and minks are the most sensitive species tested regarding dioxin-like effects, but pharmacokinetic data in minks are scant. Although the toxicological data in humans (Emmett et al. 1988a; Fischbein et al. 1979) are limited, adverse cutaneous reactions documented in humans are also seen in monkeys (Arnold 1993a, 1995), although at much lower doses. This and other effects seen in monkeys, not observed in populations occupationally or environmentally exposed to PCBs, have led some to suggest that monkeys may not represent a suitable animal model (James et al. 1993; Kimbrough 1995). However, the clinicopathologic picture in monkeys is more like humans than any other species. As these studies suggest, the monkey is more sensitive than humans on a dose basis. Attention must be paid to differences

between adults and immature animals of all species. The more rapidly growing immature animals generally have lower and distinct profiles of biotransformation enzymes as well as much smaller peripheral fat depots for sequestering the lipophilic PCBs.

Methods for Reducing Toxic Effects. The mechanism by which PCBs enter the blood stream in humans is not known; consequently, there are no established methods for reducing absorption. In experimental animals, however, administration of rice bran fiber reduced gastrointestinal absorption (Takenaka and Tarahashi 1991). Identification of additional substances that could prevent or delay absorption and that do not represent a toxic risk themselves would be valuable. There are no established methods for reducing body burden in humans, but a few reports have indicated that fasting may be effective (Imamura and Tung 1984). Studies examining the effect of fasting in animals exposed to PCBs would provide useful information that can be used to better characterize the effectiveness of this approach. The metabolism of PCBs leads to the formation of highly reactive and potentially toxic derivatives. Thus, additional studies examining the feasibility of favoring metabolic pathways leading to the formation of nontoxic metabolites would be valuable. The mechanisms of toxic actions of PCBs are not completely understood, and no methods exist to block the toxic response due to exposure to PCBs. Further studies aimed at elucidating the mechanisms of action of PCBs would help in developing possible methods for reducing toxic effects.

Children's Susceptibility. Data needs relating to developmental effects are discussed more extensively above in the Developmental Toxicity subsection. Prenatal exposure to PCBs has been associated with neurodevelopmental effects. However, many exposures to PCBs involve mixtures including other chemicals. Studies employing specific congeners of PCBs are needed to establish the association between exposure, neurotransmitter and T_4 levels in the brain, and neurobehavioral effects. Experiments aimed at defining critical windows of PCB action in the developing organism would provide valuable information, especially for pregnant women who may wish to alter their dietary habits during pregnancy. In addition, studies to define the relationship of prenatal exposure to specific PCB congeners, its activity as an endocrine disruptor, and effects on sexual differentiation are needed. Continued monitoring of children from the Dutch, Lake Michigan, Lake Ontario prospective studies is expected with particular emphasis on evaluation of immune competence, thyroid function, and cognitive abilities. Development of PBPK models that could be used to predict PCB body burdens in neonates and infants as a function of maternal body burden would be useful. Studies of the pharmacokinetics of PCBs in the fetus (i.e., assessment of placental permeability for individual congeners), infant, and child would be useful in further defining the potential for toxic effects of these compounds. Areas of focus include the

effect of the developing and changing metabolic capacities of the fetus, neonate, and child on the production of toxic metabolites and/or detoxification of the parent compound and metabolites.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Table 3-15 lists ongoing studies on the health effects of PCBs identified from the Federal Research in Progress database (FEDRIP 2000). Ongoing studies from the ATSDR Great Lakes Human Health Effects Research Program are listed in Table 3-16.

Table 3-15. Ongoing Studies on the Health Effects of PCBs

Investigator	Affiliation	Title	Sponsor
Aulerich, R	Michigan State University East Lansing, MI	Fur animal studies (mink)	USDA or cooperating state institutions
Berkowitz, Gertrud S	Mount Sinai School of Medicine of CUNY, New York, NY	Exposure of indoor pesticides and PCBs—Effects on growth and neurodevelopment	NIEHS
Bernstein, Leslie	Univ of Southern Calif Los Angeles	Organochlorine residue levels and risk of breast cancer	NIEHS
Bradfield, Christopher A	University of Wisconsin Madison	Transgenic models of dioxin action	NIEHS
Burchiel, Scott W	University of New Mexico	Effects of immunotoxic xenobiotics on human peripheral blood lymphocytes	NCRR
Bursian, S	Michigan State University	The fate and biological effects of xenobiotics in animals	USDA or cooperating state institutions
Carpenter, David O	State University of New York at Albany	Mechanisms responsible for cognitive impairment caused by exposure to PCBs	NIEHS
Charles, MJ	University of California Davis	Exploration of linkages among organochlorines, oxidative DNA damage, and breast cancer	USDA or cooperating state institutions
Chou, K	Michigan State University	Control mechanisms of male reproduction and sperm fertilizing ability	USDA or cooperating state institutions
Cohn, Barbara A	Public Health Institute, Berkeley, CA	Prenatal organochlorine exposure and human reproduction	NIEHS
Dean, Charles E	Colorado State University	Promotion of hepatic neoplasia by PCB mixtures	NIEHS
Dorgan, J	NCI, NIH	Prediagnostic breast cancer serum bank	Division of Cancer Prevention and Control
Dukelow, W Richard	Michigan State University	Toxic chemical influences on *in vivo* and *in vitro* reproduction	NIEHS
Finlay, Mary F	Benedict College, Columbia, SC	Pilot study—Toxicological effects of PCB during spermatogenesis	NCRR

Table 3-15. Ongoing Studies on the Health Effects of PCBs *(continued)*

Investigator	Affiliation	Title	Sponsor
Gammon, Marilie D	Columbia University	Breast cancer and the environment on Long Island	NCI
Ganey, PE	Michigan State University	Mechanisms and consequences of neutrophil activation by hazardous chemicals	USDA or cooperating state institutions
Gierthy, John F	State Univ of New York at Albany	PCB estrogenicity in human breast cancer cells	NIEHS
Glauert, Howard P	University of Kentucky	Mechanisms of hepatic tumor promotion by PCBs	NIEHS
Gore, Andrea	Mount Sinai School of Medicine of CUNY	Neuroendocrine mechanisms of environmental toxicity during early development	NIEHS
Grandjean, Phillippe	Boston University	Serum PCB as a risk indicator for breast cancer in women	NIEHS
Greeley, George H, Jr	University of Texas Medical Branch	Dioxin action in the alimentary canal	NIEHS
Hansen, LG	University of IL Urbana	Identification of PCB congeners associated with fish consumption	USDA or cooperating state institutions
Harris, Craig	Michigan State University	PCB effects on uterine wall	NIEHS
Hassoun, Ezdihar A	University of Toledo, Toledo, OH	TCDD induced oxidative stress in the tissues	NIEHS
Hejtmancik, Milton	Battelle Memorial Institute, Columbus, OH	Evaluation of dioxin toxic equivalency factors	NIEHS
Hennig, Bernhard	University of Kentucky	Superfund chemicals and endothelial cell dysfunction	NIEHS
Henny, Charles J	Forest and Rangeland Ecosystem Science Center Corvallis, OR	Environmental endocrine disruptors: effects and possible mechanism(s) in young male river otters	USGS Biological Resources Division
Hertz-Picciotto, Irva	University of North Carolina Chapel Hill	Fetal PCB exposure, thyroid function, and neurodevelopment	NIEHS
Hooper, Michael	University of Washington, Seattle, WA	Wildlife biomarker applications to remediation decision making	NIEHS

Table 3-15. Ongoing Studies on the Health Effects of PCBs *(continued)*

Investigator	Affiliation	Title	Sponsor
Hunter, David J	Brigham and Women's Hospital, Boston, MA	Environmental risk factors and breast cancer	NIEHS
Jefcoate, Colin R	University of Wisconsin Madison	Organochlorine compounds and human breast cytochrome P-450	NIEHS
Keefe, Thomas J	Colorado State University	Historical prospective — organochlorines/breast cancer	NCI
Klaassen, Curtis D	University of Kansas Medical Center	Environmental hormones— effects on thyroid function	NIEHS
Klebanoff, MA	NICHD, NIH	Fetal, neonatal and childhood effects of *in utero* exposure to PCBs and DDE	National Institute of Child Health and Human Development
Korrick, Susan A	Brigham and Women's Hospital, Boston, MA	Polychlorinated biphenyls and infertility	NIEHS
Korrish, Susan	Harvard University	*In utero* PCB and metal exposure and infant development	NIEHS
Laessig, Susan A	Marine Biological Laboratory, Woods Hole, MA	*Ortho*-substituted PCB on calcium homeostasis in aplysia bag cell neurons	NCRR
Longnecker, MP	NIEHS, NIH	Human health effects of exposure to organochlorine compounds	NIEHS
Matte, Thomas	Mount Sinai School of Medicine of CUNY	Prenatal PCB exposure and neurodevelopmental outcomes in adolescence and adulthood	NIEHS
Mc Coy, George L	Benedict College, Columbia, SC	Pilot study—Toxic and estrogenic actions of PCB in reproduction	NCRR
Ozonoff, David M	Boston University	Superfund basic research center at Boston University	NIEHS
Peterson, Richard E	University of Wisconsin Madison	Ah receptor independent central nervouse system/reproductive effects of PCBs	NIEHS
Quimby, Fred W	Cornell University	Model for assessment of immunotoxicity of environmental pollutants	NIEHS

Table 3-15. Ongoing Studies on the Health Effects of PCBs *(continued)*

Investigator	Affiliation	Title	Sponsor
Rattner, Barnett A	Patuxent Wildlife Research Center Laurel, MD	Effects of organochlorine contaminants on reproductive success of black-crowned night-herons (*Nycticorax nycticorax*) nesting in Baltimore Harbor, Maryland	USGS Biological Resources Division
Robertson, Larry W	University of Kentucky	Activation of PCB's to genotoxins *in vivo*	NIEHS
Rogan, WJ	NIEHS, NIH	Human exposure to halogenated aromatic compounds	NIEHS
Roth, Robert A	Michigan State University	Mechanisms and consequences of neutrophil activation by hazardous chemicals	NIEHS
Safe, SH	Texas A&M University	Endocrine toxicology studies	USDA or cooperating state institutions
Safe, Stephen H	Texas A&M University	Toxic halogenated aromatics	NIEHS
Santiago-Rivera, Azara L	State University of New York at Albany	Biopsychosocial well being among Akwesasne residents	NIEHS
Schantz, SL	University of Illinois Urbana	Developmental effects of fish-borne toxicants in rats	USDA or cooperating state institutions
Schantz, SL	University of Illinois Urbana	Developmental effects of combined PCB and MEHG exposure	USDA or cooperating state institutions
Schell, Lawrence M	State University of New York at Albany	PCBs and well being of Mohawk children and youth—growth, development, and cognition	NIEHS
Schwartz, Stephen M	Fred Hutchinson Cancer Research Center, Seattle, WA	Phytoestrogens, organochlorines, and fibroid risk	NIEHS
Seegal, Richard F	Wadsworth Center, Albany, NY	Developmental effects of fish borne toxicants in the rat	NIEHS
Shiverick, Kathleen T	University of Florida, Gainesville	Placental/uterine effects of chlorinated hydrocarbons	NIEHS

Table 3-15. Ongoing Studies on the Health Effects of PCBs *(continued)*

Investigator	Affiliation	Title	Sponsor
Spink, David C	State University of New York at Albany	Alterations in estrogen metabolism caused by exposure to PCBs	NIEHS
Stellman, Steven D	American Health Foundation, Valhalla, NY	Epidemiology of breast cancer	NCI
Thomas, Peter M	University of Texas Austin	Mechanisms of reproductive neuroendocrine toxicity	NIEHS
Trosko, James E	Michigan State University	Evaluation of Superfund chemicals as epigenetic toxicants	NIEHS
Weston, Ainsley	Mount Sinai School of Medicine of CUNY	Effects of PCB-containing river sediments on carcinogen metabolism	NIEHS
Wolff, Mary S	Mount Sinai School of Medicine of CUNY	Inner city toxicants and neurodevelopmental impairment	NIEHS
Zacharewski, T	Michigan State University	Identification and assessment of endocrine disruptors	USDA or cooperating state institutions
Zhu, Bao T	University of South Carolina at Columbia	Effects of cigarette smoking or PCBs on human estradiol	NCI
Zoeller, RT	University of Massachusetts	PCB and thyroid hormone action in developing cochlea	NIEHS

Source: FEDRIP (2000), USDA Current Research Information System (2000), USGS-BRD Science Information System (2000)

NCI = National Cancer Institute; NCRR = National Center for Research Resources; NICHD = National Institute of Child Health and Human Development; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institutes of Health; USDA = U.S. Department of Agriculture; USGS = U.S. Geological Survey

Postal abbreviations used

Table 3-16. Ongoing Studies on the Human Health Effects of PCBs Sponsored by ATSDR

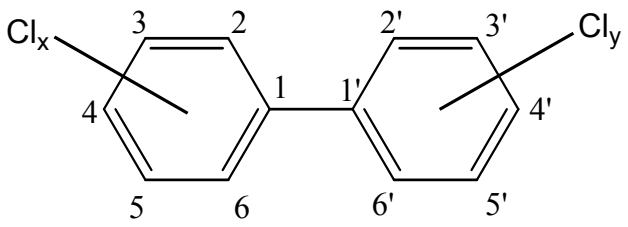
Investigator	Affiliation	Title
Anderson, HA	Wisconsin Department of Health and Social Services Madison, Wisconsin	Consortium for the health assessment of Great Lakes sport fish consumption
Darvill, T	State University of New York at Oswego Oswego, New York	Behavioral effects of consumption of Lake Ontario fish: Two methodological approaches
Dellinger, J	University of Wisconsin at Milwaukee Milwaukee, Wisconsin	Ojibwa Health Study II: Epidemiology, laboratory toxicology, and outreach
Fitzgerald, E	New York State Department of Health Albany, New York	Neurologic effects of environmental exposure to PCBs along the upper Hudson River
Karmus, W.	Michigan State University East Lansing, Michigan	Assessing effects in human reproductive health for PCB exposure via consumption of Great Lakes fish
Schantz, SL	University of Illinois at Urbana-Champaign Urbana, Illinois	Human health effects of PCB exposure from contaminated fish
Vena, J	State University of New York at Buffalo Buffalo, New York	The New York Angler Study: Exposure characterization and reproductive and developmental health
Waller, DP	University of Illinois at Chicago Chicago, Illinois	Great Lakes fish as a source of maternal and fetal exposure to chlorinate hydrocarbons

ATSDR = Agency for Toxic Substances and Disease Registry

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

PCBs are a class of chemical compounds in which 2–10 chlorine atoms are attached to the biphenyl molecule. Monochlorinated biphenyls (i.e., one chlorine atom attached to the biphenyl molecule) are often included when describing PCBs. The general chemical structure of chlorinated biphenyls is shown below.



It can be seen from the structure that a large number of chlorinated compounds are possible. The 209 possible compounds are called congeners. PCBs can also be categorized by degree of chlorination. The term “homolog” is used to refer to all PCBs with the same number of chlorines (e.g., trichloro-biphenyls). Homologs with different substitution patterns are referred to as isomers. For example, the dichlorophenyl homolog contains 12 isomers.

The numbering system for the PCBs is also shown above. Positions 2, 2', 6, and 6' are called ortho positions, positions 3, 3', 5, and 5' are called meta positions, and positions 4 and 4' are called para positions. The benzene rings can rotate around the bond connecting them; the two extreme configurations are planar (the two benzene rings in the same plane) and the nonplanar in which the benzene rings are at a 90E angle to each other. The degree of planarity is largely determined by the number of substitutions in the ortho positions. The replacement of hydrogen atoms in the ortho positions with larger chlorine atoms forces the benzene rings to rotate out of the planar configuration. The benzene rings of non-*ortho* substituted PCBs, as well as mono-*ortho* substituted PCBs, may assume a planar configuration and are referred to as planar or coplanar congeners; the benzene rings of other congeners cannot assume a planar or coplanar configuration and are referred to as non-planar congeners.

Monsanto Corporation, the major U.S. producer of PCBs from 1930 to 1977, marketed mixtures of PCBs under the trade name Aroclor. The Aroclors are identified by a four-digit numbering code in which the

first two digits indicate the type of mixture and the last two digits indicate the approximate chlorine content by weight percent. Thus, Aroclor 1242 is a chlorinated biphenyl mixture of varying amounts of mono- through heptachlorinated homologs with an average chlorine content of 42%. The exception to this code is Aroclor 1016, which contains mono- through hexachlorinated homologs with an average chlorine content of 41% (Hutzinger et al. 1974).

The trade names of some commercial PCB mixtures manufactured in other countries are Clophen (Germany), Fenclor (Italy), Kanechlor (Japan), and Phenoclor (France) (De Voogt and Brinkman 1989). The composition of commercial Clophen A-60 and Phenoclor DP-6 is similar to Aroclor 1260; that of Kanechlor 500 is similar to Aroclor 1254. Fenclor contains 100% decachlorobiphenyl (De Voogt and Brinkman 1989). The chemical identity of the Aroclors is summarized in Table 4-1. The identity of the 209 PCB congeners is shown in Table 4-2. The congeners are arranged in ascending numerical order using a numbering system developed by Ballschmiter and Zell (1980) that follow the IUPAC rules of substituent characterization in biphenyls. The resulting PCB numbers, also referred to as congener, IUPAC, or BZ numbers, are widely used for identifying individual congeners.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Physical and chemical properties of the Aroclors are summarized in Table 4-3. An important property of PCBs is their general inertness; they resist both acids and alkalis and have thermal stability. This made them useful in a wide variety of applications, including dielectric fluids in transformers and capacitors, heat transfer fluids, and lubricants (Afghan and Chau 1989). In general, PCBs are relatively insoluble in water, and the solubility decreases with increased chlorination (see Table 4-3). PCBs are also freely soluble in nonpolar organic solvents and biological lipids (EPA 1980b). PCBs are combustible liquids, and the products of combustion may be more hazardous than the material itself. By-products of combustion include hydrogen chloride, polychlorinated dibenzodioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs) (NFPA 1994).

The approximate weight percent of chlorobiphenyls in some commercial Aroclors is summarized in Table 4-4, and the congener composition of Aroclors is shown in Table 4-5. The congener composition of commercial PCBs may vary from lot to lot even in products from the same manufacturer. In addition, no two descriptions of commercial PCB mixtures, even from the same lot or a manufactured product, are identical because of slight differences in the conditions of the chlorination process or the use of different analysis procedures. For example, a late production Aroclor 1254 lot (Aroclor 1254 “Late”), with greatly

Table 4-1. Chemical Identity of Selected Technical Polychlorinated Biphenyls or Aroclors[a,b]

Characteristic	Aroclor 1016	Aroclor 1221	Aroclor 1232	Aroclor 1242	Aroclor 1248
Synonym(s)	PCB-1016; Polychlorinated biphenyl mixture with 41.5% chlorine	PCB-1221; Polychlorinated biphenyl mixture with 21% chlorine	PCB-1232; Polychlorinated biphenyl mixture with 32% chlorine	PCB-1242; Polychlorinated biphenyl mixture with 41.5% chlorine	PCB-1248; Polychlorinated biphenyl mixture with 48% chlorine
Registered trade name(s)	Aroclor[c]	Aroclor	Aroclor	Aroclor	Aroclor
Chemical formula	See Table 4-4	See Table 4-4	See Table 4-4	See Table 4-4	See Table 4-4
Chemical structure	See Section 4.1	See Section 4.1	See Section 4.1	See Section 4.1	See Section 4.1
Identification numbers:					
CAS registry	12674-11-2	11104-28-2	11141-16-5	53469-21-9	12672-29-6
NIOSH RTECS	TQ1351000	TQ1352000	TQ1354000	TQ1356000	TQ1358000
EPA hazardous waste[d]	3502[e]	3502[e]	3502[e]	3502[e]	3502[e]
OHM/TADS	8500400[f]	8500401[f]	8500402[f]	8500403[f]	8500404[f]
DOT/UN/NA/IMCO shipping	UN2315/IMO9.2[g]	UN2315/IMO9.2[g]	UN2315/IMO9.2[g]	UN2315/IMO9.2[g]	UN2315/IMO9.2[g]
HSDB	6352[g]	6353[g]	6354[g]	6355[g]	6356[g]
NCI	No data	No data	No data	No data	No data

Table 4-1. Chemical Identity of Selected Technical Polychlorinated Biphenyls or Aroclors [a,b] (*continued*)

Characteristic	Aroclor 1254	Aroclor 1260	Aroclor 1262	Aroclor 1268
Synonym(s)	PCB-1254; Polychlorinated biphenyl mixture with 54% chlorine	PCB-1260; Polychlorinated biphenyl mixture with 60% chlorine	PCB-1262; Polychlorinated biphenyl mixture with 61.5–62.5% chlorine	PCB-1268; Polychlorinated biphenyl mixture with 68% chlorine
Registered trade name(s)	Aroclor	Aroclor	Aroclor	Aroclor
Chemical formula	See Table 4-4	See Table 4-4	See Table 4-4	See Table 4-4
Chemical structure	See Section 4.1	See Section 4.1	See Section 4.1	See Section 4.1
Identification numbers:				
CAS registry	11097-69-1	11096-82-5	37324-23-5	11100-14-4
NIOSH RTECS	TQ1360000	TQ1362000	TQ1364000[h]	No data
EPA hazardous waste[d]	3502[e]	3502[e]	No data	No data
OHM/TADS	8500405[f]	8500406[f]	No data	No data
DOT/UN/NA/IMO shipping	UN2315/IMO9.2[g]	UN2315/IMO9.2[g]	UN2315[h]	UN2315[h]
HSDB	6357[g]	1822[g]	No data	No data
NCI	C02664[i]	No data	No data	No data

[a]All information obtained from SANSS 1990 and Hutzinger et al. 1974 except where noted.
[b]Chemical names used are those currently indexed by the Chemical Abstracts Service.
[c]Aroclor is the trade name for chlorinated biphenyls made by Monsanto Chemical Company.
[d]Designation prior to May 19, 1980.
[e]EPA 1980a
[f]EPA-NIH 1990
[g]HSDB 2000
[h]Chemfinder 2000
[i]NIOSH 1987a

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; PCB = polychlorinated biphenyl; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Chemical Identity of Polychlorinated Biphenyl Congeners and Homologs

PCB No.[a]	Structure	CAS No.[b]
	Biphenyl	92-52-4
	Monochlorobiphenyl	27323-18-8
1	2	2051-60-7
2	3	2051-61-8
3	4	2051-62-9
	Dichlorobiphenyl	25512-42-9
4	2,2N	13029-08-8
5	2,3	16605-91-7
6	2,3N	25569-80-6
7	2,4	33284-50-3
8	2,4N	34883-43-7
9	2,5	34883-39-1
10	2,6	33146-45-1
11	3,3N	2050-67-1
12	3,4	2974-92-7
13	3,4N	2974-90-5
14	3,5	34883-41-5
15	4,4N	2050-68-2
	Trichlorobiphenyl	25323-68-6
16	2,2N,3	38444-78-9
17	2,2N,4	37680-66-3
18	2,2N,5	37680-65-2
19	2,2N,6	38444-73-4
20	2,3,3N	38444-84-7
21	2,3,4	55702-46-0
22	2,3,4N	38444-85-8
23	2,3,5	55720-44-0
24	2,3,6	55702-45-9
25	2,3N,4	55712-37-3
26	2,3N,5	38444-81-4
27	2,3 N,6	38444-76-7
28	2,4,4N	7012-37-5
29	2,4,5	15862-07-4
30	2,4,6	35693-92-6
31	2,4N,5	16606-02-3
32	2,4N,6	38444-77-8
33	2N,3,4	38444-86-9

Table 4-2. Chemical Identity of Polychlorinated Biphenyl Congeners and Homologs *(continued)*

PCB No.[a]	Structure	CAS No.[b]
34	2N,3,5	37680-68-5
35	3,3N,4	37680-69-6
36	3,3N,5	38444-87-0
37	3,4,4N	38444-90-5
38	3,4,5	53555-66-1
39	3,4N,5	38444-88-1
	Tetrachlorobiphenyl	26914-33-0
40	2,2N,3,3N	38444-93-8
41	2,2N,3,4	52663-59-9
42	2,2N,3,4N	36559-22-5
43	2,2N,3,5	70362-46-8
44	2,2N,3,5N	41464-39-5
45	2,2N,3,6	70362-45-7
46	2,2N,3,6N	41464-47-5
47	2,2N,4,4N	2437-79-8
48	2,2N,4,5	70362-47-9
49	2,2N,4,5N	41464-40-8
50	2,2N,4,6	62796-65-0
51	2,2N,4,6N	68194-04-7
52	2,2N,5,5N	35693-99-3
53	2,2N,5,6N	41464-41-9
54	2,2N,6,6N	15968-05-5
55	2,3,3N,4	74338-24-2
56	2,3,3N,4N	41464-43-1
57	2,3,3N,5	70424-67-8
58	2,3,3N,5N	41464-49-7
59	2,3,3N,6	74472-33-6
60	2,3,4,4N	33025-41-1
61	2,3,4,5	33284-53-6
62	2,3,4,6	54230-22-7
63	2,3,4N,5	74472-35-8
64	2,3,4N,6	52663-58-8
65	2,3,5,6	33284-54-7
66	2,3N,4,4N	32598-10-0
67	2,3N,4,5	73575-53-8
68	2,3N,4,5N	73575-52-7
69	2,3N,4,6	60233-24-1
70	2,3N,4N,5	32598-11-1
71	2,3N,4N,6	41464-46-4

Table 4-2. Chemical Identity of Polychlorinated Biphenyl Congeners and Homologs *(continued)*

PCB No.[a]	Structure	CAS No.[b]
72	2,3N,5,5N	41464-42-0
73	2,3N,5N,6	74338-23-1
74	2,4,4N,5	32690-93-0
75	2,4,4N,6	32598-12-2
76	2N,3,4,5	70362-48-0
77	3,3N,4,4N	32598-13-3
78	3,3N,4,5	70362-49-1
79	3,3N,4,5N	41464-48-6
80	3,3N,5,5N	33284-52-5
81	3,4,4N,5	70362-50-4
	Pentachlorobiphenyl	25429-29-2
82	2,2N,3,3N,4	52663-62-4
83	2,2N,3,3N,5	60145-20-2
84	2,2N,3,3N,6	52663-60-2
85	2,2N,3,4,4N	65510-45-4
86	2,2N,3,4,5	55312-69-1
87	2,2N,3,4,5N	38380-02-8
88	2,2N,3,4,6	55215-17-3
89	2,2N,3,4,6N	73575-57-2
90	2,2N,3,4N,5	68194-07-0
91	2,2N,3,4N,6	68194-05-8
92	2,2N,3,5,5N	52663-61-3
93	2,2N,3,5,6	73575-56-1
94	2,2N,3,5,6N	73575-55-0
95	2,2N,3,5N,6	38379-99-6
96	2,2N,3,6,6N	73575-54-9
97	2,2N,3N,4,5	41464-51-1
98	2,2N,3N,4,6	60233-25-2
99	2,2N,4,4N,5	38380-01-7
100	2,2N,4N,4N,6	39485-83-1
101	2,2N,4,5,5N	37680-73-2
102	2,2N,4,5,6N	68194-06-9
103	2,2N,4,5N,6	60145-21-3
104	2,2N,4,6,6N	56558-16-8
105	2,3,3N,4,4N	32598-14-4
106	2,3,3N,4,5	70424-69-0
107	2,3,3N,4N,5	70424-68-9
108	2,3,3N,4,5N	70362-41-3
109	2,3,3N,4,6	74472-35-8

Table 4-2. Chemical Identity of Polychlorinated Biphenyl Congeners and Homologs *(continued)*

PCB No.[a]	Structure	CAS No.[b]
110	2,3,3N,4N,6	38380-03-9
111	2,3,3N,5,5N	39635-32-0
112	2,3,3N,5,6	74472-36-9
113	2,3,3N,5N,6	68194-10-5
114	2,3,4,4N,5	74472-37-0
115	2,3,4,4N,6	74472-38-1
116	2,3,4,5,6	18259-05-7
117	2,3,4N,5,6	68194-11-6
118	2,3N,4,4N,5	31508-00-6
119	2,3N,4,4N,6	56558-17-9
120	2,3N,4,5,5N	68194-12-7
121	2,3N,4,5N,6	56558-18-0
122	2N,3,3N,4,5	76842-07-4
123	2N,3,4,4N,5	65510-44-3
124	2N,3,4,5,5N	70424-70-3
125	2N,3,4,5,6N	74472-39-2
126	3,3N,4,4N,5	57465-28-8
127	3,3N,4,5,5N	39635-33-1
	Hexachlorobiphenyl	26601-64-9
128	2,2N,3,3N,4,4N	38380-07-3
129	2,2N,3,3N,4,5	55215-18-4
130	2,2N,3,3N,4,5N	52663-66-8
131	2,2N,3,3N,4,6	61798-70-7
132	2,2N,3,3N,4,6N	38380-05-1
133	2,2N,3,3N,5,5N	35694-04-3
134	2,2N,3,3N,5,6	52704-70-8
135	2,2N,3,3N,5,6N	52744-13-5
136	2,2N,3,3N,6,6N	38411-22-2
137	2,2N,3,4,4N,5	35694-06-5
138	2,2N,3,4,4N,5N	35065-28-2
139	2,2N,3,4,4N,6	56030-56-9
140	2,2N,3,4,4N,6N	59291-64-4
141	2,2N,3,4,5,5N	52712-04-6
142	2,2N,3,4,5,6	41411-61-4
143	2,2N,3,4,5,6N	68194-15-0
144	2,2N,3,4,5N,6	68194-14-9
145	2,2N,3,4N,6,6N	74472-40-5
146	2,2N,3,4N,5,5N	51908-16-8
147	2,2N,3,4N,5,6	68194-13-8

Table 4-2. Chemical Identity of Polychlorinated Biphenyl Congeners and Homologs *(continued)*

PCB No.[a]	Structure	CAS No.[b]
148	2,2N,3,4N,5,6N	74472-41-6
149	2,2N,3,4N,5N,6	38380-04-0
150	2,2N,3,4N,5,6N	68194-08-1
151	2,2N,3,5,5N,6	52663-63-5
152	2,2N,3,5,6,6N	68194-09-2
153	2,2N,4,4N,5,5N	35065-27-1
154	2,2N,4,4N,5,6N	60145-22-4
155	2,2N,4,4N,6,6N	33979-03-2
156	2,3,3N,4,4N,5	38380-08-4
157	2,3,3N,4,4N,5N	69782-90-7
158	2,3,3N,4,4N,6	74472-42-7
159	2,3,3N,4,5,5N	39635-35-3
160	2,3,3N,4,5,6	41411-62-5
161	2,3,3N,4,5N,6	74472-43-8
162	2,3,3N,4N,5,5N	39635-34-2
163	2,3,3N,4N,5,6	74472-44-9
164	2,3,3N,4N,5N,6	74472-45-0
165	2,3,3N,5,5N,6	74472-46-1
166	2,3,4,4N,5,6	41411-63-6
167	2,3N,4,4N,5,5N	52663-72-6
168	2,3N,4,4N,5N,6	59291-65-5
169	3,3N,4,4N,5,5N	32774-16-6
	Heptachlorobiphenyl	28655-71-2
170	2,2N,3,3N,4,4N,5	35065-30-6
171	2,2N,3,3N,4,4N,6	52663-71-5
172	2,2N,3,3N,4,5,5N	52663-74-8
173	2,2N,3,3N,4,5,6	68194-16-1
174	2,2N,3,3N,4,5,6N	38411-25-5
175	2,2N,3,3N,4,5N,6	40186-70-7
176	2,2N,3,3N,4,6,6N	52663-65-7
177	2,2N,3,3N,4N,5,6	52663-70-4
178	2,2N,3,3N,5,5N,6,	52663-67-9
179	2,2N,3,3N,5,6,6N	52663-64-6
180	2,2N,3,4,4N,5,5N	35065-29-3
181	2,2N,3,4,4N,5,6	74472-47-2
182	2,2N,3,4,4N,5,6N	60145-23-5
183	2,2N,3,4,4N,5N,6	52663-69-1
184	2,2N,3,4,4N,6,6N	74472-48-3
185	2,2N,3,4,5,5N,6	52712-05-7

Table 4-2. Chemical Identity of Polychlorinated Biphenyl Congeners and Homologs *(continued)*

PCB No.[a]	Structure	CAS No.[b]
186	2,2N,3,4,5,6,6N	74472-49-4
187	2,2N,3,4N,5,5N,6	52663-68-0
188	2,2N,3,4N,5,6,6N	74487-85-7
189	2,3,3N,4,4N,5,5N	39635-31-9
190	2,3,3N,4,4N,5,6	41411-64-7
191	2,3,3N,4,4N,5N,6	74472-50-7
192	2,3,3N,4,5,5N,6	74472-51-8
193	2,3,3N,4N,5,5N,6	69782-91-8
	Octachlorobiphenyl	31472-83-0
194	2,2N,3,3N,4,4N,5,5N	35694-08-7
195	2,2N,3,3N,4,4N,5,6	52663-78-2
196	2,2N,3,3N,4,4N,5,6N	42740-50-1
197	2,2N,3,3N,4,4N,6,6N	33091-17-7
198	2,2N,3,3N,4,5,5N,6	68194-17-2
199	2,2N,3,3N,4,5,5N,6N	52663-75-9
200	2,2N,3,3N,4,5,6,6N	52663-73-7
201	2,2N,3,3N,4,5N,6,6N	40186-71-8
202	2,2N,3,3N,5,5N,6,6N	2136-99-4
203	2,2N,3,4,4N,5,5N,6	52663-76-0
204	2,2N,3,4,4N,5,6,6N	74472-52-9
205	2,3,3N,4,4N,5,5N,6	74472-53-0
	Nonachlorobiphenyl	53742-07-7
206	2,2N,3,3N,4,4N,5,5N,6	40186-72-9
207	2,2N,3,3N,4,4N,5,6,6N	52663-79-3
208	2,2N,3,3N,4,5,5N,6,6N	52663-77-1
	Decachlorobiphenyl	2051-24-3
209	2,2N,3,3N,4,4N,5,5N,6,6N	2051-24-3

[a]Ballschmiter and Zell 1980, also referred to as BZ number
[b]Erickson 1986

Table 4-3. Physical and Chemical Properties of Some Aroclors[a]

Property	Aroclor 1016	Aroclor 1221	Aroclor 1232	Aroclor 1242
Molecular weight[b]	257.9[c]	200.7[c]	232.2[c]	266.5[c]
Color	Clear	Clear	Clear	Clear
Physical state	Oil	Oil	Oil	Oil
Melting point, EC	No data	1[d]	No data	No data
Boiling point, EC	325–356	275–320	290–325	325–366
Density, g/cm^3 at 25 EC	1.37	1.18	1.26	1.38
Odor	No data	No data	No data	Mild hydrocarbon[d]
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water, mg/L	0.42 (25 EC)[e]	0.59 (24 EC)[f]	0.45 (25 EC)	0.24[c]; 0.34 (25 EC)[e] 0.10 (24 EC)[f]
Organic solvent(s)	Very soluble[g]	Very soluble[g]	Very soluble[g]	Very soluble[g]
Partition coefficients:				
Log K_{ow}[h]	5.6	4.7	5.1	5.6
Log K_{oc}	No data	No data	No data	No data
Vapor pressure, mm Hg at 25 EC	$4x10^{-4}$ [c]	$6.7x10^{-3}$ [c]	$4.06x10^{-3}$ [c]	$4.06x10^{-4}$ [c]
Henry's law constant, atm-m^3/mol at 25 EC[i]	$2.9x10^{-4}$	$3.5x10^{-3}$	No data	$5.2x10^{-4}$
Autoignition temperature	No data	No data	No data	No data
Flashpoint, EC (Cleveland open cup)	170	141–150	152–154	176–180
Flammability limits, EC	None to boiling point	176	328	None to boiling point
Conversion factors				
Air (25 EC)[j]	1 mg/m^3=0.095 ppm	1 mg/m^3=0.12 ppm	1 mg/m^3=0.105 ppm	1 mg/m^3=0.092 ppm
Explosive limits	No data	No data	No data	No data

Table 4-3. Physical and Chemical Properties of Some Aroclors[a] *(continued)*

Property	Aroclor 1254	Aroclor 1260	Aroclor 1262	Aroclor 1268
Molecular weight[b]	328[c]	357.7[c]	389	453
Color	Light yellow	Light yellow	No data	Clear[k]
Physical state	Viscous liquid	Sticky resin	No data	Viscous liquid[k]
Melting point	No data	No data	No data	No data
Boiling point, EC	365–390	385–420	390–425	435–450
Density, g/cm^3 at 25 EC	1.54	1.62	1.64	1.81
Odor	Mild hydrocarbon[d]	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water, mg/L	0.012[c]; 0.057 (24 EC)	0.0027[c];0.08 (24 EC)[f]	0.052 (24 EC)[f]	0.300 (24 EC)[f]
Organic solvent(s)	Very soluble[g]	Very soluble[g]	No data	Soluble
Partition coefficients:				
Log K_{ow}	6.5	6.8	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure, mm Hg at 25 EC	7.71×10^{-5} [c]	4.05×10^{-5} [c]	No data	No data
Henry's law constant, atm-m^3/mol at 25 EC[i]	2.0×10^{-3}	4.6×10^{-3}	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint EC (Cleveland open cup)	No data	No data	195E C	195E C

Table 4-3. Physical and Chemical Properties of Some Aroclors[a] *(continued)*

Property	Aroclor 1254	Aroclor 1260	Aroclor 1262	Aroclor 1268
Flammability limits, EC	None to boiling point	None to boiling point	None to boiling point	None to boiling point
Conversion factors, Air (25 EC)[j]	1 mg/m^3=0.075 ppm	1 mg/m^3=0.065 ppm	1 mg/m^3=0.061 ppm	1 mg/m^3=0.052 ppm
Explosive limits	No data	No data	No data	No data

[a]All information obtained from Monsanto Chemical Company 1985 and Hutzinger et al. 1974 unless otherwise noted.
[b]Average weight from Table 3-3.
[c]EPA 1979h; data on temperature not available.
[d]NIOSH 1997
[e]Paris et al. 1978
[f]Hollifield 1979
[g]EPA 1985b
[h]These log K_{ow} values represent an average value for the major components of the individual Aroclor. Experimental values for the individual components were obtained from Hansch and Leo 1985.
[i]These Henry's law constants were estimated by dividing the vapor pressure by the water solubility. The first water solubility given in this table was used for the calculation. The resulting estimated Henry's law constant is only an average for the entire mixture; the individual chlorobiphenyl isomers vary significantly from the average. Burkhard et al. (1985) estimated the following Henry's law constants ($atm\text{-}m^3/mol$) for various Aroclors at 25 EC: 1221 (2.28×10^{-4}), 1242 (3.43×10^{-4}), 1248 (4.4×10^{-4}), 1254 (2.83×10^{-4}), and 1260 (4.15×10^{-4}).
[j]These air conversion factors were calculated by using the average molecular weight and ideal gas law.
[k]Chemical Health and Safety Data; National Toxicology Program (http://ntp-server.niehs.nih.gov)

Table 4-4. Approximate Weight Percent of PCB Homologs in Some Aroclors

Homolog	Aroclor 1016[a]	Aroclor 1221[b]	Aroclor 1232[c]	Aroclor 1242[d]	Aroclor 1248[e]
$C_{12}H_9Cl$	0.70	60.06	27.55	0.75	0.07
$C_{12}H_8Cl_2$	17.53	33.38	26.83	15.04	1.55
$C_{12}H_7Cl_3$	54.67	4.22	25.64	44.91	21.27
$C_{12}H_6Cl_4$	22.07	1.15	10.58	20.16	32.77
$C_{12}H_5Cl_5$	5.07	1.23	9.39	18.85	42.92
$C_{12}H_4Cl_6$	Not detected	Not detected	0.21	0.31	1.64
$C_{12}H_3Cl_7$	Not detected	Not detected	0.03	Not detected	0.02
$C_{12}H_2Cl_8$	Not detected	Not detected	Not detected	Not detected	Not detected
$C_{12}H_1Cl_9$	Not detected	Not detected	Not detected	Not detected	Not detected
Average molecular mass	262	206	240	272	300

Empirical Formula	Aroclor 1254[f]	Aroclor 1254[g]	Aroclor 1260[d]	Aroclor 1262[h]	Aroclor 1268
$C_{12}H_9Cl$	0.02	Not detected	0.02	0.02	No data
$C_{12}H_8Cl_2$	0.09	0.24	0.08	0.27	No data
$C_{12}H_7Cl_3$	0.39	1.26	0.21	0.98	No data
$C_{12}H_6Cl_4$	4.86	10.25	0.35	0.49	No data
$C_{12}H_5Cl_5$	71.44	59.12	8.74	3.35	No data
$C_{12}H_4Cl_6$	21.97	26.76	43.35	26.43	No data
$C_{12}H_3Cl_7$	1.36	2.66	38.54	48.48	No data
$C_{12}H_2Cl_8$	Not detected	0.04	8.27	19.69	No data
$C_{12}H_1Cl_9$	0.04	0.04	0.70	1.65	No data
Average molecular mass	334	334	378	395	453

Source: Frame et al. (1996)

[a]Lot A2 Aroclor 1016
[b]Lot A1 Aroclor 1221
[c]Lot A1.5 Aroclor 1232
[d]Mean of three Lots
[e]Lot A3.5 Aroclor 1248
[f]Lot A4 Aroclor 1254 (Monsanto Lot KI-02-6024) from abnormal late production (1974–1977)
[g]Lot G4 Aroclor 1254 (GE/118-peak analytical standard)
[h]Lot A6 Aroclor 1262

Table 4-5. Polychlorinated Biphenyl Congener Compositions (in Weight Percent)[a] in Aroclors[b]

		Aroclor						
PCB No.	Chlorine positions	1016[c]	1242[d]	1248[e]	1248[f]	1254[g] "Late"	1254[h]	1260[i]
1	2	0.52	0.54	0.05	0.02	0.02	—	0.02
2	3	0.02	0.03	—	—	—	—	—
3	4	0.15	0.18	0.01	—	—	—	—
4	2,2N	3.62	3.08	0.32	0.04	0.02	0.06	0.02
5	2,3	0.17	0.14	0.00	—	—	—	—
6	2,3N	1.64	1.43	0.13	0.00	0.01	0.02	0.01
7	2,4	0.29	0.26	0.02	—	—	—	—
8	2,4N	8.29	7.05	0.81	0.26	0.05	0.13	0.04
9	2,5	0.58	0.50	0.04	—	—	—	—
10	2,6	0.23	0.20	—	—	—	—	—
11	3,3N	—	—	—	—	—	—	—
12	3,4	0.07	0.06	—	—	—	—	—
13	3,4N	0.24	0.22	0.02	—	—	—	—
14	3,5	—	—	—	—	—	—	—
15	4,4N	2.40	2.10	0.22	0.06	0.01	0.03	0.01
16	2,2N,3	3.88	3.14	1.04	0.71	0.02	0.09	0.01
17	2,2N,4	3.98	3.13	1.05	0.93	0.02	0.08	0.02
18	2,2N,5	10.86	8.53	4.29	3.29	0.08	0.25	0.05
19	2,2N,6	0.99	0.80	0.22	0.14	—	—	—
20	2,3,3N	0.88	0.72	0.14	0.08	—	—	—
21	2,3,4	NM	NM	—	—	—	—	—
22	2,3,4N	3.50	2.84	1.33	1.38	0.02	0.04	0.01
23	2,3,5	0.01	0.01	—	0.00	—	—	—
24	2,3,6	0.16	0.13	0.01	—	—	—	—
25	2,3N,4	0.72	0.59	0.11	0.04	—	—	—
26	2,3N,5	1.57	1.28	0.40	0.23	—	0.03	—
27	2,3,6	0.51	0.41	0.12	0.07	—	—	—
28	2,4,4N	8.50	6.86	3.59	5.57	0.06	0.19	0.03
29	2,4,5	0.10	0.08	0.00	0.01	—	—	—
30	2,4,6	0.00	—	—	—	—	—	—
31	2,4N,5	9.32	7.34	5.07	5.47	0.11	0.28	0.04
32	2,4N,6	2.37	1.90	0.88	0.93	0.01	0.05	0.01
33	2N,3,4	6.21	5.01	2.23	2.21	0.05	0.16	0.03

Table 4-5. Polychlorinated Biphenyl Congener Compositions (in Weight Percent)[a] in Aroclors[b] *(continued)*

		Aroclor						
PCB No.	Chlorine positions	1016[c]	1242[d]	1248[e]	1248[f]	1254[g] "Late"	1254[h]	1260[i]
34	2N,3,5	0.03	0.02	0.00	0.00	—	—	—
35	3,3N,4	0.05	0.08	0.00	—	—	—	—
36	3,3N,5	—	—	—	—	—	—	—
37	3,4,4N	1.02	2.03	0.79	0.95	0.01	0.07	0.01
38	3,4,5	—	—	—	—	—	—	—
39	3,4N,5	—	—	—	—	—	—	—
40	2,2N,3,3N	0.58	0.76	1.13	0.92	0.15	0.12	—
41	2,2N,3,4	0.76	0.68	0.77	0.75	0.02	0.01	—
42	2,2N,3,4N	1.59	1.19	1.67	1.79	0.09	0.15	0.01
43	2,2N,3,5	0.28	0.18	0.30	0.19	—	—	—
44	2,2N,3,5N	4.47	3.55	6.31	5.09	0.67	2.31	0.03
45	2,2N,3,6	1.23	0.89	1.09	0.91	0.02	0.05	—
46	2,2N,3,6N	0.49	0.36	0.47	0.39	—	—	—
47	2,2N,4,4N	1.26	0.93	1.49	2.41	0.07	0.14	—
48	2,2N,4,5	1.61	1.18	1.66	1.54	0.05	0.12	—
49	2,2N,4,5N	3.35	2.53	4.12	4.17	0.26	1.10	0.01
50	2,2N,4,6	0.01	0.00	—	—	—	—	—
51	2,2N,4,6N	0.32	0.23	0.30	0.31	—	—	—
52	2,2N,5,5N	4.63	3.53	6.93	5.58	0.83	5.38	0.24
53	2,2N,5,6N	0.95	0.71	1.05	0.88	0.04	0.12	—
54	2,2N,6,6N	0.01	0.01	—	0.01	—	—	—
55	2,3,3N,4	—	0.10	0.06	0.05	—	—	—
56	2,3,3N,4N	0.07	1.81	3.16	3.19	1.70	0.55	0.02
57	2,3,3N,5	0.01	0.02	0.02	0.02	—	—	—
58	2,3,3N,5N	—	—	—	—	—	—	—
59	2,3,3N,6	0.41	0.32	0.37	0.23	0.01	0.02	—
60	2,3,4,4N	0.04	1.18	1.85	2.67	0.95	0.18	0.04
61	2,3,4,5	—	—	—	—	—	—	—
62	2,3,4,6	—	—	—	—	—	—	—
63	2,3,4N,5	0.06	0.12	0.17	0.19	0.07	0.02	—
64	2,3,4N,6	1.87	1.70	3.01	3.32	0.36	0.59	0.01
65	2,3,5,6	—	—	—	—	—	—	—
66	2,3N,4,4N	0.39	3.39	5.84	7.22	3.56	1.01	0.02
67	2,3N,4,5	0.06	0.16	0.13	0.10	0.01	—	—

Table 4-5. Polychlorinated Biphenyl Congener Compositions (in Weight Percent)[a] in Aroclors[b] *(continued)*

		Aroclor						
PCB No.	Chlorine positions	1016[c]	1242[d]	1248[e]	1248[f]	1254[g] "Late"	1254[h]	1260[i]
68	2,3N,4,5N	—	—	—	—	—	—	—
69	2,3N,4,6	0.00	—	—	—	—	—	—
70	2,3N,4N,5	0.59	3.73	7.28	7.39	6.83	3.49	0.04
71	2,3N,4N,6	1.16	1.03	1.67	1.86	0.11	0.15	0.01
72	2,3N,5,5N	0.00	0.01	0.02	0.01	—	—	—
73	2,3N,5N,6	0.00	0.00	—	—	—	—	—
74	2,4,4N,5	0.33	1.81	3.14	4.67	2.19	0.84	0.05
75	2,4,4N,6	0.06	0.04	0.08	0.08	—	—	—
76	2N,3,4,5	—	0.08	0.13	0.13	0.03	0.02	—
77	3,3N,4,4N	—	0.31	0.41	0.52	0.20	0.03	—
78	3,3N,4,5	—	—	—	—	—	—	—
79	3,3N,4,5N	—	—	—	—	—	—	—
80	3,3N,5,5N	—	—	—	—	—	—	—
81	3,4,4N,5	—	0.01	0.01	0.02	0.00	—	—
82	2,2N,3,3N,4	—	0.26	0.81	0.62	1.53	1.11	—
83	2,2N,3,3N,5	—	0.11	0.26	0.20	0.56	0.48	0.01
84	2,2N,3,3N,6	0.05	0.41	1.26	0.91	1.58	2.32	0.11
85	2,2N,3,4,4N	—	0.31	0.98	1.14	2.49	1.28	0.01
86	2,2N,3,4,5	—	0.03	0.11	0.09	0.10	0.06	—
87	2,2N,3,4,5N	—	0.46	1.45	1.11	3.41	3.99	0.41
88	2,2N,3,4,6	—	0.00	0.02	0.02	—	—	—
89	2,2N,3,4,6N	—	0.09	0.20	0.17	0.11	0.09	—
90	2,2N,3,4N,5	—	—	NM	NM	NM	NM	—
91	2,2N,3,4N,6	0.06	0.21	0.63	0.56	0.53	0.93	0.01
92	2,2N,3,5,5N	—	0.09	0.38	0.25	0.57	1.29	0.30
93	2,2N,3,5,6	—	0.00	0.04	0.03	—	—	—
94	2,2N,3,5,6N	—	0.01	0.03	0.02	0.01	0.02	—
95	2,2N,3,5N,6	0.31	0.61	1.96	1.43	1.84	6.25	2.45
96	2,2N,3,6,6N	0.04	0.03	0.08	0.06	0.01	0.04	—
97	2,2N,3N,4,5	—	0.38	1.22	0.97	2.78	2.62	0.09
98	2,2N,3N,4,6	—	—	—	—	—	—	—
99	2,2N,3N,4N,5	0.01	0.46	1.47	1.81	4.53	3.02	0.04
100	2,2N,4N,4N,6	—	—	—	—	—	—	—
101	2,2N,4,5,5N	0.04	0.69	2.22	1.89	5.49	8.02	3.13

Table 4-5. Polychlorinated Biphenyl Congener Compositions (in Weight Percent)[a] in Aroclors[b] *(continued)*

		Aroclor						
PCB No.	Chlorine positions	1016[c]	1242[d]	1248[e]	1248[f]	1254[g] "Late"	1254[h]	1260[i]
102	2,2N,4,5,6N	0.04	0.07	0.19	0.17	0.09	0.15	—
103	2,2N,4,5N,6	—	—	0.02	0.01	—	0.03	—
104	2,2N,4,6,6N	—	—	—	—	—	—	—
105	2,3,3N,4,4N	0.00	0.47	1.60	1.45	7.37	2.99	0.22
106	2,3,3N,4,5	—	—	—	—	—	—	—
107	2,3,3N,4N,5	—	—	—	—	—	—	—
108	2,3,3N,4,5N	—	—	—	—	—	—	—
109	2,3,3N,4,6	—	0.06	0.18	0.13	0.78	0.37	0.01
110	2,3,3N,4N,6	—	0.83	2.97	2.55	8.42	9.29	1.33
111	2,3,3N,5,5N	—	—	—	—	—	—	—
112	2,3,3N,5,6	—	—	—	—	—	—	—
113	2,3,3N,5N,6	—	—	—	—	0.01	—	—
114	2,3,4,4N,5	—	0.04	0.12	0.12	0.50	0.18	—
115	2,3,4,4N,6	—	0.04	0.11	0.11	0.37	0.20	—
116	2,3,4,5,6	—	—	—	—	—	—	—
117	2,3,4N,5,6	—	0.03	0.09	0.10	0.19	0.23	—
118	2,3N,4,4N,5	—	0.66	2.29	2.35	13.59	7.35	0.48
119	2,3N,4,4N,6	—	—	0.06	0.06	0.12	0.08	—
120	2,3N,4,5,5N	—	—	—	—	—	—	—
121	2,3N,4,5N,6	—	—	—	—	—	—	—
122	2N,3,3N,4,5	—	0.01	0.06	0.05	0.25	0.10	—
123	2N,3,4,4N,5	—	0.03	0.07	0.08	0.32	0.15	—
124	2N,3,4,5,5N	—	0.03	0.10	0.07	0.47	0.29	0.01
125	2N,3,4,5,6N	—	0.02	0.04	0.03	0.03	0.02	—
126	3,3N,4,4N,5	—	—	0.00	0.00	0.02	0.00	—
127	3,3N,4,5,5N	—	—	—	—	—	—	—
128	2,2N,3,3N,4,4N	—	0.02	0.12	0.08	1.71	1.42	0.53
129	2,2N,3,3N,4,5	—	—	0.02		0.39	0.38	0.14
130	2,2N,3,3N,4,5N	—	—	0.04	0.01	0.50	0.60	0.22
131	2,2N,3,3N,4,6	—	—	—	—	0.14	0.19	0.07
132	2,2N,3,3N,4,6N	—	0.04	0.15	0.14	1.50	2.29	2.90
133	2,2N,3,3N,5,5N	—	—	—	—	—	0.11	0.07
134	2,2N,3,3N,5,6	—	—	—	0.01	0.20	0.37	0.34
135	2,2N,3,3N,5,6N	—	—	0.04	0.04	0.28	0.61	1.08

Table 4-5. Polychlorinated Biphenyl Congener Compositions (in Weight Percent)[a] in Aroclors[b] *(continued)*

		Aroclor						
PCB No.	Chlorine positions	1016[c]	1242[d]	1248[e]	1248[f]	1254[g] "Late"	1254[h]	1260[i]
136	2,2N,3,3N,6,6N	—	—	0.05	0.06	0.24	0.70	1.46
137	2,2N,3,4,4N,5	—	—	0.03	0.02	0.52	0.42	0.02
138	2,2N,3,4,4N,5N	—	0.10	0.38	0.41	5.95	5.80	6.54
139	2,2N,3,4,4N,6	—	—	—	—	0.14	0.15	—
140	2,2N,3,4,4N,6N	—	—	—	—	—	—	—
141	2,2N,3,4,5,5N	—	0.01	0.07	0.09	0.69	0.98	2.62
142	2,2N,3,4,5,6	—	—	—	—	—	—	—
143	2,2N,3,4,5,6N	—	—	—	—	—	—	—
144	2,2N,3,4,5N,6	—	—	—	0.01	0.12	0.24	0.61
145	2,2N,3,4N,6,6N	—	—	—	—	—	—	—
146	2,2N,3,4N,5,5N	—	—	0.04	0.05	0.45	0.67	1.15
147	2,2N,3,4N,5,6	—	—	—	—	0.02	0.10	—
148	2,2N,3,4N,5,6N	—	—	—	—	—	—	—
149	2,2N,3,4N,5N,6	—	0.06	0.24	0.33	1.82	3.65	8.75
150	2,2N,3,4N,5,6N	—	—	—	—	—	—	—
151	2,2N,3,5,5N,6	—	—	0.04	0.08	0.22	0.69	3.04
152	2,2N,3,5,6,6N	—	—	—	—	—	—	—
153	2,2N,4,4N,5,5N	—	0.06	0.23	0.43	3.29	3.77	9.39
154	2,2N,4,4N,5,6N	—	—	—	—	0.02	0.04	—
155	2,2N,4,4N,6,6N	—	—	—	—	—	—	—
156	2,3,3N,4,4N,5	—	0.01	0.06	0.04	1.13	0.82	0.52
157	2,3,3N,4,4N,5N	—	—	0.01	0.00	0.30	0.19	0.02
158	2,3,3N,4,4N,6	—	0.01	0.04	0.04	0.90	0.81	0.58
159	2,3,3N,4,5,5N	—	—	—	—	—	—	—
160	2,3,3N,4,5,6	—	—	—	—	—	—	—
161	2,3,3N,4,5N,6	—	—	—	—	—	—	—
162	2,3,3N,4N,5,5N	—	—	—	—	—	—	—
163	2,3,3N,4N,5,6	—	0.01	0.06	0.08	0.70	1.03	2.42
164	2,3,3N,4N,5N,6	—	—	0.02	0.03	0.31	0.40	0.69
165	2,3,3N,5,5N,6	—	—	—	—	—	—	—
166	2,3,4,4N,5,6	—	—	—	—	0.05	0.05	—
167	2,3N,4,4N,5,5N	—	—	0.01	0.01	0.35	0.27	0.19
168	2,3N,4,4N,5N,6	—	—	—	—	—	—	—
169	3,3N,4,4N,5,5N	—	—	—	—	—	—	—

Table 4-5. Polychlorinated Biphenyl Congener Compositions (in Weight Percent)[a] in Aroclors[b] *(continued)*

		Aroclor						
PCB No.	Chlorine positions	1016[c]	1242[d]	1248[e]	1248[f]	1254[g] "Late"	1254[h]	1260[i]
170	2,2N,3,3N,4,4N,5	—	—	—	0.08	0.35	0.52	4.11
171	2,2N,3,3N,4,4N,6	—	—	—	—	0.08	0.14	1.11
172	2,2N,3,3N,4,5,5N	—	—	—	—	0.03	0.07	0.70
173	2,2N,3,3N,4,5,6	—	—	—	—	—	—	0.10
174	2,2N,3,3N,4,5,6N	—	—	—	0.08	0.14	0.34	4.96
175	2,2N,3,3N,4,5N,6	—	—	—	—	—	—	0.17
176	2,2N,3,3N,4,6,6N	—	—	—	—	0.01	0.04	0.59
177	2,2N,3,3N,4N,5,6	—	—	—	0.03	0.08	0.20	2.57
178	2,2N,3,3N,5,5N,6,	—	—	—	—	—	0.03	0.83
179	2,2N,3,3N,5,6,6N	—	—	—	0.02	0.02	0.10	2.03
180	2,2N,3,4,4N,5,5N	—	—	0.02	0.21	0.42	0.67	11.38
181	2,2N,3,4,4N,5,6	—	—	—	—	—	—	0.01
182	2,2N,3,4,4N,5,6N	—	—	—	—	—	—	—
183	2,2N,3,4,4N,5N,6	—	—	—	0.06	0.09	0.18	2.41
184	2,2N,3,4,4N,6,6N	—	—	—	—	—	—	—
185	2,2N,3,4,5,5N,6	—	—	—	—	—	—	0.55
186	2,2N,3,4,5,6,6N	—	—	—	—	—	—	—
187	2,2N,3,4N,5,5N,6	—	—	—	0.09	0.09	0.25	5.40
188	2,2N,3,4N,5,6,6N	—	—	—	—	—	—	—
189	2,3,3N,4,4N,5,5N	—	—	—	—	0.01	0.01	0.10
190	2,3,3N,4,4N,5,6	—	—	—	—	0.05	0.07	0.82
191	2,3,3N,4,4N,5N,6	—	—	—	—	—	—	0.17
192	2,3,3N,4,5,5N,6	—	—	—	—	—	—	—
193	2,3,3N,4N,5,5N,6	—	—	—	—	—	0.03	0.53
194	2,2N,3,3N,4,4N,5,5N	—	—	—	—	—	0.01	2.07
195	2,2N,3,3N,4,4N,5,6	—	—	—	—	—	—	0.84
196	2,2N,3,3N,4,4N,5,6N	—	—	—	—	—	—	1.09
197	2,2N,3,3N,4,4N,6,6N	—	—	—	—	—	—	0.07
198	2,2N,3,3N,4,5,5N,6	—	—	—	—	—	—	0.10
199	2,2N,3,3N,4,5,5N,6N	—	—	—	—	—	0.01	1.78
200	2,2N,3,3N,4,5,6,6N	—	—	—	—	—	—	0.25
201	2,2N,3,3N,4,5N,6,6N	—	—	—	—	—	—	0.24
202	2,2N,3,3N,5,5N,6,6N	—	—	—	—	—	—	0.33
203	2,2N,3,4,4N,5,5N,6	—	—	—	—	—	0.02	1.40

Table 4-5. Polychlorinated Biphenyl Congener Compositions (in Weight Percent)[a] in Aroclors[b] *(continued)*

		Aroclor						
PCB No.	Chlorine positions	1016[c]	1242[d]	1248[e]	1248[f]	1254[g] "Late"	1254[h]	1260[i]
204	2,2N,3,4,4N,5,6,6N	—	—	—	—	—	—	—
205	2,3,3N,4,4N,5,5N,6	—	—	—	—	—	—	0.10
206	2,2N,3,3N,4,4N,5,5N,6	—	—	—	—	0.03	0.03	0.53
207	2,2N,3,3N,4,4N,5,6,6N	—	—	—	—	—	—	0.05
208	2,2N,3,3N,4,5,5N,6,6N	—	—	—	—	0.01	0.01	0.13
209	2,2N,3,3N,4,4N,5,5N,6,6N	—	—	—	—	—	—	NM
Sum of weight percents =		100.0	100.0	100.2	100.2	100.2	100.4	100.3

[a]Weight percent values in table are biased high with respect to mole percent values (not calculated).
[b]Source: Frame et al. (1996)
[c]Lot A2 Aroclor 1016
[d]Mean of three Lots of Aroclor 1242
[e]Lot A3.5 Aroclor 1248
[f]Lot G3.5 Aroclor 1248
[g]Lot A4 Aroclor 1254 (Monsanto Lot KI-02-6024) from abnormal late production (1974–1977)
[h]Lot G4 Aroclor 1254 (GE/118-peak analytical standard)
[i]Mean of three Lots of Aroclor 1260

NM = congener not measured, but present at trace level.

increased levels of the high TEF (i.e., 2,3,7,8-tetrachlorodibenzo-*p*-dioxin ("dioxin") Equivalency Factor; "T" often defined as "toxic") chlorobiphenyls, were produced from 1974 to 1977 (see Section 5.1).

The pyrolysis of technical-grade PCB mixtures produces several PCDFs (Rappe et al. 1979; Schecter and Charles 1991). PCDFs are also produced during the commercial production and handling of PCBs. The amount of PCDFs formed depends upon the manufacturing conditions. The concentrations of PCDF impurities in various commercial Aroclors are shown in Table 4-6. The impurities 2,3,7,8-tetrachloro-dibenzofuran and 2,3,4,7,8-pentachlorodibenzofuran were found at concentrations of 0.33 and 0.83 ppm, respectively, in Aroclor 1248; and at 0.11 and 0.12 ppm, respectively, in Aroclor 1254 (Van den Berg et al. 1985). Concentrations of PCDFs in commercial PCB mixtures including Clophen A-60, Phenoclor DP-6, and Kanechlor 400 have been reported (De Voogt and Brinkman 1989).

Physical properties such as solubility, vapor pressure, and Henry's law constant have been reported for individual congeners (Dunnivant and Elzerman 1988; Dunnivant et al. 1992; Falconer and Bidleman 1994; Murphy et al. 1987; Sabljic and Güsten 1989). Physical and chemical properties for several PCB congeners are presented in Table 4-7 (Bidelman 1984; Dunnivant et al. 1992; Erikson 1986; Hansch and Leo 1979; Hutsinger et al. 1974; Mackay et al. 1992; Murray and Andren 1991; Yalkowsky et al. 1983). Experimentally determined log K_{ow} values for 19 congeners and an estimation method for the determination of log K_{ow} values of other PCB congeners are also available (Sabljic et al. 1993). The congeners reported are important due to their toxicity or because they occur in higher concentrations in the environment.

Table 4-6. Concentrations of Chlorinated Dibenzofurans (CDFs) in Commercial Polychlorinated Biphenyl Mixtures[a]

PCB	Tetra-CDF	Penta-CDF	Hexa-CDF	Total (PCDFs)[b]
Aroclor 1016 (1977)	Not detected	Not detected	Not detected	–
Aroclor 1016	Not detected	Not detected	Not detected	–
Aroclor 1242	0.07	0.03	0.003	0.15
Aroclor 1242	0.07	0.03	0.003	0.15
Aroclor 1242	2.3	2.2	Not detected	4.5
Aroclor 1254 (1969)	0.1	0.2	1.4	1.7
Aroclor 1254 (1970)	0.2	0.4	0.9	1.5
Aroclor 1254	0.02	0.2	0.4–0.6	0.8
Aroclor 1254	0.1	3.6	1.9	5.6
Aroclor 1260 (1969)	0.1	3.6	1.9	5.6
Aroclor 1260 (Lot AK3)	0.2	0.3	0.3	0.8
Aroclor 1260	0.3	1.0	1.1	3.8[b]
Aroclor 1260	0.8	0.9	0.5	2.2
Clopen A-60	1.4	5.0	2.2	8.6
Phenoclor DP-6	0.7	10.0	2.9	13.6
Kanechlor 400	–	–	–	. 20.0

Source: Adapted from de Voogt and Brinkman 1989

[a]in μg/g
[b]Total includes quantities of tri-CDF and hepta-CDF isomers that were analyzed.

CDF = chlorodibenzofuran; PCDFs = polychlorinated dibenzofurans

Table 4-7. Physical and Chemical Properties of Several Congeners of Polychlorinated Biphenyls

Property	PCB 77	PCB 138	PCB 153	PCB 169	PCB 180
Molecular weight	291.98[a]	360.9[b]	360.88[b]	360.86[a]	395.32[b]
Molecular formula	$C_{12}H_6Cl_4$[b]	$C_{12}H_4Cl_6$[b]	$C_{12}H_4Cl_6$[b]	$C_{12}H_4Cl_6$[b]	$C_{12}H_3Cl_7$[b]
Melting point EC	173[c]	78.5–80[c]	103–104[c]	201–202[c]	109–110[b]
Boiling point EC	360 (calc.)[b]	400 (calc.)[b]	No data	No data	240–280 (20 mmHg)[b]
Density g/cm^3 at 25 EC	1.2024 (20 EC)[b]	No data	No data	No data	No data
Odor	No data	No data	No data	No data	No data
Solubility:					
Water mg/L	0.175 ppm[c]; 0.00055[e]	0.0159–0.0159 (calc.)[b]	0.00091 ppm[d]; 0.00086[e]	0.000036–0.01230 (calc.)[b]	0.00031–0.00656 (calc.)[b]; 0.00023[e]
Organic solvents	–	–	–	–	–
Partition coefficients:					
Log K_{ow}	6.04–6.63[b]	6.50–7.44 (calc.)[b]	8.35[e]; 6.72[b]	7.408[b]	6.70–7.21 (calc.)[b]
Log K_{oc}	4.41–5.75[b]	5.21–7.3[b]	4.75–7.68[b]	6.60[b]	5.78–6.9[b]
Vapor pressure mm Hg at 25 EC	4.4×10^{-7} [d]	4.0×10^{-6} [f]	3.80×10^{-7} [f] 9.0×10^{-7} [d]	4.02×10^{-7} [b]	–
Henry's law constant atm-m^3/mol at 25 EC	0.43×10^{-4} [g] 0.94×10^{-4} [i] 0.83×10^{-4} [e]	1.07×10^{-4} [h] 0.21×10^{-4} [b]	2.78 (10^4)[g] 1.32 (10^4)[i] 1.31 (10^4)[e]	0.15×10^{-4} [b] 0.59×10^{-4} [b]	1.07×10^{-4} [e]
Explosive limits	No data	No data	No data	No data	No data

[a]HSDB 2000
[b]Yalkowsky et al. 1983
[c]Hutsinger et al. 1974
[d]Mackay et al. 1992
[e]Dunnivant et al. 1992
[f]Erikson 1986
[g]Hansch and Leo 1995
[h]Bidelman 1984
[i]Murray and Andren 1991

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Prior to the public's outcry concerning the apparent link between PCBs and widespread environmental problems and the discovery of their detrimental health effects, PCBs were produced commercially in the United States from 1929 until 1977. Marketed worldwide under trade names such as Aroclor, Askarel, and Therminol, the annual U.S. production peaked in 1970 with a total production volume of 85 million pounds (39 million kg) of Aroclors. Between 1957 and 1971, 12 different types of Aroclors, with chlorine contents ranging from 21 to 68% were produced in the United States. The manufacturing process for Aroclors involved the chlorination of biphenyl with anhydrous chlorine in the presence of a catalyst, such as iron filings or ferric chloride. The degree of chlorination, which determines the nature of the Aroclor, was controlled by the chlorine-contact time (range, 12–36 hours) in the reactor. Late production Aroclor 1254 (Aroclor 1254 "Late") was made by a two-stage chlorination procedure from 1974 to 1977. In the first stage, biphenyl was chlorinated to 42% chlorine content by weight as for Aroclor 1242 production. This was then fractionated to give a distillate that was sold as Aroclor 1016 and a residue that would have contained mostly the mono-*ortho* tetrachlorobiphenyls and higher homologs. In the second stage, this residue, which contained about 49% chlorine, was further chlorinated to 54% chlorine by weight, resulting in an Aroclor 1254 lot (Monsanto Lot KI-02-6024) with greatly increased levels of the high TEF (i.e., 2,3,7,8-tetrachlorodibenzo-*p*-dioxin ("dioxin") Equivalency Factor; "T" often defined as "toxic") chlorobiphenyls. While production records suggest that Aroclor 1254 "Late" represented <1% of the total Aroclor 1254 production, the availability of this lot during the final years of production resulted in the disproportionate use of Aroclor 1254 "Late" by standards suppliers and researchers into Aroclor 1254 toxicity (Brinkman et al. 1995; Durfee 1976; Frame 1999; IARC 1978).

During production, Aroclor mixtures were contaminated by small amounts of polychlorinated dibenzofurans (PCDFs) as impurities. Although PCDFs are formed during the pyrolysis of PCBs, in the absence of fire, PCDF levels do not appear to increase during the normal use of PCBs in electrical equipment. PCDFs have their own toxicological properties, which have been summarized in ATSDR (1994). The concentration levels for tetra-, penta-, hexa-, and total PCDFs found in commercial PCB mixtures are shown in Table 4-6 (de Voogt and Brinkman 1989).

Approximately 99% of the PCBs used by U.S. industry were produced by the Monsanto Chemical Company in Sauget, Illinois, until production was stopped in August 1977. Prior to 1971, the Monsanto

Chemical Company produced Aroclors 1221, 1232, 1242, 1248, 1254, 1260, 1262, and 1268; however, in 1971, the company voluntarily restricted the uses of PCBs and subsequently produced only Aroclor 1016, 1242, 1254, and small quantities of Aroclor 1221. In 1974, the Monsanto Chemical Company produced slightly more than 40 million pounds (18 million kg) of Aroclor mixtures. Of the total volume of Aroclors sold in the United States for that year, the percentages of the market for each of the Aroclors were: Aroclor 1016, 64%; Aroclor 1242, 17.9%; Aroclor 1254, 17.9%; and Aroclor 1221, 0.1%. The estimated, cumulative production and consumption volumes (in millions of pounds) of PCBs in the United States from 1930 to 1975 were: total production, 1,400 (635 million kg); imports, 3 (1.4 million kg); domestic sales, 1,253 (568 million kg); and exports, 150 (68 million kg). Section 5.3 provides information on amounts estimated for specific locations, as well as estimates of intermedia transfers of PCBs (Durfee 1976; EPA 1976a; Hatton 1979; IARC 1978; Kimbrough 1987).

In 1976, the U.S. Congress charged EPA with regulating the manufacture, processing, distribution in commerce, and use of PCBs. Currently regulated pursuant to the Toxic Substances Control Act (TSCA) and the Resource Conservation and Recovery Act (RCRA), the first set of effluent standards for PCBs was issued by EPA in 1977; manufacturing and importing limitations regarding PCBs were issued in 1979. After subsequent amendments, the regulations stipulate that the production of PCBs in the United States is generally banned, the use of PCB-containing materials still in service is restricted, the discharge of PCB-containing effluents is prohibited, the disposal of materials contaminated by PCBs is regulated, and the import or export of PCBs is only permitted through an exemption granted from EPA (EPA 1977b, 1979a, 1979f, 1979g, 1988c, 1988e, 1998a).

5.2 IMPORT/EXPORT

Currently, the United States neither imports nor exports PCBs. Section 6(e)(3)(A) of TSCA (Pub. L. 94-969, 90 stat. 2003, 15 USC 2601 et. seq.) prohibited all manufacture and importation of PCBs after January 1, 1979. On January 2, 1979, however, EPA announced that companies that had filed petitions for exemptions from the PCB manufacturing/importation ban could continue manufacturing or import activity until EPA acted on the application petition. As of July 7, 1997, the U.S. Court of Appeals for the Ninth Circuit overturned the Import for Disposal Rule. EPA can now only allow imports of PCBs by issuing exemptions to importers via the petition process under Section 6(e) of TSCA. See the June 29, 1998 Federal Register for further discussion of EPA's PCB export and import regulations (EPA 1979a, 1998a).

In 1973 and 1974, the United States imported PCBs mainly from Italy as decachlorobiphenyl (Fenclor), and France (Phenoclor) (Durfee 1976). It is estimated that 180,000 kg (approximately 400,000 pounds) of this compound were imported in 1974 (IARC 1978). The volume of PCBs imported through principal U.S. custom districts from unspecified countries decreased from 132,000 kg (291,000 pounds) in 1976 (IARC 1978) and 280,867 pounds (127,400 kg) in 1977 to only 11,000 pounds (5,000 kg) in 1981 (USITC 1978, 1979, 1980, 1982). The Monsanto Chemical Company exported 5.4 million pounds (2.45 million kg) of Aroclors 1016 and 1242 to unspecified countries in 1974 (Durfee 1976).

5.3 USE

Prior to 1974, PCBs were used both for nominally closed applications (e.g., capacitor and transformers, and heat transfer and hydraulic fluids) and in open-end applications (e.g., flame retardants, inks, adhesives, microencapsulation of dyes for carbonless duplicating paper, paints, pesticide extenders, plasticizers, polyolefin catalyst carriers, slide-mounting mediums for microscopes, surface coatings, wire insulators, and metal coatings) (Durfee 1976; EPA 1976a, 1988c; IARC 1978; Orris et al. 1986; Safe 1984; Welsh 1995). Table 5-1 summarizes the former uses of the various Aroclors. Currently, under 40 CFR 761.80 (June 29, 1998), individual petitioners are granted 1-year exemptions to manufacture or import PCB for use solely in the manufacture or importer's own research for the development of PCB disposal technologies. Also under 40 CFR 761.30 (June 29, 1998), individual petitioners are granted exemptions for the use of PCBs as a mounting medium in microscopy, as an immersion oil in low fluorescence microscopy, and as an optical liquid, as well as for analytical samples and research and development use (EPA 1998a).

Except for the approximate 400,000 pounds (180,000 kg) of decachlorobiphenyl imported from Italy and France used as filler for investment casting waxes (IARC 1978), most domestic use of PCBs was restricted to nominally closed applications by 1974 (IARC 1978). The production of capacitors and transformers involved filling them with Aroclors through a small hole in the unit and then sealing the hole. While smaller capacitors contained smaller amounts, the production of large capacitors generally required at least 2–3 pounds (1 kg) of Aroclors; many times that amount was required to produce the transformers. By 1976, only 5% of the transformers produced in the United States were filled with PCBs, accounting for 30% of the Monsanto Chemical Company's domestic sales; however, 95% of the capacitors produced in the United States were filled with PCBs, accounting for 70% of the company's domestic sales (IARC 1978). As of January 1979, Aroclors were no longer used in the production of capacitors and transformers. Nevertheless, the life expectancy of transformers containing PCBs is greater

Table 5-1. Summary of Former End Uses for Various Aroclors

End use	Aroclor								
	1016	1221	1232	1242	1248	1254	1260	1262	1268
Capacitors	•	•				•			
Transformers				•		•	•		
Heat transfer				•					
Hydraulics/lubricants									
Hydraulic fluids			•	•	•	•	•		
Vacuum pumps					•	•			
Gas-transmission turbines		•		•					
Plasticizers:									
Rubbers		•	•	•	•	•			•
Synthetic resins					•	•	•	•	•
Carbonless paper				•					
Miscellaneous:									
Adhesives		•	•	•	•	•			
Wax extenders				•		•			•
Dedusting agents						•	•		
Inks						•			
Cutting oils						•			
Pesticide extenders						•			
Sealants and caulking compounds						•			

Source: IARC 1979

than 30 years, and the life expectancy of capacitors ranges from 10 to 20 years, depending on the electrical application (IARC 1978). In 1981, an estimated 131,200 transformers containing PCBs were in service in the United States, representing approximately 1% of all operational transformers. Currently, the EPA maintains an up-to-date database containing the location and amount of PCBs in transformers across the United States (EPA 1999b).

5.4 DISPOSAL

According to the Toxics Release Inventory (TRI), >99% of the total PCB wastes produced in the United States in 1998 were released on-site to land. About 3,742,000 pounds (1,698,000 kg) of PCB wastes were released to land in 1998 (see Table 5-2) (TRI98 2000).

The concentration of PCBs in the environment in which some action should be considered (i.e., treatment or containment) will depend primarily on the exposure estimate determined during the baseline risk assessment for the site and on EPA's 1996 cancer slope factor, reference dose (RfD), and exposure-specific values (EPA 1990e, 1996c).

PCBs were included among the contaminants of concern at 500 of the 1,598 Superfund sites (29%) as of May 11, 2000 which were listed on the Final National Priorities List (HazDat 2000). Remedial actions taken at Superfund sites must meet the mandates of the National Contingency Plan (NCP), which implements the requirements of the Comprehensive Environmental Response Compensation and Liability Act (CERCLA) (EPA 1990e). CERCLA Section 121 provides specific statutory requirements (cleanup standards) for remediation that must be addressed when evaluating proposed remedial alternatives (U.S. Congress 1980). In order to ensure that the statutory requirements are met, the various proposed alternatives are evaluated using nine evaluation criteria that reflect these statutory requirements (U.S. Congress 1980; EPA 1988j, 1989d, 1990e). The nine criteria are categorized into three groups: threshold criteria, primary balancing criteria, and modifying criteria. The threshold criteria include the requirements to provide overall protection of human health and the environment, and to comply with applicable or relevant and appropriate (ARARs) federal and state laws (EPA 1988j, 1989d). The primary balancing criteria include provisions for evaluating long-term effectiveness and permanence; the reduction of contaminant toxicity, mobility, or volume; and short-term effectiveness for adverse health effects from human exposure, implementability, and cost. The modifying criteria include state acceptance and community acceptance (EPA 1988j, 1989d). While the primary balancing criteria are used to weigh major tradeoffs among the proposed alternatives, and the modifying criteria are not taken into account

Table 5-2. Facilities that Manufacture or Process Polychlorinated Biphenyls

Facility	Location	Range of maximum amounts on-site in pounds	Activities and uses
Norcross Safety Prods. L.L.C.	Rock Island, Illinois	100–999	Produce, by-product
Unison Transformer Services	Henderson, Kentucky	1,000–9,999	Ancillary/other use
Noranda Aluminum Inc.	New Madrid, Missouri	10,000–99,999	Ancillary/other use
Special Metals Corp.	New Hartford, New York	10,000–99,999	Ancillary/other use
Northwest Aluminum Co., Inc.	The Dalles, Oregon	10,000–99,999	Ancillary/other use

Source: TRI96 1998

until after public comments are received on the proposed remediation plans, an alternative must satisfy the threshold criteria in order to be eligible for selection (EPA 1988j, 1989d).

On April 18, 1978, EPA began to regulate the storage and disposal of PCBs. These regulations specified incineration as the only acceptable method of PCB disposal unless, by reason of the inability to dispose of the waste or contaminated materials in this manner, clearance was obtained from EPA to dispose of the materials in another way. Although in March 1983 EPA issued a procedural amendment to the PCB rule to enable new disposal technologies to receive approval on a nationwide basis, EPA's current PCB disposal rules generally require that PCBs at concentrations of $50 ppm be disposed of in an incinerator approved for that use (EPA 1998u). The recommended combustion criteria for the disposal of liquid PCB wastes by incineration is a 2-second dwell time at 1,200 EC (±100 EC) and 3% excess oxygen in the stack gas; or a 1.5-second dwell time at 1,600 EC (±100 EC) and 2% excess oxygen (EPA 1979e). Since incineration of PCBs will produce chlorine-containing products (e.g., hydrochloric acid), it is required that water scrubbers be used to remove these products before releasing the emissions into the atmosphere (EPA 1998u). Under TSCA (Toxic Substance and Control Act), the combustion efficiency of the incinerator must be 99.9% (EPA 1998u). The general acceptance of incineration as a means of disposal for PCB-contaminated materials has declined because of concerns about incomplete incineration and the possible formation of highly toxic dioxins and dibenzofurans if the combustion temperature is not held sufficiently high (Arbon et al. 1994; Chuang et al. 1995). An evaluation of the applicability of oxy-fuel technology to waste incineration conducted by Baukal et al. (1994) reported favorable results. The test results indicated that for simulated soils containing 1% PCBs and oil containing up to 40% PCBs, more than 99.9999% of the PCBs were destroyed. In controlled experiments conducted by Chuang et al. (1995), significant dechlorination was noted at 300 EC and a fully dechlorinated product occurred at 400 EC when heating a mixture of PCBs (Aroclor 1221 and 1254) and iron metal powder (Fe^0) in a muffle furnace.

The regulatory requirements implemented pursuant to TSCA also provide that chemical waste landfills and high-efficiency boilers meeting specified operating requirements are appropriate disposal facilities for mineral oil dielectric fluid from PCB-contaminated electrical equipment containing PCBs at concentrations $50 ppm, but <500 ppm. Under the land disposal restrictions promulgated at 40 CFR part 268 pursuant to RCRA (Resource Conservation & Recovery Act), PCBs are regulated as halogenated organic compounds (HOCs). Types of waste for which land disposal is prohibited include liquid hazardous wastes containing PCBs at concentrations of $50 ppm; nonliquid hazardous waste containing HOCs in total concentration greater than or equal to 1,000 mg/kg (ppm); and liquid HOC-containing

waste that are primarily water and contain HOCs in the concentration range 1,000–10,000 mg/L (ppm) HOCs. The treatment standards expressed as specified technologies (e.g., chemical reduction, carbon adsorption, biodegradation) require incineration of liquid hazardous waste containing PCBs at a concentration of 500 ppm or greater, and HOC-containing waste prohibited from land disposal (EPA 1986i, 1987c, 1987d, 1998u).

Although not widely adopted, other methods proposed for the destruction of PCBs have included wet air oxidation, biodegradation, metal-promoted dehalogenation, and electrolytic reduction (Chuang et al. 1995). Timberlake and Garbaciak (1995) detailed the results of a series of bench-scale tests applying various technologies (thermal desorption, solvent extraction, wet air oxidation, and an incineration process known as Anaerobic Thermal Process [ATP]) to PCB-contaminated sediment. The thermal desorption and solvent extraction technologies, though not designed to destroy the contaminants, indirectly separate the contaminants from a solid matrix and concentrate them into smaller volumes of treatable oily residues. The removal efficiencies of these technologies when applied to three of the river sediments tested ranged from 96 to 99%. The wet air oxidation process, which uses elevated temperatures and pressure to oxidize the organic constituents, was not very effective in destroying PCBs; it achieved only a 34% removal efficiency (Timberlake and Garbaciak 1995). Zhang and Rusling (1995) investigated electrochemical catalytic dechlorination as a method for decontaminating soils. The study achieved a 94% dechlorination level using a lead cathode and a micro emulsion of didodecylmethyl-ammonium bromide, dodecane, and water for soils containing 6.5% organic matter and contaminated with 14% Aroclor 1260 (84 mg of PCB).

A chemical destruction method that has been used for the treatment of PCBs in contaminated dielectric liquids or soil is based on the reaction of a polyethylene glycol/potassium hydroxide mixture with PCBs (De Filippis et al. 1997). This method can be used successfully for the destruction of higher chlorinated PCBs with an efficiency of >99%, but was found to be unsuitable for the treatment of di- and trichlorobiphenyls due to low destruction efficiencies (Sabata et al. 1993). Irradiation of PCBs in isooctane and transformer oil by γ-radiation resulted in degradation of PCBs to less chlorinated PCBs and PCB-solvent adducts (Arbon et al. 1996). Supercritical fluid technology has shown promise as a method for extraction of PCBs from soils, coupled with supercritical water oxidation of the extracted PCBs (Tavlarides 1993, 1998a). Hofelt and Shea (1997) demonstrated the use of semipermeable membrane devices to accumulate PCBs from New Bedford Harbor, Massachusetts water. Another method showing some promise for the treatment of PCBs in water, soil, and sediment is titanium dioxide-catalyzed photodecomposition with sunlight (Hong et al. 1998; Huang et al. 1996; Zhang and Rusling 1995; Zhang

et al. 1993). PCBs in used lubricating oils were destroyed and petroleum products, including lubricating oils, were produced with catalytic vacuum distillation/hydrotreatment technology (Brinkman et al. 1995). Treatment with metallic sodium has been suggested for PCB wastes because it yields low molecular weight polypropylene and sodium chloride which are less undesirable than products from incineration (IRPTC 1985). Bioremediation of PCB-contaminated soil has been suggested using a combination of anaerobic and aerobic treatments. Aerobic treatments would metabolize the lower chlorinated homologs (e.g., biphenyl; mono- and di-ortho chloro-substituted CBs) produced in soil from anaerobic dechlorination processes (Tiedje et al. 1993; see Section 6.3.2.3).

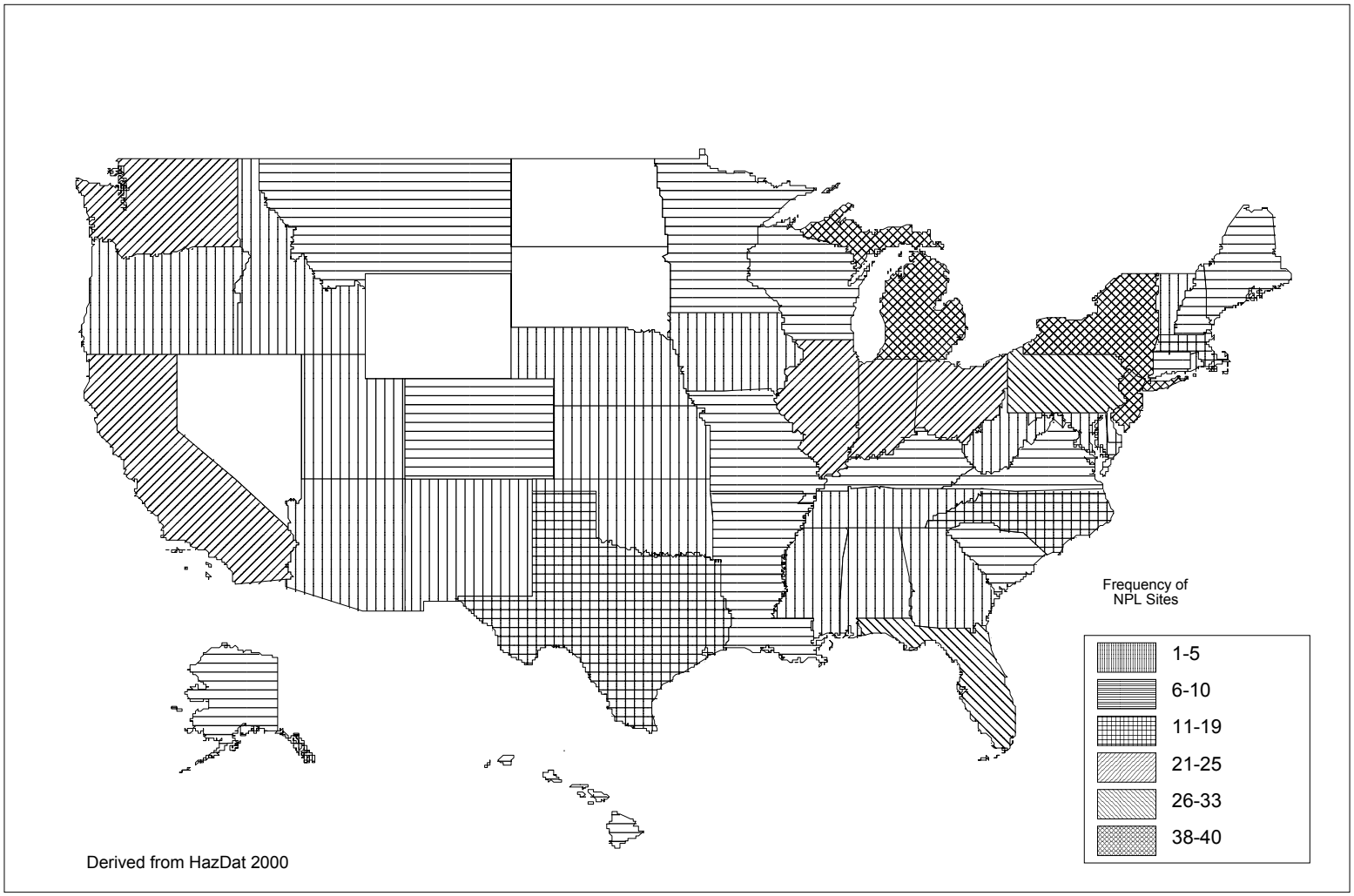
6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Polychlorinated biphenyls (PCBs) have been identified in at least 500 of the 1,598 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2000). However, the number of sites evaluated for PCBs is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 499 are located within the United States and 1 is located in the U.S. Territory of Guam (not shown).

PCBs have been released to the environment solely by human activity. Aroclors are no longer produced in the United States, except under exemption (see Section 5.3), and are no longer used in the manufacture of new products. Because PCBs are no longer manufactured or imported in large quantities, significant releases of newly manufactured or imported materials to the environment do not occur. Rather, PCBs predominantly are redistributed from one environmental compartment to another (e.g., soil to water, water to air, air to water, sediments to water) (Eisenreich et al. 1992; Larsson 1985; Larsson and Okla 1989; Lin and Que Hee 1987; Mackay 1989; Murphy et al. 1985, 1987; Swackhamer and Armstrong 1986). Thus, for example, the majority of PCBs in air result from volatilization of PCBs from soil and water. Some PCBs may be released to the atmosphere from uncontrolled landfills and hazardous waste sites; incineration of PCB-containing wastes; leakage from older electrical equipment in use; and improper disposal or spills (Blumbach and Nethe 1996; Boers et al. 1994; Bremle and Larsson 1998; Eisenreich et al. 1992; Hansen and O'Keefe 1996; Hansen et al. 1997; Hermanson and Hites 1989; Larsson 1985; Lewis et al. 1985; Morselli et al. 1985, 1989; Murphy et al. 1985; Oehme et al. 1987; Sakai et al. 1993; Sawhney and Hankin 1985; Swackhamer and Armstrong 1986; Tiernan et al. 1983; Wallace et al. 1996). PCBs may be released to water from accidental spillage of PCB-containing hydraulic fluids; improper disposal; combined sewer overflows (CSOs) or storm water runoff; and from runoff and lechate from PCB-contaminated sewage sludge applied to farmland (Crawford et al. 1995; Durell and Lizotte 1998; Gan and Berthouex 1994; Gunkel et al. 1995; Loganathan et al. 1997; Pham and Proulx 1997; Shear et al. 1996). PCBs may be released to soil from accidental leaks and spills; releases from contaminated soils in landfills and hazardous waste sites; deposition of vehicular emissions near roadway soil; and land application of sewage sludges containing PCBs (Alcock et al. 1995; Benfenati et al. 1992; Choi et al. 1974; Gan and Berthouex 1994; Gutenmann et al. 1994; Liberti et al. 1992; McLachlan et al. 1994; Morris and Lester 1994; O'Connor et al. 1990; Ohsaki and Matsueda 1994).

Figure 6-1. Frequency of NPL Sites with PCB Contamination



Derived from HazDat 2000

PCBs are globally circulated and are present in all environmental media. Atmospheric transport is the most important mechanism for global dispersion of PCBs. Biphenyls with 0–1 chlorine atom remain in the atmosphere, those with 1–4 chlorines gradually migrate toward polar latitudes in a series of volatilization/deposition cycles, those with 4–8 chlorines remain in mid-latitudes, and those with 8–9 chlorines remain close to the source of contamination (Wania and Mackay 1996). PCBs enter the atmosphere from volatilization from both soil and water surfaces (Hansen 1999). Once in the atmosphere, PCBs are present both in the vapor phase and sorbed to particles. PCBs in the vapor phase appear to be more mobile and are transported further than particle-bound PCBs (Wania and Mackay 1996). Wet and dry deposition remove PCBs from the atmosphere (Dickhut and Gustafson 1995; Eisenreich et al. 1981; Golomb et al. 1997; Hoff et al. 1996; Leister and Baker 1994; Nelson et al. 1998). The dominant source of PCBs to surface waters is atmospheric deposition; however, redissolution of sediment-bound PCBs also accounts for water concentrations (Hansen 1999). PCBs in water are transported by diffusion and currents. PCBs are removed from the water column by sorption to suspended solids and sediments as well as by volatilization from water surfaces. Higher chlorinated congeners are more likely to sorb, while lower chlorinated congeners are more likely to volatilize (Eisenreich et al. 1983, 1992; Pearson 1996). PCBs also leave the water column by concentrating in biota. PCBs accumulate most in higher trophic levels through the consumption of contaminated food, a process referred to as biomagnification (EPA 1983c; Geyer et al. 1999; Koslowski et al. 1994; Looser and Ballschmiter 1998; Oliver and Niimi 1988; Porte and Albaiges 1993; Willman et al. 1999; Wilson et al. 1995). PCBs in soil are unlikely to migrate to groundwater because of strong binding to soil (EPA 1979h, 1988a; Sklarew and Girvin 1987). Volatilization from soil appears to be an important loss mechanism; it is more important for the lower chlorinated congeners than for the higher chlorinated congeners (Hansen 1999). Vapor-phase PCBs accumulate in the aerial parts of terrestrial vegetation and food crops by vapor-to-plant transfer (Bohm et al. 1999).

The ability of PCBs to be degraded or transformed in the environment depends on the degree of chlorination of the biphenyl molecule as well as on the isomeric substitution pattern. The vapor-phase reaction of PCBs with hydroxyl radicals is the dominant transformation process in the atmosphere (Brubaker and Hites 1998), while photolysis appears to be the only viable chemical degradation process in water (EPA 1979h). Biodegradation has been demonstrated under both aerobic (Dowling et al. 1993; EPA 1983c, 1988a; Fava et al. 1993; Gibson et al. 1993; Haluska et al. 1995; Sugiura 1992; Thomas et al. 1992) and anaerobic conditions (Abramowicz 1990, 1995; Anid et al. 1993; Brown et al. 1988; Chen et al. 1988; EPA 1983c, 1988a; Larsson and Lemkemeier 1989; Pardue et al. 1988; Rhee et al. 1989) and is the major degradation process for PCBs in soil and sediment.

Typical atmospheric concentrations of PCBs have been found to be much lower in rural locations compared to urban locales. For example, the concentration of PCBs in urban Baltimore, Maryland ranged from 0.38 to 3.36 ng/m^3, while in rural Baltimore, the concentration ranged from 0.02 to 0.34 ng/m^3 (Offenberg and Baker 1999). PCB levels in more remote areas are even lower with mean concentrations ranging from 0.025 ng/m^3 over the Norwegian Sea to 0.074 ng/m^3 over the Eastern Arctic (Harner et al. 1998). Monitoring studies conducted over the years have shown that atmospheric concentrations of PCBs have decreased since the late 1970s. Water monitoring studies indicate that PCB concentrations are generally higher near sites of anthropogenic input and in in-shore waters. The concentration of PCBs in the waters of the Great Lakes (Superior, Michigan, Huron, Erie, and Ontario) typically range from 0.070 to 1.6 ng/L (Anderson et al. 1999). Concentrations of PCBs in drinking water are generally <0.1 μg/L and thus, drinking water is not considered a significant pathway for exposure. Concentrations of PCBs in most soils are generally <100 μg/kg; however, PCB concentrations in contaminated soils can be several orders of magnitude higher. Subsurface soil and sludge collected on-site at a New York hazardous waste site near Akwesasne (a Native American community) had maximum concentrations of 750 mg/kg and 41,500 mg/kg, respectively (ATSDR 1995). PCB concentrations in fish have been of particular interest due to their influence on human exposure. Composite fish samples from the U.S. North Coast analyzed from 1988 to 1991 had a mean PCB concentration of 1.64 μg/g wet weight (Kennish and Ruppel 1995). Chinook salmon sampled from Lakes Ontario and Huron from 1991 to 1994 had mean concentrations of 0.835 and 0.338 μg/g wet weight, respectively (Feeley and Jordan 1998). Even in remote areas, PCBs have been detected in fish tissue. For example, lake trout caught in the Sierra Nevada mountains from 1993 to 1994 had PCB concentrations ranging from 0.018 to 0.430 μg/g wet weight (Datta et al. 1999).

The general population may be exposed to PCBs by ingesting contaminated food, especially fish from contaminated waters, and by inhaling contaminated air. Food consumption has and continues to be the major contributor to body burden of PCBs in the general population. The estimated dietary intake of PCBs for an average adult was 0.027 μg/kg/day in 1978 and had declined to <0.001 μg/kg/day by 1991 (Gunderson 1995). Several studies indicate that diets high in fish, from PCB-contaminated waters, can significantly increase a persons dietary intake of PCBs. For example, it was found that the mean concentration of PCBs in blood of 252 males who frequently consumed contaminated fish was 4.8 ng/mL, while in 57 males who were infrequent consumers, the mean concentration was 1.5 ng/mL (Hanrahan et al. 1999). In child-bearing women, this can be especially important since PCBs can concentrate in breast milk. Infants who are breast fed may therefore be at increased risk for PCB exposure if the mother has a diet high in contaminated fish (Dewailly et al. 1993; Fitzgerald et al. 1998). PCB exposure has also been

attributed to inhalation of indoor air especially at locations which still use electrical equipment containing PCBs.

The detection of PCBs in blood, adipose tissue, breast milk, and other tissue samples from the general population indicates widespread exposure to PCBs from environmental sources. People who live near hazardous waste sites where PCBs have been detected may be exposed primarily by consuming contaminated fish from adjacent waterbodies and by breathing air that contains PCBs. Children playing near these sites or adults working near these sites may be exposed to additional PCBs by dermal contact with PCB-contaminated soil and by ingesting contaminated soil from their unwashed hands. Despite the prohibition on production and the restrictions regarding PCB use (Section 5.3), occupational exposure to PCBs can be orders of magnitude higher than general population exposure (Section 6.5).

6.2 RELEASES TO THE ENVIRONMENT

From 1929 until 1977, approximately 99% of all PCBs used by U.S. industries were manufactured by the Monsanto Chemical Company at a production facility in Sauget, Illinois (Durfee 1976; IARC 1978). During that period, over 571,000 metric tons ($1,250 \times 10^6$ pounds) of PCBs were produced and/or used in the United States (Erickson 1997; Hansen 1999). In 1976, the U.S. Congress banned the manufacture, processing, distribution in commerce, and use of PCBs under the Toxic Substances Control Act (TSCA) and the Resource Conservation and Recovery Act (RCRA). Exemptions may be granted to individual petitioners for use with optical microscopy, and for research and development (see Section 5.3; EPA 1998u).

Because PCBs are no longer manufactured or imported in large quantities, significant releases of newly manufactured or imported materials to the environment do not occur. Rather, PCBs predominantly are redistributed from one environmental compartment to another (e.g., soil to water, water to air, sediments to water) (Eisenreich et al. 1992; Larsson 1985; Larsson and Okla 1989; Lin and Que Hee 1987; Mackay 1989; Murphy et al. 1985, 1987; Swackhamer and Armstrong 1986). Thus, for example, the majority of PCBs in air result from volatilization of PCBs from soil and water. Some PCBs may be released to the atmosphere from uncontrolled landfills and hazardous waste sites; incineration of PCB-containing wastes; leakage from older electrical equipment in use; and improper disposal or spills (Blumbach 1996; Boers et al. 1994; Bremle and Larsson 1998; Eisenreich et al. 1992; Hansen et al. 1997; Hermanson and Hites 1989; Larsson 1985; Lewis et al. 1985; Morselli et al. 1985, 1989; Murphy et al. 1985; Oehme et al. 1987; Sakai et al. 1993; Sawhney and Hankin 1985; Swackhamer and Armstrong 1986; Tiernan et al.

1983; Wallace et al. 1996). PCBs may be released to water from accidental spillage of PCB-containing hydraulic fluids; improper disposal; CSOs or storm water runoff; and from runoff and lechate from PCB-contaminated sewage sludge applied to farmland (Crawford et al. 1995; Durell and Lizotte 1998; Gan and Berthouex 1994; Gunkel et al. 1995; Loganathan et al. 1997; Pham and Proulx 1997; Shear et al. 1996). PCBs may be released to soil from accidental leaks and spills; releases from contaminated soils in landfills and hazardous waste sites; deposition of vehicular emissions near roadway soil; and land application of sewage sludges containing PCBs (Alcock et al. 1995; Benfenati et al. 1992; Choi et al. 1974; Gan and Berthouex 1994; Gutenmann et al. 1994; Liberti et al. 1992; McLachlan et al. 1994; Morris and Lester 1994; O'Connor et al. 1990; Ohsaki and Matsueda 1994).

6.2.1 Air

From 1929 to 1977, unknown quantities of PCBs were released to the air during Aroclor production and processing and when PCB-contaminated equipment was incinerated (Durfee 1976). Similarly, transformer and capacitor producers discharged PCB-containing wastes to air during the various filling processes (Durfee 1976). Emissions are no longer discharged into the air through production activities; however, emissions may be discharged during the overhaul, repair, or reuse of materials containing PCBs. PCBs may have been released to the atmosphere from various past uses containing PCBs, for example, plasticizers, surface coatings, inks, adhesives, flame retardants, pesticide extenders, paints, and micro-encapsulation of dyes for carbonless duplicating paper; and, in addition, from the accidental losses of PCB fluids from capacitors and transformers (EPA 1976a; IARC 1978; Safe 1984; Welsh 1995).

The major source of PCB release to the atmosphere (2 million pounds/year) is the redistribution of the compounds that are already present in soil and water (Eisenreich et al. 1992; Murphy et al. 1985). Smaller amounts of PCBs may be released to the atmosphere from uncontrolled landfills and hazardous waste sites containing transformers, capacitors, and other PCB wastes (Bremle and Larsson 1998; Hansen and O'Keefe 1996; Hermanson and Hites 1989; Lewis et al. 1985; Murphy et al. 1985); incineration of PCB-containing wastes due to incomplete combustion of PCBs (Blumbach 1996; Boers et al. 1994; Kurokawa et al. 1996; Sakai et al. 1993); leakage from older electrical equipment still in use (Wallace et al. 1996); explosions or overheating of transformers containing PCBs (Schecter and Charles 1991); and improper (or illegal) disposal or spills of the compounds to open areas (Larsson 1985; Morselli et al. 1985, 1989; Murphy et al. 1985; Oehme et al. 1987; Sawhney and Hankin 1985; Swackhamer and Armstrong 1986; Tiernan et al. 1983). Historically, the amount of PCBs released from landfills and incinerators have been estimated to be 10–100 kg/year (22–220 pounds/year) and 0.25 kg/stack/year

(0.55 pounds/stack/year), respectively, and are small compared to the quantity of PCBs released into the atmosphere through cycling from environmental processes (Murphy et al. 1985). PCBs have been identified in 31 air samples collected at 500 of the 1,598 NPL hazardous waste sites where they were detected in some environmental media (HazDat 2000), as well as in the air surrounding landfills during fires (Ruokojarvi et al. 1995). EPA regulations under TSCA regarding the incineration of PCBs requires that the combustion efficiency should be at least 99.9% (EPA 1998b); however, the small percentage of the PCBs not destroyed by incineration will be released into the atmosphere. According to the Toxics Release Inventory (TRI), a total of 446 pounds of PCBs were directly released into the air by 10 of the 14 RCRA hazardous waste and solvent recovery industries that processed them in 1998 (TRI98 2000). The TRI data for 1998 (TRI98 2000) are shown in Table 6-1. The TRI data should be used with caution since only certain types of facilities are required to report.

6.2.2 Water

From 1929 to 1977, the Monsanto Chemical Company released some PCB-containing waste water to municipal sewers during Aroclor production and processing. Waterborne discharges of PCBs from the Monsanto plant, estimated to be <1 pound/day (0.45 kg/day) in 1974, were greatly reduced over the years leading up to production cessation (Durfee 1976). Similarly, transformer and capacitor producers also discharged PCB-containing wastes to municipal sewers (Durfee 1976). High levels of PCBs were also detected in waste water from the manufacture of carbonless copy papers; from leaking hydraulic fluids used in, for example, die cast machines in iron, steel, and aluminum foundries; from pulp and paper mill effluents due to recycling of waste papers containing carbonless copy papers; and from electrical industry waste water contaminated by, for example, accidental loss of capacitor and transformer fluids. These waste waters may also have been discharged directly into surface waters. Treated waste waters may also have entered surface waters indirectly via effluents discharged from municipal publicly owned treatment works (POTWs) and industrial treatment plants.

Currently, the major source of PCB release to surface water is the environmental cycling process (Larsson 1985; Lin and Que Hee 1987; Mackay 1989; Murphy et al. 1985, 1987; Swackhamer and Armstrong 1986). Small amounts of PCBs may enter surface water by runoff of water from accidental spillage of PCB-containing hydraulic fluids, disposal of waste oils into street drains, or from farmland to which sewage sludge containing small quantities of PCBs has been applied (Gan and Berthouex 1994;Gunkel et al. 1995). PCBs may also reach surface waters via CSOs or storm water runoff (Crawford et al. 1995; Loganathan et al. 1997; Shear et al. 1996). The annual contribution of 26 water pollution control plants

Table 6-1. Releases to the Environment from Facilities that Manufacture or Process Polychlorinated Biphenyls

		Total reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AL	1	5	0	0	579180	579185	0	579185
AZ	1	0	0	0	134160	134160	1	134161
CA	2	5	0	0	1691574	1691579	0	1691579
IL	1	0	0	0	0	0	130	130
KS	1	25	0	0	0	25	4525	4550
MI	2	10	0	0	72000	72010	95	72105
NV	1	0	0	0	5200	5200	0	5200
NY	2	1	1	0	870000	870002	1067	871069
OR	1	0	0	0	151435	151435	0	151435
SC	1	0	0	0	0	0	1	1
TN	1	0	0	0	0	0	0	0
TX	4	178	250	5	46561	46994	47	47041
UT	2	222	0	0	192026	192248	12106	204354
WI	1	0	0	0	0	0	0	0
Total	21	446	251	5	3742136	3742838	17972	3760810

Source: TRI98 2000

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations are used.
[c]The sum of fugitive and stack releases are included in releases to air by a given facility.
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[e]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTWs).

in New York City and New Jersey to the New York/New Jersey Harbor Estuary is estimated to be 88 kg (Durell and Lizotte 1998), while the Montreal, Quebec, waste water treatment plant contributed approximately 1 kg PCBs per year in 1993 to the St. Lawrence River (Pham and Proulx 1997). PCBs, particularly the lower chlorinated congeners, may enter groundwater through leaching of land-applied sewage sludge to soils containing low organic matter or through leaching from soils at hazardous waste sites (Griffin and Chou 1981). PCBs have been identified in 93 surface water and 192 groundwater samples collected at 500 of the 1,598 NPL hazardous waste sites where they were detected in some environmental media (HazDat 2000). According to the TRI, 251 and 5 pounds of PCBs were respectively discharged into surface water and injected into groundwater directly by RCRA hazardous waste and solvent recovery industries in 1998 (TRI98 2000). The TRI data for 1998 (TRI98 2000) are shown in Table 6-1. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

6.2.3 Soil

From 1929 to 1977, the Monsanto Chemical Company released some PCB-containing wastes to landfills as a result of Aroclor production. Similarly, transformer and capacitor producers disposed of PCB-containing wastes (e.g., capacitors, solid wastes, Fuller's earth media) directly into landfills (Durfee 1976). The amount of PCBs released to soil has decreased over the years due to the prohibition on production in the United States and the severe restrictions on processing and reuse of existing PCB-containing materials. PCBs may have been released to soils from various past uses containing PCBs (e.g., plasticizers, surface coatings, inks, adhesives, flame retardants, pesticide extenders, paints, and micro-encapsulation of dyes for carbonless duplicating paper) and, in addition, from the accidental losses of PCB fluids from capacitors and transformers (EPA 1976a; IARC 1978; Safe 1984; Welsh 1995).

Currently, the environmental cycling process involving deposition of atmospheric PCBs is expected to be the major source of surface soil contamination (Larsson and Okla 1989). Since PCBs are no longer produced in the United States, accidental leaks and spills from old transformers and capacitors containing PCBs and releases from containers in landfills and hazardous waste sites may be sources of PCBs in soil. Accidental spills of PCBs during transportation of electrical transformers and other PCB-containing equipment (Liberti et al. 1992); vehicular emissions (Benfenati et al. 1992; Ohsaki and Matsueda 1994) may also be sources of PCBs in soils. PCBs accumulation in POTW sewage sludge originates from domestic sources (e.g., human excretion from the recycling of PCB residues in foodstuffs) and from industrial facilities (Choi et al. 1974; McIntyre and Lester 1982; Morris and Lester 1994). Land

application of municipal sludges results in elevated PCB concentrations in these soils (Alcock et al. 1995; Gan and Berthouex 1994; Gutenmann et al. 1994; McLachlan et al. 1994; O'Connor et al. 1990).

PCB concentrations in sludge reported in the 1970s and 1980s varied from <0.01 to 1960 mg/kg (ppm) (dry weight) (Jacobs et al. 1987), but median PCB concentration in municipal sludges was in the lower end of this range, 0.99 (Clevenger et al. 1983) and 4 mg/kg (Furr et al. 1976). However, total PCBs were detected in only 1 out of 16 sewage sludge samples (4.6 ppm dry weight; limit of detection=0.25 ppm dry weight) taken from large cites in the United States (Gutenmann et al. 1994). PCBs have been identified in 465 soil samples and 219 sediment samples collected at 500 of the 1,598 NPL hazardous waste sites where they were detected in some environmental media (HazDat 2000). The amount of PCBs released to land by industry has increased from 752 pounds (341 kg) in 1988 (TRI98 2000) to 134,160 pounds (60,854 kg) in 1998 (TRI98 2000). An additional 3,607,976 pounds were released to land in 1998 by RCRA hazardous waste and solvent recovery industries not represented in the 1988 to 1997 TRI data. During 1998, PCBs were not discharged by industry into POTWs (TRI98 2000). The TRI data for 1998 (TRI98 2000) are shown in Table 6-1. The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

PCBs are globally circulated and are present in all environmental media. Atmospheric transport is the most important mechanism for global dispersion of PCBs. Biphenyls with 0–1 chlorine atoms remain in the atmosphere, those with 1–4 chlorines gradually migrate toward polar latitudes in a series of volatilization/deposition cycles, those with 4–8 chlorines remain in mid-latitudes, and those with 8–9 chlorines remain close to the source of contamination. PCBs enter the atmosphere from volatilization from both soil and water surfaces. Once in the atmosphere, PCBs are present in both the vapor phase and sorbed to particles. PCBs in the vapor phase appear to be more mobile and transported further than particle-bound PCBs. Wet and dry deposition remove PCBs from the atmosphere. The dominant source of PCBs to surface waters is atmospheric deposition; however, redissolution of sediment-bound PCBs also accounts for water concentrations. PCBs in water are transported by diffusion and currents. PCBs are removed from the water column by sorption to suspended solids and sediments as well as from volatilization from water surfaces. Higher chlorinated congeners are more likely to sorb, while lower chlorinated congeners are more likely to volatilize. PCBs also leave the water column by concentrating in

biota. PCBs accumulate more in higher trophic levels through the consumption of contaminated food, a process referred to as biomagnification. PCBs in soil are unlikely to migrate to groundwater because of strong binding to soil. Volatilization from soil appears to be an important loss mechanism; it is more important for the lower chlorinated congeners than for the higher chlorinated congeners. Vapor-phase PCBs accumulate in the aerial parts of terrestrial vegetation and food crops by vapor-to-plant transfer.

Wania and Mackay (1996) report that most PCBs are volatile enough to cycle between the air, water, and soil at environmental temperatures, and that atmospheric transport is the most important mechanism for the global movement of PCBs. These authors further categorized the transport and partitioning behavior of PCB congeners according to the number of chlorines present on the biphenyl molecule. Volatile mono-Bs remain primarily in the atmosphere. PCBs that have 1–4 chlorines and are *ortho*-rich (i.e., number of *ortho* chlorines >1) congeners tend to migrate toward polar latitudes by a series of volatilization/deposition cycles between the air and the water and/or soil. PCBs with 4–8 chlorines remain in mid-latitudes, and those with 8–9 chlorines remain close to the source of contamination. The more heavily chlorinated and *ortho*-poor (i.e., number of *ortho* chlorines #1)/*para*-rich (i.e., number of *para* chlorines >1) PCBs are less volatile and more readily condensed from the atmosphere. Thus, these PCBs are considered less mobile (Macdonald et al. 2000; Wania and Mackay 1993, 1996).

The atmosphere is a net recipient of PCBs from soil, water, and (indirect) sediment fluxes (Hansen 1999). These fluxes are the highest in summer as a result of warmer temperatures (Hoff et al. 1992). The importance of volatilization to atmospheric concentrations of PCBs is well established. This conclusion is also supported by the estimated Henry's law constants for Aroclors and PCB congeners, which range from 2.9×10^{-4} to 4.6×10^{-3} atm-m^3/mol and 1.5×10^{-5} to 2.8×10^{-4} atm-m^3/mol, respectively (see Tables 4-3 and 4-7) (Thomas 1982). The Great Lakes in particular appear to be a source of PCBs to the atmosphere (Arimoto 1989; Hornbuckle et al. 1993; Swackhamer and Armstrong 1986). The estimated PCB gas fluxes out of the Great Lakes to the atmosphere in 1994 were 1,700, 2,700, 420, and 440 kg/year for Lakes Superior, Michigan, Erie, and Ontario, respectively (Hoff et al. 1996). A pseudo first-order rate constant for the volatilization of total PCBs from Lake Superior is estimated to be 0.4/year ($t_{½}$=2 years) (Jeremiason et al. 1994). This latter estimated rate indicates that approximately one-half of the total water-borne mass of PCBs in Lake Superior enters the atmosphere over a 7-month period.

PCBs are transported from soil and sediment to the atmosphere. In the absence of water, the rate of movement of PCBs from the soil surface to the atmosphere is controlled by diffusive transfer (Cousins and Jones 1998). For example, Agrell et al. (1999) demonstrated that diffusive exchange from soils is the

dominant transport mechanism of PCBs cycling between the atmosphere and terrestrial surfaces along the Baltic Sea region. As atmospheric sources of PCBs diminish, the flux between the atmosphere and soil will eventually achieve equilibrium (i.e., fluxes in and out of soil will be equal). For instance, Harner et al. (1995) estimated the net volatilization/accumulation of PCBs from soil for four congeners (PCBs 28, 52, 138, and 153) during the period 1942 through 1992. Presently, the more mobile PCBs 28 and 52 should have achieved equilibrium between the soil and air. However, PCBs 138 and 153 are much slower to volatilize from soil and will continue to slowly out-gas until equilibrium is attained. Contaminated sediments exposed directly to the atmosphere during water level changes (e.g., tidal fluctuations) or during removal to landfills may rapidly transfer the volatile congeners directly to the air through covaporization with water (Chiarenzelli et al. 1996, 1997). This is illustrated by Bremle and Larsson (1998), who studied the concentration of PCBs in air during the landfilling of wet contaminated sediment. They found that the overlying air was enriched in the more volatile, lower molecular weight congeners compared to the deposited sediment, which suggests that volatilization was the major transport process out of the sediment for these congeners. However, other studies have demonstrated that once sediments become dehydrated, the binding of PCBs is tighter and the net volatilization is reduced (Chiarenzelli et al. 1996, 1997).

PCBs in air are present in both the vapor phase and adsorbed to aerosol particles (Eisenreich et al. 1981; Hermanson and Hites 1989; Wania and Mackay 1996). PCBs in the vapor phase appear to be more mobile and are transported further than particle-bound PCBs, while the heavier and coplanar PCBs tend to be particle-bound and/or more readily degraded in the atmosphere (Hansen 1999). PCBs with vapor pressures $>10^{-4}$ mm Hg (mono- and di-CBs) appear to exist in the atmosphere almost entirely in the vapor phase, while PCBs with vapor pressures $<10^{-8}$ mm Hg appear to exist almost entirely in the adsorbed phase, and PCBs with vapor pressures #10^{-4} and 10^{-8} mm Hg (tri- to hepta-CBs) exist in both the adsorbed and vapor phase (Eisenreich et al. 1981; Erickson 1992). The vapor pressures of the Aroclors and several PCB congeners are found in Tables 4-2 and 4-7. PCBs in the vapor phase are enriched (relative to commercial Aroclor mixtures) in di- and tri-*ortho* congeners within each homolog group due to their higher vapor pressures and limited tendency to bind to aerosol particulates. Also, being less volatile, coplanar non-*ortho* and higher chlorinated PCBs are present at very low proportions in the vapor phase, and tend to be associated with aerosols, thereby increasing their chances of removal from the atmosphere by wet and dry deposition (Falconer and Bidleman 1994; Hippelein and McLachlan 1998; Jones et al. 1992; Monosmith and Hermanson 1996; Muir et al. 1996a, 1996b; Panshin and Hites 1994; Simcik et al. 1998; Wania and Mackay 1993). For example, Falconer and Bidleman (1995) reported

preferential sorption of non- and mono-*ortho* PCBs to urban aerosols to a greater extent than multi-*ortho* congeners of the same homolog.

PCBs are physically removed from the atmosphere by wet deposition (i.e., rain and snow scavenging of vapors and aerosols); by dry deposition of aerosols; and by vapor adsorption at the air-water, air-soil, and air-plant interfaces (Cousins et al. 1999; Currado and Harrad 1999; Dickhut and Gustafson 1995; Eisenreich et al. 1981; Franz and Eisenreich 1998; Golomb et al. 1997; Gregor et al. 1996; Hart et al. 1993; Hoff et al. 1996; Leister and Baker 1994; Nelson et al. 1998; Wania et al. 1999). Wet deposition occurs episodically by in-cloud scavenging or rain-out of vapor phase PCBs, and by below-cloud scavenging or wash-out of aerosol PCBs. At low temperatures, wet deposition may fall as snow. Franz and Eisenreich (1998) found that snow can be a very efficient medium for aerosol scavenging to an even greater extent than for rain; and they found that aerosol washout accounted for between 79 and 88% of the total PCB content in snow. However, Wania et al. (1999) recently reevaluated this study and pointed out that the contribution of gaseous scavenging may have been underestimated by these authors. Also, Wania et al. (1998) pointed out that adsorption of PCBs to ice surfaces is a major scavenging mechanism for gaseous PCBs in the atmosphere. In contrast to wet deposition, dry removal of PCBs from the atmosphere results from the gravitational settling of particulate PCBs (i.e., dry particulate deposition) and by the impaction of vapor phase PCBs on terrestrial or aquatic surfaces (i.e., dry gaseous deposition). Dry gaseous deposition is a complex process which depends on the physical-chemical properties of the PCBs, characteristics of the adsorbing surface, and environmental conditions (e.g., windspeed). In the ambient atmosphere, dry particulate deposition is predominantly in the form of fine aerosols (<1 μm), which deposit on surfaces by rapid, vibratory (Brownian) diffusion (Holsen and Noll 1992). However, in urban areas, PCBs are associated with course aerosols (>1 μm), and these particulates represent the majority of the dry deposition flux even though PCBs are largely in the vapor phase (Holsen et al. 1991).

PCB inputs into aquatic and marine reservoirs are predominantly from wet and dry deposition and from the recycling of sediment-sorbed PCBs into the water column. Eisenreich et al. (1983) demonstrated for the Great Lakes water column that the concentration of PCBs is elevated at both the air/water and water/ sediment interfaces as a result of inputs from the atmosphere and sediments, respectively. In addition, Eisenreich et al. (1992) estimated that the upper Great Lakes receive the majority of the total inputs from deposition from the atmosphere (Superior 90%, Michigan 58%, Huron 78%), while the lower Great Lakes receive a lower but significant percentage from these sources (Erie 13%, Ontario 7%). The lower lakes receive a large loading of PCBs from the connecting channels (Detroit River and Niagara River) by neighboring industrial discharges and leakage from waste dump sites. In another study, Franz et al.

(1998) concluded that dry deposition dominates atmospheric PCB loadings to Lake Michigan, suggesting that these loadings are more than 3 times greater than loadings from wet deposition. Similarities between the pattern of PCB congeners in the dry deposition and surficial sediments, and also the magnitude of their fluxes to the water column support their assertion. However, Pearson et al. (1996) concluded that input/output budgets for Lake Michigan also showed large imbalances, indicating failure to understand all of the processes of PCB transport to the water column to this body of water. For Lake Superior, Jeremiason et al. (1994) estimated PCBs inputs for 1984 from riverine, wet deposition, dry deposition, and other sources as 110 (36%), 125 (41%), 32 (10%), and 41 (13%) kg PCBs/year, respectively. Thus, wet deposition contributed the largest load of PCBs to this lake. However, for all of the Great Lakes, Hoff et al. (1996) noted that wet and dry deposition fluxes into the lakes appear to be getting smaller, and the net PCB flux is out of the lakes, i.e., volatilization.

Recycling of PCBs, due to volatilization of PCBs from the water column and subsequent release of PCBs from the sediments, occurs when inputs from the atmosphere decrease (Achman et al. 1996; Sanders et al. 1996). The process of recycling tends to increase with higher PCB solubility (Sanders et al. 1996). There are several mechanisms by which PCBs can exchange between the sediment bed and the overlying water. For example, PCBs dissolved or associated with colloidal particles can exchange across the sediment-water interface by diffusive and/or advective processes (Berner 1980; Formica et al. 1988). The rate of redissolution of PCBs from sediment to water will always be greater in summer than in winter because of more rapid volatilization of PCBs from water with higher summer temperatures (Larsson and Sodergren 1987). In summer, recycling of PCBs directly to the water column by dissolution appears to be the most important process (Sanders et al. 1996), while in winter, sediment resuspension is the predominant mechanism for recycling of PCBs (Sanders et al. 1996). Environmental redistribution of PCBs from aquatic sediment is most significant for the top sediment layers, while PCBs in the lower layers may be effectively sequestered from redistribution (Baker et al. 1985; EPA 1979h, 1988a; Kleinert 1976; Swackhamer and Armstrong 1986). In the lower Hudson River estuary, a high surface sediment concentration of PCBs resulted in the exchange of PCBs from sediment to water (Achman et al. 1996). The average fluxes from sediments were between 2 and 100 times more than the flux coming down the river, and clearly dominated other fluxes from direct atmospheric deposition and waste water treatment plant discharges.

PCBs in water are transported by diffusion and currents. PCBs in surface water essentially exist in three phases: dissolved, particulate, and colloid associated (Baker and Eisenreich 1990). The heavier and less soluble congeners in the water column are more likely to be associated with particulates and colloids, and

do not freely exchange into the vapor phase. However, the more water soluble, lower chlorinated (and *ortho*-rich) congeners are predominantly in the dissolved state in the water column and can readily partition into the vapor phase. In New Bedford Harbor, Massachusetts, Burgess et al. (1996) reported that the ratio of colloid associated PCBs to freely dissolved PCBs increased from 1.2 to 8.0 (di-CBs to octa-CBs, respectively) as the degree of chlorination increased. However, at this site, the majority of the PCBs were associated with the particulate phase regardless of solubility or chlorination.

Experimental and monitoring data have shown that PCB concentrations in sediment and suspended matter are higher than in the associated water column (Eisenreich et al. 1983). In a study of the Saginaw River in Michigan, Verbrugge et al. (1995) reported that the ratio of the total PCBs bound to suspended particulates relative to dissolved PCBs, was 2 to 1. However, in a study examining the water column in Lake Superior, 75% of PCBs were in the dissolved phase, while 25% exist in the suspended particulate phase (Eisenreich et al. 1983). These studies suggest that the partitioning behavior of PCBs in the water column is location specific.

PCBs leave the water column by partitioning onto sediments and suspended particulates, and by volatilization at the air/water interface. PCBs can be immobilized for relatively long periods of time in aquatic sediments. The adsorption of dissolved PCBs onto solids (suspended particulates and sediments) is greatest for solids composed primarily of organic matter and clay (EPA 1980b). The more highly chlorinated components (and *ortho*-poor) PCBs, which have lower water solubilities and higher octanol-water partition coefficients (K_{ow}), have a greater tendency to bind to solids as a result of strong hydrophobic interactions (see Table 4-2). In contrast, the low molecular weight PCBs, which have higher water solubilities and lower K_{ow}s, sorb to a lesser extent on solids and remain largely in the water column (see Table 4-2). Volatilization of highly chlorinated PCBs in the water column is reduced significantly by the sequestration on solids compared to the lightly chlorinated PCBs, in which volatilization may be only slightly effected (EPA 1985b; Lee et al. 1979). The estimated residence times (in years) of PCBs in the water columns of the Great Lakes are: Superior (3.3), Michigan (1.3), Huron (1.0), Erie (0.2), and Ontario (1.1); and the percent loss of PCBs from these lakes due to sedimentation, volatilization, and outflow to other water bodies are summarized in Table 6-2 (Arimoto 1989; Eisenreich et al. 1992). For PCBs in the Great Lakes, sedimentation and volatilization were the primarily loss mechanisms, while the contribution of outflow was comparatively low. For Lake Michigan between 1980 and 1991, the calculated half-lives for the PCB homologs (assuming a first-order processes; in years) due to both sedimentation and volatilization were: di- (11), tri- (15), tetra- (10), penta- (12), hexa- (5.3), hepta- (7), and octa- (5) (Pearson et al. 1996).

Table 6-2. Percentage of Loss of Polychlorinated Biphenyls from the Great Lakes Waters

Waterbody	Volatilization	Sedimentation	Outflow to other bodies of water
Lake Superior	86.6	11.4	2.0
Lake Michigan	68.1	30.6	1.3
Lake Huron	75.3	19.4	5.3
Lake Erie	46.0	45.2	8.8
Lake Ontario	53.4	29.3	17.3

Source: Eisenreich et al. 1992

In addition to volatilization and sorption onto sediments, PCBs can leave the water column by concentrating in biota directly from water (EPA 1983c; Porte and Albaiges 1993). Bioconcentration is defined as uptake of a chemical from water alone; and bioaccumulation is the result of combined uptake via food, sediment, and water. The bioconcentration factors (BCFs; ratio of the concentration of PCBs in the organism over the concentration of PCBs in water) of PCBs in aquatic organisms are directly proportional to partition coefficients and lipid contents of the organism, and are congener specific (Geyer et al. 1999). BCFs in various fresh water and marine species are generally in the range of $5x10^2$–$4x10^4$ for lower chlorinated PCB congeners and about $1x10^3$–$3x10^5$ for tetra- to hexa-PCBs (70, 101, 110, and 136) (Geyer et al. 1999; see Table 6-3). Median BCFs for accumulation from water by phytoplankton range from $1x10^4$ to $1x10^6$, and are generally the greatest for the tetra- to hepta-PCBs and for the coplanar tri-, tetra-, and penta-PCBs (Willman et al. 1999). Coplanar PCBs and the more highly chlorinated congeners can have aquatic organism BCFs as high as $2x10^6$ (Hansen 1999). However, the BCFs for the higher chlorinated homologs drop off after a certain point because these larger molecules do not readily pass through biological membranes. BCFs for freshwater and marine species are illustrated in Tables 6-4 and 6-5, respectively, for Aroclors mixtures (ASTER 1996).

Bioaccumulation factors (BAFs; the ratio of the concentration of PCBs in the organism over the combined concentration of PCBs in sediment, food, and water) of PCBs increase with higher chlorination and lower water solubility (Coristine et al. 1996; Zhang et al. 1983). In contrast to BCFs, a direct relationship between bioaccumulation, partition coefficients, and organism lipid content does not always exist, and other factors (e.g., reproductive cycles) may affect the uptake and accumulation of PCBs (Hansen 1999; Stow et al. 1997). Less chlorinated PCBs (1–4 chlorines) are readily taken up by organisms, but are readily eliminated and metabolized. Thus, these homologs are not bioaccumulated to a great extent (see Section 6.3.2; McFarland and Clarke 1989). The most highly chlorinated congeners (7–10 chlorines) occur in low concentrations in the environment, and are tightly bound with soil, sediment, and organic matter. Thus, these PCBs are also not significantly bioaccumulated (Bergen et al. 1993; Lacorte and Eggens 1993; McFarland and Clarke 1989). These PCBs, which have log K_{ow} values >5, appear to enter biota through food-web transfer from sediment, which is less efficient (Koslowski et al. 1994). On the other hand, the penta-, hexa-, and hepta-PCBs are both bioavailable and resistant to degradation in organisms; and these PCB homologs bioaccumulate in organisms to the greatest extent (see Section 6.3.2; Bremle et al. 1995; Koslowski et al. 1994; McFarland and Clarke 1989; Porte and Albaiges 1993; Willman et al. 1997). For example, the PCBs that dominate congener profiles in the tissues of mussels, crabs, and seals are hexa-PCB isomers 138 and 153 (Hansen 1999; Porte and Albaiges 1993). The differences in congener retention in organisms apparently accounts for the differences in

Table 6-3. Bioconcentration Factors (BCFs) and Bioaccumulation Factors (BAFs) for Select Congeners and Total Polychlorinated Biphenyls in Various Aquatic Organisms

PCB	Organism	Laboratory BCF	Field BAF	Location	Reference
PCB 18	Rainbow trout *(Oncorhynchus mykiss)*	81,000	590,000	Lake Ontario	Oliver and Niimi 1985
PCB 40	Rainbow trout *(O. mykiss)*	49000	240,000	Lake Ontario	Oliver and Niimi 1985
PCB 52	Rainbow trout *(O. mykiss)*	200,000	1,900,000	Lake Ontario	Oliver and Niimi 1985
PCB 101	Rainbow trout *(O. mykiss)*	200,000	8,400,000	Lake Ontario	Oliver and Niimi 1985
PCB 153	Rainbow trout *(O. mykiss)*	740,000	10,000,000	Lake Ontario	Oliver and Niimi 1985
Total	Perch *(Perca fluviatilis)*		2,050–7,580	Lake Jarnsjon, Sweden	Bremle et al. 1995
Total	Tilapia *(Oreochromis mossambicus)*		10,000	Shing Mun River, Hong Kong	Chui et al. 1991
Total	Pumpkinseed *(Lepomis gibbonsus)*		187,000–2,079,000	Hudson River, New York	Sloan et al. 1985
Total	Amphipods *(Pontoporeia affinis)*		718,000	Lake Ontario	Oliver and Niimi 1988
Total	Oligochaetes *(Tubifex tubifex and Limnodrilus hoffmeisteri)*		164,000	Lake Ontario	Oliver and Niimi 1988
Total	Slimy sculpin *(Cottus cognatus)*		1,450,000	Lake Ontario	Oliver and Niimi 1988
Total	Alewife *(Alosa pseudoharengus)*		1,180,000	Lake Ontario	Oliver and Niimi 1988
Total	Rainbow smelt (small) *(Osmerus mordax)*		564,000	Lake Ontario	Oliver and Niimi 1988
Total	Rainbow smelt (large) *(O. mordax)*		1,272,000	Lake Ontario	Oliver and Niimi 1988
Total	Salmonids		3,910,000	Lake Ontario	Oliver and Niimi 1988

Table 6-4. Bioconcentration Factors (BCFs) for Various Aroclors in Fresh Water Species

Species	BCF	Duration (days)
Aroclor 1232		
White sucker (*Catostomus commersoni*)	5,500	30
Aroclor 1242		
Scud (*Gammarus pseudolimnaeus*)	36,000	60
Fathead minnow (male) (*Pimephales promelas*)	274,000	255
Atlantic salmon (*Salmo salar*)	600	4
Aroclor 1248		
Scud (*G. pseudolimnaeus)*	108,000	60
Fathead minnow (female) *(P. promelas)*	120,000	240
Channel catfish *(Ictalurus punctatus)*	56,400	77
Bluegill *(Lepomis macrochirus)*	52,000	77
Aroclor 1254		
Cladoceran *(Daphnia magna)*	3,800	4
Scud *(G. pseudolimnaeus)*	6,200	21
Crayfish *(Orconectes nais)*	750	21
Dobsonfly *(Corydalus cornutus)*	1,500	7
Stonefly *(Pteronarcys california)*	740	21
Mosquito *(Culex tarsalis)*	3,500	7
Phantom midge *(Chaoborus punctipennis)*	2,700	14
Fathead minnow (female) *(P. promelas)*	238,000	240
Rainbow trout *(Oncorhynchus mykiss)*	46,000	30
Brook trout *(Salvelinus fontinalis)*	47,000	118
Brook trout *(S. fontinalis)*	42,000	500
Brook trout *(S. fontinalis)*	3,000[a]	500
Steelhead trout *(Salmo gairdneri)*	38,000	24
Channel catfish *(I. punctatus)*	61,200	77
Aroclor 1260		
Fathead minnow (female) *(P. promelas)*	270,000	240

Source: ASTER 1998

[a]Fillet sample rather than whole body sample

Table 6-5. Bioconcentration Factors (BCFs) for Various Aroclors in Salt Water Species

Species	BCF	Duration (days)
Aroclor 1016		
Eastern oyster *(Crassostrea virginica)*	13,000	84
Horseshoe crab *(Limulus polyphemas)*	1,298	96
Sheepshead minnow (adult) *(Cyprinodon variegatus)*	25,300	28
Sheepshead minnow (juvenile) *(C. variegatus)*	43,100	28
Sheepshead minnow (fry) *(C. variegatus)*	14,400	28
Pinfish *(Lagodon rhomboides)*	17,000	21–28
Aroclor 1242		
Diatom *(Cylindrotheca closterium)*	1,000	14
Aroclor 1254		
Ciliate protozoans *(Tetrahymena pyriformis)*	60	7
Eastern oyster *(C. virginica)*	8,100	2
Eastern oyster *(C. virginica)*	101,000	245
Polychaete *(Arenicola marina)*	236	5
Polychaete *(Nereis diversicolor*)	373	5
Grass shrimp *(Palaemonetes pugio*)	27,000	16
Pink shrimp *(Penaeus duorarum)*	140	2
Spot *(Leiostomus xanthurus)*	37,000	28
Sheepshead minnow (adult) *(C. variegatus)*	30,000	28
Pinfish *(L. rhomboides)*	980	2

Source: ASTER 1996

congener concentration profiles seen in the higher trophic levels. PCB bioaccumulation is also effected by the stereochemistry of the congener; optimal bioaccumulation occurs for planar molecules substituted with 5 or 7 chlorines (Koslowski et al. 1994). For instance, median BAFs for zooplankton and zebra mussels ranged from $1x10^4$ to $1x10^6$, and were the greatest for the planar tetra- to hepta-PCBs, which had 54% larger BAFs compared to values for the non-coplanar homologs (Willman et al. 1999). Typical field- measured BAFs range from $2.1x10^3$ to $3.9x10^6$ for total PCBs (Table 6-3). BAFs for PCB isomer groups in a Lake Ontario food web ranged from $4.2x10^4$ to $1.3x10^7$ (Table 6-6). The highest BAFs occur at the lower end of the food chain. For example, Oliver and Niimi (1988) determined that the water-plankton-mysid food chain had the highest bioaccumulation of PCBs in the Lake Ontario trophic system.

Bioaccumulation of PCBs in aquatic animals depends on the water zone in which the animals predominantly reside and feed. Certain benthic organisms, such as crabs, clams, sandworms, and grass shrimp, accumulate PCBs from water at the water/sediment interface (PCB concentration is higher at this interface than in the surrounding water column, see above) and via intake of phytoplankton and zooplankton, which contain higher levels of PCBs than the water (Porte and Albaiges 1993; Pruell et al. 1993; Secor et al. 1993). When airborne PCBs are deposited onto the surface of water, lower chlorinated and *ortho*-rich congeners, especially, become enriched in the surface microlayer which results in concentrations that are 500 times higher than the average concentration in water. As a result, bioaccumulation by fish is several orders of magnitude higher in this zone (Sodergren et al. 1990). Greater bioaccumulation will occur in the fatty tissues (lipids) than in the muscle or whole body of aquatic organisms (EPA 1980b). Thus, organisms with higher lipid concentrations will accumulate a greater burden of PCBs via tropic transfer. Fish species, such as lake trout (*Salvelinius namaycush*) and coho salmon (*Oncorhynchus kisutch*), with high lipid contents, have a net trophic transfer efficiency from food ranges of 75–89 and 38% (average for tetra-CBs; however, higher chlorinated congeners ranged from 43 to 56%), respectively (Madenjian et al. 1999). In addition, insects that have lipid-rich cuticular (skin) layers can capture significant amounts of vapor-phase PCBs in their tissues and enter these PCBs into the food chain (Saghir and Hansen 1999).

Biomagnification of PCBs within the aquatic food chain results from higher trophic transfer and has been observed in aquatic organisms (Koslowski et al. 1994; Looser and Ballschmiter 1998; Oliver and Niimi 1988; Wilson et al. 1995). Biomagnification is apparent in shellfish that accumulate PCBs from the consumption of phytoplankton and zooplankton, and in marine mammals (seals, dolphins, and whales) that accumulate PCBs from plankton and fish (Andersson et al. 1988; Kuehl and Haebler 1995; Lake et al. 1995a; Salata et al. 1995; Schantz et al. 1993c; Secor et al. 1993). Food chain biomagnification also

Table 6-6. Field Measured Bioaccumulation Factors for Isomeric Groups of Polychlorinated Biphenyls

	PCB Group					
Organism	Tri-	Tetra-	Penta-	Hexa-	Hepta-	Octa-
Amphipods	387,000	667,000	615,000	938,000	2,400,000	1,400,000
Oligochaetes	127,000	180,000	154,000	150,000	259,000	310,000
Slimy sculpin	87,000	633,000	1,490,000	3,125,000	5,185,000	7,500,000
Alewife	173,000	833,000	1,380,000	2,125,000	2,960,000	3,100,000
Rainbow smelt						
Small	42,000	367,000	590,000	1,063,000	1,590,000	1,600,000
Large	93,000	933,000	1,380,000	2,375,000	3,148,000	3,300,000
Salmonids	293,000	2,170,000	4,100,000	8,125,000	11,300,000	13,000,000

Source: Oliver and Niimi 1988

occurs in several species of fish-consuming birds (Ankley et al. 1993; Hebert et al. 1994; Mackay 1989; Metcalfe and Metcalfe 1997; Shaw and Connell 1982; Winter and Streit 1992). Biomagnification of PCBs in the aquatic food chain is congener specific and is more predominant for congeners with K_{ow} values between 5 and 7 (Koslowski et al. 1994; Metcalfe and Metcalfe 1997). For example, in the food web of the western basin of Lake Erie, concentrations of PCB 138 increased from plankton (14 μg/kg) to piscivores ($1.4x10^3$ μg/kg in silver bass muscle tissue) to herring gulls ($3.0x10^4$ μg/kg) (Koslowski et al. 1994). However, no biomagnification was observed for PCBs 77, 126, and 169 (Koslowski et al. 1994). As previously observed for bioaccumulation, differences in retention also account for differences in congener biomagnification in higher trophic levels.

PCBs are strongly sorbed to soils as a result of low water solubility and high K_{ow} (see Table 4-2), and will not leach extensively (EPA 1979h, 1988a; Sklarew and Girvin 1987). The tendency to leach will be greatest among the least chlorinated congeners and is expected to be greatest in soil with low organic carbon (Sklarew and Girvin 1987; Strek and Weber 1982a). Leaching of PCBs in most soils should not be extensive, particularly for the more highly chlorinated congeners. However, PCBs will leach significantly in the presence of organic solvents that may be present at municipal landfills or hazardous waste sites (Griffin and Chou 1981). Partition coefficients (K_d) for PCBs 8, 52, and 153 for sorption onto soil with variable organic carbon content (0.2–2.3 by weight percent) are 74–825, 533–5,508, and 14,258–68,485 L/kg, respectively (Girvin and Scott 1997). Soil and sediment sorption coefficients (K_{oc}) for biphenyl and PCB congeners are listed in Table 6-7.

Soils received net PCB inputs from water and air during the peak emissions of the 1960s and early 1970s. However, at present, soils appear to be reservoirs for releasing PCBs into the atmosphere (Hansen 1999). The mechanisms involved in the soil-to-air transfer of PCBs will involve a combination of direct soil organic matter-to-air transfer and soil pore water-to-air transfer (Cousins et al. 1997). Wicking (i.e., the movement of a compound in solution to replace evaporative surface water loss) has been demonstrated as a process that can increase the volatilization of PCBs from soil; thus, volatilization rates will be greatest in moist soils from the co-vaporization of PCBs and water (Bushart et al. 1998; Chiarenzelli et al. 1996, 1997, 1998). For example, Chiarenzelli et al. (1996, 1997) demonstrated that for small amounts of St. Lawrence River solids originally contaminated with Aroclor 1248, several *ortho*-chlorinated congeners were preferentially lost by volatilization, which could be positively correlated with water loss by vaporization. Soils with low organic carbon will have the greatest rate of volatilization of PCBs (Shen and Tofflemire 1980). For example, researchers at General Electric demonstrated that the rate of volatilization of Aroclor 1242 from soil is much less from the organic topsoil than from the course sand

Table 6-7. Observed Soil and Sediment Sorption Coefficients (K_{oc}) for Polychlorinated Biphenyls Congeners

Compound	Log K_{oc}	Reference(s)
Biphenyl	3.27	Meylan et al. 1992
2-CB	3.47	Chiou et al. 1983
2,2'-CB	3.92	Chiou et al. 1983
2,4'-CB	4.13	Chiou et al. 1983
	4.57, 4.56	Girvin and Scott 1997
2,2',4-CB	4.84	Chiou et al. 1987
2,2',5-CB	4.57	Chin and Weber 1989
2,4,4'-CB	4.62	Chiou et al. 1983
2,2',5,5'-CB	3.43	Haque and Schmedding 1976
	4.23–5.15	Hassett et al. 1984
	4.97	Chin and Weber 1989
	5.42, 5.38	Girvin and Scott 1997
2,2',6,6'-CB	5.11	Steen et al. 1978
2,3',4',5-CB	5.02	Steen et al. 1978
2,2',4,5,5'-CB	5.79, 5.93	Gschwend and Wu 1985
2,2',3,4,4',5'-CB	6.16	Gschwend and Wu 1985
2,2',4,4',5,5'-CB	5.62	Karickhoff 1981
	4.78–6.87	Horzempa and Di Toro 1983
	6.85, 6.47	Girvin and Scott 1997
2,2',4,4',6,6'-CB	6.08	Karichoff 1981

Sources: Saçan and Balcioğlu (1996); Sklarew and Girvin (1987); McGroddy et al. (1996)

fraction (Shen and Tofflemire 1980). In another study, Grundy et al. (1996) examined nine soil plots treated with Aroclors 1254 and 1260 representing dry barren, dry moss, and wet grass cover in the Canadian Arctic (Northwest Territory). Rate constants (first-order processes) for loss of total PCBs of approximately 0.5/year ($t_{½}$ =1.1 year), with a range of 0.3–1.0/year for individual congeners, was estimated. For the dry barren area, loss was correlated with vapor pressure. For the two vegetated areas, the volatilization rate appeared to be reduced by organic matter from both living and dead vegetation.

PCBs accumulate in terrestrial vegetation by the following possible mechanisms: (1) uptake from soil through the roots; (2) dry deposition on aerial parts (particle-bound or gaseous); and (3) wet deposition on aerial parts (particle-bound or solute). The primary mode of uptake for total PCBs in terrestrial vegetation is by vapor-to-plant transfer (Bohm et al. 1999; Lober et al. 1994; O'Connor et al. 1990; Schönherr and Riederer 1989). However, Bohm et al. (1999) reported that vapor-to-plant partioning is most important for tri-CBs, while aerial dry deposition is most important for hepta- and octa-CBs. For example, Ye et al. (1992b) found that the more highly chlorinated congeners ($7 -chlorines) are adsorbed by aerial plant tissues (e.g., tomato plant leaves) primarily by vapor-to-plant transfer, while the lower chlorinated congeners (3–6 -chlorines) are both adsorbed on and absorbed in aerial plant tissues. The lower chlorinated (and *ortho*-enriched) congeners, which have the highest concentrations in the atmosphere, are the most efficiently scavenged by terrestrial vegetation by vapor-to-plant transfer (Jones and Duarte-Davidson 1997; Thomas et al. 1998); and leafy vegetation (e.g., lettuce, grass) appears to accumulate the highest levels of total PCBs by this mechanism (Cullen et al. 1996). The air-to-grass transfer is the first link in the grass-to-cattle-to-human food chain, and this food chain provides an appreciable fraction of human exposure to PCBs (Currado and Harrad 1999; see Section 6.4). Strong sorption of PCBs to soil organic matter and clay inhibits the uptake of PCBs in plants through the roots (Bacci and Gaggi 1985; Chu et al. 1999; Gan and Berthouex 1994; Paterson et al. 1990; Strek et al. 1982b; Webber et al. 1994; Ye et al. 1992a). As a result, below-ground vegetation, such as potatoes, will accumulate the lowest levels of total PCBs, lower proportions of the more lightly chlorinated congeners, and will predominately accumulate the moderately chlorinated congeners (e.g., penta-CBs 99, 101, and 110) directly from soil (Cullen et al. 1996). However, higher uptake from soil can occur in certain root crops (e.g., carrots) by the partitioning of PCBs into the lipid-rich epidermal layer (skin) or by soil particles adhering to the root (Cullen et al. 1996; O'Connor et al. 1990; Pal et al. 1980). Plants grown on PCB-contaminated sludge or sludge-amended soils will be free of vapor-phase PCB contamination as a result of strong sorption of PCBs to sludge organic matter (Gan and Berthouex 1994; O'Connor et al. 1990). For example, Gan and Berthouex demonstrated that for corn grown on PCB contaminated sludge-amended farmland, bioconcentration of PCBs did not occur in either the grain or stover. Plant BCFs of

PCBs from soil are summarized in Table 6-8, and are estimated to be <0.02 for most terrestrial plant species (Cullen et al. 1996; O'Connor et al. 1990; Pal et al. 1980).

6.3.2 Transformation and Degradation

The ability of PCBs to be degraded or transformed in the environment depends on the degree of chlorination of the biphenyl molecule as well as on the isomeric substitution pattern. The vapor-phase reaction of PCBs with hydroxyl radicals is the dominant transformation process in the atmosphere, while photolysis appears to be the only viable abiotic degradation process in water. Biodegradation in the environment, although slow, occurs under both aerobic and anaerobic conditions. In sediments, aside from the aerobic surface layer, anaerobic microbial degradation will be primarily responsible for transformation, particularly of the more highly chlorinated congeners. Aerobic biodegradation in soil, surface water, and sediments is limited to the less chlorinated congeners.

6.3.2.1 Air

In the atmosphere, the vapor-phase reaction of PCBs with hydroxyl radicals (photochemically formed by sunlight) is the dominant transformation process (Brubaker and Hites 1998). The calculated tropospheric lifetime values for this reaction increases as the number of chlorine substitutions increases. The tropospheric lifetime values (determined using the calculated OH radical reaction rate constant and assuming an annual diurnally averaged OH radical concentration of $5x10^5$ molecule/cm^3) are: 5–11 days for monochlorobiphenyls, 8–17 days for dichlorobiphenyls, 14–30 days for trichlorobiphenyls, 25–60 days for tetrachlorobiphenyls, and 60–120 days for pentachlorobiphenyls (Atkinson 1987). In another study, the estimated tropospheric lifetimes of PCBs (calculated using the estimated OH radical reaction rate constant and assuming a 24-hour average OH radical concentration of $9.7x10^5$ molecule/cm^3) range from 2 days for biphenyl to 75 days for hexachlorobiphenyl, and a total global PCB loss rate of 8,300 tons/year was estimated (Anderson and Hites 1996; Atkinson 1996). Rate constants for PCBs more chlorinated than hexa are not easily measured due to their low vapor pressures. It is difficult to introduce a significant amount of these PCBs into the gas phase and to collect their gas phase reaction products which could have even lower volatilities. For the PCBs that do react with OH radicals, a possible reaction scheme is the formation of a 2-hydroxybiphenyl intermediate, which quickly degrades by a series of dark reactions to chlorinated benzoic acid (see Figure 6-2; Brubaker and Hites 1998). The little information available suggests that photolysis of gas-phase PCBs in the troposphere will be negligible for those PCBs with #4 chlorine atoms, and this may be the case for the more chlorinated PCBs as well (Atkinson 1996).

Table 6-8. Plant Uptake (Bioaccumulation) of PCBs[a]

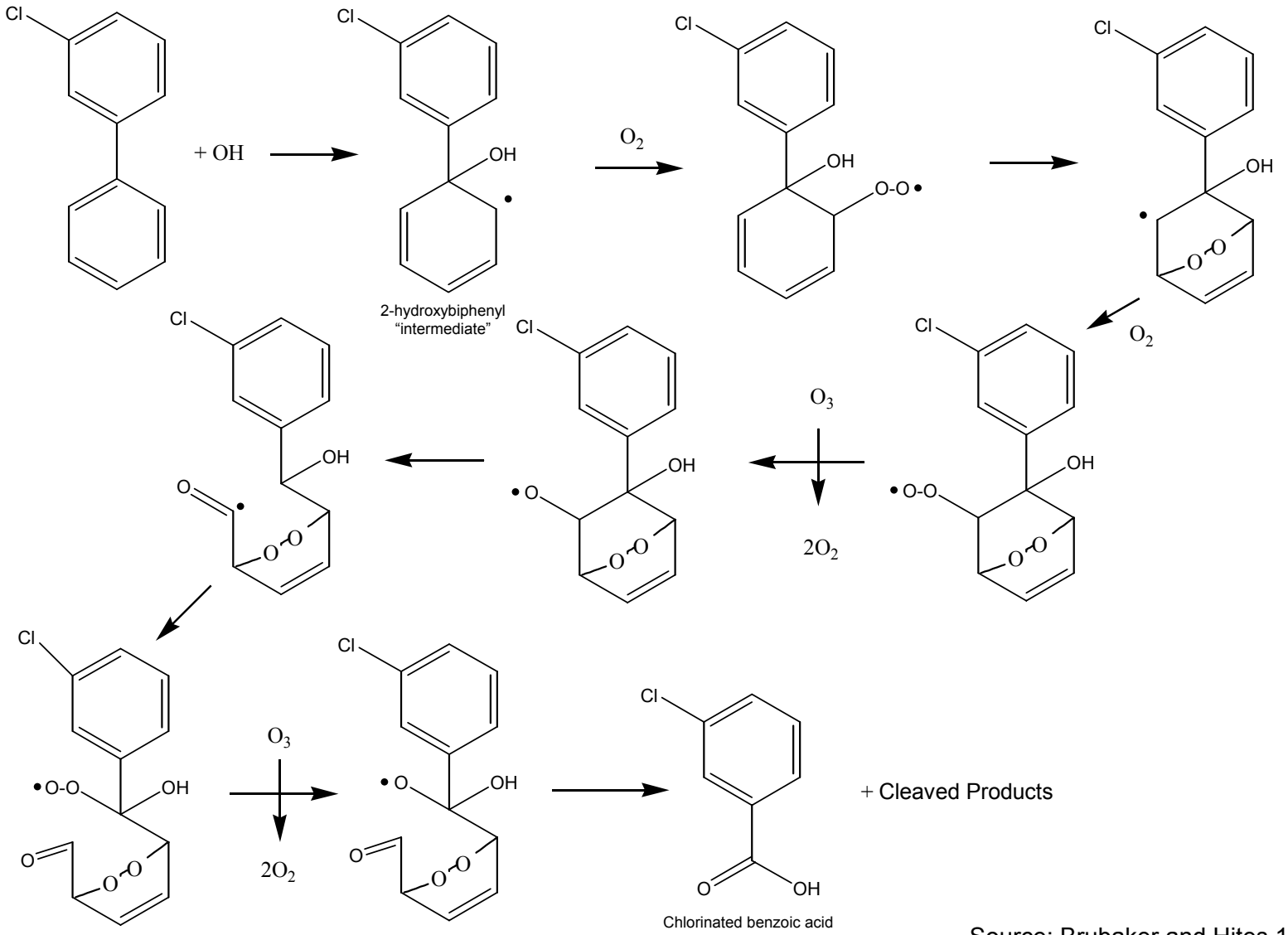
Crop (growth media)	Application rate	BAF[b]	Reference[a]
Carrot (soil)	Aroclor 1254 at 100 ppm mixed in top 6 inches of soil	<1 (Aroclor 1254) #0.16 (roots)	Iwata et al. 1974
Carrot (acid soil and brown sand)	Aroclor 1254 at 0.05, 0.5, and 5 ppm (acid soil); 0.5 ppm (brown sand)	0, << 1, <1, 0.16 (roots) <1, 0.16 (roots peels)	Wallnöfer et al. 1975
Carrot (soil)	PCB 4 at 1 ppm in dry soil, mixed in top 10 cm	<1 (di-PCB) 0.25 (roots) 0.25 (leaves)	Moza et al. 1976
Carrot (soil)	None	1.5 (PCB 52) 0.35 (PCB 101) 0.38 (PCB 138) 0.28 (PCB 153)	Cullen et al. 1996
Corn (field)	Aroclor 1254 and 1260 contaminated sludge (92–144 μg PCBs/L sludge)	<1	Lawrence et al. 1977
Lettuce (soil)	None	6.0 (PCB 52) 1.5 (PCB 101) 1.1 (PCB 138) 0.74 (PCB 153)	Cullen et al. 1996
Potato (soil)	None	0.29 (PCB 52) 0.01 (PCB 101) 0.17 (PCB 138) 0.28 (PCB 153)	Cullen et al. 1996
Radish (acid soil and brown sand)	Aroclor 1254 at 0.05 ppm (acid soil or brown sand), 0.5 ppm (acid soil); Aroclor 1224 at 0.2 ppm (brown sand);	0, 0, 0.02	Wallnöfer et al. 1975
	Aroclor 1254 at 5 ppm (acid soil) with moisture 40% of maximum water holding capacity	0.005	
Soybean sprouts (sandy soil)	Aroclor 1242 at 100 ppm	0.002	Suzuki et al. 1977
Sugarbeet (brown soil)	Aroclor 1254 at 0.3 ppm in soil	0.01 (leaves) to 0.5 (whole plant) 0.17 (root peels) 0.03 (peeled root)	Wallnöfer et al. 1975
Sugarbeet (field soil)	PCB 4 at 0.24 ppm in 0–10 cm soil layer and 0.17 ppm in 10–20 cm soil layer	0.07 (roots) 0.03 (leaves)	Moza et al. 1976
Tomato (soil and vermiculite)	PCB 4; PCB 7; PCB 18; PCB 52; PCB 101 (concentration not specified)	0 for all PCBs (mature plants)	Pal et al. 1980

Table 6-8. Plant Uptake (Bioaccumulation) of PCBs[a] *(continued)*

Crop (growth media)	Application Rate	BAF[b]	Reference[a]
Tomato	None	0.64 (PCB 52) 0.23 (PCB 101) 0.15 (PCB 138) 0.01 (PCB 153)	Cullen et al. 1996

[a]Sources: Cullen et al. 1996; Pal et al. 1980
[b]BAF = bioaccumulation factor; concentration of PCBs in plant tissue divided by the concentration in growth medium

Figure 6-2. Pathways for OH Radical-initiated Reaction of 3-Chlorobiphenyl



Source: Brubaker and Hites 1998

At the present time, insufficient data are available to assess the importance of photolysis and/or chemical reactions of particle phase congeners, although studies of Tysklind and Rappe (1991) and Koester and Hites (1992) on the photodegradation of polychlorinated dioxins and furans suggest that photolysis for particulate phase PCBs is not important (Atkinson 1996).

6.3.2.2 Water

In water, abiotic transformation processes such as hydrolysis and oxidation do not significantly degrade PCBs (EPA 1979h). Photolysis appears to be the only significant abiotic degradation process in water (EPA 1979h). Photolysis of PCBs occurs by photolytic cleavage of a carbon-chlorine bond followed by a stepwise replacement of chlorine with hydrogen which degrades PCBs (Barr et al. 1997; EPA 1979h). In all cases, the ring with the greatest degree of chlorination is the primary ring where dechlorination occurs. These dechlorination reactions have been reported to proceed by the loss of chlorine in the order of *ortho>para>meta* (Barr et al. 1997). Lepine et al. (1991) reported that for dechlorination of Aroclor 1254 (in cyclohexane) under natural sunlight, preferential removal of *ortho* chlorines led not only to decreases in many of the highly chlorinated PCB congeners but also to an increase in the concentrations of the toxic non-*ortho* coplaner congeners, PCBs 77 and 126. The estimated photolysis half-lives of mono- through tetrachlorobiphenyls with summer sunlight at a shallow water depth (<0.5 m) range from 17 to 210 days (EPA 1979h). Photolysis rates with sunlight are slower during winter (EPA 1979h). Nonetheless, as the number of chlorine substitutions increases, the light absorption band shifts toward longer wavelengths, and the photolysis rate for hepta- through deca-chlorinated biphenyls increases (EPA 1979h). The estimated photolysis half-lives (first-order) of 4-monoCB, 2,4-diCB, 2,4,6-triCB, 2,2',5,5'-tetraCB, and decachloro-CB (in 75% acetonitrile) were 210, 17, 53, 180, and <0.06 days, respectively (EPA 1983c). Bunce et al. (1978) predicted that for PCBs in shallow waters, on average up to 5% of the lightly chlorinated PCBs might lose a chlorine atom each year, but that at least one chlorine should be lost from every highly chlorinated PCB molecule annually. However, because the conditions of their experiments do not represent actual conditions in the environment, the PCB photolysis rate may be significantly lower.

The rate of PCB biodegradation in water is dependent on both individual congener structure and environmental conditions, as is explained in more detail in Section 6.3.2.3. Biodegradation in surface waters is primarily an aerobic process; in some, particularly oligotrophic waters, a substantial percentage of the total PCB concentration can be found in the dissolved phase (see Section 6.3.1; Eisenreich et al. 1983). The less chlorinated mono- and dichlorobiphenyl congeners are more likely to dissolve in water

than the more chlorinated congeners. These congeners are also more likely to biodegrade under aerobic conditions (Bailey et al. 1983; Wong and Kaiser 1975). In a river die-away study using filtered river water, the individual monochlorobiphenyl congeners were degraded by 50% within 2–5 days (Bailey et al. 1983). However, 2,2',4,4'-tetrachlorobiphenyl was not degraded over the 98-day study. The biodegradation of Aroclor 1221 proceeded rapidly in unfiltered lake water after a 4-day lag phase; within 1 month, the original mixture was completely degraded into metabolites of lower molecular weight (Wong and Kaiser 1975). However, Aroclor 1260 was not degraded over a 12-week period in three different unfiltered natural water samples (Oloffs et al. 1972). An Aroclor 1254 mixture was not mineralized over 96 days in a fresh water study; a further study using individual congeners, 2-chlorobiphenyl and 2,4'-dichlorobiphenyl, showed that the former was degraded to chlorobenzoic acid, a common intermediate in the aerobic biodegradation of PCBs, while the latter was not biodegraded (Shiarls and Sayler 1982). In general, these results are similar to those reported in aerobic soil and sediment studies where mono-, di-, and trichlorobiphenyl structures are fairly readily biodegraded, biphenyl rings containing five or more chlorine substituents are considered to be persistent, and tetrachlorobiphenyl congeners exhibit an intermediate persistence (Abramowitz 1990; Alcock et al. 1996; EPA 1979i; Gan and Berthouex 1994). Biodegradation rates in marine water may be slower than those reported in freshwater. The monochlorobiphenyl congeners had half-lives of approximately 8 months in sea water incubated at 10 EC (Carey and Harvey 1978). Aroclors 1221 and 1254 were individually added to sea water and exposed for 4–8 weeks in enclosures in the North Sea; no degradation of either PCB mixture was reported over this time (Kuiper and Hanstveit 1988). Biodegradation is potentially a more important process in soil and sediment than in water, particularly for the more highly-chlorinated congeners, for at least three reasons: the higher numbers of microorganisms present, the opportunity for anaerobic biodegradation, and the preferential partitioning of PCBs to soil and sediment (see Section 6.3.2.3).

6.3.2.3 Sediment and Soil

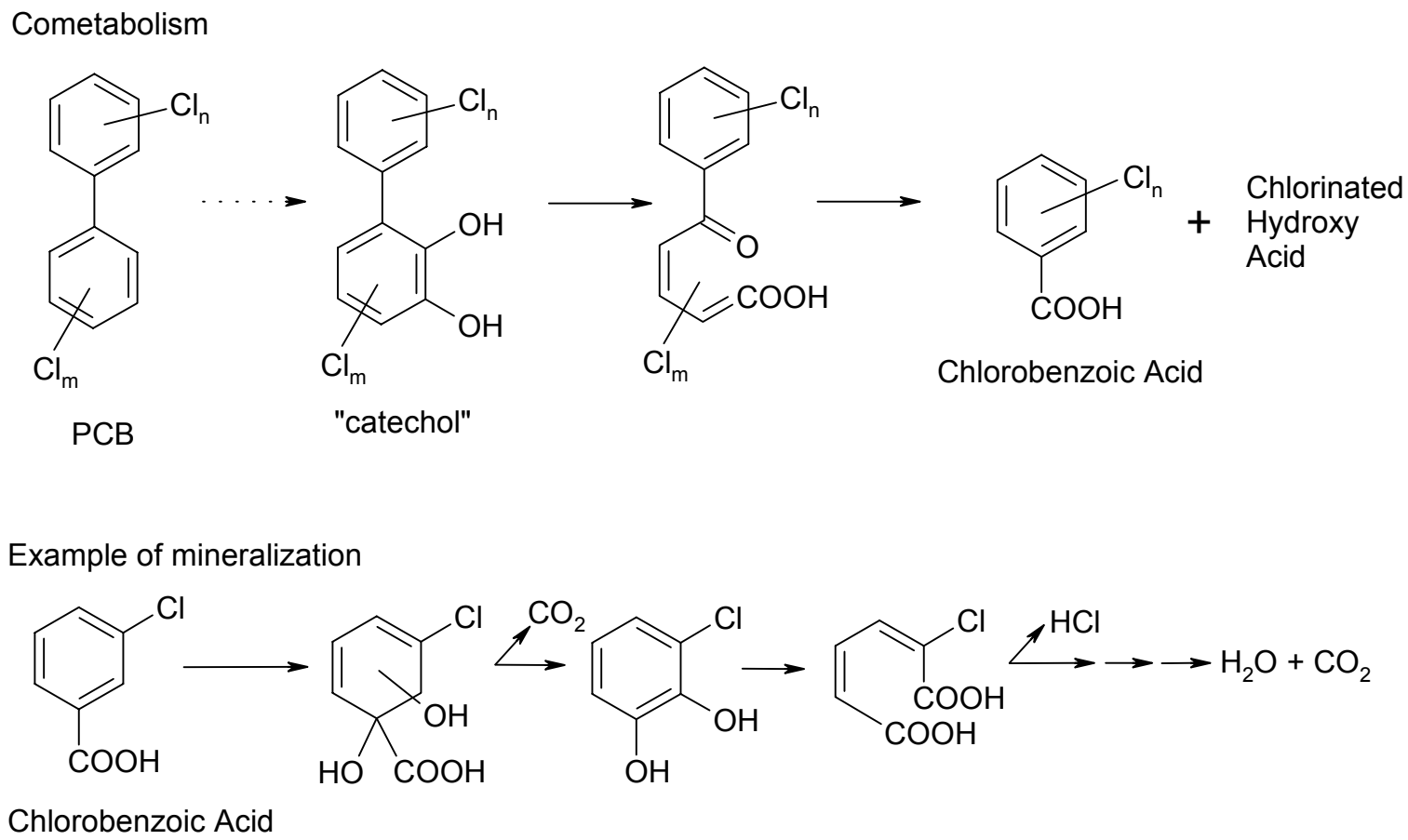
PCBs, particularly the highly chlorinated congeners, adsorb strongly to sediment and soil where they tend to persist with half-lives on the order of months to years (see Section 6.3.1; Gan and Berthouex 1994; Kohl and Rice 1998). There is no abiotic process known that significantly degrades PCBs in soil and sediment. However, photolysis of PCBs from surface soil may occur, and PCBs may also undergo base-catalyzed dechlorination (Chiarenzelli et al. 1995; Taniguchi et al. 1997); albeit, both of these processes are likely to be insignificant removal mechanisms.

Biodegradation has been shown to occur under both aerobic and anaerobic conditions and is a major degradation process for PCBs in soil and sediment, as reviewed by Higson (1992), Robinson and Lenn (1994), Bedard and Quensen (1995), and most recently by Wiegel and Wu (2000). While photolysis of PCBs from soil surfaces may also occur, and PCBs may also undergo base-catalyzed dechlorination (Chiarenzelli et al. 1995; Taniguchi et al. 1997), neither of these processes is likely to be a significant removal mechanism in soil and sediment.

Numerous bacterial and some fungal isolates have been reported to aerobically biodegrade PCBs in the literature (Abramowicz 1990). Experiments with both pure and mixed microbial cultures show that some congeners of PCBs, usually containing from one to four chlorine substituents, are readily biodegraded aerobically (Abramowitz 1990), although biodegradation of congeners containing up to six or seven chlorine atoms has been shown under enrichment conditions (Abramowitz 1990; EPA 1983c; Gibson et al. 1993). The most common process for the aerobic degradation of PCBs by bacterial cultures proceeds in two distinct steps: first bioconversion to the corresponding chlorinated benzoic acid and secondly, mineralization of the chlorobenzoate to carbon dioxide and inorganic chlorides (Robinson and Lenn 1994; Thomas et al. 1992). Each step requires a separate group of genes (Afghan and Chau 1989; Robinson and Lenn 1994; Sondossi et al. 1992; Unterman et al. 1989). This pathway is further detailed in Figure 6-3 (Abramowicz 1990; Robinson and Lenn 1994). The initial attack of the biphenyl structure involves addition of O_2 by a biphenyl 2,3-oxygenase forming the corresponding unstable dihydro-dihydroxybiphenyl, subsequent dehydrogenation to the dihydroxybiphenyl, followed by *meta* ring cleavage to the corresponding chlorinated benzoic acid and a 5-carbon hydroxy-acid (Abramowicz 1990; Flanagan and May 1993; Robinson and Lenn 1994; Sylvestre and Sondossi 1994; Thomas et al. 1992). Steric hindrance of 2,3-dioxygenation, where the chlorine substituents prevent access of the 2,3 carbon atoms to the enzyme's active site is believed to be responsible for the inability of many higher chlorinated congeners to be oxidized (Abramowitz 1990; Sylvestre and Sondossi 1994). Aerobic oxidation of PCBs has been identified in the environment. A study by Flanagan and May (1993) reported the presence of chlorobenzoic acids, as well as other metabolites where the biphenyl ring is retained and in contaminated sediment cores taken from the Hudson River, but not in uncontaminated cores obtained upstream from the site of contamination. 2,3-Dioxygenase attack can also result in the formation of ring-chlorinated acetophenone from 3-chlorophenyl, 2,5- or 2,4,5-chlorophenyl PCB rings (Bedard 1990; Bedard et al. 1987).

Aerobic biodegradation of PCBs in the environment occurs mainly in soils and surficial sediments. PCB congeners with three or less chlorine substituents (major components in Aroclors 1221 and 1232) are

Figure 6-3. Pathways for Aerobic Degradation of PCBs



Source: adapted from Adrigens et al. 1991; Robinson and Lenn 1994

considered to be non-persistent, while those with five or more chlorines (major components in Aroclors 1248, 1254, and 1260) are not readily degraded and considered to be persistent (Abramowitz 1990; Alcock et al. 1996; EPA 1979i; Gan and Berthouex 1994; Iwata et al. 1973). Tetrachlorobiphenyls (major components in Aroclors 1016 and 1242) are intermediate in persistence. Thus, the addition of a PCB mixture to an aerobic environment results in a fractionating effect where the less chlorinated species biodegrade first and leave behind, for long-term build-up, the more highly chlorinated species. For example, Williams and May (1997) report that the addition of Aroclor 1242 to aerobic Hudson River sediment samples and incubated at 4 EC for several months resulted in biodegradation following an initial lag phase of 1.4 months. More than 50% loss was reported in 5 months, particularly among specific di- and trichlorobiphenyls. A single added hexachlorobiphenyl congener (2,2',4,4',6,6'-hexachlorobiphenyl) was not degraded over 300 days. In sludge-amended soil, the dissipation half-lives (first-order kinetics) of PCB 18 and 28, and total PCBs were reported to be on the order of <1–8.5 years (Alcock et al. 1996). Gan and Berthouex (1994) reported that the disappearance of PCBs in farmland soil amended with PCB-contaminated sludge was slow with half-lives (first-order kinetics) of di-CBs ranging from 7 to 11 months, while the half-lives of the tri-CBs and tetra-CBs ranged from 5 to 17 months and from 11 to 58 months, respectively. The mineralization of 2-, 3-, 4-, 2,2',5,5'-, 2,2',4,4'-, 2,2',3,3',5,5'-, and 2,2',4,4',5,5'-chlorobiphenyl was measured in a Flanagan silt loam containing 3% organic material; after 98 days, 19.7, 16.5, 16.1, 0.7, 0.4, 0.8, and 0.1% of the initially added radiolabel was found as CO_2 (Fries and Marrow 1984). In addition to the degree of chlorination, the chlorine substitution pattern affects the biodegradation rate of PCBs. For example, Afghan and Chau (1989) and Furukawa and Matsumura (1976) demonstrated that PCBs containing chlorine substituents on only one ring are degraded more quickly than PCBs containing an equivalent number of chlorine substituents distributed between both rings. Additionally, PCBs with chlorines found in *ortho* positions, such as 2,2'- and 2,6-dichlorobiphenyl, are more resistant to aerobic biodegradation than those with chlorines found in either the *para* or *meta* positions (Bedard and Haberl 1990; Furukawa et al. 1978; Robinson and Lenn 1994). The incubation of Aroclor 1242 in aerobic Hudson River sediment resulted in an enrichment of di- and trichlorobiphenyl congeners with di-*ortho* chlorines on one ring or di-*para* chlorines; other di- and trichlorobiphenyls in the mixture were readily degraded (Williams and May 1997).

Aerobic degradation rates of PCBs can be highly variable, depending not only on structural characteristics as outlined above, but also on a number of other factors including previous exposure to PCBs or PCB-like compounds, bioavailability, initial concentration, moisture, temperature, available nutrients such as carbon sources, and the presence of inhibitory compounds. Biodegradation of PCBs in aerobic soil is slow, especially in soils that have a high organic carbon content. PCBs that remain firmly bound in soil

and sediment may not be bioavailable to the degrading organisms at sufficient concentrations. For example, in two soils containing >10% organic matter, only 5% biodegradation of Aroclor 1254 was observed after 1 year (Iwata et al. 1973). However, >25% biodegradation was observed after 1 year in a loamy, sandy soil containing only 0.1% organic carbon. In this study, the authors also observed that the less chlorinated PCB congeners were biodegraded more rapidly than the more highly chlorinated and tightly bound congeners (Iwata et al. 1973). Temperature also influences the rate of aerobic degradation. Williams and May (1997) evaluated the low temperature (4 EC) aerobic degradation of PCBs in sediment using Aroclor 1242-spiked samples of PCB-contaminated sediment from the Hudson River for several months. A 3- to 4-fold decrease in the rate of degradation was noted for sediment samples incubated at 4 EC versus those incubated at 25 EC. The aerobic biotransformation and biodegradation of PCBs can be enhanced by the use of adapted (pre-exposed) microbial populations and the addition of amenable substrates for co-metabolic and co-oxidative biotransformation. In a controlled laboratory aerobic microcosm sediment/water system, the half-lives (first-order kinetics) of Aroclors 1232, 1248, and 1254 were 61, 78, and 82 days, respectively, with no addition of substrates; 33, 39, and 36 days, respectively, with the addition of an amenable substrate; and 27, 32, and 36 days, respectively, with the addition of an amenable substrate and adapted microbes (Portier and Fujisaki 1988). Biphenyl or monochlorobiphenyls are commonly added as both growth substrates; they act to increase degradation rates through a cometabolic effect (Hurme and Puhakka 1997), as well as to induce the catabolic pathway required to sustain the growth of the PCB-degrading microbial population (Abramowicz 1990). Other studies report enhanced degradation rates in the presence of an added carbon source, such as sodium acetate, due to cometabolism (Pal et al. 1980). The efficiency of PCB degradation may also be controlled by the metabolite production pattern. Mono- and dichlorobenzoates, and possibly other higher chlorobenzoates formed from aerobic degradation of PCBs, have been shown to act as inhibitors towards further degradation of higher chlorinated PCBs (Guilbeault et al. 1994; Hickey et al. 1993; Robinson and Lenn 1994).

PCBs are slowly biodegraded in anaerobic environments by reductive dechlorination resulting in the formation of less toxic mono- and dichlorobiphenyl congeners, which are aerobically biodegradable (Abramowicz 1990, 1995; Anid et al. 1993; Brown et al. 1988; Chen et al. 1988; EPA 1983c; Larsson and Lemkemeier 1989; Pardue et al. 1988; Rhee et al. 1989). Until the 1980s, PCBs were not believed to be susceptible to anaerobic biodegradation based on studies measuring total PCB concentrations over time. Previous studies measured PCB loss as the change in total number of moles of PCBs over time. This generally remained the same as the biphenyl ring is not metabolized and only chlorine is released during reductive dechlorination. However, the overall congener distribution profile is markedly different

following anaerobic biodegradation. The profile shows a decrease in concentration of the more highly chlorinated congeners and a corresponding increase in overall proportion of the less chlorinated congeners (Bedard and Quensen 1995). For example, Aroclor 1242 added to anaerobic Hudson River sediment was incubated for 73 weeks; at the end of this period, di-, tri-, tetra-, penta-, and hexachlorinated congeners were reduced by 11, 73, 66, 73, and 94%, respectively, while the concentration of monochlorobiphenyl congeners increased by 76% (Anid et al. 1993). The original homolog distribution of Aroclor 1254 versus that after 13 months incubation in anaerobic sediment (100 mg/L treatment) is as follows (in mole percent): tri-, 2 versus 18%; tetra-, 22 versus 51%; penta-, 48 versus 22%; hexa-, 21 versus 8.5%; hepta-, 6 versus 0.5% (Hurme and Puhakka 1997). Microbial PCB dechlorination is widespread in many anaerobic environments, including freshwater (pond, lake, and river) (Bedard and Quensen 1995; Wiegel and Wu 2000), estuarine (Brown and Wagner 1990; Tiedje et al. 1993), and marine sediments (Ofjord et al. 1994) for congeners with up to 10 chlorine substituents (Hartcamp-Commandeur et al. 1996), although other authors report dechlorination occurring for up to 7 (Quensen et al. 1990), 8 (Abramowitz 1990; Kuipers et al. 1999), or 9 (Kuipers et al. 1999) chlorines only. During reductive dechlorination, anaerobic bacteria use chlorine as the terminal electron acceptor in a two-electron transfer reaction involving the addition of the electron to the carbon-chlorine bond, followed by chlorine (Cl^-) loss and subsequent hydrogen abstraction. The process of reductive dechlorination is illustrated in Figure 6-4 (Abramowicz 1990). Hydrogen (H_2) is assumed to be directly or indirectly the electron donor and water the source of protons (Nies and Vogel 1991), although other sources are possible. For reductive dechlorination to occur, a low redox potential similar to methanogenesis (Eh <-400 mV) and the absence of oxygen are thought to be required (May et al. 1992; Oremland 1988; Ye et al. 1992a), although some studies have shown that sulfidogenic redox conditions may also allow reductive dechlorination to proceed, but at a comparatively slower rate (Bedard and Quensen 1995; Hartkamp-Commandeur et al. 1996).

The most important structural factors determining whether a chlorine atom will be removed from a particular congener during anaerobic biodegradation include the position of the chlorine in relation to the opposite phenyl ring, the configuration of the surrounding chlorine atoms, the chlorine configuration of the opposite ring and, as summarized above, the total number of chlorine atoms. There are at least eight distinct, documented, reductive dechlorination pathways or processes, each resulting in a different congener distribution profile. These processes, M, Q, H, H', P, and N (and LP and T as in Wiegel and Wu 2000) are summarized in Table 6-9 (Bedard and Quensen 1995; Wiegel and Wu 2000; Wu et al. 1997). In any particular anaerobic environment, one or several of these processes may be occurring depending on the specificity that is developed by the adapted microbial population for dechlorination at a

Table 6-9. Positions of Chlorines Removed by Each Dechlorination Process[a]

Dechlorination process	Characteristic dechlorination products[a]	Susceptible chlorines	Susceptible Aroclors	Source of microorganisms
M	2 2, 2N / 2, 6[b] 2, 4N 2, 2N,4 2, 4, 4N 2, 2N, 6	Flanked and unflanked *meta*	1242 1248[a] 1254[a]	Upper Hudson Silver Lake
Q	2 2, 2N / 2, 6[b] 2, 3N 2, 2N, 5 2, 2N, 6 2, 3N, 6	Flanked and unflanked *para* *Meta* of 2, 3 group	1242 1248 1254	Upper Hudson
H !	2, 3N 2, 4N 2, 2N, 4 2, 2N, 5 2, 3N, 4 2, 3N, 5 2, 3N, 6 2, 4, 4N / 2, 4N, 5[b] 2, 2N, 4, 4N [c] 2, 2N, 4, 5N 2, 2N, 5, 5N 2, 2N, 3, 4N, 5[c] 2, 2N, 3, 5, 5N[c] 2, 2N, 3, 4N, 6[c] 2, 2N, 3, 5N, 6[c]	Flanked *para* *Meta* of 2, 3 and 2, 3, 4 groups	1242 1248 1254 1260	Upper Hudson Lower Hudson New Bedford

Table 6-9. Positions of Chlorines Removed by Each Dechlorination Process[a] *(continued)*

Dechlorination process	Characteristic dechlorination products[a]	Susceptible chlorines	Susceptible Aroclors	Source of microorganisms
H	2, 3N 2, 3N, 4 2, 3N, 5 2, 3N, 6 2, 4, 4N/ 2, 4N, 5[c] 2, 2N, 4, 4N 2, 2N, 4, 5N 2, 2N, 5, 5N 2, 2N, 2, 4N, 5 2, 2N, 3, 5, 5N 2, 2N, 3, 4N, 6 2, 2N, 3, 5N, 6	Flanked *para* Doubly flanked *meta*	1242 1248 1254 1260	Upper Hudson Lower Hudson New Bedford Silver Lake
P	2, 2N, 3, 5N 2, 2N, 4, 5N 2, 2N, 5, 5N 2, 2N, 3, 3N, 5 2, 2N, 3, 5, 5N	Flanked *para*	1254[a] 1260	Woods Pond Silver Lake
N	2, 4, 4N 2, 2N, 4, 4N 2, 2N, 4, 5N 2, 2, 4, 6N 2, 2N, 4, 4N, 6 2, 2N, 3, 4N, 5, 6	Flanked *meta*	1254 1260	Upper Hudson Silver Lake Woods Pond
LP	2, 2N, 4 2, 2N, 5 2, 2N, 6	Flanked and unflanked *para*	1260	Woods Pond
T	2, 2N, 4, 4N, 5, 5N 2, 2N, 3N, 4, 4N, 5 2, 2N, 3, 4, 4N, 5N, 6	Flanked *meta* of 2, 3, 4, 5 group in hepta- and octa-CBs	1260	Woods Pond

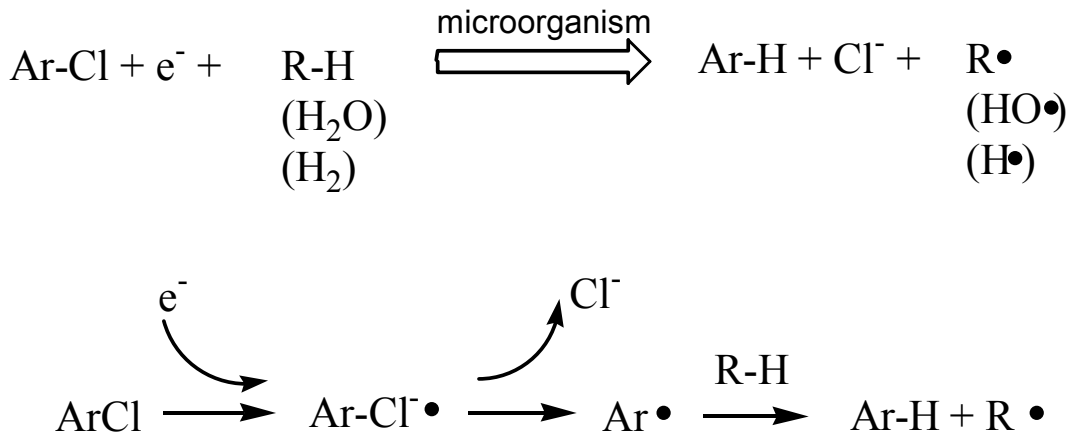
Source: Wiegel and Wu 2000; Wu et al. 1997; Bedard and Quensen 1995

[a]Products will vary depending on the congener composition of the PCB mixture being dechlorinated.

[b]Overlapping gas chromatograph peaks

[c]Proposed products from Aroclors 1254 and 1260

Figure 6-4. Possible Mechanism for Reductive Dechlorination by Anaerobic Microorganisms



Source: Abramowicz 1990

particular position or dechlorination of a particular type of PCB (Alder et al. 1993; Bedard and Quensen 1995; Kuipers et al. 1999; May et al. 1989; Morris et al. 1992; Quensen et al. 1998; Robinson and Lenn 1994; Sokol et al. 1994; Tiedje et al. 1993; Wiegel and Wu 2000; Ye et al. 1992a; Zwiernik et al. 1998).

These processes can be combined at a single site producing different distribution profiles; combinations of M and H or M and H' have been observed (Bedard and Quensen 1995) as well as a combination of processes M and Q commonly called process C (Bedard and Quensen 1995). For example, it was observed that chlorine substituents were removed from only *meta* and *para* positions in Hudson River sediment contaminated with Aroclor 1242 resulting in a high proportion of *ortho* substituted mono- and di-chlorinated PCBs. The distribution profile of this sediment was believed to be due to dechlorination processes M, Q, and H or H' (Abramowicz et al. 1995; Bedard and Quensen 1995; Brown et al. 1984, 1987a, 1987b). In Silver Lake sediment contaminated with both Aroclor 1254 and 1260, *meta* and *para* chlorines were also preferentially removed (Williams 1994). However, *ortho* dechlorination of 2,4,6-CB was observed in cultures of Silver Lake sediment, suggesting a combination of dechlorination processes H, P, N, M, and Q (Bedard and Quensen 1995; Brown et al., 1984, 1987a, 1987b). While *ortho* dechlorination has been shown in the environment (Berkaw et al. 1996; Van Dort and Bedard 1991; Wu et al. 1998), most of the commonly reported processes outlined in Table 6-9 do not dechlorinate *ortho* chlorines resulting in the accumulation of less chlorinated, primarily *ortho*-substituted, PCB congeners due to anaerobic biodegradation (Abramowicz 1990, 1995; Bedard and May 1996; Berkaw et al. 1996; Brown et al. 1987; David et al. 1994; Morris et al. 1992; Nies and Vogel 1990; Rhee et al. 1993a, 1993b; Robinson and Lenn 1994; Tiedje et al. 1993; Van Dort and Bedard 1991; Wiegel and Wu 2000; Ye et al. 1992a).

The rate, extent, and specificity of anaerobic dechlorination can vary greatly even in the same sediment based on a number of environmental factors (Wiegel and Wu 2000). These include previous exposure to PCB or PCB-like compounds, electron acceptor availability, bioavailability, presence of co-contaminants, oxygen tension, redox level, temperature, pH, salinity, inhibitory compounds, available carbon and nutrients, and trace metals. Optimum rates of PCB dechlorination usually occur in the concentration range of 100–1,000 ppm (wet weight). Below a certain threshold concentration (<50 ppm), the rate of dechlorination is often very slow or non-quantifiable (Quensen et al. 1988; Rhee et al. 1993a; Robinson and Lenn 1994; Sokol et al. 1995, 1998). For example, Abramowicz et al. (1995) found that 93% of sediment samples containing >100 μg/g PCBs were extensively dechlorinated compared with only 63% of samples containing 5–10 μg/g. However, it should be noted that the reductive dechlorination of many PCB congeners in Aroclor mixtures has been observed even when their individual concentrations were

<1 μg/g (Quensen et al. 1990; Schultz et al. 1989). PCBs generally remain tightly bound in soil and sediment, and may not be bioavailable to the biodegrading organisms even at optimum concentrations. The requirement of an optimum concentration (>50 ppm) may make this bioavailability factor critical for dechlorination of PCBs (Robinson and Lenn 1994; Tiedje et al. 1993). Bimodal desorption kinetics with both PCB-spiked and environmental sediments has been observed; approximately 50% of the initially present PCB mixture was found to be resistant to desorption with 50% of the resistant fraction desorbed over the following 6 months (Carroll et al. 1994; Harkness et al. 1993). Other authors report that desorption may not be as important given the slow rate of dechlorination of the more chlorinated congeners (Alder et al. 1993; Bedard et al. 1993). Addition of compounds, such as sodium lignisulfonate, that can increase the solubility of PCBs in soil and sediment has been shown to increase the rate of biodegradation (Sugiura 1992). Temperature is also an important factor controlling the rate of microbial dechlorination (Tiedje et al. 1993; Wiegel and Wu 2000; Wu et al. 1996, 1997). Temperatures in the range of 12–25 EC supported dechlorination, while dechlorination was not observed at temperatures >37 EC (Tiedje et al. 1993). Wu et al. (1997) reported optimal temperatures for overall chlorine removal of 20–27 EC in Woods Pond sediment contaminated with Aroclor 1260. Acid/base conditions may also affect the reductive dechlorination process. For example, the optimal pH for removal of chlorines in Woods Pond sediment contaminated with Aroclor 1260 and spiked with 2,3,4,6-tetraCB was approximately 7.0–7.5 (Wiegel and Wu 2000). The stereospecificity of dechlorination also varied as a function of pH with flanked *meta* dechlorination (Process N) occurring at pH 5.0–8.0, unflanked *para* dechlorination (Process LP) at pH 6.0–8.0, and *ortho* dechlorination at pH 6.0–7.5 (Wiegel and Wu 2000). As PCB-dechlorinating microorganisms are not able to cleave and utilize the biphenyl ring as a carbon and electron source, other compounds (e.g., mineral nutrients, electron donors, and carbon compounds) are required to help co-metabolize PCBs (Alder et al. 1993; Klasson et al. 1996; Sugiura 1992; Tiedje et al. 1993; Wiegel and Wu 2000). Alder et al. (1993) demonstrated that repeated addition of fatty acids (e.g., acetate, propionate, butyrate, and hexanoic acid) stimulated dechlorination of PCBs in carbon-limited sediment slurries, but not in sediment slurries with higher organic carbon contents. The omission of trace metals resulted in a slight reduction in the rate and extent of Aroclor 1242 dechlorination by Hudson River microorganisms (Abramowicz et al. 1993). Inhibition of PCB dechlorination can occur in the environment. Sokol et al. (1994) reported that high concentrations of co-contaminants at a site in the St. Lawrence River prevented dechlorination from occurring. Electron acceptors present in the environment may influence PCB reductive dechlorination. While most studies show reductive dechlorination of PCBs only under methanogenic and sometimes sulfidogenic conditions (Kuo et al. 1999; Ye et al. 1999), Morris et al. (1992) reports that dechlorination was shown under

denitrifying and iron(III) reducing conditions as well (Bedard and Quensen 1995). Rates of dechlorination have been shown to be fastest in methanogenic (the most reducing) environments.

In the environment, aerobic and anaerobic biodegradation processes are often not readily separated and a combination of the two may be fairly common in aquatic environments. Hudson River sediment microcosms, spiked with Aroclor 1242, were designed with an aerobic surface sediment layer overlying a deeper anaerobic layer (Fish and Principe 1994). The distribution profile of congeners following degradation, was characterized by the authors as corresponding to a combination of process M dechlorination and aerobic biodegradation. Total PCB concentration decreased from 64.8 to 18.0 μmol/kg sediment in 140 days. More recent studies have examined the potential of sequential anaerobic-aerobic treatment to degrade PCBs. As shown above, reductive dechlorination of PCBs in the environment often results in the accumulation of mono- and dichlorobiphenyls, the most commonly reported being the *ortho*-substituted congeners: 2-chlorobiphenyl, and 2,2'-, 2,4'-, 2,6-, 2,4-, and 2,3-dichlorobiphenyls (Adriaens and Grbic-Galic 1994). Hudson River sediment, containing 700 μg/g Aroclor 1242, showed 55% removal of total chlorine after 16 weeks, but only from *meta* and *para* positions; the percentage of mono- and dichlorobiphenyls increased from 9 to 88% (Quensen et al. 1988). In a 73-day field study, aerobic biodegradation of a anaerobic sediment previously contaminated with Aroclor 1242 (upon release containing 9%, but at the time of the study containing 62–73%, mono- and dichlorobiphenyls) resulted in 35–55% further degradation of the less chlorinated PCBs, particularly when oxygen, biphenyl, and inorganic nutrients were provided (Harkness et al. 1993). However, the extent and type of dechlorination is not predictable from site to site, and congeners remaining from anaerobic biodegradation may also be resistant to aerobic biodegradation. For example, dechlorination of Aroclor 1254 in sediment resulted in the accumulation of tri- and tetrachlorobiphenyl congeners; they were not dechlorinated further to mono- and dichlorobiphenyls in this sediment and would be expected to be comparatively more resistant to aerobic biodegradation (Hurme and Puhakka 1997). The reductive dechlorination of Aroclor 1254 in a marine sediment system resulted in the accumulation of *ortho* tetra- and pentachlorobiphenyls. When this culture was then subjected to aerobic biodegradation, no biodegradation was shown over 2 months. Many of the remaining congeners had either two *ortho* or two *para* groups, making them resistant to aerobic biodegradation as well (Mannisto et al. 1997).

Biodegradation of PCBs in aerobic or anaerobic groundwater has not been studied, although PCBs have been reported in groundwater environments (Section 6.4.2). In aerobic groundwater, the less-chlorinated PCB congeners, which would be more likely to leach, would presumably degrade based on studies in aerobic surface waters and soil. However, groundwater is also commonly anaerobic and, as is covered in

this section, microbial degradation under this oxygen condition proceeds for even the more highly chlorinated congeners. In a contaminant plume, as might be seen at a landfill site, sequential dechlorination of the more highly chlorinated PCB congeners may occur in the anaerobic plume while aerobic biodegradation at the anaerobic/aerobic interface of the plume edge may degrade some of the less chlorinated PCBs.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to PCBs depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. With respect to PCB analysis, comparisons among various studies are complicated by the fact that authors may report PCB concentrations as Aroclors, as homologs, or as congeners. Historically, Aroclor analysis has been performed by most laboratories. This procedure can, however, result in significant error in determining total PCB concentrations (Schwartz et al. 1987) and in assessing the toxicological significance of PCBs because it is based on the assumption that distribution of PCB congeners in environmental samples and parent Aroclors is similar. The distribution of PCB congeners in Aroclors is, in fact, altered considerably by physical, chemical, and biological processes after their release into the environment, particularly when the process of biomagnification is involved (Oliver and Niimi 1988; Smith et al. 1990). Only recently has it become more common to determine the concentration of individual PCB congeners. However, major problems have been associated with the identification of the individual congeners, as only a limited number of standards have been available (Larsen 1995). In addition, in those studies that report results as total PCBs, the definition of what constitutes total PCBs (i.e., how many and which congeners are summed) is often not the same in the various studies. Problems related to chemical analysis procedures and reporting of total PCBs are discussed in greater detail in Chapter 7. In reviewing data on levels monitored or estimated in the environment, it should be noted that the amount of the chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. Monitoring studies indicate that atmospheric concentrations of PCBs tend to be dominated by lower chlorinated, more volatile congeners, especially at northern latitudes (Halsall et al. 1999; Harner et al. 1998; Ockenden et al. 1998). Concentrations in soils and sediments, which are dominated by highly chlorinated congeners, have followed a downward trend over time and appear to have reached a steady state concentration in several locations (Bopp et al. 1998; Lead et al. 1997; Van Metre et al. 1998). Water monitoring studies indicate that PCB concentrations have also decreased since the late 1970s due to the cessation of production and manufacturing (Anderson et al. 1999; Jeremiason et al. 1998). Aquatic species, including fish and sea mammals, have shown a similar downward trend in PCB contamination with highly chlorinated

congeners being preferentially bioconcentrated (Troisi et al. 1998; Ylitalo et al. 1999; Young et al. 1998). Studies indicate that PCB concentrations increase with respect to trophic level; organisms that reside higher on the food chain tend to have higher concentrations of PCBs (Kucklick and Baker 1998; Letcher et al. 1998).

6.4.1 Air

PCB atmospheric concentrations have been detected in all areas of the world due to the high amount of past usage and their great persistence. Because of variations of several orders of magnitude, units in the following section will vary; caution is recommend. Based on several observations, atmospheric concentrations of PCBs are generally higher during summer than winter months due to higher rates of vaporization associated with higher summer temperatures (Franz and Eisenreich 1993; Haugen et al. 1999; Ockenden et al. 1998). In studies that have consistently monitored PCB concentrations in a single location, researchers have noticed a decreasing trend. Due the high degree of PCB contamination, the Great Lakes region of the United States has been closely monitored. From 1991 to 1997, scientists studied the change in atmospheric PCB concentration at the city of Chicago and Lakes Superior, Michigan, and Erie (Simcik et al. 1999). Gas-phase concentrations were found to have decreased in Chicago and near Lake Michigan and Erie, but remained fairly constant near Lake Superior. Atmospheric half-lives for all individual congeners near Lake Michigan ranged from 0.5 to 5.9 years and averaged 2.1±0.1 years; half-lives at Lake Erie ranged from 0.7 to 7.5 years and averaged 2.6±0.1 years, while half-lives at Chicago ranged from 0.6 to 5.6 years and averaged 2.7±1.3 years (Simcik et al. 1999). In another study, high volume air samples collected in Green Bay in 1989 and from several Great Lakes in 1990 were analyzed for PCB concentrations (McConnell et al. 1998). The concentration of PCBs over Green Bay ranged from 0.060 to 0.560 ng/m^3, while over Lakes Michigan, Huron, Erie, and Ontario, concentrations ranges were 0.17–0.44, 0.16–0.20, 0.12–1.30, and 0.24–0.37 ng/m^3, respectively. Air concentrations of PCBs over Lake Huron were consistently lower than the other Great Lakes, while the highest PCB concentrations were detected in the eastern- and western-most regions of Lake Erie, with 1.30 ng/m^3 observed near Detroit, Michigan and 1.10 ng/m^3 observed near Buffalo, New York (McConnell et al. 1998). Overall, the mean total concentration of PCBs over all five Great Lakes was 0.385 ng/m^3. Interestingly, the relative composition of PCBs detected over Green Bay was dominated by tri- and tetrachlorinated biphenyls with these two homologs representing approximately 70–85% of total PCBs. Over the Great Lakes, however, researchers noticed a shift towards the higher chlorinated congeners with tri-, tetra-, and pentachlorinated biphenyls contributing 25–35% each to total PCBs (McConnell et al. 1998). The difference in congener speciation in air samples is explained by increased

air temperatures during air sampling done in summer over the Great Lakes compared to the measurements taken during the winter and spring at Green Bay. Wind direction has also been shown to play a role in atmospheric PCB concentrations over the Great Lakes. Atmospheric concentrations were measured from 1994 to 1995, 15 km from Chicago above Lake Michigan (Zhang et al. 1999). Researchers found that the concentration of PCBs ranged from 0.132 to 1.120 ng/m^3. During periods of southerly winds from urban Chicago, researchers noticed that the average concentration of PCBs in the atmosphere became 5 times higher (Zhang et al. 1999). The same phenomenon was observed in Green Bay where atmospheric concentrations of PCBs were elevated in samples taken closest to the city of Green Bay, Wisconsin. From late 1989 to mid 1990, air samples collected over water and nearby land in the Green Bay region were analyzed for PCBs (Hornbuckle et al. 1993). Researchers found that PCB concentrations were greater in air samples collected from southern Green Bay (0.670–2.200 ng/m^3) than over northern Green Bay (0.160–0.520 ng/m^3). PCB concentrations detected over land ranged from 0.070 to 0.760 ng/m^3. At all sites, tri-, tetra-, and pentachlorinated biphenyls were detected most frequently and at the highest concentrations (Hornbuckle et al. 1993). Analysis of Green Bay water samples revealed that the congener distribution in the atmosphere directly correlated with the congener distribution in adjacent water samples.

Inputs of PCBs to the Great Lakes region is influenced heavily by atmospheric transport and deposition (Franz et al. 1998, Jeremiason et al. 1998). Based on current and temporal studies, it appears that the amount of PCBs being added to the Great Lakes region through dry deposition has decreased over time. From 1993 to 1995, the dry deposition of PCBs was studied for the Lake Michigan Air Basin (Franz et al. 1998). The geometric mean fluxes of total PCBs at Chicago (Illinois), over Lake Michigan, South Haven (Michigan), and Sleeping Bear Dunes (Michigan) were 0.21, 0.079, 0.14, and 0.057 μg/m^2-day, respectively. Annually, PCB input to Lake Michigan by dry deposition is expected to be approximately 1,100 kg. This is approximately 3 times less compared to measurements conducted in 1979. The study also found a strong correlation between sediment accumulation of PCBs and dry deposition to Lake Michigan. It suggests that dry deposition may account for most of the particulate PCBs accumulating in the sediments of Lake Michigan (Franz et al. 1998).

The atmospheric concentration of PCBs in various geographic locations worldwide are summarized in Table 6-10. In general, atmospheric levels of PCBs appear to be decreasing over time with higher levels of PCBs being detected in urban sites compared to rural locations. For example, the atmospheric concentrations of PCBs measured in urban and rural Baltimore locations in June of 1996 were 0.38–3.36 and 0.02–0.34 ng/m^3, respectively (Offenberg and Baker 1999). The study found that total

Table 6-10. Atmospheric Concentrations of Polychlorinated Biphenyls

Location[a]	Year	Concentration[b] (ng/m^3)	Reference
URBAN AREAS			
Urban areas	Late 1970s–early 1980s	5–10 (0.5–30)	Eisenreich et al. 1981
Boston, MA	1978	7.1	Bidleman 1981
Columbia, SC	1978	4.4	Bidleman 1981
College Station, TX	1979–1980	0.29 (0.11–0.48)	Atlas and Giam 1987
Columbia, SC	1985	2.3	Foreman and Bidleman 1987
Bloomington, IN	1986–1988	Summer: 1.74–3.84[c], Winter: 0.31–0.62	Hermanson and Hites 1989
Newport News, VA	1988	0.39±0.434[d]	Knap and Binkley 1991
Chicago, IL	1988	1.3 (geometric) (0.3–9.9)	Cotham and Bidlemen 1995
Chicago, IL	1989–1990	13.5 (7.55–20.26)	Holsen et al. 1991
Urban areas	Late 1980s–early 1990s	5 (1–10)	Eisenreich et al. 1992
Manchester, England	1991–1992	1.160 (0.223–2.260)	Halsall et al. 1999
Cardiff, England	1991–1992	1.490 (0.415–3.710)	Halsall et al. 1999
Chicago, IL	1994	(0.27–14)	Simcik et al. 1997
New Bedford, MA	1994–1995	0.4–5.3, near harbor sediment remediation 0.1–8.2 background reference	Vorhees et al. 1997
Baltimore, MD	1996	(0.38–3.36)	Offenberg and Baker 1999
New Brunswick, NJ	1997	0.482 (0.092–3.200)	Brunciak et al. 1999
Sturgeon Point, NY	1997	0.369	Brunciak et al. 1999
RURAL AREAS			
Rural areas	Late 1970s–early 1980s	0.8 (0.1–2)	Eisenreich et al. 1981
Adirondack, NY	1985	0.95±0.277[d]	Knap and Binkley 1991

Table 6-10. Atmospheric Concentrations of Polychlorinated Biphenyls *(continued)*

Location[a]	Year	Concentration[b] (ng/m^3)	Reference
RURAL AREAS *(contd)*			
Ontario, Canada	1988–1989	0.2 (0.55–0.823)	Hoff et al. 1992
Continental areas	Late 1980s–early 1990s	0.5 (0.2–1.5)	Eisenreich et al. 1992
Northwest England	1990–1991	(0.0463–0.471)	Halsall et al. 1999
Lista, Norway	1992–1995	0.114	Haugen et al. 1999
Arctic Sites (Canada, Siberia)	1993	0.17, 0.34	Stern et al. 1997
Lake Tahoe Basin, CA, NV	1995	average 0.072	Datta et al. 1998a
Lancaster University, UK	1995	0.190 (summer), 0.080 (winter)	Ockenden et al. 1998
Baltimore, MD	1996	(0.02–0.34)	Offenberg and Baker 1999
MARINE/COASTAL AREAS			
Marine	Late 1970s–early 1980s	0.5 (0.05–2)	Eisenreich et al. 1981
Bermuda	1986	0.2±0.175[d]	Knap and Binkley 1991
Chesapeake Bay	1990–1991	0.21 (0.017–0.508)	Leister and Baker 1994
Marine/coastal	Late 1980s–early 1990s	0.1 (0.01–0.7)	Eisenreich et al. 1992
Green Bay, WI	1989–1990	(0.070–0.760)	Hornbuckle et al. 1993
Baltic Sea	1990–1993	0.057 (0.032–0.080)	Agrell et al. 1999
Chesapeake Bay	1996	(0.21–0.74)	Offenberg and Baker 1999
Chesapeake Bay	1997	0.210	Brunciak et al 1999
GREAT LAKES REGION			
Great Lakes	Late 1970s–early 1980s	1 (0.4–3.0)	Eisenreich et al. 1981
Lake Superior	1986	1.25	Baker and Eisenreich 1990
Green Bay	1989	0.330	McConnell et al. 1998
Great Lakes	Late 1980–early 1990s	1 (0.2–4.0)	Eisenreich et al. 1992

Table 6-10. Atmospheric Concentrations of Polychlorinated Biphenyls *(continued)*

Location[a]	Year	Concentration[b] (ng/m^3)	Reference
GREAT LAKES REGION *(contd)*			
South Green Bay	1989–1990	(0.670–2.200)	Hornbuckle et al. 1993
North Green Bay	1989–1990	(0.160–0.520)	Hornbuckle et al. 1993
Lake Michigan	1990	(0.170–0.440)	McConnell et al. 1998
Lake Huron	1990	(0.160–0.200)	McConnell et al. 1998
Lake Erie	1990	(0.120–1.300)	McConnell et al. 1998
Lake Ontario	1990	(0.240–0.370)	McConnell et al. 1998
Great Lakes	1990	(0.089–0.370)[e]	Hillery et al. 1997
Southern Lake Michigan	1994	(0.014–1.1)	Simcik et al 1997
Lake Michigan	1994–1995	(0.132–1.120)	Zhang et al. 1999
REMOTE AREAS			
Remote areas	Late 1970s–early 1980s	0.1 (0.02–0.5)	Eisenreich et al. 1981
Antarctica	1981–1982	(0.02–0.18)	Tanabe et al. 1983
Arctic	1986–1987	0.02	Baker and Eisenreich 1990
Barents Sea	1996	0.126	Harner et al. 1998
Eastern Arctic	1996	0.074	Harner et al. 1998
Norwegian Sea	1996	0.025	Harner et al. 1998

[a]Post office state abbreviations used
[b]Values are given as mean concentrations. The ranges are given in parentheses unless otherwise noted.
[c]Values at three different sites
[d]Standard deviation
[e]Values for three sites

PCBs detected in air were dominated by tri- and tetrachlorinated congeners. Atmospheric deposition of PCBs to the New York/New Jersey Bight area were monitored in 1997 (Brunciak et al. 1999). The average atmospheric concentrations of total PCBs at New Brunswick New Jersey, Sturgeon Point, New York, and Chesapeake Bay, Maryland were 0.482, 0.369, and 0.210 ng/m^3, respectively. From 1991 to 1992, air samples from the urban cities of Manchester and Cardiff, England and from three rural sites located in northwestern England were analyzed for PCBs (Halsall et al. 1999). As was expected, urban locations had much higher PCB concentrations than rural sites. The cities of Manchester and Cardiff had average PCB concentrations of 1.160 ng/m^3 (range, 0.223–2.360) and 1.490 ng/m^3 (range, 0.415–3.710), respectively, while rural sites had average PCB concentrations ranging from 0.0463 to 0.471 ng/m^3. Irrespective of location, air samples were dominated by tri- and tetrachlorinated biphenyls (Halsall et al. 1999). Air samples at a semirural site near Lancaster University, United Kingdom were monitored for PCBs in 1995 (Ockenden et al. 1998). The mean concentration of PCBs during the summer and winter months were 0.190 and 0.080 ng/m^3, respectively. Concentrations of trichlorobiphenyls dominated both the winter and summer sampling months. A 4-year study monitored atmospheric concentrations each week in Lista, Norway from 1992 to 1995 to determine temporal and seasonal changes in PCB concentrations (Haugen et al. 1999). The geometric mean concentration of PCBs was 0.114 ng/m^3 with concentrations approximately 3 times higher during summer than winter season. The congeners found in the highest concentrations were PCBs 101 (30.5% at 0.0482 ng/m^3), 138/163 (33.2% at 0.0484 ng/m^3), and 153 (23.8% at 0.0373 ng/m^3) (Haugen et al. 1999). Overall, there was no significant change in total PCB concentrations from 1992 to 1995.

Even in remote areas of the world, atmospheric concentrations of PCBs have been observed. From 1986 to 1987, the mean concentration of PCBs was 0.02 ng/m^3 in the Arctic while from 1981 to 1982, PCBs ranged from 0.02–0.18 ng/m^3 in the Antarctic (Baker and Eisenreich 1990; Tanabe et al. 1983) (see Table 6-10). From 1988 to 1990, atmospheric levels of two pentachlorobiphenyls (PCBs 101 and 110) in Antarctic air were 0.0025 and 0.0022 ng/m^3, respectively, while two hexachlorobiphenyls (PCBs 135 and 153) were 0.0021 and 0.0023 ng/m^3, respectively (Lohmann and Jones 1998). Stern et al. (1997) measured PCB levels in air at five Arctic locations in 1993 and reported that, while there was no correlation with temperature, the atmospheric trichlorinated PCB congeners tended to be lower during the warmer months than during colder months. In the summer of 1996, researchers analyzed Arctic air samples for PCB concentrations (Harner et al. 1998). Average concentrations in the Barents Sea, eastern Arctic, and Norwegian Sea were 0.126, 0.024, and 0.075 ng/m^3, respectively. The study also monitored the levels of some of the more toxic coplanar PCBs. It was found that the concentrations of PCBs 77 and 126 in Arctic air samples were 3–40 and 0.3–8 fg/m^3, respectively. These values were approximately an

order of magnitude lower than levels found in urban areas. For example, air samples obtained from Chicago in 1995 had mean concentrations of PCBs 77 and 126 of 420 and 63 fg/m^3, respectively (Harner et al. 1998). Interestingly, the northeast Arctic Ocean profile was dominated by lower molecular weight tri- and tetrachlorinated biphenyls, while the more southern Barents Sea air samples were enriched in the higher penta- and hexachlorinated biphenyls.

Several studies have indicated that indoor air concentrations of PCBs are generally greater than outdoor concentrations. In 1984, indoor air samples from seven public buildings in Minnesota were monitored for several Aroclors (Oatman and Roy 1986). The mean total Aroclor concentration in indoor air of the three buildings using PCB transformers (457±223 ng/m^3) was found to be nearly twice as high as that in the air of the four buildings not using PCB transformers (229±106 ng/m^3). The Aroclor levels detected in the indoor air of all seven buildings were significantly higher than those detected in ambient outdoor air (Balfanz et al. 1993; Eisenreich et al. 1992; MacLeod 1981; Oatman and Roy 1986). When the indoor air in a number of laboratories, offices, and homes was monitored for various Aroclors, the "normal" indoor air concentrations of PCBs were at least one order of magnitude higher than outdoor levels (MacLeod 1981). For example, average PCB levels were 100 ng/m^3 inside an industrial research building and 210 ng/m^3 inside the laboratories themselves, compared to <20 ng/m^3 in air samples from outside the facility. The mean PCB indoor air concentration in one home was 310 ng/m^3, while the average air concentration outside the home on the same day was 4 ng/m^3. Indoor air PCB concentrations measured in public buildings in Bloomington, Indiana were 5–300 times greater than outdoor air concentrations (6–310 ng/m^3 indoor air averages, 1.5 ng/m^3 outdoor air), with indoor air concentrations highest in older buildings (Wallace et al. 1996). It has been suggested that certain electrical appliances and devices (e.g., fluorescent lighting ballasts) and building materials (elastic sealant), which have PCB-containing components, may emit PCBs into the indoor air, thereby elevating indoor PCB levels significantly above outdoor background levels (Balfanz et al. 1993).

Indoor air concentrations of PCBs in 34 homes near New Bedford Harbor, Massachusetts were measured between April 1994 and April 1995 during the dredging of contaminated river sediments. PCB levels in indoor air samples ranged from 7.9 to 61 ng/m^3 in homes closest to the dredging operation compared to more distant houses which had levels ranging from 5.2 to 51 ng/m^3 (Vorhees et al. 1997). However, these indoor concentrations exceeded outdoor concentrations by an average ratio of 32, indicating the importance of indoor air concentrations to human exposures. House dust was also analyzed for PCB contamination at these homes (Vorhees et al. 1999). House dust samples had PCB concentrations ranging from 260 to 23,000 ng/g, but did not differ significantly between houses closest to the dredging operation

and those a few miles away from the dredging operation. In general, the house dust samples contained higher concentrations of the more volatile, less chlorinated PCBs. The results of the house dust data were then compared to house dust samples from homes that were not located near known PCB sources. In nine Seattle, Washington homes, house dust had PCB concentrations ranging from 240 to 760 ng/g and in eight Columbus, Ohio homes, concentrations ranged from 210 to 1,900 ng/g (Vorhees et al. 1999). It appeared that PCB concentrations were generally lower in these locations compared to the New Bedford Harbor neighborhood homes.

In 1987, PCB concentrations in the workplace air of unspecified PCB disposal facilities in the United States ranged from 850 to 4,000 ng/m^3; in 95 of the 96 air samples collected for analysis, PCB concentrations exceeded the NIOSH-recommended exposure limit of 1,000 ng/m^3 (Bryant et al. 1989; NIOSH 1992). The average PCB concentration (Aroclors 1242 and 1260) emitted from gas vents at a hazardous waste landfill in North Carolina was 126,000 ng/m^3 (Lewis et al. 1985). The maximum total PCB concentration detected in air samples collected at Raquette Point within the Mohawk Nation Reservation at Akwesasne, New York (adjacent to a Superfund site) was 50 ng/m^3 (ATSDR 1995).

Even though the production and use of PCBs has been discontinued in the United States, PCBs are still released during some industrial processes. It is well known that PCBs may be formed whenever a carbon source and chlorine are combusted together, such as during municipal and hazardous waste incineration (Alcock et al. 1999; Bergman et al. 1984; Brown et al. 1995). However, depending upon the combustion conditions, the distribution of PCB congeners can vary greatly. For example, some combustion conditions support the production of the lower chlorinated congeners, while other conditions mainly produce nona- and decachlorobiphenyls (Brown et al. 1995). PCB concentrations ranged from 0.01 to 1.5 μg/m^3 in fly ash from five municipal incinerators operating under different technological and working conditions (Morselli et al. 1985). Stack effluents from several Midwest municipal refuse and sewage incinerators contained PCB concentrations of 0.3–3.0 μg/m^3 (Murphy et al. 1985). The total PCB concentration measured in the flue gas effluent from a municipal waste incinerator in Ohio was 0.26 μg/m^3 (Tiernan et al. 1983). PCB concentrations ranged from 0.002 to 0.010 μg/m^3 in effluents from coal and refuse combustion in Ames, Iowa (EPA 1988a). From 1995 to 1997, atmospheric PCB concentrations were measured from cement kilns and sinter plant operations located in the United Kingdom (Alcock et al. 1999). Emissions from cement kilns contained PCB concentrations ranging from 1.3×10^{-5} to 2.5×10^{-5} μg/m^3, while from sinter plants, the mean PCB concentration was 1.9 μg/m^3. Tri-, tetra-, and pentachlorinated congeners contributed between 65 and 85% of total PCBs in sinter plant emissions with PCB 28 being detected at the highest concentrations.

6.4.2 Water

Assessing the PCB contamination of surface waters has been of great interest due to the environmental and health risks PCBs present for the human populations living near them. Countless studies have been conducted that describe the ambient levels found in aquatic systems across the United States. The Great Lakes, in particular, have been monitored extensively due to the widespread PCB contamination and proximity to residential areas. Several studies indicate that PCB concentrations have continued to decrease in the Great Lakes since the early 1980s. Table 6-11 displays the change in PCB concentrations in water over time in several of the Great Lakes. In those lakes with water analyses over several years, PCB concentrations appear to be decreasing over time. In the spring of 1993, water samples were collected and analyzed for PCB concentrations from all five Great Lakes (Anderson et al. 1999). It was found that Lake Erie had the highest degree of contamination with total PCB concentrations ranging from 0.20 to 1.6 ng/L, while Lake Superior had the lowest concentrations ranging from 0.070 to 0.10 ng/L. In 1980, the average PCB concentration measured in Lake Michigan was 1.8 ng/L, with higher levels in near-shore samples (3.2 ng/L) than in open lake samples (1.2 ng/L) (Swackhamer and Armstrong 1987). Comparison of Lake Michigan water samples from 1980 to 1993 indicated a decline in PCB concentrations according to a first-order rate constant of 0.078/year. Average total PCB concentrations in water decreased from 1.2 ng/L in 1980 to 0.47 ng/L in 1991 and ranged from 0.17 to 0.27 ng/L in 1993 (Anderson et al. 1999; Pearson et al. 1996). Mean PCB concentrations of 0.63–3.3 ng/L were detected in the waters of western Lake Superior during 1978–1983 (Baker et al. 1985). PCB concentrations in Lake Superior surface waters decreased from 2.4 to 0.18 ng/L at a first-order rate of 0.20/year between 1980 and 1992 (Jeremiason et al. 1998). Volatilization was the dominant removal mechanism over this time period, while permanent sediment burial was of minor importance (Jeremiason et al. 1998). Sediment traps were also used to study the flux of PCB deposition in Lake Superior from 1987 to 1991. Total PCB settling fluxes from the upper 35 m of water averaged 121± 40 ng/m^{2}Cd in 1987 and 48±23 ng/m^{2}Cd in 1991 (Jeremiason et al. 1998). The major PCB congeners detected in settling solids were tri- to pentachlorobiphenyls. A mean concentration of 0.49 ng/L was detected in the water column of Lake Huron in 1981 (Rodgers and Swain 1983). For the San Francisco Bay and estuary, water samples collected from 1993 to 1995 had total PCB concentrations ranging from 340 to 1,600 ng/L in combined dissolved and particulate fractions (Jarman et al. 1997). Total PCB concentrations studied from 1990 to 1991 in the Saginaw River ranged from 11 to 31 ng/L, with 1.9–16 ng/L detected in the dissolved phase (Verbrugge et al. 1995).

Table 6-11. PCB Concentrations in Water Samples Collected from the Great Lakes

Great Lake	Year	Dissolved (ng/g)	Particulate (ng/g)	Total (ng/L)[a]	Source
Huron	1981			0.49	Rodgers and Swain 1983
	1993	44–92	37–60	(0.12–0.16)	Anderson et al. 1999
Michigan	1980			1.8 (1.2–3.2)	Swackhamer and Armstrong 1987
	1980			1.2	Pearson et al. 1996
	1991	0.34–0.56	142–431	0.47	Pearson et al. 1996
	1993	110–140	48–100	(0.17–0.27)	Anderson et al. 1999
Superior	1978–1983			(0.63–3.3)	Baker et al. 1985
	1980			2.4	Jeremiason et al. 1994
	1992			0.18	Jeremiason et al. 1994
	1993	56–160	28–93	(0.070–0.10)	Anderson et al. 1999
Erie	1993	52–330	45–250	(0.20–1.6)	Anderson et al. 1999
Ontario	1993	110–190	75–160	(0.19–0.25)	Anderson et al. 1999

[a]Ranges presented in parenthesis

The world's oceans have also been monitored for PCB concentrations. PCB levels reported in sea water from various oceans include 0.04–0.59 ng/L in the north Pacific, 0.02–0.20 ng/L in the north Atlantic, and 0.035–0.069 ng/L in the Antarctic (Giam et al. 1978; Tanabe et al. 1983, 1984). PCB levels were several orders of magnitude higher in sea-surface microlayer samples taken from industrial areas, compared to sites further offshore (Cross et al. 1987). PCB concentrations of 0.3–3 ng/L, have been detected in sea water from the North Sea (Boon and Duinker 1986).

Although PCBs are widely found in surface waters, their low solubility generally prevents them from reaching high concentrations, especially in groundwater (EPA 1980b). However, under extreme conditions, such as at hazardous waste sites, PCB contamination of groundwater can occur. A maximum total PCB concentration of 1,200 μg/L was detected in groundwater samples collected on-site at the General Motors Foundry Operation, a Superfund site only 100 yards from the boundary of the Mohawk Nation Reservation at Akwesasne. The maximum off-site groundwater concentration of PCBs (3 ppb) was collected at nearby Raquette Point, New York, which is within the Mohawk Nation Reservation at Akwesasne (ATSDR 1995). In the Mezquital Valley of Mexico, untreated waste water from Mexico City is used to irrigate croplands (Downs et al. 1999). Excess irrigation, however, has resulted in recharging near-surface aquifers used as domestic water supplies. To determine the potential for PCB exposure, researchers analyzed groundwater samples and found that levels of PCBs were #36 pg/L. In general, groundwater is not expected to be significantly impacted by PCB contamination.

Due to the presence of PCBs in the atmosphere, they are often associated with precipitation. In Table 6-12, typical mean PCB concentrations in rain water from various locations are presented. PCB concentrations measured in the late 1970s to early 1980s declined by a factor of 4–10 compared to those measured in the late 1980s and early 1990s (Eisenreich et al. 1981, 1992). Although PCB levels appear to have decreased during this time, more recent studies show both decreasing and steady state conditions. Precipitation sampled from the Great Lakes region from 1991 to 1997 was studied for temporal trends in PCB concentrations (Simcik et al. 2000). It was found that PCB concentrations decreased in precipitation collected over Lakes Michigan and Ontario; data collected for Lakes Michigan and Ontario showed half-lives of 6.9±3.5 and 4.0±1.4 years, respectively. Lakes Erie, Huron, and Superior, however, did not show any significant decrease in PCB concentrations in precipitation. The study also compared its results to other research that has monitored temporal trends in PCB concentrations over the Great Lakes. It was determined that the deposition rate of PCBs from the atmosphere to the Great Lakes is approximately equal to the amount evaporating from the lakes to the atmosphere. This suggests that a steady state equilibrium of PCBs has developed in the Great Lakes ecosphere (Simcik et al. 2000).

Table 6-12. Comparison of PCB Levels (ng/L) in Rainwater Samples from the 1970s to the 1990s

Location	1970s–1980s[a] mean (range)	1980s–1990s[b] mean (range)
Remote	5 (1–30)	No data
Rural/continental	20 (1–50)	5 (0.5–20)
Great Lakes	20–50 (10–150)	5 (0.5–20)
Urban	50 (10–250)	10
Marine/coastal	1–5 (0.5–10)	0.5 (0.1–1.0)

[a]late 1970s to early 1980s (Eisenreich et al. 1981)
[b]late 1980s to early 1990s (Eisenreich et al. 1992)

Some recent studies have reported the following mean concentrations of total PCBs in rain water: sites along the eastern shore of Green Bay had a mean PCB concentration of 2.2 ng/L (range, 0.9–11.7 ng/L) (Franz and Eisenreich 1993); on Lake Michigan near Chicago, 4.1–189 ng/L in 1994/1995 (Offenberg and Baker 1997); Chesapeake Bay, 1.6 ng/L (range, 0.04–34 ng/L) (Leister and Baker 1994); and Pelee Island on the western end of Lake Erie, 10.2 ng/L, and Wolfe Island on the eastern end of Lake Ontario, 8.7 ng/L from 1986 to 1991 (Chan et al. 1994). Concentrations of PCBs have also been determined in remote regions of the world. In snow collected from the Antarctic, PCB concentrations ranged from 0.16 to 1.0 ng/L (Tanabe et al. 1983). In a study conducted in 1996, PCB concentrations in snow samples from western Canada's mountain ranges were twice as high in higher altitudes compared to lower altitudes (Blais et al. 1998). For example, the concentrations of di-, tri-, tetra-, penta-, hexa-, and heptachlorobiphenyls in snow samples from Saskatchewan River Crossing (elevation of 1,402 meters above sea level (masl)) in Alberta, Canada were 0.05, 0.15, 0.25, 0.35, 0.15, and 0.10 ng/L, respectively. At Parker Ridge, which has an elevation of 2,011, the concentrations for di-, tri-, tetra-, penta-, hexa-, and heptachlorobiphenyls were 0.30, 0.25, 0.15, 0.15, 0.10, and 0.05 ng/L, respectively (Blais et al. 1998). It was also noted that at higher elevations, di- and trichlorinated congeners dominated total PCBs while at lower altitudes, tetra- and pentachlorinated congeners were higher.

In a literature review of 140 articles containing information on urban storm water quality, Makepeace et al. (1995) reported that total PCB concentrations in urban storm water ranged from 27 to 1,100 ng/L. From 1995 to 1996, PCB concentrations in water samples collected from the Trenton Channel stretch of the Detroit River, Michigan, ranged from <5 to 22 ng/L in particulate and from <5 to 13 ng/L in dissolved fractions of water (Froese et al. 1997). It was estimated that 600 kg of PCBs passed through the Channel in 1995. A maximum total PCB concentration of 15,000 ng/L was detected in surface water samples from the St. Lawrence River downstream from a Superfund site (General Motors Foundry Division) (ATSDR 1995). Based on large-volume water sampling from the ship canal between Hamilton Harbor and the start of the St. Lawrence River, an annual PCB loading of 2.8 kg/year was estimated for Lake Ontario (Fox et al. 1996).

6.4.3 Sediment and Soil

PCB levels in soils and sediments have decreased in many areas across the United States since its ban in the late 1970s. Sediment core samples were used to study the temporal change of PCB deposition at 11 riverine systems located in Texas, Florida, Iowa, Virginia, New Mexico, and Georgia (Van Metre et al. 1998). In almost every sediment core sample, PCB concentrations peaked around 1970 and decreased

linearly afterwards. The only sediment sample that did not have a downward trend in PCB concentration was at Lake Seminole in Florida, where the PCB concentration did not decrease or increase significantly from 1955 to 1995. Overall, the mean half-life of PCBs in riverine sediments was calculated to be 9.5 (±2.2) years. To determine the temporal change in PCB concentrations within the Hudson River basin, researchers obtained sediment core samples from 18 locations and analyzed them for PCBs (Bopp et al. 1998). The study found that from the mid-1960s to early 1990s, PCB concentrations decreased significantly over time. For example, PCB concentrations in the upper Hudson River were 350 ppm in the mid-1960s compared to 34 ppm in 1991. In sediment samples taken from the base of the Hudson River, sediment core samples had a mean concentration of 3.03 ppm in the mid-1960s which decreased to 0.80 ppm by 1992 (Bopp et al. 1998). The historic profiles of PCB concentrations in sediments of the lower Passaic River, New York were also studied. The authors concluded that total PCB sediment concentrations peaked in the 1970s and that PCB concentrations declined dramatically from 4.7 mg/kg (dry weight) in the 1970s to 1.1 mg/kg (dry weight) in the 1990s (Wenning et al. 1994). A similar study of dated sediments from the Newark Bay Estuary, New Jersey (including the Passaic River), also reported that the highest concentration of PCBs occurred in buried sediments (0–140 cm) from the Passaic River and Newark Bay at depths corresponding to historic deposition during the 1960s and 1970s, the peak manufacturing period for Aroclors (Iannuzzi et al. 1995). Surficial sediments were analyzed for PCBs from Lake Ontario from 1982 to 1986 (Oliver et al. 1989). Concentrations decreased from 1,300–1,900 ng/g in 1982/1983 to 80–290 ng/g in 1985/1986. Researchers determined that the percentage of lower chlorinated congeners (tri to penta) decreased with depth, while hexachlorobiphenyls remained fairly constant throughout and the concentration of highly chlorinated congeners increased with depth (Oliver et al. 1989). Archived soil samples collected in the United Kingdom between 1951 and 1968 were analyzed for PCB concentrations and compared to soil samples from the same region collected in 1993 (Lead et al. 1997). The study found that in 9 out of 10 cases, PCB concentrations decreased over time. Differences in concentrations ranged from 3.6 ng/g measured in 1953 to 1.1 ng/g in 1993 as well as 1,400 ng/g measured in 1966 to 2.6 ng/g in 1993 (Lead et al. 1997). While the tri-chlorinated congeners decreased by a factor of approximately 1,000 between 1968 and 1993, octachlorinated biphenyls only decreased by a factor of approximately 5 over the same time period. The researchers contributed the high degree of loss for the lower chlorinated biphenyls to higher rates of volatilization and biodegradation (Lead et al. 1997). These decreasing trends in sediment and soil samples, however, have not been observed in all parts of the world. PCB concentrations in sediment samples taken from the Seine River in France were studied from 1984 to 1992 to determine temporal changes (Chevreuil et al. 1998). In Europe, the Seine River is known for having some of the highest levels of PCBs. During the course of the 9-year study, no significant change in PCB concentration was observed.

The concentrations and congener profile of PCBs in sediments depend on the depth at which the samples are collected (Lake et al. 1992; Pereira et al. 1994). In 1988, the concentration of PCBs in surface core sediments (0–2.5 cm) from heavily contaminated upper New Bedford Harbor, Massachusetts, ranged from 1.02×10^6 to 9.12×10^6 ng/g (Lake et al. 1992). At a depth of 15–17.5 cm, PCB concentrations ranged from 7.53×10^6 to 2.96×10^7 ng/g. At greater depths, however, the concentration of PCBs in sediment cores decreased. The concentration range of surficial bed sediments collected from San Francisco Bay ranged from 1.3 to 8.1 ng/g dry weight (Pereira et al. 1994).

In 1972, upper sediment layers from the Hudson River and New York Harbor contained PCB concentrations ranging from 560 to 1,950 ng/g (Aroclor 1254) and from 3,950 to 33,300 ng/g (Aroclor 1242), respectively (Bopp et al. 1982). From 1968 to 1975, surface sediments from the Great Lakes contained Aroclor 1254 concentrations ranging from 2.5 to 251.7 ng/g, with the highest concentrations detected in Lake Erie (Thomas and Frank 1981). In 1976, PCB concentrations monitored in sediments from 13 streams in the Potomac River Basin ranged from 10 to 1,200 ng/g (Feltz 1980). Sediment samples collected in 1979 from Gill Creek adjacent to a hazardous waste site near Niagara Falls, New York contained 1.0×10^6 ng/g dichloro-, 3.0×10^6 ng/g trichloro-, 6.0×10^6 ng/g tetrachloro-, 3.0×10^6 ng/g pentachloro-, and 3.0×10^6 ng/g hexachlorobiphenyl (Elder et al. 1981). In 1980, an average Aroclor 1260 concentration of 120 ng/g was detected in sediment samples from eight sites along the coast of Maine (Ray et al. 1983). The mean concentrations of PCBs (ng/g dry weight) measured from 1980 to 1982 in sediments from the Great Lakes were as follows: southern Lake Huron, 34; Lake St. Clair, 29; western Lake Erie, 300; central Lake Erie, 131; and eastern Lake Erie, 91 (Oliver and Bourbonniere 1985). From 1987 to 1990, approximately 1,000 sediment samples from Green Bay, Lake Michigan, were analyzed to map the areal distribution of PCBs in the bay sediments (Manchester-Neesvig et al. 1996). The Bay sediments were estimated to contain a total of 8,500 kg of PCBs. The PCBs in these sediments are not evenly distributed, and an estimated 50% of the total PCB mass is located in the southern portion of the Bay (closest to the city of Green Bay) in an area representing 3% of the total area. An analysis of PCB homolog groups revealed that tri-, tetra-, and pentabiphenyls represented 30.8, 40.6, and 13.5%, respectively, of total PCBs detected in Green Bay sediments (Manchester-Neesvig et al. 1996).

Sediments downstream from highly contaminated sites may also be affected by PCB residues. Maximum total PCB concentrations of 5,700,000 and 36,000 ng/g were detected in sediments from the St. Lawrence River and Raquette River, respectively; these sites are within the boundaries of Akwesasne, New York, a Native American community downstream from a Superfund site (ATSDR 1995). Vanier et al. (1996)

measured PCB concentrations at three sites along the St. Lawrence River exposed to high potential PCB contamination, including two in urban Montreal, Quebec. PCB concentrations in the top 10 cm of the sediment were 3,800–16,000 ng/g dry weight Aroclor 1254 equivalent. In the most contaminated site, located in an industrial area, PCB inputs appear to have been relatively constant since about 1982. Di- and tri-chlorinated congeners make up more than 70% of the profile in the more concentrated area and less elsewhere along the river.

Although the use of PCBs has been discontinued by many countries, they are still detected in sediments from around the world. In September of 1994, researchers obtained sediment core samples along the Dnipro River in the Ukraine and analyzed them for PCB residues (Lockhart et al. 1998). In two core samples, one from the Zaporizhzhia reservoir and one from the Kakhovka reservoir along the Dnipro River, the total concentrations of PCBs were 48.1 and 30.6 ng/g, respectively. The study also found that penta- and hexachlorobiphenyls were detected more frequently than any other PCB congeners at both sites. In 1996, sediment samples from 17 sites within the Bay of Chetumal, Mexico, were analyzed for PCBs (Norena-Barroso et al. 1998). Concentrations of total PCBs ranged from 1.23 to 9.28 ng/g with a median value of 2.96 ng/g. In North Vietnam, sediment samples from the Red River Delta and the coastal area of the Thai Binh province were analyzed for PCB residues from 1995 to 1996 (Nhan et al. 1998). The mean concentration of total PCBs detected for all sediment samples was 2.12 ng/g dry weight.

In arctic regions, PCB concentrations are highest in surface sediments representing inputs from the 1980s and early 1990s. These observations support the hypothesis of a gradual movement of contaminants northward, caused by temperature-dependent partitioning (Wania and Mackay 1996). PCB concentrations ranging from 98 to 540 ng/g were detected in sediments from four remote, high-altitude lakes in Rocky Mountain National Park (Heit et al. 1984). Considering that there were no anthropogenic sources of PCBs in the vicinity, PCBs most likely accumulated via atmospheric deposition. The same phenomenon was observed in four lakes located in remote areas of Alaska where the concentration of total PCBs averaged 0.12 ng/g dry weight (Allen-Gil et al. 1997).

In contrast to sediment, PCB concentrations in soil have not been closely monitored. Of soil samples collected from three unspecified PCB disposal facilities, 74% had PCB concentrations >100 $\mu g/m^2$ (NIOSH 1977). The PCB concentrations at these sites ranged from 4 to 180,000 $\mu g/m^2$ (Bryant et al. 1989). Subsurface soils and sludges collected on-site at the General Motors Foundry Operation (a Superfund site in New York) had maximum concentrations of 750 and 41,500 ppm, respectively (ATSDR 1995). In the Canadian Arctic, a string of 21 radar stations called The Distant Early Warning (DEW)

Line stretches along 3,000 km and has been in operation since the 1950s. These radar stations have been associated with former PCB use and contamination (Bright et al. 1995a, 1995b). Site samples from the 21 DEW Line facilities, plus 3 additional Arctic radar installations, were collected from 1989 to 1992. PCBs were detected in undisturbed soils near the 21 DEW Line sites and as far as 5 km, but were not detected in soil 20 km from site. Concentrations ranged from not detected (detection limit=0.1–5.3 ng/g) to 45 ng/g in soil. These data indicate short-range redistribution of PCBs in a terrestrial environment.

6.4.4 Other Environmental Media

In order to fully assess human exposure to PCBs, several human diet studies have been conducted to monitor for PCB residues. In some cases, the analytical methodology and detection limits rendered these results inconsistent with more recent studies and some judgement is necessary. A 10-year study of ready-to-eat foods conducted by the U.S. Food and Drug Administration (FDA) from 1982 to 1991 found PCB residues 27 times out of 17,050 foods sampled (KAN-DO Office and Pesticides Team 1995). The study included 234 food items that represented about 5,000 food types in American diets covering all age groups. The average concentration of PCBs in those foods with detectable quantities was 0.0179 μg/g wet weight. The concentration of dioxin-like PCBs (including PCBs 77, 105, 118, 126, 156, 157, and 169) was studied in composite pasteurized milk samples collected in the United States from 1996 to 1997 (Lorber et al. 1998). The study found that out of a total of 48 samples, the average PCB concentration was 0.50 pg/g lipid weight. An earlier study conducted from 1969 to 1976 monitored PCBs in raw foods. They were analyzed as part of a federal monitoring programs conducted by the FDA and the U.S. Department of Agriculture (USDA). Data from this study can be found on Table 6-13. Based on this report, fish products clearly contained the highest levels of PCBs. Food either grown or processed abroad and imported into the United States is another potential source of human exposure (Kannan et al. 1997). Various fish oils used as dietary supplements were collected from around the world and analyzed for PCB levels (Jacobs et al. 1998). Researchers found that PCB congeners 138, 153, and especially 118 were detected most frequently and in the highest concentrations. None of the samples, however, exceeded the FDA regulatory limit of 2.0 mg/L for total PCBs for animal feed. In fact, total PCB concentrations ranged from not detected to 1.132 mg/L with a mean value of 0.332 mg/L (Jacobs et al. 1998). PCB concentrations measured in Australian crop products were <0.01–11 ng/g wet weight and dairy products, were 1.2–8.2 ng/g wet weight.

As previous monitoring sections have demonstrated, PCBs can be found throughout the world. Consequently, this has led to significant levels of PCBs bioaccumulating in aquatic organisms exposed to

Table 6-13. Polychlorinated Biphenyl Residues in Domestic Raw Foods for Fiscal Years 1969–1976

Commodity	Number of samples analyzed	Percent of sample with positive detections	Average concentration (ppm)[a]
Fish	2,901	46.0	0.892
Shellfish	291	18.2	0.056
Eggs	2,303	9.6	0.072
Red meat[b]	15,200	0.4	0.008
Poultry[b]	11,340	0.6	0.006
Fluid milk	4,638	4.1	0.067
Cheese	784	0.9	0.011

Source: derived from Duggan et al. 1983

[a]Average of all samples, both positive and negative (zero values were used for all samples not containing polychlorinated biphenyls). Detection limit is 0.001 ppm.
[b]Fiscal years 1972–1976

PCB-contaminated waters (EPA 1980b). PCB concentrations in seafood have therefore been closely monitored over the years. Although, in the past, PCB monitoring consisted of comparing PCB residues to Aroclor mixtures, more recent studies have concentrated on determining PCBs on a congener-specific basis (Bush et al. 1989; Huckins et al. 1988; Maack and Sonzogni 1988). Overall, the most commonly detected PCB congeners in fish samples are PCBs 138, 153, 180, 118, 110, 101, and 95 (Giesy et al. 1997; Hansen 1999; Hilbert et al. 1998; Jacobs et al. 1998; Qi et al. 1997; Ylitalo et al. 1999). Due to their high persistence and low potential for biodegradation, these PCB congeners are generally detected in the highest concentrations in biological tissues. In general, fish bioconcentrate more highly chlorinated congeners, such as penta-, hexa-, and heptachlorinated biphenyls (Datta et al. 1999, Qi et al. 1997, Ylitalo et al. 1999). In a study of bullhead fish from Bear Lake, researchers found that the relative concentrations of di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, and nonachlorobiphenyls were 0.003, 0.019, 0.015, 0.165, 0.085, 0.075, 0.018, and 0.002 μg/g dry weight, respectively (Qi et al. 1997). The same distribution of PCB homolog groups was also observed in Northern Pike and Walleye from the same lake. Similarly, rats have been shown to preferentially bioconcentrate highly chlorinated PCBs. In rats given gavage doses of Aroclor 1254 (comprised of 2.1% mono-, di-, and tri-chlorinated PCB congeners, 19.1% tetra-, 49.6% penta-, 25.9% hexa-, 2.9% hepta-, and 0.5% octa- and nona-chlorinated PCB congeners), heavily chlorinated congeners (with 6–9 chlorines) accounted for greater percentages of total PCBs in analyzed tissues than in Aroclor 1254 itself (Kodavanti et al. 1998).

The dioxin-like PCB congeners, such as PCBs 77, 126, and 169, generally make up <1% of the total amount of PCBs detected in fish (Ylitalo et al. 1999). For instance, of the three dioxin-like PCB congeners (77, 126, and 169), PCB 169 was not detected in fish and mussels collected in 1990 from marine and estuarine waters from New York State, and the sum of the concentrations of the other two congeners was <1% of the total PCB concentration (Hong et al. 1992b). In another study, PCB congeners were detected in oysters *(Crassostrea virginica)* from Galveston and Tampa Bays, but the sum of their concentrations represented <1.5% of the total PCB concentration (Sericano et al. 1992). Two of these coplanar PCB congeners (77 and 126) were retained longer than those corresponding to different PCBs within the same group when the oysters were moved to a clean water site. Because of their dioxin-like toxicity, these PCB congeners could constitute a potential health hazard to humans. These studies illustrate the importance of determining the concentration of specific congeners, in addition to the concentration of total PCBs, in fish and shellfish tissues.

Using more complete congener profiles, including PCBs 95, 101, and 110 (see below), levels of PCBs have been shown to increase with respect to the trophic level of the organism being studied. In 1994,

researchers monitored the concentration of PCBs in Lake Superior's food web to determine differences in accumulation between trophic levels (Kucklick and Baker 1998). The concentration of total PCBs ranged from 0.0056 μg/g wet weight in *Mysis relicta* to 0.180 μg/g wet weight in bloater fish. Total PCBs in all biota were dominated by hexa-, penta-, and heptachlorobiphenyl congeners, with only minor contributions from the di-, tri-, and tetrachlorobiphenyl congeners that dominate the lake's water column (Kucklick and Baker 1998). Based on their observations, researchers discovered that the increase in total PCB residues was influenced both by the organisms lipid content and trophic position. It was also noted that the relative percentage of PCB congeners did not vary significantly between trophic levels. When comparing the levels of PCBs detected in sediment to the levels found in benthic organisms, researchers found that the amount of PCBs accumulated by the benthic organisms could not be solely explained by exposure to contaminated sediments, but was also influenced by PCB concentrations in feed and water (Kucklick and Baker 1998). The same increase in PCB concentration with respect to trophic level was observed in the remote regions of the Canadian Arctic. Researchers analyzed several animals from the Canadian Arctic in April 1993 to determine the relative concentrations of PCBs stored in lipid tissues (Letcher et al. 1998). As in other food chains, PCB concentrations appeared to increase at higher trophic levels. The study found that the concentrations of total PCBs in Arctic cod, female ringed seal, male ringed seal, and polar bear were 0.0718, 0.387±73, 0.447±92, and 6.207±948 μg/g lipid weight (Letcher et al. 1998). Of the 72 PCB congeners that were analyzed for in polar bear fat samples, only 20 were found above the detection limit (5.0×10^{-5} μg/g lipid weight). Of these, PCBs 153, 180, and 138 were found in the highest concentrations. Interestingly, cod and ringed seal contained 47 and 53 congeners, respectively, above the detection limit. For Arctic cod, PCBs 110, 101, 153, and 95 were detected in high concentrations, while ringed seal contained high levels of PCBs 153, 138, and 101. On a PCB congener-specific basis, the concentration of PCBs decreased from cod to seal and finally to polar bear, revealing an increasingly simplified number of PCB congeners bioaccumulating (Letcher et al. 1998).

Eight commercially and recreationally important marine species were collected in 1993 and 1994 from 30 locations along the Atlantic and Pacific coastal regions of the contiguous United States and analyzed only for dioxin-like PCB residues (Ylitalo et al. 1999). All marine species analyzed contained 1, often $6, dioxin-like PCB congeners. Researchers noted that higher concentrations were detected in marine species collected near urban areas (Ylitalo et al. 1999). The total mean concentration of PCBs in marine tissues ranged from 0.0035 to 8.800 μg/g, wet weight. The most commonly detected PCB congeners were PCBs 153, 138, and 128. For example, in fish species, PCB 153 represented 9.3–22% of the mean total amount of PCBs detected in muscle (Ylitalo et al. 1999). Dioxin-like PCBs that were detected most frequently included PCBs 118, 105, 170, and 180. Certain dioxin-like congeners (PCBs 77 and 126) were

also detected in several tissues containing high lipid levels such as crab and lobster hepatopancrease (Ylitalo et al. 1999). However, these congeners were minor contributors to total PCB concentrations and were usually <1% of the total. The di-*ortho*-substituted congeners comprised 0.70–26% of the total PCB concentrations while mono-*ortho*-substituted PCBs contributed 4.8–31% (Ylitalo et al. 1999). Although PCBs were the most frequently detected contaminant in environmental samples, the concentrations usually fell well below the FDA tolerance limit of 2.0 μg/g wet weight in edible tissues of fish and shellfish from the United States (Ylitalo et al. 1999). The highest levels of PCBs occurred in hepatopancreas samples from crustaceans, which are typically not consumed.

The Great Lakes region has accumulated persistent toxic substances, including PCBs, to the extent that fish, other wildlife, and human populations face potentially high exposures to these constituents (Hicks 1996). The concern for potential exposures of human populations to PCBs as well as other persistent constituents in fish has spawned a number of studies of fish PCB body-burdens. A survey of salmonid species (chinook salmon, coho salmon, lake trout, brown trout, rainbow trout, and brook trout) in the sport catch from western Lake Michigan showed significant interspecies differences in PCB residues (Miller et al. 1993a). When standardized to fish length, the maximum PCB concentration in muscle was found in lake trout, followed by brown trout, chinook salmon, brook trout, rainbow trout, and coho salmon. However, in all species of fish surveyed, the levels of PCBs in 1990 declined 20–50% from levels found in 1985. Stow (1995a) evaluated data for these same five species, collected from Lake Michigan from 1972 through 1992 and found that PCB levels have remained fairly constant since the early 1980s when corrected for differences in species, location, and length.

Other studies support the downward trend in PCB concentration in fish from the Great Lakes region. Total PCB concentrations were studied from 1985 to 1992 in Coho salmon and rainbow trout caught near various Wisconsin Lake Michigan fishing ports (Eggold et al. 1996). The mean PCB concentrations in Coho salmon in 1985, 1990, and 1992 were 0.99±0.6, 0.83±0.25, and 0.78±0.29 μg/g wet weight, respectively while the mean PCB concentrations in rainbow trout in 1985, 1990, and 1992 were 1.13±1.38, 0.61± 0.33, and 0.44±0.19 μg/g wet weight, respectively. One study followed the change in PCB concentrations in sport fish and juvenile forage fish in the Canadian waters of the Great Lakes over a 15–20 year period (Scheider et al. 1998). According to the study, the concentrations of PCBs in sport fish declined in both Lake Huron and Lake Ontario from 1976 to 1994. Mean concentrations of PCBs in 65 cm lake trout from southern Lake Huron declined from 8.07 ppm in 1976 to 0.47 ppm in 1994 (Scheider et al. 1998). The same pattern was observed in 60 cm rainbow trout from Lake Ontario where PCB concentrations declined from 3.9 ppm in 1976 to 0.97 ppm in 1994. Among trout from Lake

Ontario, PCB concentrations (total and individual congeners) have decreased by as much as 80% between 1977 (9.06 μg/g) and 1993 (1.72 μg/g) (Huestis et al. 1996). For more information concerning PCB concentrations in fish from the Great Lakes region, refer to Table 6-14.

A study was begun in 1975 by the New Jersey Department of Environmental Protection (NJDEP) to monitor the concentration of PCBs in fish from the estuarine and coastal marine waters of New Jersey (Kennish and Ruppel 1996). The NJDEP monitored the concentration of PCB congeners exclusively found in Aroclors1248, 1254, and 1260. Although their studies indicate that PCB contamination is highest in the Hudson-Raritan estuary, there is evidence that PCB concentrations are declining in some fish species. For example, the mean PCB level for striped bass and white perch decreased from 2.14 to 1.80 ppm wet weight and from 2.06 to 1.28 ppm wet weight, respectively, between the 1986–1987 and 1988–1991 survey periods (Kennish and Ruppel 1996). However, the proportion of striped bass in the 1986–1987 study that exceeded the U.S. proposed action level of 2.0 ppm was 38%, while the 1988–1991 study showed relatively the same result with 36% exceeding 2.0 ppm. The mean PCB concentration for composite fish samples from the North Coast region also declined. While the 1986–1987 study found a mean concentration of 2.33 ppm wet weight, the 1988–1991 study had a mean concentration of 1.64 ppm wet weight. Also, the percentage of samples with concentrations exceeding 2.0 ppm was lower in the 1988–1991 (33%) study than in the 1986–1987 (70%) study. The Belgian Fisheries Research Station monitored PCB concentrations in marine samples from 1983 to 1993 and noticed a similar downward trend in PCB contamination (Roose et al. 1998). The study followed four different species: cod, flounder, blue mussel, and brown shrimp. All species, except blue mussel, showed a statistically significant decrease in PCB concentration. In 1983, the median PCB concentration in cod muscle tissue was 0.81±0.34 μg/g, while by 1993, the median concentration declined to 0.40±0.15 μg/g; flounder muscle tissue had a median concentration of 3.3±0.8 μg/g in 1983, while by 1993, the median concentration declined to 0.9±2.0 μg/g; blue mussel had a median PCB concentration of 2.4±0.3 μg/g in 1983, while by 1993, the median concentration declined to 1.6±0.1 μg/g; and for brown shrimp, the median PCB concentration was 0.49±0.08 μg/g in 1983, while by 1993, the median concentration declined to 0.28±0.05 μg/g (Roose et al. 1998). Several studies support a gradual decrease in PCB concentrations in fish tissue over time. For more information concerning PCB concentrations in fish species, refer to Table 6-15.

Decreasing PCB concentrations in fish, however, has not always been observed. For instance, cod liver oil samples from the Baltic Sea, were collected and analyzed for PCB concentrations every 5 years from 1971 to 1989 (Falandysz 1994). Researchers found that PCB concentrations did not decline from the

Table 6-14. Mean PCB Concentrations in Fish from the Great Lakes Region

Species	Location	Year	PCB concentration µg/g (wet weight)[a]	Source
Coho salmon	Lake Michigan, Wisconsin	1985 1990 1992	0.99±0.6 0.83±0.25 0.78±0.29	Eggold et al. 1996
Rainbow trout	Lake Michigan, Wisconsin	1985 1990 1992	1.13±1.38 0.61±0.33 0.44±0.19	Eggold et al. 1996
Lake trout	Lake Huron	1976 1994	8.07 0.47	Scheider et al. 1998
Rainbow trout	Lake Ontario	1976 1994	3.9 0.97	Scheider et al. 1998
Trout	Lake Ontario	1976 1994	9.06 1.76	Huestis et al. 1996
Forage fish	Tittabawassee River	1990	(0.408–3.445)	Giesy et al. 1997
Forage fish	Saginaw River	1990	(0.452–1.875)	Giesy et al. 1997
Forage fish	Saginaw Bay	1990	(0.349–0.523)	Giesy et al. 1997
Forage fish	Lower Green Bay	1991	(0.048–0.458)[b]	Brazner and De Vita 1998
Forage fish	Middle Green Bay	1991	(0.040–0.078)[b]	Brazner and De Vita 1998
Forage fish	Upper Green Bay	1991	(0.003–0.011)[b]	Brazner and De Vita 1998
Chinook salmon	Lake Huron	1991–1994	0.338	Feeley and Jordan 1998
Chinook salmon	Lake Ontario	1991–1994	0.835	Feeley and Jordan 1998
Whitefish	Lakes Superior, Huron, and Michigan	1994	(0.0711–0.2025)	Dellinger et al. 1996
Lake trout	Lakes Superior, Huron, and Michigan	1994	(0.378–0.158)	Dellinger et al. 1996

[a]Ranges in parenthesis
[b]Lipid weight

Table 6-15. Mean PCB Concentrations in Fish

Species	Location	Year	PCB concentration µg/g (wet weight)[a]	Source
Fish	U.S. national rivers and lakes	1976–1977 1978–1979 1980–1981 1984	0.88 0.85 0.53 0.38	Schmitt et al. 1985
Cod	Belgian fisheries	1983 1993	0.81±0.34 0.40±0.15	Roose et al. 1998
Flounder	Belgian fisheries	1983 1993	3.3±0.8 0.9±2.0	Roose et al. 1998
Striped bass	New York Harbor/Long Island Sound	1984 1990	4.13 1.30	NYSDEC 1991
Striped bass	Eastern Long Island	1985	1.8±0.4	Bush et al. 1989
Striped bass	Western Long Island	1985	1.9±0.2	Bush et al. 1989
Striped bass	Eastern Atlantic Shore	1985	3.0±0.5	Bush et al. 1989
Striped bass	Western Atlantic Shore	1985	7.5±1.9	Bush et al. 1989
Striped bass	Hudson River	1985	15.0±3.0	Bush et al. 1989
Striped bass	Hudson-Raritan Estuary	1986–1987 1988–1991	2.14 1.80	Kennish and Ruppel 1996
White perch	Hudson-Raritan Estuary	1986–1987 1988–1991	2.06 1.28	Kennish and Ruppel 1996
Composite fish samples	U.S. North Coast	1986–1987 1988–1991	2.33 1.64	Kennish and Ruppel 1996
Young carp	Buffalo River	1991	2.40	Loganathan et al. 1995
Middle-aged carp	Buffalo River	1991	4.30	Loganathan et al. 1995
Old carp	Buffalo River	1991	5.00	Loganathan et al. 1995
Herring	Baltic Sea	1991–1992	(0.688–1.555)[b]	Strandberg et al. 1998

Table 6-15. Mean PCB Concentrations in Fish *(continued)*

Species	Location	Year	PCB concentration µg/g (wet weight)[a]	Source
Perch	Baltic Sea	1991–1992	(1.034–5.418)[b]	Strandberg et al. 1998
Deep sea fish	Suruga Bay, Japan	1993	0.910	Takahashi et al. 1998
Deep sea velvet fish	Nordfjord, Norway	1993	2.39[b]	Berg et al. 1998
Deep sea tusk fish	Nordfjord, Norway	1993	11.7[b]	Berg et al. 1998
Fish	Kremenchuck Reservoir, Ukraine	1994	(0.0107–0.0196)	Lockhart et al. 1998
Fish	Kakhovka Reservoir, Ukraine	1994	(0.0437–0.0767)	Lockhart et al. 1998
Northern pike	Bear Lake, Michigan	1995	(0.161–0.275)[c]	Qi et al. 1997
Walleye	Bear Lake, Michigan	1995	(0.156–209)[c]	Qi et al. 1997
Bullhead	Bear Lake, Michigan	1995	(0.0727–0.473)[c]	Qi et al. 1997
Brook trout	Kaweah River, California	1996	(0.0049–0.0081)	Datta et al. 1998a
Fish	Brunswick River	1996	(0.0025–0.48)	Maruya and Lee 1998
Bullhead	Lac St-Louis/St Lawrence Seaway	1996–1997	0.029	Chan et al. 1999
Perch	Lac St-Louis/St Lawrence Seaway	1996–1997	0.070	Chan et al. 1999
Pike	Lac St-Louis/St Lawrence Seaway	1996–1997	0.050	Chan et al. 1999
Smallmouth bass	Lac St-Louis/St Lawrence Seaway	1996–1997	0.115	Chan et al. 1999
Sturgeon	Lac St-Louis/St Lawrence Seaway	1996–1997	0.154	Chan et al. 1999
Walleye	Lac St-Louis/St Lawrence Seaway	1996–1997	0.067	Chan et al. 1999

[a]Ranges in parenthesis
[b]Lipid weight
[c]dry weight

early 1970s to the late 1980s and that they appeared to have been in a steady state condition. For example, the concentration of hexachlorobiphenyls in cod-liver oil were 3.2 (1971), 2.5 (1975), 7.3 (1980), 3.3 (1985), 4.0 (1986), and 3.8 μg/g (1989). In general, the hexa- and pentachlorobiphenyls were most predominant in the cod liver oil samples (Falandysz 1994).

Proximity to industrialized regions has been shown to influence PCB concentrations in fish. Forage fish collected in 1991 from coastal wetlands and beaches in Green Bay, Lake Michigan were analyzed for PCB concentrations (Brazner and DeVita 1998). The concentration of PCBs in fish species appeared to vary spatially within Green Bay, according to proximity to the city. For example, PCB concentrations in fish (lipid normalized) ranged from 0.048 to 0.458 μg/g in the lower bay (closest to the city), 0.040–0.078 μg/g in middle bay, and 0.003–0.011 μg/g in the upper bay (furthest from the city). Mean levels of PCBs were also measured in fish above and below dams on rivers that feed into Lakes Michigan and Huron (Giesy et al. 1995). Researchers found that concentrations were higher downstream from the dams than upstream. For example, mean PCB concentrations in fish below dams found along the Manistee, Muskegon and Au Sable Rivers were 1.90, 3.40, and 1.10 μg/g wet weight, respectively, while above the dam, mean concentrations were 0.020, 0.195, and 0.061 μg/g wet weight, respectively. In a National Study of Chemical Residues in Fish conducted by EPA between 1986 and 1989, PCBs were detected at a mean concentration of 1.90 μg/g in bottom-feeding and game fish collected from 91% of 362 sites surveyed (EPA 1992c; Kuehl et al. 1994). Fish collected from 26% of the sites contained PCB residues >1 μg/g, and fish from 2.5% of the sites contained PCB residues at >10.0 μg/g. Fish collected at sites near wood-preserving facilities, industrial/urban areas, pulp and paper mills, refineries/other industrial sites, and Superfund sites were more highly contaminated with PCBs than fish collected near agricultural areas, near POTW sites, or at U.S. Geologic Survey (USGS) National Stream Quality Accounting Network sites (EPA 1992c; Kuehl et al. 1994). Concentration patterns of various homologs in fish tissues were as follows: mean concentrations of total mono-, di-, octa-, nona-, and decachlorobiphenyl were <0.025 ppm; mean concentrations of total tri- and heptachlorobiphenyl were <0.150 ppm; and mean concentrations of total tetra-, penta-, and hexachlorobiphenyl were 0.699, 0.565, and 0.356 ppm, respectively (EPA 1992c). Table 6-16 compares PCB concentrations in tissues of six species of fish collected near the Mohawk Reservation at Akwesasne adjacent to the PCB contaminated General Motors Foundry site and downstream in the St. Lawrence River and its tributaries (ATSDR 1995). The highest mean concentration of PCBs in standard fillet tissues (20.55 μg/g) was detected in brown bullheads collected at the General Motors Corporation site. These values are far higher than the background concentrations of <0.100 μg/g for the total PCBs in fish fillets in New York State (Sloan and Jock 1990).

Table 6-16. Mean Total PCB Levels in Standard Fillets of Fish Collected from the Vicinity of a Superfund Site

Species	CM-CFD[a] site mean (range)[b]	St. Lawrence River and tributaries[c] mean (range)[b]
Brown bullhead	20.55 (<0.15–81.49)	1.82 (<0.15–10.73)
Northern pike	2.73 (0.48–5.12)	0.42 (<0.15–3.52)
Rock bass	1.04 (<0.15–4.02)	0.18 (0.15–0.86)
White sucker	6.39 (0.29–11.0)	0.17 (<0.15–0.63)
Yellow perch	3.41 (0.20–12.26)	0.61 (0.15–0.86)

Source: ATSDR 1995

[a]General Motors Corporation/Central Foundry Division, Massena, New York, plant is a Superfund site adjoining the Mohawk Indian Nation at Akwesasne. Fish and wildlife studies and human health studies have been conducted at this site.
[b](ppm, wet/weight)
[c]PCB contamination has been detected within the Akwesasne reservation boundaries in the St. Lawrence River and several tributaries downstream from the General Motors Corporation site.

Fish that inhabit remote areas of the world have also been shown to bioaccumulate PCBs. From 1993 to 1994, PCB residues were evaluated in Kokanee fish and lake trout from the Sierra Nevada ecosystem to determine the extent of organochlorine pollution in high altitude, alpine regions (Datta et al. 1999). Analysis of fish muscle revealed that the concentration of total PCBs ranged from 0.018 to 0.430 μg/g wet weight for lake trout. Compared to trout, Kokanee fish generally had lower PCB concentrations ranging from 0.013 to 0.044 μg/g wet weight. Residue analysis indicated that the congeners most commonly found ranged from penta- to heptachlorobiphenyls (Datta et al. 1999). Although Lake Tahoe does not have any known point sources of pollution from industry or agriculture, the levels of PCBs in lake trout samples were approximately equal to or slightly lower than those found in lake trout from Lake Superior. This suggests that PCBs have been introduced to Lake Tahoe through atmospheric deposition. For further information, refer to Table 6-17.

The remediation of contaminated sediments has been shown to decrease PCB concentrations in fish inhabiting contaminated rivers. For example, one study monitored PCB concentrations in fish before and after remediation of PCB contaminated sediment (Bremle and Larsson 1998). It was found that PCB concentrations in lake water decreased from 0.0086 to 0.0027 μg/L, while concentrations in fish were halved after remediation was completed. Although concentrations of PCBs in fish decreased after remediation, the relative composition of PCB congeners remained relatively the same as before remediation. Fish still concentrated higher chlorinated congeners relative to levels detected in lake water (Bremle and Larsson 1998).

PCB concentrations have also been monitored in zebra mussels collected from the lower Saginaw River and Saginaw Bay, Michigan in the winter of 1991 (Endicott et al. 1998). The results indicated that the concentration of PCBs decreased in zebra mussels collected further away from the mouth of the Saginaw River. For example, the PCB concentration in zebra mussels from the mouth of the river was approximately 1.1 μg/g, while concentration in zebra mussels collected 20 km away was approximately 0.45 μg/g. The same concentration gradient was also observed in water samples taken from the zebra mussel collection sites. This suggests that PCB levels in zebra mussels are directly related to PCB concentrations in water (Endicott et al. 1998). Data from the Mussel Watch, plus additional data on shellfish (oysters) from North and South American coastal locations, indicate PCB congeners in shellfish were highest from South American locations and lowest in Central America (Sericano et al. 1995). Among 51 sites along the north Gulf of Mexico coast, samples with concentrations >0.100 μg/g were reported from 15 sites. Nevertheless, average concentrations of PCBs in shellfish from these 51 Gulf of

Table 6-17. Mean PCB Concentrations in Fish from Remote Areas

Species	Location	Year	PCB concentration µg/g (wet weight)[a]	Source
Char	Arctic Quebec, Canada	1989–1990	0.152 ± 0.042[b]	Dewailly et al. 1993
Trout	Schrader Lake in the Alaskan Arctic	1992	0.0066	Wilson et al. 1995
Grayling	Schrader Lake in the Alaskan Arctic	1992	0.0013	Wilson et al. 1995
Lake trout	Sierra Nevadas	1993–1994	0.018–0.430	Datta et al. 1999
Kokanee fish	Sierra Nevadas	1993–1994	0.013–0.044	Datta et al. 1999
Lake trout	Siskiwit Lake	1996–1997	(0.040–0.460)	Kannan et al. 2000

[a]Ranges in parenthesis

[b]Lipid weight

Mexico sites decreased between 1986 and 1993. For more information on PCB concentrations in crustaceans, refer to Table 6-18.

PCB concentrations in the tissues of edible turtles, and in some cases frogs, are also of concern with respect to human exposure, particularly for populations engaged in recreational and subsistence hunting. Hebert et al. (1993) evaluated the concentrations of PCBs in muscle tissue of 78 adult snapping turtles collected from 16 sites in southern Ontario, Canada. Mean concentrations (wet weight) of PCBs from all 16 sites ranged from <0.200 to 0.655 μg/g. Skinner (1992) also reported concentrations of PCBs in fat, liver, and muscle tissue from snapping turtles collected near Akwesasne, where turtles are a source of food for a Native American community of nearly 10,000 people. This author reported concentrations of total PCBs (wet weight) ranging from 36.10 to 1,347 ppm in fat, 2.85–94.77 ppm in liver tissue, and not detected to 2.98 ppm in muscle tissue of snapping turtles. Northern leopard frogs from six wetlands located along the Fox River and around Green Bay were collected from 1994 to 1995 and analyzed for total PCB concentrations (Huang et al. 1999). PCB levels in frog tissues ranged from 0.002 to 0.200 μg/g wet weight with the highest concentrations found in frogs from the upper Fox River, furthest away from Green Bay, Wisconsin. Mean residues of Aroclors 1254 and 1260 in tissues of frogs, collected along the Canadian shores of Lakes Erie and Ontario, and the St. Lawrence River, ranged from 0.310 to 1.699 μg/g lipid weight in green frogs and 0.276–1.566 μg/g lipid for leopard frogs (Gillan et al. 1998). Based on frog tissue content and sediment PCB content, biota-sediment accumulation factors of 33.28–1.06 and 23.02–0.42 were calculated for leopard frogs and green frogs, respectively.

PCB concentrations were analyzed in fat, liver, and muscle tissue of commonly hunted red and grey squirrels, beaver, muskrat, snowshoe hares, cottontail rabbits, and white-tailed deer (Skinner 1992). PCBs were typically found only in fatty tissues and occasionally in liver tissues, but were not detected in muscle tissue. Only two liver-tissue samples from muskrats contained detectable concentrations of PCBs. The highest concentration 0.7 μg/g wet weight was detected in a male muskrat. Total PCBs were above detection limits more frequently in mammalian fatty tissues, but only in muskrat and cottontail rabbits. Maximum concentrations of 0.8 μg/g wet weight and 4.0 μg/g lipid weight occurred in male muskrat from the St. Lawrence River near Raquette Point and the St. Regis River, respectively (both sites are within the New York State portion of the Mohawk Nation Reservation at Akwesasne). Wild game provides an important food source for both recreational and subsistence hunters; eating wild game is also a significant cultural activity for many Native Americans (Skinner 1992).

Table 6-18. Mean Concentration of PCBs in Crustaceans

Species	Location	Year	PCB concentration µg/g (wet weight)	PCB concentration µg/g (lipid weight)	Source
Blue mussel	Belgian Fisheries	1983 1993		2.4±0.3 1.6±0.1	Roose et al. 1998
Brown shrimp	Belgian Fisheries	1983 1993		0.49±0.08 0.28±0.05	Roose et al. 1998
Oysters	Galveston Bay, Texas	1986 1988 1990 1992 1993	0.098[a] 0.100[a] 0.099[a] 0.058[a] 0.036[a]		Jackson et al. 1998
Mussels/Oysters	U.S. Nationwide	1986	(0.009–6.808)[a]		Sericano et al. 1995
Blue mussels	Nordic Seas	1989–1990		(0.038–3.3)	Gustavson and Jonsson 1999
Zebra mussels	Mouth of Saginaw River	1991	1.1		Endicott et al. 1998
Zebra mussels	Saginaw Bay (59 km from mouth of Saginaw River)	1991	0.076		Endicott et al. 1998
Flat tree oysters	Morrocoy National Park, Venezuela	1991	(0.0006–0.012)		Jaffe et al. 1998
Zebra mussels	Saginaw Bay	1991	0.45		Endicott et al. 1998
Grass shrimp	Coastal Georgia	1996	0.33		Maruya and Lee 1998
Gei wai shrimp	Mai Po, Hong Kong	1997	0.0064		Liang et al. 1999
Caridean shrimp	Mai Po, Hong Kong	1997	0.0046		Liang et al. 1999

[a]Dry weight; Ranges in parenthesis

Waterfowl may also be an important source of human exposure, especially for avid hunters. Table 6-19 presents temporal PCB concentrations found in several species. Tissues of fish- and shellfish-eating waterfowl (i.e., goldeneye and mergansers) contained significantly higher PCB concentrations than tissues of dabbling ducks (i.e., black ducks and mallards), which, in turn, contained higher concentrations of PCBs than tissues of grazers (i.e., Canada geese) whose food preferences include aquatic vegetation, upland grass, and grain (Rathke and McRae 1989). The concentration of total PCBs was determined in breast meat of Canadian geese collected from northeastern Illinois in 1994 (Levengood et al. 1999). Breast meat samples were baked, allowing fat to drip free, and assayed for PCB residues. Overall, PCBs were detected in only 5 of 87 tissue samples in baked breast meat (detection limit 0.01 μg/g) with residues occurring more frequently in muscle than in skin. PCB concentrations ranged from 0.114 to 0.480 μg/g (Levengood et al. 1999).

Herring gull eggs have routinely been collected by the Canadian Wildlife Service since 1974 to monitor contaminant trends. The PCB concentrations in eggs taken from several nesting colonies on the Great Lakes decreased from 1974 to 1986 (Rathke and McRae 1989). The trend analysis determined that the PCB concentration in herring gull eggs taken from two colonies on Lake Ontario was . 140 mg/kg wet weight in 1974 and fell to approximately 40 mg/kg in 1986. Similarly, the concentration of PCBs in eggs from a colony on Lake Erie was 60 mg/kg in 1974, but fell to <40 mg/kg in 1986. An analysis of PCB concentration in gull eggs in the Great Lakes from 1978 to 1992 indicates that egg concentrations have stabilized (Stow 1995b). Similar conclusions have been determined by other research efforts. Levels of PCBs in herring gull eggs from Great Lakes breeding colonies declined rapidly following the ban of PCBs in 1972. Since the mid 1980s, however, the concentration of PCBs in gull eggs has essentially stabilized in Lakes Superior, Michigan, Huron, and Ontario (Donaldson et al. 1999). In Lake Ontario, herring gull egg PCB concentrations show annual variation due to increased feeding on alewives during colder weather when alewives are particularly abundant (Hebert et al. 1997). Unhatched eggs and plasma samples from prefledged bald eagles were analyzed for PCB concentrations in the Canadian Great lakes Basin (Donaldson et al. 1999). The study found the mean PCB concentration in unhatched bald eagle eggs collected along Lake Erie from 1974 to 1980 was 84 mg/kg wet weight and decreased to 26.4 mg/kg wet weight from 1989 to 1994. From 1990 to 1996, however, no significant decrease in plasma residue levels was observed from either Lake Erie or Lake Superior (Donaldson et al. 1999).

Bottlenose dolphins *(Tursipos truncatus)* collected during a 1990 mortality event along the Gulf Coast of the United States contained mean PCB concentrations of 93, 7.2, 49, 21, and 4 μg/g lipid basis in adult males, adult females, immature dolphins, suckling dolphins, and fetuses, respectively (Kuehl and Haebler

Table 6-19. Mean PCB Concentrations in Animals

Species	Location	Year	PCB concentration µg/g (wet weight)[a]	Source
Bufflehead duck	New York State	1983–1984	0.15±0.19	Foley 1992
Scaup duck	New York State	1983–1984	0.13±0.12	Foley 1992
Mallard duck	New York State	1983–1984	0.08±0.06	Foley 1992
Black duck	New York State	1983–1984	0.07±0.07	Foley 1992
Wood duck	New York State	1983–1984	0.05±0.01	Foley 1992
Canada geese	New York State	1983–1984	0.05±0.01	Foley 1992
Waterfowl	Eastern Lake Ontario/ St. Lawrence River	1983–1985	(<0.01–0.27)	Rathke and McRae 1989
Mallard duck	Wisconsin	1984–1989	(ND–0.021)	Botero et al. 1996
Grebe duck	British Columbia	1989	0.542 (liver tissue)	Elliott and Martin 1998
Seaduck	British Columbia	1989	1.770 (liver tissue)	Elliott and Martin 1998
Polar bear	Arctic Quebec	1989–1990	7.002±1.276 (lipid weight)	Dewailly et al. 1993
Mink	Georgia	1989–1991	0.154 (liver tissue)	Osowski et al. 1995
Mink	South Carolina	1989–1991	0.219 (liver tissue)	Osowski et al. 1995
Mink	North Carolina	1989–1991	0.216 (liver tissue)	Osowski et al. 1995
Mallard duck	Hamilton Harbor, Canada	1990	0.161	Gebauer and Weseloh 1993
Mink	Northwest Territories, Canada	1991–1995	0.007–0.0731 (liver tissue)	Poole et al. 1998
Sea otters	Aleutian Islands	1992–1998	0.310±0.480	Bacon et al. 1999
Sea otters	California Coast	1992–1998	0.190±0.350	Bacon et al. 1999
Sea otters	Southeast Alaska	1992–1998	0.008±0.014	Bacon et al. 1999

[a]Ranges in parenthesis

ND = not detected

1995). This trend generally reflects increased accumulation with age, with the exception of the adult females. The lower PCB residues in adult females are possibly due to the loss of PCBs via placental transfer and via lactation by the adult females who are suckling their young (Kuehl and Haebler 1995). In a similar study with stranded bottlenose dolphins, Salata et al. (1995) reported a mean total PCB concentration of 36.1 μg/g. The mean concentrations of homolog groups di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and decachlorobiphenyls were 0.046, 1.1, 2.2, 6.16, 15.1, 8.58, 2.23, 0.42, and 0.264 μg/g, respectively. Similar to what is observed in other aquatic organisms, highly chlorinated PCB congeners are preferentially bioconcentrated. Blubber and liver samples from six striped dolphins found dead in the Mediterranean sea from 1989 to 1990 were analyzed for PCBs (Reich et al. 1999). Researchers found that the mean concentration of total PCBs in dolphin blubber was 35.6±47.7 μg/g wet weight and in liver samples was 8.74±11.7 μg/g wet weight. Of the 37 congeners monitored in dolphin tissue, PCBs 138, 153, 170, and 180 comprised approximately 60% of total PCBs (Reich et al. 1999). Non-*ortho* and mono-*ortho* PCB congeners, however, contributed <1% of total PCBs in blubber and liver tissues. Of these, PCB 77 was detected most frequently and in the highest concentrations.

By comparing concentrations of PCBs in a mother dolphin and her unborn calf, the authors determined that the mother transferred 3.7% of her total PCB body burden to the calf during her pregnancy. It was also found that the lower molecular weight PCB congeners were more easily transferred than the higher molecular weight congeners and that congeners with 9 or 10 chlorine atoms may not have been transferred at all transplacentally. PCB concentrations were measured in milk from five captive bottlenose dolphins originally collected in the Gulf of Mexico (Ridgway and Reddy 1995). Maximum concentrations of PCBs in the milk were 4.45 ppm wet weight (14.1 ppm lipid weight) as Aroclor 1254, found in the milk produced by a 34-year-old female, the oldest of the population sampled. The lowest concentration, 0.281 ppm wet weight (1.38 ppm lipid weight), was in milk from one of the youngest, a 16-year-old female. For more information concerning PCB concentrations detected in blubber of several sea mammals, see Table 6-20. Based on a review of the literature on PCB residues in mammalian species, Kamrin and Ringer (1994) concluded that the lowest residues were found in the Antarctic, while the highest were in northern latitudes, particularly the Baltic Sea, with overall trends showing decreasing residues of PCBs over the past 10–15 years. Among male beluga whales from the St. Lawrence River estuary, tissue PCB concentrations decreased by a factor of 1.9 from 1982 to 1994 (Muir et al. 1996a). In the 1993–1994 samples, male and female beluga whales had geometric mean total PCB concentrations of 29.6 and 78.9 μg/g lipid basis, respectively (Muir et al. 1996b). PCB 126 was detected most often and in the highest concentrations of the four coplanar PCBs (77, 81, 126, and 169).

Table 6-20. Mean PCB Concentrations in Blubber of Sea Mammals

Species	Location	Year	PCB concentration µg/g wet weight[a]	PCB concentration µg/g lipid weight	Source
Harbour porpoise	Kattegat-Skagerrak Seas, Norway	1978–1981 1989–1990		40±22 13±5.2	Berggrena et al. 1999
Porpoise	Irish Sea	1987–1989		6.19	Troisi et al. 1998
Dolphin	Irish Sea	1987–1989		(2.80–15.48)	Troisi et al. 1998
Striped dolphin	Mediterranean Sea	1989–1990	35.6±47.7		Reich et al. 1999
Beluga whale	Arctic Quebec	1989–1990		1.002±0.469	Dewailly et al. 1993
Seal	Arctic Quebec	1989–1990		0.527±0.692	Dewailly et al. 1993
Bottlenose dolphin (adult male)	U.S. Gulf Coast	1990		93	Kuehl and Haebler 1995
Bottlenose dolphin (adult female)	U.S. Gulf Coast	1990		7.2	Kuehl and Haebler 1995
Bottlenose dolphin (juvenile)	U.S. Gulf Coast	1990		49	Kuehl and Haebler 1995
Bottlenose dolphin (suckling)	U.S. Gulf Coast	1990		21	Kuehl and Haebler 1995
Bottlenose dolphin (fetus)	U.S. Gulf Coast	1990		4	Kuehl and Haebler 1995
Harbor seal pup	Mouth of Puget Sound	1990	(1.3–2.1)		Hong et al. 1996
Harbor seal pup	Head of Puget Sound	1990	(9.2–16)		Hong et al. 1996
Adult harbor seal	Mouth of Puget Sound	1990	(0.17–0.32)		Hong et al. 1996
Adult harbor seal	Head of Puget Sound	1990	(1.1–2.3)		Hong et al. 1996

Table 6-20. Mean PCB Concentrations in Blubber of Sea Mammals *(continued)*

Species	Location	Year	PCB concentration µg/g wet weight[a]	PCB concentration µg/g lipid weight	Source
Striped dolphin	Aegean Sea	1991		21.52±2.76	Troisi et al. 1998
Harbor seal	San Francisco Bay	1991–1992	0.050[a]		Young et al. 1998
Beluga whale (fetus)	Alaskan North Coast	1992	1.35		Wade et al. 1997
Beluga whale (adult female)	Alaskan North Coast	1992	(0.70–2.16)		Wade et al. 1997
Beluga whale (adult male)	Alaskan North Coast	1992	(5.24–9.42)		Wade et al. 1997
Ringed seal (female)	Canadian Arctic	1993		0.387±0.073	Letcher et al. 1998
Ringed seal (male)	Canadian Arctic	1993		0.447±0.092	Letcher et al. 1998
Beluga whale (adult male)	St. Lawrence River	1993–1994		29.6	Muir et al. 1996b
Beluga whale (adult female)	St. Lawrence River	1993–1994		78.9	Muir et al. 1996b
Sperm whale (male)	North Sea	1994–1995		4.5	Holsbeek et al. 1999
Seal	Caspian Sea	1996–1997		(1.12–19.08)	Hall et al. 1999

[a]Concentration reported in blood; ranges in parenthesis

PCBs have also been detected in several consumer products manufactured outside the United States. PCB concentrations in recycled paper products (envelopes, toilet paper, tissue paper, and cardboard boxes) of central European origin were in the range of 5–6,000 μg/kg (ppb) (Welling et al. 1992). PCBs (Aroclor 1254) also were detected in both anhydrous lanolin and lanocerin and in finished cosmetic products produced in Italy (Mariani et al. 1994). PCB concentrations detected in the various products included 1.2 ppm in anhydrous lanolin, 4.8 ppm in lanocerin, 0.64 ppm in anhydrous cream for children, 0.52 ppm in oil/water emulsion-emollient cream, and 3.8 ppm in water/oil emulsion-emollient cream.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

PCBs are no longer manufactured or used (except under exemption) in the United States. Nonetheless, PCBs are present in the environment due to the recycling of the compounds released into the environment by historic anthropogenic production activities. The general population may be exposed to PCBs primarily via consumption of contaminated foods, particularly fish, meat, and poultry, and inhalation (Gunderson 1988). No known consumer product currently manufactured in the United States contains PCBs. Exposure of the general population to PCBs is evidenced by the body burden of the compounds among the nonoccupationally exposed population. PCBs have been detected in the blood, adipose tissue, and breast milk of nonoccupationally exposed members of the general population (EPA 1986b; Greizerstein et al. 1999; Gunderson 1995; Ouw et al. 1976). Overall, PCBs 138, 153, and 180 are the most consistently detected and quantitatively dominant congeners found in human tissues (Hansen 1998). These three congeners have been used to monitor both geographical and temporal trends in human exposure studies due to their high prevalence and persistence (Koopman-Esseboom et al. 1994a, 1994b; Schecter et al. 1989). Other congeners that are commonly detected include PCBs 28, 118, and 170. As the summaries in Section 6.4 indicate, there is a general overall trend for decreasing concentrations of PCBs in most environmental media over the past 2 decades; air concentrations have decreased slightly, and levels in water, sediments, and fish have decreased, in some cases significantly. As noted in this section, PCB body burdens in humans also have decreased, as evidenced by lower levels reported in human adipose tissue, blood serum, and breast milk.

The National Human Adipose Tissue Survey (NHATS), conducted in 1982 using packed column gas chromatography (GC), found that the concentrations of total PCBs in composite human adipose tissue ranged from 14 to 1,700 ng/g (0.014–1.7 ppm) (lipid basis) (EPA 1986b). The maximum concentration was found in a sample composite collected from the South Atlantic region (Virginia, North Carolina, South Carolina, Georgia, and Florida). PCBs were detected in 83% of 46 composite samples analyzed in

the NHATS study. In a subsequent study, Kutz et al. (1991) reported that an examination of the NHATS data from 1970 to 1983 revealed that 93.5% of the U.S. population had detectable concentrations of PCBs, 66.4% had concentrations <1 ppm, 28.9% had concentrations >1 ppm, and 5.1% had concentrations >3 ppm. The 0–14-year-old age group had the smallest percentage of individuals with detectable concentrations of PCBs and the smallest percentage of individuals exceeding the 1 and 3 ppm PCB concentrations; males had a higher percentage of individuals exceeding 1 ppm PCBs than did females; and the Northeast Census Region had the greatest percentage of individuals exceeding 3 ppm. A time-trend analysis of the data also revealed that the percentage of the population having PCB concentrations from 1 to 3 ppm steadily declined from over 62% in 1972 to <2% in 1984. The percentage of the population that had tissue levels >3 ppm also declined during this same period from a high near 10% in 1978 to zero in 1984 (Fensterheim 1993). PCB concentrations in human adipose tissues in the United States appear to have decreased significantly over the years.

Results of congener-specific analysis of PCBs in human adipose tissues obtained from Atlanta, Georgia, in 1986 have been reported (Lordo et al. 1996; Patterson et al. 1994). The sums of three coplanar PCB congeners (77, 126, and 169) were 0.24 ng/g in 14 males with a mean age of 43 and 0.18 ng/g in 14 females with a mean age of 54. Age was significantly correlated with the concentrations of the three congeners such that older people had higher concentrations of PCBs than did younger individuals. From 1990 to 1994, 105 autopsied bodies from Greenland were analyzed for PCBs (Dewailly et al. 1999). Researchers also found that the mean concentration of total PCBs in omental fat increased with age. The study found that in people ages 41–54, 55–69, and $70, mean PCB concentrations were 4,909, 5,337, and 7,357 ng/g lipid weight, respectively. The concentrations of congener-specific PCBs in intra-abdominal, subcutaneous, adrenal, liver, kidney, muscle, and spleen tissues obtained from five North American patients with no known occupational exposure are also available (Schecter et al. 1989, 1994). Differences were observed in the PCB congener pattern of distribution within a given tissue and between the various tissues of the donors. On a lipid weight basis, the highest concentrations of PCBs typically were detected in the adipose and liver tissue. Preferential accumulation in adipose tissue was also noticed in the Dewailly et al. (1999) study.

PCB serum levels measured from 1973 to 1996 in the general population are summarized in Table 6-21. Since the 1970s, researchers have noticed a decrease in PCB concentrations in human blood serum. In a study of 1,631 individuals from 1978 to 1979 living in the United States, the mean PCB concentration in human blood serum was 6.4 ng/g (Kreiss et al. 1982). Currently, mean serum PCB levels range from

Table 6-21. Serum Polychlorinated Biphenyl (PCB) Levels in Non-occupationally Exposed U.S. Populations That Do Not Consume Fish from PCB-Contaminated Waters (1973–1996)

			PCB level ng/mL (ppb)					
Area and sampling method	Number of subjects	Year	Arithmetic mean	Geometric mean	Arithmetic standard deviation	95% Confidence interval	Range	Reference
Nonconsumers of Great Lakes sport fish	41	1996		1.2			0.46–2.9	Anderson et al. 1998
Infrequent male consumers of Great Lakes sport caught fish	57	1994–1995		1.5			0.5–9.7	Hanrahan et al. 1999
Infrequent female consumers of Great Lakes sport caught fish	42	1994–1995		0.9			0.5–3.3	Hanrahan et al. 1999
Females from Cornwall and Mississauga Ontario, Canada	35	1992		3.2[b]			1.3–12.0	Kearney et al. 1999
Males from Cornwall and Mississauga Ontario, Canada	45	1992		3.9[b]			1.1–12.0	Kearney et al. 1999
Los Angeles–Long Beach, California work force[a]	738	1982–1984	5	4[b]	4.37	–	<1–37	Sahl et al. 1985a, 1985b
Jefferson, Ohio, volunteers	59	1983	5.8	4.4	6.5	4–8	1–45	Welty 1983
Fairmont, West Virginia, volunteers	40	1983	6.7	5	5.3	5–8	1–23	Welty 1983
Norwood, Massachusetts, volunteers	990	1983	4.9	4.2	3.5	4–6	2–30	Condon 1983
Old Forge, Pennsylvania, volunteers	138	1981	3.6	–	–	–	<3–43	Reid and Fox 1982

Table 6-21. Serum Polychlorinated Biphenyl (PCB) Levels in Non-occupationally Exposed U.S. Populations That Do Not Consume Fish from PCB-Contaminated Waters (1973–1996) *(continued)*

Area and sampling method	Number of subjects	Year	PCB level ng/mL (ppb) Arithmetic mean	Geometric mean	Arithmetic standard deviation	95% Confidence interval	Range	Reference
Maternity patients from western Michigan control group of nonfisheaters	71	1982	4	–	–	–	–	Schwartz et al. 1983
Lake Michigan random nonfisheaters	418	1980	–	6.6[b]	–	–	<3–60	Humphrey 1983
Canton, Massachusetts, volunteers	10	1980	7.1	5.2	5.2	3–11	1–18	Condon 1983
Billings, Montana, random packinghouse workers	17	1979	7.5	5.8	6.8	4–11	2–30	Drotman 1981
Franklin, Idaho, volunteers	105	1979	–	–	–	–	<5	Drotman 1981
Random unexposed railroad workers at unspecified location	19	1979	12	–	–	–	10–27	Chase et al. 1982
Newton, Kansas, volunteers	7	1979	4.9	4.2	3.1	2–8	2–11	Vernon 1981
Michigan PBB cohort	1,631	1978–1979	7.7	6.4	–	–	<1–57	Kreiss et al. 1982
Bloomington, Indiana, volunteers and controls	110	1977	18.8	–	10.8	17–21	6–79	Baker et al. 1980
Lake Michigan random nonfisheaters	29	1973	17.3	15[b]	–	–	<5–41	Humphrey 1983

Source: Adapted from Kreiss 1985; Massachusetts Department of Public Health 1987; Sahl et al. 1985a, 1985b

[a]Pre-employment survey of utility company workers
[b]Median

0.9 to 1.5 ng/mL in individuals who do not have a diet high in fish, especially fish from the Great Lakes (Anderson et al. 1998; Hanrahan et al. 1999).

Congener-specific analysis of PCBs in serum show that the mean concentration of three coplanar congeners (77, 126, and 169) in the general population in the United States (sampled in 1988) is 176 pg/g (ppt) (lipid basis) (Patterson et al. 1994). Analysis of pooled serum samples show a decrease in the level of three coplanar (77, 126, and 169) PCBs from 1982 to 1989 (Patterson et al. 1994). The mean concentration of the total non-*ortho*-, mono-*ortho*-, and di-*ortho*-substituted PCBs in the whole blood of 50 Vietnam veterans in Michigan measured in 1991–1992 was 167 ng/g (ppb) with a concentration range of 50–628 ng/g (ppb) (Schecter et al. 1993). A breakdown of total PCBs revealed that 0.227 ng/g were contributed by the coplanar PCBs (77, 126, and 169), 50 ng/g by the mono-*ortho* PCBs (28, 74, 105, 118, and 156), and 117 ng/g by the di-*ortho* PCBs (99, 128, 138, 153, 170, 180, 183, 185, and 187) (Schecter et al. 1993). The three most predominant congeners in the whole blood samples were congener 153 (40 ppb), 138 (26 ppb), and 180 (19 ppb). The PCB levels in the veterans did not reflect exposure in Vietnam (Schecter et al. 1993).

PCB concentrations in human breast milk have also been closely monitored since the early 1970s (Mes and Davies 1979; Mes et al. 1986; Newsome and Ryan 1999). Temporal trend studies indicate that the PCB levels detected in human breast milk have decreased over time (Lunden and Noren 1998; Schade and Heinzon 1998). Recent studies indicate that the mean concentration of PCBs in human breast milk appears to range from 238 to 271 ng/g lipid weight (Kostyniak et al. 1999; Newsome et al. 1995). For more information concerning concentrations in human breast milk, please refer to Section 6.6 Exposures of Children.

Since the early 1960s, the FDA has conducted Total Diet Studies, also known as the Market Basket Surveys. These annual studies analyze ready-to-eat foods collected in markets from cities nationwide to determine the intake of selected contaminants in the American diet. Tables 6-22 through 6-25 present the results of the Total Diet Studies from 1976 to 1997 with respect to PCBs. Since the mid-1970s, individual diets for adult males, toddlers, and infants have been analyzed, and the total PCB levels have shown a downward trend in concentration from the mid-1970s to the mid-1980s. For example, the estimated daily dietary intake of PCBs in an adult diet in 1977 was 0.016 μg/kg/day while in the study from 1982 to 1984, the estimated daily intake was 0.0005 μg/kg/day (Gartrell et al. 1985a, 1985b, 1986a). Temporal monitoring studies of PCBs in Total Diet Studies from 1982 to 1997 have revealed that PCB intake has remained relatively steady (Bolger 1999; Gunderson 1995). For example, total diet studies

Table 6-22. Estimated Daily Dietary Intake (μg/kg/day) of Polychlorinated Biphenyls for Adults, Toddlers, and Infants[a]

Fiscal year	Adult	Toddler	Infant
1982–1984	0.0005	0.0008	0.0012
1981–1982	0.003	Not detected	Not detected
1980	0.008	Not detected	Not detected
1979	0.014	Not detected	Not detected
1978	0.027	0.099	0.011
1977	0.016	0.030	0.025
1976	Trace	Not detected	Trace

Source: Derived from Gartrell et al. 1985a, 1985b, 1986a, 1986b; Gunderson 1988
[a]From food components (not individual food items) analysis

Table 6-23. Mean Daily Intakes of PCBs Per Unit of Body Weight (μg/kg body weight/day)[a,b]

Children						Adult males					
6 months			2 years			14–16 years			25–30 years		
82/84	84/86	86/91	82/84	84/86	86/91	82/84	84/86	86/91	82/84	84/86	86/91
0.001	0.001	<0.001	0.001	0.002	0.002	<0.001	0.002	<0.001	<0.001	0.001	<0.001

[a]Gunderson 1995
[b]Study years: 1982–1984, 1984–1986, 1986–1991

Table 6-24. Children Total Diet Studies — PCB Intakes from 265 Foods for the Years 1991–1997[a]

	Dietary intake of PCBs µg/kg/day					
	6–11 months	2 years	6 years	10 year	14–16 years	14–16 years
Total Diet Study	Infant	Child	Child	Child	Female	Male
1991 (3rd quarter)	0.002	0.015	0.023	0.021	0.013	0.013
1993 (1st quarter)	<0.001	0.003	<0.001	<0.001	<0.001	0.002
1993 (2nd quarter)	0.001	0.011	<0.001	<0.001	0.002	<0.001
1994 (1st quarter)	0.001	0.034	0.018	0.018	0.010	0.011
1994 (2nd quarter)	0.003	0.002	0.002	0.002	<0.001	<0.001
1995 (1st quarter)	0.008	0.006	0.007	0.004	0.001	0.003
1997 (3rd quarter)	<0.001	0.008	0.003	0.003	0.001	0.003
Average intake	0.002	0.012	0.008	0.007	0.004	0.005

[a] Bolger 1999

Table 6-25. Adult Total Diet Studies — PCB Intakes from 265 Foods for the Years 1991–1997[a]

	Dietary intake of PCBs µg/kg/day							
	25–30 years		40–45 years		60–65 years		70 years	
Total Diet Study	Female	Male	Female	Male	Female	Male	Female	Male
1991 (3rd quarter)	0.007	0.008	0.006	0.009	0.008	0.012	0.008	0.012
1993 (1st quarter)	<0.001	<0.001	<0.001	<0.001	0.001	0.001	0.001	0.001
1993 (2nd quarter)	<0.001	0.001	0.001	0.001	<0.001	0.001	0.001	0.001
1994 (1st quarter)	0.012	0.013	0.011	0.015	0.012	0.014	0.011	0.010
1994 (2nd quarter)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
1995 (1st quarter)	0.003	0.002	0.004	0.003	0.004	0.005	0.002	0.004
1997 (3rd quarter)	0.002	0.002	0.001	0.002	0.002	0.003	0.001	0.003
Average intake	0.004	0.004	0.003	0.004	0.004	0.005	0.003	0.004

[a] Bolger 1999c

conducted from 1982 to 1984 for adults between the ages of 25 and 30 indicated that the mean daily intake of PCBs was <0.001 μg/kg body weight/day while in the 1997 study, the mean was 0.002 μg/kg body weight/day. The FDA reported that the source of PCBs in the past was the meat-fish-poultry composite (63–100% of total dietary intake) with fish being the major contributing source (Jelinek and Corneliussen 1976). This observation appears to have continued in the recent Total Diet Studies conducted from 1991 to 1997 where meat, fish, and poultry remain the primary sources of PCBs in the human diet with fish being the major contributing factor (Bolger 1999). A recent market-basket study analyzed PCB congener levels in pooled food samples from supermarkets in five U.S. cities representing the northeast, mid-south, south, mid-west, and west (Schecter et al. 1997). Coplanar PCB concentrations ranged from 0.2 pg/g wet weight in a simulated vegetarian diet to 531.4 pg/g wet weight in fresh fish. Mono-*ortho* PCBs ranged from 15 pg/g wet weight in a vegetarian diet to 2,350 pg/g wet weight in fresh fish. Di-*ortho* PCBs ranged from 144 pg/g in a vegetarian diet to 4,600 pg/g in fresh fish. Schecter and Lingjun (1995) measured levels of mono-*ortho* and di-*ortho* PCBs in three types of fast foods sampled at the same five representative U.S. cities. Average total concentrations for mono-*ortho* PCBs were 380, 440, and 500 pg/g for hamburger, pizza, and chicken, respectively, and for di-*ortho* PCBs were 577, 740, and 670 pg/g for hamburger, pizza, and chicken, respectively.

As is the case with U.S. dietary exposure, PCB exposure via ingestion of drinking water and inhalation has also decreased over time. The average adult inhales . 20 m^3 of air per day while the average numbers of hours a person spends outdoors, within vehicles, and indoors are approximately 1.77, 1.77, and 20.4 hours, respectively (EPA 1997d). Assuming that outdoor air at a typical urban location contains an average PCB concentration of 5 ng/m^3 (range, 1–10 ng/$m^{3)}$ (Eisenreich et al. 1992), the average daily exposure via inhalation would be 100 ng (range, 20–200 ng). However, the concentrations of PCBs in indoor air can be at least an order of magnitude higher than outdoor air concentrations (see Section 6.4.1) (Balfanz et al. 1993; MacLeod 1981; Wallace et al. 1996). It has been suggested that the emissions from certain appliances and devices (e.g., fluorescent lighting ballasts) that have PCB-containing components contribute to these higher indoor air concentrations. Individuals who spend more time indoors in these types of surroundings may be exposed to higher PCB concentrations than people who spend more time outdoors. The exact inhalation exposure for the general population depends on the amount of time an individual spends outdoors and indoors.

The general population is exposed to <200 ng/day PCBs from drinking water (assuming drinking water concentrations of <0.1 μg/L [ppb] PCBs and a consumption rate of 2 L/day). However, the daily exposure to PCBs via most drinking water in the United States is likely to be much lower than 200 ng,

since PCBs were detected in only one finished groundwater supply and two finished surface water supplies surveyed in NOMS I and II out of 113 cities surveyed nationwide. This value (<0.1 μg/L) is based on the NOMS study conducted from 1975 to 1977. A study of municipal drinking water sources in Canada from 1985 to 1988 detected PCBs in only 1 out of 280 water samples at a concentration of 0.006 μg/L (O'Neill et al. 1992). Consequently, for persons in the general population, food consumption and inhalation appear to represent greater sources of human exposure to PCBs than ingestion of drinking water.

From 1970 to 1976, occupational exposure to PCBs in the United States may have affected . 12,000 individuals per year (NIOSH 1977). PCB levels in blood, plasma, serum, and body tissues were 10–1,000 times higher in individuals exposed to PCBs in the workplace than in nonoccupationally exposed individuals (Wolff 1985; Yakushiji et al. 1978). Serum PCB levels in some occupationally exposed populations are reported in Table 6-26. Within 46 months following the cessation of PCB use, serum PCB levels of the lower chlorinated (mostly tri- and tetra-chlorinated) PCBs in capacitor manufacturing workers in the United States decreased by an average of 25–90%, although the higher chlorinated congeners did not decrease significantly (Wolff et al. 1992). A study conducted in Finland found that the median serum levels of three co-planar PCB congeners (77, 126, and 169) in capacitor manufacturing workers were 3–20 times higher than levels in the control population (Luotamo et al. 1993). The same congeners in the blood of exposed Finnish laboratory personnel, however, were not elevated above those of a control group (Hesso et al. 1992). PCB blood levels were compared for employees in the scrap metal industry where soils were contaminated with PCBs (Malkin 1995). Serum PCB levels of <1–65.3 μg/L were observed. No difference in PCB serum levels were found between outdoor or indoor workers. This lack of difference was associated with the workers' practice of eating lunch outdoors and consequent hand-to-mouth transmission.

Occupational exposure to PCBs via inhalation was estimated to be more than an order of magnitude higher than exposure via dermal contact in workers at a facility that recovers PCBs from transformers (Perkins and Knight 1989). Although occupational exposure to PCBs in the United States is no longer due to the production of PCBs or PCB-containing products (e.g., capacitors, transformers, and electrical equipment), it may still occur as a result of repairing electrical equipment that contains PCBs or accidents involving such equipment (Schecter and Charles 1991; Wolff 1985).

Table 6-26. Serum Polychlorinated Biphenyl (PCB) Levels in Populations with Occupational Exposure

Facility	Number of subjects	PCB levels ng/mL (ppb)				Reference
		Arithmetic mean	Geometric mean	95% Confidence interval	Range	
Railway car maintenance	86	33.4	–	–	10–312	Chase et al. 1982
Capacitor plant	34	394.0[a]	–	234–554	trace–1,700	Ouw et al. 1976, 1979
Capacitor plant	290	48.0[a]	21.0[b]	38–546[b]	1–546[c]	Wolff et al. 1982a
Capacitor plant	80	342.0[a]	–	–	41–1,319	Maroni et al. 1981a
Capacitor plant	221	–	119.0[c] 25.3[b]	– –	1–2,220[c] 1–250[b]	Smith et al. 1982
Public utility	14	–	24.0[c] 24.0[c]	15–39[c] 16–35[b]	5–52[c] 7–24[b]	Smith et al. 1982
Transformer repair workers (recent exposure)	35	–	43.7[d]	–	4.3–253	Fait et al. 1989
Transformer repair workers (past exposure)	17	–	30.0[c]	–	1.5–143	Fait et al. 1989
Scavenging copper from PCB-contaminated capacitors at waste sites	11	–	12.0	–	–	Stehr-Green et al. 1986b
Private utility	25	–	22.0[c] 29.0[b]	17–25[c] 20–43[b]	9–48[c] 7–250[b]	Smith et al. 1982
Utility	1,058	4.0	3.0[d]	3.65[f]	<1–26	Sahl et al. 1985b

Source: Adapted from Kreiss 1985

[a]Blood level
[b]Higher-chlorinated PCBs
[c]Lower-chlorinated PCBs
[d]Median
[e]Standard deviation

In addition, occupational exposure to PCBs may occur as a result of waste site cleanup or disposal activities. The median serum levels of two PCB congeners (77 and 81) in Finnish workers at a hazardous waste incinerator site where PCB-containing capacitors are destroyed were 3–4 times higher than control population levels (Luotamo et al. 1993). The serum levels of two other coplanar congeners (126 and 169) in incinerator workers were not significantly different from control population levels. Elevated PCB levels in blood (compared with background levels) were found in some exposed workers, including firefighters, electricians, and others who entered the building following the Binghamton State Office Building transformer fire in Binghamton, New York (Schecter 1987). In seven firefighters, the serum PCB levels measured approximately 10 months after the fire decreased by 20–95% from levels measured immediately after the exposure (Schecter et al. 1994). Compared to persons not occupationally exposed to PCBs, electrical workers appeared to retain more of PCB congener 126 after exposure than any other congener; however, the unusually high concentration of PCB 126 in serum of electrical workers was later attributed to an unidentified peak by the analyst (see Hansen 1999, Appendix Table 5) (Fait et al. 1989). Maintenance workers and welders who work with metals coated with PCB-containing paints may also be at higher risk of exposure because scraps from different railroad car paints were found to contain 4–625 mg/kg of Aroclor 1254 (Welsh 1995).

According to the National Occupational Exposure Study (NOES) conducted by NIOSH from 1981 to 1983, the following estimated number of workers were potentially exposed to Aroclors in the workplace: 2,214 to Aroclor 1242; 3,702 to Aroclor 1254; 991 to Aroclor 1260; and 1,558 to Aroclor 1016 (NIOSH 1989). Occupational exposure to Aroclors occurs in miscellaneous workers in the transformer industry, noncellulose fiber industry, semiconductor and related industries, and in sawmills and planing mills. It also occurs in clinical laboratory technicians and technologists of general medical and surgical hospitals. The NOES database does not contain information on the frequency, concentration, or duration of occupational exposure to any of the chemicals listed. The survey provides estimations of the numbers of workers for whom potential exposure in the workplace is an issue. Since this study was conducted from 1981 to 1983, it does not accurately represent current workplace exposure to PCBs.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children are exposed to PCBs in the same manner as the general population—primarily via consumption of contaminated foods, particularly meat, fish, and poultry (Bolger 1999; Gunderson 1985). Infants and young children consume a greater amount of food per kilogram of body weight and, therefore, may have a proportionately greater exposure to PCBs than adults (Cordle et al. 1982). Infants and children also have different diets than adults due to their age. This has been reflected in the FDA total diet studies (Gunderson et al. 1995). Breast-fed infants may be exposed to higher than average concentrations of PCBs because PCBs tend to accumulate in breast milk fat. Factors that can affect the levels of PCBs in human breast milk include mother's age, number of deliveries and lactations, place of residence, and changes in the mother's weight during lactation (Czaja et al. 1999a, 1999b). Women with the highest number of deliveries have higher levels of PCBs in their breast milk (Czaja et al. 1997a). However, while lactation may be one of the means of excreting PCBs from the body, it is age rather than the number of deliveries that seems to affect the concentration of PCBs with older women having higher concentrations. Also, women in industrial areas can have elevated levels of PCBs in their breast milk compared to women living in rural areas (Czaja et al. 1997b). It is estimated that an infant that is breast fed for 6 months will receive 6.8–12% of its lifetime PCB body burden (Kimbrough 1995; Patandin et al. 1999). Blood samples were taken from 80 full-term German neonates within the first 12 hours of life, before the first oral feeding (Lackmann et al. 1999). The median serum concentration of total PCBs was 0.96 μg/L (<0.30–3.14, range), with PCBs 138, 153, and 180 detected at median levels of 0.34 (<0.10–1.01), 0.42 (<0.10–1.42), and 0.17 (<0.10–0.78) μg/L, respectively. Lanting et al. (1998a) measured the levels of PCB congeners 118, 138, 153, and 180 in plasma from 42-month-old children (n=126) living in the Groningen area, The Netherlands. In 42-month-old children who were fully breast-fed for at least 6 weeks, the median total plasma PCB level 0.81 μg/L (range, 0.23–2.2), compared to the formula-fed children that had levels of 0.18 μg/L (range, 0.07–1.49) (see Section 3.7).

A recent study conducted from 1991 to 1993 of human breast milk from 213 women living along Lake Ontario in New York State determined that the mean concentration of PCBs was 271±116 ng/g lipid weight (Kostyniak et al. 1999). In 1992, breast milk from 497 women living in Canada had a mean PCB concentration of 238 ng/g lipid weight (Newsome et al. 1995). Several studies indicate that PCB concentrations in human breast milk have decreased since the early 1970s (Hansen 1999; Lunden and Noren 1998). For example, in a study of human breast milk of Swedish women studied from 1972 to 1992, researchers determined that the concentration of PCBs decreased over time. PCB concentrations in 1972, 1980, 1984–1985, 1990, and 1992 were 1,090, 780, 600, 510, and 380 ng/g lipid weight, respectively (Lunden and Noren 1998). In Germany, researchers studied PCB levels from 1986 to 1996 in human breast milk of women between the ages of 27 and 31 who had only given birth once. They found that the concentrations of PCBs in 1986, 1988, 1990, 1992, 1994, and 1996 were 1,300, 1,050, 1,000, 750, 650, and 450 ng/g lipid weight, respectively (Schade and Heinzow 1998). Congener-specific analysis of human milk indicates that the congeners 138, 153, 118, 180, and 105 are most prevalent and that the three coplanar congeners (77, 126, and 169) were either not detected or detected at concentrations <1 ng/g (ppb) on a milk fat basis (Bohm et al. 1993; Mes et al. 1993). For a representative trend analysis of PCB concentrations in human breast milk over time, please refer to Table 6-27. PCB exposure of infants whose mothers have a diet high in fish is discussed in Section 3.7 and 6.7. In general, mothers who consume fish contaminated with PCBs have higher levels in their breast milk compared to nonconsumers.

Unborn children may also be at risk of higher PCB exposure, especially in areas that have been heavily contaminated with PCBs. To illustrate this, researchers analyzed placental cord serum of 755 infants born to mothers residing in towns adjacent to a PCB-contaminated harbor in southeastern Massachusetts (Altshul et al. 1999). Infants whose cord serum was analyzed were born between 1993 and 1998 in the towns of New Bedford, Acushnet, Fairhaven, and Dartmouth, Massachusetts. Of the 51 PCB congeners analyzed, only 13 were above the detection limit (0.01 ng/g serum). The median concentration of PCBs was 0.56 ng/g serum (Altshul et al. 1999). Researchers found that the relative predominance of less chlorinated congeners in the cord blood was generally consistent with the characteristics of the contaminated site. PCB concentrations were also measured in cord blood from both 134 women who consumed Great Lakes fish and 145 women who had never consumed Great Lakes fish (Stewart et al. 1999). Although researchers did not find any difference between fish consumption levels and total PCBs in umbilical cord serum, it was established that fish eaters had marked elevations of the most heavily chlorinated PCB homologues. In particular, levels of hepta- to nonachlorobiphenyls were greater in fish eaters than non-fish eaters (Stewart et al. 1999). Another study examined PCB concentrations in nine

Table 6-27. Mean Concentration of PCBs in Human Breast Milk

Location	Sample Size	Year	PCB concentration (ng/g lipid)[a]	PCB concentration (ng/g milk)	Source
National Canadian Study	No data	1970		6	Mes and Davies 1979
	100	1975		12	Mes and Davies 1979
	210	1982		26	Mes et al. 1986
	412	1986		6.35	Mes et al. 1993
	497	1992	238	7.21	Newsome et al. 1995
National Sweden Study	135	1972	1,090		Lunden and Noren 1998
	153	1976	910		
	431	1980	780		
	102	1984–1985	600		
	120	1988–1989	650		
	60	1990	510		
	60	1991	410		
	40	1992	380		
Akwesasne Indian Reservation	19	1986–1989	602		Fitzgerald et al. 1998
	38	1990	352		
	40	1991–1992	254		
Warren and Schoharie County, New York (rural)	52	1986–1989	375		Fitzgerald et al. 1998
	57	1990	404		
	45	1991–1992	318		
Northern Germany (age 27–31, primiparae)	15	1986	1,300		Schade and Heinzow 1998
	68	1988	1,050		
	84	1990	1,000		
	43	1992	750		
	29	1994	650		
	14	1996	450		

Table 6-27. Mean concentration of PCBs in Human Breast Milk *(continued)*

Location	Sample Size	Year	PCB concentration (ng/g lipid)[a]	PCB concentration (ng/g milk)	Source
Zagreb, Croatia	40 54 45	1987–1990 1991–1993 1994–1995	243[b] 213[b] 212[b]		Krauthacker et al. 1998
16 Counties in New York state adjacent to Lake Ontario	213	1991–1993	271±116	8.28±4.66	Kostyniak et al. 1999
New York State	7	1991–1993	(239–428)	3.5–14.1	Greizerstein et al. 1999
Helsinki, Finland (urban)	20	1992–1994	296		Kiviranta et al. 1999
Kuopio, Finland (rural)	64	1992–1993	198		Kiviranta et al. 1999
New Bedford Harbor, Massachusetts (near superfund site)	4	1993	(1,107–2,379)		Korrick and Altshul 1998
Murmansk, Russia (industrialized area)	15	1993	429.4		Polder et al. 1998
Monchegorsk, Russia (industrialized area)	15	1993	490.5		Polder et al. 1998
Keewatin, Northern Canada	12	1996–1997	247		Newsome and Ryan 1999

[a]Ranges in parenthesis
[a]Median

stillborn fetuses from the Netherlands in 1993 and found that median (range) concentration of PCBs in adipose tissue was 235 (97–768) ng/g lipid weight (Lanting et al. 1998b).

As indicated above, PCB measurements of breast milk and placental cord blood have been used as surrogate measures of exposure in studies of children. Cord blood is the most direct marker of fetal exposure, but because of its relatively low fat content, it requires sensitive analytical methods for accurate PCB analysis; analysis of breast milk does not present this difficulty. Analytical techniques have improved enormously in recent years, such that cord blood analysis of PCBs is now more accurate and reliable, but still of concern due to the low concentration of fat in cord blood.

For most young children, it appears that the dietary intake of PCBs has reached a steady state in the United States. During the 1980s, dietary intake of PCBs for infants (6–11 months) declined from 0.011 to 0.0012 μg/kg/day, and dietary intake of PCBs for toddlers (2 years) declined from 0.099 to 0.0008 μg/kg/day (Gartrell et al. 1985a, 1985b, 1986a, 1986b; Gunderson 1988). In the most recent study conducted in 1997, the estimated dietary intakes for infants (6 months) and toddlers (2 years) are <0.001 and 0.008 μg/kg/day, respectively (Bolger 1999). Assuming that the average infant weighs 9 kg, the average daily dietary exposure would be <0.009 μg. Assuming that the average toddler weighs 13 kg, the average daily dietary exposure would be 0.104 μg. See Tables 6-22 through 6-25 in Section 6.5 for more details. A potential source of dietary intake of PCBs for infants may also come from the consumption of contaminated baby formulas. In a study of eight soybean infant formulas obtained in Spain, researchers discovered detectable quantities of PCBs (Ramos et al. 1998). The mean total concentration of PCBs in soybean infant formula was 10.25 ng/g lipid weight. Of the 15 congeners analyzed for, PCB 101 contributed the most to the total amount of PCBs.

Additional exposure to PCBs could occur for children who live near hazardous waste sites. Since children spend a lot of time playing on the ground, both indoors and out, they come into more contact with contaminants found on dust and dirt particles. They may be exposed to PCBs by dermal contact with PCB-contaminated soil and by ingesting contaminated soil from their unwashed hands and other hand-to-mouth behavior. The determination of PCBs in dust and dirt can therefore be important for predicting children's exposure. However, quantitative information regarding the bioavailability and amount of PCBs that children are exposed to through contact with contaminated soils are unavailable.

Between 1994 and 1995, house dust and yard soil were analyzed for PCB concentrations from 34 homes surrounding New Bedford Harbor, Massachusetts during the dredging of PCB-contaminated sediments

(Vorhees et al. 1999). House dust samples were collected from the carpet, while yard soil was collected from the main entryway. The results indicated that house dust samples were 10 times higher (260–23,000 ng/g) than yard soil concentrations (15–1,800 ng/g). Although yard soil concentrations from neighborhoods closest to the harbor were significantly higher than comparison neighborhoods distant from the harbor, house dust concentrations did not differ significantly between the two locales (Vorhees et al. 1999). In general, the house dust samples contained higher concentrations of the more volatile, less chlorinated PCBs than the soil samples. The results of the house dust data were compared to results obtained from homes that were not located near known PCB sources. PCBs measured in house dust in nine Seattle, Washington homes had concentrations ranging from 240 to 760 ng/g and eight Columbus, Ohio, homes had concentrations ranging from 210 to 1,900 ng/g (Vorhees et al. 1999). Clearly, PCB concentrations were generally lower in these locations compared to the New Bedford Harbor neighborhood homes. Street dust and dirt samples, analyzed in August 1993, from the streets of Buffalo, New York, also contained detectable amounts of PCBs (Irvine and Loganathan 1998). Total PCB concentrations for the dust and dirt samples ranged from 90 to 1,700 ng/g, dry weight. In every case, the higher-chlorinated congeners were detected more frequently and in greater concentrations. In particular, PCBs 153, 138, 101, 118, and 180 contributed >50% of the total concentration of PCBs in each sample (Irvine and Loganathan 1998). Residing in proximity to incinerators may also increase exposure levels for children. Blood samples from 298 children living near a toxic waste incinerator in Germany had a mean concentration of PCBs of 0.49 μg/L (Osius et al. 1999). Given that PCB congeners have $\log K_{oc}$ values ranging from 3.27 to 6.87 (Horzempa and DiToro 1983; Meylan et al. 1992), they will generally adsorb strongly to soil and dust particles. This should decrease bioavailability of PCBs. More scientific data, however, are necessary to determine the degree of PCB exposure through hand-to-mouth activities. This is suggested as a data need for future study.

Consumption of contaminated groundwater may be an additional source of PCB exposure for children. PCBs have been detected in groundwater samples at 500 of the 1,598 NPL sites where they were detected in some environmental media (HazDat 2000).

Indoor air at schools could be a potential source of PCB exposure for children. Indoor air in seven public buildings (schools and offices) in Minnesota was monitored during 1984 for Aroclors 1242, 1254, and 1260 (Oatman and Roy 1986). The mean total Aroclor concentration (±1 standard deviation) in the indoor air of the three buildings using PCB transformers (457±223 ng/m^3) was found to be nearly twice as high as that in the air of the four buildings not using PCB transformers (229±106 ng/m^3). The Aroclor

levels detected in the indoor air of all seven buildings were significantly higher than those detected in ambient outdoor air (Balfanz et al. 1993; Eisenreich et al. 1992; MacLeod 1981; Oatman and Roy 1986).

Children may also be exposed to PCBs through play activities involving PCB containing materials. Children who had played with parts of a capacitor that had once contained PCBs had elevated serum PCB (similar to Aroclor 1242) levels compared with a background population consisting of other household members and a reference group of persons in the same geographical area (Wolff and Schecter 1991). The serum PCB levels in the exposed children declined to about half of the initial values over a period of 11 months. Exposure could also occur if children were to play near an area where there was a transformer fire. Although there are no data on children, elevated PCB levels in blood were found in some workers who entered a building following a transformer fire (Schecter 1987).

PCBs have been detected in several consumer products manufactured outside the United States, and it has not been determined whether any of these products would be likely to be imported into the United States. Many of these products could be used by children. PCB concentrations detected in various products include 1.2 ppm in anhydrous lanolin, 4.8 ppm in lanocerin, 0.64 ppm in anhydrous cream for children, 0.52 ppm in oil/water emulsion-emollient cream, and 3.8 ppm in water/oil emulsion-emollient cream (Welling et al. 1992). Various fish oils used as dietary supplements were collected from around the world between 1994 and 1995 and analyzed for PCB levels (Jacobs et al. 1998). Researchers found that PCB congeners 138, 153, and especially 118 were detected most frequently and in the highest concentrations. None of the samples, however, exceeded the FDA regulatory limit of 2.0 ppm for total PCBs. In fact, total PCB concentrations ranged from <5 to 1,132 μg/L with a mean of 332.0 μg/L (Jacobs et al. 1998). Due to the lack of data concerning the amount of these products that are used by children, it is difficult to determine the degree of importance these items have on a child's exposure to PCBs.

Studies also have indicated that PCBs may be transported from the workplace to the home. Children living with parents who work with PCBs (i.e., occupations associated with hazardous waste) may have higher exposure levels. There have been several cases reported of the transport of PCBs from the workplace to the home and in some cases, the secondary exposure of family members. PCBs with a pattern resembling Aroclor 1254 were found in the blood of two railway maintenance workers who repaired transformers (77 and 101 ng/mL). The PCB levels for the wives who laundered their husbands' clothes were not elevated, but their PCB pattern resembled the Aroclor 1254 pattern of their husbands, suggesting that the PCBs found in the women's blood were derived from contact with their husbands (Fischbein and Wolff 1987). In Indiana, PCBs were released into the municipal sewage treatment plant

by an electrical manufacturing firm. PCBs were found in the blood serum of sewage treatment workers (75.1 ppb), their family members (33.6 ppb), community residents (24.4 ppb), and people who applied sludge from the plant in their yards (17.4 ppb) (Baker et al. 1980). Thus, the worker's family members had higher concentrations of PCBs in their blood serum than the other nonoccupational groups. Based on these observations, children living in homes of parents who are exposed to PCBs may in turn be exposed through contaminated clothing and shoes.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to PCBs (Section 6.5), there are several groups within the general population with potentially high exposures (higher than background levels) to PCBs. These groups include recreational and subsistence fishers who typically consume larger amounts of locally caught fish than the general population; Native American populations such as the North American Inuits or other subsistence hunters/fishers; breast-fed infants of mothers who consume large amounts of contaminated fish or wild game; farmers and their families who were exposed to PCB-contaminated foods via food stored in PCB contaminated silos; and individuals living in proximity to incinerators, other PCB-disposal facilities, or the 500 current or former NPL hazardous waste sites where PCBs have been detected (HazDat 2000).

Consumption of sportfish, particularly from waters contaminated with PCBs, will increase the level of human exposure to PCBs. PCB exposures for adults and children associated with the consumption of contaminated fish are available for residents of the Great Lakes region (Anderson et al. 1999; Hanrahan et al. 1999), Massachusetts (Massachusetts Department of Public Health 1987), Michigan (Anderson 1989; Courval et al. 1996; Hovinga et al. 1992; Humphrey 1983; Humphrey and Budd 1996; Schwartz et al. 1983), New York (Fitzgerald et al. 1996); Wisconsin (Anderson 1989; Fiore et al. 1989), northern Illinois (Pellettieri et al. 1996), and Alabama (Anderson 1989; Kreiss et al. 1981) as well as for populations in Canada (Ryan et al. 1997). Direct relationships are found between serum PCB levels and the quantities of fish consumed or numbers of fish meals consumed (Fiore et al. 1989; Hovinga et al. 1993; Humphrey and Budd 1996; Schwartz et al. 1983). One recent study monitored the PCB concentrations in blood serum from both frequent and infrequent consumers of Great Lakes sport fish (Hanrahan et al. 1999). It was found that the mean concentration of PCBs in blood of 252 males who were frequent consumers was 4.8 ng/mL while in 57 males who were infrequent consumers, the concentration was 1.5 ng/mL. A similar study conducted in 1992 compared PCB blood serum levels between males from Cornwall and Mississauga, Canada who consumed waterfowl and fish from Lake Ontario and non-consumers (Kearney

et al. 1999). The PCB concentrations in blood serum of 101 male consumers and 45 non-consumers were 5.5 and 3.9 ng/mL wet weight, respectively. A multivariate regression analysis was used to show that the significantly elevated serum PCB levels observed in sportfish eaters in Michigan compared with controls was due to historic fish consumption rather than recent consumption (Hovinga et al. 1993). In a study of maternity patients from western Michigan, Schwartz et al. (1983) reported an increase in serum PCB levels in women who consumed larger numbers of fish meals per year than those who consumed no fish meals per year. For example, in the control group of non-fish eaters, the mean serum PCB level was 4 ppb. However, for women consuming 6–11, 12–23, 24–51, and 52–183 fish meals per year, the mean serum PCB levels were 5.5, 5.5, 5.9, and 9.0 ppb, respectively. A recent multimedia study characterized environmental exposures to PCBs among residents in nine homes in the Lower Rio Grand Valley of Texas (Berry et al. 1997; Butler et al. 1997). As part of this study, PCB blood serum concentrations were obtained and compared to the National Health and Nutrition Examination Survey II (NHANES II) 95th percentile. Blood plasma PCB concentrations for two individuals with maximum values, as Aroclor 1260, exceeded the NHANES II 95th percentile for PCBs. Upon further investigation, it was found that the residents caught and ate carp from a nearby irrigation ditch. Analysis of the fish showed high PCB concentrations of 399 mg/kg (ppm), indicating a likely source for the high blood serum concentration in these individuals. For all of the other participants in the study, blood serum PCB concentrations were less than 4.2 μg/L, the NHANES II median value. PCBs were not detected in drinking water or dietary samples other than the fish samples. Serum PCB levels were 2.5 times higher in people who regularly eat fish (consumption rate of >24 pounds/year [>11 kg/year]) compared to those who occasionally or never eat fish (consumption rate of 0–6 pounds/year [0–2.7 kg/year]) (Humphrey 1988). For more information concerning PCB serum levels in people who consume fish, please refer to Table 6-28.

Recreational and subsistence fishers within the general population consume larger quantities of fish and shellfish than the general population. Because of this, these populations are at greater risk of exposure to PCBs and other chemical contaminants if the waters they fish frequently are contaminated. The EPA advises states to use a screening value of 0.01 ppm of total PCBs (sum of Aroclors) as a criteria to evaluate their fishable waterbodies (EPA 1993h). Currently, 678 advisories have been issued by 35 states, the District of Columbia, and American Samoa restricting the consumption of PCB-contaminated fish and shellfish (EPA 1999l). In one study, however, of 8,306 Great Lakes sportfishers surveyed, only about 8.4% of them consumed fish from the Great Lakes (Tilden et al. 1997). Of those,

Table 6-28. Serum Polychlorinated Biphenyl (PCB) Levels in Non-occupationally Exposed U.S. Populations that Consume Fish from PCB-contaminated Waters (1973–1995)

			PCB level ng/mL (ppb)				
Population	Number of subjects	Year	Arithmetic mean	Geometric mean	Arithmetic standard deviation	Range	Reference
Frequent male consumers of Great Lakes sport caught fish	252	1994–1995		4.8		0.7–58.2	Hanrahan et al. 1999
Frequent female consumers of Great Lakes sport caught fish	187	1994–1995		2.1		0.5–12.1	Hanrahan et al. 1999
Native American Indian males from Akwesasne near the St. Lawrence River in New York, Ontario, and Quebec	139	1992–1995	4.9	2.8	5.6	<0.10–31.7	Fitzgerald et al. 1999
Sport fisherman who ate fish from Lake Michigan	10	1993		8.6		3.6–15.2	Anderson et al. 1998
Sport fisherman who ate fish from Lake Huron	11	1993		5.7		1.3–12.9	Anderson et al. 1998
Sport fishermen who ate fish from Lake Erie	11	1993		2.2		1.2–3.2	Anderson et al. 1998
Females from Cornwall and Mississauga Ontario, Canada	51	1992		3.4[a]		0.7–23.0	Kearney et al. 1999
Males from Cornwall and Mississauga Ontario, Canada	101	1992		5.5[a]		0.9–21.0	Kearney et al. 1999
Lake Michigan volunteers eating <6 lbs sportfish annually	95	1989	–	6.8	–	2–42.1	Hovinga et al. 1993

Table 6-28. Serum Polychlorinated Biphenyl (PCB) Levels in Non-occupationally Exposed U.S. Populations that Consume Fish from PCB-contaminated Waters (1973–1995) *(continued)*

			PCB level ng/mL (ppb)				
Population	Number of subjects	Year	Arithmetic mean	Geometric mean	Arithmetic standard deviation	Range	Reference
Lake Michigan volunteer sportfishers eating >24 lbs sportfish annually	112	1989	–	19.0	–	4.9–173.8	Hovinga et al. 1993
Wisconsin anglers that consumed both sport-caught fish meals and meals of species listed on PCB consumption advisory	191	1985–1988	–	–	–	–	Fiore et al. 1989
19.6 fish meals; 7.1 advisory fish meals	$6.x10^7$					<0.6	
25.3 fish meals; 10.9 advisory fish meals						0.6–2.0	
32.0 fish meals; 12.8 advisory fish meals						2–5.0	
33.3 fish meals; 16.9 advisory fish meals						>5.0	
Maternity patients from western Michigan	193	1982	5.5	4.6[a]	3.7	–	Schwartz et al. 1983
6–11 fish meals/year			5.5	–	–	–	
12–23 fish meals/year			5.5	–	–	–	
24–51 fish meals/year			5.9	–	–	–	
52–183 fish meals/year			9.0	–	–	–	
New Bedford, Massachusetts, known exposure to contaminated seafood	110	1981–1982	13.34	9.48[a]	14.02	1.40–87.97	Massachusetts Department of Public Health 1987

Table 6-28. Serum Polychlorinated Biphenyl (PCB) Levels in Non-occupationally Exposed U.S. Populations that Consume Fish from PCB-contaminated Waters (1973–1995) *(continued)*

Population	Number of subjects	Year	PCB level ng/mL (ppb)				Reference
			Arithmetic mean	Geometric mean	Arithmetic standard deviation	Range	
New Bedford, Massachusetts, random sample	840	1981–1982	5.84	3.88[a]	7.78	0.38–154.2	Massachusetts Department of Public Health 1987
Lake Michigan volunteer sportfishers	572	1980	–	21.0[a]	–	<3–203	Humphrey 1983
Lake Michigan volunteer sportfishers	90	1973	72.7	56.0[a]	–	25–366	Humphrey 1983
Triana, Alabama, volunteer sportfishers	458	1973	22.2	17.2	22.3	3–158	Kreiss et al. 1981

Source: Adapted from Kreiss 1985; Massachusetts Department of Public Health 1987; Sahl et al. 1985a, 1985b

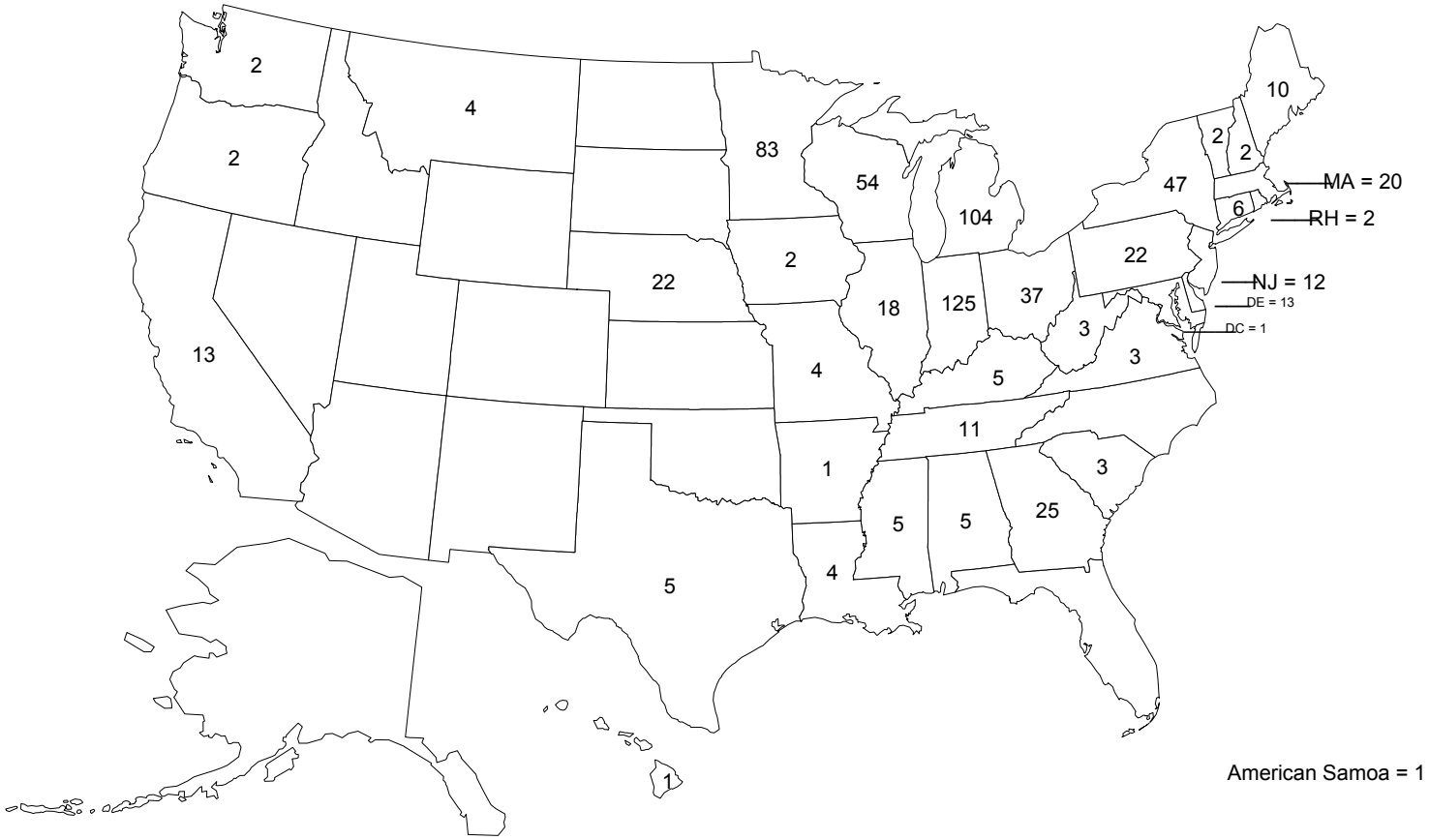
[a]Median

58% of males were aware of a health advisory, while only 39% of women were aware of a health advisory. It appears that although health advisories do exist, there is a need to better communicate these warnings to the public. The number of waterbodies under advisory for PCBs in each state is shown in Figure 6-5.

Elevated PCB concentrations have also been detected in human adipose tissue from populations with diets high in fish and seafood. Levels of PCBs were determined in liver, brain, omental fat, and subcutaneous abdominal fat samples collected from 105 deceased Inuit Greenlanders between 1992 and 1994 (Dewailly et al. 1999). The population studied represented individuals who had a history of a diet high in sea mammal fat and fish. Of the 14 congeners analyzed for, PCBs 138, 153, and 180 were found in the highest concentrations in all tissue samples and represented 63–68% of total PCB concentration. The mean concentration of total PCBs in omental fat samples from 41 Greenlanders was 5,719 μg/kg lipid basis (range=1,019–12,716 μg/kg lipid basis). Using the same analytical methods, the total concentrations of PCBs 138, 153, and 180 were compared to adipose tissue from 17 women living in Quebec City, Canada from 1991 to 1992. Researchers found that PCB concentrations in the Greenlanders were 18 times higher than those from Canada. The study also found that older individuals had higher levels of PCBs in their adipose tissue. For example, the mean PCB concentrations for people ages 41–54, 55–69, and $70 years were 4,909, 5,337, and 7,357 μg/kg lipid basis, respectively (Dewailly et al. 1999). In general, PCBs accumulated preferentially in omental/subcutaneous fat followed by liver, and accumulated the least in brain tissue.

Fat extracted from the Ooligan fish is a widely consumed traditional condiment and medicine among the indigenous people of coastal British Columbia. The average total PCB concentrations of 24–57 ng/g (ppb) lipid were reported in Ooligan fish fat and in fish from various coastal locations in the region (Chan et al. 1996). High consumption patterns of these products could increase PCB exposure of the native peoples of this region. In the summer of 1996, research was conducted to estimate the daily average intake of PCBs from consumption of local fish by the Mohawk community at the Kahnawake reservation, located south of Montreal, Canada (Chan et al. 1999). A total of 131 fish, representing 6 species, were caught and analyzed for total PCB concentrations. The mean concentration of PCBs in the fish ranged from 29.23 to 153.89 ng/g wet weight. Based on an average diet of 23 g of fish/day (compared to 1.2 g/day in the average Canadian diet), the estimated daily intake of PCBs were 0.026 μg/kg body weight/day for men and 0.033 μg/kg body weight/day for women. Based on an average body weight of 81 kg for men and 65 kg for women, the daily intake of PCBs for the Mohawk Indians would be 2.106 and 2.145 μg, respectively (Chan et al. 1999). Similar results were found in a study conducted in

Figure 6-5. 1998 Fish Advisories for Polychlorinated Biphenyls



1994 of the Dene and Metis Inuits of Western Northwest Territories, Canada whose diet consists mainly of herbivorous animals and fish (Berti et al. 1998). Researchers analyzed their dietary intake and found that the mean dietary intake of PCBs was 0.023 μg/kg/day. Researchers noted that individuals with diets high in whale blubber were at increased risk of high PCB exposure. Some examples of other populations that have diets high in fish and sea mammals include Alaskan Inuits who consume 304 g/day (Wolfe and Walker 1987), recreational anglers from Michigan who consume 27 g/day (Hovinga et al. 1992), and Indian tribes from Oregon and Washington who consume 58.7 g/day (CRITFC 1994). Since the average daily intake of fish in the U.S. diet is 6.2 g/day (EPA 1993h), these high fish consuming populations represent communities at higher risk for PCB exposure.

Infants that are breast fed by women living in the these communities may also be exposed to higher PCB concentrations. It is estimated that an infant that is breast fed for 6 months will receive 6.8–12% of its lifetime PCB body burden in that period (Kimbrough 1995; Patandin et al. 1999). For example, the diet of the Mohawk Indians from the Akwesasne reservation in New York has been impacted by the General Motors Foundry Mill, which released PCBs into the St. Lawrence River (Fitzgerald et al. 1998). Fish consumed by the Mohawk Indians come from the St. Lawrence River and have consequently been contaminated. Comparison studies were conducted to determine whether PCB levels in breast milk differed from that of the general population that was not affected by the mill. The study found that in milk samples collected in 1986–1989, the mean concentration of PCBs in American Indian milk was 602 ng/g lipid weight, while in the control group, the mean concentration was 375 ng/g lipid weight (Fitzgerald et al. 1998). From 1991 to 1992, however, PCB levels decreased to a mean of 254 ng/g lipid in Mohawk Indian breast milk, while in the control group, it only decreased to 318 ng/g lipid weight. The reduction in breast milk PCB concentrations paralleled a corresponding decrease in local fish consumption (Fitzgerald et al. 1998). The authors found that from 1986 to 1992, the number of fish meals consumed by pregnant Mohawk women decreased from 10.7 meals per year in 1986–1989, to 3.6 meals per year in 1990, and to 0.9 meals per year in 1991–1992. No such decreasing trend in consumption was noted among the Caucasian control group whose PCB levels did not change significantly over the course of the study. The mean concentration of total PCBs in human milk from native Inuit women who consumed large quantities of marine mammal tissue was 1,052 ng/g lipid weight in a 1989–1990 study (Dewailly et al. 1993). This was 7 times greater than levels measured in Caucasian women from southern Quebec (157 ng/g, lipid basis). The concentrations of PCB congeners in breast milk from a remote maritime population from Arctic Quebec (Inuit women) were compared with those of control Caucasian women in Quebec, Canada (Dewailly et al. 1994). Di-*ortho* congeners (138, 153, 170, and 180), mono-*ortho* congener (118), and non-*ortho* coplanar congeners (126 and 169) were detected at

concentrations of 862.5, 58.7, and 0.455 ng/g lipid weight in Inuit women compared to 106, 17.4, and 0.121 ng/g lipid weight in Caucasian women. Because of their high consumption of marine mammal tissues and seafood, the Inuit women have high concentrations of PCBs in their breast milk, in spite of the remoteness of Arctic Quebec (Dewailly et al. 1993, 1994). Daily PCB intake for native northern Quebec women was calculated to be 0.3 μg/kg (ppb) body weight while daily intake among infants was calculated to be 10 μg/kg due to breast feeding. This level is 143 times greater than the reference dose (RfD) of 0.07 μg/kg body weight established by the EPA (Ayotte et al. 1995). In general, these studies indicate that lactating women whose diets are high in contaminated fish can potentially increase the PCB exposure for their breast-fed infants. For more information concerning PCB concentrations in human breast milk, please refer to Table 6-27 in Section 6.6.

Unborn children may also be at risk of higher PCB exposure, especially in areas that have been heavily contaminated with PCBs. To illustrate this, researchers analyzed placental cord serum of 755 infants born to mothers residing in towns adjacent to a PCB-contaminated harbor in southeastern Massachusetts (Altshul et al. 1999). Infants whose cord serum was analyzed were born between 1993 and 1998 in the towns of New Bedford, Acushnet, Fairhaven, and Dartmouth, Massachusetts. Of the 51 PCB congeners analyzed, only 13 were above the detection limit (0.01 ng/g serum). The median concentration of PCBs was 0.56 ng/g serum (Altshul et al. 1999). Researchers found that the relative predominance of less chlorinated congeners in the cord blood was generally consistent with the characteristics of the contaminated site. PCB concentrations were also measured in cord blood from both 134 women who consumed Great Lakes fish and 145 women who had never consumed Great Lakes fish (Stewart et al. 1999). Although researchers did not find any difference between fish consumption levels and total PCBs in umbilical cord serum, it was established that fish eaters had marked elevations of the most heavily chlorinated PCB homologues. In particular, levels of hepta- to nonachlorobiphenyls were greater in fish eaters than non-fish eaters (Stewart et al. 1999). Another study examined PCB concentrations in nine stillborn fetuses from the Netherlands in 1993 and found that median (range) concentration of PCBs in adipose tissue was 235 (97–768) ng/g lipid weight (Lanting et al. 1998b).

Similarly, Native American populations such as the Inuit of Alaska or other subsistence hunters (particularly those living in high-latitude areas of the United States) may be exposed to higher levels of PCBs in wild game (e.g., beluga whales, seals, polar bears, and other game species) (Dewailly et al. 1993; Kuhnlein et al. 1995; Schantz et al. 1993c). Because these populations typically are hunters of the highest trophic levels, they are particularly exposed to PCBs (Ayotte et al. 1995). Kuhnlein et al. (1995) compared PCB concentrations in the diet of Arctic indigenous women from both eastern and western

Canada. These authors reported that PCB intakes in the western Arctic population were lower than the eastern Arctic population because of the food preferences for caribou, moose, and fish as compared to ringed seals, caribou, narwhal, and walrus. Mean total blood plasma PCB concentrations among 499 Inuit adults from Nunavik in the Quebec Arctic was 4.1 mg/kg (ppm) lipid weight, compared to 0.13 mg/kg lipid weight for control samples from individuals in southern Quebec (Ayotte et al. 1997). Hing (1998) summarized data from northern and Arctic Canadian studies associated with exposure to PCBs from consumption of native foods. Mean total PCB concentrations in traditional foods, expressed as μg/g (ppm) wet weight, were 0.080, 1.90, 0.006, 0.010, 0.052, 0.290, and 0.006, respectively, for marine mammal meat, marine mammal blubber, terrestrial mammal meat, terrestrial mammal organs, fish, birds, and plants. Based on dietary habits among two individual communities, total dietary PCB intakes were estimated to be 16 μg/day from marine mammal meat, 57 μg/day from marine mammal blubber, 1.2 μg/day from terrestrial mammal meat, 0.3 μg/day from terrestrial mammal organs, 0.4 μg/day for fish, 0.4 μg/day for birds, and 0 μg/day for plants. Total estimated PCB intakes for the two communities were 6.0 and 7 μg/day, respectively. Samples from herds of Yukon Territory and Northwest Territory caribou in Canada showed relatively low non-*ortho* PCB concentrations, considered equivalent to background levels, although PCB congener 126 and 169 concentrations were higher among caribou sampled from eastern herds (Bathurst, Northwest Territory), probably due to differences in atmospheric transport patterns (Hebert et al. 1996). Wilson et al. (1995) also reported high concentrations of PCBs in two fish species from remote Arctic lakes in Alaska. The most abundant group of organochlorine compounds detected in the fish were PCBs. Concentrations of 6.6 and 1.3 ng/g (ppb) wet weight were detected in lake trout and grayling muscle tissue, respectively. While the problem of PCB contamination in the Arctic is clearly greater in the eastern Arctic, it is increasingly being detected in Alaska as well. Clearly, increased exposure of native hunting and fishing peoples to PCBs can occur, and their infants are also at risk of greater exposure via consumption of PCB-contaminated breast milk.

During the 1940s and 1950s, concrete silos on many Midwest farms were coated on the inside with sealants containing the PCB mixture Aroclor 1254. Over time, the sealant peeled off and became mixed with silage used to feed beef and dairy cattle. Farmers and their families who lived on farms where PCB-containing sealants were used in silo construction, and who regularly ate beef and dairy products produced on their own farms, were exposed to PCB-contaminated foods (Hansen 1987a; Humphrey 1983). Most of these silos, however, have been dismantled and removed. The high serum PCB levels (100–200 μg/L [ppb]) detected in the most exposed individuals, however, suggests that monitoring should be continued (Humphrey 1983). Schantz et al. (1994) monitored serum PCB levels in Michigan mothers and children from farms with PCB-contaminated silos. These authors reported blood serum PCB levels

of 9.6 ng/mL (ppb) for mothers and 6.8 ng/mL (ppb) for children. Maternal serum PCB levels and the number of weeks of breast-feeding accounted for 47% of the variance in the children's serum PCB levels, confirming that breast milk was a primary source of the PCB exposure for the children.

Another population that may receive higher PCB exposures than the general population includes people who live in the vicinity of incinerators, PCB disposal facilities, or hazardous waste sites. PCB concentrations measured downwind from a landfill were at least an order of magnitude higher than those measured upwind from the landfill, although effective dilution reduced concentrations of PCBs in air samples monitored 15 km from the landfill to a level comparable or even slightly lower than urban air levels (Hermanson and Hites 1989). This dilution effect was also evident from the observed decrease in the atmospheric concentrations of PCBs within a short distance from another landfill during remediation (Hermanson and Hites 1989). This study suggests that people who reside in the immediate vicinity of PCB-containing landfills may be exposed to PCBs in the air at levels higher than the general population. Despite the potential for individuals living near processing facilities or hazardous waste sites to be exposed to higher levels of PCBs in air, water, and soil, higher PCB levels in human tissues have not been conclusively demonstrated (i.e., elevated levels of PCBs in the serum/blood of the susceptible population). One possible explanation for the low prevalence of elevated PCB levels in the serum/blood of people who live near these contaminated sites is that most of these people are not exposed to PCBs at elevated levels or that the PCB concentrations to which they are exposed are not completely bioavailable. Another explanation is that, unlike occupational exposure scenarios where concentrations can be orders of magnitude higher than background levels, slightly elevated environmental exposure may not result in appreciable elevation of PCB levels in serum/blood. Beginning in 1982, pilot studies involving a total of 766 subjects were conducted at 12 hazardous waste sites in the United States to determine human exposure to PCBs (Stehr-Green et al. 1988). Although environmental PCB contamination levels as high as 2.5 ppb in well water and 330,000 ppb in soil samples were measured, serum PCB levels in people from 10 of the 12 sites were not any higher than serum PCB levels in unexposed individuals in the general population. The higher serum PCB levels found in people at two sites may be attributable to the historic prevalence of occupationally related exposures. Another study that evaluated the PCB exposure of 89 individuals living near a toxic waste site in Paoli, Pennsylvania, also reported similar serum PCB levels in exposed individuals and unexposed populations (ATSDR 1987).

Individuals living near processing sites or NPL sites where PCBs have been detected may also be exposed to higher levels of PCBs in their drinking water if they obtain tap water from wells located near these sites. PCBs have been detected in groundwater samples at 192 of the 500 NPL sites where they were

detected in some environmental media (HazDat 2000). Consumption of contaminated groundwater, therefore, may be an additional source of PCB exposure for both adults and children. Children and adults may also receive higher PCB exposures from dermal contact if they play or work with PCB-contaminated soils. In an *in vivo* study with Rhesus monkeys, percutaneous absorption of Aroclor 1242 and 1254 from a clay loam soil containing 0.9% organic matter was determined to be in the range of 13.8–14.1% (Wester et al. 1993). In addition, children and adults may receive potentially higher oral exposures from ingestion of PCB-contaminated soils from their unwashed hands, while playing or working in PCB-contaminated areas.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PCBs is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of PCBs.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Some of the physical and chemical properties (i.e., octanol/water partition coefficient [K_{ow}], Henry's law constant, reaction rate constants) often useful in estimating environmental fate and transport processes for PCBs are available primarily for the Aroclors as mixtures and not for the individual congeners (see Table 4-2) (Burkhard et al. 1985; EPA 1979h, 1985b; Hollifield 1979; Paris et al. 1978). The experimental determination of the physical and chemical properties of many more of the individual congeners is needed for accurately predicting the environmental fate of the individual congeners.

Production, Import/Export, Use, and Release and Disposal. PCBs are no longer produced, imported/exported, or used on an industrial scale in the United States. The available literature contains adequate documentation of their past production (Durfee 1976; EPA 1976a; IARC 1978; Kimbrough 1987), import/export volume (Durfee 1976; EPA 1988c; IARC 1978; USITC 1978, 1979, 1980, 1982), use (EPA 1976a; IARC 1978; Safe 1984; Welsh 1995), release (Durfee 1976; EPA 1979e; Larsson 1985; Liberti et al. 1992; Mackay 1989; Morselli et al. 1985; Murphy et al. 1985; Swackhamer and Armstrong 1986; Tiernan et al. 1983; TRI93 1995), and disposal (Arbon et al. 1994; Baukal et al. 1994; Chuang et al. 1995; EPA 1979e, 1995a; IRPTC 1985; Timberlake and Garbaciak 1995; TRI93 1995; Zhang and Rusling 1995; Zhang et al. 1993). There are current EPA regulations regarding the disposal of PCBs; however, information on current disposal practices in the case of accidental transformer leakage would be useful.

Environmental Fate. A number of studies indicate that PCBs are very persistent in the environment (Brown et al. 1988; EPA 1979h, 1983c; Gan and Berthouex 1994; Portier and Fujisaki 1988). The volatilization of PCBs from soil and water, followed by dry/wet deposition of airborne PCBs into soil and water, results in the continuous recycling of undegraded PCBs in the environment (Macdonald et al. 2000; Wania and Mackay 1993, 1996). Sediment is a repository for PCBs that can later be released to air and water. However, some critical data regarding the potential for long-term release of PCBs from sediments and the role of deep ocean sediments as an ultimate sink for PCBs are lacking. There is a lack of quantitative data on the photodegradation potential of PCBs in air, water, and soil in the presence of natural sunlight. Information on the concentrations of chlorinated benzoic acids in the vicinity of PCB sources is need to access the degree of importance of OH-radical reactions in the atmosphere for degrading PCBs (Brubaker and Hites 1998). No extensive and systematic studies have been done on the influence of different types of soil/sediment (including with different PCB adsorption properties) on the reductive dehalogenation of PCBs (Wiegel and Wu 2000). Since the toxicity and the environmental fate of PCBs depend on specific PCB congeners, development of more data regarding congener-specific fate and transport of PCBs in the environment are needed.

Bioavailability from Environmental Media. The absorption and distribution of PCBs as a result of inhalation, ingestion, and dermal exposure are discussed in Sections 3.3.1, 3.3.2, and 3.3.3. Few studies that describe the bioavailability of PCBs from ambient air, surface water and groundwater, or soil exist. Additional studies determining the effect of particle size and organic matter content on the bioavailability of PCBs from soil and the role of microparticle-sorbed PCBs on the bioavailability of PCBs from

drinking water are needed. Such studies would be useful in assessing the health effects of PCBs on people living near hazardous waste sites.

Food Chain Bioaccumulation. Based on available information, estimates can be made about the bioaccumulation of PCBs in fish, shellfish, and marine mammals (Andersson et al. 1988; ASTER 1996; EPA 1983c; Kuehl and Haebler 1995; Kuehl et al. 1994; Lake et al. 1995a, 1995b; Porte and Albaiges 1993; Salata et al. 1995; Schantz et al. 1993a; Zhang et al. 1983), the bioconcentration potential from soil to plants (Bohm et al. 1999; Lober et al. 1994; O'Connor et al. 1990; Schönherr and Riederer 1989) and from atmospheric vapors and particulates to plants (Jones and Duarte-Davidson 1997; O'Connor et al. 1990; Thomas et al. 1998; Ye et al. 1992a). The existing data indicate that PCBs bioaccumulate significantly in aquatic and terrestrial food chains and biomagnify in predators, due to consumption of contaminated prey. More information on bioaccumulation and biomagnification of PCB congeners in edible fish and shellfish species is needed in assessing human health risks.

Exposure Levels in Environmental Media. The relative importance of different routes of exposure to PCBs in the past (late 1970s through early 1980s) is detailed in the current literature. FDA studies indicate that the dietary intake of PCBs has steadily decreased since 1978 (Gartrell et al. 1985a, 1985b, 1986a). According to these studies, the major contributing factor in dietary PCB intake has changed from fish to meat in recent years (Gunderson 1988). However, the FDA dietary intake values are estimated for marketed foods and do not provide an indication of PCB intake from consumption of fish obtained by sport and subsistence fishing. Despite recent studies by Berry et al. (1997) and Buckley et al. (1997), more recent data on the concentrations of PCBs in foods, collected using a market-basket approach, are needed to determine whether concentrations of PCBs in foods consumed by the general population have declined further since the mid-1980s. Data on the PCB concentrations in foods grown in contaminated areas, particularly in the vicinity of hazardous waste sites, are also needed. Also, more data on congener-specific PCB analysis of food, especially plant products, would be useful. Recent investigations also show that the concentration of PCBs in indoor air can be at least an order of magnitude higher than outdoor air (Balfanz et al. 1993; Vorhees et al. 1997; Wallace et al. 1996). Therefore, due to the decreased intake of PCBs from food in recent years, it is possible that the intake from inhalation exposure may currently exceed PCB intake from food. However, a direct comparison of the importance of exposure from inhalation and diet is difficult because the reported data do not always include the same PCBs (e.g., Aroclor 1016, 1254, etc.) for the purpose of quantifying the total PCB concentrations and in evaluating the subsequent intake. It would be useful to conduct further research to resolve this important issue. More recent monitoring data on the concentrations of total PCBs as well as congeners in air in

urban areas near hazardous waste sites and incinerators are needed. More recent survey data on PCB concentrations in finished drinking water nationwide would be helpful in assessing the importance of this exposure route. Congener-specific analysis of drinking water would also be useful in determining exposure risks, particularly for the dioxin-like congeners.

Exposure Levels in Humans. PCB levels are reported in the current literature for blood (Schecter et al. 1993, 1994), serum (Anderson et al. 1998; Fitzgerald et al. 1999; Hanrahan et al. 1999; Hovinga et al. 1992, 1993; Kearney et al. 1999; Massachusetts Department of Public Health 1987; Patterson et al. 1994), breast milk (Dekoning and Karmaus 2000; Fitzgerald et al. 1998; Kostyniak et al. 1999; Newsome and Ryan 1999; Newsome et al. 1995; Schade and Heinzow 1998), and adipose tissue of the general population (Dewailly et al. 1999; EPA 1986b; Fensterheim 1993; Jensen 1989; Kutz et al. 1991; Ouw et al. 1976; Patterson et al. 1994; Schecter et al. 1989, 1991, 1994) and occupationally exposed individuals (Fait et al. 1989; Perkins and Knight 1989; Schecter and Charles 1991; Schecter et al. 1994; Welsh 1995; Wolff 1985; Yakushiji et al. 1978). However, few systematic surveys have ever been conducted in the United States to evaluate the trend of PCB concentrations in human tissues over the years, and the reasons for the apparent slower decrease in PCB concentrations in tissues (compared to the more rapid decrease in environmental levels) are not completely known. It would be helpful to develop a database of information on congener-specific PCB levels in tissues of exposed and control cases for studying clinical and epidemiological outcomes. In particular, a comprehensive study that monitors congener specific concentrations in fish species and relates them directly to congener levels in human tissue would be extremely useful. Additional data regarding the concentrations of PCBs in body fluids or tissues of people who reside near hazardous waste sites are needed. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children may be exposed to PCBs by a variety of exposure pathways. The most important pathway appears to be consumption of contaminated foods, particularly meat, fish, and poultry (Gunderson 1988). Children can also be exposed to PCBs from mother's milk (Fitzgerald et al. 1998; Kimbrough 1995; Patandin et al. 1999; Rogan et al. 1987; Wickizer et al. 1981). More data are needed on the levels of PCB exposure in nursing women from occupational situations or consumption of fish or wild game and of from those of the general population. Exposure and body burden studies related to consumption of fish in the U.S. population are needed to determine exposure levels, particularly in children of recreational and subsistence fishers. Exposure and body burden studies are also needed in Native American communities that consume high levels of game and marine mammals. Information related to the exposure of children living near hazardous waste sites is also needed. In particular,

information related to the potential for children to be exposed to PCBs bound to soil and dust particles through pica or unintentional hand-to-mouth activity within homes located in these areas. Quantitative information regarding the bioavailability and amount of PCBs that children are exposed to through contact with contaminated soils are unavailable. Therefore, any information concerning this subject would be useful in evaluating children's exposure.

Additional information on weight-adjusted intakes would be helpful for determining the health risks for young children, particularly those in Native American populations. Infants and young children consume a greater amount of food per kilogram of body weight and, therefore, may have a proportionately greater exposure to PCBs than adults (Cordle et al. 1982).

Child health data needs relating to susceptibility are discussed in Section 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for PCBs were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this substance.

Information is particularly needed on the size of the populations potentially exposed to PCBs through contact with contaminated media in the vicinity of hazardous waste sites. The development of an exposure registry would provide a useful reference tool in assessing exposure levels and frequencies. It would also facilitate the conduct of epidemiological or health studies to assess any adverse health effects resulting from exposure to PCBs. In addition, a registry developed on the basis of exposure sources would allow an assessment of the variations in exposure levels from one source to another and the effect of geographical, seasonal, and regulatory action on the level of exposure within a certain source. These assessments, in turn, would provide a better understanding of the needs for research or data acquisition on the current exposure levels.

6.8.2 Ongoing Studies

A search in Federal Research in Progress (FEDRIP 2000) identified ongoing research studies that may fill some of the data needs discussed in Section 6.8.1. These studies are listed in Table 6-29.

Table 6-29. Ongoing Studies on Environmental Fate and Treatment of Polychlorinated Biphenyls

Investigator	Affiliation	Title	Sponsor
Bopp, Richard	Mount Sinai School of Medicine New York, New York	Sources and pathways of persistent chlorinated hydrocarbon exposure in New York City	NIEHS
Bush, Brian	Wadsworth Center	Adsorption/desorption of PCBs on Hudson River clay	National Center for Research Resources
Custer, Christine M	Upper Midwest Environmental Sciences Center	Bioaccumulation and effects of PCBs on tree swallows nesting along the Housatonic River, Massachusetts	U.S. EPA, Boston, Massachusetts and U.S. Fish and Wildlife Service
Estes, James A	Western Ecological Research Center	Monitoring program for environmental contaminants in the nearshore marine ecosystem at Adak Island, Alaska	U.S. Department of Agriculture, Cooperative State Research Service
Fischer, Lawrence	Michigan State University	Health hazards from groundwater contamination	NIEHS
Hansen, LG	Veterinary Bioscience, University of Illinois	Identification of PCB congeners associated with fish consumption	U.S. Department of Agriculture, Cooperative State Research Service
Hickey, William J	University of Wisconsin Madison, Wisconsin	Research on molecular and biochemical diversity of chlorobenzoate degrading bacteria	NSF, Division of International Programs
Hong, Chia-swee	State University of New York Albany, New York	Photocatalytic remediation of PCB-contaminated water and sediment	NIEHS
Huwe, JK	Agricultural Researcher Service	Dioxins and other environmental contaminants in food	U.S. Department of Agriculture
Landrigan, Philip J	Mount Sinai School of Medicine New York, New York	Study the current urban sources, environmental distribution and toxic effects on human health of PCBs in New York City	National Institute of Environmental Health Sciences
Manny, Bruce A	Great Lakes Science Center	Contamination of surface soils and wildcelery tubers at Grassy Island in the Wyandotte National Wildlife Refuge in the Detroit River	U.S. Department of Agriculture, Cooperative State Research Service
Matthews, HB	NIEHS, NIH RTP, North Carolina	Bioavailability of PCBs from soil	NIEHS
Mora, Miguel A	Columbia Environmental Researcher Center	Effects of environmental contaminants on major wildlife species of the lower Rio Grande Valley, Texas	Department of the Interior
Rhee, G-Yull	State University of New York Albany, New York	Bioremediation of PCB- contaminated sediments in the St. Lawrence River	NIEHS
Richmond, Milo E	New York Cooperative Fish and Wildlife Research Unit	Organochlorine and *meta*l contaminants in Hudson River mammals	New York State
Santerre, CR	Food and Nutrition Purdue University	Xenobiotics in farm-raised and wild fish	Indiana State
Sarofim, Adel F	Massachusetts Institute of Technology	The formation of PCBs during the pyrolysis and oxidation of wastes at Superfund sites	NIEHS

Table 6-29. Ongoing Studies on Environmental Fate and Treatment of Polychlorinated Biphenyls *(continued)*

Investigator	Affiliation	Title	Sponsor
Tiedje, J	Michigan State University, Crop and Soil Sciences East Lansing, Michigan	Microbial ecology of soil and biodegradation	U.S. Department of Agriculture, Cooperative State Research Service

Source: FEDRIP 2000

EPA = Environmental Protection Agency; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institute of Health; NSF = National Science Foundation; RTP = Research Triangle Park

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring PCBs, its metabolites, and other biomarkers of exposure and effect to PCBs. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

Methodology for PCB analysis includes several steps: sample collection and storage, extraction, cleanup, and determination (EPA 1995c, 1999k; Hess et al. 1995). Care must be taken to assure that the sample collection follows quality assurance protocols and that equipment and containers are free from contamination. Most sample collections are by grab sampling; however, PCBs may be concentrated from water or air onto sorbents. PCBs are typically separated from the sample matrix by solid-phase extraction (SPE), separatory funnel extraction, continuous liquid/liquid extraction (CLLE), Soxhlet extraction, or Soxhlet/Dean-Stark extraction. PCBs may be difficult to extract from oily matrices in which they are soluble. Some problems that may occur during extraction include evaporative losses during concentration, sorption onto labware, and contamination of samples. Cleanup steps are necessary to remove compounds that may interfere with the determination. Chromatography (e.g., gel permeation, silica gel, Florisil, activated carbon, high-performance liquid) is often used to remove matrix interferences, and sometimes to fractionate PCBs into several groups. Cleanup by chromatography has been used extensively to separate the non-*ortho* and the mono-*ortho* CBs from the remaining congeners before quantitative analysis (Hess et al. 1995). The identification and quantitation of PCBs are most often accomplished by gas chromatographic (GC) techniques. Capillary or high resolution gas chromatography (HRGC) columns capable of separating a substantial proportion of the congeners are indispensable, and GC detectors possessing high selectivity and sensitivity for the PCBs are required. The more universal and less sensitive flame-ionization detector (FID) is used much less often than the electron capture detector (ECD), which has exceptional sensitivity to multiply chlorinated compounds. The mass spectrometer-selected-ion-monitoring (MS-SIM) or ion-trap mass spectrometer (ITMS) detectors have sensitivities somewhat lower than ECD, and they have even greater selectivity for PCBs and can

distinguish and individually measure homologs that may coelute on a particular HRGC column (EPA 1999k).

Some methods in use are multi-residue methods in which PCBs along with many other analytes such as pesticides, are determined. In general, PCB methods analyze for Aroclor mixtures, PCB homologs, or individual PCB congeners. Until recently, packed column GC/ECD was used most often for the determination of PCBs as Aroclor mixtures. The Webb-McCall technique was used for quantitation. The weight percent and homolog identification were determined for several Aroclors. Response factors were generated to calculate the amount in each sample peak; with packed columns, each peak contains several congeners. The amounts found in each sample peak were then summed (Webb-McCall 1973). Alternately, the total area in the Aroclor region of the chromatogram was used for quantitation. However, Aroclor analyses are estimations that are prone to error as a result of the subjective assignment of Aroclor speciation and response factors. Also, the practice of comparing CB patterns in environmental samples with those of technical mixtures can be misleading since mixtures emanating from different sources are mixed at differing rates by diffusion, evaporation, and adsorption onto solids. Many congeners are metabolized, while others bioconcentrate in lipophilic material. Therefore, the final pattern in the environment is often highly modified and may not resemble the original commercial formulation or mixture of formulations (Draper et al. 1991; Duinker and Hillebrand 1979; Hess et al. 1995). The maximum detection limits (MCLs) for Aroclors vary in the range of 0.054–0.90 μg/L in water and 57–70 μg/kg in soils (EPA 1995c). Another approach is to determine PCBs by level of chlorination (or homolog group). One PCB for each homolog (isomer group) is typically used for calibration. Total PCB concentration is obtained by summing isomer group concentrations (Alford-Stevens et al. 1986). However, since the congener distribution is not determined with this method, an accurate calculation of PCB toxic equivalency (TEQ) can not be accessed. Recently, capillary or HRGC has made it possible to achieve lower detection limits and better separation of individual PCB congeners for quantitation (Frame 1997; Mullin et al. 1984; Newman et al. 1998), although complete separation of all PCB congeners on a single column has not yet been achieved (Duebeleis et al. 1989). The commonly used capillary columns (DB-5, C-18, DB-1701, SE-54, SIL-8, SP-2330, and CP-SIL-8) provide poor or no resolution for the following groups of congeners: 15/18, 28/31, 49/52, 66/95, 77/110, 84/90/101, 118/149, 138/163/164, 105/132/153, 170/190, and 182/187 (Liem 1999; Schantz et al. 1993b). Nevertheless, the trend is toward congener-specific analysis by HRGC. Recent advances include analytical methods that are able to quantify individual PCBs congeners to enable TEQ calculations (EPA 1999k; Frame 1999; Patterson et al. 1994). EPA Method 1668 (Revision A) is the current methodology used to measure individual PCB congeners in water, soil, sediment, and tissue by HRGC/high resolution mass spectrometry (HRMS)

(EPA 1999k). Estimated detection limits (EDL) of selected PCB congeners range from 109 to 193 pg/L for water and 11–19 ng/kg for soil, tissue, and mixed-phase samples. EDLs are listed in Table 7-1 for EPA Method 1668 (Revision A; EPA 1999k). This method has been used to measure specific PCBs in EPA projects such as the assessment of PCBs in fish consumed by four Native American tribes in the Columbia River Basin in Washington state (EPA 1996f). As for all analytical methods, determining the quality and usability of Aroclor, PCB homolog, or specific congener data by formal data validation procedures is recommended; EPA has developed data validation guidelines for HRGC/ECD Aroclor data and HRGC/LRMS (low resolution mass spectrometry) PCB specific congener data (EPA 1994h, 1995g).

7.1 BIOLOGICAL SAMPLES

The quantitation of PCBs in biological samples usually consists of three distinct steps: extraction of PCBs from the sample matrix by a solvent or a combination of solvents; cleanup of PCBs from impurities on single or multiple columns; and finally, quantitation by GC with a suitable detector. A summary of some available methods for biological samples is shown in Table 7-2.

PCBs are extracted from blood or serum by solvent extraction techniques using hexane (EPA 1980; Needham et al. 1980), benzene (Mes et al. 1994, 1995a, 1995b, 1995c), or mixed solvents such as hexane/ethyl ether (Koopman-Esseboom et al. 1994b; Luotamo et al. 1985; Needham et al. 1981), or by solid phase micro-extraction techniques (Poon et al. 1999). A variety of adsorbents may be used for cleanup and/or fractionation of extracts: deactivated silica gel (Burse et al. 1989), Florisil (Mes et al. 1994, 1995a, 1995b, 1995c), alumina (Koopman-Esseboom et al. 1994b), or multiple columns (Patterson et al. 1989). GC/ECD is used most often for determination of biological samples (Burse et al. 1989; Mes et al. 1994, 1995a, 1995b; NIOSH 1984b; Schantz et al. 1994). Confirmation by mass spectrometry is recommended (Burse et al. 1994; Mes et al. 1994). Detection limits are in the low- to sub-ppb range (Luotamo et al. 1985; Mes et al. 1994, 1995a, 1995b; Needham et al. 1981; NIOSH 1984b; Poon et al. 1999). Recovery, where reported, ranges from . 80 to 96% (Koopman-Esseboom et al. 1994b; Mes et al. 1994; Needham et al. 1980, 1981; NIOSH 1984b; Poon et al. 1999). The accuracy and precision of the results of PCB analysis in serum using a packed column GC/ECD method were studied in a collaborative study. The mean recovery (for Aroclor 1254) was 82.2%; inter-laboratory precision was <21% for samples spiked at 10–100 ng/mL (Burse et al. 1989). Cord blood, which is the most direct marker of fetal exposure, requires especially sensitive analytical methods for accurate PCB analysis because of its

Table 7-1. EPA Method 1668-Estimated Method Detection Limits (EMDL) and Estimated Minimal Levels (EML) of Selected PCB Congeners[a,b]

	Detection limits and minimal levels-matrix and concentration[c]				
	Water (pg/L)		Other[d] (ng/kg)		Extract (pg/μL)
Congener	EMDL	EML	EMDL	EML	EML
77	169	500	17	50	20
105	109	200	11	20	10
114	120	500	12	50	20
118	193	500	19	50	20
123	150	500	15	50	20
126	136	500	14	50	20
156	132	500	13	50	20
157	132	500	13	50	20
167	115	500	11	50	20
169	161	500	16	50	20
180	136	500	14	50	20
189	177	500	18	50	20

[a]Source: EPA 1999k
[b]for SPB-Octyl gas chromatography column
[c]EMDLs and EMLs with common laboratory interferences present. Without interferences, EMDLs and EMLs will be respectively, 5 and 10 pg/L for aqueous samples, and 0.5 and 1.0 ng/kg for soil, tissue, and mixed-phase samples, and EMLs for extracts will be 0.5 pg/μL.
[d]soil, tissue, and mixed-phase samples

EMDL = estimated method detection limits; EML = estimated minimal levels; EPA = U.S. Environmental Protection Agency

Table 7-2. Analytical Methods for Determining Polychlorinated Biphenyls in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Serum	Extraction with mixed solvents; treatment with methanolic KOH; extraction with hexane; cleanup on silica gel column	HRGC/ECD	1.0 ng/mL on 1 mL sample	>80 at 25–400 ng/mL	NIOSH 1984b (method 8004)
Serum	Extraction with mixed solvents; cleanup on silica gel column	GC/ECD	No data	82.2 (average)	Burse et al. 1989
Serum	Solvent extraction; cleanup on 10% silver nitrate on silica gel column	GC/ECD	No data	93.7 at 41 μg/L	Needham et al. 1980
Serum	Extraction with mixed solvents; cleanup on hydrated silica gel column for separation of PCBs from PBBs	GC/ECD	2.5 ng/mL	95.3 at 100 μg/L and 105–127 at 10 μg/L	Needham et al. 1981
Serum	Extraction with diethyl ether and hexane; wash of extract with sulfuric acid; cleanup on silica column	HRGC/EC	0.1 ng/mL	85 at 25–125 ng/mL	Luotamo et al. 1985
Serum (congener specific)	Addition of surrogate congener standard PCB 46 and 142, extraction with hexane, cleanup with Florisil.	HRGC/ECD	1 pg/g (PCB 200) - 634 pg/g (PCB 99)	95.1±12.5 (PCB 153)	Greizerstein et al. 1997
Serum	Extraction with SPME; thermal desorption of PCBs into GC column	GC/ECD	1.0 ppb (total PCBs)	<93	Poon et al. 1999
Blood	Solvent extraction; cleanup on Florisil	GC/ECD; confirmation by HRGC/MS-SIM	2 ng/g	81–96	Mes et al. 1994
Plasma	Solvent extraction; cleanup on alumina	Dual column HRGC/ECD	0.01 ng/g	>95	Koopman-Esseboom et al. 1994b

Table 7-2. Analytical Methods for Determining Polychlorinated Biphenyls in Biological Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Serum (congener specific)	Extraction of ^{13}C-labeled PCB-spiked sample with ethanol/ hexane; wash of extract with concentrated sulfuric acid; cleanup and fractionation by multi-column chromatography	HRGC/NICI/MS and IDMS	2 ppq	605 for PCB-77[a], 48 for PCB-126, and 16 for PCB-169	Patterson et al. 1989
Blood	Methanolic KOH hydrolysis; extraction with hexane; cleanup on silica gel and alumina column if necessary	GC/ECD	2 pg	100±4 at 1.09–109 ng/g	Que Hee et al. 1983
Adipose tissue	Solvent extraction; cleanup on sulfuric acid/silica gel and 10% silver nitrate/silica gel columns	GC/ECD	No data	91–93 at 3 μg/g	Smrek and Needham 1982
Adipose tissue	Extraction with acetone/hexane; fractionation by GPC; cleanup on Florisil column	Two dimensional HRGC/MS	No data	>80 at 10–500 ng/g	Le Bel and Williams 1986
Adipose tissue and serum (congener specific)	Extraction of ^{13}C-labeled PCB-spiked sample with ethanol/ hexane; wash of extract with concentrated sulfuric acid; cleanup and fractionation by multi-column chromatography	HRGC/ID/HRMS	No data	No data	Patterson et al. 1994
Human milk	Extraction with mixed solvents; cleanup on Florisil-silicic acid column	HRGC/ECD	No data	94 at ng/mL	Mes et al. 1984; Safe et al. 1985b
Human milk (congener specific)	Extraction with ethanol/hexane; clean up on Florisil column; fractionation on porous graphitic carbon	HRGC/ECD	3 pg/g	90–104	Hong et al. 1992a
Human milk (congener specific)	Addition of surrogate congener standard PCB 46 and 142, extraction with hexane, cleanup with Florisil.	HRGC/ECD	1 pg/g (PCB 200) - 129 pg/g (PCB 48)	No data	Greizerstein et al. 1997

Table 7-2. Analytical Methods for Determining Polychlorinated Biphenyls in Biological Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human milk	Fat separation; cleanup on adsorption columns	HRGC/ECD	0.4 ng/g fat	No data	Abraham et al. 1994
Human hair (congener specific)	Ultrasonic extraction with acetone/hexane; wash of extract with concentrated sulfuric acid and alkaline hydrolysis; cleanup on Florisil column; fractionation on carbon column	HRGC/ECD	No data	No data	Zupancic-Kralj et al. 1992
Liver, kidney, brain tissue (Rhesus monkeys)	Homogenization; solvent extraction; cleanup on Florisil	GC/ECD	12–33 ng/g	78–100 (corn oil)	Mes et al. 1995a, 1995b
Tissue (congener specific)	Homogenized; extracted in methylen chloride:hexane (1:1) using Soxhlet extractor; cleanup using sulfuric acid and chromatography	HRGC/HRMS	See Table 7-1	No data	EPA 1999k (method 1668)

[a]The high recovery for PCB 77 was due to interference from other congeners. The low recovery for PCB 126 and PCB-169 is not critical since ID/MS makes correction for recovery unnecessary.

ECD = electron capture detector; GC = gas chromatography; GPC = gel permeation chromatography; HRGC = high resolution gas chromatography; HRMS=high resolution mass spectroscopy; ID/HRMS = isotope dilution high resolution mass spectrometry; IDMS = isotope dilution mass spectrometry; KOH = potassium hydroxide; MS = mass spectrometry; MS-SIM = mass spectrometer-selected-ion-monitoring; NICI/MS = negative ion chemical ionization mass spectrometry; PBBs = polybrominated biphenyls; PCBs = polychlorinated biphenyls

relatively low fat content. Analysis of breast milk does not present this difficulty. While analytical techniques have improved enormously in recent years, the low concentration of fat in cord blood may still present difficulties in achieving accurate and reliable PCB levels.

Methods for determining PCBs in adipose tissue are similar to those for blood. Solvent extraction is used to separate the PCBs along with other soluble organics from the tissue. The PCBs are then separated from the lipids, usually by column chromatographic techniques. Most procedures include a step for determining the percent fat since results are often reported on a percent fat basis. Very little performance data are available for PCBs in adipose tissue. Detection limits of 51–144 ng/g have been reported for adipose tissue from Rhesus monkeys (Mes et al. 1994, 1995b).

A congener-specific analysis of a commercial PCB preparation and the PCB composition of a human milk sample were reported originally by Safe et al. (1985b). Recent studies have demonstrated the analysis of non-*ortho* coplanar and mono-*ortho* coplanar PCBs in breast milk (Dewailly et al. 1991) and coplanar PCBs in serum and adipose tissue (Patterson et al. 1994). Determination of these congeners (PCBs 77, 126, 169) is useful in assessing the toxic potential of breast milk for infants.

Recently, supercritical fluid extraction (SFE) has been utilized for extraction and cleanup of biological samples. The procedure is quick and avoids the use of flammable or toxic organic solvents (Anitescu and Tavlarides 1998; Djordjevic et al. 1994). Packed-column GC techniques are still widely used; however, HRGC has made it possible to achieve better separation of PCB congeners for quantitation (Ballschmiter and Zell 1980; Mullin et al. 1984).

The congeners to be determined in samples may be selected on the basis of their abundance in the samples, their toxicity, or the availability of analytical standards. The coplanar, non-*ortho*-substituted congeners are PCB-77, PCB-126, and PCB-169. The mono-*ortho*-substituted congeners, PCB-28, PCB-74, PCB-105, PCB-118, and PCB-156, are also frequently determined, along with the non-*ortho*-substituted PCB congeners. PCBs 138, 153, and 180 are frequently measured in higher amounts than other congeners (Safe 1993; Schecter et al. 1994) and are often included in sets of congeners for quantitation.

Variables in sampling methods greatly influence results. For example, PCB levels in milk fat may decrease during lactation, with maternal age and weight, and with number of children born (Jensen 1987). It has been shown by Lawton et al. (1985b) that random error, inter-laboratory variations in procedure,

and methods used for reporting data may have considerable impact on the reported PCB levels in human tissues. Caution should be exercised when comparing exposure estimates or health effect studies reported by different investigators unless similar analysis methodologies are employed. Also, without the separation and quantitation of individual PCB congeners during analysis, PCB concentrations can not be directly correlated to toxic equivalency. Currently, EPA Method 1668 (Revision A) is a standard method for analysis of individual PCB congeners in biological tissues (EPA 1999k).

7.2 ENVIRONMENTAL SAMPLES

An overview of PCB analysis, including sampling technique, extraction, cleanup procedures, and quantification is reported in EPA Method 1668 (Revision A; EPA 1999k). A summary of representative methods is shown in Table 7-3. The table includes methods that have been standardized by NIOSH, EPA, American Society for Testing and Materials (ASTM), AOAC, and Food and Drug Administration (FDA). Most of these methods were developed for the determination of Aroclors (noncongener-specific PCBs) in environmental samples.

Air samples are usually collected by pumping air through a sampler containing a glass fiber filter and adsorbent trap to separate the particle bound and vapor phase fractions. Adsorbents used most often include Florisil (Lin and Que Hee 1985, 1987; NIOSH 1984a), XAD-2 (EPA 1988b; Hippelein et al. 1993), and polyurethane foam (PUF) (Bremle and Larsson 1998; EPA 1988b). Florisil traps are solvent desorbed (Lin and Que Hee 1985, 1987; NIOSH 1984a) and XAD-2 traps are Soxhlet extracted (Bremle and Larsson 1998; EPA 1988b; Hippelein et al. 1993). PCBs are determined by GC/ECD (Bremle and Larsson 1998; EPA 1988b; Irvine and Loganathan 1998; Lin and Que Hee 1985, 1987; NIOSH 1984a) or HRGC/MS (Hippelein et al. 1993). Detection limits depend upon the volume of air sampled; however, detection limits in the low ng/m^3 (EPA 1988b) to low pg/m^3 (Hippelein et al. 1993) have been reported. Recovery, where reported, is good (>80%) (Bremle and Larsson 1998; Brownlow and Que Hee 1985; EPA 1988b; Irvine and Loganathan 1998; Lee et al. 1996; Lin and Que Hee 1985, 1987).

EPA Method 1668 (Revision A) is the current methodology used to measure specific toxic, dioxin-like PCB congeners in surface, ground, and drinking water by HRGC/HRMS (EPA 1999k). Drinking water samples are typically extracted with solvent prior to analysis by GC/ECD, HRGC/ECD, and HRGC/HRMS (EPA 1989c, 1999k). Detection limits are in the sub-ppb range and recovery is good (>80%) (EPA 1989c). Preconcentration techniques may be used for extraction of large water volumes, thus lowering the method detection limit (Leister and Baker 1994; Swackhamer and Armstrong 1987).

Table 7-3. Analytical Methods for Determining Polychlorinated Biphenyls in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (occupational)	Adsorption on glass fiber filter and Florisil; hexane desorption	GC/ECD	0.0006 mg/m^3 for 50 L sample	No data	NIOSH 1984a (method 5503)
Air	Adsorption on water-deactivated Florisil; hexane desorption; perchlorination	GC/ECD	No data	84–103 at 4–49 μg/m^3	Lin and Que Hee 1985, 1987
Air	Adsorption on Florisil or Chromosorb 102 or Tenax GC or XAD-2; hexane desorption	GC/ECD	10 μg/m^3 for 4 L sample	>80 at 300 μg/m^3	Brownlow and Que Hee 1985
Ambient Air	Sample collection on glass fiber filter and PUF cartridge; Soxhlet extraction; alumina column cleanup	GC/ECD	>1 ng/m^3	36–94	EPA 1988b (method TO-4)
Ambient air (target congeners)	Sample collection on glass fiber filter and XAD-2 trap; Soxhlet extraction; adsorption column cleanup and fractionation	HRGC/MS	low pg/m^3 (calculated)	No data	Hippelein et al. 1993
Water (congener specific)	Extracted using SPE, SFE, CLLE; cleanup using sulfuric acid and chromatography	HRGC/HRMS	See Table 7-1	No data	EPA 1999k (method 1668)
Drinking water	Extraction with hexane	HRGC/ECD	0.08–0.15 μg/L	84–97 (tap water)	EPA 1989c (method 505)
Finished drinking water and groundwater	Extraction with methylene chloride; solvent exchange to methyl tert-butyl ether	GC/ECD or HRGC/ECD	No data	No data	EPA 1989c (method 508)
Drinking water (screening)	Extraction with methylene chloride; solvent exchange to chloroform; perchlorination to decachlorobiphenyl	GC/ECD or HRGC/ECD	0.14–0.23 μg/L	82–136 ng/g	EPA 1989c (method 508A)
Drinking water	Extraction on SPE cartridges or disks; elution with methylene chloride	HRGC/MS	0.045–0.24 μg/L	65–100	EPA 1987f (method 525)
Drinking water (congener specific)	Sample spiked with ^{13}C-labeled PCBs; solvent extraction of sample (filtered water and particles); cleanup and fractionation by adsorption chromatography	HRGC/HRMS	0.02–0.04 pg/L	No data	Miyata et al. 1993

Table 7-3. Analytical Methods for Determining Polychlorinated Biphenyls in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Rain water (congener specific)	Passage through filter and XAD-2 resin; solvent extraction; cleanup on Florisil column	2-dimensional HRGC/ECD	<1–30 pg/L	79–83	Leister and Baker 1994
Waste water	Extraction with methylene chloride; exchange to hexane; cleanup on Florisil column; removal of elemental sulfur if necessary	GC/ECD	0.065 μg/L (PCB-1242)	88–96 at 25–110 μg/L	EPA 1982a, 1988b (method 608)
Waste water	Extraction with methylene chloride	GC/MS	30–36 μg/L (PCB-1221, 1254)	77–80 at 5–2,400 μg/L	EPA 1982a (method 625)
Lake water	Passage through glass fiber filter and XAD-2; Soxhlet extraction; cleanup on alumina and silica gel column	HRGC/ECD	No data	93	Swackhamer and Armstrong 1987
Sea water (congener specific)	Collection of particulate and filtered water in a pressurized extraction-filtration system; cleanup with sodium hydroxide, alumina, and silica column	HRGC/ECD	0.1–3.0 ng/L	67–106	Kelly et al. 1993
Soil, sediments, and other solid sample matrices	Extraction with hexane/acetone; cleanup on Florisil column; desulfurization if necessary	GC/ECD	<1 μg/g	No data	EPA 1994f (method 8080A)[c]
Soil, sediments, and other solid sample matrices (congener specific)	Filtered and homogenized; extracted using Soxhlet/Dean-Stark extractor; cleanup using sulfuric acid and chromatography	HRGC/HRMS	See Table 7-1	No data	EPA 1999k (method 1668)
Solid wastes (Aroclors or congeners)	Soxhlet extraction; sulfuric acid/potassium permanganate cleanup	HRGD/ECD; confirmation on second column	57–70 μg/kg (soil)	62–125 (multiple lab)	EPA 1995c (Method 8082)[c]
Hazardous wastes	Extraction with hexane/acetone; cleanup on silica gel column; desulfurization by copper or mercury if necessary	HRGC/ECD	60–70 μg/kg	104–107 (for soil)	Lopez-Avila et al. 1988

Table 7-3. Analytical Methods for Determining Polychlorinated Biphenyls in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil/sediment (low level)	Extraction with methylene chloride/acetone (1:1); cleanup by gel permeation and micro-alumina column	GC/ECD	80 µg/kg (required quantitation limit)	No data	EPA 1987a (CLP)[b]
Sediment (congener specific)	Ultrasonic extraction with acetone/hexane; sulfur removal; cleanup on Florisil; fractionation by HPLC	HRGC/ECD	No data	70–93	Fuoco et al. 1993
Sediment	Supercritical fluid extraction; mini-Florisil column cleanup sulfur removal	HRGC/ECD; confirmation by MS	No data	. 90	Lee and Peart 1994
Railcar paint scrapings	Extraction with 90% methylene chloride/10% methanol; cleanup on Florisil column	HRGC/ECD	1 mg/kg	74–86	Welsh 1995
Fly ash	Soxhlet extraction; optional column cleanup	GC/ECD or GC/MS-SIM	No data	80–100	Ko..an et al. 1994
Fish (congener specific)	Extraction of homogenized tissue with petroleum ether/ethyl acetate; cleanup by gel permeation chromatography	HRGC/NICI/MS	0.2–3 pg	65–115	Schmidt and Hesselberg 1992
Fish (congener specific)	Homogenized; extracted in methylene chloride:hexane (1:1) using Soxhlet extractor; cleanup using sulfuric acid and chromatography	HRGC/HRMS	See Table 7-1	No Data	EPA 1999k (method 1668)
Fish, fish egg, and bird egg (congener specific)	Extraction of homogenized ^{13}C-PCB labeled tissues with methylene chloride; removal of lipid by gel permeation or dialysis; cleanup by multi-layer and multiple chromatography; fractionation by HPLC	HRGC/ECD	0.1–0.73 ng/g (lipid)	62–92	Schwartz et al. 1993
Mammal blubber	Sample ground; solvent extraction; micro-Florisil column cleanup	dual column HRGC/ECD	30 µg/kg	95.2 (mean)	Newman et al. 1994
Marine animals	Microextraction	GC/ECD	1 ng	95 (Aroclor 1254)	Wirth et al. 1994
Cow's milk (congener specific)	Mixing of sample fortified with ^{13}C-labeled PCBs with sodium oxalate and methanol; solvent extraction; cleanup and fractionation by porous carbon and alumina	HRGC/MS	0.1–0.5 pg/g (fat) for tetra- to hexa-congeners of PCB	50–60	Van der Velde et al. 1994

Table 7-3. Analytical Methods for Determining Polychlorinated Biphenyls in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Eggs, fish	Supercritical fluid extraction combined with Florisil separation	GC/ECD	No data	91–95	Alley and Lu 1995
Fatty foods	Solvent extraction; liquid-liquid partitioning; cleanup on Florisil column	GC/ECD	No data	No data	AOAC 1990

[a]This method converts the different congeners to decachlorobiphenyl and cannot differentiate between commercial mixtures (e.g., Aroclor 1242, 1260).
[b]As required by Contract Laboratory Program
[c]Method 8080A is proposed for deletion from SW-846; method 8082 is proposed for inclusion in SW-846.

CLLE = continuous liquid/liquid extraction; ECD = electron capture detection; GC = gas chromatography; HPLC = high performance liquid chromatography; HRGC = high resolution gas chromatography; HRMS = high resolution mass spectrometry; MS = mass spectrometry; NICI/MS = negative ion chemical ionization mass spectrometry; ng = nanogram (10^{-9} g); pg = picogram (10^{-12} g); PUF = polyurethane foam; SIM = selected ion monitoring; SFE= separatory funnel extraction; SPE = solid phase extraction

Detection limits in the low pg/L range have been reported (Leister and Baker 1994). Some of the methods are noncongener-specific; that is, the results are reported as PCB mixtures (Aroclors) (EPA 1982a, 1989c), and some are congener-specific (EPA 1987f, 1999k; Kelly et al. 1993; Leister and Baker 1994; Miyata et al. 1993). EPA Method 508A, which converts all of the PCBs to decachlorobiphenyl, is a screening method for quantifying total PCBs (EPA 1989c). The method is likely to show interference due to perchlorination of biphenyl or related compounds (EPA 1991b) and the method cannot quantify individual commercial Aroclors in a PCB mixture. Some waters, particularly surface and waste waters, may require cleanup on adsorption columns prior to analysis (EPA 1982a, 1988b; Miyata et al. 1993). SPE media may be used, reducing the use of flammable or toxic solvents (EPA 1987f).

Soil, sediment, and solid waste samples are usually Soxhlet extracted (EPA 1994f, 1995c, 1999k). Ultrasonic extraction with various solvent combinations (Fuoco et al. 1993) and SFE (Lee and Peart 1994) are utilized as well. Recoveries using these methods are comparable to Soxhlet extraction (80–100%). Cleanup procedures include sulfur removal (EPA 1994f; Fuoco et al. 1993; Lee and Peart 1994; Lopez-Avila et al. 1988) and separation on adsorbent columns (Bandh et al. 1996; EPA 1994f; Fuoco et al. 1993; Lee and Peart 1994; Lopez-Avila et al. 1988). HRGC/ECD is used most often for determination of PCBs (Fuoco et al. 1993; Lee and Peart 1994; Lopez-Avila et al. 1988). Detection limits are generally in the ppb range (60–80 μg/kg) (EPA 1987a, 1995c; Lopez-Avila et al. 1988). Recovery of 62–125% of PCBs in clay and soil samples has been reported for a multiple lab study (EPA 1995c). Methods using the enzyme-linked immunosorbent assay are commercially available for screening PCB contamination in soils (Baek 1993; EPA 1995d). These methods are inexpensive and have a fast turnaround time.

Methods are available for measuring the concentration of PCBs in fish and animal tissues. Tissues are homogenized, and then dried by blending with anhydrous sodium sulfate prior to Soxhlet or column extraction (EPA 1999k; Newman et al. 1994). Direct extraction has also been utilized (Schwartz et al. 1993). After cleanup, PCBs are determined by HRGC/ECD (Schwartz et al. 1993), dual column HRGC/ECD (Newman et al. 1994), or HRGC/MS (Schmidt and Hesselberg 1992). A micro extraction method for very small sample masses (25 μg) has been developed (Wirth et al. 1994). A limit of detection of 1 ng/kg sample, and good recovery (95%) and precision were reported (Wirth et al. 1994). Few methods are available for the determination of PCBs in foods. Little performance data have been reported as well. A method is available for the determination of Aroclors in poultry fat, fish, and dairy products (AOAC 1990).

A number of Standard Reference Materials (SRMs) with certified PCB congener concentrations are available from the National Institute of Standards and Technology (NIST); these include SRM 1588, PCBs in Cod Liver Oil; SRM 1939, PCBs in River Sediment; SRM 1941, PCBs in Marine Sediment; and SRM 1974, PCBs in Mussel Tissue (Schantz et al. 1993a, 1993b). These SRMs are useful in validating the accuracy of methods for the determination of PCBs, and for verifying that the method remains within acceptable levels of error in during analysis. A summary of available SRMs with certified PCB concentrations is shown in Table 7-4. SRMs with non-certified concentration data for PCBs are included in the table as well.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PCBs is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of PCBs.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Several investigators have used whole blood, serum, breast milk, and hair as biomarkers for environmental exposure to PCBs (Brown and Lawton 1984; Fait et al. 1989; Furst et al. 1994; Luotamo 1988; Safe et al. 1985b; Zupancic-Kralj et al. 1992). Consequently, levels of PCBs in these media can provide estimates of exposure to PCBs. Analytical methods of satisfactory accuracy are available for determining congener- and noncongener-specific PCBs in blood, serum, breast milk, and human hair; these methods are shown in Table 7-2. Some methods for determining biomarkers are shown in Table 7-5. The method developed by several investigators can be used for the determination of the three non-*ortho* substituted PCB congeners

Table 7-4. NIST Standard Reference Materials for the Determination of Polychlorinated Biphenyls (PCBs)[a]

SRM	Description	PCBs certified	PCBs quantified
1589 PCBs (as Aroclor 1260) in human serum		1[b]	
1588 Organics in cod liver oil	Surrogate for a tissue extract with high lipid content	4	43
1649 Urban dust/organics	Air particulate material		10
1939 PCB congeners in river sediment	Sediment with high levels of PCB congeners	3	17
1941a Organics in marine sediment	Collected in Baltimore Harbor		15
1974 Organics in mussel tissue	Frozen powder-like homogenate		13
1945 Whale blubber	Frozen blubber homogenate		26

[a]Source: Schantz et al. 1993a
[b]certified as Aroclor 1260

NIST = National Institute of Standards and Technology

Table 7-5. Analytical Methods for Determining Biomarkers for Polychlorinated Biphenyls

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Liver and adipose tissue of gray seal (methyl sulfone metabolite)	Homogenization; extraction with methylene chloride/cyclohexane; removal of lipids by dialysis; cleanup by gel permeation chromatography; fractionation on carbon and Florisil columns	HRGC/ECNI/MS	No data	No data	Buser et al. 1992
Serum (major metabolites of PCB-77)	Solvent extraction; methylation; partition with H_2SO_4	HRGC/ECD and HRGC/MS	No data	low nmol/mL	Morse et al. 1995

ECD = electron capture detection; ECNI = electron capture negative ionization; HRGC = high resolution gas chromatography; MS = mass spectrometry

(77, 126, and 169) in human milk, adipose tissue, and serum at levels normally found in these tissues of control population (Harrad et al. 1992; Hong et al. 1992a; Patterson et al. 1989, 1994).

While blood, serum, breast milk, adipose tissue, and hair have been used as biomarkers of exposure, the possible equivalency of these biomarkers has not been intensively investigated. At least two of these biomarkers, serum and breast milk, did not appear to give equivalent measures of exposure even when expressed on a lipid basis. (The theory of equivalency is based on the assumption that the steady state concentration of a persistent lipophilic substance in different body compartments is the same when expressed on a lipid basis.) Greizerstein et al. (1999) compared levels of PCB congeners between serum and milk from seven women in the New York Angler Study. The congener profiles for serum and milk samples were similar for each individual, but different among all subjects. The sum of the congener concentrations was used to estimate the total PCB concentration. The ratio of serum to milk concentrations in the women ranged from 0.18 to 1.66 with a mean of 0.65±0.49, showing no consistency among individuals. Considerable differences were also found in the lipid-adjusted concentrations of PCBs among individuals. The range of lipid-adjusted serum-to-milk ratios was 1.1–2.8 with a mean of 1.9±0.5. The lipid-adjusted serum levels were also >1 for the most abundant congeners, PCBs 118, 153, 138, and 180. The lipid-adjusted ratios of these four non-planar congeners in serum and milk were similar to those found by Koopman-Esseboom et al. (1994b) in a study involving 418 mother-infant pairs. This latter study found that correlation coefficients between PCB congener levels (PCBs 118, 138, 153, and 180) in maternal plasma, human milk (lipid-basis), and cord plasma were highly significant within one biological sample (0.71–0.98) as well as between different biological samples. However, the correlation between other PCB congeners in human milk varied considerably. The study by Greizerstein et al. (1999) was small and collection of blood and milk samples was not uniform for all subjects.

Therefore, more data are needed to establish whether equivalency factors can be established between various measures of body burden so as to allow normalization of measurements between different studies.

Biomarkers of effects of exposure to PCBs are detailed Chapter 3 (Section 3.8.1). No single effect or combination of effects that could be used specifically as an indicator of exposure to PCBs are being developed to screen large numbers of food samples for PCBs and related compounds (J.K. Huwe et al. of Agricultural Research Service, Fargo, North Dakota). New screening methods for trace detection of PCBs in the environment and feeds are being developed by M. Franek et al. (Ministerstvo Zemedelstvi, Czech Republic). Development and application of semipermeable membrane devices (SPMDs) as environmental dosimeters for PCB contaminants in water, air, sediment, and soil is the subject of ongoing

research by Huckins and Petty at Columbia Environmental Research Center in Missouri. Also at the Columbia Environmental Research Center, C. Orazio et al. are developing analytical methods for determining PCBs in environmental matrices. A reliable method for continuous monitoring of PCBs in incinerator stack gas emissions using resonance-enhanced multiphoton ionization spectroscopy in conjunction with time-of-flight mass spectroscopy (REMPI/TOFMS) is the topic of current research by T.A. Cool at Cornell University. No additional information or ongoing studies regarding analytical methods for determining PCBs in environmental and biological samples resulting from exposure were located. Accordingly, new and improved analytical methods for trace detection of PCBs that could be used specifically as indicators of exposure in environmental and biological samples to PCBs are needed.

8. REGULATIONS AND ADVISORIES

Table 8-1 summarizes international, national, and state regulations and guidelines on human exposure to PCBs.

ATSDR has derived an MRL of 0.03 µg/kg/day for intermediate-duration oral exposure to PCBs. The intermediate oral MRL is based on a LOAEL of 0.0075 mg/kg/day for neurobehavioral effects in infant monkeys that were exposed to a PCB congener mixture representing 80% of the congeners typically found in human breast milk from birth to 20 weeks of age (Rice 1997, 1998, 1999b; Rice and Hayward 1997, 1999a). An uncertainty factor of 300 was applied (10 for extrapolating from a LOAEL to a NOAEL, 3 for extrapolating from monkeys to humans, and 10 for human variability).

ATSDR has derived an MRL of 0.02 µg/kg/day for chronic-duration oral exposure to PCBs. The chronic oral MRL is based on a LOAEL of 0.005 mg/kg/day for immunological effects in adult monkeys that were evaluated after 23 and 55 months of exposure to Aroclor 1254 (Tryphonas et al. 1989, 1991a). An uncertainty factor of 300 was applied (10 for extrapolating from a LOAEL to a NOAEL, 3 for extrapolating from monkeys to humans, and 10 for human variability).

EPA has verified an oral reference dose (RfD) of 0.02 µg/kg/day for Aroclor 1254 (IRIS 2000) based on dermal/ocular and immunological effects in monkeys, and an oral RfD of 0.07 µg/kg/day for Aroclor 1016 based on reduced birth weight in monkeys (IRIS 2000).

The EPA has determined that PCBs are probable human carcinogens and assigns them the cancer weight-of-evidence classification B2 (IRIS 2000). The EPA has developed an approach for assessing cancer risk from environmental PCBs by considering both toxicity and environmental processes (Cogliano 1998; EPA 1996c; IRIS 2000). This approach uses animal studies of commercial PCB mixtures to develop a range of human cancer potency estimates and then considers the effect of environmental processes to determine appropriate values for representative classes of environmental mixtures. Additional discussion on EPA's cancer risk assessment, including the cancer slope factors and their corresponding exposure pathways, is provided in Chapter 3 (Section 3.2.8.3.2). IARC has determined that PCBs are probably carcinogenic to humans (Group 2A) (IARC 1987). The Department of Health and Human Services (DHHS) concluded that PCBs are reasonably anticipated to be carcinogenic in humans based on sufficient evidence of carcinogenicity in animals (NTP 2000).

OSHA requires employers of workers who are occupationally exposed to PCBs to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs). The employer must use engineering and work practice controls, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 1 mg/m^3 for chlorodiphenyl (54% chlorine). Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls (OSHA 1998a).

The Food and Drug Administration (FDA) sets tolerance limits for PCBs as “unavoidable poisonous or deleterious substances” in both animal and human food, and food-packaging materials (FDA 1998c).

PCBs haves been designated as a hazardous substance pursuant to the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 (EPA 1998i) and as a toxic chemical under Section 313 of Title III of the Superfund Amendments and Reauthorization Act (SARA) of 1986 (EPA 1998i). Title III of SARA is also known as "The Emergency Planning and Community Right-to-Know Act (EPCRA) of 1986." As a chemical subject to the emergency planning and release reporting requirements of EPCRA, owners and operators of certain facilities that have PCBs on their sites in amounts exceeding a specified reporting threshold are required to report annually releases of PCBs to any environmental medium (EPA 1998d). The owners and operators of these facilities are also required to immediately report releases of PCBs to any environmental media if the amount released exceeds the “reportable quantity” of 1 pound (0.454 kg) (EPA 1998h). The statutory sources for designating PCBs as CERCLA hazardous substance are sections 311(b)(4) and 307(a) of the Clean Water Act (CWA), and section 112 of the Clean Air Act (CAA). The statutory reportable quantity for PCBs established by Section 102 of CERCLA is 10 pounds (4.54 kg) (EPA 1998h).

PCBs are regulated by the Clean Water Effluent Guidelines as stated in Title 40. Sections 400–475, of the Code of Federal Regulations (CFR). For each point source category, PCBs may be regulated as a group of chemicals controlled as Total Toxic Organics or may have a specific Regulatory Limitation. The point source categories for which PCBs are controlled as a Total Toxic Organic include electroplating (EPA 1981) and metal finishing (EPA 1983a). The point source category for which PCBs has a specific regulatory limitation is steam electric power generating (EPA 1982b).

If waters and their sediments become contaminated from sources such as atmospheric deposition and discharges from industrial, municipal, or agricultural operations, toxic substances could concentrate in the tissue of fish and wildlife. Currently, 679 advisories restricting the consumption of PCB-contaminated

fish, shellfish, and wildlife have been issued in 37 states and in one U.S. Territory (American Samoa) (EPA 2000b).

The Toxic Substances Control Act (TSCA) bans manufacturing, processing, and distributing PCBs in commerce. It also bans the use of PCBs outside of totally enclosed systems (EPA 1998a). In addition to authorizing the EPA to regulate PCBs, TSCA also provides the EPA with the authority to modify these bans if it is shown that such modifications would not present unreasonable risks to human health and the environment. On June 29, 1998, the EPA published amendments in the Federal Register to the regulatory requirements for the manufacture, processing, distribution in commerce, use, cleanup, storage, and disposal of PCBs (EPA 1998a). These amendments add regulatory provisions authorizing certain uses of PCBs; authorizing the manufacture, processing, and distribution in commerce of PCBs for use in research and development activities; specifying additional alternatives for the cleanup and disposal of PCBs; and clarifying the processing for disposal exemption. These amendments also add sections establishing standards and procedures for disposing of PCB remediation waste and certain products manufactured with PCBs; establishing procedures for determining PCB concentration; establishing standards and procedures for decontamination; establishing controls over the storage of PCBs for reuse; and establishing a mechanism for coordinating TSCA disposal approvals for the management of PCB wastes among various Federal programs. They also update several marking, recordkeeping, and reporting requirements.

The amendments contained in the final rule will be codified in the CFR at 40 CFR 750 and 40 CFR 761. The final rule authorizes certain uses of PCBs and materials contaminated with PCBs to continue if exposures can be controlled, and if removal and disposal of the material would be costly or impractical. More flexibility in selecting disposal technologies for PCBs is also allowed, and the list of available decontamination procedures has been expanded. The final rule allows disposal of PCBs from decontamination activities, but does not require previously needed disposal approval (EPA 1998a). The amendments add provisions for disposing of PCB remediation waste and certain products containing PCBs. TSCA does not allow state disposal rules for PCBs to be preempted, particularly if the method of disposal is described.

Some of the substances regulated by the requirements in 40 CFR 761 are dielectric fluids, solvents, oil, waste oils, heat transfer fluids, hydraulic fluids, paints or coatings, sludges, slurries, sediments, dredge spoils, soils, and materials containing PCBs as a result of spills. The regulatory applicability for these substances depends in part on the concentration of PCBs present (EPA 1998a). Numerical standards are usually expressed as the weight of PCBs per weight of liquid (e.g., milligrams per liter) or non-liquid

matrix (e.g., milligrams per kilogram). The final rule provides two option for determining what regulatory requirements apply to materials PCB-containing materials. The first option requires that the PCB concentration be determined (weight-to-weight or weight-to-volume) and then the regulatory requirements for the found concentration and the type of material are applied. Unless it is otherwise noted in the regulation, the weight or volume is determined using the total weight of the material and not the calculated weight or volume of PCBs within the substance. For non-liquid PCBs, the concentration must be determined on a dry weight basis. The concentration of PCBs in liquids and multi-phasic materials must determined on a wet weight basis and an analysis of each phase, respectively. The second option allows an assumption to be made that the PCB concentration is $500 ppm. When the second option is chosen, it would not be necessary to determine the PCB concentration; however, the most restrictive regulatory requirements will need to be met.

Although there are exceptions, such as waste oils used for energy recovery, PCB wastes are generally regulated for disposal under TSCA at concentrations of $50 ppm. The requirements for the disposal of PCB liquids and PCB items will be codified at 40 CFR 761.60. Disposal requirements for PCB remediation waste or PCB bulk product waste will be codified in 40 CFR 761.61 and 761.62, respectively. When the components of a waste are PCBs and non-PCB contaminants, and the PCB component is approved for disposal, the non-PCB component must meet the requirements of all other applicable statues or regulatory authorities prior to disposal (EPA 1998a).

Table 8-1. Regulations and Guidelines Applicable to PCBs

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenic classification	Group 2A [a]	IARC 1987
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV for occupational exposure (8-hour TWA)		ACGIH 1998
	Aroclor 1242 - (53469-21-9)	1 mg/m^3	
	Aroclor 1254 - (11097-69-1)	0.5 mg/m^3	
NIOSH	REL (10-hour TWA)		NIOSH 2000
	Chlorodiphenyl (42% chlorine) - (53469-21-9)	0.001 mg/m^3	
	Chlorodiphenyl (54% chlorine) - (11097-69-1)	0.001 mg/m^3	
OSHA	PEL (8-hour TWA)		OSHA 1998a
	Aroclor 1242 (53469-21-9)	1 mg/m^3	29 CFR
	Aroclor 1254 (11097-69-1)	0.5 mg/m^3	1910.1000[3]
	PEL (TWA) for shipyards		OSHA 1998b
	Aroclor 1242 (53469-21-9)	1 mg/m^3	29 CFR
	Aroclor 1254 (11097-69-1)	0.5 mg/m^3	1915.1000
	PEL (TWA) for construction		OSHA 1998c
	Aroclor 1242 (53469-21-9)	1 mg/m^3	29 CFR
	Aroclor 1254 (11097-69-1)	0.5 mg/m^3	1926.55
b. Water			
EPA	Drinking water standard for PCBs	$5x10^{-4}$ ppm	EPA 1999e 40 CFR 141.32
	MCL for community water systems and non-transient, non-community water systems for PCBs	$5x10^{-4}$ mg/L	EPA 1999g 40 CFR 141.61
	MCLG for PCBs	0 mg/L	EPA 1999f 40 CFR 141.50
	MCL	$5x10^{-4}$ mg/L	EPA 1996d
	Concentration at cancer risk of 10^{-4}	$5x10^{-4}$ mg/L	
	Cancer classification	B2[b]	

Table 8-1. Regulations and Guidelines Applicable to PCBs *(continued)*

Agency	Description	Information	References
NATIONAL (cont'd)			
	Human health consumption of:		EPA 1999a
	water and organism[c]	1.7×10^{-4} µg/L	
	organism only[c]	1.7×10^{-4} µg/L	
	Groundwater PQL[d]	50 µg/L	EPA 1999c 40 CFR 264 App. IX
	Universal Treatment Standards		EPA 1998e
	waste water standard[e]	0.10 mg/L[2]	40 CFR 268.48
	non-waste water standard[e]	10 mg/kg[3]	
FDA	Bottled water		FDA 1999a
	PCBs (1336-36-3)	0.0005 mg/L	21 CFR 165.110
c. Food			
FDA	Tolerances for PCB residues		FDA 1996c
	Infant and junior foods	0.2 ppm	
	eggs	0.3 ppm	
	milk (fat basis)	1.5 ppm	
	manufactured dairy products (fat basis)	1.5 ppm	
	fish and shell fish (edible portion; excludes head, scales, viscera, and inedible bones)	2 ppm	
	poultry (fat basis)	3 ppm	
	Action level for PCB residues in red meat on a fat basis	3 ppm	FDA 1996b
	Use of PCBs in the production, handling, and storage of animal feeds which then transfer to human food produced by animals	Yes	FDA 1998a 21 CFR 500.45
	Indirect food additives, manufacturing of food-packaging material	Yes	FDA 1998b 21 CFR 509.15
	Temporary tolerances for residues of PCBs as unavoidable environmental or industrial contaminants		FDA 1998c 21 CFR 509.30
	Finished animal feed for food-producing animals (except feed concentrates, feed supplements, and feed premixes)	0.2 ppm	

Table 8-1. Regulations and Guidelines Applicable to PCBs *(continued)*

Agency	Description	Information	References
NATIONAL (cont'd)			
c. Food			
	Animal feed components of animal origin, including fishmeal and other by-products of marine origin and in finished animal feed concentrates, supplements, and premixes intended for food-producing animals	2 ppm	
	Paper food-packaging material intended for or used with finished animal feed and any components intended for animal feeds	10 ppm	
d. Other			
ACGIH	Aroclor 1242 (53469-21-9)		ACGIH 1998
	Biological Exposure Index	No data	
	Carcinogenic classification	No data	
	Aroclor 1254 (11097-69-1)		
	Biological Exposure Index	No data	
	Carcinogenic classification	A3[f]	
EPA	Aroclor 1254 (11097-69-1)		IRIS 2000
	Carcinogenic classification	Evaluation incomplete	
	Oral slope factor	See PCBs	
	RfD (oral)	$2x10^{-5}$ mg/kg-day	
	Aroclor 1248 (12672-29-6)		IRIS 2000
	Carcinogenic classification	Evaluation incomplete	
	Oral slope factor	See PCBs	
	RfD (oral)	Not verified	
	Aroclor 1016 (12674-11-2)		IRIS 2000
	Carcinogenic classification	Evaluation incomplete	
	Oral slope factor	See PCBs	
	RfD (oral)	$7x10^{-5}$ mg/kg-day	

Table 8-1. Regulations and Guidelines Applicable to PCBs *(continued)*

Agency	Description	Information	References
NATIONAL (cont'd)			
d. Other (cont'd)			
EPA			
	Polychlorinated biphenyls (PCBs) (1336-36-3)		IRIS 2000
	Carcinogenic classification	B2[g]	
	Oral slope factor		
	Environmental exposure routes:		
	High risk and persistence	2.0 per (mg/kg)/day	
	Low risk and persistence	0.4 per (mg/kg)day	
	Lowest risk and persistence	0.07 per (mg/kg)/day	
	RfD (oral)	See Aroclor 1016, 1248, and 1254	
	Reportable quantity pursuant to Section 311 of the Clean Water Act	1 pound	EPA 1999h 40 CFR 117.3
	Toxic Pollutant Effluent Standards and Prohibitions	Yes	EPA 1998a 40 CFR 129.4
	Toxics Chemical Release effective date under section 372.30	1/1/87	EPA 1999d 40 CFR 372.65
	PCB waste regulated under Toxic Substance Control Act	Yes	EPA 1998b 40 CFR 261.8
	Toxic pollutant designated pursuant to section 307(a)(1) of the Act	Yes	EPA 1999j 40 CFR 401.15
	Hazardous substance in accordance with section 311(b)(2)(A) of the Act	Yes	EPA 1999i 40 CFR 116.4
	Hazardous constituent	Yes	EPA 1998r 40 CFR 261, app. viii
	Application to land used for the production of food chain crops and animal feed	Yes	EPA 1998q 40 CFR 257.3-5
USC	List of hazardous air pollutants	Yes	USC 1999 42 USC 7412
	Manufacture of PCB	Banned 2 years after 1/1/77	USC 1998 15 USC 2605
	Process or distribution in commerce	Banned 2.5 years after 1/1/77	

Table 8-1. Regulations and Guidelines Applicable to PCBs *(continued)*

Agency	Description	Information	References
STATE			
Regulations and Guidelines:			
a. Air:			
HI	List of hazardous air pollutants	Yes	UATW 1999d
AL	Human health consumption of: water and organism[h] organism only[i] for Aroclor 1016 (12674-11-2) Aroclor 1221 (11104-28-2) Aroclor 1232 (11141-16-5) Aroclor 1242 (53469-21-9) Aroclor 1248 (12672-29-6) Aroclor 1254 (11097-69-1) Aroclor 1260 (11096-82-5)	 9.7×10^{-8} mg/L 9.7×10^{-8} mg/L	UATW 1999a
AZ	PCBs (1336-36-3) Oral HBGL MCL Aroclor (12674-11-2) Oral HBGL	 0.005 µg/L 0.5 µg/L 0.49 µg/L	FSTRAC 1999
CO	Groundwater for PCBs (1336-36-3)	0.005 µg/L	CDC 1999c
	Human health consumption of PCBs (1336-36-3): water and organism water only	 4.4×10^{-5} µg/L 0.005 µg/L	CDC 1999d
HI	MCL for community and non-transient, and non-community water systems PCBs (1336-36-3)	5×10^{-4} mg/L	UATW 1999b
	Freshwater Acute Chronic	 2.0 µg/L 0.014 µg/L	UATW 1999c
	Saltwater Acute Chronic	 10 µg/L 0.03 µg/L	
	Fish consumption	7.9×10^{-5} µg/L	
ID	Primary water standard	5×10^{-4} mg/L	UATW 1999e

Table 8-1. Regulations and Guidelines Applicable to PCBs *(continued)*

Agency	Description	Information	References
STATE (cont'd)			
b. Water:	Acceptable water concentrations		
KS	Aquatic life		CDC 1999e
	Acute	2 mg/L	
	Chronic	0.014 mg/L	
	Public health		
	Food procurement	7.9×10^{-6} mg/L	
	Domestic water supply	0.5 mg/L	
NJ	Groundwater quality criteria for PCBs (1336-36-3)	0.02 µg/L	CDC 1999a
c. Fish and Wildlife Advisory for PCB[j]:			EPA 2000b
AL		Fish	
AR		Fish	
CT		Fish	
DE		Fish	
HI		Fish	
IA		Fish	
IN		Fish	
KY		Fish	
LA		Fish	
MA		Fish, turtles, and frogs	
ME		Fish	
MI		Fish	
MO		Fish	
MS		Fish	
NJ		Fish	
NY		Fish, and waterfowl	
OH		Fish	
PA		Fish	
RI		Fish	
SC		Fish	
TN		Fish	

Table 8-1. Regulations and Guidelines Applicable to PCBs *(continued)*

Agency	Description	Information	References
STATE (cont'd)			
c. Fish and Wildlife Advisory for PCB[j]: (cont'd)			EPA 2000b
TX		Fish	
VA		Fish	
WI		Fish	

[a]Probably carcinogenic to humans
[b]Sufficient evidence from animal studies to assume probable human carcinogen
[c]This criterion is based on carcinogenicity of 10^{-6} risk. Alternate risk levels may be obtained by moving the decimal point (e.g., for a risk level of 10^{-5}, move the decimal point in the recommended criterion one place to the right.)
[d]PQL: practical quantitation limit; this PQL is an average value for PCB congeners.
[e]The waste water and non-waste water standard applies to all PCB isomers.
[f]Confirmed animal carcinogen with unknown relevance to humans
[g]Probable human carcinogen
[h]derived from equation 18 for consumption of water and fish which is as follows:
Conc. (mg/L) = (HBW x RL)/(CPF x [(FCR x BCF) + WCR])
Where:
HBW = human body weight, set at 70 kg
RL = risk level, $1x10^{-5}$
CPF = cancer potency factor, 7.7 (kg-day)/mg
FCR = fish consumption rate, set at 0.030 kg/day
BCF = bioconcentration factor, given in appendix A, 31200 l/kg
WCR = water consumption rate, 2 l/kg
[i]derived from equation 19 for consumption of fish only which is as follows:
Conc. (mg/L) = {HBW x RL}/(CPF x FCR x BCF)
Where:
HBW = human body weight, set at 70 kg
RL = risk level, $1x10^{-5}$
CPF = cancer potency factor, 7.7 (kg-day)/mg
FCR = fish consumption rate, set at 0.030 kg/day
BCF = bioconcentration factor, given in appendix A, 31200 l/kg

[j]This information, current as of 2000, is based on the EPA Fish and Wildlife Advisory Database searched 8/00 on the Internet at http://www.epa.gov/OST/fishadvice/. For more detailed information, consult your state public health or natural resources department. A fish or wildlife advisory will specify the bodies of water or hunting areas with restrictions. The advisory will indicate the species and size of fish or game of concern. The advisory may completely ban consumption or recommend limiting the number of servings of a certain fish or wildlife species to less than a particular frequency. The advisory may indicate that only certain parts of the fish or game should be consumed and recommend preparation methods to minimize exposure. The advisory may have stricter restrictions than for the general public to protect pregnant women, nursing mothers, and young children. Each state, Native American tribe, or U.S. territory chooses its own criteria for issuing fish and wildlife advisories.

CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HBGL = health based guidance levels for drinking water; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; MCL = maximum contaminant limit; MCLG = maximum contaminant limit goal; NIOSH = National Institute of Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation limit; RfD = oral reference dose; REL = recommended exposure release; TLV = threshold limit value; TWA = time-weighted average; USC = United States Code

9. REFERENCES

*Aarts JMMJG, Denison MS, Cox MA, et al. 1995. Species-specific antagonism of Ah receptor action by 2,2',5,5'-tetrachloro- and 2,2',3,3'4,4'-hexachlorobiphenyl. Eur J Pharmacol 293(4):463-474.

*Abraham K, Hille A, Ende M, et al. 1994. Intake and fecal excretion of PCDDs, PCDFs, HCB, and PCBs (138, 153, 180) in a breast-fed and a formula-fed infant. Chemosphere 29(9-11):2279-2286.

*Abrahamson LJ, Allen JR. 1973. The biological response of infant nonhuman primates to a polychlorinated biphenyl. Environ Health Perspect 4:81-86.

*Abramowicz DA. 1990. Aerobic and anaerobic biodegradation of PCBs: A review. Crit Rev Biotechnol 10(3):241-251.

*Abramowicz DA. 1994. Aerobic PCB biodegradation and anaerobic PCB dechlorination in the environment. Res Microbiol 145(1):42-6.

*Abramowicz DA. 1995. Aerobic and anaerobic PCB biodegradation in the environment. Environ Health Perspect Suppl 103(5):97-99.

*Abramowicz DA, Brennan MJ, Van Dort HM, et al. 1993. Factors influencing the rate of polychlorinated biphenyl dechlorination in Hudson River sediments. Environ Sci Technol 27:1125-1131.

ACGIH. 1994. Threshold limit values for chemical substances and physical agents and biological exposure indices for 1994-1995. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH. 1995. Threshold limit values for chemicals substances and physical agents and biological exposure indices for 1995-1996. American Conferences of Governmental Industrial Hygienists, Cincinnati, OH.

*ACGIH. 1998. 1998 TLVs and BEIs. Threshold limit values for chemical substances and physical agents. Biological exposure indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

*Achman DR, Brownawell BJ, Zhang L. 1996. Exchange of polychlorinated biphenyls between sediment and water in the Hudson River estuary. Estuaries 19(4):950-965.

*Acquavella JF, Hanis NM, Nicolich MJ, et al. 1986. Assessment of clinical, metabolic, dietary, and occupational correlations with serum polychlorinated biphenyl levels among employees at an electrical capacitor manufacturing plant. J Occup Med 28(11):1177-1180.

*Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. Dev Med Child Neurol 27:532-537.

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect Suppl 103(7):103-112. Endocrine section

_____
*Cited in text

9. REFERENCES

*Adriaens P, Grbic-Galioc D. 1994. Cometabolic transformation of mono- and dichlorobiphenyls and chlorohydroxybiphenyls by methanotrophic groundwater isolates. Environ Sci Technol 28:1325-1330.

*Afghan BK, Chau ASY. 1989. Analysis of trace organics in the aquatic environment. Boca Raton, FL: CRC Press, Inc., 33-68.

*Agrawal AK, Tilson HA, Bondy SC. 1981. 3,4,3',4'-Tetrachlorobiphenyl given to mice prenatally produces long-term decreases in striatal dopamine and receptor binding sites in the caudate nucleus. Toxicol Lett 7:417-424.

*Agrell C, Okla L, Larsson P, et al. 1999. Evidence of latitudinal fractionation of polychlorinated biphenyl congeners along the Baltic Sea region. Environ Sci Technol 33(8):1149-1156.

Ahlborg MG, Becking GC, Birnbaum LS, et al. 1994. Toxic equivalency factors for dioxin-like PCBs. Chemosphere 28(6):1049-1067.

Ahlborg UG, Lipworth L, Titus-Ernstoff L, et al. 1995. Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: An assessment of the biological and epidemiological evidence. Crit Rev Toxicol 25(6):463-531.

Albrecht WE. 1987. Central nervous system toxicity of some common environmental residues in the mouse. J Toxicol Environ Health 21:405-421.

*Albro PW, Fishbein L. 1972. Intestinal absorption of polychlorinated biphenyls in rats. Bull Environ Contam Toxicol 8:26-31.

Albro PW, Parker CE. 1979. Comparison of the compositions of Aroclor 1242 and Aroclor 1016. J Chromatogr 169:161-166.

*Albro PW, Corbett JT, Schroeder JL. 1981. Quantitative characterization of polychlorinated biphenyl mixtures (Aroclors 1248, 1254, and 1260) by gas chromatography using capillary columns. J Chromatogr 205:103-111.

*Alcock RE, Bacon J, Bardget RD, et al. 1996. Persistence and fate of polychlorinated biphenyls (PCBs) in sewage sludge-amended agricultural soils. Environ Pollut 93(1):83-92.

*Alcock RE, McGrath SP, Jones KC. 1995 . The influence of multiple sewage sludge amendments on the PCB content of an agricultural soil over time. Environ Toxicol Chem 14(4):553-560.

*Alcock RE, Sweetman AJ, Juan C-Y, et al. 1999. The intake and clearance of PCBs in humans - a generic model of lifetime exposure. Organohalogen Compounds 44:61-65.

*Alder AC, Haggblom MM, Oppenheimer SR, et al. 1993. Reductive dechlorination of polychlorinated biphenyls in anaerobic sediments. Environ Sci Technol 27:530-538.

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect Suppl 103(7):103-112.

9. REFERENCES

*Alford-Stevens AL, Bellar TA, Eichelberger JW, et al. 1986. Accuracy and precision of determinations of chlorinated pesticides and polychlorinated biphenyls with automated interpretation of mass spectrometric data. Anal Chem 58:2022-2029.

Alford-Stevens AL, Budde WL, Bellar TA. 1985. Interlaboratory study on determination of polychlorinated biphenyls in environmentally contaminated sediments. Anal Chem 57:2452-2457.

*Allen JR. 1975. Response of the nonhuman primate to polychlorinated biphenyl exposure. Fed Proc 34:1675-1679.

*Allen JR, Abrahamson LJ. 1973. Morphological and biochemical changes in the liver of rats fed polychlorinated biphenyls. Arch Environ Contam Toxicol 1:265-280.

*Allen JR, Barsotti DA. 1976. The effects of transplacental and mammary movement of PCBs on infant Rhesus monkeys. Toxicology 6:331-340.

*Allen JR, Norback DH. 1973. Polychlorinated biphenyl- and triphenyl-induced gastric mucosal hyperplasia in primates. Science 179:498-499.

*Allen JR, Norback DH. 1976. Pathobiological responses of primates to polychlorinated biphenyl exposure. In: Proceedings of the National Conference on Polychlorinated Biphenyls, EPA 560/6-75-004, 43-49.

*Allen JR, Abrahamson LJ, Norback DH. 1973. Biological effects of polychlorinated biphenyls and triphenyls on the subhuman primate. Environ Res 6:344-354.

*Allen JR, Barsotti DA, Carstens LA. 1980. Residual effects of polychlorinated biphenyls on adult nonhuman primates and their offspring. J Toxicol Environ Health 6:55-66.

Allen JR, Barsotti DA, Lambrecht LK, et al. 1979. Reproductive effects of halogenated aromatic hydrocarbons on nonhuman primates. Ann NY Acad Sci 320:419-424.

*Allen JR, Carstens LA, Barsotti DA. 1974a. Residual effects of short-term, low-level exposure of nonhuman primates to polychlorinated biphenyls. Toxicol Appl Pharmacol 30:440-451.

*Allen JR, Norback DH, Hsu IC. 1974b. Tissue modifications in monkeys as related to absorption, distribution, and excretion of polychlorinated biphenyls. Arch Environ Contam Toxicol 2:86-95.

*Allen-Gil SM, Gubala CP, Wilson R, et al. 1997. Organochlorine pesticides and polychlorinated biphenyls (PCBs) in sediments and biota from four US Arctic lakes. Arch Environ Contam Toxicol 33(4):378-387.

*Alley EG, Lu G. 1995. Analysis of polychlorinated biphenyls in fatty biological matrixes by on-line supercritical fluid extraction and supercritical fluid cleanup. J AOAC Int 78(4):1051-1054.

Altenkirch H, Stoltenburg G, Haller D, Hopmann D, Walter G. 1996. Clinical data on three cases of occupationally induced PCB-intoxication. Neurotoxicology 17(3-4):639-643.

*Althaus FR, Lawrence SD, Sattler GL, et al. 1982. Chemical quantification of unscheduled DNA synthesis in cultured hepatocytes as an assay for the rapid screening of potential chemical carcinogens. Cancer Res 42:3010-3015.

9. REFERENCES

Altman NH, New AE, McConnell EE, et al. 1979. A spontaneous outbreak of polychlorinated biphenyl (PCB) toxicity in Rhesus monkeys (*macaca mulatta*): Clinical observations. Lab Anim Sci 29(5):661-665.

*Altman PK, Dittmer DS. 1974. In: Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.

*Altmann L, Lilienthal H, Hany J, et al. 1998. Inhibition of long-term potentiation in developing rat visual cortex but not hippocampus by *in utero* exposure to polychlorinated biphenyls. Dev Brain Res 110:257-260.

*Altmann L, Weinand-Haerer A, Lilienthal H, et al. 1995. Maternal exposure to polychlorinated biphenyls inhibits long-term potentiation in the visual cortex of adult rats. Neurosci Lett 202(1-2):53-56.

*Altshul L, Korrick S, Tolbert P, et al. 1999. Cord blood levels of PCBs, *p,p'*-DDE and HCB in infants born in communities adjacent to a PCB-contaminated hazardous waste site. Organohalogen Compounds 44:67-70.

*Alvares AP, Fischbein A, Anderson KE, et al. 1977. Alterations in drug metabolism in workers exposed to polychlorinated biphenyls. Clin Pharmacol Ther 22:140-146.

*American Liver Foundation. 2000. Gilbert's Syndrome. October 22, 2000. Http://www.gastro.com/liverpg/gilberts.htm.

*Andersen ME, Krishnan K. 1994. Relating in vitro to in vivo exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, replacement. New York: Marcel Dekker, Inc., 9-25.

*Andersen ME, Clewell HJ III, Gargas ML, et al. 1987a. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205.

Andersen ME, MacNaughton MG, Clewell HJ, et al. 1987b. Adjusting exposure limits for long and short exposure periods using a physiological pharmacokinetic model. Am Ind Hyg Assoc J 48(4):335-343.

*Andersen ME, Mills JJ, Gargas ML, et al. 1993. Modeling receptor-mediated processes with dioxin: implications for pharmacokinetics and risk assessment. Risk Anal 13:25-36.

*Anderson DJ, Bloem TB, Blankenbaker RK, et al. 1999. Concentrations of polychlorinated biphenyls in the water column of the Laurentian Great Lakes: Spring 1993. J Great Lakes Res 25(1):160-170.

Anderson HA. 1985. Utilization of adipose tissue biopsy in characterizing human halogenated hydrocarbon exposure. Environ Health Perspect 60:127-131.

*Anderson HA. 1989. General population exposure to environmental concentrations of halogenated biphenyls. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd ed. Amsterdam, The Netherlands: Elsevier Science Publishers, 325-344.

*Anderson HA, Falk C, Hanrahan L, et al. 1998. Profiles of Great Lakes critical pollutants: A sentinel analysis of human blood and urine. Environ Health Perspect 106(5):279-289.

9. REFERENCES

*Anderson JW, Rossi SS, Tukey RH, et al. 1995. A biomarker, P450 RGS, for assessing the induction potential of environmental samples. Environ Toxicol Chem 14:1159-1169.

*Anderson LM, Beebe LE, Fox SD, et al. 1991. Promotion of mouse lung tumors by bioaccumulated polychlorinated aromatic hydrocarbons. Exp Lung Res 17:455-471.

*Anderson LM, Fox SD, Riggs CW, et al. 1993. Selective retention of polychlorinated biphenyl congeners in lung and liver after single-dose exposure of infant mice to Aroclor 1254. J Environ Pathol Toxicol Oncol 12(1):3-16.

*Anderson LM, Logsdon D, Ruskie S, et al. 1994. Promotion by polychlorinated biphenyls of lung and liver tumors in mice. Carcinogenesis 15(10):2245-2248.

*Anderson LM, van Havere K, Budinger JM. 1983. Effects of polychlorinated biphenyls on lung and liver tumors initiated in suckling mice by *N*-nitrosodimethylamine. J Natl Cancer Inst 71:157-163.

*Anderson LM, Ward JM, Fox SD, et al. 1986. Effects of a single dose of polychlorinated biphenyls to infant mice on N-nitrosodimethylamine-initiated lung and liver tumors. Int J Cancer 38:109-116.

*Anderson PN, Hites RA. 1996. OH radical reactions: The major removal pathway for polychlorinated biphenyls from the atmosphere. Environ Sci Technol 30(5):1756-1763.

*Andersson L, Nikolaidis E, Brunstrom E, et al. 1991. Effects of polychlorinated biphenyls with *Ah* receptor affinity on lymphoid development in the thymus and the bursa of Fabricius of chick embryos *in ovo* and in mouse thymus anlagen *in vitro*. Toxicol Appl Pharmacol 107:183-188.

*Andersson O, Linder CE, Olsson M, et al. 1988. Spatial differences and temporal trends of organochlorine compounds in biota from the northwestern hemisphere. Arch Environ Contam Toxicol 17:755-765.

Andersson O, Nordlund-Moller L, Barnes HJ, et al. 1994. Heterologous expression of human uteroglobin/polychlorinated biphenyl-binding protein. J Biol Chem 269:19081-19087.

*Andersson PL, Blom A, Johannisson A, et al. 1999. Assessment of PCBs and hydroxylated PCBs as potential xenoestrogens: *In vitro* studies based on MCF-7 cell proliferation and induction of vitellogenin in primary culture of rainbow trout hepatocytes. Arch Environ Contam Toxicol 37:145-150.

*Ando M, Saito H, Wakisaka I. 1985. Transfer of polychlorinated biphenyls (PCBs) to newborn infants through the placenta and mothers' milk. Arch Environ Contam Toxicol 14:51-57.

*Andrews JE. 1989. Polychlorinated biphenyl (Aroclor 1254) induced changes in femur morphometry calcium metabolism and nephrotoxicity. Toxicology 57:83-96.

Angus WGR, Contreras ML. 1994. The effects of Aroclor 1254 on undifferentiated and NGF-stimulated differentiating PC12 cells. Neurotoxicology 15:809-818.

*Angus WGR, Mousa MA, Vargas VM, et al. 1997. Inhibition of L-aromatic amino acid decarboxylase by polychlorinated biphenyls. Neurotoxicology 18:857-868.

*Anid PJ, Ravest-Webster BP, Vogel TM. 1993. Effect of hydrogen peroxide on the biodegradation of PCBs in anaerobically dechlorinated river sediments. Biodegradation 4(4):241-248.

*Anitescu G, Tavlarides LL. 1998. Solubility of individual polychlorinated biphenyl (PCB) congeners in supercritical fluids: CO_2,CO_2/MeOH and CO_2/*n*-C_4H_{10}. Journal of Supercritical Fluids 14(3):197-211.

9. REFERENCES

*Ankley GT, Niemi GJ, Lodge KB, et al. 1993. Uptake of planar polychlorinated biphenyls and 2,3,7,8-substituted polychlorinated dibenzofurans and dibenzo-p-dioxins by birds nesting in the lower Fox River and Green Bay, Wisconsin, USA. Arch Environ Contam Toxicol 24:332-344.

*AOAC. 1990. Association of Official Analytical Chemists. Agricultural chemicals; contaminants; drugs. Pesticides and industrial chemical residues. 1:274-280.

Aono S, Tanabe S, Fujise Y, et al. 1997. Persistent organochlorines in minke whale (*balaenoptera acutorostrata*) and their prey species from the Antarctic and the North Pacific. Environ Pollut 98(1):81-89.

*Apfelbach R, Engelhart A, Behnisch P, et al. 1998. The olfactory system as a portal of entry for airborne polychlorinated biphenyls (PCBs) to the brain? Arch Toxicol 72(5):314-317.

*Arbon RE, Mincher BJ, Knighton WB. 1994. Gamma-X-Ray destruction of individual PCB congeners in neutral 2-propanol. Environ Sci Technol 28(12):2191-2196.

*Arbon RE, Mincher BJ, Knighton W. 1996. Gamma-ray destruction of PCBs in isooctane and transformer oil. Environ Sci Technol 30(6):1866-1871.

*Arcaro KF, Vakharia DD, Yang Y, et al. 1998. Lack of synergy by mixtures of weakly estrogenic hydroxylated polychlorinated biphenyls and pesticides. Environ Health Perspect Suppl 106(4):1041-1046.

*Arcaro KF, Yi L, Seegal RF, et al. 1999. 2,2',6,6'-Tetrachlorobiphenyl is estrogenic in vitro and in vivo. J Cell Biochem 72:94-102.

*Arimoto R. 1989. Atmospheric deposition of chemical contaminants to the Great Lakes. J Great Lakes Res 15:339-356.

*Ariyoshi N, Koga N, Oguri K, et al. 1992. Metabolism of 2,4,5,2',4',5'-hexachlorobiphenyl with liver microsomes of phenobarbital-treated dog; the possible formation of PCB 2,3-arene oxide intermediate. Xenobiotica 22(11):1275-1290.

*Ariyoshi N, Oguri K, Koga N, et al. 1995. Metabolism of highly persistent PCB congener, 2,4,5,2', 4', 5'-hexachlorobiphenyl, by human CYP2B6. Biochem Biophys Res Comm 212(2): 455-460.

Armstrong DE, Swackhamer DL. 1983. PCB accumulation in southern Lake Michigan sediments: Evaluation from core analysis. In: Mackay D, et al., eds. Physical behavior of PCBs in the Great Lakes. Ann Arbor, MI: Ann Arbor Science Press, 229-244.

*Arnold DL, Bryce F, Karpinski K, et al. 1993b. Toxicological consequences of Aroclor 1254 ingestion by female Rhesus (*macaca mulatta*) monkeys. Part 1B. Prebreeding phase: Clinical and analytical laboratory findings. Food Chem Toxicol 31(11):811-824.

*Arnold DL, Bryce F, McGuire PF, et al. 1995. Toxicological consequences of Aroclor 1254 ingestion by female Rhesus (*macaca mulatta*) monkeys. Part 2. Reproduction and infant findings. Food Chem Toxicol 33:457-474.

*Arnold DL, Bryce F, Mes J, et al. 1999. Toxicological consequences of feeding PCB congeners to infant Rhesus (*macaca mulatta*) and Cynomolgus (*macaca fascicularis*) monkeys. Food Chem Toxicol 37:153-167.

9. REFERENCES

*Arnold DL, Bryce F, Stapley R, et al. 1993a. Toxicological consequences of Aroclor 1254 ingestion by female Rhesus (*macaca mulatta*) monkeys. Part 1A. Prebreeding phase: Clinical health findings. Food Chem Toxicol 31(11):799-810.

*Arnold DL, Mes J, Bryce F, et al. 1990. A pilot study on the effects of Aroclor 1254 ingestion by Rhesus and Cynomolgus monkeys as a model for human ingestion of PCBs. Food Chem Toxicol 28:847-857.

*Arnold DL, Nera EA, Stapley R, et al. 1996. Prevalence of endometriosis in Rhesus (*macaca mulatta*) monkeys ingesting PCB (Aroclor 1254): Review and evaluation. Fundam Appl Toxicol 31(1):42-55.

*Arnold DL, Nera EA, Stapley R, et al. 1997. Toxicological consequences of Aroclor 1254 ingestion by female rhesus (*macaca mulatta*) monkeys and their nursing infants. Part 3: Post-reproduction and pathological findings. Food Chem Toxicol 35(12):1191-1207.

*Arnold DL, Stapley R, Bryce F, et al. 1998. A multigeneration study to ascertain the toxicological effects of Great Lakes salmon fed to rats: Study overview and design. Regul Toxicol Pharmacol 27:S1-S7.

Arnold SF, Klotz DM, Collins BM, et al. 1996. Synergistic activation of estrogen receptor with combinations of environmental chemicals. Science 272:1489-1492.

*Aronson KJ, Miller AB, Woolcott CG, et al. 2000. Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. Cancer Epidemiol Biomarkers Prev 9:55-63.

Assaf-Anid N, Nies L, Vogel TM. 1992. Reductive dechlorination of a polychlorinated biphenyl congener and hexachlorobenzene by vitamin B_{12}. Appl Environ Microbiol 58:1057-1060.

*ASTER. 1996. ASTER (Assessment Tools for the Evaluation of Risk) ecotoxicity profile. Duluth, MN: U.S. Environmental Protection Agency, Environmental Research Laboratory.

*ASTER. 1998. ASTER (Assessment Tools for the Evaluation of Risk) ecotoxicity profile. Duluth, MN: U.S. Environmental Protection Agency, Environmental Research Laboratory.

*Astroff B, Safe S. 1990. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin as an antiestrogen: Effect on rat uterine peroxidase activity. Biochem Pharmacol 39:485-488.

*Atkinson R. 1987. Estimation of OH radical reaction rate constants and atmospheric lifetimes for polychlorobiphenyls, dibenzo-*p*-dioxins, and dibenzofurans. Environ Sci Technol 21:305-307.

*Atkinson R. 1996. Atmospheric chemistry of PCBs, PCDDs and PCDFs. Issues Environ Sci Technol 6:53-72.

*Atlas E, Giam CS. 1988. Ambient concentration and precipitation scavenging of atmospheric organic pollutants. Water Air Soil Pollut 38:19-36.

9. REFERENCES

*ATSDR. 1987. Final report: Exposure study of persons possibly exposed to polychlorinated biphenyl in Paoli, Pennsylvania. Atlanta, GA: U.S. Department of Health and Human Services, Office of External Affairs, Exposure and Disease Registry Branch, Agency for Toxic Substances and Disease Registry.

*ATSDR. 1989. Agency for Toxic Substances and Disease Registry. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Federal Register 54(174):37617-37634.

ATSDR. 1992. Draft toxicological profile for chlorinated dibenzofurans (CDFs). Atlanta, GA: U.S Department of Health and Human Services, Office of External Affairs, Exposure and Disease Registry Branch, Agency for Toxic Substances and Disease Registry.

*ATSDR. 1994. Toxicological profile for chlorodibenzofurans. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

*ATSDR. 1995. Exposure to PCBs from hazardous waste among Mohawk women and infants at Akwesasne. Atlanta, GA.: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

*ATSDR. 1998. Toxicological profile for chlorinated dibenzo-*p*-dioxins. Atlanta, GA: U.S Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

*ATSDR/CDC. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary, and immune systems. Subcommittee on Biomarkers of Organ Damage and Dysfunction, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

*Atuma SS, Aune M. 1999. Method for the determination of PCB Congeners and Chlorinated Pesticides in human blood serum. Bull Environ Contam Toxicol 62: 8-15.

*Aulerich RJ, Ringer RK. 1977. Current status of PCB toxicity to mink, and effect on their reproduction. Arch Environ Contam Toxicol 6:279-292.

*Aulerich RJ, Bursian SJ, Breslin WJ, et al. 1985. Toxicological manifestations of 2,4,5, 2',4',5'-, 2,3,6,2',3',6'-, and 3,4,5,3',4',5'-hexachlorobiphenyl and Aroclor 1254 in mink. J Toxicol Environ Health 15:63-79.

*Aulerich RJ, Bursian SJ, Evans MG, et al. 1987. Toxicity of 3,4,5,3',4',5'-hexachlorobiphenyl to mink. Arch Environ Contam Toxicol 16:53-60.

*Aulerich RJ, Ringer RK, Safronoff J. 1986. Assessment of primary vs. secondary toxicity of Aroclor® 1254 to mink. Arch Environ Contam Toxicol 15:393-399.

Aulerich RJ, Ringer RK, Safronoff J. 1990. Assessment of primary vs secondary toxicity of Aroclor® 1254 to mink. Michigan State University, Department of Animal Science, East Lansing, MI.

Aust SD, Bourquin A, Loper JC, et al. 1994. Biodegradation of hazardous wastes. Environ Health Perspect Suppl 102(1):245-252.

*Ayotte P, Dewailly E, Bruneau S, et al. 1995. Arctic air pollution and human health: what effects should be expected? Sci Total Environ 160/161:529-537.

9. REFERENCES

*Ayotte P, Dewailly E, Ryan JJ, et al. 1997. PCBs and dioxin-like compounds in plasma of adult Inuit living in Nunavik (Arctic Quebec). Chemosphere 34(5-7):1459-1468.

*Bacci E, Gaggi C. 1985. Polychlorinated biphenyls in plant foliage: Translocation or volatilization from contaminated soils? Bull Environ Contam Toxicol 35:673-681.

*Bachour G, Failing K, Georgii S, et al. 1998. Species and organ dependence of PCB contamination in fish, foxes, roe deer, and humans. Arch Environ Contam Toxicol 35:666-673.

*Backlin BM, Bergman A. 1995. Histopathology of postpartum placental sites in mink (*mustela vison*) exposed to polychlorinated biphenyls or fractions thereof. APMIS 103(12):843-54.

*Backlin BM, Gessbo A, Forsberg M, et al. 1998a. Expression of the insulin-like growth factor II gene in polychlorinated biphenyl exposed female mink (mustela vison) and their fetuses. Mol Pathol 51(1):43-7.

*Backlin BM, Madej A, Forsberg M. 1997. Histology of ovaries and uteri and levels of plasma progesterone, oestradiol-17beta and oestrone sulphate during the implantation period in mated and gonadotrophin-releasing hormone-treated mink (mustela vison) exposed to polychlorinated biphenyls. J Appl Toxicol 17(5):297-306.

*Backlin BM, Persson E, Jones CJ, et al. 1998b. Polychlorinated biphenyl (PCB) exposure produces placental vascular and trophoblastic lesions in the mink (*mustela vison*): a light and electron microscopic study. APMIS 106(8):785-99.

*Bacon CE, Jarman WM, Estes JA, et al. 1999. Comparison of organochlorine contaminants among sea otter (enhydra lutris) populations in California and Alaska. Environ Toxicol Chem 18(3):452-458.

*Baek NH. 1993. Evaluation of immunoassay tests in screening soil contaminated with polychlorinated biphenyls. Bull Environ Contam Toxicol 51:844-851.

*Bager Y, Hemming H, Flodstom S, et al. 1995. Interaction of 3,4,5,3',4'-pentachlorobiphenyl and 2,4,5,2',4',5'-hexachlorobiphenyl in promotion of altered hepatic foci in rats. Pharmacol Toxicol 77:149-154.

*Bager Y, Kato Y, Kenne K, et al. 1997. The ability to alter the gap junction protein expression outside GST-P positive foci in liver of rats was associated to the tumour promotion potency of different polychlorinated biphenyls. Chem Biol Interact 103(3):199-212.

*Bahn AK, Grover P, Rosenwaike I, et al. 1977. PCB and melanoma [Letter]. N Engl J Med 296:108.

*Bahn AK, Rosenwaike I, Herrmann N, et al. 1976. Melanoma after exposure to PCB's [Letter]. N Engl J Med 295:450.

*Bailey RE, Gonsior SJ, Rhinehard WL. 1983. Biodegradation of the monochlorobiphenyls and biphenyl in river water. Environ Sci Technol 17(10):617-624.

*Baker EL Jr., Landrigan PJ, Glueck CJ, et al. 1980. Metabolic consequences of exposure to polychlorinated biphenyls (PCB) in sewage sludge. Am J Epidemiol 112(4):553-563.

9. REFERENCES

Baker FD, Bush B, Tumasonis CF, et al. 1977. Toxicity and persistence of low-level PCB in adult Wistar rats, fetuses, and young. Arch Environ Contam Toxicol 5:143-156.

*Baker JE, Eisenreich SJ. 1990. Concentrations and fluxes of polycyclic aromatic hydrocarbons and polychlorinated biphenyls across the air-water interface of Lake Superior. Environ Sci Technol 24:342-352.

*Baker JE, Eisenreich SJ, Johnson TC, et al. 1985. Chlorinated hydrocarbon cycling in the benthic nepheloid layer of Lake Superior. Environ Sci Technol 19:854-861.

*Balfanz E, Fuchs J, Kieper H. 1993. Sampling and analysis of polychlorinated biphenyls (PCB) in indoor air due to permanently elastic sealants. Chemosphere 26(5):871-880.

*Ballschmiter K, Zell M. 1980. Analysis of polychlorinated biphenyls (PCB) by glass capillary gas chromatography: Composition of technical Aroclor and Clophen-PCB mixtures. Fresenius Z Anal Chem 302:20-31.

*Ballschmiter K, Niemczyk R, Schaefer W, et al. 1987. Isomer-specific identification of polychlorinated benzenes (PCBs) and -biphenyls (PCB) in effluents of municipal waste incineration. Fresenius Z Anal Chem 328:583-587.

Ballschmiter K, Rappe C, Buser HR. 1989. Chemical properties, analytical methods and environmental levels of PCBs, PETs, PCNs and PBBs. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd ed. Amsterdam, The Netherlands: Elsevier Science Publishers, 47-102.

*Bandh C, Ishaq R, Broman D, et al. 1996. Separation for subsequent analysis of PCBs, PCDD/Fs and PAHs according to aromaticity and planarity using a two-dimensional HPLC system. Environ Sci Technol 30(1):214-219.

*Bandiera S, Farrell K, Mason G, et al. 1984. Comparative toxicities of the polychlorinated dibenzofuran (PCDF) and biphenyl (PCB) mixtures which persist in Yusho victims. Chemosphere 13:507-512.

Bandiera S, Safe S, Okey AB. 1982. Binding of polychlorinated biphenyls classified as either phenobarbitone-, 3-methylcholanthrene- or mixed-type inducers to cytosolic *Ah* receptor. Chem Biol Interact 39:259-277.

*Bank PA, Cullum ME, Jensen RK, et al. 1989. Effect of hexachlorobiphenyl on vitamin A homeostasis in the rat. Biochim Biophys Acta 990:306-314.

*Bannister R, Davis D, Zacharewski T, et al. 1987. Aroclor 1254 as a 2,3,7,8-tetrachlorodibenzo-*p*-dioxin antagonist: Effects on enzyme induction and immunotoxicity. Toxicology 46:29-42.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessment. Regul Toxicol Pharmacol 8:471-486.

Barnes D, Alford-Stevens A, Birnbaum L, et al. 1991. Toxicity equivalency factors for PCBs? Quality Assurance: Good Practice, Regulation, and Law 1(1):70-81.

9. REFERENCES

*Barr JR, Oida T, Kimata K, et al. 1997. Photolysis of environmentally important PCBs. Organohalogen Compounds 33:199-204.

*Barsotti DA, Van Miller JP. 1984. Accumulation of a commercial polychlorinated biphenyl mixture (Aroclor 1016) in adult Rhesus monkeys and their nursing infants. Toxicology 30:31-44.

*Barsotti DA, Marlar RJ, Allen JR. 1976. Reproductive dysfunction in Rhesus monkeys exposed to low levels of polychlorinated biphenyls (Aroclor 1248). Food Cosmet Toxicol 14:99-103.

*Battershill JM. 1994. Review of the safety assessment of polychlorinated biphenyls (PCBs) with particular reference to reproductive toxicity. Hum Exp Toxicol 13:581-597.

*Baukal CE, Schafer LL, Papadelis EP. 1994. PCB cleanup using an oxygen/fuel-fired mobile incinerator. Environmental Progress 13(3):188-191.

*Becker GM, McNulty WP, Bell M. 1979. Polychlorinated biphenyls-induced morphologic changes in the gastric mucosa of the Rhesus monkey. Lab Invest 40:373-383.

*Bedard DL. 1990. Bacterial transformation of polychlorinated biphenyls. In: Kamely D, Chakrabarty A, Omenn GS, eds. Biotechnology and biodegradation. Houston, TX: Portfolio Publishing Co., 369-388.

*Bedard DL, Haberl ML. 1990. Influence of chlorine subsitution pattern on the degradation of polychlorinated biphenyls by eight bacterial strains. Microb Ecol 20:87-102.

*Bedard DL, May RJ. 1996. Characterization of the polychlorinated biphenyls in the sediments of Woods Pond: Evidence for microbial dechlorination of Aroclor 1260 in situ. Environ Sci Technol 30(1):237-245.

*Bedard DL, Quensen JF. 1995. Microbial reductive dechlorination of polychlorinated biphenyls. In: Young LY, Cerniglia CE, ed. Ecological and applied microbiology; Microbial transformation and degradation of toxic organic chemicals. New York, NY: Wiley-Liss, 127-216.

*Bedard DL, Haberl ML, May RJ, et al. 1987. Evidence for novel mechanisms of polychlorinated biphenyl metabolism in *alcaligenes eutrophus* H850. Appl Environ Microbiol 53(5):1103-1112.

*Bedard DL, Van Dort HM, Bunnell SC, et al. 1993. Stimulation of reductive dechlorination of Aroclor 1260 contaminants in anaerobic slurries of Woods Pond sediment. In: Rogers JE, Abramowicz DA, eds. Anaerobic dehalogenation and its environmental implications. Abstracts of the 1992 American Society for Microbiology Conference. Athens, GA: U.S. Environmental Protection Agency, Office of Research and Development, 19-21.

Beebe LE, Fornwald LW, Alworth WL, et al. 1995. Effect of dietary Aroclor 1254 exposure on lung and kidney cytochromes P450 in female rats: evidence for P4501A2 expression in kidney. Chem Biol Interact 97(3):215-227.

*Beebe LE, Kim YE, Amin S, et al. 1993. Comparison of transplacental and neonatal initiation of mouse lung and liver tumors by *N*-nitrosodimethylamine (NDMA) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and promotability by a polychlorinated biphenyls mixture (Aroclor 1254). Carcinogenesis 14(8):1545-1548.

9. REFERENCES

*Bell FP, Iverson F, Arnold D, et al. 1994. Long-term effects of Aroclor 1254 (PCBs) on plasma lipid and carnitine concentrations in rhesus monkey. Toxicology 89(2):139-153.

*Bell M. 1983. Ultrastructural features of the murine cutaneous microvasculature after exposure to polychlorinated biphenyls compounds (PCBs) and benzo-(a)-pyrene (BAP). Virchows Arch B Cell Pathol 42:131-142.

*Belpaeme K, Delbeke K, Zhu L, et al. 1996. PCBs do not induce DNA breakage *in vitro* in human lymphocytes. Mutagenesis 11(4):383-389.

*Bemis JC, Seegal RF. 1999. Polychlorinated biphenyls and methylmercury act synergistically to reduce rat brain dopamine content *in vitro*. Environ Health Perspect 107(11):879-885.

*Benfenati E, Valzacchi S, Mariani G, et al. 1992. PCDD, PCDF, PCB, PAH, cadmium and lead in roadside soil: Relationship between road distance and concentration. Chemosphere 24(8):1077-1083.

*Benthe HF, Knop J, Schmoldt A. 1972. [Absorption and distribution of polychlorinated biphenyls (PCB) after inhalatory application]. Arch Toxikol 29:85-95. (German)

*Bercovici M, Wassermann, M, Cucos S, et al. 1983. Serum levels of polychlorinated biphenyls and some organochlorine insecticides in women with recent and former missed abortions. Environ Res 30:169-174.

*Berg V, Polder A, Skaare JU. 1998. Organochlorines in deep-sea fish from the Nordfjord. Chemosphere 38(2):275-282.

*Bergen BJ, Nelson WG, Pruell RJ. 1993. Bioaccumulation of PCB congeners by blue mussels (mytilus edulis) deployed in New Bedford Harbor, Massachusetts. Environ Toxicol Chem 12(9):1671-1681.

*Berger G S. 1994. Epidemiology of endometriosis. In: Modern surgical management of endometriosis. New York: Springer-Verlag.

*Berggrena P, Ishaq R, Zebuhr Y, et al. 1999. Patterns and levels of organochlorines (DDTs, PCBs, non-*ortho* PCBs and PCDD/Fs) in male harbour porpoises (*phocoena phocoena*) from the Baltic Sea, the Kattegat-Skagerrak Seas and the west coast of Norway. Mar Pollut Bull 38(12):1070-1084.

Bergman, A. 1992. Written communication (December 1) to Stephen J. Bosch, Syracuse Research Corporation, regarding studies of effects of PCBs on reproduction in mink. Department of Environmental Chemistry, Stockholm University, Stockholm, Sweden.

*Bergman A, Olsson M. 1985. Pathology of Baltic grey seal and ringed seal females with special reference to adrenocortical hyperplasia: Is environmental pollution the cause of a widely distributed disease syndrome? Finnish Game Research 44:47-62.

*Bergman A, Athanasiadou M, Bergek S, et al. 1992. PCB and PCB methyl sulfones in mink treated with PCB and various PCB fractions. Ambio 21(8):570-576.

*Bergman A, Hagman A, Jacobsson S, et al. 1984. Thermal degradation of polychlorinated alkanes. Chemosphere 13(2):237-250.

9. REFERENCES

*Bergman A, Klasson-Wehler E, Kuroki H. 1994. Selective retention of hydroxylated PCB metabolites in blood. Environ Health Perspect 102(5):464-469.

*Berkaw M, Sowers KR, May HD. 1996. Anaerobic *ortho* dechlorination of polychlorinated biphenyls by estuarine sediments from Baltimore harbor. Appl Environ Microbiol 62(7):2534-2539.

Berkowitz GS, Lapinski RH, Wolff MS. 1996. The role of DDE and polychlorinated biphenyl levels in preterm birth. Arch Environ Contam Toxicol 30(1):139-41.

*Bernhoft A, Nafstad I, Engen P, et al. 1994. Effects of pre- and postnatal exposure to 3,3',4,4',5-pentachlorobiphenyl on physical development, neurobehavioral and xenobiotic metabolizing enzymes in rats. Environ Toxicol Chem 13(10):1589-1597.

*Berry DL, DiGiovanni J, Juchau MR, et al. 1978. Lack of tumor-promoting ability of certain environmental chemicals in a two-stage mouse skin tumorigenesis assay. Res Commun Chem Pathol Pharmacol 20:101-108.

*Berry DL, Slaga TJ, DiGiovanni J, et al. 1979. Studies with chlorinated dibenzo-*p*-dioxins, polybrominated biphenyls, and polychlorinated biphenyls in a two-stage system of mouse skin tumorigenesis: Potent anticarcinogenic effects. Ann NY Acad Sci 320:405-414.

*Berry MR, Johnson LS, Jones JW, et al. 1997. Dietary characterizations in a study of human exposures in the lower Rio Grande Valley: I. Foods and beverages. Environ Int 23(5):675-692.

*Bertazzi PA, Riboldi L, Pesatori A, et al. 1987. Cancer mortality of capacitor manufacturing workers. Am J Ind Med 11:165-176.

*Berti PR, Receveur O, Chan HM, et al. 1998. Dietary exposure to chemical contaminants from traditional food among adult Dene/Metis in the western Northwest territories, Canada. Environ Res 76:131-142.

Bevelhimer MS, Adams SM, Miranda LE, et al. 1996. Assessing contaminant distribution and effects in a reservoir fishery. American Fisheries Society Symposium 16:119-132.

*Bidleman TF. 1981. Interlaboratory analysis of high molecular weight organochlorines in ambient air. Atmos Environ 15:619-624.

*Biegel L, Harris M, Davis D, et al. 1989a. 2,2',4,4',5,5'-hexachlorobiphenyl as a 2,3,7,8-tetrachlorodibenzo-p-dioxin antagonist in C57BL/6J mice. Toxicol Appl Pharmacol 97:561-571.

*Biegel L, Howie L, Safe S. 1989b. Polychlorinated biphenyl (PCB) congeners as 2,3,7,8-TCDD antagonists: Teratogenicity studies. Chemosphere 19:955-958.

*Billings RE, McMahon RE. 1978. Microsomal biphenyl hydroxylation: the formation of 3-hydroxybiphenyl and biphenyl catechol. Mol Pharmacol 14:145-154.

*Biocca M, Gupta BN, Chae K, et al. 1981. Toxicity of selected symmetrical hexachlorobiphenyl isomers in the mouse. Toxicol Appl Pharmacol 58:461-474.

*Birnbaum LS, DeVito MJ. 1995. Use of toxic equivalency factors for risk assessment for dioxins and related compounds. Toxicology 105(2-3):391-401.

9. REFERENCES

*Birnbaum LS, Harris MW, Crawford DD, et al. 1987. Teratogenic effects of polychlorinated dibenzofurans in combination in C57BL/6N mice. Toxicol Appl Pharmacol 91:246-255.

*Birnbaum LS, Weber H, Harris MW, et al. 1985. Toxic interaction of specific polychlorinated biphenyls and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin: Increased incidence of cleft palate in mice. Toxicol Appl Pharmacol 77:292-302.

Bishop CA, Ng P, Norstrom RJ, et al. 1996. Temporal and geographic variation of organochlorine residues in eggs of the common snapping turtle (c*helydra serpentina serpentina*) (1981-1991) and comparisons to trends in the herring gull (*larus argentatus*) in the Great Lakes basin in Ontario, Canada. Arch Environ Contam Toxicol 31(4):512-524.

*Bitman J, Cecil HC. 1970. Estrogenic activity of DDT analogs and polychlorinated biphenyls. J Agric Food Chem 18:1108-1112.

Bjerregaard, P. 1995. Health and environment in Greenland and other circumpolar areas. Sci Total Environ 160/161:521-527.

*Blais JM, Schindler DW, Muir DCG, et al. 1998. Accumulation of persistent organochlorine compounds in mountains of western Canada. Nature 395:585-588.

*Blazak WF, Marcum JB. 1975. Attempts to induce chromosomal breakage in chicken embryos with Aroclor 1242. Poultry Sci 54:310-312.

*Bleavins MR, Aulerich RJ, Ringer RK. 1980. Polychlorinated biphenyls (Aroclors 1016 and 1242): Effects on survival and reproduction in mink and ferrets. Arch Environ Contam Toxicol 9:627-635.

*Bleavins MR, Breslin WJ, Aulerich RJ, et al. 1984. Placental and mammary transfer of a polychlorinated biphenyl mixture (Aroclor 1254) in the European ferret (*mustela putorius furo*). Environ Toxicol Chem 3:637-644.

*Blumbach J, Nethe LP. 1996. Organic components reduction (PCDD/PCDF/PCB) in flue-gases and residual materials from waste incinerators by use of carbonaceous adsorbents. Chemosphere 32(1):119-131.

*Boers JP, De Leer EWB, Gramberg L, et al. 1994. Levels of coplanar PCB in flue gases of high temperature processes and their occurrence in environmental samples. Fresenius J Anal Chem 348(1-2):163-166.

*Bohm V, Schulte E, Thier H-P. 1993. Polychlorinated biphenyl residues in food and human milk: Determination of co-planar and mono-*ortho* substituted congeners. Z Lebensm Unters Forsch 196(5):435-440.

*Bohme F, Welsch-Pausch K, McLachlan MS. 1999. Uptake of airborne semivoatile organic compounds in agricultural plants: Field measurements of interspecies variability. Environ Sci Technol 33:1805-1813.

*Bolger PM. 1999. Personal communications, September 28, 1999. U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition Contaminants Branch.

9. REFERENCES

Bonin J, DesGranges J-L, Bishop CA, et al. 1995. Comparative study of contaminants in the mudpuppy (*amphibia*) and the common snapping turtle (*reptilia*), St. Lawrence River, Canada. Arch Environ Contam Toxicol 28:184-194.

*Bonnyns M, Bastomsky CH. 1976. Polychlorinated biphenyl-induced modification of lymphocyte response to plant mitogens in rats. Experientia 15(4):522-523.

*Book SA, Goldman M. 1975. Thyroidal radioiodine exposure of the fetus. Health Phys 29:874-877.

*Boon JP, Duinker JC. 1986. Monitoring of cyclic organochlorines in the marine environment. Environ Monit Assess 7:189-208.

Boon JP, Ouderans RCHM, Duinkeys JC. 1984. Kinetics of individual polychlorinated biphenyl (PCB) components in juvenile sole (*solea solea*) in relation to their concentrations in food and to lipid metabolism. Comp Biochem Physiol 79:131-42.

*Bopp RF, Chillrud SN, Shuster EL, et al. 1998. Trends in chlorinated hydrocarbon levels in Hudson River Basin sediments. Environ Health Perspect Suppl 106(4):1075-1081.

*Bopp RF, Simpson HJ, Olsen CR, et al. 1982. Chlorinated hydrocarbons and radionuclide chronologies in sediments of the Hudson River and estuary, New York. Environ Sci Technol 16:666-676.

*Borchard RE, Welborn ME, Wiekhorst WB, et al. 1975. Pharmacokinetics of polychlorinated biphenyl components in swine and sheep after a single oral dose. J Pharm Sci 64:1294-1302.

*Borlakoglu JT, Walker CH. 1989. Comparative aspects of congener specific PCB metabolism. Eur J Drug Metab Pharmcokinet 14:127-131.

*Borlakoglu JT, Wilkins JPG. 1993a. Correlations between the molecular structures of polyhalogenated biphenyls and their metabolism by hepatic microsomal monooxygenases. Comp Biochem Physiol 105C(1):113-117.

*Borlakoglu JT, Wilkins JPG. 1993b. Metabolism of di-, tri-, tetra-, penta- and hexachlorobiphenyls by hepatic microsomes isolated from control animals and animals treated with Aroclor 1254, a commercial mixture of polychlorinated biphenyls (PCBs). Comp Biochem Physiol 105C(1):95-106.

*Botero JE, Meyer MW, Hurley SS, et al. 1996. Residues of organochlorines in mallards and blue-winged teal collected in Colombia and Wisconsin, 1984-1989. Arch Environ Contam Toxicol 31(2):225-231.

*Bove FJ, Slade BA, Canady RA. 1999. Evidence of excess cancer mortality in a cohort of workers exposed to polychlorinated biphenyls. J Occup Environ Med 41(9):739-740.

Bowadt S, Larsen B. 1992. Rapid screening of chlorobiphenyl congeners by GC-ECD on a carborane-polydimethylsiloxane copolymer. J High Resolut Chromatogr 15(5):350-351.

Bowerman WW, Giesy JP, Best DA, et al. 1995. A review of factors affecting productivity of bald eagles in the Great Lakes region: Implications for recovery. Environ Health Perspect Suppl 103(4):51-59.

*Bowes GW, Mulvihill MJ, Simoneit BRT, et al. 1975. Identification of chlorinated dibenzofurans in American polychlorinated biphenyls. Nature 256:305-307.

9. REFERENCES

*Bowman RE, Heironimus MP. 1981. Hypoactivity in adolescent monkeys perinatally exposed to PCBs and hyperactive as juveniles. Neurobehav Toxicol Teratol 3:15-18.

*Bowman RE, Heironimus MP, Allen JR. 1978. Correlation of PCB body burden with behavioral toxicology in monkeys. Pharmacol Biochem Behav 9:49-56.

*Boyages SC. 2000. The neuromuscular system and brain in hypothyroidism. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's the thyroid: A fundamental and clinical text. Eighth edition. Philadelphia, PA: Lippincott Williams & Wilkins, 804-810.

Bradlaw JA, Casterline JL. 1979. Induction of enzyme activity in cell culture: A rapid screen for detection of planar polychlorinated organic compounds. J Assoc Off Anal Chem 62:904-916.

*Brandt, I, Bergman A. 1987. PCB methyl sulfones and related compounds: Identification of target cells and tissues in different species. Chemosphere 16:1671-1676.

*Brandt I, Lund J, Bergman A, et al. 1985. Target cells for the polychlorinated biphenyl metabolite 4,4'-bis(methylsulphonyl)-2,2',5,5'-tetrachlorobiphenyl in lung and kidney. Drug Metab Dispos 13:490-496.

*Brandt-Rauf PW, Niman HL. 1988. Serum screening for oncogene proteins in workers exposed to PCBs. Br J Ind Med 45:689-693.

*Brazner J, DeVita W. 1998. PCBs, DDE, and mercury in young-of-the year littoral fishes from Green Bay, Lake Michigan. J Great Lakes Res 24(1):83-92.

*Bremle G, Larsson P. 1998. PCB in the air during landfilling of a contaminated lake sediment. Atmos Environ 32(6):1011-1019.

*Bremle G, Okla L, Larsson P. 1995. Uptake of PCBs in fish in a contaminated river system: Bioconcentration factors measured in the field. Environ Sci Technol 29:2010-2015.

*Brezner E, Terkel J, Perry AS. 1984. The effect of Aroclor 1254 (PCB) on the physiology of reproduction in the female rat-I. Comp Biochem Physiol 77:65-70.

*Bright DA, Dushenko WT, Grundy SL, et al. 1995a. Effects of local and distant contaminant sources: Polychlorinated biphenyls and other organochlorines in bottom-dwelling animals from an Arctic estuary. Sci Total Environ 160-161:265-283.

*Bright DA, Dushenko WT, Grundy SL, et al. 1995b. Evidence for short-range transport of polychlorinated biphenyls in the Canadian Arctic using congener signatures of PCBs in soils. Sci Total Environ 160-161:251-263.

*Brinkman DW, Dickson JR, Wilkinson D. 1995. Full scale hydrotreatment of polychlorinated biphenyls in the presence of used lubricating oils. Environ Sci Technol 29:87-91.

Brouwer A, Ahlbord UG, van Leeuwn FXR, et al. 1998a. Report of the WHO working group on the assessment of health risks for human infants from exposure to PCDDs, PCDFs and PCBs. Chemosphere 37(9-12):1627-1643.

9. REFERENCES

Brouwer A, Klasson-Wehler E, Bokdam M, et al. 1990. Competitive inhibition of thyroxin binding to transthyretin by monohydroxy metabolites of 3,4,3',4'-tetrachlorobiphenyl. Chemosphere 20:1257-1262.

*Brouwer A, Morse DC, Lans MC, et al. 1998b. Interactions of persistent environmental organohalogens with the thyroid hormone system: mechanisms and possible consequences for animal and human health. Toxicol Ind Health 14:59-84.

*Brown AP, Ganey PE. 1995. Neutrophil degranulation and superoxide production induced by polychlorinated biphenyls are calcium dependent. Toxicol Appl Pharmacol 131:198-205.

Brown AP, Schultze AE, Holdan WL, et al. 1996. Lipopolysaccharide-induced hepatic injury is enhanced by polychlorinated biphenyls. Environ Health Perspect 104(6):634-640.

*Brown BR. 1987a. Studies on inhalation anesthetic hepatotoxicity. Crisp Data Base National Institutes of Health.

*Brown DP. 1987b. Mortality of workers exposed to polychlorinated biphenyls -An update. Arch Environ Health 42(6):333-339.

*Brown DP, Jones M. 1981. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. Arch Environ Health 36:120-129.

*Brown JF. 1994. Determination of PCB metabolic, excretion, and accumulation rates for use as indicators of biological response and relative risk. Environ Sci Technol 28:2295-2305.

*Brown JF, Lawton RW. 1984. Polychlorinated biphenyl (PCB) partitioning between adipose tissue and serum. Bull Environ Contam Toxicol 33:277-280.

*Brown JF, Wagner RE. 1990. PCB movement, dechlorination, and detoxication in the Acushnet estuary. Environ Toxicol Chem 9:1215-1233.

*Brown JF, Bedard DL, Brennan MJ, et al. 1987a. Polychlorinated biphenyl dechlorination in aquatic sediments. Science 236:709-712.

*Brown JF, Fish KM, Silkworth JB, et al. 1998. A proposed general mechanism for rodent liver carcinogenesis by persistent organohalogen compounds at the maximum tolerated dose. Organohalogen Compounds 37:67-70.

*Brown JF, Frame GM, Olson DR, et al. 1995. The sources of coplanar PCBs. Organohalogen Compounds 26:427-430.

*Brown JF, Lawton RW, Ross MR, et al. 1989. Persistence of PCB congeners in capacitor workers and yusho patients. Chemosphere 19(1-6):829-834.

Brown JF, Silkworth JB, Mayes BA. 1997. Characterization of PCB composition, tissue accumulation, and correlations with tumorigenicity in chronically dosed male and female Sprague-Dawley rats. Schenectady, NY: General Electric Corporate Research and Development. Batelle Study No. SC920192.

*Brown JF, Wagner RE, Bedard DL, et al. 1984. PCB transformations in upper Hudson sediments. Northeast Environ Sci 3(3/4):166-178.

9. REFERENCES

*Brown JF, Wagner RE, Bedard DL. 1988. PCB dechlorination in Hudson River sediment. Science 240:1674-1676.

*Brown JF, Wagner RE, Feng H, et al. 1987b. Environmental dechlorination of PCBs. Environ Toxicol Chem 6:579-593.

*Brown NM, Lamartiniere CA. 1995. Xenoestrogens alter mammary gland differentiation and cell proliferation in the rat. Environ Health Perspect 103:708-713.

*Brownlow CS, Que Hee SS. 1985. Comparison of solid sampling media for Aroclor 1254 vapor under dry and humid conditions. Am Ind Hyg Assoc J 46:421-426.

*Brozoski TJ, Brown RM, Rosvold HE, et al. 1979. Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of Rhesus monkey. Science 205(31):929-931.

*Brubaker WW, Hites RA. 1998. Gas-phase oxidation products of biphenyl and polychlorinated biphenyls. Environ Sci Technol 32:3913-3918.

*Bruce RW, Heddle JA. 1979. The mutagenic activity of 61 agents as determined by the micronucleus, *salmonella*, and sperm abnormality assays. Can J Genet Cytol 21:319-333.

*Bruckner JV, Jiang WD, Brown JM, et al. 1977. The influence of ingestion of environmentally encountered levels of a commercial polychlorinated biphenyl mixture (Aroclor 1254) on drug metabolism in the rat. J Pharmacol Exp Ther 202:22-31.

*Bruckner JV, Khanna KL, Cornish HH. 1973. Biological responses of the rat to polychlorinated biphenyls. Toxicol Appl Pharmacol 24:434-448.

*Bruckner JV, Khanna KL, Cornish HH. 1974. Effect of prolonged ingestion of polychlorinated biphenyls on the rat. Food Cosmet Toxicol 12:323-330.

*Brunciak PA, Lavorgna CL, Nelson ED, et al. 1999. Trends and dynamics of persistent organic pollutants in the coastal atmosphere of the mid-Atlantic states. Prepr Ext Abst Div Environ Chem Am Chem Soc 39(1):64-67.

Brunner MJ, Sullivan TM, Singer AW et al. 1996. An assessment of the chronic toxicity and oncogenicity of Aroclor 1016, Aroclor 1242, Aroclor 1254, and Aroclor 1260 administered in diet to rats. Battelle study no. SC920192, Columbus, OH.

*Brunstrom B, Kihlstrom I, Lundkvist U. 1982. Studies of foetal death and foetal weight in guinea pigs fed polychlorinated biphenyls (PCB). Acta Pharmacol Toxicol 50(2):100-103.

*Bryant CJ, Hartle RW, Crandall MS. 1989. Polychlorinated biphenyl, polychlorinated dibenzo-p-dioxin, and polychlorinated dibenzofuran contamination in PCB disposal facilities. Chemosphere 18:569-576.

*Buchmann A, Ziegler S, Wolf A, et al. 1991. Effects of polychlorinated biphenyls in rat liver: Correlation between primary subcellular effects and promoting activity. Toxicol Appl Pharmacol 111:454-468.

9. REFERENCES

Buck GM. 1996. Epidemiologic perspective of the developmental neurotoxicity of PCBs in humans. Neurotoxicol Teratol 18(3):239-241.

*Buck GM, Mendola P, Vena JE, et al. 1999. Paternal Lake Ontario fish consumption and risk of conception delay, New York State angler cohort. Environ Res 80:S13-S18.

*Buck GM, Sever LE, Mendola P, et al. 1997. Consumption of contaminated sport fish from Lake Ontario and time-to-pregnancy. Am J Epidemiol 146:949-954.

*Buck GM, Vena JE, Schisterman EF, et al. 2000. Parental consumption of contaminated sport fish from Lake Ontario and predicted fecundability. Epidemiology 11:388-393.

*Buckley TJ, Liddle J, Ashley DL, et al. 1997. Environmental and biomarker measurements in nine homes in the lower Rio Grande Valley: Multimedia results for pesticides, metals, PAHs, and VOCs. Environ Int 23(5):705-732.

*Buhler F, Schmid P, Schlatter CH. 1988. Kinetics of PCB elimination in man. Chemosphere 17:1717-1726.

*Bunce NJ, Kumar Y, Ravanal L, et al. 1978. Photochemistry of chlorinated biphenyls in iso-octane solution. Journal of the Chemical Society II:880-884.

*Burgess RM, McKinney RA, Brown WA. 1996. Enrichment of marine sediment colloids with polychlorinated biphenyls: Trends resulting from PCB solubility and chlorination. Environ Sci Technol 30:2556-2566.

*Burkhard LP, Armstrong DE, Andren AW. 1985. Henry's law constants for the polychlorinated biphenyls. Environ Sci Technol 19:590-596.

*Burse VW, Groce DF, Caudill SP, et al. 1994. Determination of polychlorinated biphenyl levels in the serum of residents and in the homogenates of seafood from the New Bedford, Massachusetts, area: A comparison of exposure sources through pattern recognition techniques. Sci Total Environ 144:153-177.

Burse VW, Kimbrough RD, Villanueva EC, et al. 1974. Polychlorinated biphenyls: Storage, distribution, excretion, and recovery: Liver morphology after prolonged dietary ingestion. Arch Environ Health 29:301-307.

*Burse VW, Korver MP, Needham LL, et al. 1989. Gas chromatographic determination of polychlorinated biphenyls (as Aroclor 1254) in serum: Collaborative study. J Assoc Off Anal Chem 72(4):649-659.

Burse VW, Needham LL, Korver MP, et al. 1983a. Gas-liquid chromatographic determination of polychlorinated biphenyls and a selected number of chlorinated hydrocarbons in serum. J Assoc Off Anal Chem 66:32-39.

Burse VW, Needham LL, Lapeza CR, Jr, et al. 1983b. Evaluation of potential analytical approach for determination of polychlorinated biphenyls in serum: Interlaboratory study. J Assoc Off Anal Chem 66:956-968.

9. REFERENCES

*Buser H-R, Zook DR, Rappe C. 1992. Determination of methyl sulfone-substituted polychlorobiphenyls by mass spectrometric techniques with application to environmental samples. Anal Chem 64(10):1176-1183.

*Bush B, Bennett AH, Snow JT. 1986. Polychlorobiphenyl congeners, *p,p′*-DDE, and sperm function in humans. Arch Environ Contam Toxicol 15:333-341.

*Bush B, Streeter RW, Sloan RJ. 1989. Polychlorobiphenyl (PCB) congeners in striped bass (*morone saxatilis*) from marine and estuarine waters of New York State determined by capillary gas chromatography. Arch Environ Contam Toxicol 19(1):49-61.

*Bushart SP, Bush B, Barnard EL, et al. 1998. Volatilization of extensively dechlorinated polychlorinated biphenyls from historically contaminated sediments. Environ Toxicol Chem 17(10):1927-1933.

*Bushnell PJ, Rice DC. 1999. Behavioral assessments of learning and attention in rats exposed perinatally to 3,3',4,4',5-pentachlorobiphenyl (PCB 126). Neurotoxicol Teratol 21(4):381-392.

*Byrne JJ, Carbone JP, Hanson EA. 1987. Hypothyroidism and abnormalities in the kinetics of thyroid hormone metabolism in rats treated chronically with polychlorinated biphenyl and polybrominated biphenyl. Endocrinology 121:520-527.

*Byrne JJ, Carbone JP, Pepe MG. 1988. Suppression of serum adrenal cortex hormones by chronic low-dose polychlorobiphenyl or polybromobiphenyl treatments. Arch Environ Contam Toxicol 17:47-53.

Bysshe SE. 1990. Bioconcentration factor in aquatic organisms. In: Lyman WJ et al., eds. Handbook of chemical property estimation methods. Environmental behavior of organic compounds. Washington, DC: American Chemical Society, 5-1 to 5-30.

*Calabrese EJ, Sorenson AJ. 1977. The health effects of PCBs with particular emphasis on human high risk groups. Rev Environ Health 2:285-304.

*Capen CC. 2000. Anatomy. In: Braverman LE, Utiger RD, ed. Werner and Ingbar's the thyroid: A fundamental and clinical text. Philadelphia, PA: Lippincott-Raven, 19-43.

*Carey AE, Harvey GR. 1978. Metabolism of polychlorinated biphenyls by marine bacteria. Bull Environ Contam Toxicol 20:527-534.

Carey AE, Douglas P, Tai H, et al. 1979b. Pesticide residue concentrations in soils of five United States cities, 1971-Urban soils monitoring program. Pestic Monitor J 13:17-22.

Carey AE, Gowen JA, Tai H, et al. 1979a. Pesticide residue levels in soils and crops from 37 states, 1972 - National Soils Monitoring Program (IV). Pestic Monit J 12:209-229.

*Carroll KM, Harkness MR, Bracco AA, et al. 1994. Application of a permeant/polymer diffusional model to the desorption of polychlorinated biphenyls from Hudson River sediments. Environ Sci Technol 28:253-258.

*Carter JW. 1984. Hypercholesterolemia induced by dietary PCBs (Aroclor 1254) in Fischer rats. Bull Environ Contam Toxicol 33:78-83.

9. REFERENCES

*Carter JW. 1985. Effects of dietary PCBs (Aroclor 1254) on serum levels of lipoprotein cholesterol in Fischer rats. Bull Environ Contam Toxicol 34:427-431.

*Carter JW, Koo SI. 1984. Effects of dietary Aroclor 1254 (PCBs) on serum levels of lipoprotein cholesterol and tissue distribution of zinc, copper and calcium in Fischer rats. Nutr Rep Int 29:223-232.

*Casey AC, Berger DF, Lombardo JP, et al. 1999. Aroclor 1242 inhalation and ingestion by Sprague-Dawley rats. J Toxicol Environ Health 56:311-342.

*CDC. 1999a. New Jersey. Center for Disease Control & Prevention. July 9, 1999. http://search.cdc.gov/shd/search2.html

CDC. 1999b. Colorado. Center for Disease Control & Prevention. July 9, 1999. http://search.cdc.gov/shd/search2.html

*CDC. 1999c. Colorado. Center for Disease Control & Prevention. July 9, 1999. http://search.cdc.gov/shd/search2.html

*CDC. 1999d. Colorado. Center for Disease Control & Prevention. July 9, 1999. http://search.cdc.gov/shd/search2.html

*CDC. 1999e. Kansas. Center for Disease Control & Prevention. July 9, 1999. http://search.cdc.gov/shd/search2.html

CELDS. 1994. Computer-aided Environmental Legislative Data Systems. United States Army Corps of Engineers Environmental Technical Information Systems, University of Illinois, Urbana, IL.

*Chadwick RW, George SE, Kohan MJ, et al. 1993. Potentiation of 2,6-dinitrotoluene genotoxicity in Fischer-344 rats by pretreatment with Aroclor 1254. Toxicology 80(2-3):153-171.

*Chakraborty D, Bhattacharyva A, Chatterjee J, et al. 1978. Biochemical studies on polychlorinated biphenyl toxicity in rats: Manipulation by vitamin C. Int J Vitam Nutr Res 48:22-31.

*Chan CH, Bruce G, Harrison B. 1994. Wet deposition of organochlorine pesticides and polychlorinated biphenyls to the Great Lakes. J Great Lakes Res 20(3):546-560.

Chan HM. 1998. A database for environmental contaminants in traditional foods in northern and Arctic Canada: development and applications. Food Addit Contam 15(2):127-134.

*Chan HM, El Khoury M, Sedgemore M, et al. 1996. Organochlorine pesticides and polychlorinated biphenyl congeners in ooligan grease: a traditional food fat of British Columbia first nations. J Food Comp Anal 9(1):32-42.

*Chan HM, Trifonopoulos M, Ing A, et al. 1999. Consumption of freshwater fish in Kahnawake: Risks and benefits. Environ Res 80:S213-S222.

*Chang KJ, Hsieh KH, Lee TP, et al. 1980. Studies on patients with polychlorinated biphenyl poisoning: 2. Determination of urinary coproporphyrin, uroporphyrin, γ-aminolevulinic acid and porphobilinogen. Res Commun Chem Pathol Pharmacol 30:547-554.

*Chang KJ, Hsieh KH, Lee TP, et al. 1981. Immunologic evaluation of patients with polychlorinated biphenyl poisoning: Determination of lymphocyte subpopulations. Toxicol Appl Pharmacol 61:58-63.

*Chang K-J, Hsieh K-H, Lee T-P, et al. 1982a. Immunologic evaluation of patients with polychlorinated biphenyl poisoning: Determination of phagocyte Fc and complement receptors. Environ Res 28:329-334.

*Chang K-J, Hsieh K-H, Tang S-Y, et al. 1982b. Immunologic evaluation of patients with polychlorinated biphenyl poisoning: Evaluation of delayed-type skin hypersensitivity response and its relation to clinical studies. J Toxicol Environ Health 9:217-223.

*Chao W-Y, Hsu C-C, Guo YL. 1997. Middle-ear disease in children exposed prenatally to polychlorinated biphenyls and polychlorinated dibenzofurans. Arch Environ Health 52(4):257-262.

*Chapin R, Stevens J, Hughes C, et al. 1996. Symposium overview; endocrine modulation of reproduction. Fundam Appl Toxicol 29:1-17.

*Chase KH, Wong O, Thomas D, et al. 1982. Clinical and metabolic abnormalities associated with occupational exposure to polychlorinated biphenyls (PCBs). J Occup Med 24:109-114.

*Chauhan KR, Kodavanti PRS, McKinney JD. 2000. Assessing the role of *ortho*-substitution on polychlorinated biphenyl binding to transthyretin, a thyroxine transport protein. Toxicol Appl Pharmacol 162:10-21.

*Cheek AO, Kow K, Chen J, et al. 1999. Potential mechanisms of thyroid disruption in humans: Interaction of organochlorine compounds with thyroid receptor, transthyretin, and thyroid-binding globulin. Environ Health Perspect 107(4):273-278.

*Chemfinder. 2000. Chlorodiphenyl (62% Cl) [37324-23-5]. http://www.chemfinder.com

*Chen LC, Berberian I, Koch B, et al. 1992. Polychlorinated and polybrominated biphenyl congeners and retinoid levels in rat tissues: Structure-activity relationships. Toxicol Appl Pharmacol 114:47-55.

*Chen M, Hong CS, Bush B, et al. 1988. Anaerobic biodegradation of polychlorinated biphenyls by bacteria from Hudson River sediments. Ecotoxicol Environ Saf 16:95-105.

*Chen PH, Luo ML, Wong CK, et al. 1982. Comparative rates of elimination of some individual polychlorinated biphenyls from the blood of PCB-poisoned patients in Taiwan. Food Chem Toxicol 20:417-425.

*Chen R-C, Tang S-Y, Miyata H, et al. 1985. Polychlorinated biphenyl poisoning: Correlation of sensory and motor nerve conduction, neurologic symptoms, and blood levels of polychlorinated biphenyls, quaterphenyls, and dibenzofurans. Environ Res 37:340-348.

*Chen Y-CJ, Yu M-LM, Rogan WJ, et al. 1994. A 6-year follow-up of behavior and activity disorders in the Taiwan Yu-chen children. Am J Public Health 84(3):415-421.

*Chevreuil M, Blanchard M, Teil MJ, et al. 1998. Polychlorobiphenyl behaviour in the water/sediment system of the Seine river, France. Water Res 32(4):1204-1212.

*Chia LG, Chu FL. 1984. Neurological studies on polychlorinated biphenyl (PCB)-poisoned patients. Am J Ind Med 5:117-126.

9. REFERENCES

*Chia L-G, Chu F-L. 1985. A clinical and electrophysiological study of patients with polychlorinated biphenyl poisoning. J Neurol Neurosurg Psychiatry 48:894-901.

*Chiarenzelli J, Scrudato R, Arnold G, et al. 1996. Volatilization of polychlorinated biphenyls from sediment during drying at ambient conditions. Chemosphere 33(5):899-911.

*Chiarenzelli J, Scrudato R, Bush B, et al. 1998. Do large-scale remedial and dredging events have the potential to release significant amounts of semivolatile compounds to the atmosphere? Environ Health Perspect 106:47-49.

*Chiarenzelli J, Scrudato R, Wunderlich M, et al. 1995. Photodecomposition of PCBs absorbed on sediment and industrial waste: Implications for photocatalytic treatment of contaminated solids. Chemosphere 31(5):3259-3272.

*Chiarenzelli JR, Scrudato RJ, Wunderlich ML, et al. 1997. PCB volatile loss and the moisture content of sediment during drying. Chemosphere 34(11):2429-2436.

*Chin Y-P, Weber WJ Jr. 1989. Estimating the effects of dispersed organic polymers on the sorption of contaminants by natural solids. 1. A predictive thermodynamic humic substance-organic solute interaction model. Environ Sci Technol 23:978-984.

*Chiou CT, Porter PE, Schmedding DW. 1983. Partition equilibria of nonionic organic compounds between soil organic matter and water. Environ Sci Technol 17:227-231.

*Choi PSK, Nack CH, Flinn JE. 1974. Distribution of polychlorinated biphenyls in an aerated biological oxidation wastewater treatment system. Bull Environ Contam Toxicol 11:12-17.

*Choksi NY, Kodavanti PR, Tilson HA, et al. 1997. Effects of polychlorinated biphenyls (PCBs) on brain tyrosine hydroxylase activity and dopamine synthesis in rats. Fundam Appl Toxicol 39(1):76-80.

*Chou SM, Miike T, Payne WM, et al. 1979. Neuropathy of "spinning syndrome" induced by prenatal intoxication with a PCB in mice. Ann NY Acad Sci 320:373-395.

Christensen ER, Lo CK. 1986. Polychlorinated biphenyls in dated sediments of Milwaukee Harbor, Wisconsin, USA. Environ Poll 12:217-232.

*Chu I, Lecavalier P, Valli T, et al. 1998a. Toxicity of polychlorinated biphenyl congeners in rats. In: Johansson N, Bergman A, Broman D, et al., ed. Organohalogen compounds. Akademitryck, Edsbruk: Vol. 37, 105-107.

*Chu I, Lecavalier P, Yagminas A, et al. 1999. Mixture effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin and polychlorinated biphenyl congeners in rats. Organohalogen Compounds 42:409-412.

*Chu I, Poon R, Yagminas A, et al. 1998b. Subchronic toxicity of PCB 105 (2,3,3',4,4'-pentachlorobiphenyl) in rats. J Appl Toxicol 18:285-292.

*Chu I, Villeneuve DC, Becking GC, et al. 1980. Short-term study of the combined effects of mirex, photomirex, and kepone with halogenated biphenyls in rats. J Toxicol Environ Health 6:421-432.

*Chu I, Velleneuve DC, Tagimnas A, et al. 1994. Subchronic toxicity of 3,3',4,4',5-pentachlorobiphenyl in the rat. Fundam Appl Toxicol 22:457-468.

9. REFERENCES

*Chu I, Villeneuve DC, Yagminas A, et al. 1995. Toxicity of PCB 77 (3,3',4,4'-tetrachlorobiphenyl) and PCB 118 (2,3',4,4',5-pentachlorobiphenyl) in the rat following subchronic dietary exposure. Fundam Appl Toxicol 26:282-292.

*Chu I, Villeneuve DC, Yagminas A, et al. 1996a. Toxicity of 2,2',4,4',5,5'-hexachlorobiphenyl in rats: Effects following a 90-day oral exposure. J Appl Toxicol 16(2):121-128.

*Chu I, Villeneuve DC, Yagminas A, et al. 1996b. Toxicity of 2,4,4'-trichlorobiphenyl in rats following 90-day dietary exposure. J Toxicol Environ Health 49(3):301-318.

*Chuang FW, Larson RA, Wessan N. 1995. Zero-valent iron promoted dechlorination of polychlorinated biphenyls. Environ Sci Technol 29(9):2460-2463.

*Chui VWD, Lam-Leung SY, Chan TC. 1991. Residues of polychlorinated biphenyls (PCBs) in fish, water and sediment from Shing Mun River. Biomed Environ Sci 4:399-408.

Clark DR Jr, Stafford CJ. 1981. Effects of DDE and PCB (Aroclor 1260) on experimentally poisoned female little brown bats (*myotis lucifugus*): lethal brain concentrations. J Toxicol Environ Health 7(6):925-934.

Clark T, Clark K, Paterson S, et al. 1988. Wildlife monitoring, modeling, and fugacity. Environ Sci Technol 22:120-127.

*Cleland GB, McElroy PJ, Sonstegard RA. 1989. Immunomodulation in C57BI/6 mice following consumption of halogenated aromatic hydrocarbon-contaminated coho salmon (*Oncorhynchus kisutch*) from Lake Ontario. J Toxicol Environ Health 27:477-486.

*Clevenger MA, Roberts SM, Lattin DL, et al. 1989. The pharmacokinetics of 2,2',5,5'-tetrachlorobiphenyl and 3,3',4,4'-tetrachlorobiphenyl and its relationship to toxicity. Toxicol Appl Pharmacol 100:315-327.

*Clevenger TE, Hemphill DD, Roberts K, et al. 1983. Chemical composition and possible mutagenicity of municipal sludges. J Water Pollut Control Fed 55(12):1470-1475.

*Clewell HJ III, Andersen M. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

Cobb GP, Wood PD. 1997. PCB concentrations in eggs and chorioallantoic membranes of loggerhead sea turtles (*caretta caretta*) from the Cape Romain National Wildlife Refuge. Chemosphere 34(3):539-549.

Cobb GP, Wood PD, O'Quinn M. 1997. Polychlorinated biphenyls in eggs and chorioallantoic membranes of American alligators (*alligator mississippiensis*) from coastal South Carolina. Environ Toxicol Chem 16(7):1456-1462.

Cocco P, Kazerouni N, Zahm SH. 2000. Cancer mortality and environmental exposure to DDE in the United States. Environ Health Perspect 108(1):1-4.

*Cogliano VJ. 1998. Assessing the cancer risk from environmental PCBs. Environ Health Perspect 106(6):317-323.

Cole DC, Kearney J, Ryan JJ, et al. 1997. Plasma levels and profiles of dioxin and dioxin-like compounds in Ontario Great Lakes anglers. Chemosphere 34(5-7):1401-1409.

*Collins WT, Capen CC. 1980a. Ultrastructural and functional alterations of the rat thyroid gland produced by polychlorinated biphenyls compared with iodide excess and deficiency, and thyrotropin and thyroxine administration. Virchow Arch B Cell Pathol 33:213-231.

*Collins WT, Capen CC. 1980b. Biliary excretion of ^{125}I-thyroxine and fine structural alterations in the thyroid glands of Gunn rats fed polychlorinated biphenyls (PCB). Lab Invest 43:158-164.

*Collins WT, Capen CC. 1980c. Fine structural lesions and hormonal alterations in thyroid glands of perinatal rats exposed *in utero* and by the milk to polychlorinated biphenyls. Am J Pathol 99:125-142.

*Collins WT, Capen CC, Kasza L, et al. 1977. Effect of polychlorinated biphenyl (PCB) on the thyroid gland of rats: Ultrastructural and biochemical investigations. Am J Pathol 89:119-136.

*Colombi A, Maroni M, Ferioli A, et al. 1982. Increase in urinary porphyrin excretion in workers exposed to polychlorinated biphenyls. J Appl Toxicol 2:117-121.

*Condon SK. 1983. Personal communications, August 25 and 28, 1983. Commonwealth of Massachusetts Department of Public Health.

*Connor K, Ramamootrhy K, Moore M, et al. 1997. Hydroxylated polychlorinated biphenyls (PCBs) as estrogens and antiestrogens: Structure-activity relationships. Toxicol Appl Pharmacol 145:111-123.

*Connor K, Safe S, Jefcoate CR, et al. 1995. Structure-dependent induction of CYP2B by polychlorinated biphenyl congeners in female Sprague-Dawley rats. Biochem Pharmacol 50(11):1913-1920.

*Conolly RB, Szabo S, Jaeger RJ. 1979. Vinylidene fluoride: Acute hepatotoxicity in rats pretreated with PCB or phenobarbital. Proc Soc Exp Biol Med 162:163-169.

*Cooke PS, Zhao Y-D, Hansen LG. 1996. Neonatal polychlorinated biphenyl treatment increases adult testis size and sperm production in the rat. Toxicol Appl Pharmacol 136:112-117.

*Cordle F, Locke R, Springer J. 1982. Risk assessment in a federal regulatory agency: An assessment of risk associated with the human consumption of some species of fish contaminated with polychlorinated biphenyls (PCBs). Environ Health Perspect 45:171-182.

*Corey DA, Juarez de Ku LM, Bingman VP, et al. 1996. Effects of exposure to polychlorinated biphenyl (PCB) from conception on growth, and development of endocrine, neurochemical, and cognitive measures in 60 day old rats. Growth Dev Aging 60:131-143.

*Coristine S, Haffner GD, Ciborowski JJH, et al. 1996. Elimination rates of selected di-*ortho*, mono-*ortho*, and non-*ortho* substituted polychlorinated biphenyls in rainbow trout (*oncorhynchus mykiss*). Environ Toxicol Chem 15(8):1382-1387.

Corrigan FM, Murray L, Wyatt CL, et al. 1998. Diorthosubstituted polychlorinated biphenyls in caudate nucleus in Parkinson's disease. Exp Neurol 150(2):339-42.

9. REFERENCES

*Cotham WE, Bidleman TF. 1995. Polycyclic aromatic hydrocarbons and polychlorinated biphenyls in air at an urban and a rural site near Lake Michigan. Environ Sci Technol 29(11):2782-2789.

*Courval JM, DeHoog JV, Holzman CB, et al. 1996. Fish consumption and other characteristics of reproductive-aged Michigan anglers-a potential population for studying the effects of consumption of Great Lakes fish on reproductive health. Toxicol Ind Health 12(3-4):347-359.

*Courval JM, DeHoog JV, Stein AD, et al. 1999. Sport-caught fish consumption and conception delay in licensed Michigan anglers. Environ Res 80:S183-S188.

*Cousins IT, Jones KC. 1998. Air-soil exchange of semi-volatile organic compounds (SOCs) in the UK. Environ Pollut 102:105-118.

*Cousins IT, Beck AJ, Jones KC. 1999. A review of the processes involved in the exchange of semi-volatile organic compounds (SVOC) across the air-soil interface. Sci Total Environ 228:5-24.

*Cousins IT, Hartlieb N, Teichmann C, et al. 1997. Measured and predicted volatilisation fluxes of PCBs from contaminated sludge-amended soils. Environ Pollut 97(3):229-238.

*Crawford DW, Bonnevie NL, Wenning RJ. 1995. Sources of pollution and sediment in Newark Bay, New Jersey. Ecotoxicol Environ Saf 36:85-100.

Creaser CS, Fernandes AR. 1986. Background levels of polychlorinated biphenyls in British soils. Chemosphere 15:499-508.

Creaser CS, Krokos F, Startin JR. 1992. Analytical methods for the determination of non-ortho substituted chlorobiphenyls: A review. Chemosphere 25(12):1981-2008.

*Crisp T, Clegg E, Cooper R, et al. 1998. Environmental endocrine disruption: An effects assessment and analysis. Environ Health Perspect 106(Suppl 1):11-56.

*CRITFC. 1994. A fish consumption survey of the Umatilla, Nez Perce, Yakima and Warm springs tribes of the Columbia River basin. Portland, OR: Columbia River Inter-Tribal Fish Commission.

*Crofton KM, Rice DC. 1999. Low-frequency hearing loss following perinatal exposure to 3,3',4,4',5-pentachlorobiphenyl (PCB 126) in rats. Neurotoxicol Teratol 21(3):299-301.

*Cross JN, Hardy JT, Hose JE, et al. 1987. Contaminant concentrations and toxicity of sea-surface microlayer near Los Angeles, California. Mar Environ Res 23:307-323.

*Cullen AC, Vorhees DJ, Altshul LM. 1996. Influence of harbor contamination on the level and composition of polychlorinated biphenyls in produce in Greater New Bedford, Massachusetts. Environ Sci Technol 30(5):1581-1588.

Cunningham PA, Smith SL,Tippett JP, et al. 1994. A national fish consumption advisory data base: A step toward consistency. Fisheries 19:14-23.

*Curley A, Burse VW, Grim ME, et al. 1971. Polychlorinated biphenyls: Distribution and storage in body fluids and tissues of Sherman rats. Environ Res 4:481-495.

*Currado GM, Harrad S. Air-to-grass transfer of PCBs. Organohalogen Compounds 41:409-411.

Custer TW, Sparks DW, Sobiech SA, et al. 1996. Organochlorine accumulation by sentinel mallards at the Winston-Thomas sewage treatment plant, Bloomington, Indiana. Arch Environ Contam Toxicol 30(2):163-169.

*Czaja K, Ludwicki JK, Goralczyk K, et al. 1997a. Effect of age and number of deliveries on mean concentration of organochlorine compounds in human breast milk in Poland. Bull Environ Contam Toxicol 59:407-413.

*Czaja K, Ludwicki JK, Goralczy K, et al. 1997b. Organochlorine in pesticides, HCB, and PCBs in human milk in Poland. Bull Environ Contam Toxicol 58:769-775.

*Czaja K, Ludwicki JK, Goralczyk K, et al. 1999a. Effect of changes in excretion of persistent organochlorine compounds with human breast milk on related exposure of breast-fed infants. Arch Environ Contam Toxicol 36:498-503.

*Czaja K, Ludwicki JK, Robson MG, et al. 1999b. Concentrations of persistent organochlorine compounds in the placenta and milk of the same women. Prepr Ext Abst Div Environ Chem Am Chem Soc 39(1):150-152.

*Czygan P, Greim H, Garro AJ, et al. 1973. Microsomal metabolism of dimethylnitrosamine and the cytochrome P-450 dependency of its activation to a mutagen. Cancer Res 33:2983-2986.

*Dahl P, Lindstrom G, Wiberg K, et al. 1995. Absorption of polychlorinated biphenyls, dibenzo-p-dioxins and dibenzofurans by breast-fed infants. Chemosphere 30(12):2297-2306.

Daly H, Darvill T, Lonky E, et al. 1996. Behavioral effects of prenatal and adult exposure to toxic chemicals found in Lake Ontario fish: Two methodological approaches. Toxicol Ind Health 12:419-426.

*Daly JW, Jerina DM, Witkop B. 1972. Arene oxides and the NIH shift: the metabolism, toxicity and carcinogenicity of aromatic compounds. Experientia 28:1129-1149.

Danse IR, Jaeger RJ, Kava R, et al. 1997. Position paper of the American Council on Science and Health: Public health concerns about environmental polychlorinated biphenyls (PCBs). Ecotoxicol Environ Saf 38(2):71-84.

*Dar E, Kanarek MS, Anderson HA, et al. 1992. Fish consumption and reproductive outcomes in Green Bay, Wisconsin. Environ Res 59(1):189-201.

*Darnerud PO, Morse D, Klasson-Wehler E, et al. 1996a. Binding of a 3,3', 4,4'-tetrachlorobiphenyl (CB-77) metabolite to fetal transthyretin and effects on fetal thyroid hormone levels in mice. Toxicology 106(1-3):105-114.

Darnerud PO, Sinjari T, Jonsson CJ. 1996b. Foetal uptake of coplanar polychlorinated biphenyl (PCB) congeners in mice. Pharmacol Toxicol 78(3):187-192.

*Daston GP, Gooch JW, Breslin WJ, et al. 1997. Environmental estrogens and reproductive health: A discussion of the human and environmental data. Reprod Toxicol 1(4):465-481.

Datta S, Hansen L, McConnell L, et al. 1998b. Pesticides and PCB contaminants in fish and tadpoles from the Kaweah River basin, California. Bull Environ Contam Toxicol 60:829-836.

*Datta S, McConnell LL, Baker JE, et al. 1998a. Evidence for atmospheric transport and deposition of polychlorinated biphenyls to the Lake Tahoe basin, California-Nevada. Environ Sci Technol 32(10):1378-1385.

*Datta S, Ohyama K, Dunlap DY, et al. 1999. Evidence for organochlorine contamination in tissues of salmonids in Lake Tahoe. Ecotoxicol Environ Saf 42:94-101.

*David M, Brondyk LM, Sonzogni WC. 1994. Distribution of PCB congeners in Sheboygan River (Wisconsin) sediments. J Great Lakes Res 20(3):510-522.

*Davidorf FH, Knupp JA. 1979. Epidemiology of ocular melanoma: Incidence and geographic relationship in Ohio (1967-1977). Ohio State Med J 75:561-564.

Davis DL, Bradlow HL. 1995. Can environmental estrogens cause breast cancer? Sci Am (October 1995):166-172.

*Davis D, Safe S. 1989. Dose-response immunotoxicities of commercial polychlorinated biphenyls (PCBs) and their interaction with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Toxicol Lett 48:35-43.

*Davis D, Safe S. 1990. Immunosuppressive activities of polychlorinated biphenyls in C57BL/6N mice: Structure-activity relationships as Ah receptor agonists and partial antagonists. Toxicology 63:97-111.

Davis DL, Bradlow HL, Wolff M, et al. 1993. Medical hypothesis: Xenoestrogens as preventable causes of breast cancer. Environ Health Perspect 101(5):372-377.

*De Filippis P, Chianese A, Pochetti F. 1997. Removal of PCBs from mineral oils. Chemosphere 35(8):1659-1667.

De Guise S, Martineau D, Beland P, et al. 1995. Possible mechanisms of action of environmental contaminants on St. Lawrence beluga whales (*delphinapterus leucas*). Environ Health Perspect Suppl 103(4):73-77.

*de Haan LHJ, Halfwerk S, Hovens SEL, et al. 1995. Inhibition of intercellular communication and induction of ethoxyresorufin-*O*-deethylase activity by polychlorobiphenyls, dibenzo-*p*-dioxins and dibenzofurans in mouse hepa1c1c7 cells. Environ Toxicol Pharmacol 1(1):27-37.

De Haan LHJ, Simons JFA, Bos AT, et al. 1994. Inhibition of intercellular communication by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and dioxin-like PCBs in mouse hepatoma cells (Hepa1c1c7): Involvement of the Ah receptor. Toxicol Appl Pharmacol 129:283-293.

*Dekoning EP, Karmaus W. 2000. PCB exposure *in utero* and via breast milk. A review. J Expo Anal Environ Epidemiol 10:285-293.

*Dellinger, JA, Gerstenberger, SL, Hansen, LK, et al. 1997. Ojibwa health study: Assessing the health risks from consuming contaminated Great Lakes fish. Health Conference '97 Great Lakes and St. Lawrence. Montreal, Quebec, Canada. (As cited in Johnson et al. 1998).

*Dellinger JA, Meyers RM, Gebhardt KJ, et al. 1996. The Ojibwa health study: Fish residue comparisons for Lakes Superior, Michigan, and Huron. Toxicol Ind Health 12(3-4):393-402.

9. REFERENCES

*Deml E, Oesterle D. 1982. Sex-dependent promoting effect of polychlorinated biphenyls on enzyme-altered islands induced by diethylnitrosamine in rat liver. Carcinogenesis 3:1449-1453.

*Deml E, Oesterle D. 1987. Dose-response of promotion by polychlorinated biphenyls and chloroform in rat liver foci bioassay. Arch Toxicol 60:209-211.

*Deml E, Oesterle D, Wiebel FJ. 1983. Benzo[a]pyrene initiates enzyme-altered islands in the liver of adult rats following single pretreatment and promotion with polychlorinated biphenyls. Cancer Lett 19:301-304.

Denomme MA, Bandiera S, Lambert I, et al. 1983. Polychlorinated biphenyls as phenobarbitone-type inducers of microsomal enzymes: Structure-activity relationships for a series of 2,4-dichloro-substituted congeners. Biochem Pharmacol 32:2955-2963.

*DeRosa C, Richter P, Pohl H, et al. 1998. Environmental exposures that affect the endocrine system: Public health implications. J Toxicol Environ Health, Part B 1:3-26.

*Desaulniers D, Poon R, Phan W, et al. 1997. Reproductive and thyroid hormone levels in rats following 90-day dietary exposure to PCB 28 (2,4,4'-trichlorobiphenyl) or PCB 77 (3,3'4,4'-tetrachlorobiphenyl). Toxicol Ind Health 13(5):627-638.

Desaulniers D, Leingartner K, Wade M., et al. 1999. Effects of acute exposure to PCBs 126 and 153 on anterior pituitary and thyroid hormones and FSH isoforms in adult Sprague-Dawley male rats. Toxicol Sci 47:158-169.

*des Rosiers PE, Lee A. 1986. PCBs fires: Correlation of chlorobenzene isomer and PCB homolog contents of PCB fluids with PCDD and PCDF contents of soot. Chemosphere 15:1313-1323.

DeVault DS, Clark JM, Lahvis G, et al. 1988. Contaminants and trends in fall run coho salmon. J Great Lakes Res 14:23-33.

*De Voogt P, Brinkman UA. 1989. Production, properties and usage of polychlorinated biphenyls. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd ed. Amsterdam, The Netherlands: Elsevier Science Publishers, 3-45.

De Voogt P, Klamer JC, Govers H. 1986. Simultaneous clean up and fractionation of organochlorine compounds by adsorption chromatography. J Chromatogr 363:407-411.

Devoto E, Fiore BJ, Millikan R, et al. 1997. Correlations among human blood levels of specific PCB congeners and implications for epidemiologic studies. Am J Ind Med 32(6):606-613.

*Dewailly E, Ayotte P, Bruneau S, et al. 1993. Inuit exposure to organochlorines through the aquatic food chain in Arctic Quebec. Environ Health Perspect 101(7):618-620.

*Dewailly E, Ayotte P, Bruneau S, et al. 2000. Susceptibility to infections and immune status in Inuit infants exposed to organochlorines. Environ Health Perspect 108(3):205-211.

Dewailly E, Ayotte P, Laliberte C, et al. 1996. Polychlorinated biphenyl (PCB) and dichlorodiphenyl dichloroethylene (DDE) concentrations in the breast milk of women in Quebec. Am J Public Health 86(9):1241-1246.

*Dewailly E, Mulvad G, Pedersen HS, et al. 1999. Concentration of organochlorines in human brain, liver, and adipose tissue autopsy samples from Greenland. Environ Health Perspect 107(10):823-828.

*Dewailly E, Ryan JJ, Laliberte C, et al. 1994. Exposure of remote maritime populations to coplanar PCBs. Environ Health Perspect Suppl 102(1):205-209.

*Dewailly E, Weber JP, Gingras S, et al. 1991. Coplanar PCBs in human milk in the province of Quebec, Canada: Are they more toxic than dioxin for breast fed infants? Bull Environ Contam Toxicol 47:491-498.

*Dickhut RM, Gustafson KE. 1995. Atmospheric inputs of selected polycyclic aromatic hydrocarbons and polychlorinated biphenyls to southern Chesapeake Bay. Mar Pollut Bull 30(6):385-396.

*DiGiovanni J, Viaje A, Berry DL, et al. 1977. Tumor-initiating ability of 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin (TCDD) and Aroclor 1254 in the two-stage system of mouse skin carcinogenesis. Bull Environ Contam Toxicol 18:552-557.

*Dikshith TSS, Rockwood W, Abraham R, et al. 1975. Effects of a polychlorinated biphenyl (Aroclor 1254) on rat testis. Exp Mol Pathol 22:376-385.

Dilling WL, Miracle GE, Boggs GU. 1983. Tropospheric phototransformation rates of 2-, 3-, and 4-chlorobiphenyls. 186th ACS National Meeting. [Abstract]

*Djordjevic MV, Hoffman D, Fan J, et al. 1994. Assessment of chlorinated pesticides and polychlorinated biphenyls in adipose breast tissue using a supercritical fluid extraction method. Carcinogenesis 15(11):2581-2585.

*Dluhy, RC. 2000. The adrenal cortex in hypothyroidism. In: Braverman LE, Utiger RD, ed. Werner and Ingbar's the thyroid: A fundamental and clinical text. Philadelphia, PA: Lippincott-Raven, 815-819.

*DOI. 1986. Polychlorinated biphenyl hazards to fish, wildlife, and invertebrates: A synoptic review. U.S. Department of the Interior, Fish and Wildlife Service. Biological Report 85(1.7).

*DOI. 1996. Planar PCB hazards to fish, wildlife, and invertebrates: A synoptic review. Washington, DC: U.S. Department of the Interior, National Biological Service. Biological Report 31.

*Donaldson GM, Schutt JL, Hunter P. 1999. Organochlorine contamination in bald eagle eggs and nestlings from the Canadian Great Lakes. Arch Environ Contam Toxicol 36:70-80.

*Dorgan JF, Brock JW, Rothman N, et al. 1999. Serum organochloride pesticides and PCBs and breast cancer risk: results from a prospective analysis (USA). Cancer Causes Control 10:1-11.

*Dowling DN, Pipke R, Dwyer DF. 1993. A DNA module encoding *bph* genes for the degradation of polychlorinated biphenyls (PCBs). FEMS Microbiol Lett 113(2):149-154.

*Downs TJ, Cifuentes-Garcia E, Suffet IM. 1999. Risk screening for exposure to groundwater pollution in a wastewater irrigation district of the Mexico City region. Environ Health Perspect 107(7):553-561.

*Draper WM, Wijekoon D, Stephens RD. 1991. Speciation and quantitation of aroclors in hazardous wastes based on PCB congener data. Chemosphere 22(1-2):147-163.

9. REFERENCES

*Drotman DP. 1981. Human exposure to PCBs in southern Idaho: Internal report. Atlanta, GA: Centers for Disease Control. EPA 79-105-2.

*Duarte-Davidson R, Jones KC. 1994. Polychlorinated biphenyls (PCBs) in the UK population: estimated intake, exposure and body burden. Sci Total Environ 151:131-152.

*Dubois M, Pfohl-Leszkowicz A, Grosse Y, Kremers P. 1995. DNA adducts and P450 induction in human, rat and avian liver cells after exposure to polychlorobiphenyls. Mutat Res 345(3-4):181-190.

*Duebelbeis DO, Pieczonka G, Kapila S, et al. 1989. Application of a dual column reaction chromatography system for confirmatory analysis of polychlorinated biphenyl congeners. Chemosphere 19:143-148.

*Duggan RE, Corneliussen PE, Duggan MB, et al. 1983. Pesticide residue levels in foods in the United States from July 1, 1969 to June 30, 1976. Washington, DC: Food and Drug Administration, 10-14.

*Duignan DB, Sipes IG, Ciaccio PJ, et al. 1988. The metabolism of xenobiotics and endogenous compounds by the constitutive dog liver cytochrome P450 PBD-2. Arch Biochem Biophys 267:294-304.

*Duignan DB, Sipes IG, Leonard TB, et al. 1987. Purification and characterization of dog hepatic cytochrome P-450 isozyme responsible for the metabolism of 2,2',4,4',5,5'-hexachlorobiphenyl. Arch Biochem Biophys 225:290-303.

*Duinker JC, Hillebrand MTJ. 1979. Behaviour of PCB, pentachlorobenzene, hexachlorobenzene, alpha-HCH, gamma-HCH, beta-HCH, dieldrin, endrin and p,p'-DDD in the Rhine-Meuse estuary and the adjacent coastal area. Neth J Sea Res 13:256-281.

Duinker JC, Schulz DE, Petrick G. 1988. Multidimensional gas chromatography with electron capture detection for the determination of toxic congeners in polychlorinated biphenyl mixtures. Anal Chem 60:478-482.

*Dunnivant FM, Elzerman AW. 1988. Aqueous solubility and Henry's law constant data for PCB congeners for evaluation of quantitative structure-property relationships (QSPRs). Chemosphere 17:525-541.

*Dunnivant FM, Eisenman AW, Jurs PC, et al. 1992. Quantitative structure-property relationships for aqueous solubilities and Henry's law constants of polychlorinated biphenyls. Environ Sci Technol 26:1567-1573.

*Durell GS, Lizotte RD Jr. 1998. PCB levels at 26 New York City and New Jersey WPCPs that discharge to the New York/New Jersey Harbor estuary. Environ Sci Technol 32(8):1022-1031.

*Durfee RL. 1976. Production and usage of PCB's in the United States. In: Proceedings of the National Conference on Polychlorinated Biphenyls, Chicago, 1975. EPA-560/6-75-004. Washington, DC: U.S. Environmental Protection Agency, 103-107.

Eduljee G, Badsha K, Price L. 1985. Environmental monitoring for PCB and heavy metals in the vicinity of a chemical waste disposal facility-I. Chemosphere 14:1371-1382.

Eduljee G, Badsha K, Scudamore N. 1986. Environmental monitoring for PCB and trace metals in the vicinity of a chemical waste disposal facility-II. Chemosphere 15:81-93.

9. REFERENCES

*Eggold BT, Amrhein JF, Coshun MA. 1996. PCB accumulation by salmonine smolts and adults in Lake Michigan and its tributaries and its effect on stocking policies. J Great Lakes Res 22(2):403-413.

*Eisenreich SJ, Baker JE, Franz T, et al. 1992. Atmospheric deposition of hydrophobic organic contaminants to the Laurentian Great Lakes. In: Schnoor JL, ed. Fate of pesticides and chemicals in the environment. New York, NY: John Wiley & Sons, Inc., 51-78.

*Eisenreich SJ, Capel PD, Looney BB. 1983. PCB dynamics in Lake Superior water. In: Mackay D, ed. Physical behavior of PCBs in the Great Lakes. Ann Arbor, MI: Ann Arbor Science Press, 181-211.

Eisenreich SJ, Capel PD, Robbins JA, et al. 1989. Accumulation and diagnosis of chlorinated hydrocarbons in lacustrine sediments. Environ Sci Technol 23:1116-1126.

*Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15:30-38.

*Elder VA, Proctor BL, Hites RA. 1981. Organic compounds found near dump sites in Niagara Falls, New York. Environ Sci Technol 15(10):1237-1243.

*Elliott JE, Martin PA. 1998. Chlorinated hydrocarbon contaminants in grebes and seaducks wintering on the coast of British Columbia, Canada: 1988-1993. Environ Monit Assess 53:337-362.

Elliott JE, Norstrom RJ, Smith GE. 1996. Patterns, trends, and toxicological significance of chlorinated hydrocarbon and mercury contaminants in bald eagle eggs from the Pacific Coast of Canada, 1990-1994. Arch Environ Contam Toxicol 31(3):354-367.

*Elo O, Vuojolahti P, Janhunen H, et al. 1985. Recent PCB incidents in Finland. Environ Health Perspect 60:315-319.

*Emmett EA. 1985. Polychlorinated biphenyl exposure and effects in transformer repair workers. Environ Health Perspect 60:185-192.

Emmett EA. 1986. Toxic responses of the skin. In: Casarett and Doull's toxicology: The basic science of poisons. 3rd ed. New York, NY: Macmillan Publishing Company, 427-428.

*Emmett EA, Maroni M, Jeffery JS, et al. 1988b. Studies of transformer repair workers exposed to PCBs: II. Results of clinical laboratory investigations. Am J Ind Med 14:47-62.

*Emmett EA, Maroni M, Schmith JM, et al. 1988a. Studies of transformer repair workers exposed to PCBs: I. Study design, PCB concentrations, questionnaire, and clinical examination results. Am J Ind Med 13:415-427.

*Endicott D, Kreis RG, Mackelburg L, et al. 1998. Modeling PCB bioaccumulation by the zebra mussel (*dreissena polymorpha*) in Saginaw Bay, Lake Huron. J Great Lakes Res 24(2):411-426.

EPA. 1973a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 136, Method 625.

EPA. 1973b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 136, Method 608.

9. REFERENCES

EPA. 1975a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.24.

EPA. 1975b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.32.

*EPA. 1976a. PCBs in the United States: Industrial use and environmental distribution. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. NTIS PB252012.

EPA. 1976b. Review of PCB levels in the environment. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA 560/7/76-001. NTIS PB253735.

EPA. 1977a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 129.4.

*EPA. 1977b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 129.105.

EPA. 1977c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 750.39.

EPA. 1977d. U.S. Environmental Protection Agency. Toxic pollutants effluent standards. Code of Federal Regulations. 40 CFR 129.

EPA. 1978a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4.

EPA. 1978b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 750.11.

*EPA. 1978c. U.S. Environmental Protection Agency. Support document: Draft voluntary environmental impact statement for polychlorinated biphenyls (PCBs) manufacturing, processing, distribution in commerce and use ban regulation (Section 6(e) of TSCA).

*EPA. 1979a. U.S. Environmental Protection Agency. Polychlorinated biphenyls (PCBs) in manufacturing, processing, distribution in commerce, and use prohibition; Final rule. Federal Register 44:31514-31568.

EPA. 1979b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 401.15.

EPA. 1979c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 257. 3-5.

EPA. 1979d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 750.31.

*EPA. 1979e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 761.70

*EPA 1979f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 761.60-761.65.

*EPA. 1979g. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 761.20.

*EPA. 1979h. Water-related environmental fate of 129 priority pollutants, Vol. II. Washington, DC: U.S. Environmental Protection Agency, 40-2 to 43-10. EPA 440/4-79-029a.

*EPA. 1979i. Water-related environmental fate of 129 priority pollutants, Vol. I. Washington, DC: U.S. Environmental Protection Agency, 36-1 to 36-18. EPA 440/4-79-029a.

*EPA. 1980a. Hazard waste generation and commercial hazardous waste management capacity: An assessment, SW-894. Washington, DC: U.S. Environmental Protection Agency, D-4.

*EPA. 1980b. Ambient water quality criteria for polychlorinated biphenyls. Washington, DC: U.S. Environmental Protection Agency, Criteria and Standards Division, Office of Water Regulations and Standards. EPA 440/5-80-068.

EPA. 1980c. U.S. Environmental Protection Agency. Chemical imports and exports. Code of Federal Regulations. 40 CFR 707.20.

EPA. 1980d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261 App. IX.

EPA. 1980e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 707.60.

*EPA. 1980f. Toxicity of the polychlorinated biphenyl Aroclor 1016 to mink. Duluth, MN: U.S. Environmental Protection Agency, Environmental Research Laboratory. EPA-600 3-80-033.

*EPA. 1981. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 413.02.

*EPA. 1982a. Test methods. Methods for organic chemical analysis of municipal and industrial wastewater. Cincinnati, OH: U.S Environmental Protection Agency, Office of Research and Development, Environmental Monitoring and Support Laboratory, 608-1 to 608-11; 625-1 to 625-12. EPA 600/4-82-057.

*EPA. 1982b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 423 App. A.

EPA. 1982c. Polychlorinated biphenyls in human adipose tissue and mother's milk. Washington, DC: U.S. Environmental Protection Agency. PB83-253179.

*EPA. 1983a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 433.11.

EPA. 1983b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 270.10.

*EPA. 1983c. Environmental transport and transformation of polychlorinated biphenyls. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances. EPA-560/5-83-025. PB84-142579.

EPA. 1984a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 125.

EPA. 1984b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 704.43.

EPA. 1984c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 704.45.

*EPA. 1984d. Intrauterine exposure of humans to PCBs (polychlorinated biphenyls): Newborn effects. Duluth, MN: U.S. Environmental Protection Agency. EPA 600/3-84-060. NTIS PB84-188887.

EPA. 1985a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.50.

*EPA. 1985b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

9. REFERENCES

*EPA. 1985c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 797.

EPA. 1985d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 798.5265.

EPA. 1986a. Broad scan analysis of the FY82 national human adipose tissue survey specimens. Volume III - Semi-volatile organic compounds. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA 560/5-86-037.

*EPA. 1986b. Method 8080: Organochlorine pesticides and PCB. In: Test methods for evaluating solid waste. SW-846. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, 8080-1 to 8080-27.

EPA. 1986c. Development of advisory levels for polychlorinated biphenyls (PCBs) cleanup. Washington, DC: U.S. Environmental Protection Agency. EPA 600/6-86-02.

EPA. 1986d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3.

EPA. 1986e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 403 App. B.

EPA. 1986f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 403, App. B.

EPA. 1986g. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 286.6.

EPA. 1986h. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.50.

*EPA. 1986i. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.42.

EPA. 1986j. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.42.

EPA. 1986k. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.5.

*EPA. 1987a. U.S. Environmental Protection Agency. Statement of work for organics analyses, multi-media, multiconcentration. U.S. EPA Contract Laboratory Program. Revised 8/87.

EPA. 1987b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264 App. IX.

*EPA. 1987c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.32.

*EPA. 1987d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268 App. III.

EPA. 1987e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 795.120.

*EPA. 1987f. Method 525.1: Determination of organic compounds in drinking water by liquid-solid extraction and capillary column gas chromatography/mass spectrometry. In: Methods for the determination of organic compounds in drinking water. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory. EPA-600/4-88/039.

EPA. 1987g. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.32.

EPA. 1987h. U.S. Environmental Protection Agency. Toxic chemical release reporting: Community right-to-know. Specific toxic chemical listings. chemicals and chemical categories to which this part applies. Code of Federal Regulations. 40 CFR 372.65.

*EPA. 1988a. Drinking water criteria document for polychlorinated biphenyls (PCBs). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. ECAO-CIN-414.

*EPA. 1988b. U.S. Environmental Protection Agency. Method 608: Organochlorine pesticides and PCBs. Code of Federal Regulations. 40 CFR 136, App. A, 354-374.

*EPA. 1988c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR Part 761.

EPA. 1988d. U.S. Environmental Protection Agency. Toxic chemical release reporting: Community right-to-know. Code of Federal Regulations. 40 CFR 372.

*EPA. 1988e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 148.12.

EPA. 1988f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261 App. VIII.

EPA. 1988g. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.43.

EPA. 1988h. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

EPA. 1988i. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 795.54.

*EPA. 1988j. Guidance for conducting remedial investigations and feasibility studies under CERCLA (Interim Final). U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. EPA/540/G-89/004.

EPA. 1989a. Interim methods for development of inhalation reference doses. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA 600/8-88-066F.

EPA. 1989b. Drinking water regulations and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Drinking Water.

*EPA. 1989c. Methods for the determination of organic compounds in drinking water. Method No. 505, 508 and 508A. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development, Environmental Monitoring Systems Laboratory. EPA/600/4-88-039.

*EPA. 1989d. Guidance on preparing Superfund decision documents: The proposed plan, the record of decision, explanation of significant differences, the record of decision amendment. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. NTIS PB91-921256

EPA. 1990a. Drinking water criteria document for polychlorinated biphenyls (PCBs). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. ECAO-CIN-414.

EPA. 1990b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.8.

EPA. 1990c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.2.

EPA 1990d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 761.80.

*EPA. 1990e. Guidance on remedial actions for Superfund sites with PCB contamination. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. EPA 540/G-90/007.

EPA. 1990f. U.S. Environmental Protection Agency. Standards of performance for volatile organic compounds (VOC) emissions from synthetic organic chemical manufacturing industry (SOCMI) distillation operation. Code of Federal Regulations. 40 CFR 60.667.

*EPA. 1990g. Interim methods for development of inhalation reference concentrations. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA 600/8-90/066A.

*EPA. 1991a. Workshop report on toxicity equivalency factors for polychlorinated biphenyl congeners. Risk Assessment Forum. Washington, DC: U.S. Environmental Protection Agency.

*EPA. 1991b. U.S. Environmental Protection Agency. National primary drinking water regulations--synthetic organic chemicals and inorganic chemicals; monitoring for unregulated contaminants; National primary drinking water regulations implementations; National secondary drinking water regulations. 40 CFR parts 141, 142, and 143. Federal Register 58:3526-3597.

EPA. 1991c. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.61.

EPA. 1991d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 142.62.

EPA. 1991e. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 258.20.

EPA. 1991f. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266 App. VII.

EPA. 1991g. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268 App. Vll.

EPA. 1991h. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 131.61.

EPA. 1991i. Risk assessment guidance for Superfund. Volume 1: Human health evaluation manual (part B). Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. NTIS PB92-963339.

EPA. 1992a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.45.

EPA. 1992b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 279.10.

*EPA. 1992c. National study of chemical residues in fish. Volume I. U.S. Environmental Protection Agency. EPA 823-R-92-008a.

EPA. 1992d. U.S. Environmental Protection Agency. Land disposal restrictions. Prohibitions on storage of restricted wastes. Code of Federal Regulations. 40 CFR 268.50.

EPA. 1992e. U.S. Environmental Protection Agency. National primary drinking water regulations. Maximum contaminant level goals for organic contaminants. Code of Federal Regulations. 40 CFR 141.50

EPA. 1992f. U.S. Environmental Protection Agency. Guidelines for exposure assessment; Notice. Federal Register 57(104):22888.

EPA. 1993a. U.S. Environmental Protection Agency. Federal Register. 40 FR 20802.

EPA. 1993b. U.S. Environmental Protection Agency. Federal Register. 58 FR 65622-65632.

EPA. 1993c. U.S. Environmental Protection Agency. Federal Register. 58 FR 60970-60976.

EPA. 1993d. U.S. Environmental Protection Agency. Federal Register. 58 FR 54702-54810.

EPA. 1993e. U.S. Environmental Protection Agency. Federal Register. 58 FR 54836-54862.

EPA. 1993f. U.S. Environmental Protection Agency. Federal Register. 58 FR 48092-48204.

EPA. 1993g. U.S. Environmental Protection Agency. Federal Register. 58 FR 46052-46056.

*EPA. 1993h. Guidance for assessing chemical contaminant data for use in fish advisories. U.S. Environmental Protection Agency, Office of Water. EPA 823-R-93-002.

EPA. 1994a. U.S. Environmental Protection Agency. Federal Register. 59 FR 15968-16039.

EPA. 1994b. U.S. Environmental Protection Agency. Federal Register. 59 FR 15504-15571.

EPA. 1994c. Drinking water regulations and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water.

EPA. 1994d. U.S. Environmental Protection Agency. Disposal of polychlorinated biphenyls. Federal Register. 59 FR 62788-62887.

*EPA. 1994f. Method 8080A. Organochlorine pesticides and polychlorinated biphenyls by gas chromatography. U.S. Environmental Protection Agency.

EPA. 1994g. Land disposal restrictions. Treatment standards for hazardous debris. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.45.

*EPA. 1994h. USEPA contract laboratory program: National functional guidelines for organic data review. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. NTIS PB94-963501.

*EPA. 1995a. Toxic chemical release inventory reporting form R and Instructions. U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA 745-K-95-051.

EPA. 1995b. Guidance for assessing chemical contaminant data for use in fish advisories. Vol 1: Fish sampling and analysis. Second edition. U.S. Environmental Protection Agency, Office of Science and Technology, Office of Water. EPA 823-R-95-007.

*EPA. 1995c. Method 8082. Polychlorinated biphenyls (PCBs) by capillary column gas chromatography. U.S. Environmental Protection Agency.

*EPA. 1995d. Method 4020. Screening for polychlorinated biphenyls by immunoassay. U.S. Environmental Protection Agency.

EPA. 1995e. U.S. Environmental Protection Agency. Designation, reportable quantities, and notification. List of hazardous substances and reportable quantities. Code of Federal Regulations. 40 CFR 302.4.

EPA. 1995f. U.S. Environmental Protection Agency. National primary drinking water regulations. Public notification. Polychlorinated biphenyls (PCBs). Code of Federal Regulations. 40 CFR 141.32.

*EPA. 1995g. EPA region 10 SOP for the validation of Method 1668 toxic, dioxin-like, PCB data. Seattle, WA: U.S. Environmental Protection Agency.

EPA. 1996a. U.S. Environmental Protection Agency. Disposal of polychlorinated biphenyls; import for disposal; Final rule. Federal Register. 61 FR 11096.

EPA. 1996b. National listing of fish and wildlife consumption advisories. U.S. Environmental Protection Agency, Office of Water. EPA-823-C-96-011.

*EPA. 1996c. PCBs: Cancer dose-response assessment and application to environmental mixtures. Washington, DC: U.S. Environmental Protection Agency, National Center for Environmental Assessment, Office of Research and Development. EPA/600/P-96/001F.

*EPA. 1996d. Drinking water regulations and health advisories. Washington DC: U.S. Environmental Protection Agency, Office of Water. EPA 822-B-96-002.

EPA. 1996e. U.S. Environmental Protection Agency. Proposed guidelines for carcinogen risk assessment; Notice. Federal Register 61(79):17960.

*EPA. 1996f. Quality assurance project plan, assessment of chemical contaminants in fish consumed by four Native American tribes in the Columbia River Basin, Revision 6.0. Seattle, WA: U.S. Environmental Protection Agency, Office of Environmental Assessment.

EPA. 1997a. U.S. Environmental Protection Agency. Land disposal restrictions. Treatment standards expressed as specified technologies. Code of Federal Regulations. 40 CFR 268.42.

EPA. 1997b. U.S. Environmental Protection Agency. Land disposal restrictions. Universal treatment standards. Code of Federal Regulations. 40 CFR 268.48.

*EPA. 1997c. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA/630/R-96/012.

9. REFERENCES

*EPA. 1997d. Volume I - General Factors. Exposure Factors Handbook. Washington, DC: U.S. Environmental Protection Agency, National Center of Environmental Assessment, Office of Research and Development. EPA/600/P-95/002Fa.

*EPA. 1998a. U.S. Environmental Protection Agency. Disposal of polychlorinated biphenyls (PCBs); Final rule. Federal Register. 63 FR 35384-35474.

*EPA. 1998b. Update: Listing of fish and wildlife advisories. Fact Sheet. U.S. Environmental Protection Agency, Office of Water. EPA-823-F-98-009.

EPA. 1998c. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264 App IX.

*EPA. 1998d. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266 App V.

*EPA. 1998e. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.48.

EPA. 1998f. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

EPA. 1998g. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 413.10.

*EPA. 1998h. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 401.15.

*EPA. 1998i. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.32.

EPA. 1998j. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4.

EPA. 1998k. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.50.

EPA. 1998l. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 413.02.

EPA. 1998m. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 142.62.

EPA. 1998n. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.61.

EPA. 1998o. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3.

EPA. 1998p. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 52.679.

*EPA. 1998q. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 257.3-5.

*EPA. 1998r. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261 App VIII.

EPA. 1998s. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 129.4.

EPA. 1998t. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.8.

*EPA. 1998u. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 761.

9. REFERENCES

*EPA. 1999a. National recommended water quality criteria- Correction. U.S. Environmental Protection Agency, Office of Water. EPA 822-Z-99-001.

*EPA. 1999b. PCB transformer registration database. http://www.epa.gov/opptintr/pcb/xform.htm

*EPA. 1999c. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264 App IX.

*EPA. 1999d. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

*EPA. 1999e. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.32.

*EPA. 1999f. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.50.

*EPA. 1999g. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.61.

*EPA. 1999h. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3.

*EPA. 1999i. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4.

*EPA. 1999j. U. S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 401.15.

*EPA. 1999k. Method 1668, Revision A: Chlorinated biphenyl congeners in water, soil, sediment, and tissue by HRGC/HRMS. U.S. Environmental Protection Agency, Office of Water. EPA-821-R-00-002.

*EPA. 1999l. Polychlorinated biphenyls (PCBs) update: Impact on fish advisories. U.S. Environmental Protection Agency, Office of Water. EPA-823-F-99-019.

*EPA. 2000. U.S. Environmental Protection Agency. Listing of fish and wildlife advisories: Advisory information. http://fish.rti.org.

*EPA-NIH. 1990. OHM-TADS (Oil and Hazardous Materials Technical Assistance Data System). Washington, DC: U.S. Environmental Protection Agency/National Institutes of Health.

*Epling GA, McVicar WM, Kumar A. 1988. Borohydride-enhanced photo dehalogenation of Aroclor 1232, 1242, 1254, and 1260. Chemosphere 17:1355-1362.

*Erickson MD. 1986. Analytical chemistry of PCBs. Boston, MA: Butterworth Publishers.

*Erickson MD. 1992. Analytical chemistry of PCBs. Boca Raton: Lewis Publishers.

*Eriksson P. 1988. Effects of 3,3',4,4'-tetrachlorobiphenyl in the brain of the neonatal mouse. Toxicology 49:43-48.

Eriksson P. 1996. Developmental neurotoxicology in the neonate--effects of pesticides and polychlorinated organic substances. Arch Toxicol Suppl 18:81-88.

Eriksson P. 1997. Developmental neurotoxicity of environmental agents in the neonate. Neurotoxicology 18(3):719-726.

9. REFERENCES

*Eriksson P, Fredriksson A. 1996a. Developmental neurotoxicity of four ortho-substituted polychlorinated biphenyls in the neonatal mouse. Environ Toxicol Pharmacol 1(3):155-165.

*Eriksson P, Fredriksson A. 1996b. Neonatal exposure to 2,2',5,5'-tetrachlorobiphenyl causes increased susceptibility in the cholinergic transmitter system at adult age. Environ Toxicol Pharmacol 1(3):217-220.

*Eriksson P, Fredriksson A. 1998. Neurotoxic effects in adult mice neonatally exposed to 3,3'4,4'5-pentachlorobiphenyl or 2,3,3'4,4'-pentachlorobiphenyl. Changes in brain nicotinic receptors and behaviour. Environ Toxicol Pharmacol 5(1):17-27.

*Eriksson P, Lundkvist U, Fredricksson A. 1991. Neonatal exposure to 3,3',4,4'-tetrachlorobiphenyl: changes in spontaneous behaviour and cholinergic muscarinic receptors in the adult mouse. Toxicology 69:27-34.

*Evans TC, Kretzschmar RM, Hodges RE, et al. 1967. Radioiodine uptake studies of the human fetal thyroid. J Nucl Med 8:157-165.

*Exon JH, Talcott PA, Koller LD. 1985. Effect of lead, polychlorinated biphenyls, and cyclophosphamide on rat natural killer cells, interleukin 2, and antibody synthesis. Fundam Appl Toxicol 5:158-164.

*Expert Panel. 1994. Interoretive review of the potential adverse effects of chlorinated organic chemicals on human health and the environment. Regul Toxicol Pharmacol 20(1):S187-S307.

*Fait A, Grossman E, Self S, et al. 1989. Polychlorinated biphenyl congeners in adipose tissue lipid and serum of past and present transformer repair workers and a comparison group. Fundam Appl Toxicol 12:42-55.

*Falandysz J. 1994. Polychlorinated biphenyl concentrations in cod-liver oil: Evidence of a steady-state condition of these compounds in the Baltic area oils and levels noted in Atlantic oils. Arch Environ Contam Toxicol 27:266-271.

*Falck F, Ricci A, Wolff MS, et al. 1992. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. Arch Environ Health 47(2):143-146.

*Falconer RL, Bidleman TF. 1994. Vapor pressures and predicted particle/gas distributions of polychlorinated biphenyl congeners as functions of temperature and ortho-chlorine substitution. Atmos Environ 28(3):547-554.

*Falconer RL, Bidleman TF. 1995. Preferential sorption of non- and mono-ortho-polychlorinated biphenyls to urban aerosols. Environ Sci Technol 29:1666-1673.

*Falk C, Hanrahan L, Anderson HA, et al. 1999. Body burden levels of dioxin, furans, and PCBs among frequent consumers of Great Lakes sport fish. Environ Res 80:S19-S25.

*Faqi AS, Dalsenter PR, Mathar W, et al. 1998. Reproductive toxicity and tissue concentrations of 3,3',4,4'-tetrachlorobiphenyl (PCB 77) in male adult rats. Hum Exp Toxicol 17(3):151-156.

*Fava F, Di Gioia D, Marchetti L, et al. 1993. Aerobic mineralization of chlorobenzoates by a natural polychlorinated biphenyl-degrading mixed bacterial culture. Appl Microbiol Biotechnol 40(4):541-548.

FDA. 1992. Action levels for poisonous or deleterious substances in human food and animal feed. Washington, DC: U.S. Food and Drug Administration.

FDA. 1994. U.S. Food and Drug Administration. Tolerance for unavoidable contaminants poisonous or deleterious substances. Code of Federal Regulations. 21 CFR 509, Subpart B.

FDA. 1996a. U.S. Food and Drug Administration. Unavoidable contaminants in food for human consumption and food-packaging material. Code of Federal Regulations. 21 CFR 109.

*FDA. 1996b. Red meat adulterated with PCBs. Compliance Policy Guide. Section 565.200. Office of Regulatory Affairs, U.S. Food and Drug Administration.

*FDA. 1996c. Unavoidable contaminants in food for human consumption and food packaging material: Tolerances for polychlorinated biphenyls (PCBs). U.S. Food and Drug Administration. 21CFR109.30.

*FDA. 1998a. U. S. Food and Drug Administration. Use of polychlorinated biphenyls (PCB's) in the production, handling, and storage of animal feed. Code of Federal Regulations. 21 CFR 500.45.

*FDA. 1998b. U. S. Food and Drug Administration. Use of polychlorinated biphenyls (PCB's) in establishments manufacturing food-packaging materials. Code of Federal Regulations. 21 CFR 509.15.

*FDA. 1998c. U. S. Food and Drug Administration. Temporary tolerances for polychlorinated biphenyls (PCB's). Code of Federal Regulations. 21 CFR 509.30.

*FDA. 1999a. U. S. Food and Drug Administration. Bottled water. Code of Federal Regulations. 21 CFR 165.110.

FDA. 1999b. U. S. Food and Drug Administration. Equipment and utensils. Code of Federal Regulations. 21 CFR 110.40.

FEDRIP. 1998. Federal Research In Progress. September 1998.

*FEDRIP. 2000. Federal Research In Progress.

*Feeley MM, Jordan SA. 1998. Dietary and tissue residue analysis and contaminant intake estimations in rats consuming diet composed of Great Lakes salmon: A multigeneration study. Regul Toxicol Pharmacol 27(1 Part 2):S8-S17.

*Feeley MM, Jordan SA, Gilman AP. 1998. The Health Canada Great Lakes multigeneration study-summary and regulatory considerations. Regul Toxicol Pharmacol 27:S90-S98.

*Fein GG, Jacobson JL, Jacobson SW, et al. 1984a. Intrauterine exposure of humans to PCBs: Newborn effects. U.S. Environmental Protection Agency, Duluth, MN. EPA 600/53-84-060. NTIS PB84-188-887.

*Fein GG, Jacobson JL, Jacobson SW, et al. 1984b. Prenatal exposure to polychlorinated biphenyls: Effects on birth size and gestational age. J Pediatr 105:315-320.

*Felt GR, Mueller WF, Iatropoulos MJ, et al. 1977. Chronic toxicity of 2,4,5'-trichlorobiphenyl in young Rhesus monkeys: I. Body distribution, elimination, and metabolism. Toxicol Appl Pharmacol 41:619-627.

9. REFERENCES

*Feltz HR. 1980. Significance of bottom material data in evaluation water quality. In: Contaminants and sediments. Vol 1. Fate and transport, case studies, modeling, toxicity. Ann Arbor, MI: Ann Arbor Science, 271-287.

Feng H, Cochran JK, Lwiza H, et al. 1998. Distribution of heavy metal and PCB contaminants in the sediments of an urban estuary: The Hudson River. Mar Environ Res 45(1):69-88.

*Fensterheim RJ. 1993. Documenting temporal trends of polychlorinated biphenyls in the environment. Regul Toxicol Pharmacol 18:181-201.

Finklea J, Priester LE, Creason JP, et al. 1972. I. Polychlorinated biphenyl residues in human plasma expose a major urban pollution problem. Am J Public Health 62:645-651.

Finley BL, Trowbridge KR, Burton S, et al. 1997. Preliminary assessment of PCB risks to human and ecological health in the lower Passaic River. J Toxicol Environ Health 52(2):95-118.

*Fiore BJ, Anderson H, Hanrahan MS. 1989. Sport fish consumption and body burden levels of chlorinated hydrocarbons: A study of Wisconsin anglers. Arch Environ Health 44(2):82-88.

*Fischbein A. 1985. Liver function tests in workers with occupational exposure to polychlorinated biphenyls (PCBs): Comparison with Yusho and Yu-Cheng. Environ Health Perspect 60:145-150.

*Fischbein A, Wolff MS. 1987. Conjugal exposure to polychlorinated biphenyls (PCBs). Br J Ind Med 44(4):284-286.

*Fischbein A, Rizzo JN, Solomon SJ, et al. 1985. Oculodermatological findings in workers with occupational exposure to polychlorinated biphenyls (PCBs). Br J Ind Med 42:426-430.

*Fischbein A, Wolff MS, Bernstein J, et al. 1982. Dermatological findings in capacitor manufacturing workers exposed to dielectric fluids containing polychlorinated biphenyls (PCBs). Arch Environ Health 37:69-74.

*Fischbein A, Wolff MS, Lilis R, et al. 1979. Clinical findings among PCB-exposed capacitor manufacturing workers. Ann NY Acad Sci 320:703-715.

*Fischer LJ, Seegal RF, Ganey PE, et al. 1998. Symposium overview: Toxicity of non-coplanar PCBs. Toxicol Sci 41(1):49-61.

*Fish KM, Principe JM. 1994. Biotransformations of Aroclor 1242 in Hudson River test tube microcosms. Appl Environ Microbiol 60(12):4289-4296.

*Fish KM, Mayes BA, Brown JFJ, et al. 1997. Biochemical measurements on hepatic tissues from SD rats fed Aroclors 1016, 1242, 1254, and 1250. Toxicologist 36(1):87.

*Fishbein L. 1974. Toxicity of chlorinated biphenyls. Ann Rev Pharmacol 14:139-156.

*Fitzgerald EF, Brix KA, Deres DA, et al. 1996. Polychlorinated biphenyl (PCB) and dichlorodiphenyl dichloroethylene (DDE) exposure among Native American men from contaminated Great Lakes fish and wildlife. Toxicol Ind Health 12(3-4):361-368.

9. REFERENCES

*Fitzgerald EF, Deres DA, Hwang SA, et al. 1999. Local fish consumption and serum PCB concentrations among Mohawk men at Akwesasne. Environ Res 80:S97-S103.

Fitzgerald EF, Hwang S-A, Brix KA, et al. 1995. Fish PCB concentrations and consumption patterns among Mohawk women at Akwesasne. J Expo Anal Environ Epidemiol 5(1):1-19.

*Fitzgerald EF, Hwang S-A, Bush B, et al. 1998. Fish consumption and breast milk PCB concentrations among Mohawk women at Akwesasne. Am J Epidemiol 148(2):164-172.

*Fitzgerald EF, Standfast SJ, Youngblood LG, et al. 1986. Assessing the health effects of potential exposure to PCBs, dioxins, and furans from electrical transformer fires: The Binghamton state office building medical surveillance program. Arch Environ Health 41:368-376.

*Fitzgerald EF, Weinstein AL, Youngblood LG, et al. 1989. Health effects three years after potential exposure to the toxic contaminants of an electrical transformer fire. Arch Environ Health 44:214-221.

*Flanagan WP, May RJ. 1993. Metabolite detection as evidence for naturally occurring aerobic PCB biodegradation in Hudson River sediments. Environ Sci Technol 27(10):2207-2212.

*Foley RE. 1992. Organochlorine residues in New York waterfowl harvested by hunters in 1983-1984. Environ Monit Assess 21:37-48.

*Foman SJ. 1966. Body composition of the infant. Part I: The male “reference infant”. In: Falkner F, ed. Human Development. Philadelphia, PA: WB Saunders, 239-246.

*Foman, SJ, Haschke F, Ziegler EE et al. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35:1169-1175.

*Foreman WT, Bidleman TF. 1987. An experimental system for investigating vapor-particle partitioning of trace organic pollutants. Environ Sci Technol 21:869-875.

*Fox ME, Khan RM, Thiessen PA. 1996. Loadings of PCBs and PAHs from Hamilton Harbour to Lake Ontario. Water Qual Res J Can 31(3):593-608.

*Frame G. 1997. Congener-specific PCB analysis. Anal Chem 69:468A-475A.

*Frame GM. 1999. Improved procedure for single DB-XLB column GC-MS-SIM quantitation of PCB congener distributions and characterization of two different preparations sold as "Aroclor 1254". J High Resolut Chromatogr 22(10):533-540.

*Frame GM, Cochran JW, Bowadt SS. 1996. Complete PCB congener distributions for 17 Aroclor mixtures determined by 3 HRGC systems optimized for comprehensive, quantitative, congener-specific analysis. J High Resolut Chromotogr 19(12):657-668.

Frank R, Braun HE. 1990. Organochlorine residues in bird species collected dead in Ontario 1972-1988. Bull Environ Contam Toxicol 44:932-939.

Frank R, Braun HE, Thorpe B. 1993. Comparison of DDE and PCB residues in the general diet and in human blood - Ontario 1986-87. Bull Environ Contam Toxicol 51(1):146-152.

9. REFERENCES

Frank R, Braun HE, Van Hove Holdrinet M, et al. 1982. Agriculture and water quality in the Canadian Great Lakes Basin: V. Pesticide use in 11 agricultural watersheds and presence in stream water, 1975-1977. J Environ Qual 11:497-505.

*Franklin MR, Phillips JD, Kushner JP. 1997. Cytochrome P450 induction, uroporphyrinogen decarboxylase depression, porphyin accumulation and excretion, and gender influence in a 3-week rat model of porphyria cutanea tarda. Toxicol Appl Pharmacol 147:289-299.

*Franz TP, Eisenreich SJ. 1993. Wet deposition of polychlorinated biphenyls to Green Bay, Lake Michigan. Chemosphere 26(10):1767-1788.

*Franz TP, Eisenreich SJ. 1998. Snow scavenging of polychlorinated biphenyls and polycyclic aromatic hydrocarbons in Minnesota. Environ Sci Technol 32:1771-1778.

*Franz TP, Eisenreich SJ, Holsen TM. 1998. Dry deposition of particulate polychlorinated biphenyls and polycylic aromatic hydrocarbons to Lake Michigan. Environ Sci Technol 32:3681-3688.

*Freeman GB, Lordo RA, Singer AW, et al. 2000. An assessment of neurotoxicity of Aroclors 1016, 1242, 1254, and 1260 administered in diet to Sprague-Dawley rats for one year. Toxicol Sci 53:377-391.

Freeman GB, Singer AW, Lordo RA, et al. 1998. An assessment of Aroclors 1016, 1242, 1254, and 1260 administered in diet to Sprague-Dawley rats for one year. (Submitted to Toxicol. Sci., July 1998)

*Fries GF, Marrow GS. 1984. Metabolism of chlorobiphenyls in soil. Bull Environ Contam Toxicol 33:6-12.

*Froese KL, Verbrugge DA, Snyder SA, et al. 1997. PCBs in the Detroit River water column. J Great Lakes Res 23(4):440-449.

*Frumkin H, Orris P. 1999. Evidence of excess cancer mortality in a cohort of workers exposed to polychlorinated biphenyls. J Occup Environ Med 41(9):739-745.

FSTRAC. 1990. Federal State Toxicology and Regulatory Alliance Committee. Summary of state and federal drinking water standards and guidelines. U.S. Environmental Protection Agency, Chemical Communication Subcommittee.

*FSTRAC. 1999. Federal-State Toxicology and Risk Analysis Committee. Arizona. U. S. Environmental Protection Agency, Office of Water. July 9, 1999. http://www.epa.gov/ostwater/fstrac/states.html

*Fu YA. 1984. Ocular manifestation of polychlorinated biphenyls intoxication. Am J Ind Med 5:127-132.

*Funatsu I, Yamashita F, Yoshikane T, et al. 1971. A chlorobiphenyl induced fetopathy. Fukuoka Ishi 62(6):139-149.

*Fuoco R, Colombini MP, Samcova E. 1993. Individual determination of ortho and non-ortho substituted polychlorobiphenyls (PCBs) in sediments by high performance liquid chromatographic pre-separation and gas chromatography/ECD detection. Chromatographia 36:65-70.

9. REFERENCES

*Furr AK, Lawrence AW, Tong SCS, et al. 1976. Multielement and chlorinated hydrocarbon analysis of municipal sewage sludges of American cities. Environ Sci Tech 10(7):683-687.

*Furst P, Furst C, Wilmers K. 1994. Human milk as a bioindicator for body burden of PCDDs, PCDFs, organochlorine pesticides, and PCBs. Environ Health Perspect Suppl 102(1):187-193.

*Furukawa K, Matsumura F. 1976. Microbial metabolism of polychlorinated biphenyls. Studies on the relative degradability of polychlorinated biphenyl components by *alkaligenes* sp. J Agric Food Chem 24(2):251-256.

*Furukawa K, Tonomura K, Kamibayashi A. 1978. Effect of chlorine substitution on the biodegradability of polychlorinated biphenyls. Appl Environ Microbiol 35:223-227.

*Gage JC, Holm S. 1976. The influence of molecular structure on the retention and excretion of polychlorinated biphenyls by the mouse. Toxicol Appl Pharmacol 36:555-560.

*Gallenberg LA, Vodicnik MJ. 1987. Potential mechanisms for redistribution of polychlorinated biphenyls during pregnancy and lactation. Xenobiotica 17:299-310.

Gammon MD, Wolff MS, Neugut AI, et al. 1996. Treatment for breast cancer and blood levels of chlorinated hydrocarbons. Cancer Epidemiol Biomarkers Prev 5(6):467-471.

*Gan DR, Berthouex PM. 1994. Disappearance and crop uptake of PCBs from sludge-amended farmland. Water Environ Res 66(1):54-69.

*Ganey PE, Sirois JE, Denison M, et al. 1993. Neutrophil function after exposure to polychlorinated biphenyls *in vitro*. Environ Health Perspect 101:430-434.

*Gans JG, Pintauro SJ. 1986. Liver scarring induced by polychlorinated biphenyl administration to mice previously treated with diethylnitrosamine. Proc Soc Exp Biol Med 183:207-213.

*Gao X, Son D-S, Terranova PF, et al. 1999. Toxic equivalency factors of polychlorinated dibenzo-p-dioxins in an ovulation model: Validation of the toxic equivalency concept for one aspect of endocrine disruption. Toxicol Appl Pharmacol 157:107-116.

*Gao X, Terranova PF, Rozman KK. 2000. Effects of polychlorinated dibenzofurans, biphenyls, and their mixture with dibenzo-p-dioxins on ovulation in the gonadotropin-primed immature rat: Support for the toxic equivalency concept. Toxicol Appl Pharmacol 163:115-124.

*Gardner AM, Chen JT, Roach JAG, et al. 1973. Polychlorinated biphenyls: Hydroxylated urinary metabolites of 2,5,2',5'-tetrachlorobiphenyl identified in rabbits. Biochem Biophys Res Commun 55:1377-1384.

*Garner CE, Matthews HB. 1998. The effect of chlorine substitution on the dermal absorption of polychlorinated biphenyls. Toxicol Appl Pharmacol 149(2):150-158.

*Garthoff H, Friedman L, Farber TM, et al. 1977. Biochemical and cytogenetic effects in rats caused by short-term ingestion of Aroclor 1254 or Firemaster BP6. J Toxicol Environ Health 3:769-796.

*Garthoff LH, Cerra FE, Marks EM. 1981. Blood chemistry alterations in rats after single and multiple gavage administration of polychlorinated biphenyl. Toxicol Appl Pharmacol 60:33-44.

Gartner LW, Arias IM. 1966. Studies of prolonged neonatal jaundice in the breast-fed infant. J Pediatr 68:54-66.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1985a. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1979 - September 1980. J Assoc Off Anal Chem 68:1184-1197.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1985b. Pesticides, selected elements, and other chemicals in adult total diet samples. October 1979 - September 1979. J Assoc Off Anal Chem 68:862-873.

Gartrell MJ, Craun JC, Podrebarac DS, et al. 1985c. Pesticides, selected elements, and other chemicals in infant and toddler diet samples, October 1979 - September 1980. J Assoc Off Anal Chem 68:1163-1183.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986a. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1980 - March 1982. J Assoc Off Anal Chem 69:146-161.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986b. Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1980 - March 1982. J Assoc Off Anal Chem 69:123-145.

*Gebauer MB, Weseloh DV. 1993. Accumulation of organic contaminants in sentinel mallards utilizing confined disposal facilities at Hamilton Harbour, Lake Ontario, Canada. Arch Environ Contam Toxicol 25:234-243.

*Gellert RJ, Wilson C. 1979. Reproductive function in rats exposed prenatally to pesticides and polychlorinated biphenyls (PCB). Environ Res 18:437-443.

*General Electric Company. 1995a. An assessment of the chronic toxicity and oncogenicity of Aroclor-1016, Aroclor-1242, Aroclor-1254, and Aroclor-1260 administered in diet to rats. Volume I: Final neurotoxicity and neuropathology report. Environmental Research Center, General Electric Company. Battelle Study No. SC920192.

*General Electric Company. 1995b. An assessment of the chronic toxicity and oncogenicity of Aroclor-1016, Aroclor-1242, Aroclor-1254, and Aroclor-1260 administered in diet to rats. Volume II: Final neurotoxicity and neuropathology report. Environmental Research Center, General Electric Company. Battelle Study No. SC920192.

*General Electric Company. 1997a. An assessment of the chronic toxicity and oncogenicity of Aroclor-1016, Aroclor-1242, Aroclor-1254, and Aroclor-1260 administered in diet to rats. Volume I. Environmental Research Center, General Electric Company. Batelle Study No. SC920192.

*General Electric Company. 1997b. An assessment of the chronic toxicity and oncogenicity of Aroclor-1016, Aroclor-1242, Aroclor-1254, and Aroclor-1260 administered in diet to rats. Volume II. Environmental Research Center, General Electric Company. Batelle Study No. SC920192.

*Gerhard I, Daniel B, Link S, et al. 1998. Chlorinated hydrocarbons in women with repeated miscarriages. Environ Health Perspect 106:675-681.

Gerstenberger SL, Gallina MP, Dellinger JA. 1997. Polychlorinated biphenyl congeners are selected organochlorines in Lake Superior fish, USA. Environ Toxicol Chem 16(11):2222-2228.

Geyer H, Scheunert I, Korte F. 1986. Bioconcentration potential of organic environmental chemicals in humans. Regul Toxicol Pharmacol 6:313-347.

*Geyer HJ, Rimkus GG, et al. 1999. Bioaccumulation and occurrence of endocrine-disrupting chemicals (EDCs), persistent organic pollutants (POPs)... In: Hutzinger O, Beek B, eds. Handbook of environmental chemistry. Volume 2. Part J. Springer-Verlag.

*Giam CS, Chan HS, Neff GS, et al. 1978. Phthalate ester plasticizers: A new class of marine pollutant. Science 199:419-421.

*Gibson DT, Cruden DL, Haddock JD, et al. 1993. Oxidation of polychlorinated biphenyls by *Pseudomonas sp.* strain LB400 and *Pseudomonas pseudoalcaligenes* KF707. J Bacteriol 175(14):4561-4564.

*Gierthy JF, Arcaro KF, Floyd M. 1997. Assessment of PCB estrogenicity in a human breast cancer cell line. Chemosphere 34(5-7):1495-1505.

*Giesy JP, Kannan K. 1998. Dioxin-like and non-dioxin-like toxic effects of polychlorinated biphenyls (PCBs): Implications for risk assessment. Crit Rev Toxicol 28(6):511-569.

*Giesy JP, Bowerman WW, Mora MA, et al. 1995. Contaminants of fishes from Great Lakes-influenced sections and above dams of three Michigan rivers: III. Implications for health of bald eagles. Arch Environ Contam Toxicol 29(3):309-321.

*Giesy JP, Jude DJ, Tillitt DE, et al. 1997. Polychlorinated dibenzo-p-dioxins, dibenzofurans, biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin equivalents in fishes from Saginaw Bay, Michigan. Environ Toxicol Chem 16(4):713-724.

*Giesy JP, Jude DJ, Tillitt DE, et al. 1997. Polychlorinated dibenzo- *p*-dioxins, dibenzofurans, biphenyls and 2,3,7,8-tetrachlorodibenzo- *p*-dioxin equivalents in fishes from Saginaw Bay, Michigan. Environ Toxicol Chem 16(4):713-724.

Giesy JP, Ludwig JP, Tillit DE. 1994. Dioxins, dibenzofurans, PCBs and colonial, fish-eating water birds. In: Schecter A, ed. Dioxins and health. New York, NY: Plenum Press, 249-307.

*Gillan KA, Hasspieler BM, Russell RW, et al. 1998. Ecotoxicological studies in amphibian populations of southern Ontario. J Great Lakes Res 24(1):45-54.

Gillette JR. 1967. Individually different responses to drugs according to age, sex and functional or pathological state. In: Wolstenholme G, Porter R, eds. Drug responses in man. Boston, MA: Little, Brown & Company, 24-54.

*Gilroy C, Connell BJ, Singh A, et al. 1998. PCB congener 77-induced ultrastructural alterations in the rat liver: a quantitative study. Toxicology 127:179-185.

*Gilroy C, Singh A, Chu I, et al. 1996. Toxicity of PCB 156 in the rat liver: an ultrastructural and biochemical study. J Submicrosc Cytol Pathol 28(1):27-32.

*Girvin DC, Scott AJ. 1997. Polychlorinated biphenyl sorption by soils: Measurement of soil-water partition coefficients at equilibrium. Chemosphere 35(9):2007-2025.

*Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect Suppl 101:65-71.

*Gladen BC, Rogan WJ. 1991. Effects of perinatal polychlorinated biphenyls and dichlorodiphenyl dichloroethene on later development. J Pediatr 119:58-63.

*Gladen BC, Rogan WJ, Hardy P, et al. 1988. Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene transplacentally and through human milk. J Pediatr 113:991-995.

*Gladen BC, Taylor JS, Wu Y-C, et al. 1990. Dermatological findings in children exposed transplacentally to heat-degraded polychlorinated biphenyls in Taiwan. Br J Dermatol 122:799-808.

*GLWQB. 1985. Report to the International Joint Commision: Report on Great Lakes water quality. Kingston, Ontario: Great Lakes Water Quality Board.

*Goldey ES, Crofton KM. 1998. Thyroxine replacement attentuates hypothyroxinemia, hearing loss, and motor deficits following developmental exposure to Aroclor 1254 in rats. Toxicol Sci 45:94-105.

*Goldey ES, Kehn LS, Lau C, et al. 1995. Development exposure to polychlorinated biphenyls (Aroclor 1254) reduces circulating thyroid hormone concentrations and causes hearing deficits in rats. Toxicol Appl Pharmacol 135:77-88.

*Goldman PS, Rosvold HE, Vest B, et al. 1971. Analysis of the delayed-alternation deficit produced by dorsolateral prefrontal lesions in the Rhesus monkey. J Comp Physiol Psychol 77(2):212-220.

Goldstein JA, Safe S. 1989. Mechanism of action and structure-activity relationships for the chlorinated dibenzo-*p*-dioxins and related compounds. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd ed. Amsterdam, The Netherlands: Elsevier Science Publishers, 239-293.

*Goldstein JA, Hickman P, Jue DL. 1974. Experimental hepatic porphyria induced by polychlorinated biphenyls. Toxicol Appl Pharmacol 27:437-448.

*Golomb D, Ryan D, Underhill J, et al. 1997. Atmospheric deposition of toxics onto Massachusetts Bay -- II. Polycyclic aromatic hydrocarbons. Atmos Environ 31(9):1361-1368.

Golub MS, Donald JM, Reyes JA. 1991. Reproductive toxicity of commercial PCB mixtures: LOAELs and NOAELs from animal studies. Environ Health Perspect 94:245-253.

*Goto M, Sugiura K, Hattori M, et al. 1974. Metabolism of 2,3,-dichlorobiphenyl-^{14}C and 2,4,6-trichlorobiphenyl-^{14}C in the rat. Chemosphere 5:227-232.

*Gould JC, Cooper KR, Scanes CG. 1997. Effects of polychlorinated biphenyl mixtures and three specific congeners on growth and circulating growth-related hormones. Gen Comp Endocrinol 106(2):221-30.

*Grant DL, Phillips WEJ. 1974. The effect of age and sex on the toxicity of Aroclor® 1254, a polychlorinated biphenyl, in the rat. Bull Environ Contam Toxicol 12:145-152.

Grant DL, Phillips WEJ, Villeneuve DC. 1971. Metabolism of a polychlorinated biphenyl (Aroclor® 1254) mixture in the rat. Bull Environ Contam Toxicol 6:102-112.

*Gray K, Longnecker M, Klebanoff M, et al. 2000. In utero exposure to background levels of polychlorinated biphenyls and cognitive functioning among school-aged children. Am J Epidemiol 151(11):S24.

*Gray LE, Kelce WR, Monosson E, et al. 1995. Exposure to TCDD during development permanently alters reproductive function in male Long Evans rats and hamsters: Reduced ejaculated and epididymal sperm numbers and sex accessory gland weights in offspring with normal androgenic status. Toxicol Appl Pharmacol 131:108-118.

Gray LE Jr. 1996. Comments on "developmental neurotoxicity of PCBs in humans: What do we know and where do we go from here"? Neurotoxicol Teratol 18(3):243-5; Discussion 271-6.

Gray LE Jr. 1998. Chemical-induced alterations of sexual differentiation: a review of effects in humans and rodents. J Clean Technol Environ Toxicol Occup Med 7(2):121-145.

*Gray LE Jr, Ostby J, Marshall R, et al. 1993. Reproductive and thyroid effects of low-level polychlorinated biphenyl (Aroclor 1254) exposure. Fundam Appl Toxicol 20(3):288-294.

*Green S, Carr JV, Palmer KA, et al. 1975a. Lack of cytogenetic effects in bone marrow and spermatogonial cells in rats treated with polychlorinated biphenyls (Aroclors 1242 and 1254). Bull Environ Contam Toxicol 13:14-22.

*Green S, Sauro FM, Friedman L. 1975b. Lack of dominant lethality in rats treated with polychlorinated biphenyls (Aroclors 1242 and 1254). Food Cosmet Toxicol 13:507-510.

*Gregor D, Teixeira C, Rowsell R. 1996. Deposition of atmospherically transported polychlorinated biphenyls in the Canadian Arctic. Chemosphere 33(2):227-244.

*Greizerstein HB, Gigliotti P, Vena J et al. 1997. Standardization of a method for the routine analysis of polychlorinated biphenyl congeners and selected pesticides in human serum and milk. J Analytical Toxicol 21:125-133.

*Greizerstein HB, Stinson C, Mendola P, et al. 1999. Comparison of PCB congeners and pesticide levels between serum and milk from lactating women. Environ Res 80:280-286.

*Griffin RA, Chou SFJ. 1981. Movement of PCB's and other persistent compounds through soil. Water Sci Technol 13:1153-1163.

*Gschwend PM, Wu S. 1985. On the constancy of sediment-water partition coefficients of hydrophobic organic pollutants. Environ Sci Technol 19(1):90-96.

*Grimvall E, Rylander L, Nilsson-Ehle P, et al. 1997. Monitoring of polychlorinated biphenyls in human blood plasma: Methodological developments and influence of age, lactation, and fish consumption. Arch Environ Contam Toxicol 32:329-336.

*Grundy SL, Bright DA, Dushenko WT, et al. 1996. Weathering and dispersal of polychlorinated biphenyls from a known source in the Canadian Arctic. Environ Sci Technol 30(9):2661-2666.

*Guilbeault B, Sondossi M, Ahmad D, et al. 1994. Factors affecting the enhancement of PCB degradative ability of soil microbial populations. Int Biodeterior Biodegrad 33(1):73-91.

9. REFERENCES

*Gunderson EL. 1988. FDA total diet study, April 1982-April 1984: Dietary intakes of pesticides, selected elements and other chemicals. J Assoc Off Anal Chem 71:1200-1209.

*Gunderson EL. 1995. FDA total diet study, July 1986-April 1991: Dietary intakes of pesticides, selected elements, and other chemicals. J Assoc Off Anal Chem 78:1353-1363.

*Gunkel G, Mast P-G, Nolte C. 1995. Pollution of aquatic ecosystems by polychlorinated biphenyls (PCB). Limnologica 25(3/4):321-331.

*Guo YL, Lai T-J, Chen S-J, et al. 1995. Gender-related decrease in Raven's progressive matrices scores in children prenatally exposed to polychlorinated biphenyls and related contaminants. Bull Environ Contam Toxicol 55:8-13.

*Guo YL, Lai TJ, Ju SH, et al. 1993. [No title available]. Dioxin '93 14:235.

*Guo YL, Ryan JJ, Lau BPY, et al. 1997. Blood serum levels of PCBs and PCDFs in Yucheng women 14 years after exposure to a toxic rice oil. Arch Environ Contam Toxicol 33:104-108.

*Guo YL, Yu M-L, Hsu C-C, et al. 1999. Chloracne, goiter, arthritis, and anemia after polychlorinated biphenyl poisoning: 14-year follow-up of the Taiwan Yucheng cohort. Environ Health Perspect 107(9):715-719.

*Guo YL, Yu M-L, Ryan JJ. 1996. Different congeners of PCBs/PCDFs may have contributed to different health outcomes in the Yucheng cohort. Neurotoxicol Teratol 18(3):255-256.

*Gustavson K, Jonsson P. 1999. Some halogenated organic compounds in sediments and blue mussel (*Mytilus edulis*) in Nordic Seas. Mar Pollut Bull 38(8):723-736.

*Gustavsson P, Hogstedt C. 1997. A cohort study of Swedish capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am J Ind Med 32(3):234-239.

*Gustavsson P, Hogstedt C, Rappe C. 1986. Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am J Ind Med 10:341-344.

*Gutenmann HW, Rutzke M, Kuntz HT, et al. 1994. Elements and polychlorinated biphenyls in sewage sludges of large cities in the United States. Chemosphere 28(4):725-728.

*Gutleb AC, Appelman J, Bronkhorst MC, et al. 1999. Delayed effects of pre- and early-life time exposure to polychlorinated biphenyls on tadpoles of two amphibian species (*xenopus laevis* and *rana temporaria*). Environ Toxicol Pharmacol 8:1-14.

*Guttes S, Failing K, Neumann K, et al. 1998. Chlororganic pesticides and polychlorinated biphenyls in breast tissue of women with benign and malignant breast disease. Arch Environ Contam Toxicol 35:140-147.

*Guzelian PS, Henry CJ, Olin SS. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press.

*Haag-Gronlund M, Johansson N, Fransson-Steen R, et al. 1998. Interactive effects of three structurally different polychlorinated biphenyls in a rat liver tumor promotion bioassay. Toxicol Appl Pharmacol 152:153-165.

9. REFERENCES

Haag-Gronlund M, Warngard L, Flodstrom S, et al. 1997. Promotion of altered hepatic foci by 2,3',4,4',5-pentachlorobiphenyl in Sprague-Dawley female rats. Fundam Appl Toxicol 35(1):120-130.

*Haake JM, Safe S, Mayura K, et al. 1987. Aroclor 1254 as an antagonist of the teratogenicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Toxicol Lett 38:299-306.

Haglund P, Asplund L, Jarnberg U, et al. 1990. Isolation of toxic polychlorinated biphenyls by electron donor-acceptor high-performance liquid chromatography on a 2-(1-pyrenyl)ethyldimethylsilylated silica column. J Chromatogr 507:389-398.

*Hagmar L, Becher G, Heikkila A, et al. 1998. Consumption of fatty fish from the Baltic Sea and PCB in whole venous blood, plasma and cord blood from delivering women in the Aland/Turkey archipelago. J Toxicol Environ Health 53:581-591.

Hagmar L, Hallberg T, Leja M, et al. 1995. High consumption of fatty fish from the Baltic Sea is associated with changes in human lymphocyte levels. Toxicol Lett 77:335-342.

Hakansson H, Manzoor E, Ahlborg UG. 1992. Effects of technical PCB preparations and fractions thereof on vitamin A levels in the mink (*mustela vison*). Ambio 21(8):588-590.

*Hall AJ, Duck CD, Law RJ, et al. 1999. Organochlorine contaminants in Caspian and harbour seal blubber. Environ Pollut 106:203-212.

*Halsall CJ, Gevao B, Howsam M, et al. 1999. Temperature dependence of PCBs in the UK atmosphere. Atmos Environ 33:541-552.

*Haluska L, Barancikova G, Balaz S, et al. 1995. Degradation of PCB in different soils by inoculated *alcaligenes xylosoxidans*. Sci Total Environ 175(3):275-285.

Hanneman WH, Legare ME, Tiffany-Castiglioni E, et al. 1996. The need for cellular, biochemical, and mechanistic studies. Neurotoxicol Teratol 18(3):247-250.

*Hanrahan LP, Falk C, Anderson HA, et al. 1999. Serum PCB and DDE levels of frequent Great Lakes sport fish consumers-A first look. Environ Res 80:S26-S37.

*Hansch C, Leo AJ. 1985. Medchem Project. Issue No. 26. Claremont, CA: Pomona College.

*Hansen H, De Rosa CT, Pohl H, et al. 1998. Public health challenges posed by chemical mixtures. Environ Health Perspect 106(Suppl. 6):1271-1280.

*Hansen LG. 1979. Selective accumulation and depletion of polychlorinated biphenyl components: Food animal implications. Ann NY Acad Sci 320:238-246.

*Hansen LG. 1987a. Food chain modification of the composition and toxicity of polychlorinated biphenyl (PCB) residues. Rev Environ Toxicol 3:149-212.

*Hansen LG. 1987b. Environmental toxicology of polychlorinated biphenyls. In: Safe S, ed. Polychlorinated biphenyls (PCBs): Mammalian and environmental toxicology. Berlin, Germany: Springer-Verlag, 15-48.

9. REFERENCES

*Hansen LG. 1998. Stepping backward to improve assessment of PCB congener toxicities. Environ Health Perspect Suppl 106(1):171-189.

*Hansen LG. 1999. The *ortho* side of PCBs: Occurrence and disposition. Boston, MA: Kluwer Academic Publishers.

*Hansen LG, O'Keefe PW. 1996. Polychlorinated dibenzofurans and dibenzo-p-dioxins in subsurface soil, superficial dust, and air extracts from a contaminated landfill. Arch Environ Contam Toxicol 31(2):271-276.

*Hansen LG, Welborn ME. 1977. Distribution, dilution and elimination of polychlorinated biphenyl analogs in growing swine. J Pharm Sci 66:497-501.

*Hansen LG, Byerly CS, Metcalf RL, et al. 1975. Effect of a polychlorinated biphenyl mixture on swine reproduction and tissue residues. Am J Vet Res 36:23-26.

*Hansen LG, Green D, Cochran J, et al. Chlorobiphenyl (PCB) composition of extracts of subsurface soil, superficial dust and air from a contaminated landfill. F J Anal Chem 357:442-448.

*Hansen LG, Li MH, Saeed A, et al. 1995. Environmental polychlorinated biphenyls: Acute toxicity of landfill soil extract to female prepubertal rats. Arch Environ Contam Toxicol 29(3):334-343.

*Hansen LG, Welborn ME, Borchard RE, et al. 1977. Tissue distribution of PCB components in swine and sheep fed three different rations containing Aroclors 1242 and 1254. Arch Environ Contam Toxicol 5:257-278.

*Hansen LG, Wilson DW, Byerly CS. 1976. Effects on growing swine and sheep of two polychlorinated biphenyls. Am J Vet Res 37:1021-1024.

Hany J, Lilienthal H, Roth-Harer A, et al. 1999a. Behavioral effects following single and combined maternal exposure to PCB 77 (3,4,3',4'-tetrachlorobiphenyl) and PCB 47 (2,4,2',4'-tetrachlorobiphenyl) in rats. Neurotoxicol Teratol 21(2):147-156.

*Hany J, Lilienthal H, Sarasin A, et al. 1999b. Developmental exposure of rats to a reconstituted PCB mixture or Aroclor 1254: Effects on organ weights, aromatase activity, sex hormone levels, and sweet preference behavior. Toxicol Appl Pharmacol 158:231-243.

*Haque R, Schmedding. 1976. Studies on the adsorption of selected polychlorinated biphenyl isomers on several surfaces. J Environ Sci Health B 11:129-137.

*Hara I. 1985. Health status and PCBs in blood of workers exposed to PCBs and of their children. Environ Health Perspect 59:85-90.

*Haraguchi K, Athanasiadou M, Bergman A, et al. 1992. PCB and PCB methyl sulfones in selected groups of seals from Swedish waters. Ambio 21:546-549.

*Haraguchi K, Kato Y, Kimura R, et al. 1999a. Tissue distribution of methylsulfonyl metabolites derived from 2,2',4,5,5'-penta- and 2,2',3,4',5',6-hexachlorobiphenyls in rats. Arch Environ Contam Toxicol 37:135-142.

*Haraguchi K, Koga N, Yoshimura H, et al. 1999b. Comparative metabolism of polychlorinated biphenyls (Kanechlor-500) in rats, hamsters and guinea pigs. Organohalogen Compounds 42:177-179.

*Haraguchi K, Kuroki H, Masuda Y. 1986. Capillary gas chromatographic analysis of methylsulphone metabolites of polychlorinated biphenyls retained in human tissues. J Chromatogr 361:239-252.

*Hard HJ, Barnes C, Larsson G, et al. 1995. Solution structure of a mammalian PCB-binding protein in complex with a PCB. Nat Struct Biol 2:983-989.

Hardell L, Lindstrom G, van Bavel B, et al. 1998. Some aspects of the etiology of non-Hodgkin's lymphoma. Environ Health Perspect Suppl 106(2):679-681.

*Hardell L, Van Bavel B, Lindstrom G, et al. 1996. Higher concentrations of specific polychlorinated biphenyl congeners in adipose tissue from non-Hodgkin's lymphoma patients compared with controls without a malignant disease. Int J Oncol 9(4):603-608.

*Harding LE, Harris ML, Stephen CR, et al. 1999. Reproductive and morphological condition of wild mink (*mustela vison*) and river otters (*lutra canadensis*) in relation to chlorinated hydrocarbon contamination. Environ Health Perspect 107(2):141-147.

*Harkness MR, McDermott JB, Abramowicz A, et al. 1993. In situ stimulation of aerobic PCB biodegradation in Hudson River sediments. Science 259:503-507.

*Harner T, Kylin H, Bidleman TF, et al. 1998. Polychlorinated naphthalenes and coplanar polychlorinated biphenyls in Arctic air. Environ Sci Technol 32:3257-3265.

*Harner T, Mackay D, Jones KC. 1995. Model of the long-term exchange of PCBs between soil and the atmosphere in the southern UK. Environ Sci Technol 29(5):1200-1209.

*Harper N, Connor K, Safe S. 1993a. Immunotoxic potencies of polychlorinated biphenyl (PCB), dibenzofuran (PCDF) and dibenzo-*p*-dioxin (PCDD) congeners in C57BL/6 and DBA/2 mice. Toxicology 80:217-227.

*Harper N, Connor K, Steinberg M, et al. 1995. Immunosuppressive activity of polychlorinated biphenyl mixtures and congeners: Nonadditive (antagonistic) interactions. Fundam Appl Toxicol 27:131-139.

*Harper N, Howie L, Connor K, et al. 1993b. Immunosupressive effects of highly chlorinated biphenyls and diphenyl ethers on T-cell dependent and independent antigens in mice. Toxicology 85:123-135.

*Harrad SJ, Sewart AS, Boumphrey R, et al. 1992. A method for the determination of PCB congeners 77, 126 and 169 in biotic and abiotic matrices. Chemosphere 24(8):1147-1154.

Harris M, Zacharewski T, Safe S. 1993. Comparative potencies of Aroclors 1232, 1242, 1248, 1254, and 1260 in male Wistar rats--assessment of the toxic equivalency factor (TEF) approach for polychlorinated biphenyls (PCBs). Fundam Appl Toxicol 20(4):456-463.

*Hart KM, Tremp J, Molinar E, et al. 1993. The occurrence and the fate of organic pollutants in the atmosphere. Water Air Soil Pollut 68(1-2):91-112.

9. REFERENCES

*Hartkamp-Commandeur LCM, Gerritse J, Govers HAJ, et al. 1996. Reductive dehalogenation of polychlorinated biphenyls by anaerobic microorganisms enriched from Dutch sediments. Chemosphere 32(7):1275-1286.

*Hashimoto K, Akasaka S, Takagi Y, et al. 1976. Distribution and excretion of [^{14}C]polychlorinated biphenyls after their prolonged administration to male rats. Toxicol Appl Pharmacol 37:415-423.

*Hassett JP, Milicic E, Jota MAT. 1984. Equilibrium and kinetic studies of binding of a PCB compound by dissolved organic matter. Am Chem Soc Abstr Pap :ENVR 86.

*Hassoun E, d'Argy R, Dencker L, et al. 1984. Teratogenicity of 2,3,7,8-tetrachlorodibenzofuran in BXD recombinant inbred strains. Toxicol Lett 23:37-42.

*Hatton RE. 1979. Chlorinated biphenyls and related compounds. In: Grayson M, Eckroth D, eds. Kirk-Othmer encyclopedia of chemical technology, Vol. 5. New York, NY: John Wiley and Sons, 844-848.

*Hattula ML. 1985. Mutagenicity of PCBs and their pyrosynthetic derivatives in cell-mediated assay. Environ Health Perspect 60:255-257.

*Haugen J-E, Wania F, Lei YD. 1999. Polychlorinated biphenyls in the atmosphere of southern Norway. Environ Sci Technol 33:2340-2345.

*Hayes MA. 1987. Carcinogenic and mutagenic effects of PCBs. In: Safe S, Hytzinger O, eds. Environmental toxin series. Vol 1: Polychlorinated biphenyls (PCBs: Mammalian and environmental toxicology). Heidelberg: Springer-Verlag, 77-95.

*HazDat. 1998. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

*HazDat. 2000. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

*Heaton SN, Bursian SJ, Giesy JP, et al. 1995a. Dietary exposure of mink to carp from Saginaw Bay, Michigan. 1. Effects on reproduction and survival, and the potential risks to wild mink populations. Arch Environ Contam Toxicol 28:334-343.

*Heaton SN, Bursian SJ, Giesy JP, et al. 1995b. Dietary exposure of mink to carp from Saginaw Bay, Michigan: 2. Hematology and liver pathology. Arch Environ Contam Toxicol 29:411-417.

*Hebert CE, Gamberg M, Elkin BT, et al. 1996. Polychlorinated dibenzodioxins, dibenzofurans and non-ortho substituted polychlorinated biphenyls in caribou (*rangifer tarandus*) from the Canadian Arctic. Sci Total Environ 183(3):195-204.

*Hebert CE, Gloosehenko V, Haffner GD, et al. 1993. Organic contaminants in snapping turtle (*chelydra serpentiana*) populations from southern Ontario, Canada. Arch Environ Contam Toxicol 24:35-43.

*Hebert CE, Shutt JL, Norstrom RJ. 1997. Dietary changes cause temporal fluctuations in polychlorinated biphenyl levels in herring gull eggs from Lake Ontario. Environ Sci Technol 31(4):1012-1017.

9. REFERENCES

*Hebert CE, Weseloh DV, Kot L, et al. 1994. Organochlorine contaminants in a terrestrial foodweb on the Niagara Peninsula, Ontario, Canada 1987- 89. Arch Environ Contam Toxicol 26:356-366.

*Heddle JA, Bruce WR. 1977. Comparison of tests for mutagenicity or carcinogenicity using assays for sperm abnormalities, formation of micronuclei and mutations in *salmonella*. In: Hiatt HH, et al., eds. Cold Spring Harbor conference on cell proliferation: Volume 4: Origins of human cancer. Cold Spring Harbor, NY: Cold Spring Harbor Lab, 1549-1557.

Heinrich-Hirsch B, Beck H, Chahoud I, et al. 1997. Tissue distribution, toxicokinetics and induction of hepatic drug metabolizing enzymes in male rats after a single s.c. dose of 3,4,3',4'-tetrachlorobiphenyl (PCB-77). Chemosphere 34(5-7):1523-1534.

*Heit M, Klusek C, Baron J. 1984. Evidence of deposition of anthropogenic pollutants in remote Rocky Mountain lakes. Water Air Soil Pollut 22:403-416.

*Helzlsouer KJ, Alberg AJ, Huang H-Y, et al. 1999. Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. Cancer Epidemiol Biomarkers Prev 8:525-532.

*Hemming H, Bager Y, Flodstrom S, et al. 1995. Liver tumour promoting activity of 3,4,5,3',4'-pentachlorobiphenyl and its interaction with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Eur J Pharmacol 292:241-249.

*Hemming H, Flodstrom S, Fransson-Steen R, et al. 1992. Inhibition of intercellular communication in cells in culture by polychlorinated compounds. Chemosphere 25(7-10):939-945.

*Hemming H, Flodstrom S, Warngard L, et al. 1993. Relative tumour promoting activity of three polychlorinated biphenyls in rat liver. Eur J Pharmacol 248(2):163-174.

*Hennig B, Slim R, Toborek M, et al. 1999. PCB-mediated endothelial cell dysfunction: Implications in atherosclerosis. Organohalogen Compounds 42:505-508.

Henning MH, Ebert ES, Keenan RE, et al. 1997. Assessment of effects of PCB-contaminated floodplain soils on reproductive success of insectivorous songbirds. Chemosphere 34(5-7):1121-1137.

*Hermanson MH, Hites RA. 1989. Long-term measurements of atmospheric polychlorinated biphenyls in the vicinity of Superfund dumps. Environ Sci Technol 23:1253-1258.

*Herr DW, Goldey ES, Crofton KM. 1996. Developmental exposure to Aroclor 1254 produces low-frequency alterations in adult rat brainstem auditory evoked responses. Fundam Appl Toxicol 33:120-128.

*Hess P, de Boer J, Cofino WP, et al. 1995. Critical review of the analysis of non- and mono-*ortho*-chlorobiphenyls. J Chromatogr 703:417-465.

*Hesso A, Hameila M, Tornaeus J, et al. 1992. Polychlorinated dioxins, furans and non-ortho polychlorinated biphenyls in blood of exposed laboratory personnel. Chemosphere 25(7-10):1053-1059.

*Hickey WJ, Searles DB, Focht DD. 1993. Enhanced mineralization of polychlorinated biphenyls in soil inoculated with chlorobenzoate-degrading bacteria. Appl Environ Microbiol 59(4):1194-1200.

9. REFERENCES

*Hicks HE. 1996. The Great Lakes: A historical overview. Toxicol Ind Health 12(2/3):303-313.

*Higson FK. 1992. Microbial degradation of biphenyl and its derivatives. Adv Appl Microbiol 37:135-164.

*Hilbert G, Lillemark L, Balchen S, et al. 1998. Reduction of organochlorine contaminants from fish oil during refining. Chemosphere 37(7):1241-1252.

*Hill RH Jr. 1985. Effects of polyhalogenated aromatic compounds on porphyrin metabolism. Environ Health Perspect 60:139-143.

*Hillery BR, Basu I, Sweet CW, et al. 1997. Temporal and spatial trends in a long-term study of gas-phase PCB concentrations near the Great Lakes. Environ Sci Technol 31(6):1811-1816.

*Hippelein M, McLachlan MS. 1998. Soil/air partitioning of semivolatile organic compounds. 1. Method development and influence of physical-chemical properties. Environ Sci Technol 32:310-316.

*Hippelein M, Kaupp H, Door G, et al. 1993. Testing of a sampling system and analytical method for determination of semivolatile organic compounds in ambient air. Chemosphere 26(12):2255-2263.

*Hirose M, Shirai T, Tsuda H, et al. 1981. Effect of phenobarbital, polychlorinated biphenyl and sodium saccharin on hepatic and renal carcinogenesis in unilaterally nephrectomized rats given N-ethyl-N-hydroxyethylnitrosamine orally. Carcinogenesis 2:1299-1302.

*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J. Nat Cancer Inst 84:313-320.

*Hofelt CS, Shea D. 1997. Accumulation of organochlorine pesticides and PCBs by semipermeable membrane devices and *mytilus edulis* in New Bedford harbor. Environ Sci Technol 31(1):154-159.

*Hoff RM, Muir DCG, Grist NP. 1992. Annual cycle of polychlorinated biphenyls and organohalogen pesticides in air in Southern Ontario. 1: Air contamination data. Environ Sci Technol 26:266-275.

*Hoff RM, Strachan WMJ, Sweet CW, et al. 1996. Atmospheric deposition of toxic chemicals to the Great Lakes: A review of data through 1994. Atmos Environ 30(20):3505-3527.

Hoffman DJ, Rice CP, Kubiak TJ. 1996. PCBs and dioxins in birds. In: Beyer WE, Heinz GH, Redmon-Norwood AW, eds. Environmental contaminants in wildlife: Interpreting tissue concentrations. Boca Raton, FL: CRC Press, 165-207.

*Holene E, Nafstad I, Skaare JU, et al. 1995. Behavioral effects of pre- and postnatal exposure to individual polychlorinated biphenyl congeners in rats. Environ Toxicol Chem 14(6):967-976.

*Holene E, Nafstad I, Skaare JU, et al. 1998. Behavioral hyperactivity in rats following postnatal exposure to sub-toxic doses of polychlorinated biphenyl congeners 153 and 126. Behav Brain Res 94:213-224.

*Holene E, Nafstad I, Skaare JU, et al. 1999. Behavioural effects in female rats of postnatal exposure to sub-toxic doses of polychlorinated biphenyl congener 153. Acta Paediatr Scand Suppl 429:55-63.

Hollander D. 1997. Environmental effects on reproductive health: The endocrine disruption hypothesis. Fam Plann Perspect 29(2):82-6, 89.

*Hollifield HC. 1979. Rapid nephelometric estimate of water solubility of highly insoluble organic chemicals of environmental interest. Bull Environ Contam Toxicol 23:579-586.

*Holsbeek L, Joiris CR, Debacker V, et al. 1999. Heavy metals, organochlorines and polycyclic aromatic hydrocarbons in sperm whales stranded in the southern North Sea during the 1994/1995 winter. Mar Pollut Bull 38(4):304-313.

*Holsen TM, Noll KE. 1992. Dry deposition of atmospheric particles: Application of current models to ambient data. Environ Sci Technol 26:1807-1815.

*Holsen TM, Noll KE, Lu S, et al. 1991. Dry deposition of polychlorinated biphenyls in urban areas. Environ Sci Technol 25:1075-1078.

*Holson RR, Pearce B. 1992. Principles and pitfalls in the analysis of prenatal treatment effects in multiparous species. Neurotoxicol Teratol 14:221-228.

*Hong C-S, Bush B, Xiao J. 1992a. Isolation and determination of mono-ortho and non-ortho substituted PCBs (coplanar PCBs) in human milk by HPLC porous graphitic carbon and GC-ECD. Chemosphere 24(4):465-473.

*Hong C-S, Bush B, Xiao J. 1992b. Coplanar PCBs in fish and mussels from marine and estuarine waters of New York State. Ecotoxicol Environ Saf 23(1):118-131.

*Hong C-S, Calambokidis J, Bush B, et al. 1996. Polychlorinated biphenyls and organochlorine pesticides and harbor seal pups from the inland waters of Washington State. Environ Sci Technol 30(3):837-844.

*Hong CS, Wang Y, Bush B. 1998. Kinetics and products of the TiO_2 photocatalytic degradation of 2-chlorobiphenyl in water. Chemosphere 36(7):1653-1667.

Hong CS, Xiao J, Casey AC, et al. 1994. Mono-ortho- and non-ortho substituted polychlorinated biphenyls in human milk from Mohawk and control women: Effects of maternal factors and previous lactation. Arch Environ Contam Toxicol 27:431-437.

Honrath RE, Sweet CI, Plouff CJ. 1997. Surface exchange and transport processes governing atmospheric PCB levels over Lake Superior. Environ Sci Technol 31(3):842-852.

*Hood A, Hashmi R, Klaassen CD. 1999. Effects of microsomal enzyme inducers on thyroid-follicular cell proliferation, hyperplasia, and hypertrophy. Toxicol Appl Pharmacol 160:163-170.

*Hoopingarner R, Samuel A, Krause D. 1972. Polychlorinated biphenyl interactions with tissue culture cells. Environ Health Perspect 1:155-158.

*Hori M, Kondo H, Ariyoshi N, et al. 1997. Species-specific alteration of hepatic glucose 6-phosphate dehydrogenase activity with coplanar polychlorinated biphenyl: Evidence for an Ah-receptor-linked mechanism. Chemosphere 35(5):951-958.

9. REFERENCES

*Hornbuckle KC, Achman DR, Eisenreich SJ. 1993. Over-water and over-land polychlorinated biphenyls in Green Bay, Lake Michigan. Environ Sci Technol 27:87-98.

*Hornshaw TC, Safronoff J, Ringer RK, et al. 1986. LC_{50} test results in polychlorinated biphenyl-fed mink: Age, season, and diet comparisons. Arch Environ Contam Toxicol 15:717-723.

*Hornung MW, Miller L, Goodman B, et al. 1998. Lack of developmental and reproductive toxicity of 2,3,3',4,4'-pentachlorobiphenyl (PCB 105) in ring-necked pheasants. Arch Environ Contam Toxicol 35:646-653.

Hornykiewicz O. 1973. Parkinson's disease: from brain homogenate to treatment. Fed Proc 32:183-190.

*Horzempa LM, Di Toro DM. 1983. The extent of reversibility of polychlorinated biphenyl adsorption. Water Res 17(8):851-859.

Houghton DL, Ritter L. 1995. Organochlorine residues and risk of breast cancer. J Am Coll Toxicol 14(2):71-89.

*Hovinga ME, Sowers M, Humphrey HEB. 1992. Historical changes in serum PCB and DDT levels in an environmentally-exposed cohort. Arch Environ Contam Toxicol 22(4):362-366.

*Hovinga ME, Sowers M, Humphrey HEB. 1993. Environmental exposure and lifestyle predictors of lead, cadmium, PCB, and DDT levels in Great Lakes fish eaters. Arch Environ Health 48(2):98-104.

*Høyer AP, Grandjean P, Jorgensen T, et al. 1998. Organochlorine exposure and risk of breast cancer. Lancet 352:1816-1820.

*HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Program (via TOXNET), Bethesda, MD. January 1995.

*HSDB. 2000. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Program, Bethesda, MD. July 2000.

*Hsieh S-F, Yen Y-Y, Lan S-J, et al. 1996. A cohort study on mortality and exposure to polychlorinated biphenyls. Arch Environ Health 51(6):417-424.

*Hsu C-C, Yu M-LM, Chen Y-CJ, et al. 1994. The Yu-Cheng rice oil poisoning incident. In: Schecter A, ed. Dioxins and health. New York, NY: Plenum Press, 661-684.

*Hsu ST, Ma CI, Hsu SKH, et al. 1985. Discovery and epidemiology of PCB poisoning in Taiwan: A four-year followup. Environ Health Perspect 59:5-10.

*Hu K, Bunce NJ. 1999. Metabolism of polychlorinated dibenzo- *p*-dioxins and related dioxin-like compounds. J Toxicol Environ Health 2:183-210.

*Huang A, Lin S, Inglis R, et al. 1998b. Pre- and postnatal exposure to 3,3',4,4'-tetrachlorobiphenyl: II. effects on the reproductive capacity and fertilizing ability of eggs in female mice. Arch Environ Contam Toxicol 34(2):209-214.

*Huang A, Powell D, Chou K. 1998a. Pre- and postnatal exposure to 3,3',4,4'-tetrachlorobiphenyl: I. effects on breeding ability and sperm fertilizing ability in male mice. Arch Environ Contam Toxicol 34(2):204-208.

*Huang IW, Hong CS, Bush B. 1996. Photocatalytic degradation of PCBs in TiO_2 aqueous suspensions. Chemosphere 32(9):1869-1881.

*Huang S, Gibson GG. 1992. Species and congener specific induction of hepatic cytochrome P4504A by polychlorinated biphenyls. Biochem Pharmacol 43:637-639.

*Huang Y-W, Karasov WH, Patnode KA, et al. 1999. Exposure of northern leopard frogs in the Green Bay ecosystem to polychlorinated biphenyls, polychlorinated dibenzo-*p*-dioxins, and polychlorinated dibenzofurans is measured by direct chemistry but not hepatic ethoxyresorufin-*O*-deethylase activity. Environ Toxicol Chem 18(10):2123-2130.

*Huckins JN, Schwartz TR, Petty JD. 1988. Determination, fate, and potential significance of PCBs in fish and sediment samples with emphasis of selected AHH-inducing congeners. Chemosphere 17:1995-2016.

*Huestis SY, Servos MR, Whittle DM, et al. 1996. Temporal and age-related trends in levels of polychlorinated biphenyl congeners and organochlorine contaminants in Lake Ontario lake trout (salvelinus namaycush). J Great Lakes Res 22(2):310-330.

*Hughes MF, Shrivastava SP, Sumler MR, et al. 1992. Dermal absorption of chemicals: Effect of application of chemicals as a solid, aqueous paste, suspension, or in volatile vehicle. J Toxicol Environ Health. 37:57-71.

*Huisman M, Koopman-Esseboom C, Fidler V, et al. 1995a. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. Early Hum Dev 41:111-127.

*Huisman M, Koopman-Esseboom C, Lanting CI, et al. 1995b. Neurological condition in 18-month-old children perinatally exposed to polychlorinated biphenyls and dioxins. Early Hum Dev 43:165-176.

*Humphrey HEB. 1983. Population studies of PCBs in Michigan residents. In: D'Itri FM, Kamrin MA, eds. PCBs: Human and environmental hazards. Boston, MA: Butterworth, 299-310.

*Humphrey HEB. 1988. Chemical contaminants in the Great Lakes: The human health aspect. In: Evans MS, ed. Toxic contaminants and ecosystem health: A Great Lakes focus. New York, NY: John Wiley and Sons, 153-165.

*Humphrey HEB, Budd ML. 1996. Michigan's fisheater cohorts: A prospective history of exposure. Toxicol Ind Health 12(3-4):499-505.

*Humphrey HEB, Gardiner JC, Pandya JR, et al. 2000. PCB congener profile in the serum of humans consuming Great Lakes fish. Environ Health Perspect 108(2):167-172.

*Hunter DJ, Hankinson SE, Laden F, et al. 1997. Plasma organochlorine levels and the risk of breast cancer [see comments]. N Engl J Med 337(18):1253-1257.

Huntley SL, Iannuzzi TJ, Avantaggio JD, et al. 1997. Combined sewer overflow (CSOs) as sources of sediment contamination in the lower Passaic River, New Jersey. II. Polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and polychlorinated biphenyls. Chemosphere 34(2):233-250.

*Hurme TS, Puhakka JA. 1997. Polychlorinated biphenyl biotransformations by aerobic and anaerobic boreal lake sediment microorganisms. In: Alleman BC, Leeson A, eds. In situ and on-site bioremediation: Volume 2. Columbus, OH: Battelle Press, 427-432.

*Hutton JJ, Meier J, Hackney C. 1979. Comparison of the *in vitro* mutagenicity and metabolism of dimethylnitrosamine and benzo[a]pyrene in tissues from inbred mice treated with phenobarbital, 3-methylcholanthrene or polychlorinated biphenyls. Mutat Res 66:75-94.

Hutzinger O, Safe S, Zitko V. 1972. Photochemical degradation of chlorobiphenyls (PCBs). Environ Health Perspect 1:15-20.

*Hutzinger O, Safe S, Zitko V, eds. 1974. The chemistry of PCBs. Boca Raton, FL: CRC Press.

*Iannuzzi TJ, Huntley SL, Bonnevie NL, et al. 1995. Distribution and possible sources of polychlorinated biphenyls in dated sediments from the Newark Bay Estuary, New Jersey. Arch Environ Contam Toxicol 28:108-117.

Iannuzzi TJ, Huntley SL, Schmidt CW, et al. 1997. Combined sewer overflows (CSOs) as sources of sediment contamination in the lower Passaic River, New Jersey. I. Priority pollutants and inorganic chemicals. Chemosphere 34(2):213-231.

*IARC. 1978. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Volume 18: Polychlorinated biphenyls and polybrominated biphenyls. World Health Organization, Lyon, France.

IARC. 1982. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Supplement 4: Chemicals, industrial processes and industries associated with cancer in humans: IARC monographs, volumes 1 to 29. World Health Organization, Lyon, France.

*IARC. 1987. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Supplement 7: Overall evaluations of carcinogenicity: An updating of IARC monographs volumes 1 to 42. World Health Organization, Lyon, France.

*Iatropoulus MJ, Bailey J, Adams HP, et al. 1978. Response of nursing infant Rhesus to Clophen A-30 or hexachlorobenzene given to their lactating mothers. Environ Res 16:38-47.

*Imamura M, Tung TC. 1984. A trial of fasting: cure for PCB poisoned patients in Taiwan. Am J Ind Med 5:147-153.

*Imanishi J, Nomura H, Matsubara M, et al. 1980. Effect of polychlorinated biphenyl on viral infections in mice. Infect Immun 29(1):275-277.

*IRIS. 1999a. Integrated Risk Information System. Aroclor 1254. U.S. Environmental Protection Agency. http://www.epa.goc/ngispgm3/iris/subst/0289.htm

*IRIS. 1999b. Integrated Risk Information System. Aroclor 1016. U.S. Environmental Protection Agency. http://www.epa.goc/ngispgm3/iris/subst/0462.htm

9. REFERENCES

*IRIS. 1999c. Integrated Risk Information System. Polychlorinated biphenyls (PCBs). U.S. Environmental Protection Agency. http://www.epa.goc/ngispgm3/iris/subst/0294.htm

*IRIS. 1999d. Integrated Risk Information System. Aroclor 1248. U.S. Environmental Protection Agency. http://www.epa.goc/ngispgm3/iris/subst/0649.htm

*IRIS. 2000. Integrated Risk Information System. Polychlorinated biphenyls (PCBs). U.S. Environmental Protection Agency. http://www.epa.goc/ngispgm3/iris/subst/0294.htm

*IRPTC. 1985. Treatment and disposal methods for waste chemicals. IRPTC FILE. International Registry of Potentially Toxic Chemicals, United Nations Environment Programme, Geneva, Switzerland, 20, 262-264.

*Irvine KN, Loganathan BG. 1998. Localized enrichment of PCB levels in street dust due to redistribution by wind. Water Air Soil Pollut 105:603-615.

*Ito N, Nagasaki H, Arai M, et al. 1973. Histopathologic studies on liver tumorigenesis in mice by technical polychlorinated biphenyls and its promoting effect on liver tumors induced by benzene hexachloride. J Natl Cancer Inst 51:1637-1646.

Ito N, Nagasaki H, Makiura S, et al. 1974. Histopathologic studies on liver tumorigenesis in rats treated with polychlorinated biphenyls. Gann 65(6):545-549.

*Iwata Y, Gunther FA, Westlake WE. 1974. Uptake of a PCB (Aroclor 1254) from soil by carrots under field conditions. Bull Environ Contam Toxicol 11(6):523-528.

*Iwata Y, Westlake WE, Gunther FA. 1973. Varying persistence of polychlorinated biphenyls in six California soils under laboratory conditions. Bull Environ Contam Toxicol 9:204-211.

*Jackson JA, Diliberto JJ, Birnbaum LS. 1993. Estimation of octanol-water partition coefficients and correlation with dermal absorption for several polyhalogenated aromatic hydrocarbons. Fundam Appl Toxicol 21:334-344.

*Jacobs LW, O'Connor GA, Overcash MA, et al. 1987. Effects of trace organics in sewage sludges on soil-plant systems and assessing their risk to humans. In: Land application of sludge. Food chain implications. Lewis Publishers, Inc., 103-143.

*Jacobs MN, Santillo D, Johnston PA, et al. 1998. Organochlorine residues in fish oil dietary supplements: Comparison with industrial grade oils. Chemosphere 37(9-12):1709-1721.

*Jacobson JL. 1985. Human exposure to PCBs--congeners and developmental effect. Crisp Data Base National Institutes of Health.

*Jacobson JL, Jacobson SW. 1996a. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med 335(11):783-789.

*Jacobson JL, Jacobson SW. 1996b. Sources and implications of interstudy and interindividual variability in the developmental neurotoxicity of PCBs. Neurotoxicol Teratol 18(3):257-264, 271-6.

*Jacobson JL, Jacobson SW. 1997. Evidence for PCBs as neurodevelopmental toxicants in humans. Neurotoxicology 18(2):415-424.

*Jacobson JL, Fein GG, Jacobson SW, et al. 1984b. The transfer of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) across the human placenta and into maternal milk. Am J Public Health 74:378-379.

*Jacobson JL, Jacobson SW, Humphrey HEB. 1990a. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. J Pediatr 116:38-45.

*Jacobson JL, Jacobson SW, Humphrey HEB. 1990b. Effects of exposure to PCBs and related compounds on growth and activity in children. Neurotoxicol Teratol 12:319-326.

*Jacobson JL, Jacobson SW, Padgett RJ, et al. 1992. Effects of prenatal PCB exposure on cognitive processing efficiency and sustained attention. Dev Psychol 28(2):297-306.

*Jacobson JL, Jacobson SW, Schwartz PM, et al. 1984a. Prenatal exposure to an environmental toxin: A test of the multiple effects model. Dev Psychol 20:523-532.

*Jacobson SW, Fein GG, Jacobson JL, et al. 1985. The effect of intrauterine PCB exposure on visual recognition memory. Child Dev 56:853-860.

Jaffe R, Stemmler EA, Eitzer BD, et al. 1985. Anthropogenic, polyhalogenated, organic compounds in sedentary fish from Lake Huron and Lake Superior tributaries and embayments. J Great Lakes Res 11:156-162.

*James RC, Busch H, Tamburro CH, et al. 1993. Polychlorinated biphenyl exposure and human disease. J Occup Med 35:136-148.

*Jan J, Tratnik M. 1988. Polychlorinated biphenyls in residents around the river Krupa, Slovenia, Yugoslavia. Bull Environ Contam Toxicol 41:809-814.

*Jansen HT, Cooke PS, Porcelli J, et al. 1993. Estrogenic and antiestrogenic actions of PCBs in the female rat: in vitro and in vivo studies. Reprod Toxicol 7(3):237-248.

*Jarman WM, Burns SA, Bacon CE, et al. 1996. High levels of HCB and DDE associated with reproductive failure in prairie falcons (Falco mexicanus) from California. Bull Environ Contam Toxicol 57:8-15.

*Jarman WM, Johnson GW, Bacon CE, et al. 1997. Levels and patterns of polychlorinated biphenyls in water collected from the San Francisco Bay and estuary, 1993-95. Fresenius J Anal Chem 359(3):254-260.

*Jelinek CF, Corneliussen PE. 1976. Levels of PCB's in the U.S. food supply. In: Proceedings of the National Conference on Polychlorinated Biphenyls, Chicago, 1975. Washington, DC: U.S. Environmental Protection Agency, 147-154. EPA-560/6-75-004.

Jensen AA. 1983. Chemical contaminants in human milk. Res Rev 89:1-94.

*Jensen AA. 1987. Polychlorobiphenyls (PCBs), polychlorodibenzo-*p*-dioxins (PCDDs) and polychlorodibenzofurans (PCDFs) in human milk, blood and adipose tissue. Sci Total Environ 64:259-293.

9. REFERENCES

*Jensen AA. 1989. Background levels in humans. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd ed. Amsterdam, The Netherlands: Elsevier Science Publishers, 345-380.

Jensen RG, Clark RM, Ferris AM. 1980. Composition of the lipids in human milk: A review. Lipids 15:345-355.

*Jensen S, Sundström G. 1974. Structures and levels of most chlorobiphenyls in two technical PCB products and in human adipose tissue. Ambio 3:70-76.

*Jensen S, Jansson B, Olsson M. 1979. Number and identity of anthropogenic substances known to be present in Baltic seals and their possible effects on reproduction. Ann NY Acad Sci 320:436-448.

*Jeremiason JD, Eisenreich SJ, Baker JE, et al. 1998. PCB decline in settling particles and benthic recycling of PCBs and PAHs in Lake Superior. Environ Sci Technol 32:3249-3256.

*Jeremiason JD, Hornbuckle KC, Eisenreich SJ. 1994. PCBs in Lake Superior, 1978-1992: Decreases in water concentrations reflect loss by volatilization. Environ Sci Technol 28(5):903-914.

*Johansen HR, Becher G, Polder A, et al. 1994. Congener-specific determination of polychlorinated biphenyls and organochlorine pesticides in human milk from Norwegian mothers living in Oslo. J Toxicol Environ Health 42(2):157-171.

*Johanson CE. 1980. Permeability and vascularity of the developing brain: cerebellum vs cerebral cortex. Brain Res 190:3-16.

Johansson M, Nilsson S, Lund B-O. 1998. Interactions between methylsulfonyl PCBs and the glucocorticoid receptor. Environ Health Perspect 106(12):769-772.

*Johansson N, Haag-Gronlund M, Fransson-Steen R, et al. 1999. Interactive effects of different polychlorinated biphenyls in rat. In:Organohalogen Compounds 42:229-233.

*Johnson BL, DeRosa CT. 1999. Conclusion: Public health implications. Environ Res A80:S246-S248.

*Johnson BL, Hicks HE, Cibulas W, et al. 2000. Public health implications of exposure to polychlorinated biphenyls (PCBs). http://www.astdr.cdc.gov/DT/pcb007.html

*Johnson BL, Hicks HE, De Rosa CT. 1999. Key environmental human health issues in the Great Lakes and St. Lawrence River basins. Environ Res 80:S2-S12.

*Johnson BL, Hicks HE, Jones DE, et al. 1998. Public health implications of persistent toxic substances in the Great Lakes and St. Lawrence basins. J Great Lakes Res 24(2):698-722.

*Johnson KL, Cummings AM, Birnbaum LS. 1997. Promotion of endometriosis in mice by polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls. Environ Health Perspect 105(7):750-755.

Johnstone RM, Court GS, Fesser AC, et al. 1996. Long-term trends and sources of organochlorine contamination in Canadian Tundra peregrine falcons, *falco peregrinus tundrius*. Environ Pollut 93(2):109-120.

*Jones CJ, Backlin BM, Stoddart RW, et al. 1997. Environmental pollutants as aetiological agents in female reproductive pathology: Placental glycan expression in normal and polychlorinated biphenyl (PCB) - exposed mink (*mustela vison*). Placenta 18(8):689-699.

*Jones DH, Lewis DH, Eurell TE, et al. 1979. Alteration of the immune response of channel catfish (*ictalurus punctatus*) by polychlorinated biphenyls. In: Symposium on pathobiology of environmental pollutants: Animal models and wildlife as monitors. Washington, DC: National Academy of Sciences, 385-386.

Jones KC. 1988. Determination of polychlorinated biphenyls in human foodstuffs and tissues: Suggestions for a selective congener analytical approach. Sci Total Environ 68:141-159.

*Jones KC, Duarte-Davidson R. 1997. Transfers of airborne PCDD/Fs to bulk deposition collectors and herbage. Environ Sci Technol 31:2937-2943.

*Jones KC, Sanders G, Wild SR, et al. 1992. Evidence for a decline of PCBs and PAHs in rural vegetation and air in the United Kingdom. Nature 356:137-140.

*Juarez de Ku LM, Sharma-Stokkermans M, Meserve LA. 1994. Thyroxine normalizes polychlorinated biphenyl (PCB) dose-related depression of choline acetyltransferase (ChAT) activity in hippocampus and basal forebrain of 15-day-old rats. Toxicology 94:19-30.

Kaiser C, Lorenz W, Bahadir M. 1993. Residues in recycled goods from shredded plastics. II. Communication. Fresenius Environ Bull 2(7):363-369.

*Kakela R, Kakela A, Hyvarinen H, et al. 1999. Vitamins A_1, A_2, and E in minks exposed to polychlorinated biphenyls (Aroclor 1242) and copper, via diet based on freshwater or marine fish. Environ Toxicol Chem 18(11):2595-2599.

*Kalina I, Sram RJ, Konecna H, et al. 1991. Cytogenetic analysis of peripheral blood lymphocytes in workers occupationally exposed to polychlorinated biphenyls. Teratog Carcinog Mutagen 11:77-82.

*Kamei M, Ohgaki S, Kanbe T, et al. 1996. Highly hydrogenated dietary soybean oil modifies the responses to polychlorinated biphenyls in rats. Lipids 31(11):1151-1156.

*Kaminsky LS, Kennedy MW, Adams SM, et al. 1981. Metabolism of dichlorobiphenyls by highly purified isozymes of rat liver cytochrome P-450. Biochemistry 20:7379-7384.

*Kamrin MA, Ringer RK. 1994. PCB residues in mammals: A review. Toxicol Environ Chem 41:63-84.

*KAN-DO Office and Pesticides Team. 1995. Accumulated pesticide and industrial chemical findings from a ten-year study of ready-to-eat foods. J AOAC Int 78(3):614-631.

*Kannan K, Tanabe S, Borrell A, et al. 1993. Isomer-specific analysis and toxic evaluation of polychlorinated biphenyls in striped dolphins affected by an epizootic in the western Mediterranean Sea. Arch Environ Contam Toxicol 25:227-233.

*Kannan K, Tanabe S, Giesy JP, et al. 1997. Organochlorine pesticides and polychlorinated biphenyls in foodstuffs from Asian and oceanic countries. Rev Environ Contam Toxicol 152:1-55.

9. REFERENCES

*Kannan K, Yamashita N, Imagawa T, et al. 2000. Polychlorinated naphthalenes and polychlorinated biphenyls in fishes from Michigan waters including the Great Lakes. Environ Sci Technol 34:566-572.

*Karickhoff SW. 1981. Semi-empirical estimation of sorption of hydrophobic pollutants on natural sediments and soils. Chemosphere 10:833-846.

Kashimoto T, Miyata H. 1986. Differences between Yusho and other kinds of poisoning involving only PCBs. In: Waid JS, ed. PCBs and the environment, Vol. III. Boca Raton: CRC Press, 2-26.

*Kasza L, Collins WT, Capen CC, et al. 1978. Comparative toxicity of polychlorinated biphenyl and polybrominated biphenyl in the rat thyroid gland: Light and electron microscopic alterations after subacute dietary exposure. J Environ Pathol Toxicol 1:587-599.

*Kato N, Yoshida A. 1980. Effect of dietary PCB on hepatic cholesterogenesis in rats. Nutr Rep Int 21:107-112.

*Kato N, Kawai K, Yoshida A. 1981a. Effect of dietary level of ascorbic acid on the growth, hepatic lipid peroxidation, and serum lipids in guinea pigs fed polychlorinated biphenyls. J Nutr 111:1727-1733.

*Kato N, Kawai K, Yoshida A. 1982b. Effects of dietary polychlorinated biphenyls and protein level on liver and serum lipid metabolism of rats. Agric Biol Chem 46:703-707.

*Kato N, Mochizuki S, Kawai K, et al. 1982a. Effect of dietary level of sulfur-containing amino acids on liver drug-metabolizing enzymes, serum cholesterol and urinary ascorbic acid in rats fed PCB. J Nutr 112:848-854.

*Kato N, Tani T, Yoshida A. 1981b. Effect of dietary quality of protein on liver microsomal mixed function oxidase system, plasma cholesterol and urinary ascorbic acid in rats fed PCB. J Nutr 111:123-133.

*Kato S, McKinney JD, Matthews HB. 1980. Metabolism of symmetrical hexachlorobiphenyl isomers in the rat. Toxicol Appl Pharmacol 53:389-398.

*Kato Y, Haraguchi K, Kawashima M, et al. 1995. Induction of hepatic microsomal drug-metabolizing enzymes by methylsulphonyl metabolites of polychlorinated biphenyl congeners in rats. Chem Biol Interact 95:257-268.

*Kearney JP, Cole DC, Ferron LA, et al. 1999. Blood PCB, *p,p*-DDE, and mirex levels in Great Lakes fish and waterfowl consumers in two Ontario communities. Environ Res 80(A):S138-S149.

*Kelly AG, Cruz I, Wells DE. 1993. Polychlorobiphenyls and persistent organochlorine pesticides in sea water at the pg l^{1} level. Sampling apparatus and analytical methodology. Anal Chim Acta 276(1):3-13.

*Kennish MJ, Ruppel BE. 1996. Polychlorinated biphenyl contamination in selected estuarine and coastal marine finfish and shellfish of New Jersey. Estuaries 19(2A):288-295.

*Kester MHA, Bulduk S, Tibboel D, et al. 2000. Potent inhibition of estrogen sulfotransferase by hydroxylated PCB metabolites: A novel pathway explaining the estrogenic activity of PCBs. Endocrinology 141(5):1897-1900.

9. REFERENCES

*Kholkute SD, Rodriguez J, Dukelow WR. 1994a. Effects of polychlorinated biphenyls (PCBs) on in vitro fertilization in the mouse. Reprod Toxicol 8:69-73.

Kholkute SD, Rodriguez J, Dukelow WR. 1994b. Reproductive toxicity of Aroclor-1254: Effects on oocyte, spermatozoa, in vitro fertilization, and embryo development in the mouse. Reprod Toxicol 8:487-493.

Kidwell JM, Phillips LJ, Birchard GF. 1995. Comparative analyses of contaminant levels in bottom feeding and predatory fish using the National Contaminant Biomonitoring Program data. Bull Environ Contam Toxicol 54:919-923.

Kihlstrom JE, Lundberg C, Orberg J, et al. 1975. Sexual functions of mice neonatally exposed to DDT or PCB. Environ Physiol Biochem 5:54-57.

*Kihlstrom JE, Olsson M, Jensen SJ, et al. 1992. Effects of PCB and different fractions of PCB on the reproduction of the mink (*mustela vison*). Ambio 21(8):563-569.

Kilburn KH, Warshaw RH, Hanscom B. 1994. Balance measured by head (and trunk) tracking and a force platform in chemically (PCB and TCE) exposed and referent subjects. Occup Environ Med 51(6):381-385.

Kim NK, Stone DW. 1980. Organic chemicals and drinking water. New York State Department of Health, Albany, NY, 101.

*Kimbrough RD. 1987. Human health effect of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs). Ann Rev Pharmacol Toxicol 27:87-111.

*Kimbrough RD. 1995. Polychlorinated biphenyls (PCBs) and human health: An update. Crit Rev Toxicol 25:133-166.

*Kimbrough RD, Linder RE. 1974. Induction of adenofibrosis and hepatomas in the liver of Balb/cJ mice by polychlorinated biphenyls (Aroclor 1254). J Natl Cancer Inst 53:547-552.

*Kimbrough RD, Doemland ML, LeVois ME. 1999a. Mortality in male and female capacitor workers exposed to polychlorinated biphenyls. J Occup Environ Med 41(3):161-171.

*Kimbrough RD, Doemland ML, LeVois ME. 1999b. Author's reply to letter to the editor re: "Evidence of excess cancer mortality in a cohort of workers exposed to polychlorinated biphenyls". J Occup Environ Med 41(9):739-745.

*Kimbrough RD, Linder RE, Gaines TB. 1972. Morphological changes in livers of rats fed polychlorinated biphenyls: Light microscopy and ultrastructure. Arch Environ Health 25:354-364.

*Kimbrough RD, Squire RA, Linder RE, et al. 1975. Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Aroclor 1260. J Natl Cancer Inst 55:1453-1459.

*Kimura NT, Kanematsu T, Baba T. 1976. Polychlorinated biphenyl(s) as a promotor in experimental hepatocarcinogenesis in rats. Z Krebsforsch 87:257-266.

King TL, Haines BK, Uthe JF. 1996. Non-, mono-, and di-o-chlorobiphenyl concentrations and their toxic equivalents to 2,3,7,8-tetrachlorodibenzo(p)dioxin in Aroclors and digestive glands from American lobster (homarus americanus) captured in Atlantic Canada. Bull Environ Contam Toxicol 57:465-472.

*Kiviranta H, Purkunen R, Vartiainen T. 1999. Levels and trends of PCDD/Fs and PCBs in human milk in Finland. Chemosphere 38(2):311-323.

*Klasson KT, Barton JW, Evans BS, et al. 1996. Reductive microbial dechlorination of indigenous polychlorinated biphenyls in soil using a sediment-free inoculum. Biotechnology Progress 12:310-315.

*Klasson-Wehler E, Bergman A, Brandt I, et al. 1989a. 3,3',4,4'-Tetrachlorobiphenyl: Excretion and tissue retention of hydroxylated metabolites in the mouse. Drug Metab Dispos 17:441-448.

*Klasson-Wehler E, Bergman A, Kowalski B, et al. 1987. Metabolism of 2,3,4',6-tetrachlorobiphenyl: Formation and tissue localization of mercapturic acid pathway metabolites in mice. Xenobiotica 17:477-486.

*Klasson-Wehler E, Jonsson J, Bergman A, et al. 1989b. 3,3',4,4'-tetrachlorobiphenyl and 3,3',4,4',5-pentachlorobiphenyl-tissue-localization and metabolic fate in the mouse. Chemosphere 19:809-812.

*Klasson-Wehler E, Lindberg L, Jonsson CJ, et al. 1993. Tissue retention and metabolism of 2,3,4,3',4'-pentachlorobiphenyl in mink and mouse. Chemosphere 27:2397-2412.

*Kleinert SJ. 1976. Sources of polychlorinated biphenyls in Wisconsin. In: Proceedings of the National Conference on Polychlorinated Biphenyls, Chicago, 1975. Washington, DC: U.S. Environmental Protection Agency, 124-126. EPA-560/6-75-004.

Kling D, Gamble W. 1980. In vivo inhibition of citrate cleavage enzyme by polychlorinated biphenyls. Experientia 37:1258-1259.

*Kling D, Gamble W. 1982. Cholesterol biosynthesis in polychlorinated biphenyl-treated rats. Environ Res 27:10-15.

*Kling D, Kunkle J, Roller AS, et al. 1978. Polychlorinated biphenyls: *In vivo* and *in vitro* modifications of cholesterol and fatty acid biosynthesis. J Environ Pathol Toxicol 1:813-828.

*Kluwe WM, Herrmann CL, Hook JB. 1979. Effects of dietary polychlorinated biphenyls and polybrominated biphenyls on the renal and hepatic toxicities of several chlorinated hydrocarbon solvents in mice. J Toxicol Environ Health 5:605-615.

*Knap AH, Binkley KS. 1991. Chlorinated organic compounds in the troposphere over the western North Atlantic Ocean measured by aircraft. Atmos Environ 25A:1507-1516.

*Kocan A, Petrik J, Chovancova J, et al. 1994. Method for the group separation of non-*ortho*-, mono-*ortho* and multi-*ortho*-substituted polychlorinated biphenyls and polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans using activated carbon chromatography. J Chromatogr 665:139-153.

*Kodavanti PR, Tilson HA. 1997. Structure-activity relationships of potentially neurotoxic PCB congeners in the rat. Neurotoxicology 18(2):425-441.

*Kodavanti PRS, Derr-Yellin EC, Mundy WR, et al. 1998. Repeated exposure of adult rats to Aroclor 1254 causes brain region-specific changes in intracellular Ca2+ buffering and protein kinase C activity in the absence of changes in tyrosine hydroxylase. Toxicol Appl Pharmacol 153:186-198.

*Kodavanti PRS, Shin D-S, Tilson HA, et al. 1993. Comparative effects of two polychlorinated biphenyl congeners on calcium homeostasis in rat cerebellar granule cells. Toxicol Appl Pharmacol 123:97-106.

*Kodavanti PRS, Ward TR, McKinney JD, et al. 1995. Increased [^{3}H]phorbol ester binding in rat cerebellar granule cells by polychlorinated biphenyl mixtures and congeners: Structure-activity relationships. Toxicol Appl Pharmacol 130:140-148.

*Kodavanti PRS, Ward TR, McKinney JD, et al. 1996a. Increased [^{3}H]phorbol ester binding in rat cerebellar granule cells and inhibition of $^{45}Ca^{2+}$ sequestration in rat cerebellum by polychlorinated diphenyl ether congeners and analogs: Structure-activity relationships. Toxicol Appl Pharmacol 138:251-261.

*Kodavanti PRS, Ward TR, McKinney JD, et al. 1996b. Inhibition of microsomal and mitochondrial Ca^{2+}-sequestration in rat cerebellum by polychlorinated biphenyl mixtures and congeners: Structure-activity relationships. Arch Toxicol 70:150-157.

*Koester CJ, Hites RA. 1992. Photodegredation of polychlorinated dioxins and dibenzofurans adsorbed to fly ash. Environ Sci Technol 26:502-507.

*Koga N, Beppu M, Ishida C, et al. 1989. Further studies on metabolism *in vivo* of 3,4,3',4'-tetrachlorobiphenyl in rats: identification of minor metabolites in rat feces. Xenobiotica 19:1307-1318.

Koga N, Beppu M, Yoshimura H. 1990. Metabolism *in vivo* of 3,4,5,3',4'-pentachlorobiphenyl and toxicological assessment of the metabolite in rats. J Pharmacobiodyn 13:497-506.

*Koga N, Shin'yama A, Ishida C, et al. 1992. A new metabolite of 2,4,3',4'-tetrachlorobiphenyl in rat feces. Chem Pharm Bull 40(12):3338-3339.

Koga Y, Tsuda M, Ariyoshi N, et al. 1994. Induction of bilirubin UDP-glucuronyltransferase and CYP4A1 P450 by co-planar PCBs: Different responsiveness of guinea pigs and rats. Chemosphere 28:639-645.

*Kohl SD, Rice JA. 1998. The binding of contaminants to humin: a mass balance. Chemosphere 36(2):251-261.

Kokoszka L, Flood J. 1985. A guide to EPA-approved PCB disposal methods. Chem Eng 92:41-43.

*Koller LD. 1977. Enhanced polychlorinated biphenyl lesions in Moloney leukemia virus-infected mice. Clin Toxicol 11:107-116.

*Komori M, Nishio K, Kitada M et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human liver. Biochemistry 29:4430-4433.

*Kono TK, Yamana Y. 1979. [Ocular symptoms of oil disease patients (report 4): Investigation 10 years after onset.] Fukuoka Igaku Zasshi 70:181-186. (Japanese)

*Koopman-Esseboom C, Huisman M, Weisglas-Kuperus N, et al. 1994b. PCB and dioxin levels in plasma and human milk of 418 Dutch women and their infants. Predictive value of PCB congener levels in maternal plasma for fetal and infant's exposure to PCBs and dioxins. Chemosphere 28(9):1721-1732.

*Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, et al. 1994a. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. Pediatr Res 36(4):468-473.

*Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MAJ, et al. 1996. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatrics 97:700-706.

*Korach KS, Sarver P, Chae K, et al. 1988. Estrogen receptor-binding activity of polychlorinated hydroxybiphenyls: Conformationally restricted structural probes. Mol Pharmacol 33:120-126.

*Korrick SA, Altshul L. 1998. High breast milk levels of polychlorinated biphenyls (PCBs) among four women living adjacent to a PCB-contaminated waste site. Environ Health Perspect 106(8):513-518.

*Koslowski SE, Metcalfe CD, Lazar R, et al. 1994. The distribution of 42 PCBs, including three coplanar congeners, in the food web of the western basin of Lake Erie. J Great Lakes Res 20(1):260-270.

Kosson DS, Dienemann EA, Ahlert RC. 1985. Characterization and treatability studies of an industrial landfill leachate (Kin-buc I). Proceedings of the Industrial Waste Conference 39:329-341.

*Kostyniak PJ, Stinson C, Greizerstein HB, et al. 1999. Relation of Lake Ontario fish consumption, lifetime lactation, and parity to breast milk polychlorobiphenyl and pesticide concentrations. Environ Res 80:S166-S174.

Kovacevic R, Vojinovic-Miloradov M, Teodorovic I, et al. 1995. Effect of PCBs on androgen production by suspension of adult rat leydig cells *in vitro*. J Steroid Biochem Mol Biol 52(6):595-597.

*Kramer VJ, Helferich WG, Bergman A, et al. 1997. Hydroxylated polychlorinated biphenyl metabolites are anti-estrogenic in a stably transfected human breast adenocarcinoma (MCF7) cell line. Toxicol Appl Pharmacol 144:363-374.

*Kraul I, Karlog O. 1976. Persistent organochlorinated compounds in human organs collected in Denmark 1972-73. Acta Pharmacol Toxicol 38:38-48.

*Krauthacker B, Reiner E, Votava-Raic A, et al. 1998. Organochlorine pesticides and PCBs in human milk collected from mothers nursing hospitalized children. Chemosphere 37(1):27-32.

*Kreiss K. 1985. Studies on populations exposed to polychlorinated biphenyls. Environ Health Perspect 60:193-199.

*Kreiss K, Roberts C, Humphrey HEB. 1982. Serial PBB levels, PCB levels, and clinical chemistries in Michigan's PBB cohort. Arch Environ Health 37:141-147.

*Kreiss K, Zack MM, Kimbrough RD, et al. 1981. Association of blood pressure and polychlorinated biphenyl levels. J Am Med Assoc 245:2505-2509.

*Krieger N, Wolff MS, Hiatt RA, et al. 1994. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. J Natl Cancer Inst 86(8):589-599.

*Kremer H, Lilienthal H, Hany J, et al. 1999. Sex-dependent effects of maternal PCB exposure on the electroretinogram in adult rats. Neurotoxicol Teratol 21(1):13-19.

*Krishnan K, Andersen M. 1994. Physiologically-based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd edition. New York, NY: Raven Press, Ltd, 149-188.

*Krishnan K, Andersen ME, Clewell HJ III, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang R, ed. Toxicology of chemical mixtures. New York, NY: Academic Press, 399-437.

*Krishnan V, Safe S. 1993. Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), and dibenzofurans (PCDFs) as antiestrogens in MCF-7 human breast cancer cells: Quantitative structure-activity relationships. Toxicol Appl Pharmacol 120(1):55-61.

Krutovskikh VA, Mesnil M, Mazzoleni G, et al. 1995. Inhibition of rat liver gap junction intercellular communication by tumor-promoting agents *in vivo*: Association with aberrant localization of connexin proteins. Lab Invest 72:571-577.

*Kucklick JR, Baker JE. 1998. Organochlorines in Lake Superior's food web. Environ Sci Technol 32:1192-1198.

*Kuehl DW, Haebler R. 1995. Organochlorine, organobromine, metal and selenium residues in bottlenose dolphins (tursiops truncatus) collected during an unusual mortality event in the Gulf of Mexico, 1990. Arch Environ Contam Toxicol 28:494-499.

*Kuehl DW, Butterworth B, Marquis PJ. 1994. A national study of chemical residues in fish. III: Study results. Chemosphere 29(3):523-535.

*Kuhnlein HV, Receveur O, Muir CDG, et al. 1995. Arctic indigenous women consume greater than acceptable levels of organochlorines. J Nutr 125:2501-2510.

*Kuiper J, Hanstveit AO. 1988. Biodegradation rates of xenobiotic compounds in plankton communities. In: Capuzzo JM, Kester DR, eds. Oceanic processes in marine pollution. Volume 1. Malabar, FL: Robert E. Krieger Publishing Company, 79-88.

*Kuipers B, Cullen WR, Mohn WM. 1999. Reductive dechlorination of nonachlorobiphenyls and selected octachlorobiphenyls by microbial enrichment cultures. Environ Sci Technol 33:3579-3585.

*Kunita N, Hori S, Obana H, et al. 1985. Biological effects of PCBs, PCQs and PCDFs present in the oil causing Yusho and Yu-Cheng. Environ Health Perspect 59:79-84.

*Kuo C-E, Liu S-M, Liu C. 1999. Biodegradation of coplanar polychlorinated biphenyls by anaerobic microorganisms from estuarine sediments. Chemosphere 39(9):1445-1458.

*Kurachi M, Mio T. 1983a. On fluctuation of PCBs under various unnatural conditions in mice. Agric Biol Chem 47:1173-1181.

9. REFERENCES

*Kurachi M, Mio T. 1983b. On the formation of a conjugate of PCBs with glutathione and its further metabolism in mice or rats. Agric Biol Chem 47:1193-1199.

*Kuratsune M. 1989. Yusho, with reference to Yu-Cheng. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd ed. Amsterdam, The Netherlands: Elsevier Science Publishers, 381-400.

Kuratsune M, Shapiro R. 1984. PCB poisoning in Japan and Taiwan. Am J Ind Med 5:1-153.

*Kuratsune M, Nakamura Y, Ikeda M, et al. 1987. Analysis of deaths seen among patients with Yusho-A preliminary report. Chemosphere 16:2085-2088.

*Kuroiwa Y, Murai Y, Santa T. 1969. [Neurological and nerve conduction velocity studies on 23 patients with chlorobiphenyl poisoning.] Fukuoka Igaku Zasshi 60:462-463. (Japanese)

*Kurokawa Y, Matsueda T, Nakamura M, et al. 1996. Characterization of non-*ortho* coplanar PCBs, polychlorinated dibenzo-p-dioxins and dibenzofurans in the atmosphere. Chemosphere 32(3):491-500.

*Kusuda M. 1971. A study on the sexual functions of women suffering from rice-bran oil poisoning. Sanka to Fujinka 38:1062-1072.

*Kutz FW, Wood PH, Bottimore DP. 1991. Residues in human adipose tissue. Rev Environ Contam Toxicol 120:61-81.

*Kuwabara K, Yakushiji T, Watanabe I, et al. 1979. Increase in the human blood PCB levels promptly following ingestion of fish containing PCBs. Bull Environ Contam Toxicol 21:273-278.

*Lackmann GM, Angerer J, Salzberger U, et al. 1999. Influence of maternal age and duration of pregnancy on serum concentrations of polychlorinated biphenyls and hexachlorobenzene in full-term neonates. Biol Neonate 76:214-219.

*Lacorte S, Eggens ML. 1993. Influence of diet on the bioaccumulation of PCBs. Sci Total Environ Suppl(Pt 1):479-489.

*Lai T-J, Guo Y-L, Yu M-L, et al. 1994. Cognitive development in Yucheng children. Chemosphere 29(9-11):2405-2411.

*Laib RJ, Rose J, Brunn H. 1991. Hepatocarcinogenicity of PCB congeners: I. Initiation and promotion of enzyme-altered rat liver foci by 2,2',4,5'-tetra- and 2,2',4,4',5,5'-hexachlorobiphenyl. Toxicol Environ Chem 34:19-22.

*Lake CA, Lake JL, Haebler R, et al. 1995a. Contaminant levels in harbor seals from the northeastern United States. Arch Environ Contam Toxicol 29:128-134.

*Lake JL, McKinney R, Lake CA, et al. 1995b. Comparisons of patterns of polychlorinated biphenyl congeners in water, sediment, and indigenous organisms from New Bedford Harbor, Massachusetts. Arch Environ Contam Toxicol 29:207-220.

*Lake JL, Pruell RJ, Osterman FA. 1992. An examination of dechlorination processes and pathways in New Bedford Harbor sediments. Mar Environ Res 33(1):31-47.

*Lambert GH, Hsu CC, Humphrey H, et al. 1992. Cytochrome P450IA2 in-vivo induction: A potential biomarker of polyhalogenated biphenyls and their related chemical's effects on the human. Chemosphere 25:197-200.

*Lan S-J, Yen Y-Y, Yang C-H, et al. 1987. A study of the birth weights of transplancental Yu-Cheng babies. Kaohsiung J Med Sci 3:273-282.

Langer P, Kausitz J, Tajtakova M, et al. 1997. Decreased blood level of β_2-microglobulin in the employees of a factory which produced polychlorinated biphenyls. Chemosphere 34(12):2595-2600.

*Langer P, Tajtakova M, Fodor G, et al. 1998. Increased thyroid volume and prevalence of thyroid disorders in an area heavily polluted by polychlorinated biphenyls. Eur J Endocrinol 139:402-409.

Lans MC, Klasson-Wehler E, Willemsen M, et al. 1993. Structure-dependent, competitive interaction of hydroxy-polychlorobiphenyls, -dibenzo-*p*-dioxins and -dibenzofurans with human transthyretin. Chem Biol Interact 88(1):7-21.

Lans MC, Spiertz C, Brouwer A, et al. 1994. Different competition of thyroxine binding to transthyretin and thyroxine-binding globulin by hydroxy-PCBs, PCDDs and PCDFs. Eur J Pharmacol 270:129-136.

*Lanting CI, Fidler V, Huisman M, et al. 1998a. Determinants of polychlorinated biphenyl levels in plasma from 42-month-old children. Arch Environ Contam Toxicol 35:135-139.

*Lanting CI, Huisman M, Muskiety FAJ, et al. 1998b. Polychlorinated biphenyls in adipose tissue, liver, and brain from nine stillborns of varying gestational ages. Pediatr Res 44:222-225.

*Lanting CI, Patandin S, Fidler V, et al. 1998c. Neurological condition in 42-month-old children in relation to pre- and postnatal exposure to polychlorinated biphenyls and dioxins. Early Hum Dev 50:283-292.

*Larsen BR, Turrio-Baldassarri L, Nilsson T, et al. 1994. Toxic PCB congeners and organochlorine pesticides in Italian human milk. Ecotoxicol Environ Saf 28:1-13.

*Larsen JC. 1995. Levels of pollutants and their metabolites: exposure to organic substances. Toxicology 101:11-27.

*Larsson P. 1985. Contaminated sediments of lakes and oceans act as sources of chlorinated hydrocarbons for release to water and atmosphere. Nature 317:347-349.

*Larsson P, Lemkemeier K. 1989. Microbial mineralization of chlorinated phenols and biphenyls in sediment-water systems from humic and clear-water lakes. Water Res 23:1081-1085.

*Larsson P, Okla L. 1989. Atmospheric transport of chlorinated hydrocarbons to Sweden in 1985 compared to 1973. Atmos Environ 23:1699-1711.

*Larsson P, Sodergren A. 1987. Transport of polychlorinated biphenyls (PCBs) in freshwater mesocosms from sediment to water and air. Water Air Soil Pollut 36:33-46.

*Lawrence C. 1977. PCB? and melanoma [Letter]. N Engl J Med 296:108.

*Lawrence J and Toxine HM. 1977. Polychlorinated biphenyl concentrations in sewage and sludges of some waste treatment plants in southern Ontario. Bull Environ Contam Toxicol 17:49-56.

*Lawton RW, Brown JF, Ross MR, et al. 1985b. Comparability and precision of serum PCB measurements. Arch Environ Health 40:29-37.

*Lawton RW, Ross MR, Feingold J, et al. 1985a. Effects of PCB exposure on biochemical and hematological findings in capacitor workers. Environ Health Perspect 60:165-184.

*Lawton RW, Ross MR, Feingold J, et al. 1986. Spirometric findings in capacitor workers occupationally exposed to polychlorinated biphenyls (PCBs). J Occup Med 28:453-456.

*Lead WA, Steinnes E, Bacon JR, et al. 1997. Polychlorinated biphenyls in the UK and Norwegian soils: spatial and temporal trends. Sci Total Environ 193:229-236.

*Lebel G, Dodin S, Ayotte P, et al. 1998. Organochlorine exposure and the risk of endometriosis. Fertil Steril 69(2):221-228.

*Le Bel GL, Williams DT. 1986. Determination of halogenated contaminants in human adipose tissue. J Assoc Off Anal Chem 69:451-458.

Leblanc GA. 1995. Trophic-level differences in the bioconcentration of chemicals: Implications in assessing environmental biomagnification. Environ Sci Technol 29:154-160.

*Lecavalier P, Chu I, Yagminas A, et al. 1997. Subchronic toxicity of 2,2',3,3',4,4'-hexachlorobiphenyl in rats. J Toxicol Environ Health 51(3):265-277.

*Lee, H-B, Peart TE. 1994. Optimization of supercritical carbon dioxide extraction for polychlorinated biphenyls and chlorinated benzenes from sediments. J Chromatogr 663:87-95.

*Lee MC, Griffin RA, Miller ML, et al. 1979. Adsorption of water-soluble polychlorinated biphenyl Aroclor 1242 and used capacitor fluid by soil materials and coal chars. J Environ Sci Health A14:415-442.

*Lee W-J, Su C-C, Sheu H-L, et al. 1996. Monitoring and modeling of PCB dry deposition in urban area. Journal of Hazardous Materials 49:57-88.

Leece B, Denomme MA, Towner R, et al. 1985. Polychlorinated biphenyls: Correlation between in vivo and in vitro quantitative structure-activity relationships (QSARs). J Toxicol Environ Health 16:379-388.

*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: implications for practice. Pediatr Clin North Am 44:55-77.

*Leister DL, Baker JE. 1994. Atmospheric deposition of organic contaminants to the Chesapeake Bay. Atmos Environ 28(8):1499-1520.

*Leoni V, Fabiani L, Marinelli G, et al. 1989. PCB and other organochlorine compounds in blood of women with or without miscarriage: A hypothesis of correlation. Ecotoxicol Environ Safety 17:1-11.

*Leonzio C, Fossi MC, Casini S. 1996a. Porphyrins as biomarkers of methylmercury and PCB exposure in experimental quail. Bull Environ Contam Toxicol 56:244-250.

*Leonzio C, Monaci F, Fossi MC, et al. 1996b. Multiresponse biomarker evaluation of interactions between methylmercury and arochlor 1260 in quail. Ecotoxicology 5:365-376.

*Lester R, Schmid R. 1964. Bilirubin metabolism. New Engl J Med 270:779-786.

*Letcher RJ, Norstrom RJ, Bergman A. 1995. Geographical distribution and identification of methylsulphone PCB and DDE metabolites in pooled polar bear (*ursus maritimus*) adipose tissue from western hemisphere Arctic and Subarctic regions. Sci Total Environ 160:409-420.

*Letcher RJ, Norstrom RJ, Muir DCG. 1998. Biotransformation versus bioaccumulation: Sources of methyl sulfone PCB and 4,4'-DDE metabolites in the polar bear food chain. Environ Sci Technol 32:1656-1661.

*Letz G. 1983. The toxicology of PCB's: An overview for clinicians. West J Med 138:534-540.

*Leung H. 1993. Physiologically-based pharmacokinetic modelling. In: Ballantine B, Marro T, Turner T, eds. General and applied toxicology. Vol. I. New York, NY: Stockton Press, 153-164.

*Leung H-W, Ku RH, Paustenbach DJ, et al. 1988. A physiologically based pharmacokinetic model for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in C57BL/6J and DBA/2J mice. Toxicol Lett 42:15-28.

*Levengood JM, Ross SC, Stahl ML, et al. 1999. Organochlorine pesticide and polychlorinated biphenyl residues in Canada geese (*branta canadensis*) from Chicago, Illinois. Vet Hum Toxicol 41(2):71-75.

*Levin ED, Schantz SL, Bowman RE. 1988. Delayed spatial alternation deficits resulting from perinatal PCB exposure in monkeys. Arch Toxicol 62:267-273.

*Lewis RG, Martin BE, Sgontz DL, et al. 1985. Measurements of fugitive atmospheric emissions of polychlorinated biphenyls from hazardous waste landfills. Environ Sci Technol 19:986-991.

Li MH, Hansen LG. 1995. Uterotropic and enzyme induction effects of 2,2',5-trichlorobiphenyl. Bull Environ Contam Toxicol 54(4):494-500.

*Li MH, Hansen LG. 1996a. Responses of prepubertal female rats to environmental PCBs with high and low dioxin equivalencies. Fundam Appl Toxicol 33(2):282-293.

*Li MH, Hansen LG. 1996b. Enzyme induction and acute endocrine effects in prepubertal female rats receiving environmental PCB/PCDF/PCDD mixtures. Environ Health Perspect 104(7):712-722.

*Li M-H, Hansen LG. 1997. Consideration of enzyme and endocrine interactions in the risk assessment of PCBs. Reviews in Toxicology 1:71-156.

*Li M-H, Rhine C, Hansen LG. 1998. Hepatic enzyme induction and acute endocrine effects of 2,3,3',4',6'-pentachlorobiphenyl in prepubertal female rats. Arch Environ Contam Toxicol 35:97-103.

*Li M-H, Zhao Y-D, Hansen LG. 1994. Multiple dose toxicokinetic influence on the estrogenicity of 2,2',4,4',5,5'-hexachlorobiphenyl. Bull Environ Contam Toxicol 53:583-590.

*Liang Y, Wong MH, Shutes RBE, et al. Ecological risk assessment of polychlorinated biphenyl contamination in the Mai Po Marshes Nature Reserve, Hong Kong. Wat Res 33(6):1337-1346.

*Liberti L, Petruzzelli D, Tiravanti G. 1992. Accidental road spilling of polychlorobiphenyls-A case history. Water Sci Technol 25(3):239-246.

*Liem AKD. 1999. Basic aspects of methods for the determination of dioxins and PCBs in foodstuffs and human tissues. Trends in Analytical Chemistry 18(6):429-439.

*Lilienthal H, Winneke G. 1991. Sensitive periods for behavioral toxicity of polychlorinated biphenyls: Determination by cross-fostering in rats. Fundam Appl Toxicol 17:368-375.

*Lilienthal H, Neuf M, Munoz C, et al. 1990. Behavioral effects of pre- and postnatal exposure to a mixture of low chlorinated PCBs in rats. Fundam Appl Toxicol 15:457-467.

*Liljegren G, Hardell L, Lindstrom G, et al. 1998. Case-control study on breast cancer and adipose tissue concentrations of congener specific polychlorinated biphenyls, DDE and hexachlorobenzene. Eur J Cancer Prev 7:135-140.

*Lin JM, Que Hee SS. 1985. Optimization of perchlorination conditions for some representative polychlorinated biphenyls. Anal Chem 57:2130-2134.

*Lin JM, Que Hee SS. 1987. Change in chromatogram patterns after volatilization of some Aroclors, and the associated quantitation problems. Am Ind Hyg Assoc J 48:599-607.

*Linder RE, Gaines TB, Kimbrough RD. 1974. The effect of polychlorinated biphenyls on rat reproduction. Food Cosmet Toxicol 12:63-77.

*Litterst CL, Farber TM, Baker AM, et al. 1972. Effect of polychlorinated biphenyls on hepatic microsomal enzymes in the rat. Toxicol Appl Pharmacol 23:112-122.

*Livingston, AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4:301-324.

*Lober M, Cleverly D, Schaum J, et al. 1994. Development and validation of an air-to-beef food chain model for dioxin-like compounds. Sci Total Environ 156:39-65.

*Lockhart WL, Muir CG, Wilkinson P, et al. 1998. Chemical contaminants in fish and sediment core samples from the Dnipro River, Ukraine, 1994. Water Qual Res J Can 33(4):489-509.

*Loganathan BG, Irvine KN, Kannan K, et al. 1997. Distribution of selected PCB congeners in the Babcock Street sewer district: a multimedia approach to identify PCB sources in combined sewer overflows (CSOS) discharging to the Buffalo River, New York. Arch Environ Contam Toxicol 33(2):130-140.

*Loganathan BG, Kannan K, Watanabe I, et al. 1995. Isomer-specific determination and toxic evaluation of polychlorinated biphenyls, polychlorinated/brominated dibenzo-p-dioxins and dibenzofurans, polybrominated biphenyl ethers, and extractable organic halogen in carp from the Buffalo River, New York. Environ Sci Technol 29(7):1832-1838.

*Lohmann R, Jones KC. 1998. Dioxins and furans in air and deposition: a review of levels, behaviour and processes. Sci Total Environ 219:53-81.

Lokietz H, Dowben RM, Hsia DYY. 1963. Studies on the effect of Novobiocin and glucuronyl transferase. Pediatrics 32:47-51.

*Longcope C. 2000. The male and female reproductive systems in hypothyroidism. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's the thyroid: A fundamental and clinical text. Eighth edition. Philadelphia, PA: Lippincott Williams & Wilkins, 824-827.

*Longnecker MP, Gladen BC, Patterson DG, et al. 2000. Polychlorinated biphenyl (PCB) exposure in relation to thyroid hormone levels in neonates. Epidemiology 11:249-254.

Longnecker MP, Rogan WJ, Lucier G. 1997. The human health effects of DDT (dichlorodiphenyltrichloroethane) and PCBs (polychlorinated biphenyls) and an overview of organochlorines in public health. Annu Rev Public Health 18:211-244.

*Lonky E, Reihman J, Darvill T, et al. 1996. Neonatal behavioral assessment scale performance in humans influenced by maternal consumption of environmentally contaminated Lake Ontario fish. J Great Lakes Res 22(2):198-212.

*Loo JCK, Tryphonas H, Jordan N, et al. 1989. Effects of Aroclor 1254® on hydrocortisone levels in adult Rhesus monkeys (*macaca mulatta*). Bull Environ Contam Toxicol 43:667-669.

*Loomis D, Browning SR, Schenck AP, et al. 1997. Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. Occup Environ Med 54(10):720-728.

*Loose LD, Pittman KA, Benitz KF, et al. 1977. Polychlorinated biphenyl and hexachlorobenzene induced humoral immunosuppression. J Reticuloendothel Soc 22(3):253-267.

*Loose LD, Pittman KA, Benitz KF, et al. 1978b. Environmental chemical-induced immune dysfunction. Ecotoxicol Environ Saf 2:173-198.

*Loose LD, Silkworth JB, Charbonneau T, et al. 1981. Environmental chemical-induced macrophage dysfunction. Environ Health Persp 39:79-91.

*Loose LD, Silkworth JB, Mudzinski SP, et al. 1979. Modification of the immune response by organochloride xenobiotics. Drug Chem Toxicol 2:111-132.

*Loose LD, Silkworth JB, Pittman KA, et al. 1978a. Impaired host resistance to endotoxin and malaria in polychlorinated biphenyl- and hexachlorobenzene-treated mice. Infect Immun 20:30-35.

*Looser R, Ballschmiter K. 1998. Biomagnification of polychlorinated biphenyls (PCBs) in freshwater fish. Fresenius Journal of Analytical Chemistry 360:816-819.

*Lopez-Avila V, Schoen S, Milanes J, et al. 1988. Single-laboratory evaluation of EPA method 8080 for determination of chlorinated pesticides and polychlorinated biphenyls in hazardous wastes. J Assoc Off Anal Chem 71:375-386.

Lopshire RF, Watson JT, Enke CG. 1996. Composition-selective detection of polychlorinated biphenyls (PCBs) by oxygen-chlorine exchange reaction in a tandem mass spectrometer. Toxicol Ind Health 12:375-391.

*Lorber MN, Winters DL, Griggs J, et al. 1998. A national survey of dioxin-like compounds in the United States milk supply. Organohalogen Compounds 38:125-129.

*Lordo RA, Dinh KT, Schwemberger JG. 1996. Semivolatile organic compounds in adipose tissue: Estimated averages for the U.S. population and selected subpopulations. Am J Public Health 86(9):1253-1259.

*Lu F-J, Chang K-J, Lin S-C, et al. 1980. [Studies on patients with polychlorinated biphenyl poisoning: Determination of urinary coproporphyrin, uroporphyrin, γ-aminolevulinic acid and porphobilinogen.] J Formosan Med Assoc 79:990-995. (Chinese)

*Lu Y-C, Wu Y-C. 1985. Clinical findings and immunological abnormalities in Yu-Cheng patients. Environ Health Perspect 59:17-29.

*Lubet RA, Nims RW, Beebe LE, et al. 1992. Induction of hepatic CYP1A activity as a biomarker for environmental exposure to Aroclor® 1254 in feral rodents. Arch Environ Contam Toxicol 22(3):339-344.

*Lucier GW, Nelson KG, Everson RB, et al. 1987. Placental markers of human exposure to polychlorinated biphenyls and polychlorinated dibenzofurans. Environ Health Perspect 76:79-87.

Luebeck EG, Moolgavkar SH, Buchmann A, et al. 1991. Effects of polychlorinated biphenyls in rat liver: Quantitative analysis of enzyme-altered foci. Toxicol Appl Pharmacol 111:469-484.

*Lund J, Brandt I, Poellinger L, et al. 1985. Target cells for the polychlorinated biphenyl metabolite 4,4'-bis(methylsulfonyl)-2,2',5,5'-tetrachlorobiphenyl: Characterization of high affinity binding in rat and mouse lung cytosol. Mol Pharmacol 27:314-323.

*Lunden A, Noren K. 1998. Polychlorinated naphthalenes and other organochlorine contaminants in Swedish human milk, 1972-1992. Arch Environ Contam Toxicol 34:414-423.

*Lundkvist U. 1990. Clinical and reproductive effects of Clophen A50 (PCB) administered during gestation on pregnant guinea pigs and their offspring. Toxicology 6:249-257.

*Luotamo M. 1988. Isomer-specific biological monitoring of polychlorinated biphenyls. Scand J Work Environ Health 14(Suppl 1):60-62.

*Luotamo M, Iarvisalo J, Aitio A. 1985. Analysis of polychlorinated biphenyls (PCBs) in human serum. Environ Health Perspect 60:327-332.

*Luotamo, M, Jarvisalo J, Aitio A. 1991. Assessment of exposure to polychlorinated biphenyls: analysis of selected isomers in blood and adipose tissue. Environ Res 54:121-134.

*Luotamo M, Patterson DG Jr, Needham LL, et al. 1993. Concentrations of PCB congeners in sera from workers with past and present exposure. Chemosphere 27(1-3):171-177.

*Luster MI, Portier C, Pait DG, et al. 1992. Risk assessment in immunotoxicology: I. Sensitivity and predictability of immune tests. Fundam Appl Toxicol 18:200-210.

*Lutz RJ, Dedrick RL. 1987. Physiologic pharmacokinetic modeling of polychlorinated biphenyls. Environ Toxicol Series 1:111-131.

*Lutz RJ, Dedrick RL, Matthews HB, et al. 1977. A preliminary pharmacokinetic model for several chlorinated biphenyls in the rat. Drug Metab Dispos 5:386-396.

*Lutz RJ, Dedrick RL, Tuey D, et al. 1984. Comparison of the pharmacokinetics of several polychlorinated biphenyls in mouse, rat, dog, and monkey by means of a physiological pharmacokinetic model. Drug Metab Dispos 12:527-535.

Ma CY, Bayne CK. 1993. Differentiation of Aroclors using linear discrimination for environmental samples analyzed by electron capture negative ion chemical ionization mass spectrometry. Anal Chem 65(6):772-777.

*Maack L, Sonzogni WC. 1988. Analysis of polychlorobiphenyl congeners in Wisconsin fish. Arch Environ Contam Toxicol 17:711-719.

*Macdonald RW, Barrie LA, Bidleman TF, et al. 2000. Contaminants in the Canadian Arctic: 5 years of progress in understanding sources, occurrence and pathways. Sci Total Environ 254:98-234.

*Mackay D. 1989. Modeling the long-term behavior of an organic contaminant in a large lake: Application to PCBs in Lake Ontario. J Great Lakes Res 15:283-297.

*MacLellan K, Singh A, Chu I, et al. 1994a. Subchronic toxicity of 3,3',4,4'-tetrachlorobiphenyl in the rat liver: An electron microscope study. Histol Histopathol 9:453-459.

*MacLellan K, Singh A, Chu I, et al. 1994b. Subchronic toxicity of pentachlorobiphenyl congeners n. 126 or 118 in the rat liver. An electron microscope study. J Submicrosc Cytol Pathol 26(2):279-291.

*MacLellan K, Singh A, Chu I, et al. 1994c. Toxicity of 2,2',4,4',5,5'-hexachlorobiphenyl in the rat liver: An electron microscope study. Histol Histopathol 9:461-468.

*MacLeod KE. 1981. Polychlorinated biphenyls in indoor air. Environ Sci Technol 15:926-928.

*Madenjian CP, Schmidt LJ, Chernyak SM, et al. 1999. Variation in net trophic transfer efficiencies among 21 PCB congeners. Environ Sci Technol 33:3768-3773.

*Madra S, Mann F, Francis JE, et al. 1996. Modulation by iron of hepatic microsomal and nuclear cytochrome P450, and cytosolic glutathione S-transferase and peroxidase in C57BL/10ScSn mice induced with polychlorinated biphenyls (Aroclor 1254). Toxicol Appl Pharmacol 136(1):79-86.

*Madra S, Styles J, Smith AG. 1995. Perturbation of hepatocyte nuclear populations induced by iron and polychlorinated biphenyls in C57BL/10ScSn mice during carcinogenesis. Carcinogenesis 16(4):719-727.

Maier WE, Kodavanti PRS, Harry J, et al. 1994. Sensitivity of adenosine triphosphatases in different brain regions to polychlorinated biphenyl congeners. J Appl Toxicol 14:225-229.

*Makepeace DK, Smith DW, Stanley SJ. 1995. Urban stormwater quality: Summary of contaminant data. Critical Reviews in Environmental Science and Technology 25(2):93-139.

*Makiura S, Aoe H, Sugihara S, et al. 1974. Inhibitory effect of polychlorinated biphenyls on liver tumorigenesis in rats treated with 3'-methyl-4-dimethylaminoazobenzene, N-2-fluorenylacetamide, and diethylnitrosamine. J Natl Cancer Inst 53:1253-1257.

*Malkin R. 1995. Occupational and environmental lead and PCB exposure at a scrap metal dealer. Environ Res 70(1):20-23.

9. REFERENCES

*Manchester-Neesvig JB, Andren AW, Edgington DN. 1996. Patterns of mass sedimentation and of deposition of sediment contaminated by PCBs in Green Bay. J Great Lakes Res 22(2):444-462.

*Mannisto MK, Puhakka JA, Ferguson JF. 1997. Degradation of Aroclor 1221, 1242 and anaerobically transformed Aroclor 1254 by aerobic marine sediment microorganisms. In: Alleman BC, Leeson A, eds. In situ and on-site bioremediation: Volume 2. Columbus, OH: Battelle Press, 421-426.

Marczylo T, Ioannides C. 1997. Induction of the rat hepatic cytosolic arylamine oxidase by a series of polychlorinated biphenyls: association with the Ah locus. Toxicol Lett 92(2):81-91.

*Mariani E, Bargagna A, Longobardi M. 1994. Gas chromatographic determination of chlorinated pesticides and PCBs in complex cosmetic matrices. Il Farmaco 49(6):441-442.

*Mariussen E, Anderson JM, Fonnum F. 1999. The effect of polychlorinated biphenyls on the uptake of dopamine and other neurotransmitters into rat brain synaptic vesicles. Toxicol Appl Pharmacol 161:274-282.

*Maroni M, Colombi A, Feriolo A, et al. 1993. Evaluation of porphyrinogenesis and enzyme induction in workers exposed to PCB. Med Lav 75:188-199.

*Maroni M, Columbi A, Arbosti G, et al. 1981a. Occupational exposure to polychlorinated biphenyls in electrical workers. II Health effects. Br J Ind Med 38:55-60.

*Maroni M, Columbi A, Arbosti G, et al. 1981b. Occupational exposure to polychlorinated biphenyls in electrical workers. I Environmental and blood polychlorinated biphenyls concentrations. Br J Ind Med 38:49-54.

Maronpot RR, Montgomery CA, Boorman GA, et al. 1986. National Toxicology Program nomenclature for hepatoproliferative lesions of rats. Toxicol Pathol 14:263-273.

*Maruya KA, Lee RF. 1998. Aroclor 1268 and toxaphene in fish from a southeastern U.S. estuary. Environ Sci Technol 32(8):1069-1075.

*Massachusetts Department of Public Health. 1987. Final report of Greater New Bedford PCB health effects study 1984-1987. Boston, MA: Massachusetts Department of Public Health.

*Masuda Y. 1994. The Yusho rice oil poisoning incident. In: Schecter A., ed. Dioxins and health. New York, NY: Plenum Press, 633-659.

*Masuda Y, Kagawa R, Kuroki H, et al. 1978. Transfer of polychlorinated biphenyls from mothers to foetuses and infants. Food Cosmet Toxicol 16:543-546.

*Masuda Y, Kagawa R, Kuroki H, et al. 1979. Transfer of various polychlorinated biphenyls to the foetuses and offspring of mice. Food Cosmet Toxicol 17:623-627.

Matsusue K, Ishii Y, Ariyoshi N, et al. 1997. A highly toxic PCB produces unusual changes in the fatty acid composition of rat liver. Toxicol Lett 91(2):99-104.

*Matthews HB. 1982. Aryl halides. In: Jakoby WB, Bend JR, Caldwell J, eds. Metabolic basis of detoxification. Metabolism of functional groups. New York: Academic Press, 51-68.

*Matthews HB, Anderson MW. 1975. Effect of chlorination on the distribution and excretion of polychlorinated biphenyls. Drug Metab Dispos 3:371-380.

*Matthews HB, Dedrick RL. 1984. Pharmacokinetics of PCBs. Ann Rev Pharmacol Toxicol 24:85-103.

*Matthews HB, Surles JR, Carver JG, et al. 1984. Halogenated biphenyl transport by blood components. Fundam Appl Toxicol 4:420-428.

*May HD, Boyle AW, Price WA, et al. 1992. Subculturing of a polychlorinated biphenyl-dechlorinating anaerobic enrichment on solid media. Appl Environ Microbiol 58(12):4051-4054.

May RJ, Mondello FJ. 1999. Metabolite detection as a tool for the determination of naturally occurring aerobic PCB biodegradation. Schenectady, NY: General Electric Company, Corporate Research and Development. May 14, 1999.

*Mayes BA, McConnell EE, Neal BH, et al. 1998. Comparative carcinogenicity in Sprague-Dawley rats of the polychlorinated biphenyl mixtures Aroclors 1016, 1242, 1254, and 1260. Toxicol Sci 41(1):62-76.

*Mayr U, Butsch A, Schneider S. 1992. Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74:135-149.

Mazhitova Z, Jensen S, Ritzen M, et al. 1998. Chlorinated contaminants, growth and thyroid function in schoolchildren from the Aral Sea region in Kazakhstan. Acta Paediatr 87:991-995.

*McConnell E, Hass JR, Altman N, et al. 1979. A spontaneous outbreak of polychlorinated biphenyl (PCB) toxicity in Rhesus monkeys (*macaca mulatta*): Toxicopathology. Lab Animal Sci 29:666-673.

*McConnell L, Bidleman T, Cotham W, et al. 1998. Air concentrations of organochlorine insecticides and polychlorinated biphenyls over Green Bay, WI, and the four lower Great Lakes. Environ Pollut 101:391-399.

*McCormack KM, Melrose P, Rickert DE, et al. 1979. Concomitant dietary exposure to polychlorinated biphenyls and polybrominated biphenyls: Tissue distribution and arylhydrocarbon hydroxylase activity in lactating rats. Toxicol Appl Pharmacol 47:95-104.

McCoy G, Finlay MF, Rhone A, et al. 1995. Chronic polychlorinated biphenyls exposure on three generations of oldfield mice (*peromyscus polionotus*): Effects on reproduction, growth, and body residues. Arch Environ Contam Toxicol 28(4):431-435.

*McFarland VA, Clarke JU. 1989. Environmental occurrence, abundance, and potential toxicity of polychlorinated biphenyl congeners: Considerations for a congener-specific analysis. Environ Health Perspect 81:225-239.

*McGroddy SE, Farrington JW, Gschwend PM. 1996. Comparison of the *in situ* and desorption sediment-water partitioning of polycyclic aromatic hydrocarbons and polychlorinated biphenyls. Environ Sci Technol 30:172-177.

*McIntyre AE, Lester JN. 1982. Polychlorinated biphenyl and organochlorine insecticide concentrations in forty sewage sludges in England. Environ Pollut 3:225-230.

*McKinley MK, Kedderis LB, Birnbaum LS. 1993. The effect of pretreatment on the biliary excretion of 2,3,7,8-tetrachlorodibenzo-p-dioxin, 2,3,7,8-tetrachlorodibenzofuran, and 3,3',4,4'-tetrachlorobiphenyl in the rat. Fundam Appl Toxicol 21:425-432.

McKinney JD, Waller CL. 1994. Polychlorinated biphenyls as hormonally active structural analogues. Environ Health Perspect 102:290-297.

*McLachlan J. 1997. Synergistic effect of environmental estrogens: Report withdrawn. Science 277:462-463.

*McLachlan MS. 1993. Digestive tract absorption of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in a nursing infant. Toxicol Appl Pharmacol 123(1):68-72.

*McLachlan MS, Hinkel M, Reissinger M, et al. 1994. A study of the influence of sewage sludge fertilization on the concentrations of PCDD/F and PCB in soil and milk. Environ Pollut 85:337-343.

McLachlan M, Mackay D, Jones PH. 1990. A conceptual model of organic chemical volatilization at waterfalls. Environ Sci Technol 24:252-257.

*McLean MR, Robertson LW, Gupta RC. 1996. Detection of PCB adducts by the P-postlabeling technique. Chem Res Toxicol 9:165-171.

*McNulty WP, Becker GM, Cory HT. 1980. Chronic toxicity of 3,4,3',4- and 2,5,2'5'-tetrachlorobiphenyls in Rhesus macaques. Toxicol Appl Pharmacol 56:182-190.

Mehlman MA, Friend B, Tobin RB. 1974a. The effect of polychlorinated biphenyls on liver gluconeogenic enzyme activities in rats during exposure to cold. Toxicology 2:301-308.

Mehlman MA, Yin L, Nielsen RC. 1974b. Metabolic changes in "frozen-clamped" livers of rats caused by ingestion of polychlorinated biphenyls. Toxicol Appl Pharmacol 27:300-307.

Mehlman MA, Tobin RB, Friend B, et al. 1975. The effects of a polychlorinated biphenyl mixture (aroclor 1254) on liver gluconeogenic enzymes of normal and alloxan-diabetic rats. Toxicology 5:89-95.

*Meigs JW, Albom JJ, Kartin BL. 1954. Chloracne from an unusual exposure to Aroclor. J Am Med Assoc 154:1417-1418.

*Melino G, Vernole P, Antinori M, et al. 1992. Immunological and cytogenetic damage in workers accidentally exposed to polychlorinated biphenyls (PCB). Clin Chem Enzymol Commun 4(5):341-353.

*Mendola P, Buck GM, Sever LE, et al. 1997. Consumption of PCB-contaminated freshwater fish and shortened menstrual cycle length. Am J Epidemiol 146(11):955-960.

*Mendola P, Buck GM, Vena JE, et al. 1995a. Consumption of PCB-contaminated sport fish and risk of spontaneous fetal death. Environ Health Perspect 103:498-502.

*Mendola P, Vena JE, Buck GM. 1995b. Exposure characterization, reproductive and developmental health in the New York State angler cohort study. Great Lakes Res Rev 1(2):41-43.

Mergler D, Belanger S, Larribe F, et al. 1998. Preliminary evidence of neurotoxicity associated with eating fish from the upper St. Lawrence River lakes. Neurotoxicology 19(4-5):691-702.

9. REFERENCES

*Mes J. 1994. Temporal changes in some chlorinated hydrocarbon residue levels of Canadian breast milk and infant exposure. Environ Pollut 84(3):261-268.

*Mes J, Davies DJ. 1979. Presence of polychlorinated biphenyl and organochlorine pesticide residues and the absence of polychlorinated terphenyls in Canadian human milk samples. Bull Environ Contam Toxicol 21:381-387.

*Mes J, Arnold DL, Bryce F, et al. 1989. The effect of long-term feeding of Aroclor® 1254 to female Rhesus monkeys on their polychlorinated biphenyl tissue levels. Arch Environ Contam Toxicol 18:858-865.

*Mes J, Arnold DL, Bryce F. 1994. Determination of polychlorinated biphenyls in postpartum blood, adipose tissue, and milk from female Rhesus monkeys and their offspring after prolonged dosing with Aroclor® 1254. J Anal Toxicol 18(1):29-35.

*Mes J, Arnold DL, Bryce F. 1995a. The elimination and estimated half-lives of specific polychlorinated biphenyl congeners from the blood of female monkeys after discontinuation of daily dosing with Aroclor® 1254. Chemosphere 30:789-800.

*Mes J, Arnold DL, Bryce F. 1995b. Postmortem tissue levels of polychlorinated biphenyls in female Rhesus monkeys after more than six years of daily dosing with Aroclor® 1254 and in their non-dosed offspring. Arch Environ Toxicol 29:69-76.

*Mes J, Arnold DL, Bryce F. 1995c. Female Rhesus monkeys dosed with Aroclor®1254: Analysis of polychlorinated biphenyl congeners in dam's milk and in the blood of dams and their offspring before, during, and after gestation. J Anal Toxicol 19:209-217.

*Mes J, Davies DJ, Doucet J, et al. 1993. Specific polychlorinated biphenyl congener distribution in breast milk of Canadian women. Environ Technol 14(6):555-565.

*Mes J, Davies DJ, Turton D, et al. 1986. Levels and trends of chlorinated hydrocarbon contaminants in the breast milk of Canadian women. Food Additives Contaminants 3(4):313-322.

*Mes J, Doyle JA, Adam BR, et al. 1984. Polychlorinated biphenyls and organochlorine pesticides in milk and blood of Canadian women during lactation. Arch Environ Contam Toxicol 13:217-223.

Meserve LA, Murray BA, Landis JA. 1992. Influence of maternal ingestion of Aroclor 1254® (PCB) or FireMaster BP- 6® (PBB) on unstimulated and stimulated corticosterone levels in young rats. Bull Environ Contam Toxicol 48(5):715-720.

*Metcalfe TL, Metcalfe CD. 1997. The trophodynamics of PCBs, including mono- and non-ortho congeners, in the food web of North-Central Lake Ontario. Sci Total Environ 201:245-272.

Metcalfe-Smith JL, Maguire RJ, Batchelor SP. 1995. Polychlorinated biphenyl congeners and chlorinated pesticides in fish from the Yamaska River basin, Quebec. Water Qual Res J Can 30(2):179-204.

*Meylan W, Howard PH, Boethling RS. 1992. Molecular topology/fragment contribution method for predicting soil sorption coefficients. Environ Sci Technol 26(8):1560-1567.

*Miller DB, Gray LE Jr, Andrews JE, et al. 1993b. Repeated exposure to the polychlorinated biphenyl (Aroclor 1254) elevates the basal serum levels of corticosterone but does not affect the stress-induced rise. Toxicology 81(3):217-222.

Miller DT, Condon SK, Kutzner S, et al. 1991. Human exposure to polychlorinated biphenyls in Greater New Bedford, Massachusetts: A prevalence study. Arch Environ Contam Toxicol 20:410-416.

*Miller MA, Kassulke NM, Walkowski MD. 1993a. Organochlorine concentrations in Laurentian Great Lakes salmonines: Implications for fisheries management. Arch Environ Contam Toxicol 25:212-219.

Mills AG, Jefferies TM. 1993. Rapid isolation of polychlorinated biphenyls from milk by a combination of supercritical-fluid extraction and supercritical-fluid chromatography. J Chromatogr 643(1-2):409-418.

*Miyata H, Aozasa O, Ohta S, et al. 1993. Estimated daily intakes of PCDDs, PCDFs and non-ortho coplanar PCBs via drinking water in Japan. Chemosphere 26(8):1527-1536.

*Mizutani T, Hidaka K, Ohe T, et al. 1977. A comparative study on accumulation and elimination of tetrachlorobiphenyl isomers in mice. Bull Environ Contam Toxicol 18:452-461.

Monjan AA, Collector MI. 1977. Stress-induced modulation of the immune response. Science 186:307-308.

*Monosmith CL, Hermanson MH. 1996. Spatial and temporal trends of atmospheric organochlorine vapors in the central and upper Great Lakes. Environ Sci Technol 30:3464-3472.

*Monsanto Chemical Company. 1985. Monsanto material safety data: Polychlorinated biphenyls (PCBs). St. Louis, MO: Monsanto Company.

*Moore JA, Hardisty JF, Banas DA, et al. 1994. A comparison of liver tumor diagnoses from seven PCB studies in rats. Regul Toxicol Pharmacol 20:362-370.

*Moore M, Mustain M, Daniel K, et al. 1997. Antiestrogenic activity of hydroxylated polychlorinated biphenyl congeners identified in human serum. Toxicol Appl Pharmacol 142:160-168.

Mora MA. 1995. Residues and trends of organochlorine pesticide and polychlorinated biphenyls in birds from Texas 1965-88. Fish and Wildlife Research 14:1-26.

Morales NM, Matthews HB. 1979. In vivo binding of 2,3,6,2',3',6'-hexachlorobiphenyl and 2,4,5,2',4',5'-hexachlorobiphenyl to mouse liver macromolecules. Chem Biol Interact 27:99-110.

*Morgan RW, Ward JM, Hartman PE. 1981. Aroclor 1254-induced intestinal metaplasia and adenocarcinoma in the glandular stomach of F344 rats. Cancer Res 41:5052-5059.

Morita M, Nakagawa J, Rappe C. 1978. Polychlorinated dibenzofuran (PCDF) formation from PCB mixture by heat and oxygen. Bull Environ Contam Toxicol 19:665-670.

*Morris PJ, Mohn WW, Quensen JF III, et al. 1992. Establishment of polychlorinated biphenyl-degrading enrichment culture with predominantly *meta* dechlorination. Appl Environ Microbiol 58(9):3088-3094.

*Morris S, Lester JN. 1994. Behaviour and fate of polychlorinated biphenyls in a pilot wastewater. Water Res 28(7):1553-1561.

*Morrissey RE, Harris MW, Diliberto JJ, et al. 1992. Limited PCB antagonism of TCDD-induced malformations in mice. Toxicol Lett 60:19-25.

Morse DC, Brouwer A. 1995. Fetal, neonatal, and long-term alterations in hepatic retinoid levels following maternal polychlorinated biphenyl exposure in rats. Toxicol Appl Pharmacol 131:175-182.

*Morse DC, Plug A, Wesseling W, et al. 1996b. Persistent alterations in regional brain glial fibrillary acidic protein and synaptophysin levels following pre- and postnatal polychlorinated biphenyl exposure. Toxicol Appl Pharmacol 139:252-261.

*Morse DC, Seegal RF, Borsch KO, et al. 1996a. Long-term alterations in regional brain serotonin metabolism following maternal polychlorinated biphenyl exposure in the rat. Neurotoxicology 17(3-4):631-638.

*Morse DC, Wehler EK, Wesseling W, et al. 1996c. Alterations in rat brain thyroid hormone status following pre- and postnatal exposure to polychlorinated biphenyls (Aroclor 1254).

*Morse DC, Wehler EK, van de Pas M, et al. 1995. Metabolism and biochemical effects of 3,3',4,4'-tetrachlorobiphenyl in pregnant and fetal rats. Chem Biol Interact 95(1-2):41-56.

*Morselli L, Brocco D, Pirni A. 1985. The presence of polychlorodibenzo-p-dioxins (PCDDs), polychlorodibenzofurans (PCDFs), and polychlorobiphenyls (PCBs) in fly ashes from various municipal incinerators under different technological and working conditions. Ann Chim 75:59-64.

*Morselli L, Zappoli S, Liberti A, et al. 1989. Evaluation and comparison of organic and inorganic compounds between emission and emission samples from municipal solid waste incinerator. Chemosphere 18:2263-2273.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants. Clin Pharmacokin 5:485-527.

*Moslen MT, Reynolds ES, Szabo S. 1977. Enhancement of the metabolism and hepatotoxicity of trichloroethylene and perchloroethylene. Biochem Pharmacol 26:369-375.

Moya J, Garrahan KG, Poston TM, et al. 1998. Effects of cooking on levels of PCBs in the fillets of winter flounder. Bull Environ Contam Toxicol 60:845-851.

*Moysich KB, Ambrosone CB, Vena JE, et al. 1998. Environmental organochlorine exposure and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 7(3):181-188.

*Moysich KB, Shields PG, Freudenheim JL, et al. 1999. Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 8:41-44.

*Moza P, Weisgerber I, Klein W. 1976. Fate of 2,2'-dichlorobiphenyl-^{14}C in carrots, sugar beets, and soil under outdoor conditions. J Agric Food Chem 24(4):881-885.

9. REFERENCES

*Mühlebach S, Bickel MH. 1981. Pharmacokinetics in rats 2,4,5,2',4',5',-hexachlorobiphenyl, an unmetabolizable lipophilic model compound. Xenobiotica 11(4):249-257.

*Muir DCG, Ford CA, Rosenberg B, et al. 1996b. Persistent organochlorines in beluga whales (*delphinapterus leucas*) from the St. Lawrence River estuary-I. Concentrations and patterns of specific PCBs, chlorinated pesticides and polychlorinated dibenzo-*p*-dioxins and dibenzofurans. Environ Pollut 93(2):219-234.

*Muir DCG, Koczanski K, Rosenberg B, et al. 1996a. Persistent organochlorines in beluga whales (*delphinapterus leucas*) from the St. Lawrence River estuary-II. Temporal trends, 1982-1994. Environ Pollut 93(2):235-245.

*Mullin MD, Pochini CM, McCrindle S, et al. 1984. High-resolution PCB analysis: Synthesis and chromatographic properties of all 209 PCB congeners. Environ Sci Technol 18:468-476.

Mulvad G, Pedersen HS, Hansen JC, et al. 1996. Exposure of Greenlandic Inuit to organochlorines and heavy metals through the marine food chain: an international study. Sci Total Environ 186(½):137-139.

*Murk AJ, Boudewijn TJ, Meininger PL, et al. 1996. Effects of polyhalogenated aromatic hydrocarbons and related contaminants on common tern reproduction: Integration of biological, biochemical, and chemical data. Arch Environ Contam Toxicol 31:128-140.

*Murphy MJ, Piper LJ, Fasco MJ, et al. 1979. Potentiation of fluoroxene (2,2,2-trifluoroethyl vinyl ether) toxicity with polychlorinated biphenyls. Toxicol Appl Pharmacol 48:87-97.

*Murphy TJ, Formanski LJ, Brownawell B, et al. 1985. Polychlorinated biphenyl emissions to the atmosphere in the Great Lakes region. Municipal landfills and incinerators. Environ Sci Technol 19:924-946.

*Murphy TJ, Mullin MD, Meyer JA. 1987. Equilibration of polychlorinated biphenyls and toxaphene with air and water. Environ Sci Technol 21:155-162.

Murray HE, Ray LE, Giam CS. 1981. Phthalic acid esters, total DDTs and polychlorinated biphenyls in marine samples from Galveston Bay, Texas. Bull Environ Contam Toxicol 26:769-774.

*Mussalo-Rauhamaa H, Hasanen E, Pyysalo H, et al. 1990. Occurrence of beta-hexachlorocyclohexane in breast cancer patients. Cancer 66:2124-2128.

*Nagayama J, Okamura K, Iida T, et al. 1998a. Postnatal exposure to chlorinated dioxins and related chemicals on thyroid hormone status in Japanese breast fed infants. Chemosphere 37:1789-1793.

Nagayama J, Tsuji H, Iida T, et al. 1998b. Postnatal exposure to chlorinated dioxins and related chemicals on lymphocyte subsets in Japanese breast-fed infants. Chemosphere 37:1781-1787.

*Nakanishi Y, Shigematsu N, Kurita Y, et al. 1985. Respiratory involvement and immune status in Yusho patients. Environ Health Perspect 59:31-36.

Napolitano GE, Richmond JE. 1995. Enrichment of biogenic lipids, hydrocarbons and PCBs in stream-surface foams. Environ Toxicol Chem 14(2):197-201.

Narayanan PK, Carter WO, Ganey PE, et al. 1998. Impairment of human neutrophil oxidative burst by polychlorinated biphenyls: inhibition of superoxide dismutase activity. J Leukoc Biol 63(2):216-224.

*Narbonne JF, Gillet G, Daubeze M. 1978. [Effect of polychlorinated biphenyls in the rat: I. -- relation tissue level dose (author's transl)]. Toxicological European Research 1(3):145-52.

NAS/NRC. 1980. National Academy of Sciences/National Research Council. Drinking water and health. Volume 3. Washington, DC: National Academy Press, 133.

*NAS/NRC. 1989. Report of the oversight committee. In: Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press.

Nath RG, Randerath E, Randerath K. 1991. Short-term effects of the tumor promoting polychlorinated biphenyl mixture, Aroclor 1254, on I-compounds in liver, kidney and lung DNA of male Sprague-Dawley rats. Toxicology 68:275-289.

NATICH. 1992. National Air Toxics Information Clearinghouse. Report on state, local, and EPA air toxics activities. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. December 1992.

Navas JM, Segner H. 1998. Antiestrogenic activity of anthropogenic and natural chemicals. Environ Sci Pollut Res Int 5(2):75-82.

*NCI. 1978. Bioassay of Aroclor 1254 for possible carcinogenicity. NCI-GC-TR-38. Bethesda, MD: National Cancer Institute. NTIS PB279624.

Nebert DW, Adesnik M, Coon MJ, et al. 1987. The P450 gene superfamily: Recommended nomenclature. DNA 6:1-11.

*Needham LL, Burse VW, Price HA. 1981. Temperature-programmed gas chromatographic determination of polychlorinated and polybrominated biphenyls in serum. J Assoc Off Anal Chem 64:1131-1137.

*Needham LL, Smrek AL, Head SL, et al. 1980. Column chromatography separation of polychlorinated biphenyls from dichlorodiphenyltrichloroethane and metabolites. Anal Chem 52:2227-2229.

Neely WB. 1977. A material balance study of polychlorinated biphenyls in Lake Michigan. Sci Total Environ 7:117-129.

*Nelson ED, McConnell LL, Baker JE. 1998. Diffusive exchange of gaseous polycyclic aromatic hydrocarbons and polychlorinated biphenyls across the air-water interface of the Chesapeake Bay. Environ Sci Technol 32(7):912-919.

*Nelson NN, Hammond PB, Nisbet ICT, et al. 1972. PCBs - environmental impact. Environ Res 5:249-362.

*Nesaretnam K, Darbre P. 1997. 3,5,3',5'-Tetrachlorobiphenyl is a weak oestrogen agonist *in vitro* and *in vivo*. J Steroid Biochem Mol Biol 62(5-6):409-418.

*Nesaretnam K, Corcoran D, Dils RR, et al. 1996. 3,4,3',4'-Tetrachlorobiphenyl acts as an estrogen *in vitro* and *in vivo*. Mol Endocrinol 10:923-936.

Ness DK, Schantz SL, Hansen LG. 1994. PCB congeners in the rat brain: Selective accumulation and lack of regionalization. J Toxicol Environ Health 43:453-468.

*Ness DK, Schantz SL, Moshtaghian J, et al. 1993. Effects of perinatal exposure to specific PCB congeners on thyroid hormone concentrations and thyroid histology in the rat. Toxicol Lett 68:311-323.

*Newman JW, Becker JS, Blondina G, et al. 1998. Quantitation of Aroclors using congener-specific results. Environ Toxicol Chem 17(11):2159-2167.

*Newman JW, Vedder J, Jarman WM, et al. 1994. A method for the determination of environmental contaminants in living marine mammals using microscale samples of blubber and blood. Chemosphere 28(10):1795-1805.

*Newsome WH, Ryan JJ. 1999. Toxaphene and other chlorinated compounds in human milk from northern and southern Canada: A comparison. Chemosphere 39(3):519-526.

*Newsome WH, Davies D, Doucet J. 1995. PCB and organochlorine pesticides in Canadian human milk-1992. Chemosphere 30(11):2143-2153.

*NFPA. 1994. National Fire Protection Association. Hazardous chemicals data.

*Nhan DD, Am NM, Hoi NC, et al. 1998. Organochlorine pesticides and PCBs in the Red River Delta, North Vietnam. Mar Pollut Bull 36(9):742-749.

*Nicholson WJ, Landrigan PJ. 1994. Human health effects of polychlorinated biphenyls. In: Schecter A, ed. Dioxins and health. New York, NY: Plenum Press, 487-524.

Nicola RM, Branchflower R, Pierce D. 1987. Chemical contaminants in bottomfish. J Environ Health 49:342-347.

*Nies L, Vogel TM. 1990. Effects of organic substrates on dechlorination of Aroclor 1242 in anaerobic sediments. Appl Environ Microbiol 56:2612-2617.

*Nies L, Vogel TM. 1991. Identification of the proton source for the microbial reductive dechlorination of 2,3,4,5,6-pentachlorobiphenyl. Appl Environ Microbiol 57(9):2771-2774.

*Nilsson B, Ramel C. 1974. Genetic tests on *drosophila melanogaster* with polychlorinated biphenyls (PCB). Hereditas 77:319-322.

*Nims RW, Beebe LE, Dragnev KH, et al. 1992. Induction of hepatic CYP1A in male F344/NCr rats by dietary exposure to Aroclor 1254: Examination of immunochemical, RNA, catalytic, and pharmacokinetic endpoints. Environ Res 59(2):447-466.

Nims RW, Fox SD, Issaq HJ, et al. 1994. Accumulation and persistence of individual polychlorinated biphenyl congeners in liver, blood, and adipose tissue of rats following dietary exposure to Aroclor® 1254. Arch Environ Contam Toxicol 27:513-520.

*NIOSH. 1977. Criteria for a recommended standard: Occupational exposure to polychlorinated biphenyls (PCBs). Rockville Md: U.S. Department of Health, Education and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. NIOSH publ. 77-225.

9. REFERENCES

*NIOSH. 1984a. NIOSH manual of analytical methods. Vol. 1: Method no. 5503. 3rd ed. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

*NIOSH. 1984b. NIOSH manual of analytical methods. Vol. 1: Method no. 8004. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

NIOSH. 1986. National Institute for Occupational Safety and Health. Mortality of workers exposed to polychlorinated biphenyls: An update. NTIS PB86-206000.

*NIOSH. 1987a. Registry of toxic effects of chemical substances. Vol. 4. 1985-86 ed. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 3687.

NIOSH. 1987b. Health hazard evaluation report: Jacksonville Fire Department, Jacksonville, Florida. Cincinnati, OH: National Institute for Occupational Safety and Health, Hazard Evaluations and Technical Assistance Branch. HETA 84-180-1776.

*NIOSH. 1989. National occupational exposure survey as of 08/29/89. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 134, 142, 184.

*NIOSH. 1990. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health, Cincinnati, OH.

*NIOSH. 1991. Health hazard evaluation report. Westinghouse Electric Corporation, Bloomington, Indiana. Cincinnati, OH: Hazard Evaluations and Technical Assistance Branch, National Institute for Occupational Safety and Health. HETA 89-116-2094.

*NIOSH. 1992. NIOSH recommendations for occupational safety and health compendium of policy documents and statements. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Standards Development and Technology Transfer. NIOSH 92-100, B92, 162, 536.

*NIOSH. 1997. NIOSH pocket guide to chemical hazards. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute of Occupational Safety and Health.

*NIOSH. 2000. NIOSH pocket guide to chemical hazards. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute of Occupational Safety and Health. Http://www.cdc.gov/niosh/npg/.

*Nisbet ICT, Fry DM, Hatch JJ, et al. 1996. Feminization of male common tern embryos is not correlated with exposure to specific PCB congeners. Bull Environ Contam Toxicol 57:895-901.

*Nishida N, Farmer JD, Kodavanti PRS, et al. 1997. Effects of acute and repeated exposures to Aroclor 1254 in adult rats: Motor activity and flavor aversion conditioning. Fundam Appl Toxicol 40:68-74.

*Nishizumi M. 1976. Radioautographic evidence for absorption of polychlorinated biphenyls through the skin. Ind Health 14:41-44.

Nishizumi M. 1980. Reduction of diethylnitrosamine-induced hepatoma in rats exposed to polychlorinated biphenyls through their dams. Gann 71:910-912.

NOAA. 1988. PCB and chlorinated pesticide contamination in U.S. fish and shellfish: A historical assessment report. Seattle, WA: National Oceanic and Atmospheric Administration. NOAA Technical Memorandum NOS OMA 39.

*Norback DH, Weltman RH. 1985. Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. Environ Health Perspect 60:97-105.

*Norback DH, Seymour JL, Knieriem KM, et al. 1976. Biliary metabolites of 2,5,2',5'-tetrachlorobiphenyl in the rat. Res Commun Chem Pathol Pharmacol 14:527-533.

*Noren K, Lunden A, Pettersson E, et al. 1996. Methylsulfonyl metabolites of PCBs and DDE in human milk in Sweden, 1972-1992. Environ Health Perspect 104(7):766-772.

*Noren K, Weistrand C, Karpe F. 1999. Distribution of PCB congeners, DDE, hexachlorobenzene, and methylsulfonyl metabolites of PCB and DDE among various fractions of human blood plasma. Arch Environ Contam Toxicol 37:408-414.

*Norena-Barroso E, Zapata-Perez O, Ceja-Moreno V, et al. 1998. Hydrocarbon and organochlorine residue concentrations in sediment from Bay of Chetumal, Mexico. Bull Environ Contam Toxicol 61:80-87.

*NRC. 1991. National Research Council. Animals as sentinels of environmental health hazards. Washington, DC: National Academy Press.

*NRC. 1993. National Research Council. Pesticides in the diets of infants and children. Washington, DC: National Academy Press.

NTP. 1989. National Toxicology Program. Fifth annual report on carcinogens: Summary 1989. Research Triangle Park, NC: U.S. Department of Health and Human Service, Public Health Service, 239-242. NTP 89-239.

NTP. 1995. National Toxicology Program. Management status report. Research Triangle Park, NC: Division of Toxicology Research and Testing, National Institute of Environmental Health and Sciences.

NTP. 1998. National Toxicology Program. Eighth annual report on carcinogens. Summary 1998. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, 176-178.

*NTP. 2000. National Toxicology Program. Ninth annual report on carcinogens. http://ehis.niehs.nih.gov/roc/toc9.html

Nyhan WL. 1961. Toxicity of drugs in the neonatal period. J Pediatr 59:1-20.

*Oakley GG, Devanaboyina U, Robertson LW, et al. 1996. Oxidative DNA damage induced by activation of polychlorinated biphenyls (PCBs): Implications for PCB-induced oxidative stress in breast cancer. Chem Res Toxicol 9:1285-1292.

9. REFERENCES

*Oatman L, Roy R. 1986. Surface and indoor air levels of polychlorinated biphenyls in public buildings. Bull Environ Contam Toxicol 37:461-466.

*Ockenden WA, Prest HF, Thomas GO, et al. 1998. Passive air sampling of PCBs: Field calculation of atmospheric sampling rates by triolein-containing semipermeable membrane devices. Environ Sci Technol 32:1538-1543.

*O'Connor GA, Kiehl D, Eiceman GA, et al. 1990. Plant uptake of sludge-borne PCBs. J Environ Qual 19:113-118.

*Oda H, Yoshida A. 1994. Effect of feeding xenobiotics on serum high density lipoprotein and apolipoprotein A-I in rats. Biosci Biotechnol Biochem 58:1646-1651.

*Oehme M, Mano S, Mikalsen A. 1987. Formation and presence of polyhalogenated and polycyclic compounds in the emissions of small and large scale municipal waste incinerators. Chemosphere 16:143-153.

*Oesterle D, Deml E. 1983. Promoting effect of polychlorinated biphenyls on development of enzyme-altered islands in livers of weanling and adult rats. J Cancer Res Clin Oncol 105:141-147.

*Oesterle D, Deml E. 1984. Dose-dependent promoting effect of polychlorinated biphenyls on enzyme-altered islands in livers of adult and weanling rats. Carcinogenesis 5:351-355.

*Offenberg JH, Baker JE. 1997. Polychlorinated biphenyls in Chicago precipitation: Enhanced wet deposition to near-shore Lake Michigan. Environ Sci Technol 31(5):1534-1538.

*Offenberg JH, Baker JE. 1999. Influence of Baltimore's urban atmosphere on organic contaminants over the northern Chesapeake Bay. J Air Waste Manage Assoc 49:959-965.

*Ofjord GD, Puhakka JA, Ferguson JF. 1994. Reductive dechlorination of Aroclor 1254 by marine sediment cultures. Environ Sci Technol 28:2286-2294.

*Ohnishi Y, Kohno T. 1979. Polychlorinated biphenyls poisoning in monkey eye. Invest Ophthalmol Vis Sci 18:981-984.

*Ohsaki Y, Matsueda T. 1994. Levels, features and a source of non-ortho coplanar polychlorinated biphenyl in soil. Chemosphere 28(1):47-56.

*Okey AB, Riddick DS, Harper PA. 1994. The Ah receptor: Mediator of the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds. Toxicol Lett 70(1):1-22.

*Oliver BG, Bourbonniere RA. 1985. Chlorinated contaminants in surficial sediments of lakes Huron, St. Clair, and Erie: Implications regarding sources along the St. Clair and Detroit rivers. J Great Lakes Res 11:366-372.

*Oliver BG, Niimi AJ. 1985. Bioconcentration factors of some halogenated organics for rainbow trout: Limitations in their use for prediction of environmental residues. Environ Sci Technol 19:842-849.

*Oliver BG, Niimi AJ. 1988. Trophodynamic analysis of polychlorinated biphenyl congeners and other chlorinated hydrocarbons in the Lake Ontario ecosystem. Environ Sci Technol 22:388-397.

*Oliver BG, Charlton MN, Durham RW. 1989. Distribution, redistribution, and geochronology of polychlorinated biphenyl congeners and other chlorinated hydrocarbons in Lake Ontario sediments. Environ Sci Technol 23:200-208.

*Olivero J, Ganey PE. 2000. Role of protein phosphorylation in activation of phospholipase A_2 by the polychlorinated biphenyl mixture aroclor 1242. Toxicol Appl Pharmacol 163:9-16.

*Oloffs PC, Albright LJ, Szeto SY. 1972. Fate and behavior of five chlorinated hydrocarbons in three natural waters. Can J Microbiol 18:1393-1398.

*Olsen SF, Olsen J, Frische G. 1990. Does fish consumption during pregnancy increase fetal growth? A study of the size of the newborn, placental weight and gestatational age in relation to fish consumption during pregnancy. Int J Epidemiol 19(4):971-977.

*Olsson M, Karlsson B, Ahnland E. 1994. Diseases and environmental contaminants in seals form the Baltic and the Swedish west coast. Sci Total Environ 154:217-227.

*Omara FO, Flipo D, Brochu C, et al. 1998. Lack of suppressive effects of mixtures containing low levels of methylmercury (MeHg), polychlorinated dibenzo-p-dioxins (PCDDS), polychlorinated dibenzofurans (PCDFS),and aroclor biphenyls (PCBS) on mixed lymphocyte reaction, phagocytic, and natural killer cell activities of rat leukocytes in vitro. J Toxicol Environ Health A54:561-577.

*O'Neill HJ, Pollock TL, Brun GL, et al. 1992. Toxic chemical survey of municipal drinking water sources in Atlantic Canada 1985-1988. Wat Pollut Res J 27(4):715-732.

*Oremland RS. 1988. Biogeochemistry of methanogenic bacteria. In: Zehnder AJB, ed. Biology of anaerobic microorganisms. New York, NY: John Wiley & Sons, 641-705.

*Orris P, Kominsky JR, Hryhorczyk D, et al. 1986. Exposure to polychlorinated biphenyls from an overheated transformer. Chemosphere 15:1305-1311.

OSHA. 1974. U.S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910. 1000.

OSHA. 1997a. U.S. Department of Labor. Occupational Safety and Health Administration. Toxic and hazardous substances. Air contaminants. Code of Federal Regulations. 29 CFR 1915.1000.

OSHA. 1997b. U.S. Department of Labor. Occupational Safety and Health Administration. Safety and health regulations for construction. Gases, vapors; fumes, dusts, and mists. Code of Federal Regulations. 29 CFR 1926.55.

*OSHA. 1998a. U. S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

*OSHA. 1998b. U. S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000.

*OSHA. 1998c. U. S. Department of Labor. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55.

*Osius N, Karmaus W, Kruse H, et al. 1999. Exposure to polychlorinated biphenyls and levels of thyroid hormones in children. Environ Health Perspect 107(10):843-849.

*Osowski SL, Brewer LW, Baker OE, et al. 1995. The decline of mink in Georgia, North Carolina, and South Carolina: The role of contaminants. Arch Environ Contam Toxicol 29(3):418-423.

OSTP. 1985. Office of Science and Technology Policy. Chemical carcinogens; A review of the science and its associated principles, February 1985. Federal Register 50(50):10372-10381.

*OTA. 1990. Neurotoxicology: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment. OTA-BA-438.

*Ouw HK, Simpson GR, Siyali DS. 1976. Use and health effects of Aroclor 1242, a polychlorinated biphenyl, in an electrical industry. Arch Environ Health 31:189-194.

*Overmann SR, Kostas J, Wilson LR, et al. 1987. Neurobehavioral and somatic effects of perinatal PCB exposure in rats. Environ Res 44:56-70.

*Owen GM, Brozek J. 1966. Influence of age, sex, and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.

*Pal D, Weber JB, Overcash MR. 1980. Fate of polychlorinated biphenyls (PCBs) in soil-plant systems. Residue Reviews 74:45-98.

*Paneth N. 1991. Human reproduction after eating PCB-contaminated fish. Health Environ Digest 5:4-6.

Paneth N. 1996. Adopting a public health approach to developmental neurotoxicity. Neurotoxicol Teratol 18(3):233-234.

*Panshin SY, Hites RA. 1994. Atmospheric concentrations of polychlorinated biphenyls at Bloomington, Indiana. Environ Sci Technol 28:2008-2013.

*Pantaleoni G, Fanini D, Sponta AM, et al. 1988. Effects of maternal exposure to polychlorobiphenyls (PCBs) on F1 generation behavior in the rat. Fundam Appl Toxicol 11:440-449.

*Pappas BA, Murtha SJE, Park GAS, et al. 1998. Neurobehavioral effects of chronic ingestion of Great Lakes chinook salmon. Regul Toxicol Pharmacol 27:S55-S67.

*Pardue JH, Delaune RD, Patrick WH. 1988. Effect of sediment of pH and oxidation-reduction potential on PCB mineralization. Water Air Soil Pollut 37:439-447.

*Parham FM, Portier CJ. 1998. Using structural information to create physiologically based pharmacokinetic models for all polychlorinated biphenyls. II-Rates of metabolism. Toxicol Appl Pharmacol 151(1):110-116.

*Parham FM, Kohn MC, Matthews HB, et al. 1997. Using structural information to create physiologically based pharmacokinetic models for all polychlorinated biphenyls. Toxicol Appl Pharmacol 144(2):340-347.

*Paris DF, Steen WC, Baughman GL. 1978. Role of the physico-chemical properties of Aroclors 1016 and 1242 in determining their fate and transport in aquatic environments. Chemosphere 7:319-325.

Parkinson A, Robertson L, Safe L, et al. 1980. Polychlorinated biphenyls as inducers of hepatic microsomal enzymes: Structure-activity rules. Chem Biol Interact 30:271-285.

Parkinson A, Safe SH, Robertson LW, et al. 1983. Immunochemical quantitation of cytochrome P-450 isozymes and epoxide hydrolase in liver microsomes from polychlorinated or polybrominated biphenyl-treated rats. J Biol Chem 258:5967-5976.

*Patandin S, Koopman-Esseboom C, De Ridder MAJ, et al. 1998. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. Pediatr Res 44(4):538-545.

*Patandin S, Lanting CI, Mulder PGH, et al. 1999. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J Pediatr 134:33-41.

*Patandin S, Weiglas-Kuperus N, de Ridder MAJ, et al. 1997. Plasma polychlorinated biphenyl levels in Dutch preschool children either breast-fed or formula-fed during infancy. Am J Public Health 87:1711-1714.

*Paterson S, Mackay D, Tam D, et al. 1990. Uptake of organic chemicals by plants: A review of processes, correlations and models. Chemosphere 21(3):297-331.

*Patnode KA, Curtis LR. 1994. 2,2',4,4',5,5'- and 3,3',4,4',5,5'-Hexachlorobiphenyl alteration of uterine progesterone and estrogen receptors coincides with embryotoxicity in mink (*mustela vison*). Fundam Appl Toxicol 127:9-18.

*Patterson DG Jr., Lapeza CR, Barnhart ER, et al. 1989. Gas chromatographic/mass spectrometric analysis of human serum for non-ortho (coplanar) and ortho substituted polychlorinated biphenyls using isotope-dilution mass spectrometry. Chemosphere 19:127-134.

*Patterson DG Jr., Todd GD, Turner WE, et al. 1994. Levels of non-ortho-substituted (coplanar), mono- and di-ortho-substituted polychlorinated biphenyls, dibenzo-p-dioxins, and dibenzofurans in human serum and adipose tissue. Environ Health Perspect Suppl 102(1):195-204.

*Pauwels A, Covaci A, Delbeke L, et al. 1999. The relation between levels of selected PCB congeners in human serum and follicular fluid. Chemosphere 39(14):2433-2441.

*Peakall DB, Lincer JL, Bloom SE. 1972. Embryonic mortality and chromosomal alterations caused by Aroclor 1254 in ring doves. Environ Health Perspect 1:103-104.

*Pearson RF, Hornbuckle KC, Eisenreich SJ, et al. 1996. PCBs in Lake Michigan water revisited. Environ Sci Technol 30(5):1429-1436.

*Pellettieri MB, Hallenbeck WH, Brenniman GR, et al. 1996. PCB intake from sport fishing along the northern Illinois shore of Lake Michigan. Bull Environ Contam Toxicol 57(5):766-770.

*Peng J, Singh A, Ireland WP, et al. 1997. Polychlorinated biphenyl congener 153-induced ultrastructural alterations in rat liver: a quantitative study. Toxicology 120:171-183.

*Pereira MA, Herren SL, Britt AL, et al. 1982. Promotion by polychlorinated biphenyls of enzyme-altered foci in rat liver. Cancer Lett 15:185-190.

*Pereira WE, Hostettler FD, Cashman JR, et al. 1994. Occurrence and distribution of organochlorine compounds in sediment and livers of striped bass (*morone saxatilis*) from the San Francisco Bay-Delta Estuary. Mar Pollut Bull 28(7):434-441.

*Perkins JL, Knight VB. 1989. Risk assessment of dermal exposure to polychlorinated biphenyls permeating a polyvinyl chloride glove. Am Ind Hyg Assoc J 50:A171-A172.

Petersen GI, Kristensen P. 1998. Bioaccumulation of lipophilic substances in fish early life stages. Environ Toxicol Chem 17(7):1385-1395.

*Pham TT, Proulx S. 1997. PCBs and PAHs in the Montreal urban community (Quebec, Canada) wastewater treatment plant and in the effluent plume in the St. Lawrence River. Water Res 31(8):1887-1896.

Phaneuf D, DesGranges JL, Plante N, et al. 1995. Contamination of local wildlife following a fire at a polychlorinated biphenyls warehouse in St. Basile le Grand, Quebec, Canada. Arch Environ Contam Toxicol 28:145-153.

*Phillips DL, Pirkle JL, Burse VW, et al. 1989b. Chlorinated hydrocarbon levels in human serum: Effects of fasting and feeding. Arch Environ Contam Toxicol 18:495-500.

*Phillips DL, Smith AB, Burse VW, et al. 1989a. Half-life of polychlorinated biphenyls in occupationally exposed workers. Arch Environ Health 44:351-354.

*Phillips WEJ, Hatina G, Villeneuve DC, et al. 1972. Effect of parathion administration in rats following long term feeding with PCB's. Environ Physiol Biochem 2:165-169.

*Pines A, Cucos S, Ever-Hadani P, et al. 1987. Some organochlorine insecticide and polychlorinated biphenyl blood residues in infertile males in the general Israeli population of the middle 1980's. Arch Environ Contam Toxicol 16:587-597.

*Pintar JE. 2000. Normal development of the hypothalamic-pituitary-thyroid axis. In: Braverman LE, Utiger RD, ed. Werner and Ingbar's the thyroid: A fundamental and clinical text. Philadelphia, PA: Lippincott-Raven, 7-19.

*Platanow NS, Karstad LH. 1973. Dietary effects of polychlorinated biphenyls on mink. Can J Comp Med 37:391-400.

Pohl H, Holler J. 1995. Halogenated aromatic hydrocarbons and toxicity equivalency factors (TEFs) from the public health assessment perspective. Chemosphere 31(1):2547-2559.

Poland A, Glover E. 1977. Chlorinated biphenyl induction of aryl hydrocarbon hydroxylase activity: A study of the structure-activity relationship. Mol Pharmacol 13:924-938.

*Poland A, Knutson JC. 1982. 2,3,7,8-Tetrachlorodibenzo-p-dioxin and related halogenated aromatic hydrocarbons. Examinations of the mechanisms of toxicity. Annu Rev Pharmacol Toxicol 22:57-end

9. REFERENCES

*Poland A, Glover E, Kende AS. 1976. Stereospecific, high affinity binding of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin by hepatic cytosol: Evidence that the binding species is receptor for induction of aryl hydrocarbon hydroxylase. J Biol Chem 16:4936-4946.

*Poland A, Knutson J, Glover E, et al. 1983. Tumor promotion in the skin of hairless mice by halogenated aromatic hydrocarbons. In: Weinstein IB, Vogel HJ, eds. Genes and proteins in oncogenesis. New York, NY: Academic Press, 143-161.

*Polder A, Becher G, Savinova TN, et al. 1998. Dioxins, PCBs and some chlorinated pesticides in human milk from the Kola Peninsula, Russia. Chemosphere 37(9-12):1795-1806.

*Poole KG, Elkin BT, Bethke RW. 1995. Environmental contaminants in wild mink in the Northwest Territories, Canada. Sci Total Environ 160-161:473-486.

*Poole KG, Elkin BT, Bethke RW. 1998. Organochlorine and heavy metal contaminants in wild mink in western Northwest Territories, Canada. Arch Environ Contam Toxicol 34(4):406-413.

*Poon K-F, Lam PKS, Lam MHW. 1999. Determination of polychlorinated biphenyls in human blood serum by SPME. Chemosphere 39(6):905-912.

*Porte C, Albaiges J. 1993. Bioaccumulation patterns of hydrocarbons and polychlorinated biphenyls in bivalves, crustaceans, and fishes. Arch Environ Contam Toxicol 26(3):273-281.

Porte C, Barcelo D, Albaiges J. 1988. Quantitation of total *versus* selected polychlorinated biphenyl congeners in marine biota samples. J Chromatogr 442:386-393.

*Porterfield SP, Hendry LB. 1998. Impact of PCBs on thyroid hormone directed brain development. Toxicol Ind Health 14(½):103-120.

*Portier RJ, Fujisaki K. 1988. Enhanced biotransformation and biodegradation of polychlorinated biphenyls in the presence of aminopolysaccharides. In: Adams WJ, Chapman GA, Landis WG eds. Aquatic toxicology and hazard assessment: 10th volume. Philadelphia, PA: ASTM, 517-527.

*Preston BD, Miller JA, Miller EC. 1983. Non-arene oxide aromatic ring hydroxylation of 2,2',5,5'-tetrachlorobiphenyl as the major metabolic pathway catalyzed by phenobarbital-induced rat liver microsomes. J Biol Chem 258:8304-8311.

*Preston BD, Miller JA, Miller EC. 1984. Reactions of 2,2',5,5' -tetrachlorobiphenyl-3,4-oxide with methionine, cysteine and glutathione in relation to the formation of methylthio-metabolites of 2,2',5,5' -tetrachlorobiphenyl in the rat and mouse. Chem-Biol Ineract 50:289-312.

*Preston BD, Miller EC, Miller JA. 1985. The activities of 2,2',5,5'-tetrachlorobiphenyl, its 3,4-oxide metabolite, and 2,2',4,4'-tetrachlorobiphenyl in tumor induction and promotion assays. Carcinogenesis 6(3):451-453.

*Preston BD, Van Miller JP, Moore RW, et al. 1981. Promoting effects of polychlorinated biphenyls (Aroclor 1254) and polychlorinated dibenzofuran-free Aroclor 1254 on diethylnitrosamine-induced tumorigenesis in the rat. J Natl Cancer Inst 66:509-515.

Price HA, Welch RL. 1972. Occurrence of polychlorinated biphenyls in humans. Environ Health Perspect 1:73-78.

9. REFERENCES

*Price NO, Young RW, Dickinson JK. 1972. Pesticide residues and polychlorinated biphenyl levels in diets, urine, and fecal matter of preadolescent girls. Proc Soc Exp Biol Med 139:1280-1283.

*Price SC, Ozalp S, Weaver R, et al. 1988. Thyroid hyperactivity caused by hypolipodaemic compounds and polychlorinated biphenyls: The effect of coadministration in the liver and thyroid. Arch Toxicol Suppl 12:85-92.

*Provost TL, Juarez De Ku LM, Zender C, et al. 1999. Dose- and age-dependent alterations in choline acetyltransferase (ChAT) activity, learning and memory, and thyroid hormones in 15- and 30-day old rats exposed to 1.25 or 12.5 ppm polychlorinated biphenyl (PCB) beginning at conception. Prog Neuro-Psychopharmacol Biol Psychiat 23:915-928.

*Pruell RJ, Rubinstein NI, Taplin BK, et al. 1993. Accumulation of polychlorinated organic contaminants from sediment by three benthic marine species. Arch Environ Contam Toxicol 24(3):290-297.

*Puhvel SM, Sakamoto M, Ertl DC, et al. 1982. Hairless mice as models for chloracne: A study of cutaneous changes induced by topical application of established chloracnegens. Toxicol Appl Pharmacol 64:492-503.

*Qi M, Anderson M, Meyer S, et al. 1997. Contamination of PCB congeners in Bear Lake fish tissues, livers, and brains. Toxicol Environ Chem 61(1-4):147-161.

*Quazi S, Takahata M, Horio F, et al 1984. Hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase and cholesterol 7-α-hydroxylase activities in rats fed PCB. Nutr Rep Int 30(3):617627.

*Que Hee S, Ward JA, Tabor MW, et al. 1983. Screening method for Aroclor 1254 in whole blood. Anal Chem 55:157-160.

*Quenson JF III, Boyd SA, Tiedje JM. 1990. Dechlorination of four commercial polychlorinated biphenyl mixtures (Aroclor) by anaerobic microoganisms from sediments. Appl Environ Microbiol 56(8):2360-2369.

*Quensen JF III, Mousa MA, Boyd SA, et al. 1998. Reduction of aryl hydrocarbon receptor-mediated activity of polychlorinated biphenyl mixtures due to anaerobic microbial dechlorination. Environ Toxicol Chem 17(5):806-813.

*Quensen JF III, Tiedje JM, Boyd SA. 1988. Reductive dechlorination of polychlorinated biphenyls by anaerobic microorganisms from sediments. Science 242:752-754.

Ramamoorthy K, Vyhlidal C, Wang F, et al. 1997. Additive estrogenic activities of a binary mixture of 2',4',6'-trichloro- and 2',3',4',5'-tetrachloro-4-biphenylol. Toxicol Appl Pharmacol 147(1):93-100.

Ramos L, Hernandez LM, Gonzalez MJ. 1997. Variation of PCB congener levels during lactation period and relationship to their molecular structure. Arch Environ Contam Toxicol 33(1):97-103.

*Ramos L, Torre M, Laborda F, et al. 1998. Determination of polychlorinated biphenyls in soybean infant formulas by gas chromatography. J Chromatogr 823:365-372.

Rao CV, Banerji AS. 1988. Induction of liver tumors in male Wistar rats by feeding polychlorinated biphenyls (Aroclor 1260). Cancer Lett 39:59-67.

*Rao CV, Banerji SA. 1993. Effect of polychlorinated biphenyls (Aroclor 1260) on histology of adrenal of rats. J Environ Biol 14:1-6.

*Rappe C, Buser HR. 1981. Occupational exposure to polychlorinated dioxins and dibenzofurans. ACS Symp Ser 149:319-342.

*Rappe C, Buser HR. 1989. Chemical and physical properties, analytical methods, sources and environmental levels of halogenated dibenzodioxins and dibenzofurans. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd ed. Amsterdam, The Netherlands: Elsevier Science Publishers, 71-102.

*Rappe C, Buser HR, Bosshardt HP. 1979. Dioxins, dibenzofurans, and other polyhalogenated aromatics: Production, use, formation, and destruction. Ann NY Acad Sci 320:1-18.

*Rathke DE, McRae G. 1989. 1987 report on Great Lakes water quality: Appendix B: Great Lakes water surveillance. Great Lakes Water Quality Board report to the International Joint Commission, Windsor, Ontario.

*Ray LE, Murray HE, Giam CS. 1983. Organic pollutants in marine samples from Portland, Maine. Chemosphere 12:1031-1038.

Ray S, Bailey M, Paterson G, et al. 1998. Comparative levels of organochlorine compounds in flounders from the northeast coast of Newfoundland and an offshore site. Chemosphere 36(10):2201-2210.

*Reich S, Jimenez B, Marsili L, et al. 1999. Congener specific determination and enantiomeric ratios of chiral polychlorinated biphenyls in striped dolphins (*stenella coeruleoalba*) from the Mediterranean sea. Environ Sci Technol 33:1787-1793.

*Reid D, Fox JM. 1982. Polychlorinated biphenyl report: Old Forge, Lackawanna County. Pennsylvania Department of Health, Division of Environmental Health.

Requejo AG, West RH, Hatcher PG, et al. 1979. Polychlorinated biphenyls and chlorinated pesticides in soils of the Everglades national park and adjacent agricultural areas. Environ Sci Technol 13:931-935.

*Restum JC, Bursian SJ, Giesy JP, et al. 1998. Multigenerational study of the effects of consumption of PCB-contaminated carp from Saginaw Bay, Lake Huron, on mink. 1. Effects on mink reproduction, kit growth and survival, and selected biological parameters. J Toxicol Environ Health 54:343-375.

*Reynolds ES, Moslen MT, Szabo S, et al. 1975. Hepatotoxicity of vinyl chloride and 1,1-dichloroethylene. Am J Pathol 81:219-236.

*Rhee G-Y, Bush B, Bethoney CM, et al. 1993a. Reductive dechlorination of Aroclor 1242 in anaerobic sediments: Pattern, rate, and concentration dependence. Environ Toxicol Chem 12(6):1025-1032.

*Rhee GY, Bush B, Brown MP, et al. 1989. Anaerobic biodegradation of polychlorinated biphenyls in Hudson River sediments and dredged sediments in clay encapsulation. Water Res 23:957-964.

*Rhee G-Y, Sokol RC, Bush B, et al. 1993b. Long-term study of the anaerobic dechlorination of Aroclor 1254 with and without biphenyl enrichment. Environ Sci Technol 27(4):714-719.

*Rice DC. 1996. PCBs and behavioral impairment: Are there lessons we can learn from lead? Neurotoxicol Teratol 18(3):229-232.

*Rice DC. 1997. Effect of postnatal exposure to a PCB mixture in monkeys on multiple fixed interval-fixed ratio performance. Neurotoxicol Teratol 19(6):429-434.

*Rice DC. 1998. Effects of postnatal exposure of monkeys to a PCB mixture on spatial discrimination reversal and DRL performance. Neurotoxicol Teratol 20(4):391-400.

Rice DC. 1999b. Behavioral impairment produced by low-level postnatal PCB exposure in monkeys. Environ Res 80:S113-S121.

*Rice DC. 1999a. Effect of exposure to 3,3',4,4',5-pentachlorobiphenyl (PCB 126) throughout gestation and lactation on development and spatial delayed alternation performance in rats. Neurotoxicol Teratol 21(1):59-69.

*Rice DC. 2000. Parallels between attention deficit hyperactivity disorder and behavioral deficits produced by neurotoxic exposure in monkeys. Environ Health Perspect Suppl 108(3):405-408.

*Rice DC, Hayward S. 1997. Effects of postnatal exposure to a PCB mixture in monkeys on nonspatial discrimination reversal and delayed alternation performance. Neurotoxicology 18(2):479-494.

*Rice DC, Hayward S. 1998. Lack of effect of 3,3',4,4,5-pentachlorobiphenyl (PCB 126) throughout gestation and lactation on multiple fixed interval-fixed ration and DRL performance in rats. Neurotoxicol Teratol 20(6):645-650.

*Rice DC, Hayward S. 1999b. Effects of exposure to 3,3',4,4',5-pentachlorobiphenyl (PCB 126) throughout gestation and lactation on behavior (concurrent random interval-random interval and progressive ratio performance) in rats. Neurotoxicol Teratol 21(6):679-687.

*Rice DC, Hayward S. 1999a. Effects of postnatal exposure of monkeys to a PCB mixture on concurrent random interval-random interval and progressive ratio performance. Neurotoxicol Teratol 21(1):47-58.

Rice RH, Cohen DE. 1996. Toxic responses of the skin. In: Klaassen CD, ed. Cassarett and Doull's toxicology: The basic science of poisons. New York, NY: McGraw-Hill, 529-546.

*Rickenbacher U, McKinney JD, Oatley SJ, et al. 1986. Structurally specific binding of halogenated biphenyls to thyroxine transport protein. J Med Chem 29:641-648.

*Ridgway S, Reddy M. 1995. Residue levels of several organochlorines in *tursiops truncatus* milk collected at varied stages of lactation. Mar Poll Bull 30(9):609-614.

*Ringer RK, Aulerich RJ, Bleavins MR. 1981. Biological effects of PCBs and PBBs on mink and ferrets: A review. In: Khan MAQ, ed. Toxicology of halogenated hydrocarbons: Health and ecological effects. Elmsford, NY: Pergamon Press, 329-343.

*Risebrough RW. 1999. 'Endocrine disruption' and the 'wildlife connection'. Human and Ecological Risk Assessment 5(5):869-883.

*Risebrough RW, Anderson DW. 1975. Some effects of DDE and PCB on mallards and their eggs. J Wildl Manage 39(3):508-513.

9. REFERENCES

*Robbiano L, Pino A. 1981. Induction in rats of liver DNA single-strand breaks by the polychlorinated biphenyl Aroclor 1254. Boll Soc Ital Biol Sper 57:407-413.

*Robertson LW, Gupta RC. 2000. Metabolism of polychlorinated biphenyls (PCBs) generates electrophiles and reactive oxygen species that damage DNA. In: Williams GM, Aruoma OI, eds. Molecular drug metabolism and toxicology. OICA International, 1-19.

Robertson LW, Parkinson A, Bandiera S, et al. 1984. PCBs and PBBs: Biologic and toxic effects on C57BL/6J and DBA/2J inbred mice. Toxicology 31:191-206.

*Robinson GK, Lenn MJ. 1994. The bioremediation of polychlorinated biphenyls (PCBs): Problems and perspectives. Biotechnol Genet Eng Rev 12:139-188.

Rodgers JA Jr. 1997. Pesticide and heavy metal levels of waterbirds in the Everglades agricultural area of South Florida. Florida Field Naturalist 25(2):33-41.

*Rodgers PW, Swain WR. 1983. Analysis of polychlorinated biphenyl (PCB) loading trends in Lake Michigan. J Great Lakes Res 9:548-558.

*Rodriguez J, Kholkute SD, Dukelow WR. 1997. Reproductive toxicology of 3,3',4,4'-tetrachlorobiphenyl in mice. Bull Environ Contam Toxicol 58:999-1005.

*Rogan WJ. 1989. Yu-Cheng. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd ed. Amsterdam, The Netherlands: Elsevier Science Publishers, 401-415.

*Rogan WJ, Gladen BC. 1991. PCBs, DDE, and child development at 18 and 24 months. Ann Epidemiol 1(5):407-413.

*Rogan WJ, Gladen BC. 1992. Neurotoxicology of PCBs and related compounds. Neurotoxicology 13:27-36.

*Rogan WJ, Gladen BC, Guo Y-LL, et al. 1999. Sex ratio after exposure to dioxin-like chemicals in Taiwan. Lancet 353:206-207.

*Rogan WJ, Gladen BC, Hung K-L, et al. 1988. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. Science 241:334-336.

*Rogan WJ, Gladen BC, McKinney JD, et al. 1986a. Neonatal effects of transplacental exposure to PCBs and DDE. J Pediatr 109:335-341.

*Rogan WJ, Gladen BC, McKinney JD, et al. 1986b. Polychlorinated biphenyls (PCBs) and dichlorophenyl dichloroethene (DDE) in human milk: Effects of maternal factors and previous lactation. Am J Public Health 76:172-177.

*Rogan WJ, Gladen BC, McKinney JD, et al. 1987. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethane (DDE) in human milk: Effects on growth, morbidity, and duration of lactation. Am J Public Health 77:1294-1297.

*Roose P, Cooreman K, Vyncke W. 1998. PCBs in cod (*gadus morhua*), flounder (*platichthys flesus*), blue mussel (*mytilus edulis*) and brown shrimp (*crangon crangon*) from the Belgian continental shelf: Relation to biological parameters and trend analysis. Chemosphere 37(9-12):2199-2210.

*Rose N, Laib RJ, Brunn H, et al. 1985. Biotransformation and toxicity of polychlorinated biphenyls (PCB's): Investigation of initiating and promoting activities of 2,2',4,5'-tetra- and 2,2',4,4',5,5'-hexachlorobiphenyl. Naunyn-Schmiedebergs Arch Pharmacol 330(Suppl):R21.

*Rosenshield ML, Jofre MB, Karasov WH. 1999. Effects of polychlorinated biphenyl 126 on green frog (*rana clamitans*) and leopard frog (*rana pipiens*) hatching success, development, and metamorphosis. Environ Toxicol Chem 18(11):2478-2486.

*Rosin DL, Martin BR. 1981. Neurochemical and behavioral effects of polychlorinated biphenyls in mice. Neurotoxicology 2:749-764.

*Rothman N, Cantor KP, Blair A, et al. 1997. A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues. Lancet 350(9073):240-244.

Rumsby PC, Evans JG, Phillimore HE, et al. 1992. Search for Ha-*ras* codon 61 mutations in liver tumours caused by hexachlorobenzene and Aroclor 1254 in C57BL/10ScSn mice with iron overload. Carcinogenesis 13(10):1917-1920.

*Ruokojarvi P, Ruuskanen J, Ettala M, et al. 1995. Formation of polyaromatic hydrocarbons and polychlorinated organic compounds in municipal waste landfill fires. Chemosphere 31(8):3899-3908.

Rushmore TH, Pickett CB. 1990. Transcriptional regulation of the rat glutathione S-transferase Ya subunit gene. J Biol Chem 265:14648-14653.

*Ryan JJ, Dewailly E, Gilman A, et al. 1997. Dioxin-like compounds in fishing people from the lower north shore of the St. Lawrence River, Quebec, Canada. Arch Environ Health 52(4):309-316.

*Ryan JJ, Gasiewicz TA, Brown JF. 1990. Human body burden of polychlorinated dibenzofurans associated with toxicity based on the Yusho and Yucheng incidents. Fundam Appl Toxicol 15:722-731.

Ryan JJ, Lau PY, Pilon JC, et al. 1984. Incidence and levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in Lake Ontario commercial fish. Environ Sci Technol 18:719-721.

*Ryan JJ, Levesque D, Panopio LG, et al. 1993. Elimination of polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) from human blood in the Yusho and Yu-Cheng rice oil poisonings. Arch Environ Contam Toxicol 24:504-512.

Rybitski MJ, Hale RC, Musick JA. 1995. Distribution of organochlorine pollutants in Atlantic sea turtles. Copeia 1995(2):379-390.

*Rylander L and Hagmar L. 1995. Mortality and cancer incidence among women with a high consumption of fatty fish contaminated with persistent organochlorine compounds. Scand J Work Environ Health 21(6):419-426.

*Rylander L, Stromberg U, Dyremark E, et al. 1998b. Polychlorinated biphenyls in blood plasma among Swedish female fish consumers in relation to low birth weight. Am J Epidemiol 147:493-502.

*Rylander L, Stromberg U, Hagmar L. 1995. Decreased birthweight among infants born to women with a high dietary intake of fish contaminated with persistent organochlorine compounds. Scand J Work Environ Health 21:368-375.

Rylander L, Stromberg U, Hagmar L. 1998a. Agreement between reported fish consumption obtained by two interviews and its impact on the results in a reproduction study. Eur J Epidemiol 14(1):93-97.

*Sabata S, Friesova A, Rericha R, et al. 1993. Limits to the use of KOH/PEG method for destruction of PCB liquids of Czechoslovak production. Chemosphere 27(7):1201-1210.

*Sabljic A, Güsten H. 1989. Predicting Henry's law constants for polychlorinated biphenyls. Chemosphere 19:1503-1511.

*Sabljic A, Güsten H, Hermens J, et al. 1993. Modeling octanol/water partition coefficients by molecular topology: Chlorinated benzenes and biphenyls. Environ Sci Technol 27(7):1394-1402.

*Saçan MT, Balcio™lu IA. 1996. Prediction of the soil sorption coefficient of organic pollutants by the characteristic root index model. Chemosphere 32(10):1993-2001.

*Saeed A, Hansen LG. 1997. Morphometric changes in the prepubertal female rat thyroid gland following acute exposure to 2,2',4,4'-tetrachlorobiphenyl and Aroclor 1242. J Toxicol Environ Health 51(5):503-513.

Safe S. 1976. Overview of analytical identification and spectroscopic properties. In: Proceedings of the National Conference on Polychlorinated Biphenyls, Chicago, 1975. Washington, DC: U.S. Environmental Protection Agency. EPA 560/6-75-004.

*Safe S. 1980. Metabolism, uptake, storage and bioaccumulation of halogenated aromatic pollutants. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd ed. Amsterdam, The Netherlands: Elsevier Science Publishers, 81-107.

*Safe S. 1984. Polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs): Biochemistry, toxicology and mechanism of action. CRC Crit Rev Toxicol 13:319-395.

*Safe S. 1989a. Polyhalogenated aromatics: uptake, disposition and metabolism. In: Kimbrough R, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd ed. Amsterdam, The Netherlands: Elsevier Science Publishers, 131-159.

*Safe S. 1989b. Polychlorinated biphenyls (PCBs): mutagenicity and carcinogenicity. Mutat Res 220:31-47.

*Safe S. 1990. Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: Environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs). Crit Rev Toxicol 21:51-88.

*Safe S. 1993. Development of bioassays and approaches for the risk assessment of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and related compounds. Environ Health Perspect Suppl 101(3):317-325.

*Safe S. 1994. Polychlorinated biphenyls (PCBs): Environmental impact, biochemical and toxic responses, and implications for risk assessment. Crit Rev Toxicol 24(2):87-149.

*Safe SH. 1995. Environmental and dietary estrogens and human health: Is there a problem? Environ Health Perspect 103:356-351.

*Safe S. 1998a. Limitations of the toxic equivalency factor approach for the risk assessment of TCDD and related compounds. Teratogen Carcinogen Mutagen 17:285-304.

*Safe S. 1998b. Development validation and problems with the toxic equivalency factor approach for risk assessment of dioxins and related compounds. J Anim Sci 76(1):134-141.

*Safe S. 1998c. Interactions between hormones and chemicals in breast cancer. Annu Rev Pharmacol Toxicol 38:121-158.

*Safe SH. 1999. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and related environmental antiestrogens: Characterization and mechanism of action. In: Naz RK, ed. Endocrine disruptors: effects on male and female reproductive systems. Boca Raton, FL: CRC Press, 187-221.

*Safe SH, Zacharewski T. 1997. Organochlorine exposure and risk for breast cancer. In: Aldaz CM, Gould MN, McLachlan J, et al., ed. Etiology of breast and gynecological cancers. New York, NY: John Wiley & Sons, Inc., 133-145.

*Safe S, Bandiera S, Sawyer T, et al. 1985a. PCBs: Structure-function relationships and mechanism of action. Environ Health Perspect 60:47-56.

*Safe S, Bannister R, Davis D, et al. 1989. Aroclor 1254 as a 2,3,7,8-tetrachlorobenzo-p-dioxin antagonist in mice. Chemosphere 18:709-714.

*Safe S, Connor K, Ramamoorthy K, et al. 1997. Human exposure to endocrine-active chemicals: Hazard assessment problems. Reg Toxicol Pharmacol 26(1 Part 1):52-58.

*Safe SH, Connor K, Raamamorthy K, et al. 1998. Estrogenic activity of hydroxylated polychlorinated biphenyls (PCBs) and their interactions. In: Eisenbrand G, ed. Hormonally active agents in food: Symposium. Weinheim, FRG: Wiley-VCH, 200-207.

*Safe S, Hutzinger O, Jones D. 1975. The mechanism of chlorobiphenyl metabolism. J Agric Food Chem 23:851-853.

Safe S, Rodriguez LV, Goldstein LS. 1995. Toxic equivalency factor approach for risk assessment of combustion by-products. Toxicol Environ Chem 49(3):181-191.

*Safe S, Safe L, Mullin M. 1985b. Polychlorinated biphenyls: Congener-specific analysis of a commercial mixture and a human milk extract. J Agric Food Chem 33:24-29.

*Sager DB. 1983. Effect of postnatal exposure to polychlorinated biphenyls on adult male reproductive function. Environ Res 31:76-94.

*Sager DB, Girard DM. 1994. Long-term effects on reproductive parameters in female rats after translactational exposure to PCBs. Environ Res 66(1):52-76.

*Sager D, Girard D, Nelson D. 1991. Early postnatal exposure to PCBs: Sperm function in rats. Environ Toxicol Chem 10:737-746.

*Sager DB, Shih-Schroeder W, Girard D. 1987. Effect of early postnatal exposure to polychlorinated biphenyls (PCBs) on fertility in male rats. Bull Environ Contam Toxicol 38:946-953.

*Saghir SA, Hansen LG. 1999. Toxicity and tissue distribution of 2,2',4,4'- and 3,3',4,4'-tetrachlorobiphenyls in houseflies. Ecotoxicol Environ Safety 42:177-184.

*Saghir SA, Koritz GD, Hansen LG. 1994. Toxicokinetics of 2,2',4,4'-and 3,3',4.4'-tetrachlorobiphenyl in house files following topical administration. Pestic Biochem Physiol 49:94-113.

*Sahl JD, Crocker TT, Gordon RJ, et al. 1985a. Polychlorinated biphenyl concentrations in the blood plasma of a selected sample of non-occupationally exposed southern California working adults. Sci Total Environ 46:9-18.

*Sahl JD, Crocker TT, Gordon RJ, et al. 1985b. Polychlorinated biphenyls in the blood of personnel from an electric utility. J Occup Med 27:639-643.

*Sakai S, Hiraoka M, Takeda N, et al. 1993. Coplanar PCBs and PCDDs/PCDFs in municipal waste incineration. Chemosphere 27(1-3):233-240.

Salama AA, Mohamed MAM, Duval B, et al. 1998. Polychlorinated biphenyl concentrations in raw and cooked North Atlantic bluefish (pomatomus saltatrix) fillets. J Agric Food Chem 46(4):1359-1362.

*Salata GG, Wade TL, Sericano JL, et al. 1995. Analysis of Gulf of Mexico bottlenose dolphins for organochlorine pesticides and PCBs. Environ Pollut 88(2):167-175.

*Sanders G, Hamilton-Taylor J, Jones KC. 1996. PCB and PAH dynamics in a small rural lake. Environ Sci Technol 30:2958-2966.

*Sanders OT, Zepp RL, Kirkpatrick RL. 1974. Effect of PCB ingestion on sleeping times, organ weights, food consumption, serum corticosterone and survival of albino mice. Bull Environ Contam Toxicol 12:394-399.

*SANSS. 1990. Structure and Nomenclature Search System. Chemical Information System (CIS) computer database.

*Sargent L, Dragan YP, Erickson C, et al. 1991. Study of the separate and combined effects of the non-planar 2,5,2',5'- and the planar 3,4,3',4'-tetrachlorobiphenyl in liver and lymphocytes in vivo. Carcinogenesis 12:793-800.

*Sargent L, Roloff B, Meisner L. 1989. In vitro chromosome damage due to PCB interactions. Mutat Res 224:79-88.

Sargent LM, Sattler GL, Roloff B, et al. 1992. Ploidy and specific karyotypic changes during promotion with phenobarbital, 2,5,2',5'-tetrachlorobiphenyl, and/or 3,4,3',4-tetrachlorobiphenyl in rat liver. Cancer Res 52:955-962.

*Sawhney BL, Hankin L. 1985. Polychlorinated biphenyls in food: A review. J Food Protect 48:442-448.

Sawyer T, Safe S. 1982. PCB isomers and congeners: Induction of aryl hydrocarbon hydroxylase and ethoxyresorufin-o-deethylase enzyme activities in rat hepatoma cells. Toxicol Lett 13:87-94.

*Schade G, Heinzow B. 1998. Organochlorine pesticides and polychlorinated biphenyls in human milk of mothers living in northern Germany: Current extent of contamination, time trend from 1986 to 1997 and factors that influence the levels of contamination. Sci Total Environ 215:31-39.

*Schaeffer E, Greim H, Goessner W. 1984. Pathology of chronic polychlorinated biphenyl (PCB) feeding in rats. Toxicol Appl Pharmacol 75:278-288.

*Schantz MM, Koster BJ, Wise SA, et al. 1993. Determination of PCBs and chlorinated hydrocarbons in marine mammal tissues. Sci Total Environ 139/140:323-345.

*Schantz MM, Parris RM, Kurz J, et al. 1993a. Comparison of methods for the gas-chromatographic determination of PCB congeners and chlorinated pesticides in marine reference materials. Fresenius J Anal Chem 346(6-9):766-778.

*Schantz MM, Parris RM, Wise SA. 1993b. NIST standard reference materials (SRMs) for polychlorinated biphenyl (PCB) determinations and their applicability to toxaphene measurements. Chemosphere 27(10):1915-1922.

Schantz SL. 1996. Developmental neurotoxicity of PCBs in humans: What do we know and where do we go from here? Neurotoxicol Teratol 18(3):217-227.

*Schantz SL, Gardiner JC, Gasior DM, et al. 1999. Motor function in aging Great Lakes fisheaters. Environ Res 80(2):S46-S56.

*Schantz SL, Jacobson JL, Humphrey HEB, et al. 1994. Determinants of polychlorinated biphenyls (PCBs) in the sera of mothers and children from Michigan farms with PCB-contaminated silos. Arch Environ Health 49(6):452-458.

Schantz SL, Levin ED, Bowman RE. 1991. Long-term neurobehavioral effects of perinatal polychlorinated biphenyl (PCB) exposure in monkeys. Environ Toxicol Chem 10:747-756.

*Schantz SL, Levin ED, Bowman RE, et al. 1989. Effects of perinatal PCB exposure on discrimination-reversal learning in monkeys. Neurotoxicol Teratol 11:243-250.

*Schantz SL, Moshtaghian J, Ness DK. 1995. Spatial learning deficits in adult rats exposed to *ortho*-substituted PCB congeners during gestation and lactation. Fundam Appl Toxicol 26:117-126.

*Schantz SL, Seo BW, Wong PW, et al. 1997. Long-term effects of developmental exposure to 2,2',3,5',6-pentachlorobiphenyl (PCB 95) on locomotor activity, spatial learning and memory and brain ryanodine binding. Neurotoxicology 18(2):457-67.

*Schantz SL, Seo B-W, Moshtaghian J, et al. 1996b. Effects of gestational and lactational exposure to TCDD or coplanar PCBs on spatial learning. Neurotoxicol Teratol 18:305-313.

*Schantz SL, Sweeney AM, Gardiner JC, et al. 1996a. Neuropsychological assessment of an aging population of Great Lakes fisheaters. Toxicol Ind Health 12(3-4):403-417.

*Schecter AJ. 1983. Contamination of an office building in Binghamton, New York by PCBs, dioxins, furans and biphenylenes after an electrical panel and electrical transformer incident. Chemosphere 12:669-680.

*Schecter AJ. 1986. The Binghamton state office building PCB, dioxin and dibenzofuran electrical transformer incident: 1981-1986. Chemosphere 15:1273-1280.

*Schecter AJ. 1987. The Binghamton state office building PCB transformer incident: 1981-1987. Chemosphere 16:2155-2160.

*Schecter AJ. 1991. Dioxins and related chemicals in humans and in the environment. In: Banbury report 35: Biological basis for risk assessment of dioxins and related compounds. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 169-214.

Schecter AJ. 1992. Written communication (September 24) to Agency for Toxic Substances and Disease Control in peer review comments on draft toxicological profile for polychlorinated biphenyls. SUNY Health Science Center, Binghamton, NY.

*Schecter AJ, Charles K. 1991. The Binghamton state office building transformer incident after one decade. Chemosphere 23:1307-1321.

Schecter A, Li L. 1997. Dioxins, dibenzofurans, dioxin-like PCBs, and DDE in U.S. fast food, 1995. Chemosphere 34(5-7):1449-1457.

*Schecter A, Cramer P, Boggess K, et al. 1997. Levels of dioxins, dibenzofurans, PCB and DDE congeners in pooled food samples collected in 1995 at supermarkets across the United States. Chemosphere 34(5-7):1437-1447.

*Schecter AJ, Furst P, Furst C, et al. 1991. Dioxins, dibenzofurans and selected chlorinated organic compounds in human milk and blood from Cambodia, Germany, Thailand, the U.S.A., the U.S.S.R., and Vietnam. Chemosphere 23:1903-1912.

Schecter A, Kassis I, Papke O. 1998. Partitioning of dioxins, dibenzofurans, and coplanar PCBs in blood, milk, adipose tissue, placenta and cord blood from five American women. Chemosphere 37:1817-1823.

*Schecter A, McGee H, Stanley J, et al. 1993. Chlorinated dioxin, dibenzofuran, coplanar, mono-ortho, and di-ortho substituted PCB congener levels in blood and semen of Michigan Vietnam veterans compared with levels in Vietnamese exposed to Agent Orange. Chemosphere 27(1-3):241-252.

*Schecter A, Mes J, Davies D. 1989. Polychlorinated biphenyl (PCB), DDT, DDE and hexachlorobenzene (HCB) and PCDD/F isomer levels in various organs in autopsy tissue from North American patients. Chemosphere 18:811-818.

*Schecter AJ, Schaffner F, Tiernan TO, et al. 1985b. Biological markers after exposure to polychlorinated dibenzo-*p*-dioxins, dibenzofurans, biphenyls, and related chemicals. Part II: Ultrastructural characterization of human liver biopsies. In: Keith L, Rappe C, Choudhry G, eds., Chlorinated dioxins and dibenzofurans in the total environment, II. Boston, MA: Butterworth Publishers, 247-264.

*Schecter A, Stanley J, Boggess K, et al. 1994. Polychlorinated biphenyl levels in the tissues of exposed and nonexposed humans. Environ Health Perspect Suppl 102(1):149-158.

*Schecter A, Tiernan T. 1985. Occupational exposure to polychlorinated dioxins, polychlorinated furans, polychlorinated biphenyls, and biphenylenes after an electrical panel and transformer accident in an office building in Binghamton, New York. Environ Health Perspect 60:305-313.

*Schecter A, Tiernan T, Schaffner F, et al. 1985a. Patient fat biopsies for chemical analysis and liver biopsies for ultrastructural characterization after exposure to polychlorinated dioxins, furans and PCBs. Environ Health Perspect 60:241-254.

Scheele J, Teufel M, Niessen KH. 1992. Chlorinated hydrocarbons in the bone marrow of children: studies on their association with leukemia. Eur J Pediatr 151(11):802-805.

*Scheele J, Teufel M, Niessen K-H. 1994. A pilot study on polychlorinated biphenyl levels in the bone marrow of healthy individuals and leukemia patients. J Environ Pathol Toxicol Oncol 13:181-185.

*Scheider WA, Cox C, Hayton A, et al. 1998. Current status and temporal trends in concentrations of persistent toxic substances in sport fish and juvenile forage fish in the Canadian waters of the Great Lakes. Environ Monit Assess 53:57-76.

*Schlummer M, Moser GA, McLachlan MS. 1998. Digestive tract absorption of PCDD/Fs, PCBs, and HCB in humans: Mass balances and mechanistic considerations. Toxicol Appl Pharmacol 152:128-137.

Schell LM, Tarbell AM. 1998. A partnership study of PCBs and the health of Mohawk youth: Lessons from our past and guidelines for our future. Environ Health Perspect Suppl 106(3):833-840.

*Scheutz EG, Wrighton SA, Safe SH, et al. 1986. Regulation of cytochrome P-450p by phenobarbital and phenobarbital-like inducers in adult rat hepatocytes in primary monolayer culture and *in vivo*. Biochemistry 25:1124-1133.

*Schlebusch H, Wagner V, van der Ven H, et al. 1989. Polychlorinated biphenyls: The occurrence of the main congeners in follicular and sperm fluids. J Clin Chem Clin Biochem 27:663-667.

*Schmidt LJ, Hesselberg RJ. 1992. A mass spectroscopic method for analysis of AHH-inducing and other polychlorinated biphenyl congeners and selected pesticides in fish. Arch Environ Contam Toxicol 23(1):37-44.

*Schmitt CJ, Zajicek JL, Peterman PH, et al. 1990. National contaminant biomonitoring program: Residues of organochlorine chemicals in U.S. freshwater fish, 1976-1984. Arch Environ Contam Toxicol 19:748-781.

*Schmitt CJ, Zajicek JL, Ribick MA. 1985. National pesticide monitoring program: Residues of organochlorine chemicals in freshwater fish, 1980-81. Arch Environ Contam Toxicol 14:225-260.

9. REFERENCES

*Schnellmann RG, Putnam CW, Sipes IG. 1983. Metabolism of 2,2',3,3'6,6'-hexachlorobiphenyl and 2,2',4,4',5,5'-hexachlorobiphenyl by human hepatic microsomes. Biochem Pharmacol 32:3233-3239.

*Schnellmann RG, Volp RF, Putnam CW, et al. 1984. The hydroxylation, dechlorination, and glucuronidation of 4,4'-dichlorobiphenyl (4-DCB) by human hepatic microsomes. Biochem Pharmacol 33:3503-3509.

*Schoeny RS, Smith CC, Loper JC. 1979. Non-mutagenicity for salmonella of the chlorinated hydrocarbons Aroclor 1254, 1,2,4-trichlorobenzene, mirex and kepone. Mutat Res 68:125-132.

*Schönherr J, Riederer M. 1989. Foliar penetration and accumulation of organic chemicals in plant cuticles. Rev Environ Contam Toxicol 108:1-70.

Schreitmueller J, Ballschmiter K. 1994. Levels of polychlorinated biphenyls in the lower troposphere of the North- and South-Atlantic Ocean. Fresenius J Anal Chem 348(3):226-239.

*Schuetz EG, Brimer C, Schuetz JD. 1998. Environmental xenobiotics and the antihormones cyproterone acetate and spirolactone use the nuclear hormone pregnenolone X receptor to activate the CYP3A23 hormone response element. Mol Pharmacol 54:1113-1117.

*Schultz DE, Patrick G, Duinkeyr JC. 1989. Complete characterization of polychlorinated biphenyl congeners in commercial Aroclor and Clophen mixtures by multidimensional gas chromatography-electron capture detection. Environ Sci Technol 23:852-859.

*Schulze-Stack A, Altman-Hamamdzic S, Morris PJ, et al. 1999. Polychlorinated biphenyl mixtures (Aroclors) inhibit LPS-induced murine splenocyte proliferation in vitro. Toxicology 139:137-154.

*Schuur AG, Cenjin PH, van Toor H, et al. 1998a. Effect of Aroclor 1254 on thyroid hormone sulfation in fetal rats. In: Johansson N, Bergman A, Broman D, et al., ed. Organohalogen compounds. Akademitryck, Edsbruk:, Vol. 37, 249-252.

*Schuur AG, van Leeuwen-Bol I, Jong WMC, et al. 1998b. *In vitro* inhibition of thyroid hormone sulfation by polychloribiphenylols: Isozyme specificity and inhibition kinetics. Toxicol Sci 45:188-194.

*Schuur AG, Bergman A, Brouwer A, et al. 1999. Effects of pentachlorophenol and hydroxylated polychlorinated biphenyls on thyroid hormone conjugation in a rat and a human hepatoma cell line. Toxicol in Vitro 13:417-425.

*Schwartz PM, Jacobson SW, Fein G, et al. 1983. Lake Michigan fish consumption as a source of polychlorinated biphenyls in human cord serum, maternal serum, and milk. Am J Public Health 73:293-296.

*Schwartz TR, Stalling DL, Rice CL. 1987. Are polychlorinated biphenyls residues adequately described by Aroclor mixture equivalents? Isomer-specific principal components analysis of such residues in fish and turtles. Environ Sci Technol 21:72-76.

*Schwartz TR, Tillitt DE, Feltz KP, et al. 1993. Determination of mono- and non-O,O'-chlorine substituted polychlorinated biphenyls in Aroclors and environmental samples. Chemosphere 26(8):1443-1460.

*Secor CL, Mills EL, Harshbarger J, et al. 1993. Bioaccumulation of toxicants, element and nutrient composition, and soft tissue histology of zebra mussels (dreissena polymorpha) from New York State waters. Chemosphere 26(8):1559-1575.

Seegal RF. 1995. Dopaminergic bases of polychlorinated biphenyl-induced neurotoxicity. In: Chang LW, Slikker W Jr, eds. Neurotoxicology: Approaches and methods. San Diego, CA: Academic Press Inc., 347-357.

*Seegal RF. 1996a. Can epidemiological studies discern subtle neurological effects due to perinatal exposure to PCBs? Neurotoxicol Teratol 18(3):251-254.

*Seegal RF. 1996b. Epidemiological and laboratory evidence of PCB-induced neurotoxicity. Crit Rev Toxicol 26(6):709-737.

*Seegal RF. 1998. Neurochemical effects of co-planar and non-coplanar polychlorinated biphenyls. [Abstract]. Neurotoxicol Teratol 20(3):349-350.

Seegal RF, Schantz SL. 1994. Neurochemical and behavioral sequelae of exposure to dioxins and PCBs. In: A. Schecter, ed. Dioxins and health. New York, NY: Plenum Press, 409-447.

Seegal RF, Bemis JC, Okoniewski RJ. 1998. Polychlorinated biphenyls interact with other Great Lakes Fish-borne contaminants to alter dopamine function *in vitro*. In:Organohalogen Compounds 37:1-4.

*Seegal RF, Brosch KO, Bush B. 1986a. Polychlorinated biphenyls produce regional alterations of dopamine metabolism in rat brain. Toxicol Lett 30:197-202.

*Seegal RF, Brosch KO, Bush B. 1986b. Regional alterations in serotonin metabolism induced by oral exposure of rats to polychlorinated biphenyls. Neurotoxicology 7:155-166.

*Seegal RF, Brosch K, Bush, B et al. 1989. Effects of Aroclor 1254 on dopamine and norepinephrine concentrations in pheochromocytoma (PC-12) cells. Neurotoxicology 10:757-764.

*Seegal RF, Brosch KO, Okoniewski R. 1988. The degree of PCB chlorination determines whether the rise in urinary homovanillic acid production in rats is peripheral or central in origin. Toxicol Appl Pharmacol 96:560-564.

*Seegal RF, Brosch KO, Okoniewski RJ. 1997. Effects of *in utero* and lactational exposure of the laboratory rat to 2,4,2',4'- and 3,4,3',4'-tetrachlorobiphenyl on dopamine function. Toxicol Appl Pharmacol 146(1):95-103.

*Seegal RF, Bush B, Brosch KO. 1991a. Sub-chronic exposure of the adult rat to Aroclor 1254 yields regionally-specific changes in central dopaminergic function. Neurotoxicology 12:55-66.

*Seegal RF, Bush B, Brosch KO. 1991b. Comparison of effects of Aroclors 1016 and 1260 on non-human primate catecholamine function. Toxicology 66:145-163.

*Seegal RF, Bush B, Brosch KO. 1992. PCBs induce long-term changes in dopaminergic function in the non-human primate. In: Organohalogen compounds, Vol. 10: 12th International Symposium on Dioxins and Related Compounds, August 24-28, Tampere, Finland, 319-322.

*Seegal RF, Bush B, Brosch KO. 1994. Decreases in dopamine concentrations in adult, non-human primate brain persist following removal from polychlorinated biphenyls. Toxicology 86(1-2):71-87.

*Seegal RF, Bush B, Shain W. 1990. Lightly chlorinated *ortho*-substituted PCB congeners decrease dopamine in nonhuman primate brain and in tissue culture. Toxicol Appl Pharmacol 106:136-144.

*Seegal RF, Pappas BA, Park GAS. 1998a. Neurochemical effects of consumption of Great Lakes salmon by rats. Regul Toxicol Pharmacol 27:S68-S75.

*Seiler P, Fischer B, Lindenau A, et al. 1994. Effects of persistent chlorinated hydrocarbons on fertility and embryonic development in the rabbit. Human Reprod 9:1920-1926.

*Seo BW, Meserve LA. 1995. Effects of maternal ingestion of Aroclor 1254 (PCB) on the developmental pattern of oxygen consumption and body temperature in neonatal rats. Bull Environ Contam Toxicol 55:22-28.

*Seo BW, Li MH, Hansen LG, et al. 1995. Effects of gestational and lactational exposure to coplanar polychlorinated biphenyl (PCB) congeners or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on thyroid hormone concentrations in weanling rats. Toxicol Lett 78(3):253-262.

*Sericano JL, Wade TL, El-Husseini AM, et al. 1992. Environmental significance of the uptake and depuration of planar PCB congeners by the American oyster (*crassostrea viginica*). Mar Pollut Bull 24(11):537-543.

*Sericano JL, Wade TL, Jackson TJ, et al. 1995. Trace organic contamination in the Americas: An overview of the US national status and trends and the international 'mussel watch' programmes. Mar Pollut Bull 31(4/12):214-225.

*Setchell BP, Waites GMH. 1975. The blood testis barrier. In: Creep RO, Astwood EB, Geiger SR, eds. Handbook of physiology: Endocrinology V. Washington, DC: American Physiological Society.

*Shafer TJ, Mundy WR, Tilson HA, et al. 1996. Disruption of inositol phosphate accumulation in cerebellar granule cells by polychlorinated biphenyls: A consequence of altered Ca^{2+} homeostasis. Toxicol Appl Pharmacol 141:448-455.

*Shain W, Bush B, Seegal R. 1991. Neurotoxicity of polychlorinated biphenyls: Structure-activity relationship of individual congeners. Toxicol Appl Pharmacol 111:33-42.

*Shain W, Overmann SR, Wilson LR, et al. 1986. A congener analysis of polychlorinated biphenyls accumulating in rat pups after perinatal exposure. Arch Environ Contam Toxicol 15:687-707.

*Shalat SL, True LD, Fleming LE, et al. 1989. Kidney cancer in utility workers exposed to polychlorinated biphenyls (PCBs). Br J Ind Med 46:823-824.

*Shaw GR, Connell DW. 1982. Factors influencing concentrations of polychlorinated biphenyls in organisms from an estuarine ecosystem. Aust J Mar Freshwater Res 33:1057-1070.

*Shear NM, Schmidt CW, Huntley SL, et al. 1996. Evaluation of the factors relating combined sewer overflows with sediment contamination of the lower Passaic River. Mar Pollut Bull 32(3):288-304.

9. REFERENCES

*Shen TT, Tofflemire TJ. 1980. Air pollution aspects of land disposal of toxic wastes. Journal of the Environmental Engineering Division 106:211-226.

*Shiarls MP, Sayler GS. 1982. Biotransformation of PCB by natural assemblages of freshwater microorganisms. Environ Sci Technol 16:367-369.

*Shigematsu N, Norimatsu Y, Ishibashi T, et al. 1971. Clinical and experimental studies on respiratory involvement in chlorobiphenyls poisoning. Fukuoka Ishi 62(1):150-156.

Shimada T. 1987. Lack of correlation between formation of reactive metabolites and thymic atrophy caused by 3,4,3',4'-tetrachlorobiphenyl in C57BL/6N mice. Arch Toxicol 59:301-306.

*Shimada T, Imai Y, Sato R. 1981. Covalent binding of polychlorinated biphenyls to proteins by reconstituted monooxygenase system containing cytochrome *P*-450. Chem Biol Interact 38:29-44.

*Shipp EB, Restum JC, Giesy JP, et al. 1998a. Multigenerational study of the effects of consumption of PCB-contaminated carp from Saginaw Bay, Lake Huron, on mink. 2. Liver PCB concentration and induction of hepatic cytochrome P-450 activity as a potential biomarker for PCB exposure. J Toxicol Environ Health 54:377-401.

*Shipp EB, Restum JC, Bursian SJ, et al. 1998b. Multigenerational study of the effects of consumption of PCB-contaminated carp from Saginaw Bay, Lake Huron, on mink. 3. Estrogen receptor and progesterone receptor concentrations, and potential correlation with dietary PCB consumption. J Toxicol Environ Health 54:403-420.

*Shirai JH, Kissel JC. 1996. Uncertainty in estimated half-lives of PCBs in humans: impact on exposure assessment. Sci Total Environ 187:199-210.

*Silberhorn EM, Glauert HP, Robertson LW. 1990. Carcinogenicity of polyhalogenated biphenyls: PCBs and PBBs. Crit Rev Toxicol 20:440-496.

*Silkworth JB, Grabstein EM. 1982. Polychlorinated biphenyl immunotoxicity: Dependence on isomer planarity and the Ah gene complex. Toxicol Appl Pharmacol 65:109-115.

*Silkworth JP, Loose LD. 1978. Cell-mediated immunity in mice fed either Aroclor 1016 or hexachlorobenzene. Toxicol Appl Pharmacol 45:326-332.

Silkworth JP, Sutter TR, Kim JH, et al. 1999. CYP1A1 and CYP1B1 expression in Sprague-Dawley rats fed araclors 1016, 1242, 1254, and 12600 for 6 months. Organohalogen Compounds 42:481-484.

*Simcik MF, Basu I, Sweet CW, et al. 1999. Temperature dependence and temporal trends of polychlorinated biphenyl congeners in the Great Lakes atmosphere. Environ Sci Technol 33:1991-1995.

*Simcik MF, Franz TP, Zhang H, et al. 1998. Gas-particle partitioning of PCBs and PAHs in the Chicago urban and adjacent coastal atmosphere: States of equilibrium. Environ Sci Technol 32:251-257.

*Simcik MF, Hoff RM, Strachan WMJ, et al. 2000. Temporal trends of semivolatile organic contaminants in Great Lakes precipitation. Environ Sci Technol 34:361-367.

*Simcik MF, Zhang H, Eisenreich SJ, et al. 1997. Urban contamination of the Chicago/coastal Lake Michigan atmosphere by PCBs and PAHs during aeolos. Environ Sci Technol 31(7):2141-2147.

9. REFERENCES

*Sinclair PR, Bement WJ, Bonkovsky HL, et al. 1986. Uroporphyrin accumulation produced by halogenated biphenyls in chick-embryo hepatocytes. Biochem J 237:63-71.

*Singh A, Chu I, Villeneuve DC. 1996. Subchronic toxicity of 2,4,4'-trichlorobiphenyl in the rat liver: An ultrastructural and biochemical study. Ultrastruct Pathol 20:275-284.

*Singh A, Gilroy C, Chu I, et al. 1997. Toxicity of PCB 105 in the rat liver: An ultrastructural and biochemical study. Ultrastruct Pathol 21:143-151.

*Sinks T, Steele G, Smith AB, et al. 1992. Mortality among workers exposed to polychlorinated biphenyls. Am J Epidemiol 136(4):389-398.

*Sipes G, Schnellmann RG. 1987. Biotransformation of PCBs: Metabolic pathways and mechanisms. In: Safe S, ed. Environmental toxic series, Vol. 1. Polychlorinated biphenyls (PCBs): Mammalian and environmental toxicology. Secaucus, NJ: Springer-Verlag, Inc.

*Sipes IJ, Gandolfi AJ. 1986. Biotransformation of toxicants. In: Casarett and Doull's toxicology: The basic science of poisons. 3rd ed. New York, NY: Macmillan Publishing Co., 66-74.

Siren H, Hyvonen H, Saarinen M, et al. 1992. Comparison of HPLC and solid phase clean-up methods for identification of PCBs in cod-liver oil by HRGC/MS-SIM technique. Chromatographia 34(5-8):421-430.

Sittig, M. 1994. World-wide limits for toxic and hazardous chemicals in air, water and soil. Park Ridge, NJ: Noyes Publications.

*Skinner LC. 1992. Chemical contaminants in wildlife from the Mohawk nation at Akwesasne and the vicinity of the General Motors Corporation/Central Foundry Division Massena, New York plant. New York State Department of Environmental Conservation, Albany, New York.

*Sklarew DS, Girvin DC. 1987. Attenuation of polychlorinated biphenyls in soils. Rev Environ Contam Toxicol 98:1-41.

*Slim R, Toborek M, Robertson LW, et al. 1999. Antioxidant protection against PCB-mediated endothelial cell activation. Toxicol Sci 52:232-239.

*Sloan R, Brown M, Brandt R, et al. 1985. Hudson River PCB relationships between resident fish, water, and sediment. Northeastern Environmental Science 3(3/4):138-151.

*Sloan RJ, Jock K. 1990. Chemical contaminants in fish from the St. Lawrence river drainage on lands of the Mohawk nation at Akwesasne, and near the General Motors Corporation central foundry division Massena, New York Plant. Technical report 90-1 (BEP). Division of Fish and Wildlife.

*Smialowicz RJ, Andrews JE, Riddle MM, et al. 1989. Evaluation of the immunotoxicity of low level PCB exposure in the rat. Toxicology 56:197-211.

*Smialowicz RJ, DeVito MJ, Riddle MM, et al. 1997. Opposite effects of 2,2',4,4',5,5'-hexachlorobiphenyl and 2,3,7,8-tetrachlorodibenzo-p-dioxin on the antibody response to sheep erythrocytes in mice. Fundam Appl Toxicol 37:141-149.

*Smith AB, Schloemer J, Lowry LK, et al. 1982. Metabolic and health consequences of occupational exposure to polychlorinated biphenyls. Br J Ind Med 39:361-369.

*Smith AG, Francis JE, Carthew P. 1990a. Iron as a synergist for hepatocellular carcinoma induced by polychlorinated biphenyls in *Ah*-responsive C57BL/10ScSn mice. Carcinogenesis 11:437-444.

*Smith AG, Francis JE, Green JA, et al. 1990b. Sex-linked hepatic uroporphyria and the induction of cytochromes P450IA in rats caused by hexachlorobenzene and polyhalogenated biphenyls. Biochem Pharmacol 40(9):2059-2068.

*Smith BJ. 1984. P.C.B. levels in human fluids: Sheboygan case study. University of Wisconsin Sea Grant Institute, Madison, WI. Technical report WIS-SG-83-240.

Smith MA. 1997. Reassessment of the carcinogenicity of polychlorinated biphenyls (PCBs). J Toxicol Environ Health 50(6):567-579.

*Smits-van Prooije AE, Lammers JHCM, Waalkens-Berendsen DH, et al. 1993. Effects of the PCB 3,4,5,3',4',5'-hexachlorobipyenyl on the reproduction capacity of Wistar rats. Chemosphere 27(1-3):395-400.

*Smrek AL, Needham LL. 1982. Simplified cleanup procedures for adipose tissue containing polychlorinated biphenyls, DDT, and DDT metabolites. Bull Environ Contam Toxicol 28:718-722.

*Sodergren A, Larsson P, Knulst J, et al. 1990. Transport of incinerated organochlorine compounds to air, water, microlayer, and organisms. Marine Pollut Bull 21:18-24.

*Sokol RC, Bethoney CM, Rhee G-Y. 1995. Effect of PCB concentration on reductive dechlorination and dechlorination potential in natural sediments. Water Res 29(1):45-48.

*Sokol RC, Bethoney CM, Rhee G-Y. 1998. Effect of Aroclor 1248 concentration on the rate and extent of polychlorinated biphenyl dechlorination. Environ Toxicol Chem 17(10):1922-1926.

*Sokol RC, Kwon O-S, Behoney M, et al. 1994. Reductive dechlorination of polychlorinated biphenyls in St. Lawrence River sediments variations in dechlorination characteristics. Environ Sci Technol 28:2054-2064.

*Sondossi M, Sylvestre M, Ahmad D. 1992. Effects of chlorobenzoate transformation on the pseudomonas-*testosteroni* biphenyl and chlorobiphenyl degradation pathway. Appl Environ Microbiol 58(2):485-495.

*Soog D-K, Ling Y-C. 1997. Reassessment of PCDD/DFs and Co-PCBs toxicity in contaminated rice-bran oil responsible for the disease “Yu-Cheng”. Chemosphere 34:1579-1586.

Soontornchat S, Li M-H, Cooke PS, et al. 1994. Toxicokinetic and toxicodynamic influences on endocrine disruption by polychlorinated biphenyls. Environ Health Perspect 102(6-7):568-571.

*Spencer F. 1982. An assessment of the reproductive toxic potential of Aroclor 1254 in female Sprague-Dawley rats. Bull Environ Contam Toxicol 28:290-297.

Springer MA. 1980. Pesticide levels, egg and eggshell parameters of great horned owls. Ohio J Sci 80:184-187.

*Stack AS, Altman-Hamamdzic S, Morris PJ, et al. 1999. Polychlorinated biphenyl mixtures (Aroclors) inhibit LPS-induced murine splenocyte proliferation in vitro. Toxicology 139:137-154.

*Steele G, Stehr-Green P, Welty E. 1986. Estimates of the biologic half-life of polychlorinated biphenyls in human serum. New Engl J Med 314:926-927.

*Steen WC, Paris DF, Baughman GL. 1978. Partitioning of selected polychlorinated biphenyls to natural sediments. Water Res 12:655-657.

*Stehr-Green PA, Burse VW, Welty E. 1988. Human exposure to polychlorinated biphenyls at toxic waste sites: Investigations in the United States. Arch Environ Health 43:420-424.

*Stehr-Green PA, Ross D, Liddle J, et al. 1986b. A pilot study of serum polychlorinated biphenyl levels in persons at high risk of exposure in residential and occupational environments. Arch Environ Health 4:240-244.

*Stehr-Green PA, Welty E, Steele G, et al. 1986a. Evaluation of potential health effects associated with serum polychlorinated biphenyl levels. Environ Health Perspect 70:255-259.

Stein VB, Amin TA, Narang RS. 1987. Simplified method for determining polychlorinated biphenyls, phthalates, and hexachlorocyclohexanes in air. J Assoc Off Anal Chem 70:721-723.

*Steinberg KK, Freni-Titulaer LWJ, Rogers TN, et al. 1986. Effects of polychlorinated biphenyls and lipemia on serum analytes. J Toxicol Environ Health 19:369-381.

*Stellman SD, Djordjevic MV, Muscat JE, et al. 1998. Relative abundance of organochlorine pesticides and polychlorinated biphenyls in adipose tissue and serum of women in Long Island, New York. Cancer Epidemiol Biomarkers Prev 7:489-496.

*Stern GA, Halsall CJ, Barrie LA, et al. 1997. Polychlorinated biphenyls in Arctic air. 1. Temporal and spatial trends: 1992-1994. Environ Sci Technol 31(12):3619-3628.

*Stewart P, Darvill T, Lonky E, et al. 1999. Assessment of prenatal exposure to PCBs from maternal consumption of Great Lakes fish: An analysis of PCB pattern and concentration. Environ Res 80:S87-S96.

*Stewart P, Pagano J, Sargent D, et al. 2000a. Effects of Great Lakes fish consumption on brain PCB pattern, concentration, and progressive-ratio performance. Environ Res 82:18-32.

*Stewart P, Reihman J, Lonky E, et al. 2000b. Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. Neurotoxicol Teratol 22:21-29.

Stone PJ, ed. 1981. Emergency handling of hazardous materials in surface transportation. Washington, DC: Bureau of Explosives, Association of American Railroads, 418.

*Stow CA. 1995a. Factors associated with PCB concentrations in Lake Michigan salmonids. Environ Sci Technol 29(2):522-527.

*Stow CA. 1995b. Great Lakes herring gull egg PCB concentrations indicate approximate steady-state conditions. Environ Sci Technol 29(11):2893-2897.

Stow CA, Carpenter SR, Eby LA, et al. 1995. Evidence that PCBs are approaching stable concentrations in Lake Michigan fishes. Ecological Applications 5(1):248-260.

*Stow CA, Jackson LJ, Amrhein JF. 1997. An examination of the PCB: lipid relationship among individual fish. Can J Fish Aquat Sci 54(5):1031-1038.

*Strandberg B, Strandberg L, van Bavel B, et al. 1998. Concentrations and spatial variations of cyclodienes and other organochlorines in herring and perch from the Baltic Sea. Sci Total Environ 215:69-83.

*Strek HJ, Weber JB. 1982a. Behaviour of polychlorinated biphenyls (PCBs) in soils and plants. Environ Pollut 28:291-312.

*Strek HJ, Weber JB. 1982b. Adsorption and reduction in bioactivity of polychlorinated biphenyl (Aroclor 1254) to redroot pigweed by soil organic matter and montmorillonite clay. Soil Sci Am J 46(2):318-322.

*Street JC, Sharma RP. 1975. Alteration of induced cellular and humoral immune responses by pesticides and chemicals of environmental concern: Quantitative studies of immunosuppression by DDT, Aroclor 1254, carbaryl, carbofuran, and methylparathion. Toxicol Appl Pharmacol 32:587-602.

*Stripp BR, Lund J, Mango GW, et al. 1996. Clara cell secretory protein: a determinant of PCB bioaccumulation in mammals. Am J Physiol 271:L656-L664.

*Sugiura K. 1992. Microbial degradation of polychlorinated biphenyls in aquatic environments. Chemosphere 24(7):881-890.

Sundlof SF, Forrester DJ, Thompson NP, et al. 1986. Residues of chlorinated hydrocarbons in tissues of raptors in Florida. J Wildl Dis 22:71-82.

*Sundstrom G, Hutzinger O, Safe S. 1976a. The metabolism of 2,2',4,4',5,5'-hexachlorobiphenyl by rabbits, rats and mice. Chemosphere 4:249-253.

*Sundstrum G, Hutzinger O, Safe S. 1976b. The metabolism of chlorobiphenyls-A review. Chemosphere 5:267-298.

*Suzuki M, Aizawa N, Okano G, et al. 1977. Translocation of polychlorobiphenyls in soil into plants: A study by a method of culture of soybean sprouts. Arch Environ Contam 5:343-352.

*Suzuki T. 1980. Additive effects of dietary cadmium and PCB in rats. Agric Biol Chem 44:2209-2210.

*Svensson BG, Hallberg T, Nilsson A, et al. 1994. Parameters of immunological competence in subjects with high consumption of fish contaminated with persistent organochlorine compounds. Int Arch Occup Environ Health 65(6):351-358.

*Svensson B-G, Mikoczy Z, Stromberg U, et al. 1995a. Mortality and cancer incidence among Swedish fishermen with a high dietary intake of persistent organochlorine compounds. Scand J Work Environ Health 21(2):106-115.

*Svensson B-G, Nilsson A, Jonsson E, et al. 1995b. Fish consumption and exposure to persistent organochlorine compounds, mercury, selenium and methylamines among Swedish fishermen. Scand J Work Environ Health 21:96-105.

*Swackhamer DL, Armstrong DE. 1986. Estimation of the atmospheric and nonatmospheric contributions and losses of polychlorinated biphenyls for Lake Michigan on the basis of sediment records of remote lakes. Environ Sci Technol 20:879-883.

*Swackhamer DL, Armstrong DE. 1987. Distribution and characterization of PCBs in Lake Michigan water. J Great Lakes Res 13:24-36.

Swanson GM, Ratcliffe HE, Fischer LJ. 1995. Human exposure to polychlorinated biphenyls (PCBs): a critical assessment of the evidence for adverse health effects. Regul Toxicol Pharmacol 21(1):136-50.

Sykes RG, Coate AR. 1995. PCBs in sealants in water distribution reservoirs. Am Water Works Assoc J 87(4):96-100.

*Sylvestre M, Sondossi M. 1994. Selection of enhanced polychlorinated biphenyl-degrading bacterial strains for bioremediation: Consideration of branching pathways. In: Chaudhry GR, ed. Biod Degrad Biorem Toxic Chem. Portland, OR: Dioscorides Press, 47-73.

*Szabo S, Silver EH, Gallagher GT. 1983. Potentiation of duodenal ulcerogenic action of acrylonitrile by PCB or phenobarbital in the rat. Toxicol Appl Pharmacol 71:451-454.

*Takabatake E, Fujita M, Sawa Y. 1980. Combined effects of polychlorinated biphenyls and methylmercury on hepatic microsomal monooxygenases and the hepatic action of bromobenzene. JPharmDyn 3:463-469.

*Takagi Y, Aburada S, Hashimoto K, et al. 1986. Transfer and distribution of accumulated (^{14}C)polychlorinated biphenyls from maternal to fetal and suckling rats. Arch Environ Contam Toxicol 15:709-715.

*Takahashi S, Lee J-S, Tanabe S, et al. 1998. Contamination and specific accumulation of organochlorine and butyltin compounds in deep-sea organisms collected from Suruga Bay, Japan. Sci Total Environ 214:49-64.

*Takenaka S, Takahashi, K. 1991. Enhancement of fecal excretion of polychlorinated biphenyls by the addition of rice bran fiber to the diet. Chemosphere 22:375-382.

*Taki I, Hisanaga S, Amagase Y. 1969. Report on Yusho (chlorobiphenyls poisoning) pregnant women and their fetutses. Fukuoka Acta Med 60:471-474.

*Talcott PA, Koller LD. 1983. The effect of inorganic lead and/or a polychlorinated biphenyl on the developing immune system of mice. J Toxicol Environ Health 12:337-352.

*Talcott PA, Koller LD, Exon JH. 1985. The effect of lead and polychlorinated biphenyl exposure on rat natural killer cell cytotoxicity. Int J Immunopharmacol 7(2):255-261.

*Tanabe S, Hidaka H, Tatsukawa R. 1983. PCBs and chlorinated hydrocarbon pesticides in Antarctic atmosphere and hydrosphere. Chemosphere 12:277-288.

Tanabe S, Kannan N, Subramanian A, et al. 1987. Highly toxic coplanar PCBs: Occurrence, source, persistency and toxic implications to wildlife and humans. Environ Pollut 47:147-163.

*Tanabe S, Kannan N, Wakimoto T, et al. 1989. Isomer-specific determination and toxic evaluation of potentially hazardous coplanar PCBs, dibenzofurans and dioxins in the tissues of "Yusho" PCB poisoning victim and in the causal oil. Toxicol Environ Chem 24:215-231.

*Tanabe S, Nakagawa Y, Tatsukawa R. 1981. Absorption efficiency and biological half-life of individual chlorobiphenyls in rats treated with Kanechlor products. Agric Biol Chem 45:717-726.

*Tanabe S, Tanaka H, Tatsukawa R. 1984. Polychlorobiphenyls, 3DDT and hexachlorocyclohexane isomers in the western North Pacific ecosystem. Arch Environ Contam Toxicol 13:731-738.

*Taniguchi S, Murakami A, Hosomi M, et al. 1997. Chemical decontamination of PCB-contaminated soil. Chemosphere 34(5-7):1631-1637.

*Tanimura T, Ema M, Kihara T. 1980. Effects of combined treatment with methylmercury and polychlorinaed biphenyls (PCBs *on the development of mouse offspring. In: Persaud TVN, ed. Neural and behavioural teratology. Baltimore: University Park Press, 163-198.*

*Tarvis D, Hegmann K, Gerstenberger S, et al. 1997. Association of mercury and PCB levels with chronic health effects in Native Americans. Health Conference '97 Great Lakes and St. Lawrence. Montreal, Quebec, Canada. (As cited in Johnson et al. 1998)

*Tatematsu M, Nakanishi K, Murasaki G, et al. 1979. Enhancing effect of inducers of liver microsomal enzymes on induction of hyperplastic liver nodules by N-2-fluorenylacetamide in rats. J Natl Cancer Inst 63:1411-1416.

*Tavlarides L. 1998a. Multidisciplinary study of PCBs and PCDFs at a waste site elimination of PCBs by supercritical extraction and wet oxidation. Crisp Data Base National Institutes of Health.

Tavlarides L. 1998b. Supercritical fluid technology--remediation of PCB/PAH contaminated soils. Crisp Data Base National Institutes of Health.

*Taylor PR, Lawrence CE. 1992. Polychlorinated biphenyls: estimated serum half lives. Br J Ind Med 49(7):527-528.

*Taylor PR, Lawrence CE, Hwang HL, et al. 1984. Polychlorinated biphenyls: Influence on birthweight and gestation. Am J Public Health 74:1153-1154.

*Taylor PR, Stelma, Auger I, et al. 1988. The relation of occupational polychlorinated biphenyl exposure to cancer and total mortality. In: The health effect of polybrominated biphenyls. Doctoral thesis submitted to Harvard School of Public Health, Boston, MA, 86-136. (Unpublished study)

*Taylor PR, Stelma JM, Lawrence CE. 1989. The relation of polychlorinated biphenyls to birth weight and gestational age in the offspring of occupationally exposed mothers. Am J Epidemiol 129:395-406.

*Thomas G, Sweetman AJ, Ockenden WA, et al. 1998. Air-pasture transfer of PCBs. Environ Sci Technol 32:936-942.

*Thomas DR, Carswell KS, Georgiou G. 1992. Mineralization of biphenyl and PCBs by the white rot fungus phanerochaete chrysosporium. Biotechnol Bioeng 40(11):1395-1402.

*Thomas PT, Hinsdill RD. 1978. Effect of polychlorinated biphenyls on the immune responses of Rhesus monkeys and mice. Toxicol Appl Pharmacol 44:41-51.

*Thomas PT, Hinsdill RD. 1980. Perinatal PCB exposure and its effect on the immune system of young rabbits. Drug Chem Toxicol 3:173-184.

*Thomas RG. 1982. Volatilization from water. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York: McGraw-Hill Book Co., 15-16.

*Thomas RL, Frank R. 1981. PCBs in sediment and fluvial suspended solids in the Great Lakes. In: Mackay D, et al., eds. Physical behavior of PCBs in the Great Lakes. Ann Arbor, MI: Ann Arbor Science Press, 245-267.

*Tiedje JM, Quensen JF III, Chee-Sanford J, et al. 1993. Microbial reductive dechlorination of PCBs. Biodegradation 4(4):231-240.

Tiernan TO, Taylor ML, Garrett JG, et al. 1985. Sources and fate of polychlorinated dibenzodioxins, dibenzofurans and related compounds in human environments. Environ Health Perspect 59:145-158.

*Tiernan TO, Taylor ML, Garret JH, et al. 1983. Chlorodibenzodioxins, chlorodibenzofurans and related compounds in the effluents from combustion processes. Chemosphere 12:595-606.

*Tilden J, Hanrahan LP, Anderson H, et al. 1997. Health advisories for consumers of Great Lakes sport fish: Is the message being received? Environ Health Perspect 105(12):1360-1365.

*Tilson HA, Kodavanti PR. 1997. Neurochemical effects of polychlorinated biphenyls: an overview and identification of research needs. Neurotoxicology 18(3):727-743.

*Tilson HA, Kodavanti PR. 1998. The neurotoxicity of polychlorinated biphenyls. Neurotoxicology 19(4-5):517-525.

*Tilson HA, Davis GJ, McLachlan JA, et al. 1979. The effects of polychlorinated biphenyls given prenatally on the neurobehavioral development of mice. Environ Res 18:466-474.

*Tilson HA, Jacobson JL, Rogan WJ. 1990. Polychlorinated biphenyls and the developing nervous system cross-species comparisons. Neurotoxicol Teratol 12:239-248.

*Tilson HA, Kodavanti PRS, Mundy WR, et al. 1998. Neurotoxicity of environmental chemicals and their mechanism of action. Toxicol Lett 102-103:631-635.

*Timberlake DL, Garbaciak S Jr. 1995. Bench-scale testing of selected remediation alternatives for contaminated sediments. J Air Waste Manage Assoc 45:52-56.

*Tironi A, Pesatori A, Consonni D, et al. 1996. [Mortality among women workers exposed to PCB.] Epidemiol Prev 20:200-202. (Italian)

*Tithof PK, Contreras ML, Ganey PE. 1995. Aroclor 1242 stimulates the production of inositol phosphates in polymorphonuclear neutrophils. Toxicol Appl Pharmacol 131:136-143.

*Tithof PK, Schiamberg E, Peters-Golden M, et al. 1996. Phospholipase A_2 is involved in the mechanism of activation of neutrophils by polychlorinated biphenyls. Environ Health Persp 104(1):105-111.

Toborek M, Barger SW, Mattson MP, et al. 1995. Exposure to polychlorinated biphenyls causes endothelial cell dysfunction. J Biochem Toxicol 10(4):219-226.

Travis CC, Arms AD. 1988. Bioconcentration of organics in beef, milk, and vegetation. Environ Sci Technol 22:271-274.

Travis CC, Hattemer-Frey HA. 1988. Uptake of organics by aerial plant parts: A call for research. Chemosphere. 17:277-283.

Tremblay NW, Gilman AP. 1995. Human health, the Great Lakes, and environmental pollution: A 1994 perspective. Environ Health Perspect Suppl 103(9):3-5.

*Treon JF, Cleveland FP, Cappel JW, et al. 1956. The toxicity of the vapours of Aroclor 1242® and Aroclor® 1254. Am Ind Hyg Assoc Q 17:204-213.

TRI88. 1990. Toxics Release Inventory 1988. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances.

TRI92. 1994. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*TRI93. 1995. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*TRI96. 1998. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*TRI98. 2000. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*Troisi GM, Haraguchi K, Simmonds MP, et al. 1998. Methyl sulphone metabolites of polychlorinated biphenyls (PCBs) in cetaceans from the Irish and the Aegean seas. Arch Environ Contam Toxicol 35:121-128.

*Truelove J, Grant D, Mes J, et al. 1982. Polychlorinated biphenyl toxicity in the pregnant Cynomolgus monkey: A pilot study. Arch Environ Contam Toxicol 11:583-588.

*Tryphonas H. 1994. Immunotoxicity of polychlorinated biphenyls: Present status and future considerations. Exp Clin Immunogenet 11:149-162.

*Tryphonas H. 1995. Immunotoxicity of PCBs (Aroclors) in relation to Great Lakes. Environ Health Perspect Suppl 103(9):35-46.

*Tryphonas H, Fournier M, Lacroix F, et al. 1998b. Effects of Great Lakes fish consumption on the immune system of Sprague-Dawley rats investigated during a two-generation reproductive study: II. Quantitative and functional aspects. Regul Toxicol Pharmacol 27:S40-S54.

*Tryphonas H, Hayward S, O'Grady L, et al. 1989. Immunotoxicity studies of PCB (Aroclor 1254) in the adult Rhesus (*macaca mulatta*) monkey-Preliminary report. Int J Immunopharmacol 11:199-206.

*Tryphonas H, Luster MI, Schiffman G, et al. 1991b. Effect of chronic exposure of PCB (Aroclor 1254) on specific and nonspecific immune parameters in the Rhesus (*macaca mulatta*) monkey. Fundam Appl Toxicol 16:773-786.

*Tryphonas H, Luster MI, White KL Jr, et al. 1991a. Effects of PCB (Aroclor® 1254) on non-specific immune parameters in Rhesus (*macaca mulatta*) monkeys. Int J Immmunopharmacol 13:639-648.

*Tryphonas H, McGuire P, Fernie S, et al. 1998a. Effects of Great Lakes fish consumption on the immune system of Sprague-Dawley rats investigated during a two-generation reproductive study: I. Body and organ weights, food consumption, and hematological parameters. Regul Toxicol Pharmacol 27:S28-S39.

*Tryphonas L, Arnold DL, Zawidzka Z, et al. 1986b. A pilot study in adult Rhesus monkeys (*m. mulatta*) treated with Aroclor 1254 for two years. Toxicol Pathol 14:1-10.

*Tryphonas L, Charbonneau S, Tryphonas H, et al. 1986a. Comparative aspects of Aroclor 1254® toxicity in adult Cynomolgus and Rhesus monkeys: A pilot study. Arch Environ Contam Toxicol 15:159-169.

*Tryphonas L, Truelove J, Zawidzka Z, et al. 1984. Polychlorinated biphenyl (PCB) toxicity in adult Cynomolgus monkeys (m. fascicularis): A pilot study. Toxicol Pathol 12(1):10-25.

Tsai ML, Webb RC, Loch-Caruso R. 1996. Congener-specific effects of PCBs on contractions of pregnant rat uteri. Reprod Toxicol 10(1):21-28.

*Tuey DB, Matthews HB. 1977. Pharmacokinetics of 3,3',5,5'-tetrachlorobiphenyl in the male rat. Drug Metab Dispos 5:444-450.

*Tuey DB, Matthews HB. 1980. Use of a physiological compartmental model for the rat to describe the pharmacokinetics of several chlorinated biphenyls in the mouse. Drug Metab Dispos 8:397-403.

*Tysklind M, Rappe C. 1991. Photolytic transformation of polychlorinated dioxins and dibenzofurans in fly ash. Chemosphere 23:1365-1375.

*UATW. 1999a. Unified Air Toxics Website. Alabama. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. July 23, 1999. http://www.epa.gov/ttn/uatw/stprogs.html

*UATW. 1999b. Unified Air Toxics Website. Hawaii. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. July 23, 1999. http://www.epa.gov/ttn/uatw/stprogs.html

*UATW. 1999c. Unified Air Toxics Website. Hawaii. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. July 23, 1999. http://www.epa.gov/ttn/uatw/stprogs.html

*UATW. 1999d. Unified Air Toxics Website. Hawaii. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. July 23, 1999. http://www.epa.gov/ttn/uatw/stprogs.html

*UATW. 1999e. Unified Air Toxics Website. Idaho. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. July 23, 1999. http://www.epa.gov/ttn/uatw/stprogs.html

*Unger M, Kiaer H, Blichert-Toft M, et al. 1984. Organochlorine compounds in human breast fat from deceased with and without breast cancer and in a biopsy material from newly diagnosed patients undergoing breast surgery. Environ Res 34:24-28.

*Unterman R, Brennan MJ, Brooks RE, et al. 1989. Biodegradation of PCB on contaminated soils. In: Proceedings of the 197th National Meeting of the American Chemical Society, Dallas, Texas, USA, April 9-14. Abstract Paper American Chemical Society, Washington, DC, 197.

USC. 1980. United States Code. Comprehensive Environmental Response, Compensation, and Liability. 42 USC 9601.

*USC. 1998. United States Code. Regulation of hazardous chemical substances and mixtures. 15 USC 2605.

*USC. 1999. United States Code. Hazardous air pollutants. 42 USC 7412.

*U.S. Congress. 1980. Comprehensive environmental response, compensation, and liability act of 1980. Title1-Hazardous substances releases, liability, compensation. Section 121-Cleanup standards. Public Law 96-510.94 Stat. 2767; 42 USC 9601.

*USITC. 1978. Imports of benzenoid chemicals and products 1977. USITC Publ 900. Washington, DC: U.S. International Trade Commission, 26.

*USITC. 1979. Imports of benzenoid chemicals and products 1978. USITC Publ 990. Washington, DC: U.S. International Trade Commission, 26.

*USITC. 1980. Imports of benzenoid chemicals and products 1979. USITC Publ 1083. Washington, DC: U.S. International Trade Commission, 28.

*USITC. 1982. Imports of benzenoid chemicals and products 1981. USITC Publ 1272. Washington, DC: U.S. International Trade Commission, 25.

*Uzawa H, Ito Y, Notomi A, et al. 1969. [Hyperglyceridemia resulting from intake of rice oil contaminated with chlorinated biphenyls.] Fukuoka Igaku Zasshi 60:449-454. (Japanese)

Uzgiris EE, Edelstein WA, Philipp HR, et al. 1995. Complex thermal desorption of PCBs from soil. Chemosphere 30(2):377-387.

Vaman Rao C, Banerji SA. 1993. Effect of polychlorinated biphenyls (Aroclor 1260) on histology of adrenal of rats. J Environ Biol 14(1):1-6.

*van Birgelen APJM, Fase KM, van der Kolk J, et al. 1996a. Synergistic effect of 2,2',4,4',5,5'-hexachlorobiphenyl and 2,3,7,8-terachlorodibenzo-p-dioxin on hepatic porphyrin levels in the rat. Environ Health Perspect 104(5):550-557.

*Van Birgelen APJM, Smit EA, Kampen IM, et al. 1995. Subchronic effects of 2,3,7,8-TCDD or PCBs on thyroid hormone metabolism: use in risk assessment. Eur J Pharmacol 293:77-85.

Van Birgelen APJM, Ross DG, Devito MJ. 1996b . Interactive effects between 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,2',4,4',5,5'-hexachlorobiphenyl in female B6C3FL mice: Tissue distribution and tissue-specific enzyme induction. Fundam Appl Toxicol 34(1):118-131.

9. REFERENCES

*van Birgelen APJM, van der Kolk J, van den Berg M, et al. 1992. Interactive effects of 2,2',4,4',5,5'-hexachlorobiphenyl and 2,3,7,8-tetrachlorodibenzo-p-dioxin on thyroid hormone, vitamin A, and vitamin K metabolism in the rat. Chemosphere 25:1239-1244.

*Van Birgelen APJM, Van der Kolk J, Fase KM, et al. 1994a. Toxic potency of 2,3,3'4,4'5-hexachlorobiphenyl relative to and in combination with 2,3,7,8-tetrachlorodibenzo-p-dioxin in a subchronic feeding study in the rat. Toxicol Appl Pharmacol 126:202-213.

*Van Birgelen APJM, Van der Kolk J, Fase KM, et al. 1994b. Toxic potency of 3,3',4,4',5,5'-pentachlorobiphenyl relative to and in combination with 2,3,7,8-tetrachlorodibenzo-p-dioxin in a subchronic feeding study in the rat. Toxicol Appl Pharmacol 127:209-221.

*Van den Berg KJ, Van Raaij J, Bragt P, et al. 1991. Interactions of halogenated industrial chemicals with transthyretin and effects on thyroid hormone levels *in vivo*. Arch Toxicol 65:15-19.

*Van den Berg M, Birnbaum L, Bosveld ATC, et al. 1998. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ Health Perspect 106(12):775-792.

*Van den Berg M, Olic K, Hutzinger O. 1985. Polychlorinated dibenzofurans (PCDFs): Environmental occurrence and physical, chemical and biological properties. Toxicol Environ Chem Rev 9:171-217.

*van der Burght ASAM, Clijsters PJ, Horbach GJ, et al. 1999. Structure-dependent induction of CYP1A by polychlorinated biphenyls in hepatocytes of Cynomolgus monkeys (*Macaca fascicularis*). Toxicol Appl Pharmacol 155:13-23.

*van der Kolk J, van Birgelen APJM, Poiger H, et al. 1992. Interactions of 2,2',4,4',5,5'-hexachlorobiphenyl and 2,3,7,8-tetrachlorodibenzo-p-dioxin in a subchronic feeding study in the rat. Chemosphere 25(12):2023-2027.

Van der Plas SA, de Jongh J, Faassen-Peters M, et al. 1998. Toxicokinetics of an environmentally relevant-mixture of dioxin-like PHAHs with or without a non-dioxin-like PCB in a semi-chronic exposure study in female Sprague Dawley rats. Chemosphere 37:1941-1955.

*van der Plas SA, Haag-Gronlund M, Scheu G, et al. 1999. Induction of altered hepatic foci by a mixture of dioxin-like compounds with and without 2,2',4,4',5,5'-hexachlorobiphenyl in female Sprague-Dawley rats. Toxicol Appl Pharmacol 156:30-39.

*van der Schalie WH, Gardner HS, Bantle JA, et al. 1999. Animals as sentinels of human health hazards of environmental chemicals. Environ Health Perspect 107(4):309-315.

*Van der Velde EG, Marsman JA, De Jong AP, et al. 1994. Analysis and occurrence of toxic planar PCBs, PCDDs and PCDFs in milk by use of carbosphere activated carbon. Chemosphere 28(4):693-702.

*Van Dort HM, Bedard DL. 1991. Reductive ortho and meta-dechlorination of a polychlorinated biphenyl congener by anaerobic microorganisms. Appl Environ Microbiol 57:1576-1578

Van Duuren BL. 1981. Cocarcinogens and tumor promoters and their environmental importance. J Environ Pathol Toxicol 4:959-969.

*Vanier C, Sylvestre M, Planas D. 1996. Persistence and fate of PCBs in sediments of the Saint Lawrence River. Sci Total Environ 192(3):229-244.

*Van Metre PC, Wilson JT, Callender E, et al. 1998. Similar rates of decrease of persistent, hydrophobic and particle-reactive contaminants in riverine systems. Environ Sci Technol 32:3312-3317.

Varanasi U, Stein JE, Tilbury KL, et al. 1994. Chemical contaminants in gray whales (eschrichtius robutus) stranded along the west coast of North America. Sci Total Environ 145:29-53.

*Vartiainen T, Jaakkola JJK, Saarikoski S, et al. 1998. Birth weight and sex of children and the correlation to the body burden of PCDDs/PCDFs and PCBs of the mother. Environ Health Perspect 106(2):61-66.

Vater ST, Velazquez SF, Cogliano VJ. 1995. A case study of cancer data set combinations for PCBs. Regul Toxicol Pharmacol 22(1):2-10.

Veith GD, Kosian P. 1983. Estimating bioconcentration potential from octanol/water partition coefficients: In: Mackay D, et al., eds. Physical behavior of PCBs in the Great Lakes. Ann Arbor, MI: Ann Arbor Science Press, 269-282.

Vena JE, Buck GM, Kostyniak P, et al. 1996. The New York angler cohort study: Exposure characterization and reproductive and developmental health. Toxicol Ind Health 12 (3-4):327-334.

*Verbrugge DA, Giesy JP, Mora MA, et al. 1995. Concentrations of dissolved and particulate polychlorinated biphenyls in water from the Saginaw River, Michigan. J Great Lakes Res 21(2):219-233.

*Vernon AA. 1981. High levels of polychlorinated biphenyls in serum specimens, Kansas. Internal report ELI-80-23-2. Centers for Disease Control, Atlanta, GA.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

*Villeneuve DC, Grant DL, Khera K, et al. 1971. The fetotoxicity of a polychlorinated biphenyl mixture (Aroclor® 1254) in the rabbit and in the rat. Environ Physiol 1:67-71.

*Villeneuve DC, Grant DL, Phillips WEJ. 1972. Modification of pentobarbital sleeping times in rats following chronic PCB ingestion. Bull Environ Contam Toxicol 7:264-269.

ViniermPM, Crain DA, McLachlan JA, et al. 1996. Interactions of environmental chemicals with the estrogen and progesterone receptors from the oviduct of the American alligator. Environ Health Perspect 104(12):1318-1322.

*Vorhees DJ, Cullen AC, Altshul LM. 1997. Exposure to polychlorinated biphenyls in residential indoor air and outdoor air near a Superfund site. Environ Sci Technol 31(12):3612-3618.

*Vorhees DJ, Cullen AC, Altshul LM. 1999. Polychlorinated biphenyls in house dust and yard soil near a Superfund site. Environ Sci Technol 33:2151-2156.

*Vos JG, Beems RB. 1971. Dermal toxicity studies of technical polychlorinated biphenyls and fractions thereof in rabbits. Toxicol Appl Pharmacol 19:617-633.

*Vos JG, de Roij T. 1972. Immunosuppressive activity of a polychlorinated biphenyl preparation on the humoral immune response in guinea pigs. Toxicol Appl Pharmacol 21:549-555.

9. REFERENCES

*Vos JG, Notenboom-Ram E. 1972. Comparative toxicity study of 2,4,5,2',4',5'-hexachlorobiphenyl and a polychlorinated biphenyl mixture in rabbits. Toxicol Appl Pharmacol 23:563-578.

*Vos JG, Van Dreil-Grootenhuis D. 1972. PCB-induced suppression of the humoral and cell-mediated immunity in guinea pigs. Sci Total Environ 1:289-302.

Vrecl M, Pogacnik A, Sek S, et al. 1995. Quantitative alterations in the liver and adrenal gland in pregnant rats induced by Pyralene 3000. Bull Environ Contam Toxicol 54(6):900-906.

*Wade TL, Chambers L, Gardinali PR, et al. 1997. Toxaphene, PCB, DDT, and chlordane analyses of beluga whale blubber. Chemosphere 34(5-7):1351-1357.

*Wallace JC, Basu I, Hites RA. 1996. Sampling and analysis artifacts caused by elevated indoor air polychlorinated biphenyl concentrations. Environ Sci Technol 30(9):2730-2734.

Waller CL, Minor DL, McKinney JD. 1995. Using three-dimensional quantitative structure-activity relationships to examine estrogen receptor binding affinities of polychlorinated hydroxybiphenyls. Environ Health Perspect 103(7-8):33-38.

Waller DP, Presperin C, Drum ML, et al. 1996. Great Lakes fish as a source of maternal and fetal exposure to chlorinated hydrocarbons. Toxicol Ind Health 12(3/4):335-345.

*Wallnöfer PR, Kowiger M, Engelhardt G. 1975. [No title available]. Z. Plauz Pflanzeuschutz. 82:91.

Wang JS, Chou HN, Fan J-J, et al. 1998. Uptake and transfer of high PCB concentrations from phytoplankton to aquatic biota. Chemosphere 36(6):1201-1210.

*Wania F, Mackay D. 1993. Global fractionation and cold condensation of low volatility organochlorine compounds in polar regions. Ambio 22(1):10-18.

*Wania F, Mackay D. 1996. Tracking the distribution of persistent organic pollutants. Environ Sci Technol 30:390A-396A.

*Wania F, Hoff JT, Jia CQ, et al. 1998. The effects of snow and ice on the environmental behaviour of hydrophobic organic chemicals. Environ Pollut 102:25-41.

*Wania F, Mackay D, Hoff JT. 1999. The importance of snow scavenging of polychlorinated biphenyl and polycyclic aromatic hydrocarbon vapors. Environ Sci Technol 33(1):195-197.

Ward EM, Burnett CA, Ruder A, et al. 1997. Industries and cancer. Cancer Causes Control 8(3):356-370.

*Ward JM. 1985. Proliferative lesions of the glandular stomach and liver in F344 rats fed diets containing Aroclor 1254. Environ Health Perspect 60:89-95.

Warngard L, Haag-Gronlund M, Bager Y. 1998. Assessment of animal tumour promotion data for the human situation. Arch Toxicol Suppl 20:311-319.

*Warshaw R, Fischbein A, Thornton J, et al. 1979. Decrease in vital capacity in PCB-exposed workers in a capacitor manufacturing facility. Ann NY Acad Sci 320:277-283.

*Wassermann D, Wassermann M, Cucos S, et al. 1973. Function of adrenal gland-zona fasciculata in rats receiving polychlorinated biphenyls. Environ Res 6:334-338.

*Wassermann M, Bercovici B, Cucos S, et al. 1980. Storage of some organochlorine compounds in toxemia of pregnancy. Environ Res 22:404-411.

*Wassermann M, Nogueira DP, Tomatis L, et al. 1976. Organochlorine compounds in neoplastic and adjacent apparently normal breast tissue. Bull Environ Contam Toxicol 15(4):478-484.

*Wassermann M, Ron M, Bercovici G, et al. 1982. Premature delivery and organochlorine compounds: Polychlorinated biphenyls and some organochlorine insecticides. Environ Res 28:106-112.

*Webber MD, Peitz RI, Granato TC, et al. 1994. Organic chemicals in the environment: Plant uptake of PCBs and other organic contaminants from sludge-treated coal refuse. J Environ Qual 23:1019-1026.

*Weinand-Harer A, Lilienthal H, Bucholski K-A, et al. 1997. Behavioral effects of maternal exposure to an ortho-chlorinated or a coplanar PCB congener in rats. Environ Toxicol Pharmacol 3(2):97-103.

*Weisglas-Kuperus N. 2000. Immunologic effects of polychlorinated biphenyl (PCB) and dixoin exposure in Dutch toddlers. Toxicologist 54(1):300.

*Weisglas-Kuperus N, Patandin S, Berbers G, et al. 1999. Immunological effects of background exposure to polychlorinated biphenyls and dioxins in Dutch toddlers. Organohalogen Compounds 44:425.

*Weisglas-Kuperus N, Sas TCJ, Koopman-Esseboom C, et al. 1995. Immunologic effects of background prenatal and postnatal exposure to dioxins and polychlorinated biphenyls in Dutch infants. Pediatr Res 38(3):404-10.

*Weistrand C, Noren K. 1997. Methylsulfonyl metabolites of PCBs and DDE in human tissues. Environ Health Perspect 105(6):644-649.

*Weistrand C, Noren K. 1998. Polychlorinated naphthalenes and other organochlorine contaminants in human adipose and liver tissue. J Toxicol Environ Health 53:293-311.

*Welling L, Paukku R, Mantykoski K. 1992. PCB in recycled paper products. Chemosphere 25(3):293-295.

Wells DE, Echarri I. 1994. Determination of chlorobiphenyls, with the separation of non-*ortho*, mono-*ortho* and di-*ortho* chloro congeners in fish and sea mammals. Anal Chim Acta 286(3):431-449.

Welp EA, Weiderpass E, Boffetta P, et al. 1998. Environmental risk factors of breast cancer. Scand J Work Environ Health 24(1):3-7.

*Welsch F. 1985. Effects of acute or chronic polychlorinated biphenyl ingestion on maternal metabolic homeostasis and on the manifestations of embryotoxicity caused by cyclophosphamide in mice. Arch Toxicol 57:104-113.

*Welsh MS. 1995. Extraction and gas chromatography/electron capture analysis of polychlorinated biphenyls in railcar paint scrapings. Appl Occup Environ Hyg 10(3):175-181.

*Welty ER. 1983. Personal communication, August 8, 1983. (As cited in Kreiss 1985).

*Wenning RJ, Bonnevie NL, Huntley SL. 1994. Accumulation of metals, polychlorinated biphenyls, and polycyclic aromatic hydrocarbons in sediments from the lower Passaic River, New Jersey. Arch Environ Contam Toxicol 27(1):64-81.

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

*Wester RC, Bucks DAW, Maibach HI, et al. 1983. Polychlorinated biphenyls (PCBs): Dermal absorption, systemic elimination, and dermal wash efficiency. J Toxicol Environ Health 12:511-519.

*Wester RC, Maibach HI, Bucks DW, et al. 1990. Percutaneous absorption and skin decontamination of PCBs: In vitro studies with human skin and in vivo studies in the Rhesus monkey. J Toxicol Environ Health 31:235-246.

*Wester RC, Maibach HI, Sedik L, et al. 1993. Percutaneous absorption of PCBs from soil: In vivo rhesus monkey, in vitro human skin, and binding to powdered human stratum corneum. J Toxicol Environ Health 39(3):375-382.

*Whalen MM, Loganathan BG, Warren T, et al. 1998. Effect of *in vitro* exposure to individual and mixtures of PCBs and tributylin on human naltural (NK) cell function. In:Organohalogen Compounds 37:209-212.

Whitlock JP. 1987. The regulation of gene expression of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Pharmacol Rev 39:147-161.

*WHO. 1993. Polychlorinated biphenyls and terphenyls. Environmental Health Criteria, 140. Geneva, Switzerland: World Health Organization, 48-52, 444-479.

*Whysner J, Montandon F, McClain RM, et al. 1998. Absence of DNA adduct formation by phenobarbital, polychlorinated biphenyls, and chlordane in mouse liver using the 32p-postlabeling assay. Toxicol Appl Pharmacol 148(1):14-23.

*Wickizer TM, Brilliant LB, Copeland R, et al. 1981. Polychlorinated biphenyl contamination of nursing mothers' milk in Michigan. Am J Public Health 71:132-137.

*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advanced treatise, Volume II - The elements Part A. New York, NY: Academic Press.

Wierda D, Irons RD, Greenlee WF. 1981. Immunotoxicity in C57BL/6 mice exposed to benzene and Aroclor 1254. Toxicol Appl Pharmacol 60:410-417.

*Wiegel J, Wu Q. 2000. Microbial reductive dehalogenation of polychlorinated biphenyls. FEMS Microbiol Ecol 32:1-15.

*Williams WA. 1994. Microbial reductive dechlorination of trichlorobiphenyls in anaerobic sediment slurries. Environ Sci Technol 28:630-635.

*Williams WA, May RJ. 1997. Low-temperature microbial aerobic degradation of polychlorinated biphenyls in sediment. Environ Sci Technol 31(12):3491-3496.

*Willman EJ, Manchester-Neesvig JB, Agrell C, et al. 1999. Influence of *ortho*-substitution homolog group on polychlorinated bioaccumulation factors and fugacity ratios in plankton and zebra mussels (*dreissena polymorpha*). Environ Toxicol Chem 18(7):1380-1389.

*Willman EJ, Manchester-Neesvig JB, Armstrong DE. 1997. Influence of ortho-substitution on patterns of PCB accumulation in sediment, plankton, and fish in a freshwater estuary. Environ Sci Technol 31:3712-3718.

*Wilson N, Shear N, Paustenbach D, et al. 1998. The effect of cooking practices on the concentration of DDT and PCB compounds in the edible tissue of fish. J Expo Anal Environ Epidemiol 8:423-440.

*Wilson R, Allen-Gill S, Griffin D, et al. 1995. Organochlorine contaminants in fish from the Arctic Lake in Alaska, USA. Sci Total Environ 160/161:511-519.

Winneke G. 1995. Endpoints of developmental neurotoxicity in environmentally exposed children. Toxicol Lett 77(1-3):127-136.

*Winneke G, Bucholski A, Heinzow B, et al. 1998a. Neurobehavioral development and TSH-levels in human infants: associations with PCBs in the neonatal period. In: Gies A, Wenzel A, Gahr M, ed. Workshop: Effects of endocrine disruptors in the environment on neuronal development and behaviour-current knowledge, assessment, gaps. Berlin, Germany: Firma Werbung and Vertrieb, Vol. 50, 49-55.

*Winneke G, Bucholski A, Heinzow B, et al. 1998b. Developmental neurotoxicity of polychlorinated biphenyls (PCBs): cognitive and psychomotor functions in 7-month old children. Toxicol Lett 102-103:423-428.

*Winter S, Streit B. 1992. Organochlorine compounds in a three-step terrestrial food chain. Chemosphere 24(12):1765-1774.

*Wirth EF, Chandler GT, Dipinto LM, et al. 1994. Assay of polychlorinated biphenyl bioaccumulation from sediments by marine benthic copepods using a novel microextraction technique. Environ Sci Technol 28:1609-1614.

*Wolfe RJ, Walker RJ. 1987. Subsistence economies in Alaska: Productivity, geography, and development impacts. Arctic Anthropology 24(2):56-81.

*Wolff MS. 1985. Occupational exposure to polychlorinated biphenyls (PCBs). Environ Health Perspect 60:133-138.

*Wolff MS, Schecter A. 1991. Accidental exposure of children to polychlorinated biphenyls. Arch Environ Contam Toxicol 20:449-453.

*Wolff MS, Toniolo PG. 1995. Environmental organochlorine exposure as a potential etiologic factor in breast cancer. Environ Health Perspect Suppl 103(7):141-145.

*Wolff MS, Camann D, Gammon M, et al. 1997. Proposed PCB congener groupings for epidemiological studies. Environ Health Perspect 105(1):13.

Wolff MS, Fischbein A, Rosenman KD, et al. 1986. Pattern designation of PCBs in human samples. Chemosphere 15:301-307.

*Wolff MS, Fischbein A, Selikoff IJ. 1992. Changes in PCB serum concentrations among capacitor manufacturing workers. Environ Res 59(1):202-216.

*Wolff MS, Fischbein A, Thornton J, et al. 1982a. Body burden of polychlorinated biphenyls among persons employed in capacitor manufacturing. Int Arch Occup Environ Health 49:199-208.

*Wolff MS, Thornton J, Fischbein A, et al. 1982b. Disposition of polychlorinated biphenyl congeners in occupationally exposed persons. Toxicol Appl Pharmacol 62:294-306.

*Wolff MS, Toniolo PG, Lee EW, et al. 1993. Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 85(8):648-652.

*Wolff MS, Zeleniuch-Jacquotte A, Dubin N, et al. 2000. Risk of breast cancer and organochlorine exposure. Cancer Epidemiol Biomarkers Prev 9:271-277.

Wolfle D. 1998. Interactions between 2,3,7,8-TCDD and PCBs as tumor promoters: Limitations of TEFs. Teratogenesis Carcinog Mutagen 17:217-224.

*Wong O. 1995. Pancreatic cancer in workers at a transformer manufacturing plant. Am J Ind Med 27(6):905-910.

*Wong PTS, Kaiser KLE. 1975. Bacterial degradation of polychlorinated biphenyls II. Rate studies. Bull Environ Contam Toxicol 38:249-255.

*Wong PW, Pessah IN. 1996. *Ortho*-substituted polychlorinated biphenyls alter calcium regulation by a ryanodine receptor-medicated mechanism: Structural specificity toward skeletal- and cardiac-type microsomal calcium release channels. Mol Pharmacol 49:740-751.

*Wong PW, Pessah IN. 1997. Noncoplanar PCB 95 alters microsomal calcium transport by an immunophilin FKBP 12-dependent mechanism. Mol Pharmacol 51:693-702.

*Wong PW, Brackney WR, Pessah IN. 1997. *Ortho*-Substituted polychlorinated biphenyls alter microsomal calcium transport by direct interaction with ryanodine receptors of mammalian brain. J Biol Chem 272(24):15145-15153.

Wormworth J. 1995. Toxins and tradition: The impact of food-chain contamination on the Inuit of northern Quebec. Can Med Assoc J 152(8):1237-1240.

*Wren CD, Hunter DB, Leatherland JF, et al. 1987a. The effects of polychlorinated biphenyls and methylmercury, singly and in combination, on mink. I: Uptake and toxic responses. Arch Environ Contam Toxicol 16:441-447.

*Wren CD, Hunter DB, Leatherland JF, et al. 1987b. The effects of polychlorinated biphenyls and methylmercury, singly and in combination on mink. II: Reproductive and kit development. Arch Environ Contam Toxicol 16:449-454.

*Wu Q, Bedard DL, Wiegel J. 1996. Influence of incubation temperature on the microbial reductive dechlorination of 2,3,4,6-tetrachlorobiphenyl in two freshwater sediments. Appl Environ Microbiol 62(11):4174-4179.

*Wu Q, Bedard DL, Wiegel J. 1997. Temperature determines the pattern of anaerobic microbial dechlorination of Aroclor 1260 primed by 2,3,4,6-tetrachlorobiphenyl in Woods Pond sediment. Appl Environ Microbiol 63(12):4818-4825.

*Wu Q, Sowers KR, May HD. 1998. Microbial reductive dechlorination of Aroclor 1260 in anaerobic slurries of estuarine sediments. Appl Environ Microbiol 64(3):1052-1058.

Wyndham C, Safe S. 1978. In vitro metabolism of 4-chlorobiphenyl by control and induced rat liver microsomes. Biochemistry 17:208-215.

*Wyss PA, Muhlebach S, Bickel MH. 1986. Long-term pharmacokinetics of 2,2',4,4',5,5'-hexachloro-biphenyl (6-CB) in rats with constant adipose tissue mass. Drug Metab Dispos 14:361-365.

Yaffe BA, Reeder BA. 1989. An epidemiologic assessment of exposure of children to polychlorinated biphenyls (PCBs) in a Toronto community. Can J Public Health 80:325-329.

*Yakushiji T, Watanabe I, Kuwabara K, et al. 1978. Long-term studies of the excretion of polychlorinated biphenyls (PCBs) through the mother's milk of an occupationally exposed worker. Arch Environ Contam Toxicol 7:493-504.

*Yakushiji T, Watanabe I, Kuwabara K, et al. 1984. Postnatal transfer of PCBs from exposed mothers to their babies: Influence of breast-feeding. Arch Environ Health 39:368-375.

*Yamaguchi A, Yoshimura T, Kuratsune M. 1971. Investigation concerning babies born from women who consumed oil contaminated with chlorobiphenyl. Fukuoka Igaku Zasshi 62:117-22.

*Yassi A, Tate R, Fish D. 1994. Cancer mortality in workers employed at a transformer manufacturing plant. Am J Ind Med 25(3):425-437.

*Ye D, Quensen III JF, Tiedje JM, et al. 1992a. Anaerobic dechlorination of polychlorobiphenyls (Aroclor 1242) by pasteurized and ethanol-treated microorganisms from sediments. Appl Environ Microbiol 58:1110-1114.

*Ye D, Quensen JFIII, Tiedje JM, et al. 1999. 2-Bromoethanesulfonate, sulfate, molybdate, and ethanesulfonate inhibit anaerobic dechlorination of polychlorobiphenyls by pasteurized microorganisms. Appl Environ Microbiol 65(1):327-329.

*Ye Q, Puri RK, Kapila S, et al. 1992b. Studies on the transport and transformation of PCBs in plants. Chemosphere 25(7-10):1475-1479.

*Ylitalo GM, Buzitis J, Krahn MM. 1999. Analyses of tissues of eight marine species from Atlantic and Pacific coasts for dioxin-like chlorobiphenyls (Cbs) and total Cbs. Arch Environ Contam Toxicol 37:205-219.

*Yoshimura H, Yamamoto HA. 1975. A novel route of excretion of 2,4,3',4'-tetrachlorobiphenyl in rats. Bull Environ Contam Toxicol 13:681-688.

Yoshimura H, Yonemoto Y, Yamada H, et al. 1987. Metabolism *in vivo* of 3,4,3',4'-tetrachlorobiphenyl and toxicological assessment of the metabolites in rats. Xenobiotica 17:897-910.

*Yoshimura H, Yoshihara S, Ozawa N, et al. 1979. Possible correlation between induction modes of hepatic enzymes by PCBs and their toxicity in rats. Ann NY Acad Sci 320:179-192.

*Yoshimura T. 1974. [Epidemiological study on Yusho babies born to mothers who had consumed oil contaminated by PCB.] Fukuoka Igaku Zasshi 65:74-80. (Japanese)

*Yoshimura T, Ikeda M. 1978. Growth of school children with polychlorinated biphenyl poisoning or *Yusho*. Environ Res 17:416-425.

*Young D, Becerra M, Kopec D, et al. 1998. GC/MS analysis of PCB congeners in blood of the harbor seal *phoca vitulina* from San Francisco Bay. Chemosphere 37(4):711-733.

Young SS. 1985. Letter to the editor. Toxicol Appl Pharmacol 78:321-322.

*Yu M-L, Hsin J-W, Hsu C-C, et al. 1998. The immunologic evaluation of the Yucheng children. Chemosphere 37(9-12):1855-1865.

Zabik ME, Booren A, Zabik MJ, et al. 1996. Pesticide residues, PCBs and PAH in baked, charbroiled, salt boiled and smoked Great Lakes lake trout. Food Chemistry 55(3):231-239.

Zabik ME, Zabik MJ, Booren AM, et al. 1995. Pesticides and total polychlorinated biphenyls residues in raw and cooked walleye and white bass harvested from the Great Lakes. Bull Environ Contam Toxicol 54(3):396-402.

*Zhang H, Eisenreich SJ, Franz TR, et al. 1999. Evidence for increased gaseous PCB fluxes to Lake Michigan from Chicago. Environ Sci Technol 33(13):2129-2137.

*Zhang P-C, Scrudato RJ, Pagano JJ, et al. 1993. Photodecomposition of PCBs in aqueous systems using TiO_2 as catalyst. Chemosphere 26(6):1213-1223.

*Zhang S, Rusling JF. 1995. Dechlorination of polychlorinated biphenyls on soils and clay by electrolysis in a bicontinuous microemulsion. Environ Sci Technol 29(5):1195-1199.

*Zhang Y, Rott B, Freitag D. 1983. Accumulation and elimination of ^{14}C-PCBs by daphnia magna straus 1820. Chemosphere 12:1645-1651.

*Zhao F, Mayura K, Harper N, et al. 1997b. Inhibition of 3,3',4,4',5-pentachlorobiphenyl-induced fetal cleft palate and immunotoxicity in C57BL/6 mice by 2,2',4,4',5,5'-hexachlorobiphenyl. Chemosphere 34(5-7):1605-1613.

*Zhao F, Mayura K, Kocurek N, et al. 1997a. Inhibition of 3,3',4,4',5-pentachlorobiphenyl-induced chicken embryotoxicity by 2,2',4,4', 5,5'-hexachlorobiphenyl. Fundam Appl Toxicol 35(1):1-8.

*Zheng T, Holford TR, Mayne ST, et al. 2000. Risk of female breast cancer associated with serum polychlorinated biphenyls and 1,1-dichloro-2,2'-bis(p-chlorophenyl)ethylene. Cancer Epidemiol Biomarkers Prev 9:167-174.

9. REFERENCES

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

*Zoeller RT, Dowling ALS, Vas AA. 2000. Developmental exposure to polychlorinated biphenyls exerts thyroid hormone-like effects on the expression of RC3/neurogranin and myelin basic protein messenger ribonucleic acids in the developing rat brain. Endocrinology 141(1):181-189.

*Zupancic-Kralj L, Jan J, Marsel J. 1992. Assessment of polychlorobiphenyls in human/poultry fat and in hair/plumage from a contaminated area. Chemosphere 25(12):1861-1867.

*Zwiernik MJ, Quensen JF III, Boyd SA. 1998. FeSO4 amendments stimulate extensive anaerobic PCB dechlorination. Environ Sci Technol 32:3360-3365.

10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

BZ number—A system of sequential numbers for the 209 PCB congeners introduced in 1980 by Ballschmiter and Zell that identifies a given congener simply and precisely. Also referred to as congener, IUPAC, or PCB number.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Congener—A single, unique, well-defined chemical compound in the PCB category. The name of the congener specifies the total number of chlorine substituents and the position of each chlorine.

Congener number—A system of sequential numbers for the 209 PCB congeners introduced in 1980 by Ballschmiter and Zell that identifies a given congener simply and precisely. Also referred to as BZ, PCB, or IUPAC number.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Homolog—Subcategories of PCB congeners having the same number of chlorine substituents. For example, the 42 tetrachlorobiphenyls are congeners with 4 chlorine substituents in all possible arrangements.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

IUPAC number—A system of sequential numbers for the 209 PCB congeners introduced in 1980 by Ballschmiter and Zell that identifies a given congener simply and precisely. Also referred to as BZ, congener, or PCB number.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious

effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A

ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: PCBs
CAS Number: 11097-69-1
Date: September 2000
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to Figure: 87k
Species: Monkey

Minimal Risk Level: 0.03 [X] µg/kg/day [ ] ppm

Reference: Rice 1997, 1998, 1999b; Rice and Hayward 1997, 1999a

Experimental design: A series of studies were conducted that investigated effects of postnatal exposure to a PCB congener mixture, representing 80% of the congeners present in breast milk in Canadian women, on learning in monkeys. Groups of five and eight male monkeys were orally administered doses of 0 or 0.0075 mg/kg/day, respectively, from birth to 20 weeks of age. The daily dose was divided into thirds and administered prior to the first three daily feedings via syringe to the back of the mouth. The dose level represents the approximate daily intake of a nursing human infant whose mother's milk contained 50 ppb PCBs (the Health Canada guideline for maximum concentration in breast milk). At the end of the dosing period (i.e., at 20 weeks of age), the levels of PCBs in fat and blood in the treated monkeys were 1.7–3.5 ppm and 1.84–2.84 ppb, respectively. Corresponding values in the control monkeys were 0.05–0.20 ppm and 0.30–0.37 ppb. Beginning at 3 years of age, the monkeys were tested on a series of nonspatial discrimination reversal problems followed by a spatial delayed alternation task. Additional testing was done at 4.5 and 5 years of age.

Effects noted in study and corresponding doses: Treated monkeys showed decreased median response latencies and variable increases in mean response latencies across three tasks of nonspatial discrimination reversal. There was no difference in overall accuracy of the tests or correlation between performance and tissue levels of PCBs. Treated monkeys also displayed retarded acquisition of a delayed alternation task and increased errors at short delay task responses. These findings were interpreted as a learning/performance decrement rather than an effect on memory *per se.* In a separate portion of this study (Rice 1997), treated monkeys displayed shorter mean interresponse times when compared with controls. The increase in pause time for fixed-interval performance emerged more slowly across 48 sessions in treated monkeys. For fixed-ratio performance tasks, the control monkeys decreased their mean pause time across 10 sessions, whereas the treated monkeys did not. Rice (1997) interpreted these results as suggesting learning deficit, perseveration, and/or inability to inhibit inappropriate responding as a result of postnatal PCB exposure. Testing of these monkeys at 4.5–5 years of age showed that treated animals performed in a less efficient manner than controls under a differential reinforcement of low rate (DRL) schedule of reinforcement (Rice 1998). There were no differences between groups on the accuracy of performance on a series of spatial discrimination reversal tasks, although some treated monkeys made more errors than others on certain parts of the experiment. Further tests conducted at about 5 years of age did not find treatment-related effects on a series of concurrent RI-RI (random interval) schedules of reinforcement (Rice and Hayward 1999a). This schedule was designed to study behavior in transition (learning) as well as at steady state. However, there was a difference between treated and control monkeys on performance on a progressive ratio (PR) schedule. Rice and Hayward (1999a) stated that this finding may be indicative of retarded acquisition of the steady-state PR performance in treated monkeys.

Dose and end point used for MRL derivation: The tested dose level, 0.0075 mg/kg/day, is a less serious LOAEL for neurobehavioral toxicity. This LOAEL is a particularly appropriate basis for MRL derivation due to the human relevance of the tested PCB mixture (a congener mixture analogous to that in human breast milk), dose level (approximate daily intake of a nursing human infant whose mother's milk contained 50 ppb PCBs), and resulting PCB tissue and blood levels (near background concentrations found in the general human population). Support for the LOAEL is provided by the occurrence of minimal immunological alterations in the same monkeys at 0.0075 mg/kg/day (Arnold et al. 1999), as well as clinical signs of toxicity (ocular and dermal changes) and decreased antibody responses in offspring of monkeys that were exposed to a similar dose level of Aroclor 1254 (0.005 mg/kg/day) for approximately 46 weeks during gestation and nursing (Arnold et al. 1995); these studies are summarized below in the other pertinent information section.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

No

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Was a conversion used from intermittent to continuous exposure?

No

Other additional studies or pertinent information that lend support to this MRL:

The monkeys that were evaluated for neurodevelopmental toxicity by Rice and coworkers were also tested for other kinds of effects earlier in life (Arnold et al. 1999). Following exposure to 0.0075 mg/kg/day of the simulated human milk congener mixture during the first 20 weeks of life, the monkeys were periodically examined for the following endpoints for at least the following 46 weeks: bone development (at birth); general health status; formula intake; food and water consumption; body weight; tooth eruption; somatic measurements; and hematology, serum biochemistry, and immunology indices. Immunological assessment of the infants was started at 22 weeks of age and included IgM and IgG antibody production following immunization with SRBC, lymphoproliferative activity of peripheral leucocytes in response to mitogens (PHA, ConA, and PWM), numbers of peripheral leucocytes and their subsets, and NK cell activity. Few statistically significant changes were observed in any of the monitored parameters. Anti-SRBC titers were reduced in the treated monkeys but not significantly different from controls. Absolute mean numbers of B lymphocytes were significantly lower in treated monkeys (no change in mean percent), but the effect was transient because it was not observed when re-evaluated in the monkeys at 1 year of age. The investigators concluded that, overall, the effects on the infant immune system were mild and of unclear biological significance due to large inter-animal variability related to small numbers of animals.

In another study (Arnold et al. 1995), oral exposure of adult female monkeys for approximately 44 months (total exposure; pre-conception, gestation, and lactation) to a similarly low dose (0.005 mg/kg/day) of an Aroclor PCB mixture resulted in immunological and dermal/ocular effects in their offspring. Groups of 16 female Rhesus monkeys self-ingested capsules containing Aroclor 1254 in a glycerol/corn oil mixture (1:1) in doses of 0, 0.005, 0.02, 0.04, or 0.08 mg/kg/day. After 25 months of exposure, approximately 90% of the animals had attained an apparent pharmacokinetic steady state with respect to adipose concentrations of PCBs. After 37 months of exposure, the females were mated with untreated males, and dosing was continued throughout breeding and gestation and into the first part of the lactation period. Maternal treatment was discontinued when the infants were 7 weeks old (to preclude ingestion of the mother's dosing capsule) and resumed after the infants were weaned at age 22 weeks. Mothers were dosed with PCBs for 37 months prior to mating, and infants born to these mothers were exposed for a duration of approximately 46 weeks (average 24 weeks gestation plus 22 weeks nursing). Study end points included numbers of impregnations, live infants, postpartum deaths, abortions, suspected resorptions, stillbirths, and gestation length. On the day of parturition all infants were x-rayed to ascertain osseus development. Body weight, clinical health, hematology, and serum biochemistry were periodically evaluated in the infants and maternal animals during the lactation period, and subsequently in the dams until the infants were 78 weeks old and in the infants until they were 122 weeks old. The offspring were also evaluated for changes in tooth eruption and anthropometric measurements throughout the study, and immunological changes when they were 20 and 60 weeks old. Four immunological tests were performed: IgM and IgG antibodies to SRBC; lymphocyte proliferation response to PHA, ConA, and PWM mitogens; mixed lymphocyte culture assay (one-way); and natural killer cell activity. Most of the control and all treated offspring were autopsied at 122 weeks of age.

PCB-related effects were induced in the adult monkeys and their offspring (Arnold et al. 1995). Conception rate was significantly reduced at 0.02 mg/kg/day and higher doses. Because this effect occurred in the adult animals that were mated after 37 months of exposure, 0.02 mg/kg/day is a serious LOAEL for reproductive toxicity for chronic-duration exposure. Exposure during gestation and lactation resulted in both fetal toxicity and postnatal effects in the offspring. Fetal mortality was increased at 0.02 mg/kg/day and higher doses. Incidence rates for fetal mortality (combined abortions, suspected resorptions, and stillbirths) were 2/11, 5/10, 3/4, 2/6, and 4/5 in impregnated monkeys in the 0, 0.005, 0.02, 0.04, and 0.08 mg/kg/day groups, respectively, and displayed a significant increasing dose-related trend ($p=0.040$). Statistical comparison of the treated and control groups showed that the fetal mortality incidence rates were increased at 0.02 mg/kg/day ($p=0.077$) and significantly increased at 0.08 mg/kg/day ($p=0.036$). The precision of this statistical comparison is limited by the small numbers of animals, which obscures the high response rate in the 0.02 mg/kg/day group (i.e., that there were 3 fetal deaths in 4 impregnated animals, and that the combined incidence of fetal and neonatal deaths was 4/4). Evaluation of the offspring, limited by the small numbers of surviving animals, showed mild clinical manifestations of PCB exposure and some immunological test differences at 0.005 and 0.04 mg/kg/day (no infants survived beyond postpartum week 2 in the other dose groups). The major clinical signs in the surviving exposed offspring were inflammation and/or enlargement of the tarsal (Meibomian) gland, nail lesions, and gum recession. For example, in the control, 0.005, and 0.04 mg/kg/day dose groups, incidences of tarsal gland inflammation and/or enlargement were 1/9, 4/4, and 3/3; incidences of nail bed prominence were 0/9, 3/4, and 3/3; incidences of elevated nails were 0/9, 2/4, and 2/3; incidences of nails folding on themselves were 0/9, 1/4, and 3/3; and incidences of gum recession were 0/9, 1/4, and 2/3. Immunological alterations in the exposed offspring mainly included suppressed antibody responses to SRBC. IgM antibody levels to SRBCs were significantly reduced in comparison to controls at 0.005 and 0.04 mg/kg/day at week 22 ($p=0.056$ and 0.023, respectively) and week 23 ($p=0.043$ and 0.029, respectively), and at 0.005 mg/kg/day at weeks 61, 62, and 63 ($p=0.028$, 0.043, and 0.056, respectively). IgM titers were also suppressed at 0.04 mg/kg/day during weeks 61, 62, and 63, but statistical significance was precluded by the small number of infants ($n=2$) in this group. Other immunological changes included significantly reduced mitogen (ConA)-induced lymphocyte proliferation compared to

controls at 0.04 mg/kg/day at weeks 28 and 60 (p=0.036 and 0.053, respectively). Although evaluation of the offspring data is complicated by the small number of animals, it is highly relevant that the clinical and immunological effects in the infants are similar to those observed in their chronically exposed dams at the same dose levels as low as 0.005 mg/kg/day (Arnold et al. 1993a, 1993b; Tryphonas et al. 1989, 1991a, 1991b). The effects on the dams are detailed in the in the worksheet for the chronic oral MRL.

Evidence that the 0.0075 mg/kg/day less serious LOAEL is an appropriate dose level for intermediate-duration MRL derivation is provided by the observation that the next highest tested dose level in monkeys (or any other species) is 0.02 mg/kg/day (Arnold et al. 1995), which is a serious LOAEL for fetal mortality as indicated above.

Agency Contact (Chemical Manager): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: PCBs
CAS Number: 11097-69-1
Date: September 2000
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 148k
Species: Monkey

Minimal Risk Level: 0.02 [X] µg/kg/day [ ] ppm

Reference: Tryphonas et al. 1989, 1991a

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

Groups of 16 female Rhesus monkeys self-ingested capsules containing Aroclor 1254 in a glycerol/corn oil mixture (1:1) in doses of 0, 0.005, 0.02, 0.04, or 0.08 mg/kg/day. The monkeys were challenged with injected sheep red blood cells (SRBC) at 23 months of exposure and received a secondary challenge with SRBC at 55 months. The animals had achieved an apparent pharmacokinetic steady state at 23 months based on PCB concentrations in blood and fat. End points examined at 23 months (Tryphonas et al. 1989) included: antibody titers (IgG and IgM) to SRBC, lymphocyte transformation in response to two mitogens (PHA and ConA), quantitation of T- and B-lymphocytes, total serum immunoglobulin levels (IgG, IgM, and IgA), serum proteins, and serum hydrocortisone level. End points examined at 55 months (Tryphonas et al. 1991a, 1991b) included: body weights, IgM and IgG titers in response to secondary immunization with SRBC, lymphocyte proliferation in response to three mitogens (PHA, ConA, and PWM), mix lymphocyte culture assay, phagocytic activity of peripheral blood monocytes following stimulation with phorbol myristate acetate (PMA) or Zymosan, interleukin 1 production in response to *E. coli*, lymphocyte subpopulation analysis, antibody response to pneumococcus antigens, serum hydrocortisone level, serum complement activity, natural killer cell activity, levels of serum thymosins, interferon production by Con A-stimulated leukocytes, and tumor necrosis factor production. As indicated below in the other pertinent information section, clinical health findings (Arnold et al. 1993a) and reproduction and offspring findings (Arnold et al. 1995) were also reported for the monkeys that were tested for immunotoxicity.

Effects noted in study and corresponding doses:

IgM (all doses except 0.02 mg/kg/day) and IgG (all doses) antibody levels to SRBC were significantly reduced compared to controls after 23 months, although no clear dose-response relationships were observed (Tryphonas et al. 1989). Secondary challenge with SRBC after 55 months showed decreasing dose-related trends in the IgM and IgG anamnestic responses, although only IgM was significantly lower than controls at all dose levels (Tryphonas et al. 1991a). Other immunologic changes included alterations in lymphocyte T-cell subsets characterized by a significantly decreased ratio of T-inducer/helper (CD4) cells to T-cytotoxic/suppressor (CD8) cells, due to reduced CD4 and increased CD8 cells, at 0.08 mg/kg/day (not tested at lower doses) after 23 months. No effects on total lymphocytes or B-cells were found, indicating that T-cells were preferentially affected by the PCBs, although there were no exposure-related changes in T-cell subsets after 55 months suggesting that adaptation had occurred. Statistically significant dose-related trends, but no significant differences between exposed and control

groups, were observed after 55 months for decreasing lymphocyte proliferation in response to mitogens (PHA and ConA, but not PWM), increasing NK cell activity, increasing levels of serum thymosin alpha-1, decreasing phagocytic activity of peripheral blood monocytes following activation with PMA, and increasing total serum complement activity.

Dose and end point used for MRL derivation: The lowest dose level tested, 0.005 mg/kg/day, is a LOAEL for decreased antibody response. Interpretation of the adversity of this effect is complicated by a lack of data on immunocompetence and the essentially inconclusive findings in the other tested end points; however, support for the 0.005 mg/kg/day LOAEL is provided by mild clinical manifestations of toxicity at the same dose. As indicated below in the other pertinent information section, eyelid and toe/finger nail changes were observed in some monkeys at doses as low as 0.005 mg/kg/day (Arnold et al. 1993a).

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

No

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Was a conversion used from intermittent to continuous exposure?

No

Other additional studies or pertinent information that lend support to this MRL:

No other studies investigated immunological effects of chronic exposure to PCBs. Intermediate-duration studies, however, have conclusively shown that oral exposure to commercial PCB mixtures can induce morphological and functional alterations in the immune system of rats, mice, guinea pigs, and monkeys. Effects in the non-primate species occurred at relatively high doses (generally $4 mg/kg/day) and included decreased thymus and spleen weights in rats, mice, and guinea pigs exposed to Aroclors 1260, 1254, or 1248 (Allen and Abrahamson 1973; Bonnyns and Bastomsky 1976; Smialowicz et al. 1989; Street and Sharma 1975; Vos and Van Driel-Grootenhuis 1972); reduced antibody responses to tetanus toxoid in guinea pigs exposed to Clopen A-60, keyhole limpet hemocyanin in rats exposed to Aroclor 1254, and SRBC in mice exposed to Aroclor 1242 (Exon et al. 1985; Loose et al. 1977, 1978a, 1978b, 1979; Vos and Van Driel-Grootenhuis 1972); increased susceptibility to infection by Moloney leukemia virus in mice exposed to Aroclor 1254 or 1242, herpes simplex virus in mice exposed to Kanechlor 500, and bacterial endotoxin and malarial parasite in mice exposed to Aroclor 1242 (Imanishi et al. 1980; Koller 1977; Loose et al. 1979); reduced skin reactivity to tuberculin in guinea pigs exposed to Clopen A-60 (Vos and Van Driel-Grootenhuis 1972); and reduced NK cell activity in rats exposed to Aroclor 1254 (Smialowicz et al. 1989; Talcott et al. 1985).

Intermediate-duration oral studies of Aroclors in monkeys confirm the observations of PCB immunotoxicity in rats, mice, and guinea pigs, indicate that non-human primates are more sensitive than the other species, and support the findings of the chronic immunotoxicity study in monkeys (Tryphonas et al. 1989, 1991a, 1991b) used as the basis of the chronic oral MRL. Results of intermediate-duration studies in monkeys included decreased antibody responses to SRBC, increased susceptibility to bacterial infections, and/or histopathological changes in the thymus, spleen, and lymph nodes in adult monkeys and their offspring at 0.1–0.2 mg/kg/day doses of Aroclor 1254 and 1248 (Abrahamson and Allen 1973; Allen and Barsotti 1976; Allen et al. 1980; Barsotti et al. 1976; Thomas and Hinsdill 1978; Truelove et al. 1982; Tryphonas et al. 1986a). Additionally, results of studies in infant monkeys are consistent with the data in adults showing immunosuppressive effects of Aroclor 1254 at doses as low as 0.005 mg/kg/day. Evaluation of *in utero* and lactationally exposed offspring from the monkeys in the Tryphonas et al. (1989, 1991a, 1991b) studies indicated exposure-related reductions in IgM antibody levels to SRBC and mitogen-induced lymphocyte transformation that paralleled the findings in the maternal animals (Arnold et al. 1995).

Support for the chronic LOAEL of 0.005 mg/kg/day is provided by clinical observations on the same monkeys that were immunologically evaluated by Tryphonas et al. (1989, 1991a, 1991b). Examinations of the monkeys exposed to 0.005–0.08 mg/kg/day Aroclor 1254 during the first 37 months of the study showed characteristic dose-related ocular and dermal effects, including eye exudate, inflammation and/or prominence of the tarsal (Meibomian) glands, and various finger and toe nail changes (Arnold et al. 1993a). Statistical analyses found significant increasing dose-related trends in incidence rates, total frequency of observed occurrences and/or onset times for these effects, with some treated and control group comparisons showing significant differences at doses as low as 0.005 mg/kg/day. Effects that were significantly increased in the 0.005 mg/kg/day group included increased total frequencies of inflamed and/or prominent tarsal glands, toenail separations, and elevated toenails. Additionally, monkeys from this study that were mated after 37 months of exposure and continued to be exposed to $0.005 mg/kg/day Aroclor 1254 through gestation and lactation had offspring with clear clinical signs of PCB intoxication, manifested as inflammation and/or enlargement of the tarsal glands, nail lesions, and gum recession (Arnold et al. 1995). Further, the next highest dose level in this study (0.02 mg/kg/day) is a chronic serious LOAEL for reproductive toxicity (reduced conception rate) (Arnold et al. 1995). Conception rate, adjusted for the total number of matings, was significantly lower than controls at 0.02, 0.04, and 0.08 mg/kg/day (p=0.009, 0.039, and 0.005, respectively), but not at 0.005 mg/kg/day (p=0.085). Similar results were noted after adjustment for the number of matings with positive sires. There was a significant (p=0.017) decrease in conception rate with increasing dose with both types of mating adjustments. Percentages of impregnations (number impregnated/number available) in the 0, 0.005, 0.02, 0.04, and 0.08 mg/kg/day groups were 69, 63, 27, 43, and 33%, respectively. The $0.02 mg/kg/day doses in this study are also serious effect levels for developmental toxicity (fetal mortality), as discussed in the worksheet for the intermediate-duration oral MRL.

Agency Contact (Chemical Manager): Obaid Faroon

Table A-1. PCB Concentrations in Blood and Breast Milk in Epidemiology Studies

Study	Mean PCB concentrations: Blood (wet basis)	Mean PCB concentrations: Breast milk (lipid basis)	Basis of analysis	Health effects
Michigan Mother-Child Study (Fein et al. 1984a, 1984b; Jacobson and Jacobson 1996a, 1997; Jacobson et al. 1984a, 1985, 1990a, 1990b, 1992)	maternal serum: 6.1 ppb (fisheaters) 4.1 ppb (nonfisheaters) cord serum: 2.0 ppb	866 ppb (fisheaters) 622 ppb (nonfisheaters)	total PCBs	Exposure from consumption of contaminated sportfish (Lake Michigan). Reduced birth weight, head circumference and gestational age in newborns, neurobehavioral alterations in newborn and older children[a].
Oswego Newborn and Infant Development Project (Lonky et al. 1996; Stewart et al. 1999, 2000a)	cord blood: 0.8 ppb (fisheaters)[b] 1.03 ppb (nonfisheaters)	NR[c]	total PCBs (68 congeners)	Exposure from consumption of contaminated sportfish (Lake Ontario). Neurobehavioral alterations in newborn children[d].
Wives of Swedish Fisherman Cohort Study (Rylander et al. 1995, 1998b)	maternal serum: 1.0 ppb (median, fisheaters) 0.92 ppb (median, nonfisheaters)	NR	PCB 153	Exposure from consumption of fatty fish (Baltic Sea). Increased risk of low birth weight was associated with increasing maternal serum levels of PCB 153 (300–400 ppb).
Lake Michigan Aging Population Study (Schantz et al. 1996a, 1999)	adult serum: 16.0 ppb (fisheaters) 6.2 ppb (nonfisheaters)	NR	total PCBs	Exposure from consumption of contaminated sportfish (Lake Michigan). No significant effects on visual-motor coordination and hand steadiness tests in adults.
New York State Angler Cohort Study (Buck et al. 1997, 1999, 2000; Kostyniak et al. 1999; Mendola et al. 1995a, 1997)	NR[e]	NR	NA	Exposure from consumption of contaminated sportfish (Lake Ontario). Assessments of female and male reproductive endpoints found indications of fish consumption-related reductions in menstrual cycle length and female fecundability.

Table A-1. PCB Concentrations in Blood and Breast Milk in Epidemiology Studies *(continued)*

Study	Mean PCB concentrations: Blood (wet basis)	Mean PCB concentrations: Breast milk (lipid basis)	Basis of analysis	Health effects
Michigan Anglers Cohort Study (Courval et al. 1999)	NR[e]	NR	NA	Exposure from consumption of contaminated sportfish (Lake Erie, Lake Huron, or Lake Michigan). Associations between conception delay and fish consumption were found in exposed men but not their wives.
Inuit Infant Study (Dewailly et al. 2000)	NR	621 ppb	Σ 3 non-dioxin-like congeners (PCBs 138, 153, and 180)	Exposure from consumption of arctic sea mammal fat and other marine foods. Some immunologic alterations were associated with exposure to PCBs as well as other organochlorine compounds[f].
North Carolina Breast Milk and Formula Project (Gladen et al. 1988; Longnecker et al. 2000; Rogan and Gladen 1991, 1992; Rogan et al. 1986a, 1986b, 1987)	maternal serum: 9.06 ppb (median) cord serum: <4.27 ppb (median)	1.8 ppm[g]	total PCBs	General population exposure. Neurobehavioral alterations in infants[h]. No associations between PCBs and birth weight, head circumference, or thyroid hormones.

Table A-1. PCB Concentrations in Blood and Breast Milk in Epidemiology Studies *(continued)*

Study	Mean PCB concentrations: Blood (wet basis)	Mean PCB concentrations: Breast milk (lipid basis)	Basis of analysis	Health effects
Dutch Mother-Child Study (Huisman et al. 1995a, 1995b; Koopman-Esseboom et al. 1994a, 1994b, 1996; Lanting et al. 1998c; Patandin et al. 1999; Weisglas-Kuperus et al. 1995)	NR	620 ppb	total PCBs (26 congeners including 118, 138, 153, and 180)	General population exposure. Reduced birth weight. Reduced growth (weight, length, and head circumference) during first 3 months in formula-fed, but not breast-fed, children. Neurobehavioral alterations and changes in T-lymphocyte subpopulations and thyroid hormone levels in infants[i].
	maternal plasma: 2.2 ppb	430 ppb	Σ 4 non-dioxin-like congeners (PCBs 118, 138, 153, and 180)	
	cord plasma: 0.45 ppb	25.6 ppb 0.16 ppb TEQ	Σ 3 dioxin-like congeners (PCBs 77, 126, and 169)	
	child plasma: 0.75 ppb (median, breast-fed at 42 months) 0.21 ppb (median, formula-fed at 42 months)	0.046 ppb TEQ	Σ 3 dioxin-like congeners and 17 PCDD and PCDF 2,3,7,8-substituted congeners	
European Background PCB Study — German Sample (Winneke et al. 1998b)	cord plasma: 0.55 ppb	427 ppb	Σ 3 non-dioxin-like congeners (PCBs 138, 153, and 180)	General population exposure. Neurodevelopmental and thyroid hormone alterations in infants[j].

Table A-1. PCB Concentrations in Blood and Breast Milk in Epidemiology Studies *(continued)*

Study	Mean PCB concentrations: Blood (wet basis)	Mean PCB concentrations: Breast milk (lipid basis)	Basis of analysis	Health effects

[a] Newborn children from mothers who ate contaminated fish were more likely to exhibit hypoactive reflexes, more motor immaturity, poorer lability of states, and greater amount of startle. Testing at 4 years of age found that prenatal exposure was associated with poorer performance on the Verbal and the Memory scales of the McCarthy Scales of Children's Abilities, as well as less efficient visual discrimination processing and more errors in short-term memory scanning. Evaluation of the children at 11 years of age showed that prenatal exposure was significantly associated with lower full-scale and verbal IQ scores and poorer reading word comprehension.
[b]Although the concentration of total PCBs did not differ between fisheaters and controls, both the proportion (mol %) and absolute concentration (ppb) of the most heavily chlorinated PCB congeners (C17-C19) were markedly elevated in the cord blood of the fisheaters compared to the controls. PCB congeners of light (C11-C13) or moderate (C14-C16) chlorination were unrelated to fish consumption. The most heavily chlorinated congeners in cord blood were also the only congeners that correlated with breast milk levels.
[c]Actual values of PCBs in milk were not reported. The C17–C19 congeners in breast milk and cord blood were correlated while no correlation was found for the lightly (C11-C13) or moderately (C14-C16) chlorinated congeners.
[d]Children born to mothers with high consumption of contaminated fish had a greater number of abnormal reflexes and less mature autonomic responses than newborns from low-fisheaters or nonfisheaters. Heavily chlorinated congeners (C17-C19) were associated with poorer Habituation and Autonomic scores.
[e]Exposure was assessed using an index developed to estimate cumulative lifetime PCB exposure through fish consumption.
[f]Associations between increasing levels of organochlorine compounds in breast milk and risk of acute otitis media during the first year of life were found, although the data are insufficient for identifying whether the effect may be due to PCBs, hexachlorobenzene, *p,p'*-DDE, or other chemicals. No statistically significant changes in immunological indices were observed, although there were indications of reduced total serum IgA levels and altered T-lymphocyte subpopulations in breast-fed Inuit infants at 7 and 12 months of age.
[g]Average PCB levels in milk at birth. In lactating women, the levels declined about 20% over 6 months and about 40% over 18 months.
[h]Higher PCB levels were associated with less muscle tone and activity and hyporeflexia. Prenatal exposure to PCBs (levels in milk at birth) was associated with a significant decrease in PDI scores at the ages of 6 and 12 months.
[i]Prenatal exposure to PCBs (cord blood) was not significantly associated with either PDI or MDI scores at 7 months of age. Postnatal exposure was significantly associated with lower PDI scores, but not MDI scores. Cognitive abilities evaluated in these children at 42 months of age using the KABC showed a significant decreased performance associated with prenatal exposure to PCBs. PCB and CDD TEQs in maternal plasma during pregnancy were compared with thyroid T_3, T_4, and TSH concentrations in cord plasma at delivery and in the venous plasma of infants at ages 2 weeks and 3 months. Hormone levels were negatively correlated with CDD TEQs, PCB TEQs, and combined CDD and PCB TEQs, at all ages.
[j]Prenatal exposure was not significantly associated with MDI or PDI scores at 7 months of age. Postnatal exposure was significantly associated with lower MDI scores, but not with PDI scores. A positive correlation was found between serum concentrations of thyroid TSH and total PCBs in infants.

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer mortality	Capacitor workers exposed ≥3 months versus. U.S. white population	2,567	1940–1976	1940–1976	SMR	93 (no CI)	Latency <10 year	Brown and Jones 1981
						108 (no CI)	Latency 10<20 year	
						60 (no CI)	Latency >20 year	
						89 (95% CI= 63–122)	Overall SMR; further analysis revealed that risk was not related to employment duration. Analyses of mortality from cancers at various specific sites did not show statistically significantly increased risk[a].	
	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	78 (no CI)	Overall SMR; update of Brown and Jones (1981) study; seven additional years' follow-up. Analyses of mortality from cancers at various specific sites did not show statistically significantly increased risk[b].	Brown 1987b

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer mortality	Capacitor manufacturing plant workers in New York State exposed ≥90 days versus U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly elevated SMRs	Analyses for mortality from all cancers combined were stratified in the following ways: (1) hourly versus salaried compensation schedule, and gender of worker (analyses were also conducted for various cancer sites[c]); (2) gender, employment duration, and latency. Only "limited" exposure to other chemicals was reported.	Kimbrough et al. 1999a
	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	142	1965–1982	1965–1978 (mean exposure 6.5 years)	RR	1.30 (95% CI= 0.52–2.67)	Median latency time =13 years	Gustavsson et al. 1986

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer mortality	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	242	1965–1991	1965–1978	SMR	No statistically significantly elevated SMRs	Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses for mortality by all cancers combined were conducted for the entire cohort or stratified by exposure status (low versus high exposure). SMR=133 (95% CI=76–216) for the entire cohort. Analyses of mortality from cancers at various sites did not show statistically significantly increased risk[d].	Gustavsson and Hogstedt 1997
	Italian capacitor manufacturing workers employed ≥1 week versus national mortality rates	2,110 (544 males and 1,556 females)	1946–1982	1946–1978	SMR	Males: 253 (95% CI= 144–415) Females: 156 (no CI; not statistically significant)	In a follow-up study that considered nine additional years of latency (Tironi et al. 1996), mortality from all cancers was not statistically significantly increased in males (SMR=109; CI=67–168) or females (SMR=118; CI=71–184).	Bertazzi et al. 1987
	Italian capacitor manufacturing workers employed ≥1 week versus local mortality rates	2,110 (544 males and 1,556 females)	1946–1982	1946–1978	SMR	Males: 183 (95% CI= 104–300) Females: 226 (95% CI= 123–385)	NC	Bertazzi et al. 1987

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer mortality	Japanese *Yusho* food PCB contamination registrants versus national death rates	887 males	1968–1983	1968 (poisoning incident)	SMR	2.13 (no CI; p<0.01)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. SMR was not statistically significant in an evaluation of 874 females. Average follow-up was approximately 11 years. Analyses of mortality from cancers at various sites did not show statistically significantly increased risk[e].	Kuratsune et al. 1987
	Taiwanese *Yu-Cheng* food PCB contamination victims versus national mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	Males: SMR=0.69 (95% CI= 0.3–1.36) Females: SMR=0.4 (95% CI= 0.08–1.18) Total: SMR=0.58 (95% CI= 0.29–1.04)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. Similarly statistically non-significant findings were obtained in comparisons against local reference populations. Analyses of mortality from cancers at various specific sites did not show statistically significantly increased risk[f].	Hsieh et al. 1996
	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 men and 858 women)	1957–1986	1957–1977	SMR	0.8 (95% CI= 0.6–1.1)	Analyses of mortality from cancers at various specific sites did not show statistically significantly increased risk[g].	Sinks et al. 1992

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer mortality	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	0.84 (95% CI= 0.68–1.03)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents. Analyses of mortality from cancers at various specific sites also did not show statistically significantly increased risk[h].	Svensson et al. 1995a
	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	3.05 (95% CI= 0.99–7.13)	Statistically significant SMR was for squamous cell carcinomas; a statistically non-significant SMR was obtained for melanomas. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer mortality	U.S. male utility workers employed full time for ≥6 months versus U.S. general population mortality rates (adjusted for age, calendar year, and race)	138,905	1950–1988	1950–1986	SMR	0.86 (95% CI= 0.84–0.89)	Analyses of mortality from cancers at various specific sites also did not show statistically significant increased risk[i]. Possible confounding factors include co-exposures to solvents, wood preservatives, sunlight, and magnetic fields (which was associated with mortality from brain cancer in this cohort).	Loomis et al. 1997
	Canadian transformer manufacturing plant male workers employed for ≥1 month versus Canadian general male population	2,222	1947–1989	1947–1975	SMR	1.21 (95% CI= 0.90–1.60)	Analysis combined deaths from "definite", "probable", and "possible" cancer link. Analysis of "definite" cancer mortality cases yielded an SMR of 0.81 (95% CI=0.57–1.13). Statistically non-significant SMRs were also obtained in all workers employed ≥6 months (n=812) and in transformer assembly workers employed for ≥6 months (n=308). The authors noted that "considerably more exposure" to mineral oils occurred than exposure to PCB-containing askarol transformer fluids.	Yassi et al. 1994

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer incidence	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	142	1965–1982	1965–1978 (mean exposure 6.5 years)	RR	0.92 (95% CI= 0.37–1.90)	Median latency time =13 years	Gustavsson et al. 1986
	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SIR	1.02 (95% CI= 0.88–1.17)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents. Analyses of cancer incidence at various specific sites also did not show statistically significant increased risk[j].	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer incidence	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SIR	0.95 (95% CI= 0.89–1.01)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a
	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	242	1965–1991	1965–1978	SIR	No statistically significantly elevated SIRs	Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses for all cancers were conducted for the entire cohort, for the subgroup with time since first exposure >10 years, and for the high exposure group. Analysis of cancer incidence at various specific sites also did not show statistically significant increases[k].	Gustavsson and Hogstedt 1997
Liver-related cancer mortality	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	667 (no CI)	Latency <10 years	Brown and Jones 1981
						233 (no CI)	Latency 10–20 years	
						no deaths	Latency >20 years	
						280 (95% CI= 58–820)	Overall value; further analysis revealed that risk not related to employment duration	

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Liver-related cancer mortality	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	263 (no CI, $p<0.05$)	Overall value; update of Brown and Jones (1981) study; seven additional years' follow-up; no increase in risk with increasing duration of latency or employment. Five cases observed versus 1.9 expected. One liver cancer was metastatic, not primary; when exclude that case, SMR=210 ($p \geq 0.05$) (Nicholson and Landrigan 1994).	Brown 1987b
	Capacitor manufacturing plant workers in New York State exposed ≥90 days versus U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly increased SMRs	Analysis stratified by gender and hourly versus salaried compensation. Male hourly (80; CI=10–289; two deaths); female hourly (89; CI=11–321; two deaths); male salaried (79; CI=2–439; one death); female salaried (no deaths).	Kimbrough et al. 1999a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Liver-related cancer mortality	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	242	1965–1991	1965–1978	SMR	No statistically significantly elevated SMRs	Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses for mortality by liver cancer were conducted for the entire cohort or stratified by exposure status (low versus high exposure). Only one death due to liver cancer was reported, in the high exposure group. SMRs were 667 (CI=16–3,710) and 196 (CI=5–1,090) for the high exposure group and entire cohort, respectively.	Gustavsson and Hogstedt 1997

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Liver-related cancer mortality	Japanese *Yusho* food PCB contamination registrants versus national and local death rates	887 males	1968–1983	1968 (poisoning incident)	SMR	5.59 (no CI; p<0.01)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. Average follow-up was approximately 11 years. An SMR of 3.85 for males was also statistically significantly elevated (p<0.01; no CI); compared to a local reference population that had an underlying high incidence of liver cancer mortality. Evaluating only those liver cancers in males that were observed after 9 years of latency compared to the local reference population resulted in an SMR of 3.85 (p<0.05); no CI;. SMRs were not statistically significant in evaluations of 874 females.	Kuratsune et al. 1987

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Liver-related cancer mortality	Taiwanese *Yu-Cheng* food PCB contamination victims versus national mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	Males: 0.29 (95% CI= 0.01–1.62); Females: 1.08 (95% CI= 0.03–6.02)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. One male death and one female death observed. The analysis considered deaths from liver and intrahepatic bile duct cancers combined. Similarly statistically non-significant findings were reported in males and females using a local reference population.	Hsieh et al. 1996
	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 males, 858 females)	1957–1986	1957–1977	SMR	1.1 (95% CI= 0.0–6.4)	NC	Sinks et al. 1992

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Liver-related cancer mortality	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	0.48 (95% CI= 0.01–2.65)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a
	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	0.9 (95% CI= 0.41–1.7)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Liver-related cancer incidence	U.S. male utility workers employed full time for ≥6 months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	0.73 (95% CI= 0.57–0.93)	The analysis included combined mortalities from cancers of the liver, biliary passages, and gall bladder. An additional analysis of liver (not specified) cancer mortality yielded an SMR of 0.79 (95% CI=0.55-1.1)	Loomis et al. 1997
	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	242	1965–1991	1965–1978	SIR	No statistically significantly elevated SIRs	Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses for incidence of liver and bile duct cancer were conducted for the entire cohort or stratified by exposure status (low versus high exposure) or time since first exposure (>10 or >20 years). SIR=256 (95% CI=31-926) for the entire cohort. One each of cholangiocellular cancer and adenocarcinoma were reported.	Gustavsson and Hogstedt 1997

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Rectal cancer mortality	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	No deaths	Latency <10 years	Brown and Jones 1981
						417 (no CI)	Latency 10–20 years	
						556 (no CI)	Latency >20 years	
						335 (95% CI= 92–860)	Overall value; an analysis stratified by employment location and sex of worker revealed that observed mortality (3) statistically significantly greater ($p<0.05$) than expected (0.5) for females in one of two locations (Plant 2) resulting in an SMR of 600 (no CI; 3 observed deaths, 0.5 expected). An SMR of 323 (no CI; 1 observed death, 0.31 expected) was reported in males from plant 1. No deaths from rectum cancer were observed in females in plant 1 or males in plant 2. Analysis by employment duration revealed statistically significantly increased SMR only in the group exposed for 10–14 years (not for longer or shorter durations) in one or both locations, although the number of deaths was small.	

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Rectal cancer mortality	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	211 (no CI; p≥0.05)	Overall value; update of Brown and Jones (1981) study; seven additional years' follow-up. Four observed deaths versus 1.9 expected. For females in plant 2 (previously statistically significant in Brown and Jones, 1981) the observed/expected mortality ratio was 3/0.8 (p≥0.05).	Brown 1987b
	Capacitor manufacturing plant workers in New York State exposed ≥90 days vs. U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly increased SMRs	Analysis stratified by gender and hourly vs. salaried compensation. A statistically non-significant SMR of 169 (95% CI=46–434; 4 observed deaths, 2.3 expected) was reported in female hourly workers.	Kimbrough et al. 1999a
	Japanese *Yusho* food PCB contamination registrants versus national death rates	1,761 (887 males, 874 females)	1968–1983	1968 (poisoning incident)	SMR	Males: 1.60 (no CI; p>0.05) Females: no deaths	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. The analysis combined cancers of the rectum, sigmoid colon, and anus. One observed death. Average follow-up was approximately 11 years.	Kuratsune et al. 1987

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Rectal cancer mortality	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 male, 858 female)	1957–1986	1957–1977	SMR	0.8 (95% CI= 0.0–4.5)	NC	Sinks et al. 1992
	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	0.73 (95% CI= 0.2–1.86)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a
	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	1.02 (95% CI= 0.7–1.46)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Rectal cancer mortality	U.S. male utility workers employed full time for ≥6 months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	0.79 (95% CI= 0.65–0.95)	NC	Loomis et al. 1997
Respiratory-related cancer mortality	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	88 (95% CI= 35–181)	Overall SMR value	Brown and Jones 1981
	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	59 (no CI)	Overall SMR value; update of Brown and Jones (1981) study; seven additional years' follow-up	Brown 1987b
	Japanese *Yusho* food PCB contamination registrants versus national death rates	887 males	1968–1983	1968 (poisoning incident)	SMR	3.26 (no CI; p<0.01)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. The analysis combined cancers of the lung, trachea, and bronchus. SMR was not statistically significant in an evaluation of 874 females. Average follow-up was approximately 11 years.	Kuratsune et al. 1987

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Respiratory-related cancer mortality	Taiwanese *Yu-Cheng* food PCB contamination victims versus Taiwan national mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	Males: 0.85 (95% CI= 0.10–3.07); Females: 0.88 (95%CI= 0.02–4.91)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. The analysis considered deaths from trachea, bronchus, and lung cancers combined. One death in males and one death in females observed. Similarly statistically non-significant findings were reported in males and females using a local reference population.	Hsieh et al. 1996
	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 males, 858 women)	1957–1986	1957–1977	SMR	0.7 (95% CI= 0.4–1.2)	NC	Sinks et al. 1992

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Respiratory-related cancer mortality	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	0.78 (95% CI= 0.46–1.28)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a
	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	0.86 (95% CI= 0.68–1.07)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Respiratory-related cancer mortality	U.S. male utility workers employed full time for ≥6 months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	0.91 (95% CI= 0.87–0.95)	The analysis included combined mortalities from cancers of the trachea, bronchus, and lung.	Loomis et al. 1997
	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	242	1965–1991	1965–1978	SMR	No statistically significantly elevated SMRs	The analysis focused on mortality from lung cancer. Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses were conducted for the entire cohort or stratified by exposure status (low versus high exposure). SMRs were 152 (CI=31–444), 222 (27–803), and 173 (CI=56–406) for the low and high exposure groups and entire cohort, respectively. A total of five lung cancer mortalities were observed.	Gustavsson and Hogstedt 1997

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Respiratory-related cancer mortality	Canadian transformer manufacturing plant male workers employed for ≥6 months versus Canadian general male population	819	1947–1989	1947–1975	SMR	0.79 (95% CI= 0.26–1.85)	A statistically non-significant SMR was also obtained in transformer assembly workers employed for ≥6 months (n=308). The authors noted that "considerably more exposure" to mineral oils occurred than exposure to PCB-containing askarol transformer fluids.	Yassi et al. 1994
Pancreatic cancer mortality	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	53 (no CI)	One death observed; overall SMR value.	Brown and Jones 1981
	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	54 (no CI)	Overall SMR value; update of Brown and Jones (1981) study; seven additional years' follow-up.	Brown 1987b

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Parcreatic cancer mortality	Canadian transformer manufacturing plant male workers employed for ≥6 months versus Canadian general male population	2,222	1947–1989	1947–1975	SMR	5.01 (95% CI= 2.50–8.96; 11 observed deaths)	Analysis was for all workers in the transformer plant, with "definite", "probable", or "possible" link between death and pancreatic cancer. The "definite" pancreatic cancer mortality cases yielded an SMR of 2.92 (95% CI=1.17–6.01). Among all workers employed for ≥6 months (n=812) an SMR of 7.64 (3.29–15.06) was obtained, and among workers employed for ≥6 months in the transformer assembly department (n=308), an SMR of 12.9 (2.59–37.7) was calculated. The authors noted that "considerably more exposure" to mineral oils occurred than exposure to PCB-containing askarol transformer fluids. Wong (1995) identified other concerns about the positive pancreatic findings, including inclusion of cases that had neither sufficient duration of exposure nor sufficient latency to be related to PCB exposure at the plant.	Yassi et al. 1994

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Pancreatic cancer mortality	Capacitor manufacturing plant workers in New York State exposed ≥90 days versus U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly increased SMRs	Analysis stratified by gender and hourly versus salaried compensation.	Kimbrough et al. 1999a
	Japanese *Yusho* food PCB contamination registrants versus national death rates	1,761 (887 males, 874 females)	1968–1983	1968 (poisoning incident)	SMR	Males: 1.41 (no CI; p>0.05) Females: 2.18 (no CI; p>0.05)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. Average follow-up was approximately 11 years. One death in males and one death in females observed	Kuratsune et al. 1987
	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 males, 858 females)	1957–1986	1957–1977	SMR	0.7 (95% CI= 0.1–2.5)	NC	Sinks et al. 1992

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Pancreatic cancer mortality	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	0.66 (95% CI= 0.22–1.55)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a
Stomach cancer mortality	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	0.84 (95% CI= 0.58–1.18)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Pancreatic cancer mortality	U.S. male utility workers employed full time for ≥6 months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	0.84 (95% CI= 0.74–0.95)	NC	Loomis et al. 1997
Stomach cancer mortality	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	60 (no CI)	Overall SMR value; one death observed. One observed death, 1.66 expected).	Brown and Jones 1981
	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	36 (no CI)	Overall SMR value; one death observed, update of Brown and Jones (1981) study; seven additional years' follow-up. One observed death, 2.8 expected).	Brown 1987b
	Capacitor manufacturing plant workers in New York State exposed ≥90 days versus U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly increased SMRs	Analysis stratified by gender and hourly versus salaried compensation.	Kimbrough et al. 1999a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Stomach cancer mortality	Japanese *Yusho* food PCB contamination registrants versus national death rates	1,761 (887 males, 874 females)	1968–1983	1968 (poisoning incident)	SMR	Males: 1.40 (no CI; p>0.05) Females: no deaths	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. Average follow-up was approximately 11 years.	Kuratsune et al. 1987
	Taiwanese *Yu-Cheng* food PCB contamination victims versus Taiwan national and local reference mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	National reference: 0.63 (95% CI= 0.02–3.53) Local reference: 0.65 (95% CI= 0.02–3.59	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. The analysis focused on deaths from cancer of the stomach in males. One observed death. No parallel analysis was reported in females.	Hsieh et al. 1996
Stomach cancer incidence	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	1.37 (95% CI= 0.82–2.23)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Intestinal cancer mortality	Taiwanese *Yu-Cheng* food PCB contamination victims versus Taiwan national and local reference mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	National: 19.76 (95% CI= 0.5–110.3) Local: 26.46 (95% CI= 0.67–147.4)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminated. The analysis focused on deaths from cancer of the small intestine in males; one observed death. No parallel analysis was reported in females.	Hsieh et al. 1996
	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	99 (95% CI= 27–254)	Overall SMR value.	Brown and Jones 1981
	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	104 (no CI)	Overall SMR value; update of Brown and Jones (1981) study; seven additional years' follow-up.	Brown 1987b
	U.S. male utility workers employed full time for ≥6 months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	0.93 (95% CI= 0.85–1.02)	NC	Loomis et al. 1997

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
"Digestive tract" cancer mortality	Italian capacitor manufacturing male workers employed ≥1 week versus national mortality rates	544 males	1946–1982	1946–1978	SMR	346 (95% CI= 141–721)	For this analysis, cancers of the stomach (2), pancreas (2), liver (1), and biliary tract (1) were included by the authors in the "digestive tract" group. A SMR of 274 (95% CI=112-572) was also obtained in males in a comparison against a local reference group. No statistically significant digestive tract SMR was obtained for female workers compared to either national or local reference groups, or in a follow-up evaluation with an additional 9 years of latency (Tironi et al. 1996).	Bertazzi et al. 1987
"Digestive organs" cancer mortality	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 males, 858 females)	1957–1986	1957–1977	SMR	0.6 (95% CI= 0.2–1.1)	NC	Sinks et al. 1992

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
"Digestive cancer" mortality	Canadian transformer manufacturing plant male workers employed for ≥1 month versus Canadian general male population	2,222	1947–1989	1947–1975	SMR	1.45 (95% CI= 0.85–2.33)	Analysis combined deaths from "definite", "probable", and "possible" cancer link. Analysis of "definite" digestive cancer mortality cases yielded an SMR of 0.85 (95% CI=0.43–1.53; 11 observed deaths). Statistically non-significant SMRs were also obtained in all workers employed ≥6 months (n=812) and in transformer assembly workers employed for ≥6 months (n=308). The authors noted that "considerably more exposure" to mineral oils occurred than exposure to PCB-containing askarol transformer fluids.	Yassi et al. 1994

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Italian capacitor manufacturing female workers employed ≥1 week versus local mortality rates	1,556 females	1946–1982	1946–1978	SMR	377 (95% CI= 115–877)	A SMR of 266 (not statistically significant; CI not reported; 4 observed, 1.5 expected) was also obtained in females in a comparison against a national reference group. No statistically significantly elevated hematological cancer SMR was obtained for male workers compared to either local (SMR=263; no CI; 3 observed, 1.1 expected) or national (SMR=375; no CI; 3 observed, 0.8 expected) reference groups.	Bertazzi et al. 1987
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Japanese *Yusho* food PCB contamination registrants versus national death rates	1,761 (887 males, 874 females).	1968–1983	1968 (poisoning incident)	SMR	Males: 2.23 (no CI; p>0.05) Females: no deaths	Heated PCB-contaminated rice oil also contained PCDFS and other contaminants; one observed death in males. The analysis focused on leukemia. Average follow-up was approximately 11 years.	Kuratsune et al. 1987
	Taiwanese *Yu-Cheng* food PCB contamination victims versus Taiwan national and local mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	National: 61.17 (95% CI= 1.55–340.7) Local: 86.45 (95% CI= 2.19–481.5)	Heated PCB-contaminated rice oil also contained PCDFS and other contaminants. The analysis focused on Hodgkin's disease in males; no comparable analysis in females was reported. One observed death in males.	Hsieh et al. 1996

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
	Taiwanese *Yu-Cheng* food PCB contamination victims versus Taiwan national and local mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	National: 7.69 (95% CI= 0.19–42.84) Local: 8.42 (95% CI= 0.21–46.89)	Heated PCB-contaminated rice oil also contained PCDFS and other contaminants. The analysis focused on unspecified leukemia disease in males; comparable analysis in females was not reported. One observed death in males.	Hsieh et al. 1996
	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	46 (no CI)	Lymphatic and hemato-poietic cancer mortality; only two deaths; overall SMR value	Brown and Jones 1981
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	68 (no CI)	Lymphatic and hematopoietic cancer mortality; overall SMR value; update of Brown and Jones (1981) study; seven additional years' follow-up	Brown 1987b

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	3.08 (95% CI= 1.24–6.35)	The statistically significant SMR was for multiple myeloma. Statistically non-significant SMRs were obtained for Hodgkins and non-Hodgkins lymphoma and for leukemia. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	No statistically significantly increased SMRs	Statistically non-significant SMRs were obtained for Hodgkins and non-Hodgkins lymphomas, multiple myeloma, and leukemia. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a
	U.S. male utility workers employed full time for ≥6 months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	No statistically significant SMRs	Statistically non-significant SMRs were obtained for mortalities from the following hematologic-related cancers: combined neoplasms of the lymphatic and hematopoietic tissues, lymphosarcoma and reticulosarcoma, Hodgkins disease, leukemia and aleukemia, other lymphatic neoplasms.	Loomis et al. 1997

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	242	1965–1991	1965–1978	SMR	No statistically significant SMRs	Statistically non-significant SMRs were obtained for mortalities from the following hematologic-related cancers: combined hematopoietic and lymphatic malignancies, and malignant lymphomas. Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses were conducted for the entire cohort or stratified by exposure status (low vs. high exposure).	Gustavsson and Hogstedt 1997
	Canadian transformer manufacturing plant male workers employed for ≥6 months versus Canadian general male population	819	1947–1989	1947–1975	SMR	No statistically significant SMRs	Statistically non-significant SMRs were obtained in separate analyses for non-Hodgkins lymphomas and leukemias in all workers employed for ≥6 months (n=812) and in transformer assembly workers employed for ≥6 months (n=308). The authors noted that "considerably more exposure" to mineral oils occurred than exposure to PCB-containing askarol transformer fluids.	Yassi et al. 1994

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	142	1965–1982	1965–1978 (mean exposure 6.5 yrs)	Observed versus expected	1 observed case	The report identified one case of malignant lymphoma, expected number of cases was not reported, but the numbers of deaths from cancers was reported to "correspond well with those expected." Median latency time=13 years.	Gustavsson et al. 1986
	Capacitor manufacturing plant workers in New York State exposed ≥90 days versus U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly increased SMRs	Analysis stratified by gender and hourly versus salaried compensation. Three separate analyses were conducted for lymphosarcoma, leukemia and aleukemia, and other lymphatic and hematopoietic cancers.	Kimbrough et al. 1999a
	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 males, 858 females)	1957–1986	1957–1977	SMR	1.0 (95% CI= 0.4–2.0)	NC	Sinks et al. 1992

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer incidence	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SIR	No statistically significant SIRs	Statistically non-significant SIRs were obtained for Hodgkins and non-Hodgkins lymphoma, multiple myeloma, lymphatic leukemia, myeloic leukemia, and acute leukemia. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer incidence	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SIR	1.86 (95% CI= 0.96–3.25	The nearly statistically significant SIR was for acute leukemia. Statistically non-significant SIRs were obtained for Hodgkins and non-Hodgkins lymphoma, multiple myeloma, lymphatic leukemia, and myeloic leukemia. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer incidence	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	242	1965–1991	1965–1978	SIR	No statistically significantly elevated SIRs	Statistically non-significant SIRs were obtained for occurrence of the following hematologic-related cancers: combined hematopoietic and lymphatic malignancies, and non-Hodgkins lymphoma. Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses for all cancers were conducted for the entire cohort, for the subgroup with time since first exposure >10 yrs, and for the high exposure group.	Gustavsson and Hogstedt 1997

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer mortality	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 males, 858 females)	1957–1986	1957–1977	SMR	4.1 (95% CI= 1.8–8.0	All observed skin cancer deaths (8) were from malignant melanoma, while the expected number of deaths was calculated using mortality rates for basal cell carcinoma, squamous cell carcinoma, and malignant melanoma combined. However, a nested proportional hazards analysis comparing indices of PCB exposure between skin cancer cases and a comparison group showed no relationship between risk of melanoma and cumulative PCB exposure.	Sinks et al. 1992

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer mortality	Capacitor manufacturing plant workers in New York State exposed ≥90 days versus U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly elevated SMRs	The analysis focused on mortality from melanomas. Analyses were stratified by hourly versus salaried compensation schedule, and gender of worker. Only "limited" exposure to other chemicals was reported. There were statistically non-significant increases in melanoma mortality in hourly male workers (SMR=130; 95% CI=42-303; 5 observed deaths, 3.8 expected), hourly female workers (SMR=144; 95% CI=30-421; 3 observed deaths, 2 expected), and salaried male workers (SMR=210; 95% CI=57-538; 4 observed deaths, 1.9 exp).	Kimbrough et al. 1999a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer mortality	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	3.05 (95% CI= 0.99–7.13)	Statistically significant SMR was for squamous cell carcinomas (five cases observed versus 1.6 expected); a statistically non-significant SMR was obtained for melanomas. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a
	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	No deaths observed	Analysis focused on squamous cell skin cancer and melanoma. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer mortality	U.S. male utility workers employed full time for ≥6 months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	1.04 (95% CI= 0.86–1.24)	The overall analysis showed no increases in skin cancers. However, an analysis stratified by latency ("lag") and total career exposure showed a positive relationship between adjusted mortality rate ratios (RRs) and cumulative exposure within the group with a lag time of 20 years: 0–2,000 hrs total exposure (RR=1.29 [95% CI=0.76-2.17]), 2,000–10,000 hours (RR=2.56 [95% CI=1.09–5.97]), >10,000 hours [RR=4.81 (95% CI=1.49-15.1]).	Loomis et al. 1997

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer incidence	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SIR	2.28 (95% CI= 1.45–3.5	The statistically significant SIR was for squamous cell cancer of the skin. A statistically non-significant SIR was obtained for melanomas. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a
	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SIR	Non-statistically significant SIRs	Statistically non-significant SIRs were obtained for squamous cell cancers and melanomas. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer incidence	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus west coast fishermen	2,896 (east) 8,477 (west)	1965–1988	1968–1988	IRR	1.88 (95% CI= 1.15–3.09)	Exposure duration was not clearly identified. East coast fishermen had higher blood levels of PCBs than the west coast population, but they also had higher levels of dioxins and furans (Svensson et al. 1995b).	Svensson et al. 1995a
	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	242	1965–1991	1965–1978	SIR	No observed cases	The analysis focused on malignant melanomas. Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses were conducted for the entire cohort, the high exposure group, and the group with time since first exposure (TSFE) >10 years.	Gustavsson and Hogstedt 1997

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer incidence	U.S. male petrochemical plant workers versus National Cancer Survey incidence rates	31	9-year period until late 1950s	9-year period until late 1950s	NR	2 cases observed versus 0.4 expected (p=0.001)	The analysis focused on malignant melanoma. The report was an editorial letter to the journal, indicating that the men were "heavily" exposed to Aroclor 1254. A follow-up letter (Bahn et al. 1977) indicated that the men were R&D workers who were exposed to other chemicals, but another group of 20 R&D workers with less PCB exposure had no cases of malignant melanoma. A letter from Lawrence (1977) indicated that an epoxide scavenger additive to PCBs was found to have a "pronounced carcinogenic effect in a skin painting study in animals, and that the skin cancer may not be from the PCBs, per se.	Bahn et al. (1976)
Lip cancer incidence	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SIR	1.92 (95% CI= 1.29–2.8)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Lip cancer incidence	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SIR	2.6 (95% CI= 1.05–5.36)	Analysis focused on squamous cell skin cancer and melanoma. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a

Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference

[a]No statistically significant increase in SMR was obtained in the Brown and Jones (1981) overall analysis for the following cancer sites: stomach, intestine (except rectum), rectum, liver/biliary passages, pancreas, respiratory system, breast, lymphatic/hematopoietic systems, and other cancer.
[b]No statistically significant increase in SMR was obtained in the Brown (1987b) update analysis that was stratified by employment location and gender for the following cancer sites: stomach, intestine (except rectum), pancreas, respiratory, urinary, lymphatic/hematopoietic, breast, female genital organs, and other cancers.
[c]No statistically significant increase in SMR was obtained in the Kimbrough et al. (1999a) analysis that was stratified by gender of worker and hourly versus salaried compensation for the following cancer sites: tongue, buccal cavity, pharynx, esophagus, stomach, intestine, rectum, biliary passages and liver, pancreas, larynx, trachea-bronchus-lung, breast, cervix uteri, uterus, ovary-tube-broad ligament, prostate, kidney, bladder and urinary tract, skin, brain and nervous system, connective tissue, other unspecified cancer, lymphosarcoma, leukemia and aleukemia, other lymphatic and hematopoietic cancer.
[d]No statistically significant increase in SMR was obtained in the Gustavsson and Hogstedt (1997) analysis that was stratified by exposure status for the following cancer sites: esophageal, liver, lung, prostate, bladder, kidney, hematopoietic and lymphatic malignancies, and malignant lymphomas.
[e]No statistically significant increase in SMR was obtained in the Kuratsune et al. (1987) analysis that was stratified by gender for the following cancer sites: esophagus, stomach, rectum-sigmoid colon-anus, pancreas, breast, uterus, and leukemia.
[f]No statistically significant increase in SMR was obtained in the Hsieh et al. (1996) analysis using either national or local reference populations for the following cancer sites: males: nasopharynx, stomach, small intestine, liver and intrahepatic bile ducts, trachea-bronchus-lung, unspecified leukemia; females: liver and intrahepatic bile ducts, trachea-bronchus-lung, and bone.
[g]No statistically significant increase in SMR was obtained in the Sinks et al. (1992) analysis for the following cancer sites: buccal cavity-pharynx, digestive organs, liver-biliary passages-gallbladder, pancreas, rectum, respiratory system, kidney, lymphatic and hematopoietic tissue, and brain and nervous system.
[h]No statistically significant increase in SMR was obtained in the Svensson et al. (1995a) analyses stratified by east coast versus west coast fisherman for the following cancer sites: esophagus, stomach, colon, rectum, liver, pancreas, lung-larynx, breast, prostate, bladder, kidney, brain-nervous system, Hodgkins and non-Hodgkins lymphoma, and leukemia.
[i]No statistically significant increase in SMR was obtained in the Loomis et al. (1997) analyses for the following cancer sites: buccal cavity-pharynx, stomach, intestine, rectum, liver-biliary passages-gall bladder, liver (not specified), pancreas, trachea-bronchus-lung, breast, prostate, kidney, urinary organs, skin, brain and nervous system, lymphatic and hematopoietic systems, lymphosarcoma and reticulosarcoma, Hodgkins disease, leukemia and aleukemia, and other lymphatic neoplasms.
[j]No statistically significant increase in SIR was obtained in the Svensson et al. (1995a) analyses stratified by east coast versus west coast fishermen for the following sites: esophagus, colon, rectum, liver-bile ducts, pancreas, lung-larynx, prostate, renal parenchyma, urinary bladder, brain, soft tissue sarcoma, Hodgkins lymphoma, non-Hodgkins lymphoma, multiple myeloma, lymphatic leukemia, myeloic leukemia, and acute leukemia.
[k]No statistically significant increase in SIR was obtained in the Gustavsson and Hogstedt (1997) analysis conducted for the entire cohort, for the subgroup with time since first exposure >10 years, and for the high exposure group for the following cancer sites: esophageal, liver, larynx, lung, prostate, bladder, malignant melanoma, nervous system, soft tissue sarcoma, hematopoietic-lymphatic, non-Hodgkins lymphoma, and other sites.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 3.9, "Interactions with Other Substances," and 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and Figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures. The order of the above may change?

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

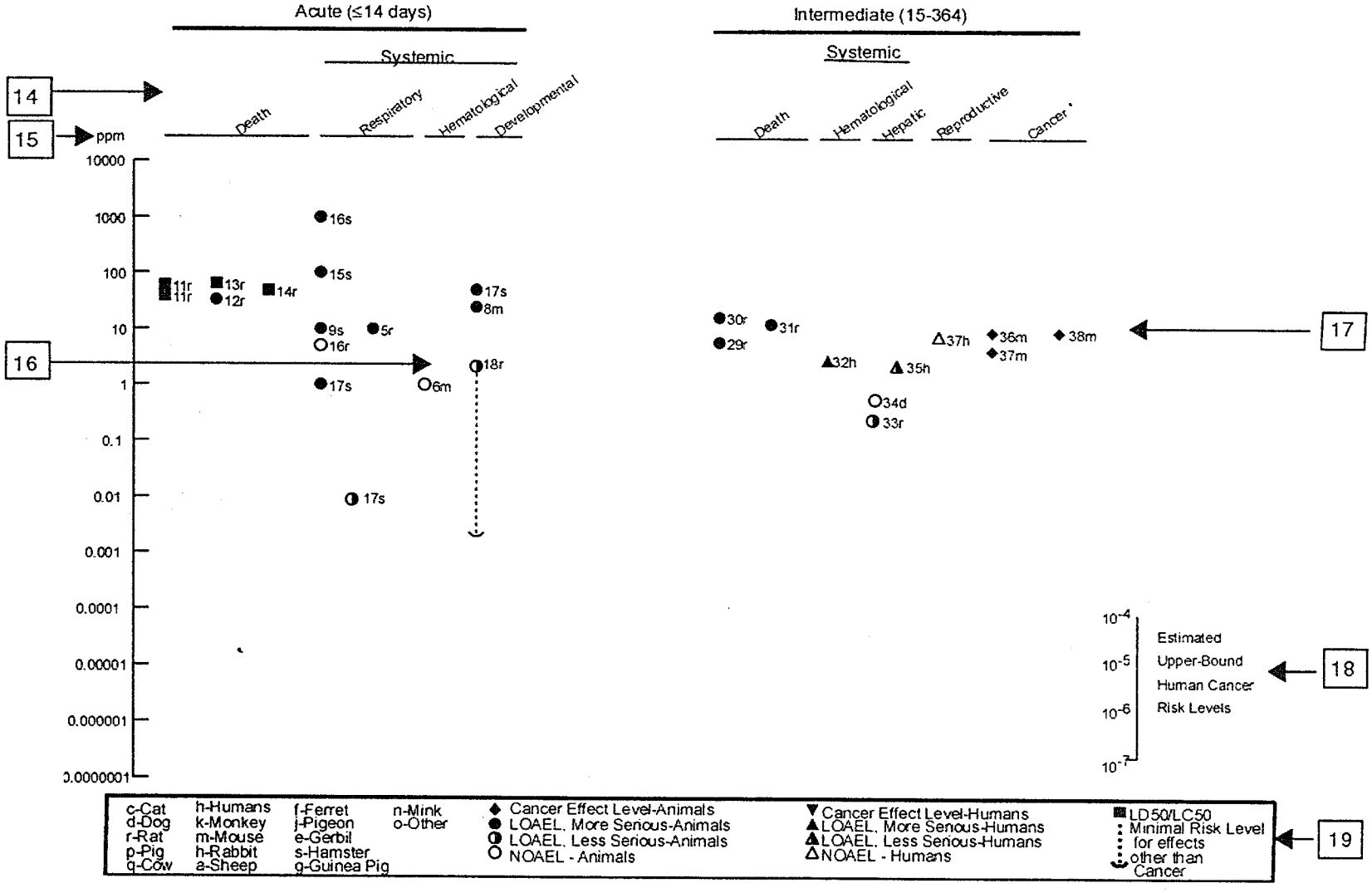
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 3-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

13 → Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram

EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter

mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector

pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short-term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week
$>$	greater than
$\geq$	greater than or equal to
$=$	equal to
$<$	less than
$\leq$	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer

APPENDIX C

μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D

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APPENDIX E

SUMMARY REPORT FOR THE EXPERT PANEL REVIEW
April 13, 2000

SUMMARY REPORT FOR THE EXPERT PANEL REVIEW OF THE TOXICOLOGICAL PROFILE FOR PCBs

Prepared for:

The Agency for Toxic Substances and Disease Registry
Division of Toxicology
Atlanta, Georgia

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NOTE

This report was prepared by Eastern Research Group, Inc. (ERG), an ATSDR contractor, as a general record of discussion for the expert panel review meeting on the Toxicological Profile for Polychlorinated Biphenyls. This report captures the main points of scheduled presentations and highlights discussions among the expert panelists. This report does not contain a verbatim transcript of all issues discussed during the meeting. Additionally, the report does not embellish, interpret, or enlarge upon matters that were incomplete or unclear. ATSDR will evaluate the panelists' recommendations and determine what modifications are necessary to the Toxicological Profile. Except as specifically noted, no statements in this report represent analyses or positions of ATSDR or of ERG.

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APPENDICES

Appendix A—List of Participants

Appendix B—Agenda

LIST OF ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
DSA	delayed spatial alteration
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
LOAEL	lowest-observed-adverse-effect level
LSE	levels of significant exposure
MRL	minimal risk level
NHEXAS	National Human Exposure Assessment Survey
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
PCBs	polychlorinated biphenyls
TEF	toxic equivalency factor

EXECUTIVE SUMMARY

A group of expert scientists extensively reviewed the Agency for Toxic Substances and Disease Registry's (ATSDR's) draft Toxicological Profile for Polychlorinated Biphenyls (PCBs), public comments on this profile, and the Agency's proposed disposition of these comments. During a 3-day meeting, the scientists thoroughly discussed and debated the scientific rigor of the toxicological profile and its criticisms. At the end of the meeting, the panelists generally commended ATSDR on its efforts in preparing the draft profile, but they identified numerous areas where the profile should be improved.

Following is a list of the general recommendations that the expert panelists highlighted during their closing statements. An overview of the discussion that led to these recommendations and specific examples of other suggested revisions are documented throughout this report.

- The panelists recommended several improvements to the organization and presentation of the profile. Most importantly, the panelists thought the Health Effects chapter should subordinate information on route of exposure to discussions on endpoints. They also recommended that this chapter of the profile include syntheses of information using a weight-of-evidence approach to develop conclusions. ATSDR agreed to make these and other improvements to the presentation of information in the profile.

- After highlighting several sections of the profile that do not adequately characterize relevant studies, omit studies, or rely too heavily on outdated information, the panelists recommended that ATSDR carefully revise parts of the Health Effects chapter to provide more accurate, balanced, and complete accounts of the past and current information on the public health implications of PCBs.

- On the topic of PCB-related cancer effects, the panelists confirmed that the profile should document carcinogenicity classifications published by the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), and the U.S. Environmental Protection Agency (EPA). The panelists also recommended that ATSDR improve its reviews of the occupational epidemiological studies, and compare and contrast their findings.

- The panelists generally agreed that the Tryphonas study is an adequate basis for deriving a chronic oral Minimal Risk Level (MRL), but they strongly recommended that ATSDR consider other studies as a supplemental basis for the final health guidance values. Specifically, panelists thought the human studies of Michigan, North Carolina, and Dutch cohorts might be a supportive basis for

a chronic oral MRL, and they thought an animal study published by Rice might be an adequate basis for an intermediate oral MRL.

- Several panelists thought the profile should offer additional insight into the general population's PCB exposures from fish consumption. They recommended that ATSDR distinguish the potential impacts of consuming fish caught in PCB-contaminated waters from those of consuming fish from supermarkets.

1.0 INTRODUCTION

In December 1998, the Agency for Toxic Substances and Disease Registry (ATSDR) released a draft updated version of the Toxicological Profile for Polychlorinated Biphenyls (PCBs) for public comment. Since then, outside agencies, scientists, special interest groups, and the public have submitted comments on the draft profile. To ensure that ATSDR adequately responds to all comments, and to evaluate the scientific merit of the profile as a whole, the Agency assembled an expert review panel of toxicologists, epidemiologists, environmental health scientists, and other experts on September 27–29, 1999, to review the disposition of comments and critique the toxicological profile itself. This report summarizes the technical discussions of the expert review panel.

1.1 Background

Before releasing a toxicological profile, ATSDR goes through great measures to ensure that the profile accurately reflects the current knowledge base of the science. These measures include various forms of scientific review. For example, every toxicological profile goes through several rounds of internal review at ATSDR (e.g., ATSDR's Intra-Agency Minimal Risk Level Workgroup), external peer review by selected expert scientists, and a public comment period, all before being published in final form. Through this process, expert scientists, special interest groups, the public, and others are all given the opportunity to recommend revisions or additions to ATSDR's toxicological profiles.

The Toxicological Profile for PCBs (Draft for Public Comment) has already been subject to extensive internal and external scientific review. However, given the large number of the public comments and their content, ATSDR decided to assemble an expert panel of scientists to critically review a large subset of the public comments and how ATSDR proposes to address them. The Agency also encouraged the expert panelists to comment on any section of the toxicological profile that they thought should be revised.

This expert panel review is an integral part of the overall review process for the Toxicological Profile for PCBs and is expected to lead to a greater understanding of the scientific issues related to PCBs in the environment. ATSDR plans to carefully consider the expert panelists' comments, as summarized in this report, as it finalizes the Toxicological Profile for PCBs.

1.2 The Expert Panel

To organize a comprehensive review, ATSDR identified expert scientists who do not work for the Agency and have demonstrated expertise in the chemical and physical properties of PCBs, human exposure to PCBs, or the health effects associated with PCB exposure, whether in laboratory animals or humans. These scientists included representatives from academia and various federal health and

environmental agencies, and their collective expertise spanned virtually every subject matter in the draft toxicological profile. Therefore, the scientists offered a broad and balanced perspective on the wide range of public comments that ATSDR received. ATSDR distributed copies of the draft toxicological profile, the Agency's proposed disposition of the public comments, and additional relevant information to the scientists roughly 2 weeks prior to the expert panel meeting.

Additionally, several other scientists attended the expert panel review meeting, and they fell into two general categories. First, between 15 and 20 scientists from ATSDR and its profile contractor attended the meeting. These scientists primarily observed the expert panelists' discussions, but offered their own comments and asked the panelists questions periodically throughout the meeting. Second, two observers representing the industry, who ATSDR invited, attended the meeting. The observers mostly listened to the expert panel review, but were given the opportunity to make comments on every topic that was discussed.

Appendix A lists the names and affiliations of the expert panelists, ATSDR scientists, and observers who registered to attend the expert panel review meeting. Note, ATSDR invited representatives of selected special interest groups and stakeholders to attend the meeting.

1.3 The Expert Panel Review Meeting

The 3-day expert panel meeting took place at ATSDR's Division of Toxicology conference room in Atlanta, Georgia, on September 27–29, 1999, and generally followed the agenda shown in Appendix B. Three scientists from ATSDR's Division of Toxicology moderated the expert panel meeting: Dr. Malcolm Williams, Dr. Obaid Faroon (Chemical Manager for the Toxicological Profile for PCBs), and Dr. Chris DeRosa (Director of the Division of Toxicology).

The meeting began with introductory remarks from Dr. Henry Falk, Assistant Administrator of ATSDR, and Dr. DeRosa. Dr. Falk opened the meeting by highlighting the importance of having meaningful and accurate toxicological profiles, not only because the profiles are a critical resource for the Superfund program, but also because they are becoming more widely used in other settings. Specifically, toxicological profiles are now being used as source documents by the World Health Organization, health and regulatory scientists, and researchers and teachers. Given the importance of the Toxicological Profile for PCBs, Dr. Falk urged the expert panelists to actively participate in the meeting's discussions. Following on these remarks, Dr. DeRosa briefly reviewed the steps ATSDR has already taken in reviewing the Toxicological Profile for PCBs (e.g., internal Agency review, external peer review, and release for public comment). He then emphasized that the expert panel review is an integral part of

ATSDR's overall scientific review of this document. After these introductory remarks, the panelists and observers introduced themselves, noting their affiliations and areas of expertise.

For the remainder of the meeting, the panelists engaged in free-flowing discussions on the various topics listed in the agenda (see Appendix B). These discussions addressed relevant public comments, ATSDR's responses to the comments, and any other issues pertaining to the agenda items. As the agenda shows, the expert panel spent most of its time discussing how the toxicological profile described the various health effects associated with exposure to PCBs. These discussions covered non-carcinogenic and carcinogenic effects, as well as the basis ATSDR used for deriving a chronic oral minimal risk level (MRL) for exposure to PCBs. Finally, the expert panelists were encouraged to submit written comments, in case they did not have the opportunity to provide comments during the 3-day meeting.

1.4 Report Organization

During the meeting, the panelists commented both on general issues that pertain to the entire toxicological profile and specific issues for particular sections in the profile. Section 2 of this report summarizes the general issues raised by the panelists, and Section 3 summarizes the specific issues. Within Section 3, each subsection reviews the panelists' comments on different chapters within the profile (e.g., Section 3.1 summarizes the comments on Chapter 1 of the profile, Section 3.2 summarizes the comments on Chapter 2, and so on). Section 4 of this report lists all references cited in the text. When citing specific passages in the toxicological profile, this report refers to page numbers in the December 1998 release of the draft profile for public comment.

As noted earlier, the appendices to this report include a list of the scientists who registered to attend the expert panel review (Appendix A) and the meeting agenda (Appendix B).

2.0 GENERAL COMMENTS ON THE TOXICOLOGICAL PROFILE

During the 3-day meeting, the expert panelists' discussions primarily focused on specific topics and public comments relevant to the toxicological profile. Section 3 of this report reviews salient features of these specific comments. Some of the panelists' comments, however, were relevant to the entire toxicological profile. These general comments addressed both format issues and content issues, as described below.

2.1 Format Issues

The panelists recommended that ATSDR consider modifying several aspects of the format of the toxicological profile. Most importantly, several panelists and observers thought the profile was very redundant due to the organization of the document: In the current profile, health effects are organized by route of exposure first (inhalation, oral, and dermal), and by endpoint second (e.g., death, systemic effects, reproductive effects, and so on). Noting that the health effects associated with PCBs are believed to be largely, though not exclusively, independent of route of exposure, the panelists almost unanimously recommended that ATSDR organize Chapter 2 of the profile by endpoint first, and by route of exposure second.

The panelists recommended several other changes to the format of the document. First, one panelist recommended the use of "running headers" on every page of Chapter 2, such that readers can easily find the subject matter of every page. Second, another panelist thought Chapter 2 would benefit from the use of sub-headers that clearly distinguish studies on acute, intermediate, and chronic exposures, and that distinguish different types of health effects for a given endpoint. Some panelists thought the use of sub-headers is particularly important for the section on developmental effects (Section 2.2.2.6), which discusses behavioral effects, thyroid effects, and so on. Third, one panelist recommended that every section in Section 2.2 open with one or two sentences explaining the section's contents and including cross-references to other sections, as appropriate. Finally, a panelist suggested that the profile include an index.

2.2 Content Issues

According to the expert panelists, the following issues and general comments apply to the content in various sections of the toxicological profile. The panelists recommended that ATSDR consider revising the relevant sections of the profile accordingly.

- **Synthesis of Information.** Several panelists thought the toxicological profile should be strengthened by including brief sections that synthesize the findings of various toxicological and epidemiological studies presented in Chapter 2. The panelists thought this was especially

important for the Relevance to Public Health section (Section 2.5). According to several panelists, this section currently lists the results of many different toxicological studies on animals and humans, leaving the reader with the burden of drawing conclusions or identifying common themes among them. A few panelists were particularly concerned about the lack of synthesis of information on developmental effects: The panelists thought the profile merely provided a list of studies, without highlighting consistencies and discrepancies between them.

- **Omission of Relevant Studies on PCBs.** Several panelists noted that the current version of the toxicological profile does not include recently published studies on PCBs, as well as some older references. Section 3 of this report identifies specific cases where relevant references were apparently missing or not cited. Responding to this comment, representatives from ATSDR noted that studies published in 1999 and in the last half of 1998 obviously could not be included in the draft profile, since it was published in December, 1998; however, some panelists noted that selected earlier studies were not referenced. The panelists debated whether the profile should include more information on the Yusho and Yu-Cheng poisoning incidents, as Section 3.2.1 of this report describes in greater detail.

- **The Profile's Emphasis on Fish Consumption.** Several panelists thought the toxicological profile overly emphasized, or incorrectly characterized, human exposure to PCBs through consumption of contaminated fish. One panelist explained that this exposure pathway is an important issue for certain populations (e.g., people who consume sport-caught fish from PCB-contaminated waters), but he thought the profile should not overstate this pathway's relevance to the general population.

  On a related note, some panelists were concerned that the profile relies too heavily on studies of health effects among fish-eating populations, assuming PCB exposure, and not heavily enough on studies that have identified health effects attributed specifically to PCB exposure. Though they agreed that fish-eating populations are undoubtedly exposed to PCBs, some panelists cautioned that fish-eaters are also exposed to other persistent, bioaccumulative toxicants, thus complicating efforts to attribute observed health effects in epidemiological studies specifically to PCBs. Accordingly, some panelists thought the profile should place a lesser emphasis on the studies of fish consumption, but others thought these studies were an important part of the profile's message.

- **Presentation of Congener-Specific Information.** A recurring topic during the meeting was the fact that the many toxicological and epidemiological studies addressed exposures to various forms of PCBs, including congeners and/or mixtures of congeners. The panelists had differing opinions

on how the profile should address congener-specific information: Some panelists thought it should be presented in separate sections of the profile; others thought including the congener-specific information under the appropriate endpoints would help highlight similarities and differences between exposures to individual congeners, commercial mixtures of PCBs, mixtures of PCBs with other contaminants, and weathered commercial PCB mixtures; and one panelist suspected that including congener-specific effects throughout the profile might make the document difficult to read.

When discussing the availability of congener-specific data, the panelists raised several related issues: One panelist noted that examining associations between total PCB exposure and observed health effects might mask statistically significant findings between exposure to individual PCB congeners and selected health effects. On another issue, one panelist explained that exposure at Superfund sites is primarily to weathered mixtures of PCBs, which might differ considerably from the various commercial mixtures used in selected animal studies. Finally, yet another panelist cautioned ATSDR about relying too heavily on congener-specific information, given the differing sensitivity of various PCB analytical methods.

- **Miscellaneous General Comments.** One panelist encouraged ATSDR to use precise terminology for symptoms (effects that you cannot see, like headaches) and signs (effects that you can see, like rashes). Since symptoms technically are subjective, this panelist thought the profile should not refer to "subjective symptoms," as it currently does, for example, on page 220.

3.0 SPECIFIC COMMENTS ON THE TOXICOLOGICAL PROFILE

This section summarizes the panelists' review of specific topics in the toxicological profile. Comments are organized by the various chapters in the profile, and comments on health effects are further classified by endpoint. Note, panelists and observers were given the opportunity to comment on every chapter in the draft toxicological profile, but the majority of their comments addressed the health effects outlined in Chapter 2.

3.1 Comments on Chapter 1—Public Health Statement

Given the number of revisions the panelists recommended to the Public Health Statement, as documented below, and the fact that the Public Health Statement is the most important chapter of the profile to certain audiences, some panelists recommended that ATSDR carefully read through and revise this entire chapter to ensure that it provides a clear and concise statement of the relevant public health issues. Specific examples of the panelists' concerns regarding this chapter follow.

Several panelists highlighted specific passages in the Public Health Statement that were either unclear or inaccurate. For example, one panelist questioned the reasoning behind one of the opening statements in Chapter 1: "Because the health effects of PCBs are difficult to evaluate, most of the information in this document is about seven types of commercially available PCB mixtures" (pages 1 and 2). This panelist suspected that the decision to evaluate seven types of mixtures was not simply due to the complexity of evaluating PCB-related health effects. Further, another panelist questioned the profile's definition of the half-life of PCBs in air ("the time it takes for one-half the PCBs to change into something else," page 3), indicating that this definition does not account for fallout or other relevant removal mechanisms. As a result, the panelists recommended that ATSDR clarify its definition of half-life in the final release of the profile.

Finally, yet another panelist was not convinced that a statement on the toxicity of PCB metabolites was accurate: "Some metabolites of PCBs may have the potential to be as harmful as unchanged PCBs, but there is no conclusive experimental evidence to support this assumption" (pages 5 and 6). The panelists suggested rewording this sentence as: "Some metabolites of PCBs may have the potential to be as harmful as unchanged PCBs; recent experimental evidence demonstrates that metabolites may also cause different kinds of toxicities." This panelist also recommended that ATSDR revise its statement, "If your PCB levels in these fluids are higher than the normal environmental levels, this will show that you have been exposed to high levels of PCBs" (page 10), because prolonged low-level exposure to PCBs might also explain elevated body burdens.

In addition to the specific comments, the panelists discussed the availability and implications of medical tests to characterize PCB levels in blood, body fat, and breast milk. Though the profile clearly states that routine clinical tests are not available, some panelists suggested that ATSDR include more detailed information on this topic, such as whether tests will be commercially available, how people can get tested by physicians and specialists, and how medical professionals should interpret the significance of measured PCB levels. During this discussion, several panelists indicated that the profile does not acknowledge that no treatments are currently available to reduce body burdens of PCBs. One panelist noted that PCB tests are currently available to physicians, but some testing methods have relatively high detection limits and inadequate quality assurance measures.

Noting that exposures to chemicals at waste sites have affected certain communities more so than others, one panelist recommended that the profile, particularly the Public Health Statement, address issues of differential exposures among various ethnic groups. Based on historical data on pesticides, this panelist thought African-Americans might be more likely to store PCBs in their bodies than other sub-populations, but he was not aware of such data on PCBs. To put this comment into perspective, one panelist noted that the African-American women and white women in a study of 912 North Carolinians generally had comparable levels of PCBs, though he added that this data does not reflect exposures at hazardous waste sites (Rogan et al. 1986). At the end of this discussion, ATSDR noted that the profile will address genetic polymorphism with regards to PCB exposure, metabolism, and health effects, if relevant data exist.

General comments on the Public Health Statement included a suggestion that the chapter include a picture indicating the chemical structure of PCBs and a discussion on PCBs in breast milk and nursing. On the latter topic, some panelists questioned whether women with elevated PCB concentrations in breast milk should nurse, but others cautioned against making such statements given the potential benefits of breast feeding. A few panelists wondered if the Public Health Statement should address this topic. Finally, a panelist thought the Public Health Statement should include some information on PCB-related immunological effects, especially considering that ATSDR proposed basing its chronic oral MRL on this endpoint.

3.2 Comments on Chapter 2—Health Effects

The expert panel discussed and debated many technical issues presented in Chapter 2 ("Health Effects") of the toxicological profile. The following subsections review these discussions, organized by endpoint. The subsections are presented in the order that topics were considered during the expert panel review; this order does not reflect any judgment on which endpoints are most important or most widely debated for PCBs.

3.2.1 Developmental Effects

The panelists reviewed public comments the Agency received regarding developmental effects following oral exposure to PCBs. With few exceptions, which are noted below, the panelists generally agreed with ATSDR's proposed approaches for responding to the comments. The observers had no comments on the profile's review of developmental effects. Discussions on developmental effects focused primarily on the following topics:

- **Inclusion of Additional Studies.** In response to a public comment, the panelists listed several relevant studies that are currently not included in the draft toxicological profile. These studies include the Oswego studies (Lonky et al. 1996; Stewart et al.1999), the Dutch cohort study (Huisman et al. 1995; Koopman-Esseboom et al. 1994, 1996a, 1996b; Lanting et al. 1998a, 1998b, 1998c, 1998d; Patandin et al. 1997, 1998a, 1998b, 1998c, 1998d, 1999a, 1999b; Weisglas-Kuperus 1998), the German cohort study (Winneke et al., 1998), studies published by Dr. Deborah Rice (Rice 1999a, 1999b), and the 2-year follow-up study of a cohort of children in North Carolina (Rogan and Gladen 1991). In addition, the panelists debated the need for providing more detailed analyses of two Asian poisoning incidents—a topic that is elaborated on below.

  Some panelists noted that information in the aforementioned studies should have been included in the levels of significant exposure (LSE) tables and could have been relevant to developing an MRL. Overall, several panelists encouraged ATSDR to reconsider the general message of the developmental effects of the toxicological profile (i.e., "The overall evidence suggesting that PCBs may represent a developmental hazard for human health is inconclusive," page 225), given the emerging weight of evidence provided by these additional studies. Moreover, given the range of suggested improvements for the section on developmental effects, some panelists thought future drafts of this section would benefit from additional expert review.

- **Yusho and Yu-Cheng Incidents.** Several panelists recommended that ATSDR consider including more information on the Yusho and Yu-Cheng poisoning incidents from Japan and Taiwan, respectively, in the Toxicological Profile for PCBs. These incidents involved two populations that consumed rice oil contaminated with complex mixtures of chemicals, which included furans, PCBs, and other compounds. Analyses of these incidents are documented in numerous journal articles (e.g., Hsu et al. 1994; Masuda 1994). The panelists offered several insights on the relevance of these studies to the profile.

  First, noting that the exposed populations in these incidents consumed mixtures of chemicals, one panelist thought this study should be included in the profile to characterize possible interactive

effects (e.g., synergism and antagonism) of PCBs, furans, and other chemicals. Second, panelists debated the extent to which PCBs, as opposed to furans, accounted for the observed health effects. One panelist indicated that toxic equivalency factor (TEF) calculations have suggested that PCBs accounted for at least 25 percent of the toxicity in the Yusho and Yu-Cheng incidents. For this reason, the panelist thought the toxicological profile should more prominently acknowledge the implications of the Yusho and Yu-Cheng incidents, while noting the uncertainty associated with TEF calculations. Third, the panelists debated whether the exposure concentrations for these incidents had been accurately characterized. One panelist thought the concentrations in the rice oil were extremely well documented. Others agreed, but wondered if heating the rice oil (as the residents of Yusho and Yu-Cheng did when cooking) might have changed the composition of contaminants considerably. As a result, these panelists suspected that levels of the lower-chlorinated PCB congeners might not have been completely characterized. These issues regarding the levels of contamination in the rice oil and potential exposure concentrations were not resolved. Finally, some panelists thought the toxicological profile for PCBs should at least include references to the toxicological profiles on dioxins and furans, which reportedly review the Yusho and Yu-Cheng incidents more thoroughly.

- **Public Comment on the Studies Published by Jacobson.** One of the public comments requested that the toxicological profile provide "a more detailed and balanced summary of the limitations" of the Michigan fisheater studies published by Dr. Joseph Jacobson (Jacobson and Jacobson 1996a, 1996b; Jacobson et al. 1984a, 1985). The panelists thought that including results from the Oswego and Dutch studies in the toxicological profile might address the concerns raised in the comment, since these studies replicate the findings of the Jacobson studies under question.

  A panelist who is a principal investigator of the Oswego studies then summarized major findings from his research (Lonky et al. 1996; Stewart et al. 1999). He explained how his series of studies overcomes many of the criticisms of Dr. Jacobson's earlier studies, such as control for confounding variables, quality of sample, and representativeness of analytical data. As a result, this panelist thought inclusion of his studies in the toxicological profile would provide a much more compelling case for links between PCB exposure and neurodevelopmental effects.

- **Public Comment on Paneth's Criticism of the Jacobson Studies.** One of the public comments suggested that ATSDR's interpretation of Paneth's critique of the Michigan fisheater studies (see page 125 of the profile) was misleading (Paneth, 1991). ATSDR's disposition of comments defended its original text by noting that "many other well known researchers," in addition to Paneth, have criticized the Michigan fisheater studies. The panelists discussed this comment and

ATSDR's response at length. One panelist recommended that ATSDR's disposition of comments cite individual scientists and their relevant reviews, rather than simply citing "well known researchers."

Two panelists were surprised at the extent to which the profile stands by Paneth's criticisms of the Michigan fisheater study. Noting that Paneth apparently misunderstood the scope of the Michigan fisheater study (e.g., by assuming that the Michigan study was a case-control study, which it was not), one panelist thought ATSDR should more carefully review Paneth's criticisms. Agreeing with this sentiment, another panelist thought ATSDR gave an imbalanced account of developmental effects by citing Paneth's criticisms of various studies without citing other reviews that refute these criticisms, especially the "Workshop Report on Developmental Neurotoxic Effects Associated with Exposure to PCBs" (EPA/630/R-92/004). None of the panelists supported Paneth's criticisms of the Michigan fisheater study.

- **Recommended Revisions to the Discussion of Neurodevelopmental Effects.** One panelist thought the profile's review of developmental and behavioral effects in animals was very vague and imprecise. As an example, the panelist noted that several passages in this section of the profile discussed how studies observed "a change" or "a behavioral effect," rather than describing the effects and changes in greater detail (e.g., "an impairment" or "an improvement"). This panelist thought ATSDR should include more specific terminology throughout this section for it to be more informative to the reader.

- **The Need for Better Synthesis of Information.** Several panelists were concerned that the toxicological profile, particularly the section on developmental effects, provides little or no synthesis of the information from the many studies presented. Some panelists thought many readers might not be able to identify or understand consistencies and inconsistencies among the myriad toxicological and epidemiological studies. As an example of how the document could better synthesize information, one panelist noted that some animal and human studies have reported similar findings that both humans and animals exposed to PCBs do poorer on tests of memory function. This panelist thought the profile should highlight such parallels between human and animal studies as converging evidence on the link between PCBs and selected health outcomes.

Another panelist thought Section 2.5 (page 224) does not adequately distinguish the implications of transplacental and breast milk exposure. This panelist thought the profile should emphasize that transplacental transfer occurs at the earliest stage of life, when humans are particularly prone

and susceptible to the potential effects of exposure to environmental contaminants, while breast milk exposure occurs slightly later in life and does not appear to be associated with adverse developmental effects.

- **Public Comment on the Findings Reported by Pantaleoni et al (1988).** One public comment suggested that passages on pages 131, 133, and 224 of the profile do not accurately characterize the findings reported by Pantaleoni et al., but the panelists disagreed with the comment and agreed that ATSDR has accurately described this study.

- **Comments on the Mechanisms for Developmental Effects.** One panelist offered three recommendations for improving the profile's discussion on mechanisms for developmental effects. First, this panelist thought Section 2.4.2 implies that neurotoxic effects are linked to exposures to only ortho-substituted PCB congeners, and not to other PCB congeners; the panelist did not think evidence existed proving that non-ortho-substituted congeners do not exhibit neurotoxic effects and recommended that this point be clarified. Second, this panelist thought effects of long-term potentiation might be a more relevant model for evaluating mechanisms of neurotoxicity (as opposed to nerve cell death or reduction in dopamine levels), since these effects appear to follow exposures to doses similar to those encountered in the environment. The panelist noted that some researchers (e.g., Winneke) have examined this mechanism. Third, this panelist recommended that relevant information on mechanisms and *in vitro* studies should be included for perspective in Section 2.2 of the profile, rather than keeping this information only in Section 2.4.

3.2.2 Neurological Effects

The panelists reviewed ATSDR's disposition of five public comments regarding neurological effects following both inhalation and oral exposure to PCBs. One observer commented on neurological effects, as noted below.

- **Distinction Between Neurological Effects and Developmental Effects.** A public comment, and several panelists, wondered why certain studies on neurological effects are presented in Section 2.2.2.6 (Developmental Effects) and others are presented in Section 2.2.2.4 (Neurological Effects). In response, the Chemical Manager explained the hierarchy ATSDR follows when classifying effects in toxicological profiles: Any effect observed between conception and maturation is considered a developmental effect, regardless of whether the effect was neurological, systemic, and so on. Though the panelists did not question this approach, several thought the profile should clearly state ATSDR's criterion for classifying neurological effects in two different parts of the document.

- **Public Comment on the Weight of Evidence for Neurological Effects.** Two public comments identified inaccuracies and misleading statements throughout Section 2.2.2.4 and questioned whether sufficient evidence is available linking PCB exposures to neurological effects. A panelist who has conducted her own research on PCB-related neurological effects agreed that this section includes gross inaccuracies and cited as examples misleading statements in the first two sentences of Section 2.2.2.4 (page 117). First, this panelist thought the opening sentence, which indicates that neurotoxic effects have occurred among Native Americans who eat PCB-contaminated fish, should include a reference; this panelist was unaware of any research that had reported such a finding.

  Second, this panelist took exception to how the second sentence of this section characterizes her own research (Schantz et al., 1996). The sentence in question implies that her research has found evidence of neurological effects among adults in a fish-eating population and that behavioral outcomes were found to be linked to exposures to ortho-substituted PCBs. However, this panelist explained that the reference cited (i.e., Schantz et al., 1996) simply describes the neurological endpoints that would be assessed and the characteristics of the sample that would be tested in her study. She explained that the actual study is still underway, data analysis is ongoing, and the final results are currently unknown. She thought these and other inaccuracies need to be corrected, because they currently imply that studies have found evidence of neurological effects in adults. Overall, this panelist did not think sufficient evidence existed linking neurological effects in adults with exposure to PCBs, primarily because no research on neurological effects in adults has been conducted.

  Other panelists also addressed these public comments. One panelist thought, and others agreed, that some peer-reviewed papers from the Yusho and Yu-Cheng incidents have reported PCB-related neurological effects in adults, including numbness and nerve conduction delays (Chen et al. 1985a; Chia and Chu 1984, 1985). An observer, on the other hand, recommended that ATSDR not include the Asian poisoning incidents under the review of neurological effects, given the uncertainties associated with attributing toxic effects to both the PCBs and furans in the contaminated rice oil. Another panelist recommended, and an observer agreed, that ATSDR review the occupational medicine literature relative to PCBs for more information on potential neurological effects. The observer, however, believed that the occupational medicine literature does not provide evidence of PCB-related neurological effects. Yet another panelist thought the profile should carefully state the overall conclusion for neurological effects: This panelist

encouraged that the profile indicate that not enough evidence is available to determine the links between PCB exposure and neurological effects, if any, rather than imply that no such links exist.

- **Public Comment on Neurological Effects Linked to Inhalation Exposure.** One comment suggested that Section 2.2.1.4 does not accurately portray findings of the three studies on neurological effects following inhalation exposure to PCBs (Fischbein et al., 1979; Emmett et al., 1988a; Smith et al., 1982). According to the disposition of comments, ATSDR plans to revise this section of the profile accordingly. The panelists had no comments on this topic.

- **Public Comment on the Neurotoxicity of Ortho-Substituted Congeners.** One public comment questioned the profile's implications that only ortho-substituted PCB congeners are neurotoxic (see page 117, for example). A panelist proposed that ATSDR address this comment by considering studies on long-term potentiation effects, which reportedly are observed following exposures to both ortho-substituted and coplanar PCBs. No other comments were offered.

3.2.3 Children's Susceptibility

The panelists reviewed the four public comments on children's susceptibility to PCBs. An overview of the panelists' views on the public comments, plus some general comments on the Children's Susceptibility section of the profile, follow. The observers had no comments on this topic.

- **Public Comment on the Relevance of Children's Susceptibility for PCBs.** A public comment indicated that the toxicological profile overemphasizes children's susceptibility to PCBs and that the potential health risks to children are no greater than those to adults. Several panelists, however, thought this comment has little substance, for various reasons. First, one panelist noted that children do consume elevated levels of PCBs from breast feeding—a route of exposure that obviously does not affect adults. This panelist also believed that some dietary surveys suggest that children consume more PCBs per body weight than adults. According to another panelist, some recent unpublished data indicate that children who live near selected PCB-contaminated sites have higher PCB tissue concentrations than adults. Given recent studies showing adverse health effects in children associated with low doses of PCBs (see Section 3.7 of this report) and the overwhelming evidence for developmental sensitivity in animal studies, one panelist recommended that ATSDR simply reject the public comment.

- **Public Comment on the Implications of Children's Susceptibility on the MRL.** A public comment suggested that ATSDR not use an uncertainty factor of 10 that accounts for children's susceptibility when developing its chronic oral MRL. (Note, ATSDR's derivation of the MRL in

the draft toxicological profile does not include such an uncertainty factor.) When responding to this comment, the panelists and ATSDR discussed at length the scientific basis for uncertainty factors, ATSDR's approach to, and requirements for, considering uncertainty factors, and the distinction between uncertainty factors and margins of safety. One panelist was concerned that health effects are currently occurring at exposure doses comparable to the proposed MRL. At the end of the discussion, some panelists recommended use of additional uncertainty factors for the purpose of being protective of children, and others did not. The panelists revisited this topic when reviewing the basis for ATSDR's proposed MRL (see Section 3.7 of this report).

- **Public Comment on the Criticisms of the Michigan Fisheaster Studies.** A public comment suggested that Section 2.7 of the toxicological profile overstates the value of the Michigan fisheater studies. Consistent with their earlier comments regarding developmental effects (see Section 3.2.1 of this report), the panelists again disagreed with the comment's implication that the findings of the Michigan studies are erroneous.

- **Public Comment on Metabolism of PCBs by Breast-fed Infants.** A public comment questioned whether the profile's reference to studies from 1966 and 1977 (page 239) regarding metabolism of PCBs by infants might be outdated and wondered whether pediatricians still prescribe novobiocin, an antibiotic that reportedly inhibits glucuronyl transferase activity (Gartner and Arias, 1966; Leeder and Kearns, 1977). One panelist suspected that more recent studies are not available from the current scientific literature, but he basically found the comment irrelevant, since he thought breast milk does not contain metabolizable PCBs. Another panelist noted that relatively small amounts of metabolizable PCBs are occasionally detected in breast milk, but in small proportions; he added that these infrequent detections presumably occur in individuals recently exposed to PCBs. This reviewer stressed that the epidemiological significance of these infrequent detections has not been established.

- **General Comments on Children's Susceptibility.** After reviewing the public comments on children's susceptibility to PCBs, some panelists offered general remarks on this topic: Two panelists thought the children's susceptibility section should acknowledge the sensitivity of the thyroid system (see Section 3.2.4 of this report), though neither cited published studies reporting a link between PCB exposure and thyroid effects in children. Another panelist indicated that the recent studies by Deborah Rice should also be included in the children's susceptibility section (Rice, 1999a; 1999b).

3.2.4 Endocrine Effects

The panelists reviewed ATSDR's disposition of every comment the Agency classified as specifically addressing endocrine effects of PCB exposure. The observers had limited comments on these discussions.

- **Inclusion of Additional Studies.** When reviewing the public comments on endocrine effects, the panelists listed several studies that ATSDR should consider incorporating in the toxicological profile. One panelist thought the profile should include more data from human studies, specifically the Yusho incident and the Dutch studies (Koopman-Esseboom et al. 1994; Nagayama et al. 1997; Weisglas-Kuperus 1998), to provide a more complete account of endocrine effects. This panelist thought data from the Yusho incident provides insight on potential interactive effects between PCBs and other compounds. Another panelist thought the profile should more prominently acknowledge *in vitro* studies of PCB congener-specific activities, human cell lines, and so on. Yet another panelist recommended, and an observer agreed, that the profile should address Arnold's studies of endometriosis (Arnold, 1996) and Helzlsouer's studies of breast cancer (Helzlsouer et al., 1999).

- **Organization, Prioritization, and Synthesis of Endocrine Effects in the Profile.** In response to a public comment regarding the profile's redundant discussions of endocrine effects, panelists noted that ATSDR could address this comment by revising the profile's format, as described in detail in Section 2.1 of this report. In addition, one panelist felt the profile placed too much emphasis on studies on endometriosis and breast cancer and not enough emphasis on thyroid effects, for which extensive animal studies and limited human studies are reportedly available. Given the large volume and complexity of information on endocrine effects, two panelists thought the toxicological profile should include a brief integration and synthesis of the many studies reviewed.

- **Public Comment on the Xenoestrogen/Breast Cancer Theory.** A public comment recommended that the discussion of xenoestrogen/breast cancer theory (pages 233 and 234) be deleted from the toxicological profile. The panelists debated at length the utility of including various theories linking PCBs to breast cancer, as described below. Overall, one panelist did not think the toxicological profile should include such theoretical discussions given that scientists have little understanding of the endocrine causal pathway for breast cancer. Other panelists thought the discussions were relevant to the toxicological profile, but recommended that ATSDR move them into the profile's sections on cancer. (In fact, the panelists continued to discuss this topic in their review of the sections on cancer; see Section 3.2.5, below, for additional comments.)

The panelists provided several different perspectives on the theory of PCBs and breast cancer. One point of agreement was that the draft toxicological profile presents a very selective review of the current literature on breast cancer and environmental contaminants; one panelist noted that the profile omits a recent study that found no association between PCB serum concentrations and breast cancer (Helzlsouer et al., 1999).

Though the panelists also generally agreed that the relevant epidemiological studies currently do not support a link between PCB exposure and breast cancer, they offered different reasons for why no such link is apparent. For example, one panelist noted that the causal pathway for breast cancer might begin very early in life, in which case, studies that examine PCB levels in adult subjects would naturally not capture the exposures that might be of greatest concern. Alternatively, other panelists noted that the epidemiological studies generally have inadequate characterization of serum levels of PCBs: Emphasizing that some PCB congeners are estrogenic and others are anti-estrogenic, one panelist thought studies that reported serum levels of total PCBs are inadequate, since this metric does not characterize the estrogenicity of the exposure concentrations; another panelist indicated that some epidemiological studies collected too few serum samples (and not at relevant times) to provide a meaningful data analysis; and yet another panelist noted that many of the epidemiological studies did not consider serum levels of dioxins and furans, which might be confounding factors in establishing links between PCBs and breast cancer. The expert panelists' varying comments and criticisms suggested that the available human studies offer little insight into the exact role PCBs have, if any, in causing breast cancer.

- **Public Comment on the Mendola Study (1997).** A public comment noted that the shortened menstrual cycles observed in women who consumed fish, as documented in the Mendola study, cannot be attributed to PCB exposure, since the fish likely contained other persistent toxins. One panelist agreed with the comment, but thought research like the Mendola study is still germane to the toxicological profile, even though the findings might indicate results of interactive effects of many contaminants. This panelist recommended that ATSDR retain such studies in the toxicological profile and bring the associated issue of interactive effects to the forefront.

- **Public Comment on the Mendola (1997) and Gerhard (1998) Studies.** A public comment suggested that the studies published by Mendola and Gerhard should be deleted from the toxicological profile because they do not provide direct evidence of PCB-related endocrine effects. Disagreeing with the comment, one panelist recommended that the studies be retained in the profile with appropriate caveats noting their limitations; this panelist also suggested reinforcing

the findings of these studies with relevant animal studies, if available. No other panelists addressed this public comment.

- **Comments on Thyroid Effects.** Two panelists thought the toxicological profile should have included more information on thyroid effects. These two panelists noted that current research has not reported consistent thyroid effects associated with exposures to PCBs: Different effects are observed in different human cohorts, thus underscoring the complexity of understanding the mechanisms of thyroid effects. Though these panelists acknowledged that inconclusive data are available for humans, they recommended that the profile review the available information. One panelist recommended that ATSDR refer to a recent issue of Environmental Health Perspectives for a review of relevant epidemiological studies that might provide additional information on thyroid effects (Brouwer et al. 1999).

- **Inclusion of Discussions on Diabetes and the Pancreas as a Target Organ.** Though he acknowledged that only limited information is available on these topics, one panelist was concerned that the toxicological profile does not discuss possible links between PCB exposure and diabetes, nor does it mention the pancreas as a target organ. This panelist noted that PCBs have been found to cause beta cells in the pancreas to release insulin. He then recommended that the profile at least mention potential links between PCBs and diabetes as an emerging issue, especially given the growing evidence of links between dioxin exposure and diabetes compiled by the National Institute of Health Sciences.

- **Additional Comments on the Endocrine System.** Some panelists thought the profile should review studies that have characterized PCB concentrations in follicular fluids, which could have implications for various target organs and effects. Others thought the profile erroneously classifies all coplanar PCBs as anti-estrogens (see page 234); these panelists indicated that some coplanar PCBs (e.g., possibly PCB #77 and #126) and their metabolites are actually estrogenic.

3.2.5 Cancer

The panelists discussed at length the public comments regarding how the toxicological profile documents PCB-related cancer effects, during which the observers offered a few comments. An overview of the panelists' discussion follows.

- **Public Comment on the Carcinogenicity of PCBs.** A public comment took exception with a passage in the toxicological profile that claimed "most of the epidemiological studies have been inconclusive or have not shown an association between PCBs and cancer" (see page 138). In their

discussions, the panelists unanimously agreed that ATSDR should, *throughout the toxicological profile and disposition of comments*, simply refer to the carcinogenicity classifications made by the U.S. Environmental Protection Agency (EPA), the International Agency for Research on Cancer (IARC), and the National Toxicology Program (NTP). The panelists encouraged that ATSDR review these classifications carefully and even incorporate EPA's, IARC's, and NTP's specific terminology regarding cancer effects in humans and animals.

During this discussion, a panelist indicated EPA's current position on the carcinogenicity of PCBs: PCBs are probable human carcinogens, based on suggestive but inadequate human studies, and animal studies that provide sufficient evidence. This panelist was surprised that the toxicological profile currently implies that there is no association between PCBs and cancer, rather than paralleling EPA's position.

Citing a different quote in the profile ("The weight of evidence does not support a causal association for PCBs and human cancer at this time," page 227), one panelist suggested that ATSDR use precise terminology and clearly differentiate discussions of causation from those of association when commenting on the carcinogenicity of PCBs. Another panelist indicated that the Public Health Statement (Chapter 1) does not clearly communicate the current state of knowledge regarding PCBs and cancer. Yet another panelist was concerned about the overview of PCBs and cancer in the section on Relevance to Public Health (Section 2.5). These panelists thought, and others agreed, that ATSDR needs to carefully revise the profile to avoid presenting a confusing, inconsistent account of carcinogenicity.

- **Public Comment Providing Evidence that PCBs Are Not Carcinogens.** One public comment suggested that the toxicological profile should conclude that PCBs are not human carcinogens, based partly on the fact that similar cancer endpoints have not been reported across the many different epidemiological studies. The panelists generally disagreed with this comment, for two reasons. First, the panelists noted that IARC's carcinogenicity classification clearly contradicts the comment's assertion.

  Second, a couple of the panelists explained that the observation of common cancers across studies is not a necessary and sufficient condition for establishing a contaminant's carcinogenicity. In fact, these panelists noted that the absence of consistent cancer outcomes might simply reflect the small cohort sizes in certain studies, the extremely low incidence of certain cancers, or latency effects. Further, noting that animal studies have reported gender differences in cancer effects, one panelist hypothesized that the varying demographics in the cohort studies might account for part

of the apparent inconsistency in cancer outcomes. Finally, one panelist was not surprised about the variable cancer outcomes, given the fact that the occupational studies considered (1) notably different plant settings, (2) employees with widely varying contacts with PCBs, and (3) exposures to different Aroclor mixtures and other contaminants. In short, the panelists did not agree with the arguments provided in the public comment.

- **Inadequate Review of Occupational Epidemiological Studies.** After citing several instances where the toxicological profile made uninformed criticisms of his epidemiological studies, one panelist recommended that ATSDR carefully review all of the profile's discussions on occupational epidemiological studies before releasing the final draft. In general, this panelist was particularly concerned that the profile characterized what he thought were strengths in his study as either weaknesses or limitations (Sinks et al., 1992). More specifically, he thought the profile unfairly criticizes the selection criteria used in his epidemiological study (see pages 39 and 40), and he defended the criteria as a strength, rather than a limitation. This panelist noted that the criteria (e.g., including all plant workers in the study, regardless of their duration of employment) were entirely appropriate for investigating potential dose-response patterns, which would not have been possible if other selection criteria were adopted.

Expanding on these concerns, another panelist identified cases where the profile unfairly criticized "limitations" of Brown's epidemiological studies (page 36) (Brown 1987; Brown and Jones 1981). This panelist did not see a flaw in "combining two plants from different geographical regions," especially because the Brown study reported results for both the combined populations and for the individual plants. This panelist also disagreed with the profile's statement that ". . . the appropriateness of grouping liver, biliary, and gall bladder cancers is questionable," partly because International Classification of Disease (ICD) codes, especially ICD codes for subjects who died more than 30 years ago, might actually support grouping these cancers. The panelist recommended that ATSDR verify whether splitting the cancers would have been defensible before citing this approach as a limitation.

In addition to the previous concerns, some panelists suggested that ATSDR's review of occupational studies comment more specifically on the differences in exposures from one plant to the next. A panelist explained that exposures at the Bloomington plant (a facility considered in one of the studies) were likely considerably different from the exposures at General Electric's plants, due to the plants' differing building configurations, industrial processes, and so on. Echoing this concern, another panelist noted that the plants she has studied use widely varying

amounts of chlorinated solvents and other chemicals that should be considered when interpreting results from these types of studies.

On another note, two panelists cautioned ATSDR about classifying occupational studies by route of exposure, since employees at many plants were exposed to PCBs through some combination of inhalation, oral, and dermal exposures, and the dominant route of exposure could have varied from subject to subject. One of these panelists noted that some of the epidemiological studies currently classified under oral exposure might actually be better classified under inhalation exposure. Both panelists thought the profile should at least acknowledge that most subjects in these studies had multiple exposure routes.

By the end of the meeting, several panelists recommended that the final toxicological profile address cancer retrospective cohort mortality studies more thoughtfully and that the revised profile portray the strengths and limitations of these studies more accurately.

- **The Need for a Comparative Overview of Occupational Cohort Studies.** Some panelists strongly recommended that the profile include a table that compares and contrasts key features of the many occupational cohort studies published on PCBs. The panelists noted that such a table should at least clearly indicate exactly what populations were considered in the cohort studies (some different studies actually considered the same cohorts), the location(s) of the cohorts, the availability of dose information, the type of study (prospective versus retrospective), and possibly a brief summary of findings.

  The panelists thought such an addition was necessary because even researchers familiar with the literature can get easily confused when trying to make sense of the occupational studies. As an example, one panelist noted that David Brown has published more than one paper that has reported elevated liver and rectal cancers among women who were highly exposed to PCBs (Brown 1987; Brown and Jones 1981), but these papers reportedly document effects observed among a single cohort and not three separate cohorts. The panelists worried that an observer unfamiliar with this literature might interpret the results of these three papers as a consistent finding among separate studies, when, in fact, the papers present a single finding that has been observed in one cohort. The panelists thought the profile should not be ambiguous in this regard.

- **Organization of the Discussions on Cancer.** Noting that he had difficulties quickly identifying the profile's review of PCBs and brain cancer, one panelist recommended that the profile have just one section in Chapter 2 on cancer, with separate sub-sections that address the different types of

cancers. Further, some panelists thought the profile should adopt a more systematic approach for presenting the studies relevant to cancer, possibly by presenting occupational studies first, followed by non-occupational studies, studies evaluating exposures from fish consumption, case-control studies, and animal studies.

- **Lack of Emphasis on Gender Differences.** During their discussions, the panelists identified several instances where gender differences were apparent, but not documented in the profile. For instance, some of the human studies have found notable gender differences, as have selected animal studies (Mayes et al., 1998). As a result, some panelists thought discussion of gender differences should not be limited to the LSE tables, but should also be discussed in the text on cancer effects, and possibly in the Relevance to Public Health or Public Health Statement sections.

- **Public Comment on the Implications of the Most Recent Kimbrough Study.** Citing quotes from a press release that reportedly overstated the findings of the recent Kimbrough cancer study (Kimbrough et al., 1999), a public comment suggested that ATSDR carefully review this study in the final profile. When discussing this comment, copies of a recent letter to the editor criticizing the Kimbrough study (prepared by ATSDR scientists) were distributed to the panelists (Bove et al., 1999). Representatives from ATSDR gave an overview of their findings, after which panelists commented on the Kimbrough study. One panelist noted that some of the limitations identified in ATSDR's review are simply inherent limitations in cohort mortality studies, but this panelist did question some of the data interpretations cited in the Kimbrough study. As an example, this panelist thought the study's data are suggestive of female intestinal cancer—a conclusion that is apparently not reached in the paper.

- **Public Comment on Links Between PCBs and Melanoma.** A public comment indicated that the profile overstates the association between PCBs and melanoma that was reported by Loomis et al (1997). The panelists disagreed with this comment, noting that Loomis' analysis of dose-response was an accurate depiction of the cancer outcomes, contrary to the arguments presented in the comment. Moreover, some panelists noted that consistent findings from another study (i.e., Sinks et al., 1992) provide compelling evidence for the association, despite the known genetic and behavioral risks of melanoma.

- **Public Comment on the Profile's Characterization of Breast Cancer Studies.** A public comment criticized the profile for providing inaccurate and incomplete information on the association between PCBs and breast cancer in humans. When reviewing ATSDR's proposed

disposition of this comment, the panelists revisited many of the topics they discussed during their earlier review of endocrine effects (see Section 3.2.4 of this report).

In general, the panelists agreed on some aspects of the profile's review of breast cancer, but disagreed on others. The main point of agreement was that the profile should discuss breast cancer primarily in the "Cancer" sections and not in the "Endocrine Effects" sections. Another point of agreement was that the profile does not provide a balanced review of the current scientific literature, but the panelists had differing recommendations for how ATSDR should address this. Some panelists thought the profile should include a more thorough review of the various studies on breast cancer, reflecting the differing quality of these studies. Several panelists, on the other hand, thought including additional information was unnecessary, suspecting that a thorough review of the literature on breast cancer and PCBs would take too much room in the profile on a topic that is still widely debated.

The main point of contention was whether the toxicological profile should discuss the xenoestrogen/breast cancer theory in the first place. Consistent with their earlier debates, some panelists thought the theory should be omitted from the profile, but others disagreed and thought the profile should briefly mention the theory, along with its uncertainties.

As general comments on PCBs and breast cancer, one panelist recommended that ATSDR integrate summary statements from Hunter's recent review article on breast cancer (Hunter et al. 1997). Another panelist thought the profile should indicate that some genetically vulnerable populations might be more susceptible to carcinogenic effects, which might explain some of the variable results from the epidemiological studies. Other panelists questioned whether the Public Health Statement (page 7) should claim that PCBs "may play an import role in causing breast cancer," given the debate that continues to surround this hypothesis. Finally, one panelist recommended that the profile should note that pre-menopausal and post-menopausal breast cancers might have different etiologies.

As noted earlier, additional comments regarding the profile's handling of breast cancer can be found in Section 3.2.4, above.

- **Comments on PCBs and Non-Hodgkin's Lymphoma.** A public comment thought the profile grossly overstated the findings of the Hardell study on the links between PCBs and non-Hodgkin's lymphoma (Hardell et al., 1996). Two panelists agreed with this comment. Noting that the Hardell study did not directly examine immune markers or any other immune effects, one panelist

thought the profile should not state that this study's ". . . data suggest that the immunosuppressive effects of PCBs may relate to the etiology of non-Hodgkin's lymphoma" (page 139). This panelist instead thought the profile should simply state the main finding of the Hardell study—elevated PCB levels were found to be associated with some cases of non-Hodgkin's lymphoma. The other panelist did not think the profile should report hypothetical mechanisms, especially when little evidence of the mechanisms exist.

The panelists discussed several general issues related to the profile's discussion on non-Hodgkin's lymphoma. First, noting that immunosuppression accounts for a very small portion of non-Hodgkin's lymphoma cases, one panelist emphasized that the absence of evidence linking PCBs to immunosuppression does not necessarily contradict apparent associations between PCBs and non-Hodgkin's lymphoma. Second, though the mechanisms of action might not be known, two panelists thought the profile should underscore the consistent findings of the Hardell study and selected occupational studies (e.g., Betrazzi et al., 1987). One panelist added that the absence of consistent evidence across every occupational study might simply result from the rarity of non-Hodgkin's lymphoma, and not from a lack of association between PCBs and this cancer. Third, the panelists suggested additions to the profile's section on mechanisms of PCBs and non-Hodgkin's lymphoma: One panelist indicated that this mechanism is clearly not Ah receptor mediated; another panelist thought the profile should acknowledge other potential mechanisms (e.g., immunosuppression and reactive oxygen species) for all types of cancers, but some panelists cautioned about including too many hypotheses and theories on cancer mechanisms in the profile.

- **Public Comment on the Rothman Study (1997).** A public comment recommended that the profile note that Rothman's 1997 research on non-Hodgkin's lymphoma was conducted primarily to generate hypotheses and that further research is required to confirm its theories. A panelist clarified that the Rothman study was not designed to generate hypotheses; rather, the study's original design was reportedly to examine associations between cancer outcomes and DDT, but the study happened to generate hypotheses by virtue of its findings specific to PCBs. No other panelists addressed this comment.

- **Public Comment on Sensitivity of Younger Animals to Carcinogenic Effects of PCBs.** A public comment indicated that experimental studies do not suggest that younger animals have greater sensitivity to carcinogenic effects of PCBs. Two panelists disagreed with this comment, however, noting that Dr. Lucy Anderson has published several studies documenting differential sensitivity of immature animals to PCB-related carcinogenic effects (Anderson et al. 1983, 1986, 1993). Further, another panelist noted that studies by Rao and Banerji have characterized PCB-

related carcinogenic effects in 5-week old rats, though these studies did not compare the sensitivity of the immature rats to adult rats (Rao and Banerji 1993).

- **Public Comment on the Bahn et al. Study (Bahn et al. 1976, 1977).** Noting that Bahn's study is in fact a letter to the editor that reports preliminary data, a Submitter suggested that the profile place a lesser emphasis on its results. One panelist thought this particular letter to the editor was an important contribution to the literature, even though Bahn's study results were never published. No other panelists commented on this study.

- **MRLs and Cancer Endpoints.** One panelist wondered if ATSDR will derive an MRL or some other advisory limit that reflects carcinogenic endpoints. Other panelists and ATSDR scientists explained that the MRLs, by definition, are based strictly on non-carcinogenic effects and that ATSDR, as per policy, does not derive advisory limits for cancer effects. Rather, the Agency simply defers to EPA's cancer slope factors for such limits, if appropriate.

- **General Comments on PCBs and Cancer.** When reviewing the profile's treatment of PCBs and cancer, some panelists made general comments that do not fit under the categories described above. Examples of these comments follow: (1) One panelist thought the toxicological profile's summary of Rothman's paper overlooked a notable finding—a potential interaction between cancerous effects and the Epstein-Barr virus. (2) One panelist noted that IARC's document on the carcinogenicity of dioxin reviews studies of cancer among the Yusho and Yu-Cheng populations that might be relevant for the profile on PCBs (Hsu et al. 1985; Kuratsune et al. 1987). (3) One panelist thought the discussion of breast cancer on pages 138 and 139 was unclear, because it did not clearly distinguish the study of fisheaters from the study of blood donors. (4) One panelist indicated that the review of the Mayes animal study should note that dibenzofurans were largely removed from the Aroclor 1254 mixtures that were administered to the rodents, thus strengthening the toxicological implications of the study. (5) One panelist recommended that the profile address cancer slope factors in the section on Relevance to Public Health (Section 2.5), given that these factors have implications to dermal and inhalation routes of exposure. (6) On the topic of PCBs and brain cancer, one panelist thought the profile should consider studies published by Health Canada, Loomis, and Greg Steele (Loomis et al. 1997; the reviewers did not provide references for the studies reportedly conducted by Health Canada and Greg Steele).

3.2.6 Reproductive Effects

The panelists stepped through the three public comments regarding reproductive effects. They had no comments on ATSDR's proposed disposition of two comments, but they did discuss the proposed

disposition of the third. An overview of this discussion, plus general comments on PCB-related reproductive effects, follow:

- **Public Comment on the Presentation of Endometriosis Studies.** A public comment took exception to how the profile presented information on PCBs and endometriosis, particularly the profile's suggestion that ". . . endometriosis is known to occur following exposure to dioxin and some dioxin-like chemicals" (page 122). One panelist thought the profile should include a summary of studies that link dioxin to endometriosis, so long as the profile clearly acknowledges that links between PCBs and endometriosis have not been identified. However, noting that the mechanisms of action of dioxins and coplanar PCBs are similar, this panelist indicated that the lack of information on PCBs and endometriosis does not necessarily imply that the two are completely unrelated.

  When discussing this topic, one panelist cited results from Arnold's study on endometriosis in rhesus monkeys: The study reportedly found no correlation between PCB exposure and the incidence of endometriosis, but the study found that monkeys who were fed Aroclor 1254 had longer average menses duration and a shorter average menstrual cycle length than the untreated monkeys (Arnold et al., 1996). Noting that the group of monkeys considered in this study was relatively old, one panelist suggested that a similar study of a younger group of monkeys might generate different results. No other panelists commented on the potential links between PCBs and endometriosis.

- **General Comments on Reproductive Issues.** One panelist thought the profile should have commented more thoroughly on the findings of the Buffalo fisheater study that are relevant to reproductive effects, such as the observed late fetal loss, changes in menstrual cycles, and time-to-pregnancy effects. Noting that some of these findings are currently classified under developmental effects (Section 2.2.2.6), this panelist recommended that the profile clearly state how ATSDR distinguishes research on developmental from research on reproductive effects. Another panelist recommended that the profile document Barsotti's findings regarding reduced reproductive performance in rhesus monkeys up to 5 years following the cessation of dosage of Aroclor 1248 (Barsotti et al., 1976).

3.2.7 Toxicokinetics

Most of the panelists did not comment on Section 2.3 of the profile. As an exception, one panelist recommended that ATSDR review its statements on distribution of PCBs to reflect the most recent information available, particularly congener-specific data. This panelist thought the profile had confusing

statements on serum-adipose partitioning (page 160) and should have offered more detail on distribution of PCBs following oral exposure. He thought the profile's treatment of metabolism was adequate.

3.2.8 Mechanisms of Action

When reviewing information on the toxicological endpoints, the panelists offered two general comments on Section 2.4 that are not listed in the previous subsections. First, one panelist recommended that the section on mechanisms of toxicity acknowledge the research by Isaac Pessah on the ryanodine receptor (Pessah 1997; Wong and Pessah 1996, 1997). This panelist believed Pessah's work has noteworthy implications both because it points to a receptor-mediated mechanism for the non-dioxin-like PCB congeners and because the structure-activity data for this receptor correlate with the structure-activities for selected neurotoxic effects. Second, two panelists strongly disagreed with the statement in the profile, "Most of the non-neural toxic and biochemical effects of PCBs occur via a signal transduction pathway involving the Ah receptor" (page 197). They believed that most of these effects occur via pathways that do not involve the Ah receptor and suggested some of these pathways be discussed in the profile.

3.2.9 Reducing Peak Absorption Following Exposure

One panelist recommended, and another agreed, that ATSDR delete or thoroughly revise Section 2.11.1 (Reducing Peak Absorption Following Exposure) because he was unaware of any method, except possibly for lactation, that effectively reduces PCB body burdens in exposed individuals. Another panelist agreed that medical intervention cannot reduce PCB body burdens, but he added that physicians can offer recommendations for minimizing the toxic effects of exposures.

3.3 Comments on Chapter 3—Chemical and Physical Information

The expert panel reviewed ATSDR's proposed disposition of the two public comments relevant to Chapter 3 and offered general comments on the chapter. A summary of the panelists' discussions follows:

- **Public Comment on "Heavy 1254."** A public comment recommended that Chapter 3 include information on "heavy 1254"—a PCB congener mixture similar to Aroclor 1254, but containing higher amounts of dioxin toxic equivalents. One panelist agreed with the comment, particularly because the congener profile for any mixture affects the results and interpretations of human and animal studies. This panelist recommended that the profile indicate the relative toxicity of "heavy 1254," to the extent that such information is available.

- **Public Comment on Revising Table 3-5.** A public comment recommended that ATSDR update Table 3-5 in the profile with more recent information on the congener composition of various Aroclors. The panelist who provided the updated information noted that the data were originally compiled by George Frame, and recommended that ATSDR cite his effort if the Agency uses the revised table in the final profile (Hansen 1999).

- **General Comments on Chapter 3.** The panelists offered several general comments on the profile's presentation of chemical and physical properties of PCBs. First, two panelists thought Chapter 3 should include text that describes, even if generally, how the various chemical and physical properties of PCBs affect environmental distribution and the potential for human exposure. These panelists also recommended that the profile indicate how PCB properties are, to a certain extent, dependent on the number of chlorine atoms in a given congener (e.g., lower-chlorinated PCBs tend to be more water soluble and volatile than the higher-chlorinated PCBs), though they acknowledged that such information could also be logically presented in other chapters of the profile.

  An observer indicated that the profile incorrectly identifies the reasons why PCBs were originally used in industry (page 274). This observer noted that fire resistance, rather than chemical inertness, was the primary factor for selecting PCBs for various applications. Consequently, this observer took exception to the profile's characterization of PCBs as "combustible liquids" (also on page 274). ATSDR's profile contractor suspected that this characterization was taken from a Department of Transportation designation of PCB properties, but no panelists or observers could confirm this explanation.

  Based on an observer comment, one panelist recommended that the profile provide more detailed information on the chemicals that can be formed upon combustion of PCBs. The observer acknowledged that data suggest that PCBs form furans upon combustion, as the profile indicates, but he did not think sufficient data were available to confirm that PCBs form dioxins. This observer noted that model compound studies have suggested that chlorinated benzenes, which are often found in PCB mixtures, form dioxins upon combustion, but he was unaware of any similar studies suggesting that PCBs form dioxins. Questioning this position, a panelist thought studies of the Yusho incident reported that trace amounts of dioxins were formed upon heating PCB mixtures, but the observers indicated that most of the data suggested otherwise and that only very limited data of questionable quality indicated that PCBs might form dioxins. Overall, the observers and some panelists recommended that ATSDR review its discussion of combustion by-products accordingly (page 274).

Finally, after discussing the history of how PCBs have been used in industry, one panelist recommended that the profile mention the different chemicals, such as chlorobenzenes, that are commonly found in PCBs. This suggestion followed an observer comment on past use of Askarels—a generic grouping of non-combustible electrical fluids that contained PCBs and often, though not always, contained chlorobenzenes. Also relevant to this discussion was the observation that many companies altered the composition of PCB mixtures that were originally prepared by manufacturers.

3.4 Comments on Chapter 4—Production, Import/Export, Use, and Disposal

The panelists reviewed the nine public comments ATSDR received on topics in Chapter 4 and the Agency's proposed disposition of these comments. With one exception, the panelists and observers had no additional comments on these topics. Two panelists, however, agreed with the public comment suggesting that ATSDR should consider deleting the entire last paragraph in Chapter 4 (pages 303 and 304), which addresses remedial options for PCB-contaminated sites. The Submitter and the two panelists were concerned that, in this paragraph, ATSDR was "identifying preferred remedial alternatives"—an issue that EPA typically addresses. One panelist suggested that ATSDR merely present the various remedial options without commenting on which options are preferred.

An ATSDR scientist provided one additional comment on Chapter 4, suggesting that ATSDR reconsider including discussions on specific clean-up levels for PCBs in soils (page 302), since some readers might infer that the listed levels should apply to all PCB-contaminated sites. If ATSDR retains the information on soil clean-up levels, one panelist recommended that the profile indicate the soil depth over which these levels apply.

3.5 Comments on Chapter 5—Potential for Human Exposure

The expert panel and observers discussed selected public comments ATSDR received on Chapter 5 of the profile. A summary of this discussion follows:

- **Clarification of Exposures Due to Fish Consumption.** One panelist strongly recommended that ATSDR reconsider the profile's summary statements about how the general population is exposed to PCBs. This panelist emphasized an important distinction that the profile should make: Consumption of fish caught in PCB-contaminated waters leads to notably different exposures than consumption of fish purchased in stores. Moreover, this panelist added that the general population primarily consumes tuna, shrimp, catfish, and salmon, all of which reportedly have extremely low PCB levels or no measurable PCBs. Another panelist agreed with this comment.

- **Public Comment on the Reported Serum Levels of PCBs.** A Submitter recommended that ATSDR provide additional context for the serum levels of PCBs (4–8 ppb) reported in the toxicological profile. Some panelists strongly agreed with this sentiment. One suspected that the reported serum levels are based on relatively old data and should be updated with recent figures, if available. After emphasizing that the reported serum levels can have great implications on current public health studies, this panelist recommended that ATSDR carefully consider this public comment and properly caveat the estimated serum levels as necessary. Further, an observer thought the profile should indicate that PCB serum levels generally increase with age. Finally, two panelists suggested that Health Canada might have more recent data for commenting on serum levels of PCBs.

- **Public Comment on the Presentation of Dated Information.** Noting that the profile currently cites some dated exposure concentrations, one Submitter recommended that the document clearly differentiate typical exposure concentrations observed in the past from those observed today. Agreeing with this comment, some panelists noted that much of the exposure concentration data in Chapter 5 is dated. For instance, one panelist indicated that the U.S. Food and Drug Administration (FDA) has recently published information on dietary levels of PCBs that the profile does not cite (a citation for this study was not provided). Reviewing trends in these data, this panelist indicated that current quarterly "market basket" studies now rarely show PCBs at quantitative levels (50 ppb). He added that these current PCB levels are considerably lower than levels that were observed during the 1970s—a trend that several panelists thought the profile should mention. Some panelists wondered whether the average daily intake, when normalized to body weight, suggested by the market basket studies currently exceeds ATSDR's proposed MRL. This issue was not resolved during the meeting.

- **Public Comment on Current Occupational Exposures to PCBs.** One Submitter thought the profile included an inaccurate account of current occupational exposures to PCBs (". . . occupational exposures to PCBs remains several orders of magnitude higher than general population exposure," page 308). Agreeing with this comment, one panelist noted that elevated PCB body burdens in individuals with occupational exposures might primarily reflect past exposures, and provide little insight into current exposure levels. Based on this and other arguments, some panelists recommended (and an observer agreed) that Chapter 5 better reflect how PCB exposures have changed in occupational settings over the years and specifically identify the occupations that likely have the greatest potential for exposure to PCBs today.

- **Public Comment on Comparability of Various Human Monitoring Findings.** One Submitter suggested that the toxicological profile summarize the significance of the different sampling media (e.g., blood serum, breast milk, and adipose tissue). One panelist indicated that ATSDR could respond to this comment by providing general guidelines for estimating PCB levels in one medium from reported PCB levels in another medium. Other panelists cautioned, however, that such simple partitioning guidelines would likely not apply to all PCB congeners and that congener-specific partitioning has not been extensively documented in the scientific literature.

- **Public Comment on PCB Exposures via Contaminated Drinking Water.** A Submitter took exception to statements in the profile which imply that ingesting contaminated drinking water might be a relevant source of exposure to PCBs ("The general population may be exposed to PCBs by inhaling contaminated air and ingesting contaminated water and food," page 307). Noting that PCBs are extremely hydrophobic compounds, one panelist agreed with the public comment, even for historical exposures. Another panelist, on the other hand, did not think such statements should be removed from the profile entirely, since "raw water" with high amounts of suspended solids could be a viable exposure pathway for PCBs and since PCBs in water are the major source of contamination to fish. Accordingly, this panelist encouraged that ATSDR acknowledge (rather than ignore) the various potential exposure pathways for PCBs, and put them into proper perspective.

- **Public Comment on Atmospheric Removal Processes.** A public comment questioned whether photolysis is the dominant removal pathway for airborne PCBs, as the profile currently suggests (page 306). One panelist thought precipitation, not photolysis, is the dominant removal pathway.

- **General Comments on Chapter 5.** When addressing the public comments, the panelists offered the following general insights on the technical content of Chapter 5. First, one panelist thought the profile should clearly indicate that the PCB congener profile in most inhalation exposures considerably differs from that in oral exposures. This panelist also thought the profile's discussion of indoor air exposures places too great an emphasis on PCBs in occupational settings, especially considering that PCBs are now almost never used in industry. Second, one panelist noted that the profile currently uses inconsistent terminology when referring to FDA's tolerance on PCBs in fish. He explained that this tolerance is a regulatory standard (not a guidance) and is based on PCBs in edible tissue (not a lipid-adjusted value). Another panelist, in response to a public comment, recommended that the profile include a reference for its information on PCB degradation in contaminated sewage sludge (page 305). Yet another panelist, when responding to a different

public comment, suggested that ATSDR consider data from the National Human Exposure Assessment Survey (NHEXAS), if these data are available.

3.6 Comments on Chapter 6 to Chapter 9

The panelists did not specifically discuss topics in Chapters 6 through 9 of the profile. It should be noted that ATSDR received very few public comments on Chapters 6 and 7, and no public comments on Chapters 8 and 9. However, one panelist mentioned a paper by Brock et al., 1996, in the Journal of Analytical Toxicology, which outlines a specific approach for determining PCBs and pesticides in serum using capillary gas chromatography with electron capture detection.

3.7 Comments on Appendix A—ATSDR Minimal Risk Levels and Worksheets

The panelists discussed at length the scientific basis of ATSDR's proposed approach for deriving MRLs for PCBs. The draft toxicological profile includes only a chronic oral MRL (0.02 μg/kg/day), which is based on immunological effects observed in rhesus monkeys. Before the panelists commented on the MRL for PCBs, ATSDR distributed handouts that define the MRL and how it is typically derived, including how uncertainty factors enter into MRL derivations. After the panelists reviewed this information, they discussed many topics relevant to the MRL for PCBs.

Overall, the panelists' discussion raised several important issues. First, though the panelists generally approved of ATSDR's derivations of the MRL based on the Tryphonas study (see Section 3.7.1 of this report), they highly recommended that ATSDR consider the human studies reviewed by Tilson et al. (1990) as a supplemental basis for the MRL. This study is reviewed in Section 3.7.2, below. Moreover, the panelists recommended that ATSDR consider an additional animal study as a basis for developing an intermediate oral MRL. Section 3.7.3 of this report summarizes their discussion regarding this study by Dr. Deborah Rice. Section 3.7.4 then reviews general comments the panelists made when discussing MRLs for PCBs, including mention of an additional human study that could be used to derive the MRL, but was not reviewed extensively during this discussion.

As reviewed below, the panelists suggested ATSDR conduct evaluations of studies in addition to the Tryphonas study to support the proposed MRL. Specifically, the panelists presented some information suggesting that neurological endpoints might be more sensitive than immunological endpoints and therefore a more appropriate basis for the MRL. The panelists reached no conclusions on this hypothesis, though, due to recognized limitations in the human studies reviewed by Tilson et al. (1990) and questions regarding ATSDR's use of uncertainty factors. Nonetheless, *the panelists underscored the fact that the dose-response data from two considerably different studies (and possibly more) paint a very consistent picture regarding health-guidance values for PCBs: An animal study and a*

human study, both of which considered different exposure doses and toxicological endpoints, suggest notably similar chronic oral MRL levels. The panelists recommended that ATSDR carefully evaluate the strengths and limitations of both studies before proposing its final chronic oral MRL for PCBs.

The observers made no comments on the panelists' discussion of MRLs.

3.7.1 Tryphonas Study (Tryphonas et al. 1989, 1991b)

Before the panelists discussed the public comments on ATSDR's proposed MRL, the Chemical Manager for the Toxicological Profile for PCBs described how ATSDR derived the chronic oral MRL for PCBs from the research conducted by Dr. Helen Tryphonas. The Chemical Manager explained that this study examined immunological effects among female rhesus monkeys that were exposed to Aroclor 1254 for 55 months. In general, monkeys that received Aroclor 1254 doses as low as 0.005 mg/kg/day had significantly reduced levels of antibody production in responses to challenges of sheep red blood cell antigens, while monkeys that received no doses did not have impaired immune responses. Therefore, the study reported a lowest-observed-adverse-effect level (LOAEL) of 0.005 mg/kg/day. The Chemical Manager then explained why ATSDR proposed applying three uncertainty factors to this LOAEL to derive an MRL: The Agency used a factor of 10 to extrapolate the LOAEL to a no-observed-adverse-effect level (NOAEL); a factor of 3 to extrapolate from animal studies to humans; and a factor of 10 to account for human variability. Accounting for these factors, the Chemical Manager noted that ATSDR proposed a chronic oral MRL of 0.02 μg/kg/day.

Some panelists highlighted the strengths of the Tryphonas study. For instance, one panelist noted that the study used a relatively large sample size, especially when compared to other studies involving rhesus monkeys. Another panelist added that the Tryphonas study was very carefully controlled and provides data on immunological effects for a wide range of PCB doses, while controlling for confounding factors that are unavoidable in human studies (e.g., exposures to other persistent, bioaccumulative toxins). After extensive debate and discussion on the merits of this study, none of the panelists identified critical shortcomings of the Tryphonas study.

The expert panel subsequently reviewed the public comments that ATSDR received on this study, and Dr. Tryphonas herself provided key insights to her work. An overview of these comments, and the panelists' responses, follows:

- **Public Comment on the Improper Selection of Toxicologic Endpoint for the MRL.** Based on concerns regarding the Tryphonas study (as outlined below), one public comment suggested that ATSDR should not base its chronic oral MRL on the immunotoxicity of PCBs. None of the

panelists agreed with the Submitter's criticisms, and Dr. Tryphonas was particularly confident that the immunological endpoint was an appropriate basis for ATSDR's MRL. Dr. Tryphonas acknowledged that evidence of PCB-related immunotoxicity has not been closely monitored in human studies. Nonetheless, she noted that many human studies provide accounts of adverse immunological effects following exposures to PCBs. As examples, she highlighted findings of relevant human studies:

Children born to women in Michigan and Wisconsin who ate fish from the Great Lakes suffered from higher incidence of infections (primarily bacterial) during their first 4 months of life, when compared to other infants (Swain 1991); infants born to women who were exposed to Kanechlor 500 and Kanechlor 300 had a higher incidence of colds and other infections when compared to infants born to women who were not exposed to these Kanechlors (Hara 1985); and 6-year old children from the Yusho and Yu-Cheng incidents had a higher incidence of bronchitis and ear infections, thus suggesting an immunological impairment[1] (Chao et al. 1997; Rogan et al. 1988). Though she noted that the aforementioned human studies all have limitations preventing one from concluding that PCBs cause immunological effects in humans, Dr. Tryphonas felt that the combined evidence from these and other studies suggest that PCBs are indeed toxic to the human immune system and that basing the MRL on immunotoxic effects is entirely appropriate.

Another panelist agreed with Dr. Tryphonas' arguments. He added that his experience as a researcher for EPA on Aroclor 1254 has found that immunotoxicity is a critical adverse effect associated with exposure to PCBs. This panelist noted that the Levinskas study found a dose-response relationship for clinical manifestations of PCB-related immunotoxicity in rhesus monkeys (Levinskas et al. 1984). Based on this study and other studies, this panelist was also convinced that basing the MRL on immunotoxic effects was appropriate.

- **Public Comment on the Clinical Relevance of the Tryphonas Study.** One public comment suggested that ATSDR not base its MRL on the Tryphonas study because the observed immunological effects have little clinical relevance to humans. Dr. Tryphonas again disagreed, for

[1] Dr. Tryphonas indicated that the children considered in the Yusho and Yu-Cheng incidents did not have abnormally low levels of natural killer (NK) cells or immunoglobulin. However, Dr. Tryphonas noted that the NK cell numbers do not necessarily correlate with the functional activity of the NK cells and that immunoglobulin levels typically are only lowered by "great insults" to the immune system. Therefore, she concluded that people with normal NK cell numbers and immunoglobulin levels might still have compromised immune function. Similarly, Dr. Tryphonas also explained why a study of immunotoxic effects in transformer repairmen found negative results (Emmett et al. 1988): She noted that this study's negative results were for *secondary* immune responses, and that examining changes in secondary responses might fail to identify important effects to the primary (humoral) response.

several reasons. First, she defended her choice of the sheep red blood cell antigen partly due to its widespread use in animal studies to characterize immunotoxic effects of pollutants. In fact, Dr. Tryphonas noted that during the November 1996 meeting of the "Ad Hoc Organization for Economic Cooperation and Development (OECD) Workshop on Immunotoxicity Testing," the use of the plaque-forming cell assay, which uses the sheep red blood cell antigens, was unanimously proposed as the standard functional assay for the screening of chemicals for potential immunotoxic effects using animal models.

Second, Dr. Tryphonas indicated that other researchers have reported that immune responses to the sheep red blood cell antigen in animals are highly predictive of these animals' responses to selected infectious agents (Luster et al. 1988, 1992). Moreover, her ongoing research on the immunotoxic effects of toxaphene has indicated that Cynomolgus monkeys have immune responses to the tetanus toxoid comparable to the responses to sheep red blood cells, thus providing evidence that animal responses to the sheep red blood cells might be clinically relevant to the toxins that humans encounter.

Finally, Dr. Tryphonas explained that the general mechanism of the primary immune response to the sheep red blood cells in rhesus monkeys (e.g., uptake and processing of the antigen by macrophages, presentation of the antigen fragments to T lymphocytes, and subsequent production of specific antibodies by the B lymphocytes) is similar to the humoral response expected to occur in humans. However, noting that researchers will likely never conduct human testing with sheep red blood cells, Dr. Tryphonas acknowledged that the clinical relevance of humans' immune response to sheep red blood cell antigens can only be hypothesized and not quantified.

For these reasons, Dr. Tryphonas believed that the implications of her research are clinically relevant to humans. Other panelists did not comment on this topic.

- **Public Comments that Rhesus Monkeys are a Poor Model of PCB Toxicity in Humans.** Two public comments argued that rhesus monkeys and humans have different metabolic pathways for PCBs, which, in turn, lead to different health effects in exposed rhesus monkeys and humans. The Submitters thus concluded that the immunologic effects observed in rhesus monkeys might be completely irrelevant to humans. None of the panelists agreed with this comment, as described below.

First, Dr. Tryphonas discussed the Submitters' assertion that rhesus monkeys are more sensitive to PCBs than humans. Noting that this comment on sensitivity is apparently based on information

documented in an abstract ("Gillis and Price, 1996"), and not in the peer-reviewed literature, Dr. Tryphonas questioned the validity of the assertion. On another note, Dr. Tryphonas did not agree that pathways for PCB metabolism differ qualitatively between rhesus monkeys and humans, as one Submitter suggests. In fact, according to research carried out in monkeys (Arnold et al. 1993), Dr. Tryphonas indicated that the congener profile of PCBs measured in rhesus monkeys that were administered orally a mixture of PCB congeners typically found in human breast milk tends to match closely the profile observed in human blood (Kreiss 1995) and human breast milk (Dillon et al. 1981). Even if qualitative metabolic differences existed, however, Dr. Tryphonas still cautioned that they would not necessarily imply that rhesus monkeys are somehow more sensitive to PCBs than humans.

Other panelists provided additional insight on this public comment. For instance, based on the studies reviewed by Tilson et al. (1990) (see Section 3.7.2, below), one panelist noted that published research has suggested that rhesus monkeys might actually be less sensitive than humans for developing PCB-related health effects—in this case, behavioral or neurodevelopmental effects. Another panelist agreed, and added that his experience reviewing animal studies has not suggested a considerable sensitivity among rhesus monkeys to PCBs.

- **Public Comment on the Proposed Uncertainty Factors for the MRL.** One public comment suggested that the chronic oral MRL for PCBs should be based only on an overall uncertainty factor of 30, instead of 300.[2] Noting that her study examined immunological effects only among middle-aged rhesus monkeys, Dr. Tryphonas advocated the use of conservative uncertainty factors for deriving the MRL, since certain human groups—children, the elderly, and immunosuppressed populations—might be much more susceptible to PCB-related immunological effects; she thought an uncertainty factor of 300 was appropriate. Another panelist agreed, and recommended the Agency continue to use an overall uncertainty factor of at least 300; yet another panelist thought a case could be made for applying an additional uncertainty factor of 10 (for a total factor of 3,000) to account for children's susceptibility. On the other hand, because the Tryphonas study considered some elderly rhesus monkeys, one panelist added that a case can be made for using less conservative uncertainty factors.

[2] Technically, the Submitter's recommendation was that the MRL should be based on the dermal, ocular, and nail effects observed in the rhesus monkeys of the Tryphonas study. The Submitter proposed using an uncertainty factor of 30 for an MRL based on that endpoint. However, the panelists' comments focused on the use of uncertainty factors for the endpoint of immunological effects. In response to an earlier comment, the panelists agreed that basing the MRL on immunological effects was appropriate.

- **Public Comment on the Representativeness of an MRL Based on Exposure to Aroclor 1254.** One Submitter noted that the Tryphonas study used doses of unweathered Aroclor 1254, rather than doses of weathered PCBs, like those typically observed in the environment. Speculating that weathered PCBs are more toxic than the unweathered mixtures, this Submitter thought the MRL based on the Tryphonas study might understate risks of ingesting PCBs. Disagreeing with the Submitter's reasoning, one panelist did not think the available environmental sampling and toxicological data supported a blanket judgment that weathered PCBs in the environment are indeed more toxic than unweathered Aroclor 1254. As a result, this and another panelist did not agree with the Submitter's comment. No other panelists commented on this issue.

3.7.2 Studies Reviewed by Tilson et al. (1990)

Dr. Walter Rogan recommended that ATSDR consider deriving its MRL based on the findings of the studies reviewed by Tilson et al., which included Dr. Rogan as a contributing author (Tilson et al., 1990). This study examined neurodevelopmental effects in cohorts of children in Michigan and North Carolina and reported a NOAEL for 95 percent of the cohort of 0.093 μg/kg/day—a NOAEL that represents the estimated daily dose that mothers can receive before adverse neurodevelopmental effects are observed in their offspring. The mothers in this study were not exposed to PCBs in occupational settings. Before the panelists commented on this recommendation, Dr. Rogan briefly reviewed key aspects of the studies reviewed by Tilson et al. (1990).

Dr. Rogan explained that this study used various metrics (e.g., the Brazelton Neonatal Behavioral Assessment Scale or the Bayley Scales of Infant Development) to determine whether children in the two cohorts developed normally or abnormally. Based on the motor development index, which quantifies children's abilities to stack blocks, dump raisins out of bottles, and so on, Dr. Rogan found that the children whose mothers had PCB concentrations in breast milk fat of 3.4 ppm or greater had statistically significant lower test results than the other children in the cohorts. In short, the breast milk fat concentration of 3.4 ppm was the highest PCB level in mothers below which no adverse health effects were observed in their children. This general trend was reportedly observed among the children at age 6 months, 12 months, 18 months, and 24 months, and was also observed for various other developmental metrics (e.g., IQ data). In fact, Dr. Rogan indicated that decreased visual recognition memory actually occurred among children whose mothers' breast milk fat concentration was 1.0 ppm, but this metric was used only in the Michigan cohort and not in the North Carolina cohort.

Because PCB doses were not measured in the Michigan and North Carolina studies, the researchers had to estimate the daily exposure of PCBs that would result in a mother having a breast milk fat concentration of 3.4 ppm at the time of delivering a child. Dr. Rogan listed the computational steps

and assumptions that were made to estimate this dose. First, the researchers estimated that a 25 year old woman who weighed 60 kg, had 25 percent body fat, and had 3.4 ppm of PCBs in her breast milk, likely had an overall body burden of 51 mg of PCBs. Dr. Rogan indicated the assumptions that were made in this calculation, such as the concentration of PCBs in a woman's breast milk fat were assumed to be equal to the concentration of PCBs in the fat throughout the rest of the body. Second, assuming that the 51 mg body burden is a result of a lifetime of low-level PCB exposure without any excretion, the researchers estimated that women with 3.4 ppm in their breast milk fat had an average daily PCB intake of 5.6 μg/day. Normalizing this to the average body weight of a 25-year-old woman (60 kg), this daily intake translates into a daily dose of 0.093 μg/kg/day—the dose that Dr. Rogan and his colleagues reported as a NOAEL for neurodevelopmental effects.[3]

Before the panelists commented on this study, Dr. Rogan listed several uncertainties associated with his dose calculations. First, because losses of PCBs through excretion, lactation, and metabolism were not factored into the dose calculations, the actual dose that results in 3.4 ppm of PCBs in breast milk fat would be higher than the reported NOAEL. Second, if dose calculations were based on women older than 25 years, the estimated daily dose would be lower than the reported NOAEL. Moreover, a difference in the analytical methods used in the Michigan study and the North Carolina study also might have caused the researchers to overestimate the actual NOAEL, possibly by a factor of 2.

Following this presentation, the panelists and ATSDR scientists discussed whether the studies reviewed by Tilson et al. (1990) can serve as an alternative basis for the chronic oral MRL. Some panelists noted that the data from the paper provide a very realistic account of environmental exposures, since the study considered humans who are exposed to low-level PCB doses through their everyday activities. However, other panelists highlighted corresponding limitations, such as the fact that the subjects in the Michigan and North Carolina studies were undoubtedly exposed to many other persistent, bioaccumulative toxins (e.g., dioxins) that might account, at least in part, for the observed health effects. In short, some panelists cautioned that one cannot be certain that the health effects resulted directly from PCB exposure, even though the study's evidence strongly suggests this is the case. Finally, some panelists recommended that ATSDR consider the uncertainties inherent in back-calculating exposure

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[3] The calculations described above can be summarized as:

Body Burden = (Body Weight) x (Body Fat Percentage) x (PCB Concentration in Fat)
= (60 kg) x (25%) x (3.4 mg PCB/kg fat)
= 51 mg PCBs

Dose (NOAEL) = (Body Burden) / (Assumed Exposure Duration) / (Body Weight)
= (51 mg PCBs) / (25 years x 365 days/year) / (60 kg)
= 0.000093 mg/kg/day
= 0.093 μg/kg/day

doses when considering the studies reviewed by Tilson et al. (1990) as a basis for the chronic oral MRL—a potential shortcoming that does not apply to the carefully controlled animal studies.

Some panelists debated which uncertainty factors should be applied to the reported NOAEL to derive an MRL. Some suggested using only a factor of 10 to account for intra-species variability, but others suggested using an additional factor of 10 to account for children as a sensitive population. As Section 3.7.4 notes, the panelists discussed the applicability of this additional factor at length, but did not agree on the appropriateness of this factor for deriving an MRL. Despite these debates, several panelists noted that the NOAEL reported in the Tilson et al. 1990 paper (0.1 μg/kg/day, when rounded to one significant digit) is comparable to ATSDR's extrapolation of a NOAEL in humans from the Tryphonas study (0.2 μg/kg/day).[4] Recognizing the similarity in these levels, some panelists thought ATSDR should stress that its final MRL can be defended both by considering immunological effects in rhesus monkeys and neurodevelopmental effects in humans. In other words, some panelists recommended that ATSDR use a weight-of-evidence approach in developing its MRL.

Regardless of whether ATSDR eventually adopts the studies reviewed by Tilson et al. (1990) as the basis for its MRL, the panelists suggested that the NOAEL dose from the North Carolina study should at least be cited in the toxicological profile's LSE tables.

3.7.3 Rice Studies

Several panelists and the Submitter of a public comment suggested that ATSDR consider the findings from Dr. Deborah Rice's recent studies on behavioral effects in monkeys as a basis for an intermediate oral MRL (Rice, 1999a; 1999b). These panelists briefly summarized Dr. Rice's study, which reportedly considered doses of mixtures of PCBs at 7.5 μg/kg/day for 20 weeks to infant monkeys. According to the panelists, this dose level is comparable to that which can be observed environmentally. The monkeys were then tested for various behavioral effects at ages of 2.5 and 5 years. According to the panelists familiar with this research, Dr. Rice's study observed that the exposed monkeys had significant

[4] Two notes deserve mention. First, Dr. Rogan provided evidence that his NOAEL might be overstated by a factor of two, due to the use of an analytical method that is known to overstate PCB concentrations. As a result, a NOAEL of 0.05 μg/kg/day can be reported for the studies reviewed by Tilson et al. (1990) for the most sensitive population (i.e., embryos and children). (Note, some panelists thought an additional factor of 10 should be applied to his NOAEL to account for sensitive populations, but other panelists disagreed.) Second, the extrapolated NOAEL for the Tryphonas study was derived as follows: The LOAEL in rhesus monkeys of 5 μg/kg/day was divided by a factor of 10 to convert the LOAEL to a NOAEL of 0.5 μg/kg/day in monkeys. This NOAEL was then divided by 3 to account for interspecies variation. Therefore, ATSDR calculated the NOAEL in the non sensitive human population as 0.166 μg/kg/day, rounded up to 0.2 μg/kg/day. To account for the most sensitive population, such as the developing embryo and fetuses, ATSDR divided the 0.2 μg/kg/day by a factor of 10 and resulted in an MRL of 0.02 μg/kg/day. As a result, ATSDR's MRL (i.e., 0.02 μg/kg/day) is lower than the NOAEL in the most sensitive human subpopulation reported in the studies reviewed by Tilson et al. (1990) (i.e., 0.05 μg/kg/day).

behavioral deficits in numerous cognitive tests. These deficits include, but are not limited to, slowed learning and decreased performance on delayed spatial learning and memory tests.

Several panelists thought this study provides an adequate basis for deriving an MRL. Specifically, since the duration of exposure in this particular study was 20 weeks, the panelists noted that Dr. Rice's findings are an appropriate basis for an intermediate oral MRL.

3.7.4 Additional Comments on MRLs

In addition to the specific comments on the Tryphonas study, the Tilson review, and the Rice study, the panelists addressed several other issues pertaining to MRLs for PCBs, as summarized below:

- **Consideration of the Dutch Cohort Studies as an Alternative Basis for the Chronic Oral MRL.** Several panelists thought ATSDR should consider basing its chronic oral MRL on data recently published for the Dutch cohorts (Huisman et al. 1995; Koopman-Esseboom et al. 1994, 1996a, 1996b; Lanting et al. 1998a, 1998b, 1998c, 1998d; Pantandin et al. 1997, 1998a, 1998b, 1998c, 1998d, 1999a, 1999b; Weisglas-Kuperus 1998). Though the panelists did not specify which endpoint was found to be most sensitive in these cohorts, one panelist thought the Agency might be able to develop dose-response relationships for thyroid effects among the subjects.

  When reviewing the Dutch cohort study, some panelists identified a critical potential confounding factor: The human subjects were exposed to many chemicals of concern, including persistent, bioaccumulative toxins other than PCBs (e.g., dioxins). One panelist noted that the Dutch study reported that some adverse effects correlated with the combined exposure of dioxins and PCBs, while other effects correlated strictly with PCB exposures. As an example, this panelist indicated that learning effects among 4-year-olds were found to be PCB-specific. Several panelists agreed that working with the combined exposures to PCBs and dioxin might be complicated, but these panelists suggested that ATSDR should at least investigate the relevance of the data from the Dutch cohort studies for developing a chronic oral MRL.

- **Public Comment on Carcinogenic Effects and MRLs.** A public comment suggested that ATSDR's failure to consider carcinogenic effects when developing the MRL was "a mistake or serious oversight." ATSDR scientists explained that the MRLs, by definition, do not account for cancer effects. The panelists discussed at length various pros and cons of this approach—a discussion that focused primarily on ATSDR's health guideline policies and not specifically on PCBs, and is therefore not summarized in this report.

- **Use of Uncertainty Factors that Account for Children's Exposures.** Several panelists asked about the need for including additional uncertainty factors that account for childrens' sensitivity to PCB exposures. ATSDR scientists explained that the Agency's mandate is to *consider* use of such additional factors when developing health guidance values (i.e., the Agency is not *required* to use these factors) and that the origin of this mandate was for evaluating pesticide chemical residues, and not for PCBs. Nonetheless, some panelists recommended that ATSDR consider applying an additional uncertainty factor of 10 to the proposed MRL to protect children. Other panelists disagreed, noting that the uncertainty factor of 10 for intra-species variability was sufficient for this purpose.

- **Public Comment on an MRL Based on Other Endpoints.** One public comment suggested that ATSDR consider basing its chronic oral MRL on the reproductive and developmental effects observed in an animal study by Arnold (Arnold et al. 1995). The Submitter argued that the results of this study suggest an MRL of 0.5 μg/kg/day. None of the panelists advocated the use of this MRL, presumably because the MRLs based on the studies discussed in Sections 3.7.1 and 3.7.2 are both considerably lower than the MRL derived using the Arnold study.

4.0 REFERENCES

Anderson LM, Fox SD, Riggs CW, et al. 1993. Selective retention of polychlorinated biphenyl congeners in lung and liver after single-dose exposure of infant mice to Aroclor 1254. J Environ Pathol Toxicol Oncol 12(1):3-16.

Anderson LM, van Havere K, Budinger JM. 1983. Effects of polychlorinated biphenyls on lung and liver tumors initiated in suckling mice by N-nitrosodimethylamine. J Natl Cancer Inst 71:157-163.

Anderson LM, Ward JM, Fox SD, et al. 1986. Effects of a single dose of polychlorinated biphenyls to infant mice on N-nitrosodimethylamine-initiated lung and liver tumors. Int J Cancer 38:109-116.

Arnold, DL, Bryce F, Karpinski K, et al. 1993. Toxicological consequences of Aroclor 1254 ingestion by female rhesus (Macaca mulatta) monkeys. Part 1B. Prebreeding phase: clinical and analytical laboratory findings. Food Chem Toxicol 31(11):811-824.

Arnold DL, Bryce F, McGuire PF, et al. 1995. Toxicological consequences of Aroclor 1254 ingestion by female rhesus (Macaca mulatta) monkeys. Part 2. Reproduction and infant findings. Food Chem Toxicol 33:457-474.

Arnold DL, Nera EA, Stapley R, et al. 1996. Prevalence of endometriosis in Rhesus (*Macaca mulatta*) monkeys ingesting PCB (Aroclor 1254): Review and evaluation. Fundamental and Applied Toxicology 31(1):42-55.

Bahn AK, Grover P, Rosenwaike I, et al. 1977. PCB and melanoma [Letter]. N Engl J Med 296:108.

Bahn AK, Rosenwaike I, Herrmann N, et al. 1976. Melanoma after exposure to PCB's [Letter]. N Engl J Med 295:450.

Barsotti DA, Marlar RJ, Allen JR. 1976. Reproductive dysfunction in rhesus monkeys exposed to low levels of polychlorinated biphenyls (Aroclor 1248). Food Cosmet Toxicol 14:99-103.

Betrazzi PA, Riboldi L, Pesatori A, et al. 1987. Cancer mortality of capacitor manufacturing workers. Am J Ind Med 11:165-176.

Bove FJ; Slade, BA; Canady, RA. 1999. Evidence of Excess Cancer Mortality in a Cohort of Workers Exposed to Polychlorinated Biphenyls. Journal of Occupational and Environmental Medicine 41(9):739-741.

Brouwer A, Longnecker MP, Birnbaum LS, et al. 1999. Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. Environ Health Perspect Suppl 107(4):639-649.

Brown DP. 1987. Mortality of workers exposed to polychlorinated biphenyls -An update. Arch Environ Health 42(6):333-339.

Brown DP, Jones M. 1981. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. Arch Environ Health 36:120-129.

Chao W-Y, Hsu C-C, Guo YL. 1997. Middle-ear disease in children exposed prenatally to polychlorinated biphenyls and polychlorinated dibenzofurans. Arch Environ Health 52(4):257-262.

Chen RC, Tang SY, Miyata H, et al. 1985a. Polychlorinated biphenyl poisoning: Correlation of sensory and motor nerve conduction, neurologic symptoms, and blood levels of polychlorinated biphenyls, quaterphenyls, and dibenzofurans. Environ Res 37:340-348.

Chia LG, Chu FL. 1984. Neurological studies on polychlorinated biphenyl (PCB)-poisoned patients. Am J Ind Med 5;117-126.

Chia LG, Chu FL. 1985. A clinical and electophysiological study of patients with polychlorinated biphenyl poisoning. J Neurol Neurosurg Psychiatry 48:894-901.

Dillon et al. 1981. Food and Cosmetics Toxicology 19:437-442.

Emmett EA, Maroni M, Jefferys, et al. 1988. Studies of transformer repair workers exposed to PCBs: II. Results of clinical laboratory investigations. Am J Ind Med 14:47-62.

Fischbein A, Rizzo JN, Solomon SJ, et al. 1985. Oculodermatological findings in workers with occupational exposure to polychlorinated biphenyls (PCBs). Br J Ind Med 42:426-430.

Gartner LW, Arias IM. 1966. Studies of prolonged neonatal jaundice in the breast-fed infant. J Pediatr 68:54.

Gerhard I, Daniel B, Link S, et al. 1998. Chlorinated hydrocarbons in women with repeated miscarriages. Env Health Persp 106:675-681.

Hara I. 1985. Health status and PCBs in blood of workers exposed to PCBs and their children. Environ Health Perspect 59:85-90.

Hansen LG. 1999. PCB congener weight%s in Aroclors of 5 types. In: Hansen LG, ed. The *ortho* side of PCBs: Occurrence and disposition. Boston, MA: Kluwer Academic Publishers, 205.

Hardell L, Van Bavel B, Lindstrom G, et al. 1996. Higher concentrations of specific polychlorinated biphenyl congeners in adipose tissue from non-Hodgkin's lymphoma patients compared with controls without a malignant disease. International Journal of Oncology 9(4):603-608.

Helzlsouer KJ Alberg AJ, Huang HY, et al. 1999. Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. Cancer Epidemiology, Biomarkers, and Prevention 8:525-532.

Hsu C-C, Yu M-LM, Chen Y-CJ, et al. 1994. The Yu-Cheng rice oil poisoning incident. In: Schecter A, ed. Dioxins and health. New York, NY: Plenum Press, 661-684.

Hsu ST, Ma CI, Hsu SKH, et al. 1985. Discovery and epidemiology of PCB poisoning in Taiwan: A four-year followup. Environ Health Perspect 59:5-10.

Huisman M, Koopm-Esseboom C, Fidler V, et al. 1995. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. Early Hum Dev 41:111-127.

Hunter DJ, Hankinson SE, Laden F, et al. 1997. Plasma organochlorine levels and the risk of breast cancer. N Engl J Med 337:1253-1258.

Jacobson JL, Jacobson SW. 1996a. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med 335:783-789.

Jacobson JL, Jacobson SW. 1996b. Dose-response in perinatal exposure to polychlorinated biphenyls (PCBs): The Michigan and North Carolina cohort studies. Toxicol Ind Health 12(3/4):435-445.

Jacobson JL, Jacobson SW, Humphrey HEB. 1990a. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. J Pediatr 116:38-45.

Jacobson JL, Jacobson SW, Schwartz PM, et al. 1984a. Prenatal exposure to an environmental toxin: A test of the multiple effects model. Dev Psychol 20:523-532.

Jacobson SW, Fein GG, Jacobson JL, et al. 1985. The effect of intrauterine PCB exposure on visual recognition memory. Child Dev 56:853-860.

Kimbrough RD, Doemland ML, LeVois ME. 1999. Mortality in male and female capacitor workers exposed to polychlorinated biphenyls. Journal of Occupational and Environmental Medicine 41:161-171.

Koopman-Esseboom C, Huisman M, Weisglas-Kuperus N, et al. 1994. PCB and dioxin levels in plasma and human milk of 418 Dutch women and their infants. Predictive value of PCB congener levels in maternal plasma for fetal and infant's exposure to PCBs and dioxins. Chemosphere 28(9):1721-1732.

Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MAJ, et al. 1996a. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatrics 97:700-706.

Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MAJ, et al. 1996b. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatrics 97(5):700-706.

Kreiss, K. 1985. Studies on populations exposed to polychlorinated biphenyls. Environ Health Perspect 60:193-199.

Kuratsune M, Nakamura Y, Ikeda M, et al. 1987. Analysis of deaths seen among patients with Yusho- A preliminary report. Chemosphere 16:2085-2088.

Lanting CI, Fidler V, Huisman M, et al. 1998a. Determinants of polychlorinated biphenyls levels in plasma from 42-month-old children. Arch Environ Contam Toxicol 35:135-139.

Lanting CI, Huisman M, Muskiety FAJ, et al. 1998b. Polychlorinated biphenyls in adipose tissue, liver, and brain from nine stillborns of varying gestational ages. Pediatr Res 44(2):222-225.

Lanting CI, Patandin S, Fidler V, et al. 1998c. Neurological condition in 42-month-old children in relation to pre- and postnatal exposure to polychlorinated biphenyls and dioxins. Early Hum Dev 50:283-292.

Lanting CI, Patandin S, Weisgals-Kuperus N, et al. 1998d. Breastfeeding and neurological outcome at 42 months. Acta Paediatr 87:1224-1229.

Leeder JS, Kearns GL 1997. Pharmacogenetics in pediatrics: implications for practice. Pediatric Clinics of North America 44:55-77.

Levinskas GJ, Martin DP, Seibold HR, et al. 1984. Aroclor 1254: Reproduction study with Rheseus monkeys (macaca mulatta). [Unpublished study]

Lonky E, Reihman J, Darvill T, et al. 1996. Neonatal behavioral assessment scale performance in humans influenced by maternal consumption of environmentally contaminated Lake Ontario fish. J Great Lakes Res 22(2):198-212.

Loomis D, Browning SR, Schenck AP, Gregory E, Savitz DA. 1997. Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. Occup Envrion Med 54(10):720-8.

Luster MI, Munson AE, Thomas PT, et al. 1988. Development of a testing battery to assess chemical-induced immunotoxicity: National Toxicology Program's guidelines for immunotoxicity evaluation in mice. Fundam Appl Toxicol 10:2-9.
Luster MI, Portier C, Pait DG, et al. 1992. Risk assessment in immunotoxicology: I. Sensitivity and predictability of immune tests. Fundam Appl Toxicol 18:200-210.

Masuda Y. 1994. The Yusho rice oil poisoning incident. In: Schecter A., ed. Dioxins and health. New York, NY: Plenum Press, 633-659.

Mayes BA, McConnell EE, Neal BH, et al. 1998. Comparative carcinogenicity in Sprague-Dawley rats of the polychlorinated biphenyl mixture aroclors 1016, 1242, 1254, and 1260. Toxicol Sci 41(1):62-76.

Mendola P, Buck GM, Sever LE, et al. 1997. Consumption of PCB-contaminated freshwater fish and shortened menstrual cycle length. American Journal of Epidemiology 146(11)955-960.

Nagayama J, Iida T, Hirakawa H, et al. 1997. Effects of lactational exposure to chlorinated dioxins and related chemicals on thyroid functions in Japanese babies. Organohalogen Compounds 33:446-450.

Paneth N. 1991. Human reproduction after eating PCB-contaminated fish. Health Environ Digest 5:4-6.

Pantaleoni G, Fanini D, Sponta AM, et al. 1988. Effects of maternal exposure to polychlorinated biphenyls (PCBs) on F1 generation behavior in the rat. Fund Appl Toxicol 11:440-449.

Patandin S, Weiglas-Kuperus N, de Ridder MAJ, et al. 1997. Plasma polychlorinated biphenyl levels in Dutch preschool children either breast-fed or formula-fed during infancy. Am J Public Health 87:1711-1714.

Patandin S, Dagnelie PC, Mulder PGH, et al. 1998a. Dietary exposure to polychlorinated biphenyls and dioxins from infancy until adulthood: A comparison between breast-feeding, toddler, and long-term exposure. Environ Health Perspect 107:45-51.

Patandin S, Dagnelie PC, Weisglas-Kuperus N, et al. 1998b. Exposure to PCBs, PCDDs and PCDFs through breast milk compared with long-term dietary exposure. Organohalogen Compounds 38:214A-214F.

Patandin S, Koopman-Esseboom C, De Ridder MAJ, et al. 1998c. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. Pediatr Res 44(4):538-545.

Patandin S, Koopman-Esseboom C, De Ridder MAJ, et al. 1998d. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. Pediatr Res 44(4):538-545.

Patandin S, Dagnelie PC, Mulder PGH, et al. 1999a. Dietary exposure to polychlorinated biphenyls and dioxins from infancy until adulthood: A comparison between breast-feeding, toddler, and long-term exposure. Environ Health Perspect 107:45-51.

Patandin S, Lanting CI, Mulder PGH, et al. 1999b. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J Pediatr 134:33-41.

Pessah IN. 1997. Non-coplanar PCBs alter neuronal Ca^{2+} regulation and neuroplasticity by a FKBP12/ryanodine receptor-mediated mechanism. Toxicologist 36:333.

Rao CV, Banerji SA. 1993. Effect of polychlorinated biphenyls (Aroclor 1260) on histology of adrenal of rats. J Environ Biol 14:1-6.

Rice DC. 1999a. Behavioral impairment produced by low-level postnatal PCB exposure in monkeys. Environ Res 80:S113-S121.

Rice DC. 1999b. Effect of exposure to 3,3',4,4',5-pentachlorobiphenyl (PCB 126) throughout gestation and lactation on development and spatial delayed alternation performance in rats. Neurotoxicol Teratol 21(1):59-69.

Rogan WJ, Gladen BC. 1991. PCBs, DDE, and child development at 18 and 24 months. Ann Epidemiol 1(5):407-413.

Rogan WJ, Glad BC, Hung KL, et al. 1988. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. Science 241:334-336.

Rogan WJ, Gladen BC, McKinney JD, et al. 1986. Neonatal effects of transplacental exposure to PCBs and DDE. J Pediatr 109:335-341.

Rothman N, Canter KP, Blair A, et al. 1997. A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues. Lancet (British Edition) 350(9073):240-244.

Schantz SL. 1996. Developmental neurotoxicity of PCBs in humans: What do we know and where do we go from here? Neurotoxicol Teratol 18(3)212-27, 229-76.

Sinks T, Steele G, Smith AB, et al. 1992. Mortality among workers exposed to polychlorinated biphenyls. Am J Epidemiol 136(4):389-398.

Smith AB, Schloemer J, Lowry LK, et al. 1982. Metabolic and health consequences of occupational exposure to polychlorinated biphenyls. Br J Ind Med 39:361-369.

Stewart P, Darvill T, Lonky E, et al. 1999. Assessment of prenatal exposure to PCBs from maternal consumption of Great Lakes fish: An analysis of PCB pattern and concentration. Environ Res 80:S87-S96.

Swain WR. 1991. Effects of organochlorine chemicals on the reproductive outcome of humans who consumed contaminated Great Lakes fish: An epidemiologic consideration. J Toxicol Environ Health 33:587-639.

Tilson et al. 1990. Polychlorinated Biphenyls and the Developing Nervous System: Cross-Species Comparisons. Neurtoxicology and Teratology 12:239-248.

Tryphonas H, Hayward S, O'Grady L, et al. 1989. Immunotoxicity studies of PCB (Aroclor 1254) in the adult rhesus (Macaca mulatta) monkey—preliminary report. Int J Immunopharmacol 11:199-206.

Tryphonas H, Luster MI, Schiffman G, et al. 1991b. Effect of chronic exposure of PCB (Aroclor 1254) on specific and low specific immune parameters in the rhesus (Macaca mulatta) monkey. Fund Appl Toxicol 16:773-786.

Weiglas-Kuperus N. 1998. Neurodevelopmental, immunological and endocrinological indices of perinatal human exposure to PCBs and dioxins. Chemosphere 37(9-12):1845-1853.

Winneke G, Bucholski A, Heinzow B, et al. 1998. Developmental neurotoxicity of polychlorinated biphenyls (PCBs): cognitive and psychomotor functions in 7-month old children. Toxicol Lett 102-103:423-428.

Wong PW, Pessah IN. 1996. *Ortho*-substituted polychlorinated biphenyls alter calcium regulation by a ryanodine receptor-mediated mechanism: structural specificity toward skeletal- and cardiac-type microsomal calcium release channels. Mol Pharmacol 49:740-751.

Wong PW, Pessah IN. 1997. Noncoplanar PCB 95 alters microsomal calcium transport by an immunophilin FKBP12-dependent mechanism. Mol Pharmacol 51:693-702.

APPENDIX A
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List of Participants and Observers for the Expert Panel Review for PCBs (September 27 - 29, 1999)

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APPENDIX B

AGENDA

Agenda for the Expert Panel Review of the Toxicological Profile for PCBs

September 27, 1999

Morning Session

10:00 Meeting convenes
Welcome and Introduction:
Dr. Henry Falk, Assistant Administrator, ATSDR

Review of Agenda and Meeting Objectives:
Dr. Christopher T. De Rosa, Director, Division of Toxicology

10:15 Developmental Effects (Chapter 2)

12:00 **Lunch**

Afternoon Session

1:00 Continue Developmental Effects Discussion

2:00 Neurobehavioral, Neurodevelopmental, Children (Chapter 2)

3:15 Break

3:30 Endocrine Disruption (Chapter 2)

5:00 Adjourn Meeting

September 28, 1999

Morning Session

8:30 Discussion of Other Health Effects

- Reproductive
- Dermal
- Respiratory
- Other

10:30 Discussion of Chronic Oral MRL and Immunological Effects

- Comparison of studies' merits as critical MRL study
- Appropriateness of study end-points for use in MRL derivation
- Potential confounders in epidemiologic studies
- Applicability\comparison of end-points across studies
- Critical effects and uncertainty factor selection
- Animal Sensitivities
- Congeners
- PCB planar vs coplanar
- Dioxin-like; phenobarbital-like; estrogen-like PCBs
- Other issues

12:00 **Lunch**

Afternoon Session

1:15 Discussion of the Following Cancer Issues:

- Weight-of-the-evidence
- Breast Cancer
- GIT Cancer
- Non-Hodgkins Lymphoma
- Hepatocellular Carcinoma
- Melanoma and Squamous Cell Carcinoma
- Yusho and Yu-Cheng incidents and cancer

2:30 Break

2:45 Continue Cancer Discussion

5:00 Adjourn meeting

September 29, 1999

Morning Session

8:30 Review of Chemical and Physical Information (Chapter 3)
Response to Public Comments

9:15 Review of Production, Import, Use and Disposal (Chapter 4)

9:45 Review of Potential for Human Exposure (Chapter 5)

10:30 Review of Analytical Methods (Chapter 6) and Other Issues

11:15 Break

11:30 Discussion of Public Health Statement (Chapter 1)
Response to public comments regarding general issues

12:00 - 12:30 Wrap-up and Next Steps